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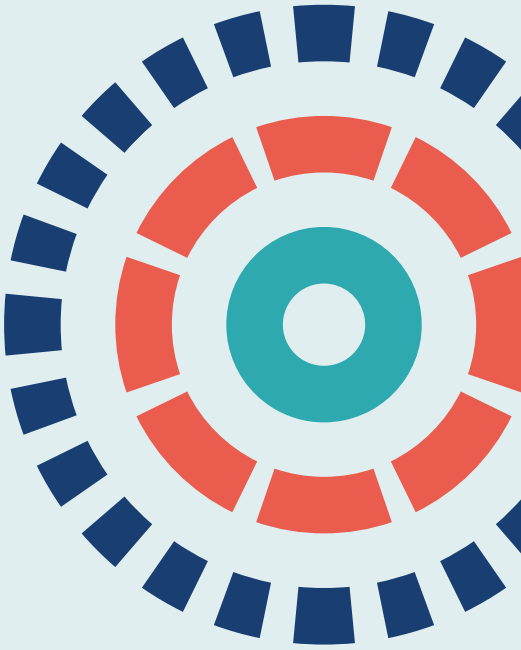

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Prophylactic removal of impacted mandibular third molars: a systematic review and economic evaluation

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This report

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Abstract

Prophylactic removal of impacted mandibular third molars: a systematic review and economic evaluation

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Background: Impacted third molars are third molars that are blocked, by soft tissue or bone, from fully erupting through the gum. This can cause pain and disease. The treatment options for people with impacted third molars are removal or retention with standard care. If there are pathological changes, the current National Institute for Health and Care Excellence guidance states that the impacted third molar should be removed.

Objective: The objective of this study was to appraise the clinical effectiveness and cost-effectiveness of the prophylactic removal of impacted mandibular third molars compared with retention of, and standard care for, impacted third molars.

Methods: Five electronic databases were searched (1999 to 29 April 2016) to identify relevant evidence [The Cochrane Library (searched 4 April 2016 and 29 April 2016), MEDLINE (searched 4 April 2016 and 29 April 2016), EMBASE (searched 4 April 2016 and 29 April 2016), EconLit (searched 4 April 2016 and 29 April 2016) and NHS Economic Evaluation Database (searched 4 April 2016)]. Studies that compared the prophylactic removal of impacted mandibular third molars with retention and standard care or studies that assessed the outcomes from either approach were included. The clinical outcomes considered were pathology associated with retention, post-operative complications following extraction and adverse effects of treatment. Cost-effectiveness outcomes included UK costs and health-related quality-of-life measures. In addition, the assessment group constructed a de novo economic model to compare the cost-effectiveness of a prophylactic removal strategy with that of retention and standard care.

Results: The clinical review identified four cohort studies and nine systematic reviews. In the two studies that reported on surgical complications, no serious complications were reported. Pathological changes due to retention of asymptomatic impacted mandibular third molars were reported by three studies. In these studies, the extraction rate for retained impacted mandibular third molars varied from 5.5% to 31.4%; this variation can be explained by the differing follow-up periods (i.e. 1 and 5 years). The findings from this review are consistent with the findings from previous systematic reviews. Two published cost-effectiveness studies were identified. The authors of both studies concluded that, to their knowledge, there is currently no economic evidence to support the prophylactic removal of impacted mandibular third molars. The results generated by the assessment group's lifetime economic model indicated that the incremental cost-effectiveness ratio per quality-adjusted life-year gained for the comparison of a prophylactic removal strategy with a retention and standard care strategy is £11,741 for people aged 20 years with asymptomatic impacted mandibular third molars. The incremental cost per person associated with prophylactic extraction is £55.71, with an incremental

quality-adjusted life-year gain of 0.005 per person. The base-case incremental cost-effectiveness ratio per quality-adjusted life-year gained was found to be robust when a range of sensitivity and scenario analyses were carried out.

Limitations: Limitations of the study included that no head-to-head trials comparing the effectiveness of prophylactic removal of impacted mandibular third molars with retention and standard care were identified with the assessment group model that was built on observational data. Utility data on impacted mandibular third molars and their symptoms are lacking.

Conclusions: The evidence comparing the prophylactic removal of impacted mandibular third molars with retention and standard care is very limited. However, the results from an exploratory assessment group model, which uses available evidence on symptom development and extraction rates of retained impacted mandibular third molars, suggest that prophylactic removal may be the more cost-effective strategy.

Future work: Effectiveness evidence is lacking. Head-to-head trials comparing the prophylactic removal of trouble-free impacted mandibular third molars with retention and watchful waiting are required. If this is not possible, routine clinical data, using common definitions and outcome reporting methods, should be collected.

Study registration: This study is registered as PROSPERO CRD42016037776.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 30. See the NIHR Journals Library website for further project information.

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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 as a result of 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 treatment and the last treatment for a given diagnosis.

List of abbreviations

2M	second molar
3M	third molar
AG	assessment group
BAOS	British Association of Oral Surgeons
BDA	British Dental Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
DCC	distal cervical caries
FDS	Faculty of Dental Surgery
FGDP	Faculty of General Dental Practice
GI	Gingival Index
HRQoL	health-related quality of life
I3M	impacted third molar
ICER	incremental cost-effectiveness ratio
IM3M	impacted mandibular third molar
M2M	mandibular second molar
M3M	mandibular third molar
MTA	multiple technology appraisal
NHS EED	NHS Economic 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
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TA	technology appraisal
UDA	unit of dental activity

Plain English summary

Third molars, commonly known as wisdom teeth, may come through the gum (erupt) without any problems, usually during young adulthood (aged 18–24 years). 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 reviewed this practice and recommended that these teeth should not be removed if they are 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 later in life, 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 effectiveness 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 those of nine previous reviews. There is also very little research reported that relates to the cost-effectiveness of the procedure, with only three studies identified.

With the available evidence on the rates of extraction and the symptoms experienced by people who keep their impacted mandibular third molar, we built an exploratory economic model to assess the cost-effectiveness of recommending prophylactic removal compared with that of recommending watchful waiting. Results from the model suggested 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 that are associated with the two strategies are compared, the resulting statistic is £11,741 per quality-adjusted life-year gained, which would probably be good value for money for the NHS.

Scientific summary

Background

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

The treatment options for people with impacted third molars are either surgical removal or standard care without prophylactic removal of the third molars.

The decision to remove or retain an impacted third molar depends on whether or not it is asymptomatic and/or pathology free. When there are pathological changes, the current National Institute for Health and Care Excellence guidance states that the impacted third molar should be removed. Even if an impacted third molar 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 effectiveness and cost-effectiveness of the prophylactic removal of impacted mandibular third molars compared with that of standard care without prophylactic removal of impacted mandibular third molars.

Methods

Clinical effectiveness review

Five electronic databases were searched (from 1999 to 29 April 2016) for clinical trials (randomised and non-randomised), observational studies, systematic reviews, decision analyses and UK costs. Studies that compared the prophylactic removal of impacted mandibular third molars with standard care without prophylactic removal or studies that assessed the outcomes of either approach were considered. The outcomes of interest were the pathology associated with the 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 the relevant publications; and quality assessed the included studies. The results of the data extraction and (clinical) quality assessment are summarised in structured tables and in a narrative description in the main report. No meta-analysis or network meta-analyses were undertaken.

Cost-effectiveness review

The search strategy that was 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 impacted third molars. As part of the search strategy, the NHS Economics Evaluation Database located

within The Cochrane Library and EconLit (via EBSCO*host*) were also searched. Two reviewers independently screened all titles and/or abstracts and applied inclusion criteria to identify relevant studies.

Economic model

Owing to the absence of cost–utility analyses that were relevant to the decision problem and generalisable to the NHS in England, the assessment group constructed a de novo economic model. Two pathways are considered: (1) the intervention, namely prophylactic removal of impacted mandibular third molars, and (2) the comparator, namely current standard of care (watchful waiting). The pathways were modelled as a combination of Markov model processes and decision trees. The model perspective was that of the UK NHS, the time horizon was a lifetime (80 years), the outcomes were measured in quality-adjusted life-years and both costs and quality-adjusted life-years 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

In total, 13 studies from 22 publications were included in the systematic review (four cohort studies and nine systematic reviews).

Cohort studies

The four cohort studies included one observational cohort that investigated the prophylactic removal of pathology-free or asymptomatic impacted mandibular third molars in comparison with the standard care and retention of these pathology-free or asymptomatic impacted mandibular third molars. Annual assessment over 5 years identified patients as requiring and subsequently having an impacted mandibular third molar removed, requiring and refusing extraction of an impacted mandibular third molar and not requiring removal of the impacted mandibular third molar.

No serious surgical complications were reported in the 52 participants who had an impacted mandibular third molar removed. Of those requiring removal but refusing, five out of seven participants required extraction within the follow-up period. Finally, out of those not requiring removal, zero out of 25 participants required extraction within the follow-up period.

Two single-cohort studies investigated standard care without removal of pathology-free or asymptomatic impacted mandibular third molars. For one study, assessments were conducted over the telephone every 6 months for 5 years, and for the other study a clinician questioned and assessed clinical outcomes at 1 year. The difference in the length of follow-up periods explains the differences in the rates of extraction reported by each paper: 5.5% for the study with a 1-year follow-up and 31.4% for the study with a 5-year follow-up. The reasons for extraction also varied between the studies. One study reported that, at 1 year, 46% of participants did not know why the impacted mandibular third molar had been removed. Of those participants who did know why, 50% of the impacted mandibular third molars 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-free or asymptomatic impacted mandibular third molars. An assessment of periodontal health was conducted prior to and at 6 months after removal and post-surgical complications were reported. There was no statistically significant change in plaque index and Gingival Index, but there was a statistically significant reduction in the mean probing pocket depth and probing attachment level. A total of 20 post-surgical complications were reported; the most frequently reported were intense pain for > 1 day (12/78 participants), post-operative infection (5/78 participants) and wound dehiscence (3/78 participants). No instances of secondary bleeding or nerve damage were reported.

Systematic reviews

Nine systematic reviews of the management of third molars were included in this review, although none was limited to impacted mandibular third molars. The inclusion criteria for the systematic reviews differed, resulting in a wide range of included primary studies. Despite the differences in systematic reviews, the conclusions were similar, with seven out of the nine systematic reviews stating that there was insufficient evidence on which to base a decision. One systematic review that looked at the risk of future extraction following the retention of trouble-free third molars found that the mean incidence rate of future extraction was 3% 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 provided economic evidence on the cost-effective prophylactic removal of impacted third molars. Two of the studies reported details about the cost-effectiveness of the prophylactic removal of impacted third molars. One of these studies is a cost-effectiveness study from a UK NHS perspective, whereas one study is of less direct relevance, as the estimates are based on the Australian health-care system and the results are presented in Australian dollars. The third study reports findings that relate to an assessment of oral health-related quality of life after the removal of impacted third molars.

Economic model

Comparing prophylactic removal with watchful waiting, exploratory model results show that the incremental cost per person that is associated with prophylactic extraction is £56 and the incremental quality-adjusted life-year gain is 0.005 per person. Combining the cost and the quality-adjusted life-year results that were generated by the model suggests an incremental cost-effectiveness ratio for the comparison of a prophylactic removal strategy with a watchful waiting strategy of £11,741 per quality-adjusted life-year gained for people aged 20 years with asymptomatic impacted mandibular third molars. The base-case incremental cost-effectiveness ratio per quality-adjusted life-year 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 systematic review of clinical evidence found no randomised controlled trial data to support or refute the prophylactic removal of pathology-free/trouble-free impacted mandibular third molars. The review, however, did identify evidence from two longitudinal studies that demonstrated the outcomes when asymptomatic impacted mandibular third molars are left in situ. No studies reported the impact of retention on the status of the second molars, although this may have been a result of the narrow inclusion criteria, which included people with pathology-free or trouble-free impacted mandibular third molars. This criterion 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 impacted mandibular third molars with 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 concluded that there is currently no economic evidence to support the prophylactic removal of impacted third molars. This is in contrast to the results generated by the assessment group's economic model, which suggest that prophylactic removal may be the more cost-effective strategy.

The strengths of the assessment group's exploratory economic model include its simplicity and the minimal use of assumptions. It is constructed around two key parameters: (1) the annual rates of symptom development and (2) the extraction of pathology-free/trouble-free impacted mandibular third molars. Unfortunately, the economic model is limited by the lack of utility evidence around impacted mandibular third molar symptoms; however, suitable proxies were found for utility values and cost-effectiveness findings are robust across a range of utility values that could be used.

A further limitation of the assessment group's exploratory economic model is that head-to-head trial evidence of a closely adhered to policy of watchful waiting as opposed to prophylactic removal could not be found and is therefore not used to inform model assumptions. For this reason, real-world observational evidence on symptom development and extractions with NHS dentistry operating under a recommendation of watchful waiting were used in the model. The findings of the model should be interpreted as a comparison of a strategy to recommend watchful waiting with a strategy of recommending prophylactic removal of impacted mandibular third molars.

Conclusions

Clinical effectiveness conclusions

The findings from this review are consistent with previous systematic reviews in that there is no available randomised controlled trial evidence to support or refute the practice of the prophylactic removal of asymptomatic/pathology-free impacted mandibular third molars. However, the review did identify evidence from longitudinal studies demonstrating what happens when asymptomatic impacted mandibular third molars 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 concluded that there is currently no economic evidence to support the prophylactic removal of impacted third molars.

The base-case results generated by the assessment group economic model indicated that the incremental cost-effectiveness ratio per quality-adjusted life-year gained for the comparison of the cost-effectiveness of a prophylactic removal strategy with that of a watchful waiting strategy is markedly less than the £20,000 per quality-adjusted life-year gained threshold widely accepted by the National Institute for Health and Care Excellence's Appraisal Committees.

Implications for service provision

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

The results that were generated by the economic model, supported by published observational studies, suggest that most people with impacted mandibular third molars will have their impacted teeth removed at some point and that, although prophylactic removal is probably more costly than a watchful waiting strategy, the improvements in health-related quality of life for people from a reduction in impacted mandibular third molar symptoms suggest that prophylactic removal may, in the authors' opinion, be 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 impacted mandibular third molars could be designed to record the impaction status and health of the retained impacted mandibular third molar with results being presented separately for maxillary and mandibular teeth.

Study registration

This study is registered as PROSPERO CRD42016037776.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 30. See the NIHR Journals Library website for further project information.

Chapter 1 Background

Description of health problem

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

For some patients, 3Ms erupt fully, whereas, 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; 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.*[3] assert that, although there is extensive literature regarding the extraction of 3Ms, '[t]here 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 . . . [w]ith the current emphasis in dentistry being placed on clinicians to make evidence-based decisions.'[3]

There is a 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, whereas 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 that is 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 to relate to the removal of pathology-free 3Ms to avoid potential problems in the future.

Aetiology, pathology and prognosis

Impacted third molars are classified on the basis of their location (mandibular or maxillary), eruption status, nature of impaction, angulation of impaction and 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 be observed only through radiographic assessment.[5] Eruption status is described in *Table 1*.

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; this is known as 'partial bony impaction' when partially erupted or as 'complete bony impaction' when unerupted and not communicating with the mouth.

TABLE 1 Eruption status

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 angulation can be based on Winter's classification,[6] whereby the 3M could be:

- mesioangular [angled towards the second molar (2M)]
- distoangular (angled away from the 2M)
- horizontal
- vertical
- buccal (angled towards the cheek)
- lingual (angled towards the tongue).

Based on Pell and Gregory's[7] classification 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 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.*,[8] the prevalence of pathological changes in I3Ms is higher in impacted mandibular third molars (IM3Ms) than in impacted maxillary 3Ms.

Pericoronitis

Pericoronitis is an infection of the soft tissue surrounding the crown of the tooth and is caused by an accumulation of bacteria and debris beneath the soft tissue. This can result in inflammation and pain. When 3Ms are impacted, an area is created that is difficult to clean properly with a toothbrush, which makes 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 teeth 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

The early stages of gum disease include red and swollen gums and bleeding gums after tooth-brushing, which 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, can lead to chronic gum inflammation that 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 that is caused by bacteria that metabolise sugar in the diet to form acids. A longitudinal study[10] in the USA followed patients with at least one 3M below the occlusal plane at baseline that had erupted during the follow-up period

(median follow-up period 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 a study[12] of 1231 non-veteran volunteers revealed that the presence of a 3M that was soft-tissue impacted increased the risk of incident 2M pathology by 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 56.6% for those with bony impaction.[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, although 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: dentigerous cysts (14.1%), calcifying odontogenic cysts (6.6%) and odontogenic keratocysts (2.5%).[15]

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 that 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]

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 2016 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[18] 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 that there was no difference in the incidence of impaction between 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 who were 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 a hospital for assessment. Details of the eruption and symptom status of all 3Ms at the time of presentation are shown in *Table 2*. In the data available/recorded, the majority of mandibular third molars (M3Ms) (69.4%) were impacted, whereas maxillary 3Ms were more likely to be classified as 'present and functional' or 'absent'.

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% vs. 71%, respectively). The most frequent indication for extraction was prophylactic removal ($n = 8772$, 44%), followed by pericoronitis ($n = 7896$, 40%). There were differences in the rates of 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 as a result of pericoronitis, compared with 8% of maxillary 3Ms.

TABLE 2 Eruption status and symptom status of all 3M teeth

	3M teeth (%)			
	Maxillary		Mandibular	
Status	Right ($n = 5191$)	Left ($n = 5700$)	Left ($n = 7049$)	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

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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 and Renton[19] reported that the mean age of patients having 3Ms removed had increased from 25 years in 2000 to 32 years in 2010, with the most common age increasing from 26 to 29 years (CIs not reported).

Impact of the health problem

Prior to the introduction of the NICE guidance in 2000,[2] the removal of 3Ms was one of the most common of all surgical procedures performed in the UK, with > 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 £30M per year, with additional estimated costs of £20M in the private sector.[20]

The authors of a 2012 study[19] investigating the effects of the 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) had reduced from ≈ 60,000 in the 1990s to ≈ 40,000 in 2003. However, since 2003, the number of removals appeared to have increased to ≈ 65,000 during 2009/10 (inpatient/day case only).

Information provided to NICE in the British Dental Association (BDA) (McArdle LW, British Dental Association, 2016, NICE submission) and the Faculty of General Dental Practice (FGDP) (Renton T, FGDP, 2016, NICE submission) submissions suggested that the prophylactic removal of 3Ms prevents future harm to patients. These organisations argue that the introduction of the 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 aged > 25 years are at a higher risk of surgical morbidity relating to 3M extraction (Renton T, NICE submission). 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 (McArdle LW, NICE submission).

Current service provision

Management of disease

The treatment options for people with I3Ms are surgical removal or standard care without prophylactic removal of 3Ms.

Surgical removal

A report[21] by the Royal College of Surgeons of England states that 3M surgical procedures are generally suitable for day case management, and that it is recognised that treatment under local anaesthesia, with or without sedation, is associated with reduced complication rates.

Removal of I3Ms can be carried out by a dentist, or patients can be referred to an oral surgeon if the degree of impaction or position of the tooth indicates that a more complex surgical procedure is required. If 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.[22] 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). Furthermore, nerve damage may occur; this 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%.[23] The removal of M3Ms (regardless of eruption status) is much more likely to be associated with post-surgical complications than the removal of maxillary 3Ms.[24] 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.[25] 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) of patients, the damage is permanent.[22] 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% likely to experience permanent damage.[22]

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 time between recalls.[26] 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 or not it is asymptomatic (pathology or trouble free). When there are pathological changes, current NICE guidance[2] states that the I3M should be removed.

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 (Renton T, NICE submission), 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 (Renton T, NICE submission).

There is significant geographical variation in current practice when international guidelines are examined.[21,27–34] The American[31] 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.

There is variation between services relating to the use of either general anaesthesia or local anaesthesia and sedation. There are published data[35] that illustrate that only 3% of IM3M cases in a London teaching hospital required general anaesthetic, with 40% of cases requiring intravenous sedation. However, our clinical advisor has pointed out that not all district general hospitals offer sedation services for dental extractions; therefore, the proportion of patients who receive 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 patients of these practices 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, the provision of patient information, the provision of pre-operative mouth rinses, the provision of analgesia and the rates of antibiotic prescription (Renton T, NICE submission).

Relevant UK guidelines

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

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 that 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.

BOX 1 Current NICE guidance[2] on the extraction of wisdom teeth

1. The practice of prophylactic removal of pathology-free impacted third molars should be discontinued in the NHS.
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).
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.
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.

Description of the technology under assessment

Summary of the 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[36] clearly outlines social, medical and dental factors that dictate the optimal setting (Renton T, NICE submission).

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

Identification of important subgroups

There is intrapatient variance in the presentation of I3Ms, that is a single patient can have multiple 3Ms (i.e. maxillary as well as mandibular and bilateral presence) with different types of impaction (i.e. vertical, horizontal, distoangular and mesioangular). These are the most common impaction types considered as subgroups, although 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 (McArdle LW, NICE submission).

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 (Renton T, NICE submission).

Chapter 2 Definition of the decision problem

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

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*.

Overall aims of assessment

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

What is not included in the assessment

It is beyond the remit of this assessment report to comment on or to 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. 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.'

TABLE 3 Decision problem issued by NICE[11]

Criteria	Inclusion criteria
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 and 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 effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies that are being compared Costs will be considered from an NHS and Personal Social Services perspective
Other considerations	If evidence allows, consideration may be given to people with mesioangular or horizontally impacted third molars

Reproduced with permission from NICE.[11] © NICE (2016). *Third Molars (Impacted) – Prophylactic Removal [ID898]. Final Scope.* All rights reserved and subject to NICE 'Notice of Rights'. Available from www.nice.org.uk/guidance/indevelopment/gid-tag525. NICE guidance is prepared for the National Health Service in England. It is subject to regular review and updating and may be withdrawn.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

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 from 1999 onwards: MEDLINE, EMBASE, The Cochrane Library, NHS Economic Evaluation Database (NHS EED) and EconLit. The search strategies used are presented in *Appendix 1*.

In addition to the electronic databases, information on studies that were in progress were sought by searching the International Standard Randomised Controlled Trial Number registry.

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 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA].

Inclusion and exclusion criteria

Two out of the three reviewers (JH, GP and RD) independently screened all of the titles and abstracts identified by the initial search using Covidence (Melbourne, VIC, Australia). Full-text copies of any titles/abstracts that may have been eligible were obtained and assessed for inclusion by two reviewers (JH and 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 were summarised. For studies that were identified as not meeting the criteria at the data abstraction stage, the bibliographic details and reasons for exclusion were summarised.

The eligibility criteria reflected the decision problem from NICE;[11] additional criteria were that studies were based in settings with a similar dental system to that in the UK (i.e. Europe, North America, Australasia), English-language papers (owing to a lack of resources to translate non-English-language papers) and the time frame of 1999 onwards, because this was a partial update of the previous NICE guidance.[2] The inclusion criteria for SRs were necessarily broader and were not restricted to those looking at IM3Ms only.

Data abstraction strategy

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

TABLE 4 Inclusion and exclusion criteria (clinical effectiveness)

	Criteria	
	Inclusion	**Exclusion**
Study design	• Clinical trials (randomised and non-randomised) • Observational studies • Systematic reviews • Decision analyses	• Case studies • Non-SRs
Patient population	People with IM3Ms	
Intervention	Prophylactic removal of IM3Ms (as defined by study authors)	
Comparator	Standard care without prophylactic removal of IM3Ms	
Outcomes	The outcome measures to be considered included: • Pathology associated with retention of 3Ms • 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 people with mesioangular or horizontally I3Ms	
Limits	• 1999 onwards • English language only	

Critical appraisal strategy

The quality of the included studies was assessed by one reviewer (Juliet Hounsome or Joanne Fisher) and independently checked for agreement by a second reviewer (Juliet Hounsome or Joanne Fisher). Disagreements were resolved through consensus. The quality of the cohort studies was assessed using an adapted version of the Newcastle–Ottawa Scale for assessing the quality of cohort studies[37] and SRs were assessed according to criteria outlined by the Centre for Reviews and Dissemination.[38]

Methods of data synthesis

The results of the data extraction and quality assessment for each included study are presented in structured tables (see *Tables 5–9* and *Appendices 3* and *4*) and as a narrative summary (see following section).

Results

Quantity and quality of research available

The results of the electronic searches (conducted on 4 April 2016) and the application of the inclusion criteria are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in *Figure 1*.

In total, 22 citations,[20,39–59] reporting the results of nine SRs[20,40,42–46,50,56] and four cohort studies,[47,48,58,59] 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 2*.

As shown in *Figure 1*, a total of 72 papers were initially included at full-text review. However, on further inspection, no relevant data for the specific population of interest for this review were available for 50 papers; these papers were subsequently excluded. The bibliographic details, with the reasons for exclusion, for these 50 studies are also reported in *Appendix 2*.

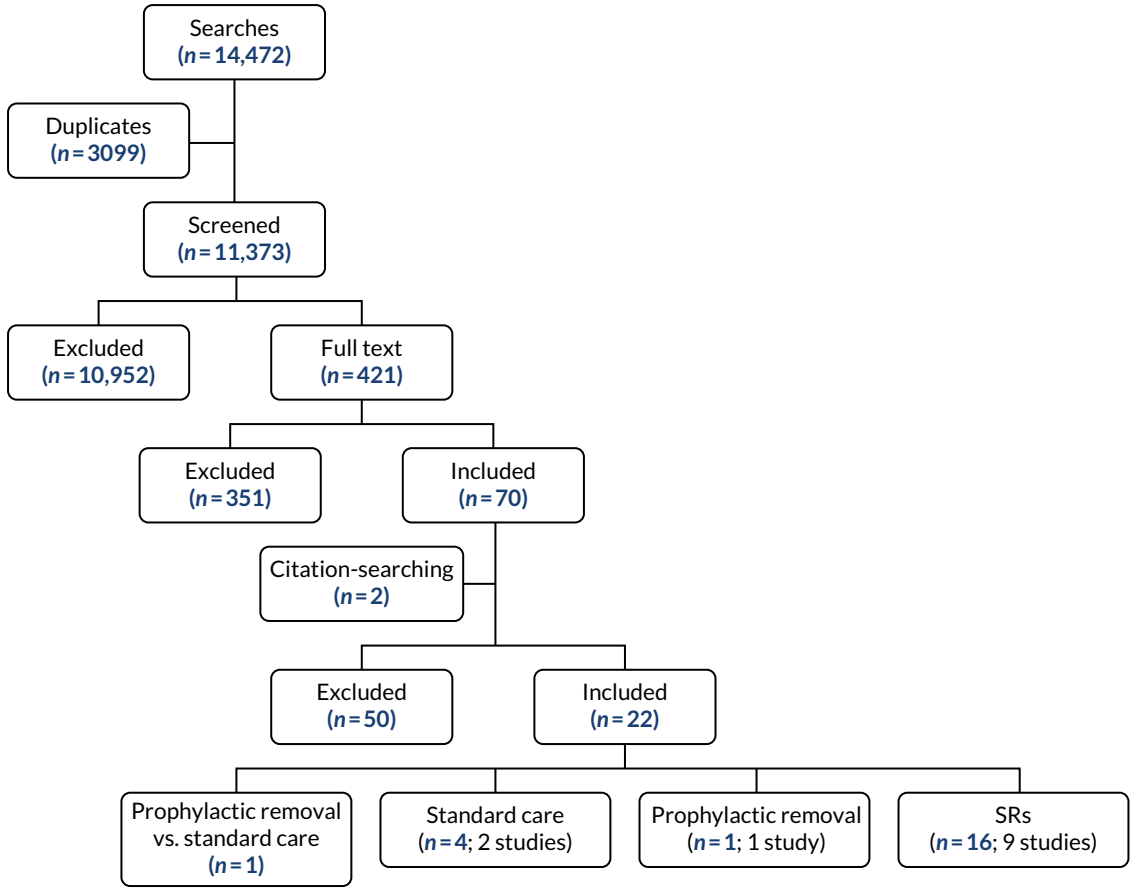

FIGURE 1 The PRISMA flow diagram: clinical evidence review.

One study[58] reported on outcomes both for standard care with and standard care without prophylactic removal of IM3Ms. Four papers[39,47,48,57] reported on two studies that assessed the outcomes of standard care without prophylactic removal of IM3Ms, and one paper[59] reported on a study that assessed prophylactic removal of IM3Ms. A further 16 papers[20,40–46,49–56] reported on nine SRs that assessed whether or not I3Ms should be removed prophylactically.

Quality assessment: cohort studies

The quality of the four included cohort studies[47,48,58,59] was assessed using an adapted version of the Newcastle–Ottawa Scale;[37] the results are tabulated in *Table 5*.

TABLE 5 Quality assessment of cohort studies

Characteristic	Study			
	Vares and Kyyak, 2014[58]	Fernandes *et al.*, 2010[48]	Hill and Walker, 2006[47]	Petsos *et al.*, 2016[59]
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 rate (%)	No description	31	9	14

All of the studies, with the exception of the Vares and Kyyak[58] study, included patients who were representative of the population of interest. Clinical records were used in all four studies[47,48,58,59] to ascertain whether or not patients were 'exposed' to the intervention (either retention and 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 that the assessment of the 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%,[47] 14%[59] and 31%.[48] No details of study attrition were reported by Vares and Kyyak.[58] To conclude, the AG considered all but one[58] of the studies to be generally good-quality cohort studies. However, missing information in the Vares and Kyyak[58] paper meant that it was not possible to adequately assess the quality of this study.

Quality assessment: systematic reviews

The quality of the nine SRs[20,40,42–46,50,56] was assessed in accordance with criteria outlined by the Centre for Reviews and Dissemination.[38] The results of the quality assessment are shown in *Appendix 3*.

Seven of the SRs had defined clear review questions in terms of population, interventions, comparators and outcomes;[20,40,42–44,46,50] however, these details were missing in two SRs.[45,56] Only three reviews[20,45,46] had an adequate search strategy without language or date restrictions. Two reviews were limited by language only: one review to English, Dutch, French or German[40] and one review to English.[44] One review[43] was restricted by both language (English, Danish, Norwegian or Swedish) and date (1999–2003). Another review was restricted by date only (1999–2003).[50] The search terms used were not reported in the clinical evidence publications[56] or in the Canadian Agency for Drugs and Technologies in Health (CADTH) SR,[42] which were also restricted by date and language. Three SRs[20,40,46] provided adequate information to facilitate the assessment of whether or not preventative steps had been taken to minimise bias and errors in the selection process. Four SRs[20,40,45,46] reported adequate methods for assessing the quality of included studies. One SR[43] reported using a recognised quality assessment tool, but did not provide details on how it was used. The remaining four SRs[42,44,50,56] did not report whether or not they had conducted a quality assessment of the included studies. Adequate details of the primary studies were presented in seven of the SRs.[20,40,43,44,46,50,56] In the CADTH publication,[42] details were presented only narratively for each primary study; although Costa *et al.*[45] 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[44,56] reported a narrative synthesis, three SRs[20,40,42] summarised each study individually and one SR[46] did not include any studies. Costa *et al.*[45] reported the results of the quality assessment only and Suska *et al.*[43] did not provide any synthesis. It was not possible to assess the Senter for Medisinsk Metodevurdering report for this item (were appropriate methods used for data synthesis?).[50]

Assessment of the effectiveness of the included studies

Prophylactic removal versus retention and standard care

One study[58] reported on outcomes for both the 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 and was conducted in Ukraine between 2009 and 2013. It was designed to develop and assess a pre-operative assessment and to create a rationale for the prophylactic removal of asymptomatic IM3Ms. The assessment included clinical and roentgenological parameters; the 84 patients who were included were assigned to one of three groups: (1) requiring removal and subsequently having the tooth removed ($n = 52$), (2) requiring removal but the patient refused ($n = 7$) and (3) 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 the 5 years, the study[58] authors reported that there were 'no considerable intra- or post-operative complications in the first subgroup',[58] 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'.[58]

Of the seven patients who refused extraction, five required the tooth to be extracted within the 5 years' follow-up. 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[58] 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'.[58]

Further details of the study characteristics and outcomes are reported in *Appendix 4*.

Retention and standard care

We included two studies, Fernandes *et al.*[48] and Hill and Walker[47] (reported in four publications[39,47,48,57]), 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[48] and 5 years.[47] Both studies were conducted in the UK; the number of patients with trouble-free IM3Ms was 421 in one study[48] and 153 in the other.[47] The number of trouble-free IM3Ms examined was reported in one study only ($n = 676$).[48] Participants in one study[47] were aged 16–30 years (median age 23 years); in the other study,[48] participants were aged 18–70 years (18–34.9 years, $n = 400$; 35–49.9 years, $n = 149$; and 50–70 years, $n = 64$).[48] The percentage of males was 41% in one study[48] and 34% in the other study[47] (*Table 6*). Further study and participant characteristics are reported in *Appendix 4*.

Outcomes were assessed by Hill and Walker[47] using a questionnaire or telephone call every 6 months and a clinical examination every year, if the patient were willing to attend. A research dentist questioned and assessed the clinical outcomes of patients at the 1-year follow-up in Fernandes *et al.*[48]

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*. Fernandes *et al.*[48] reported an extraction rate over 1 year of 5.5%, whereas Hill and Walker[47] 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.*[48] 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 common reason for removal (27%, 50% of known reasons), followed by pericoronitis (13.5%, 25% of known reasons). Hill and Walker[47] reported that pericoronitis was the most common reason

TABLE 6 Study and participant characteristics of retention and standard care studies

	Characteristic			
Study	**Setting**	**Follow-up period**	**Description of I3Ms and patients**	**Participant demographics**
Fernandes *et al.*, 2010[48]	Multicentre, Scotland, UK (primary care setting)	1 year	IM3Ms ($n = 676$). 613 patients assessed at baseline, 583 patients eligible, 421 patients with follow-up	• Full sample: $n = 613$ • Males: 40.1% • Age (years): ○ 18–34.9 – $n = 400$ ○ 35–49.9 – $n = 149$ ○ 50–70 – $n = 64$
Hill and Walker, 2006[47]	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 years

TABLE 7 Outcomes of retention and standard care studies

Outcomes assessed	Rate, *n/N* (%)
Extraction rate	
[a]Fernandes *et al.*[48]	37/676 (5.5)
Hill and Walker[47]	
Without a history of pericoronitis	48/153 (31.4)
With a history of pericoronitis	23/66 (34.8)
Reasons for extraction	
[a]Fernandes *et al.* 2010[48]	
Pericoronitis	5/37 (13.5)
Pain	10/37 (27.0)
Caries in distal of adjacent molar	1/37 (2.7)
Caries in the 3M	2/37 (5.4)
Contralateral	2/37 (5.4)
Unknown	17/37 (46.0)
[a]Hill and Walker 2006[47] (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 2M	4/48 (8.3)
Painful when eating	2/48 (4.2)
Earache/TMJ pain	2/48 (4.2)
Survived asymptomatically	
Fernandes *et al.* 2010[48]	
From any symptom	562/676 (83.1)
From SIGN symptoms only	623/676 (92.2)
Hill and Walker 2006[47]	150/222[b] (67.6)
Symptoms developed by tooth	
Fernandes *et al.* 2010[48]	
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)

SIGN, Scottish Intercollegiate Guidelines Network; TMJ, temporomandibular joint.
a Per tooth.
b Includes 66 patients with a history of pericoronitis.

for removal (62.5%), followed by cosmetic/orthodontic reasons (12.5%). Both studies reported the number of patients having teeth removed as a result of caries in the 2M: 2.7% in one study[48] and 8.3% in the other.[47]

The number of patients who did not experience any symptoms over the period of the studies was 83.1% in one study[48] and 67.6% in the other.[47] Fernandes *et al.*[48] reported the number of patients who did

not experience symptoms that indicated the need for removal according to the Scottish Intercollegiate Guidelines Network (SIGN) guidelines[34] as 92.2%. The authors also reported the rates for the different symptoms, with discomfort/irritation, which is not a symptom that SIGN includes as a reason for removal, being the most frequently reported reason (47.4%).[48]

Fernandes *et al.*[48] also investigated the relationship between symptoms and several factors. The authors found that there was a statistically significant relationship between the presence of symptoms and age, angulation, eruption status and the reason for the 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 Index (GI), '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 per week or deprivation category.

Prophylactic removal

The final included study, by Petsos *et al.*,[59] 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 4*.

The study[59] was a prospective cohort study conducted in Germany that was self-funded and recruited patients over 5 months in 2014 after they underwent extraction of asymptomatic IM3Ms. The study[59] was designed to assess the 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 IM3M removed and 20 had a fully impacted M3M. The mean age of patients was 16 years and 37% of patients were male. Only four patients were smokers. At baseline, the plaque index, GI, probing pocket depth (PPD) and probing attachment level (PAL) were measured, with measurements being obtained at six sites around the 2M (i.e. mesiobuccal, buccal, distobuccal, distolingual, lingual, mesiolingual).

To assess the change in the 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.

Although no significant change was reported in the plaque index 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, the 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).[59]

The surgical complications following the prophylactic removal of the IM3Ms were recorded. A total of 20 patients (25.6%) reported complications. Intense pain for > 1 day was the most frequent complication, which was reported by 12 patients. A further five patients (6.4%) reported post-operative infection (infiltrate or abscess), and the remaining three patients experienced wound dehiscence. No incidences of secondary bleeding or nerve damage were reported.[59]

The authors[59] concluded that 'young patients may benefit from an early removal of mandibular M3, especially in the presence of certain cofactors'.

Systematic reviews

Nine SRs,[20,40,42–46,50,56] reported in 16 publications,[20,40–46,49–56] met the review inclusion criteria and their details are summarised in *Tables 8* and *9*, with further details shown in *Appendix 4*.

TABLE 8 Systematic review characteristics

Study	Characteristic		
	Publication type; date of search	Objective/research questions	Inclusion criteria
Bouloux *et al.* 2015[44] AAOMS M3Taskforce	SR; NR	*To determine, clinically, whether or not 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 • At least one 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[42]	Rapid review/HTA; 2000–10	*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?* *Reproduced with permission from CADTH[42]*	• English language • Study design: HTAs, SRs, RCTs, non-RCTs • Comparing clinical outcomes between one group that underwent prophylactic surgery for 3M removal and one group that retained their asymptomatic teeth
Clinical evidence[41,51–56]	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 • > 20 patients
Costa *et al.* 2013[45]	SR; up to 30 August 2012	*To investigate whether or not there is evidence justifying the prophylactic extraction of 3Ms*	• Study design: RCT, SR and meta-analyses • All languages • The effect of prophylactic 3M extraction • The non-intervention (maintenance) of asymptomatic I3Ms
Mettes *et al.* 2012[46]	SR; 1950 to 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

TABLE 8 Systematic review characteristics (*continued*)

Study	Characteristic		
	Publication type; date of search	Objective/research questions	Inclusion criteria
Senter for Medisinsk Metodevurdering 2003[50]	SR/HTA (English summary only); 1999–2003	To evaluate the evidence on the incidence of surgical complications following the prophylactic removal of I3Ms, and the morbidity, quality-of-life and economic aspects associated with retention of I3Ms	NR in English summary
Song *et al.* 2000[20]	SR/HTA/clinical guidance; 1984–99	*To provide a summary of the 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 owing to associated pathological changes • Outcomes: pathological changes associated with retention of 3Ms, or post-operative complications following extraction
Stordeur and Eyssen 2012[40]	Rapid assessment; December 2010 to 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
Suska *et al.* 2010[43]	HTA/SR; May 2003 to December 2009. Based on the Norwegian HTA, so searches conducted after 2003 only	*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?*	• Study design: studies with some kind of control group, case series 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 languages only

AAOMS, American Association of Oral and Maxillofacial Surgeons; CPG, clinical practice guideline; HTA, health technology assessment; NR, not reported.

TABLE 9 Systematic review results and conclusions

Study	Number/type of studies included	Author conclusions as quoted in publications
Bouloux *et al.* 2015[44]	Cohort studies, $n = 7$	*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[42]	SRs, $n = 4$ Non-RCTs, $n = 1$ Guidelines, $n = 2$	*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 towards a potentially unnecessary surgical procedure* *Reproduced with permission from CADTH[42]*
Clinical evidence[41,51–56]	Extraction of asymptomatic I3Ms: SR, $n = 5$ 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[56]*
Costa *et al.* 2013[45]	SR, $n = 1$ RCT, $n = 3$	*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[46]	RCT, $n = 1$	Insufficient evidence was found to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults The single RCT compared removal with retention of asymptomatic impacted wisdom teeth and reported only one relevant outcome (late lower incisor crowding at 5 years). No difference was found Watchful monitoring of asymptomatic third molar teeth may be a more prudent strategy
Senter for Medisinsk Metodevurdering 2003[50]	Patient series, $n = 13$ Cohort studies, $n = 3$ Case–control studies, $n = 2$ Cross-sectional studies, $n = 6$ Decision analysis, $n = 1$	Removal of asymptomatic fully retained wisdom teeth is not recommended. However, Norwegian dentists recommend prophylactic removal of 3Ms when the likelihood of 3Ms causing problems in the future is high and the incidence of post-operative complications is low (including partially erupted wisdom teeth). Because this report is based on studies that are not optimal, the patient's preferences need to be decisive
Song *et al.* 2000[20]	RCT, $n = 2$ Decision analysis, $n = 4$ Literature reviews, $n = 34$	*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*

TABLE 9 Systematic review results and conclusions (*continued*)

Study	Number/type of studies included	Author conclusions as quoted in publications
Stordeur and Eyssen 2012[40]	SRs, *n* = 2 HTAs, *n* = 2 CPG, *n* = 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. Preventative 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* *Reproduced with permission from the Belgian Health Care Knowledge Centre. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nd/4.0/), which permits reproduction, provided the original author and source are credited*
Suska *et al.* 2010[43]	HTA report/SRs, *n* = 2 Case series, *n* = 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* *Reproduced with permission from HTA-centrum*

CPG, clinical practice guideline; HTA, Health Technology Assessment.

Two reports[40,42] were rapid reviews that applied SR methodology. All but one review[44] attempted to assess the evidence for the prophylactic removal of 3Ms compared with standard care without prophylactic removal. Bouloux *et al.*[44] assessed only whether or not retention of asymptomatic 3Ms led to future extraction.

No review restricted the population to trouble-free IM3Ms. Instead, four reviews[40,42,44,45] included all trouble-free 3Ms regardless of their impaction status or location, two reviews[46,56] included trouble-free I3Ms regardless of their location, one review[20] included all 3Ms regardless of whether or not there were symptoms and one review[43] included I3Ms regardless of their symptoms or location. A further review was published in Norwegian and had an English summary only,[50] so the specific population was unclear. Different types of study design were included across the SRs: five[40,42,43,45,56] included SRs and five[42–44,50,56] included non-RCTs (e.g. cohort studies and case series). One[46] SR limited inclusion to RCTs and another[44] limited inclusion to cohort studies only. One[20] review also included literature reviews and the dates of the searches ranged from 1950[46] to 2014.[56]

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[20,49,50,60–63] being identified by more than one review:

- Mettes *et al.*[49] (SR) was included in five SRs.[40,42,43,45,56]
- Harradine *et al.*[61] (RCT) was included in four SRs.[20,45,46,56]
- NICE guidance[2]/Song *et al.*[20,64] publications were identified by three SRs.[40,42,56]
- The Senter for Medisinsk Metodevurdering[50] report was included in three SRs.[42,43,56]
- Lindqvist and Thilander[63] (RCT) was included in three SRs.[45,49,56]
- Edwards *et al.*[60] (decision analysis) was included in two SRs.[20,50]
- Kruger *et al.*[62] (cohort study) was included in two SRs.[44,50]

Despite the differences in inclusion criteria across the SRs, the conclusions were similar. Seven SRs[20,40,42,43,45,46,56] stated that there was insufficient evidence to support or refute the prophylactic removal of trouble-free 3Ms. Two[42,56] 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[20,40] SRs recommended that, in the light of insufficient evidence, retention/'first do no harm' may be appropriate. Watchful monitoring was recommended in the Cochrane review by Mettes *et al.*[46] The Senter for Medisinsk Metodevurdering report[50] 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[44] 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'.[44]

Additional evidence

References from included systematic reviews

We reviewed all of the references included in the identified SRs for inclusion in this review. Of the 84 cited references, nine met our inclusion criteria and all of the references 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 5*.

Professional stakeholder's submissions

As part of the NICE process, three submissions from professional stakeholders were received: the first on behalf of the BDA; the second was 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.

The submission forms that are provided by NICE to professional stakeholders enable health-care professionals to provide their perspectives on the technology in the context of clinical practice, and include questions in 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-focused 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 or not they included any data that could inform this appraisal report.

Much of the content of the submissions was professional opinions and perspectives, and the full submissions are available for the committee to consider. In terms of the references 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 5*.

The key points from each submission are summarised in the following sections.

The British Dental Association submission

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.

The Faculty of Dental Surgery, Faculty of General Dental Practice and British Association of Oral Surgeons submission

The key points highlighted in the submission are that, as a result of NICE guidance,[2] patients are retaining M3Ms, 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.

The British Association of Oral and Maxillofacial Surgeons submission

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,[65] 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 antiresorptive or antiangiogenic drugs and those who are to receive radiotherapy to the head and neck). The routine prophylactic removal of 3Ms would put significant strain on NHS resources in both primary and secondary care.

Summary of clinical results

Searching 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[20,40–46,49–56] and four cohort studies[39,47,48,57–59]).

Of the four cohort studies, one investigated the prophylactic removal of pathology-free or asymptomatic IM3Ms in comparison with the standard care and retention of these pathology-free or asymptomatic IM3Ms,[58] two studies investigated the standard care and retention of pathology of asymptomatic IM3Ms without a comparison group[47,48] and one study investigated the prophylactic removal of pathology-free or asymptomatic IM3Ms.[59] All of the studies described teeth as asymptomatic. All four studies were European, and the two studies looking at the standard care and retention of pathology-free or asymptomatic IM3Ms, without a comparison group, were UK based.[47,48] Follow-up across the studies varied from 6 months to 5 years, with outcomes assessed through clinical assessment. In the two studies reporting on surgical complications,[59,60] no serious complications were reported, although intense pain and post-operative infection were reported in one study. The pathological changes due to retention of pathology-free or asymptomatic IM3Ms were reported in three studies.[47,48,59] The extraction rate for retained teeth varied from 5.5%[48] to 31.4%,[47] although this variation can be explained by the differing follow-up periods (1 and 5 years, respectively).

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, compared 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 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[1,3,4,16,66–69] and there are a number of international clinical guidelines[2,21,27–34,41–43,70] 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, focusing 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 3Ms.

Discussion of the results of the cohort studies is hampered by the different outcomes reported by the studies, as different approaches to 3M 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 that 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, although intense pain and infection were reported at rates of 15% and 6%.[59]

None of the nine SRs 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 the study design. This led to a disparate collection of studies being included, with 73 of the 84 studies being included in one SR only. 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 SRs 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.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

This section presents the methods and results of a SR of the published literature comparing the cost-effectiveness of prophylactic removal of I3Ms with that of no prophylactic removal.

Search strategy

The search strategy developed for the clinical searches (see *Appendix 1*), 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*host*) were also searched. All databases were searched on 29 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 (Google Inc., Mountain View, CA, USA). The Google Scholar search was updated on 1 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.

Study selection and inclusion criteria

Studies were selected based on their relevance to the decision problem and on the specific economic criteria displayed in *Table 10*. Two reviewers (AB and SB) independently examined the titles and abstracts of all of the studies identified by the search to find potentially eligible publications (stage 1). In the next stage (stage 2), two reviewers (AB and 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:

1. Owing to limited information about UK costs being available, studies that included any costs were included in the review.
2. Papers reporting short-term health-related quality-of-life (HRQoL) outcomes were excluded from the review (i.e. papers with only long-term HRQoL outcomes were included) to align HRQoL outcomes with the outcomes reported in the clinical papers.

TABLE 10 Economic inclusion criteria (costs and outcomes)

Criteria	Inclusion
Patient population	People with I3Ms
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

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.

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[17,20,71–76] were initially included at stage 2. However, on further inspection, five[71–75] of the eight studies did not include information that was relevant to the population of interest; these papers were, therefore, subsequently excluded from the review. Bibliographic details and summary data from these five studies[71–75] are available in *Appendix 2*. Of the 34 papers considered for inclusion after stage 1, 31 were excluded during stage 2, which left three papers[17,20,76] to be included in the review. The reasons for excluding the 31 studies are listed in *Table 11*.

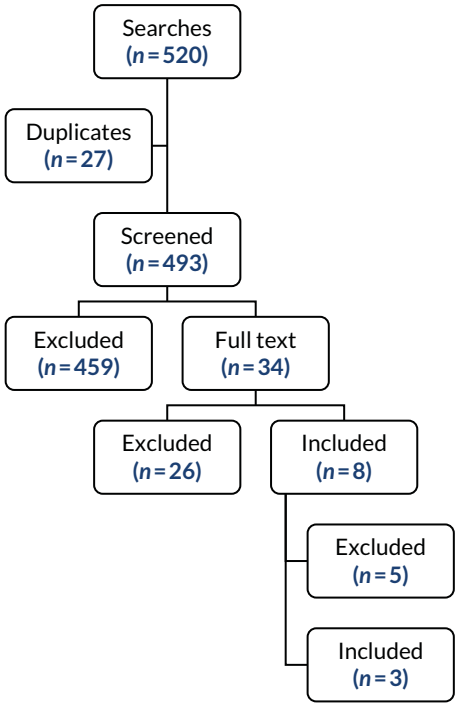

FIGURE 2 The PRISMA flow diagram: economic evidence review.

TABLE 11 Reasons for excluding papers from the cost-effectiveness review at stage 2

Study	Reason for exclusion
Aravena and Cartes-Velasquez 2011[77]	Literature review describing the signs and symptoms used to evaluate post-operative complications in 3M surgery. Abstract only
Bienstock *et al.* 2011[78]	Short-term study of the duration of disability after 3M surgery (mean 1.4 ± 1.8 days) and risk factors associated with prolonged recovery (maximum 26 days)
Bienstock 2012[79]	Indirect costs (mean number of work days missed and risk factors associated with prolonged return to work after 3M surgery)
Chuang *et al.* 2007[80]	Estimates of post-surgery complication rates and risk factors after removal of 3Ms
Chuang *et al.* 2008[81]	Risk factors for post-surgery inflammatory complications after removal of 3Ms

TABLE 11 Reasons for excluding papers from the cost-effectiveness review at stage 2 (*continued*)

Study	Reason for exclusion
Colorado-Bonnin *et al.* 2006[82]	Short-term (7-day) post-operative HRQoL data
Conrad *et al.* 1999[83]	Short-term (14-day) patients' perceptions of recovery after 3M surgery
Deepti *et al.* 2009[84]	Short-term (7-day) post-operative HRQoL data after I3M removal
Edwards *et al.* 1999[60]	Data were included in the HTA review by Song *et al.*[20] that informed TA1
Gutierrez-Perez 2004[85]	Signs and symptoms of 3M infections. Written in Spanish
Inverso *et al.* 2014[86]	The value of telephone vs. clinical follow-up after 3M surgery
Inverso *et al.* 2014[71]	No information relating to I3Ms
Koumaras 2012[72]	No information relating to I3Ms
Kunkel *et al.* 2006[74]	No information relating to I3Ms
Kunkel *et al.* 2007[73]	No information relating to I3Ms
Liedholm *et al.* 2010[87]	No figures relating to I3Ms were specifically reported
Leidholm *et al.* 2005[75]	No information relating to I3Ms
Matijević *et al.* 2014[88]	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[89]	A study of visible 3Ms and probing depths
Osunde *et al.* 2011[90]	A review of literature on different modalities for minimising inflammatory complications associated with 3M surgery
Pandurić *et al.* 2009[91]	Short-term (14-day) post-operative HRQoL data reported for patients (after 3M surgery) in Croatia
Phillips *et al.* 2003[92]	Short-term (14-day) diary designed to assess a patient's perception of recovery after removal of all four 3Ms
Phillips *et al.* 2010[93]	Short-term (14-day) diary used to study the effect of age and sex on recovery after 3M surgery
Ruvo *et al.* 2005[94]	Short-term (14-day) outcomes after removal of all four 3Ms
Sancho-Puchades *et al.* 2012[95]	Short-term (7-day) study of HRQoL after 3M surgery when using conscious sedation
Sato *et al.* 2009[96]	Short-term (7-day) outcomes: data about post-operative signs and symptoms collected daily from patients and surgeons
Shugars and White 2003[97]	Editorial linked to McGrath *et al.*[76] paper: no rates, frequencies or other statistics provided
Shugars *et al.* 2006[98]	Short-term (14-day) HRQoL outcomes collected using two different instruments
Slade *et al.* 2004[99]	Short-term (pre and 7 days post) oral health outcomes after removal of 3Ms
White *et al.* 2003[100]	Short-term (14-day) clinical and HRQoL outcomes after removal of all four 3Ms
White 2004[101]	List of citations (with comments) summarising clinical and HRQoL outcomes after 3M surgery

HTA, Health Technology Assessment.

The three papers[17,20,76] that were included in the review are listed in *Table 12*. Two studies[17,20] provided information on costs and one study[76] provided information on patient HRQoL. The characteristics of these studies are presented in *Table 13*.

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 because only one paper[20] directly considers the cost-effectiveness of prophylactic removal of I3Ms in a UK setting [and a summary of this paper and its quality are located in the clinical evidence section of this report (see *Tables 8* and *9* and *Appendix 4*)].

Economic review: overview of included papers

The AG concludes that relevant data on I3Ms are limited to three studies.[17,20,76] 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 the cost-effectiveness from a UK NHS perspective, whereas 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 the results are presented in Australian dollars. The third paper[76] reports findings that relate to an assessment of oral HRQoL after the removal of I3Ms.

Key results: cost-effectiveness of prophylactic removal of impacted third molars

Cost-effectiveness: Song *et al.*[20]

This publication by Song *et al.*[20] is the AG's report for TA1 (The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth).[1] It includes a summary of the findings from a study reported by Edwards *et al.*,[60] who estimated the cost-effectiveness of removal and retention of disease-free 3Ms and concluded that the cost of prophylactic removal of I3Ms was approximately 33% higher than the cost of retention. The report by Song *et al.*[20] also includes findings from a paper by Walters,[102] who identified that the compensation awarded for permanent nerve damage after 3M surgery ranged from £4000 to £14,000 per case, or higher.

Song *et al.*[20] concluded 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 with the costs associated with prophylactic removal under general anaesthetic. Data were obtained from the Western Australian Hospital Morbidity Data system. All of the episodes of discharge from all hospitals (private and public)

TABLE 12 The three studies included in the AG's economic evidence review

Study	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[76]	6-month study of patients' perceptions of oral HRQoL after removal of impacted 3Ms

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 costs from private and public hospitals	20 years	2009 (unless otherwise stated)
Song *et al.* 2000[20]	UK	I3Ms	SR (and decision analysis)	NA	NA	NHS	NA	NA
McGrath *et al.* 2003[76]	UK	I3Ms	Evaluation of patients' perceptions of changes in (OHRQoL) over a 6-month period after I3M surgery	Patients awaiting I3M surgery	Change in OHRQoL as measured by OHIP-14 and OHRQoL-UK scores	Patient questionnaires and patient 'recovery log' diaries	From the day of the I3M surgery until 7 days after I3M surgery	NA

GA, general anaesthetic; NA, not applicable; OHIP, Oral Health Impact Profile-14; OHRQoL, oral health-related quality of life.

in Western Australia for the financial year 2008–9 for the removal of impacted or embedded teeth as the principal oral condition were included. The rate calculations for Western Australian hospitalisation were measured using Australian population 2006 data.

The annual direct cost to the state for I3M removal in hospital was estimated to be AUS$259M, which equates to a direct cost of AUS$2644 for each hospitalisation (i.e. £1536 using the conversion rate of 22 August 2016). The time frame for the analysis was 20 years. The average watchful waiting strategy cost per participant was AUS$1077. This cost included the 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 that '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'.[17]

Health-related quality of life: McGrath *et al.*[76]

The study by McGrath *et al.*[76] in 2003 assessed oral HRQoL in patients after the removal of their 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 significant and clinically significant.

Cost-effectiveness review: conclusions

As there is very limited clinical effectiveness evidence comparing the prophylactic removal of I3M with 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[17,20] 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.

Independent economic assessment

To our knowledge, 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 carried out (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.[103]

In the AG's model, in line with the age of the youngest patient recruited to the Fernandes *et al.*[48] study, the AG chose 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's model, the base-case time horizon is 80 years (i.e. up to the point when people reach the age of 100 years, when < 1% of patients are still alive). The time horizon is varied in scenario analyses (10, 20, 30, 40 and 50 years) to assess the impact that this change has on model outputs.

Model pathways

The elements of both the intervention (prophylactic removal) and the comparator (watchful waiting) pathways were determined through consultation with clinical experts and examination of clinical data identified via the AG's SR of clinical effectiveness evidence. Clinical consultation was conducted through a combination of face-to-face meetings, telephone conversations and comments on draft versions of the report.

In the NHS watchful waiting pathway, there are many different points at which an IM3M may, or should, be extracted. For example, the decision to extract an IM3M 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 with extraction driven by, for example, a decayed adjacent tooth or number of instances of pericoronitis are absent and clinical advice to the AG was that patient preference would probably play a significant role in the decision to extract.

The AG has, therefore, chosen to design an economic model that is based on what actually happens in terms of the current extraction rates of IM3Ms (i.e. use available data) rather than on what might or should happen under a watchful waiting pathway following symptom development. This approach minimises the use of assumptions around when extraction occurs and allows analysis of the true current situation in the NHS against a change in extraction rates if prophylactic removal was recommended. However, how far the results can be interpreted as a comparison of a watchful waiting strategy with strict adherence to extraction only after certain symptom-related criteria is met, against a prophylactic removal strategy, is unclear.

A visual representation of the intervention pathway (prophylactic removal) is shown in *Figure 3*. The pathway is modelled as a combination of a Markov model process to move people between different IM3M health states, with decision trees to determine the probability of complications and severity of complications at each cycle and to determine the outcomes from the extraction of an IM3M.

The cycle length is 1 year. In each cycle, a person can develop IM3M symptoms (the severity of which is determined by decision trees) but not have the IM3M extracted, have the IM3M extracted (either with or without complications, determined by decision trees), remain in a post-extraction state (with or without permanent nerve damage) 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 their IM3M will be extracted. The probability of extraction is independent of symptom development. The possible symptoms are pericoronitis, mild pain and severe pain, which is determined in the model by a decision tree. If a person has only symptoms in a cycle without extraction, they remain in the 'IM3M in situ' state.

When a tooth is extracted, the person might be found by the dental surgeon to have developed a DCC in the adjacent mandibular second molar (M2M). The AG has assumed that the probability of extraction of an IM3M is independent of the development of a M2M DCC. This assumption has been made because the data that are available describe the proportion of people with M2M DCC in a population who had an IM3M extracted only, and not on whether or not this was the reason for the extraction.[104] If 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'). If a person has IM3M extraction in a given cycle, these events are determined by a decision tree. After extraction, people can enter

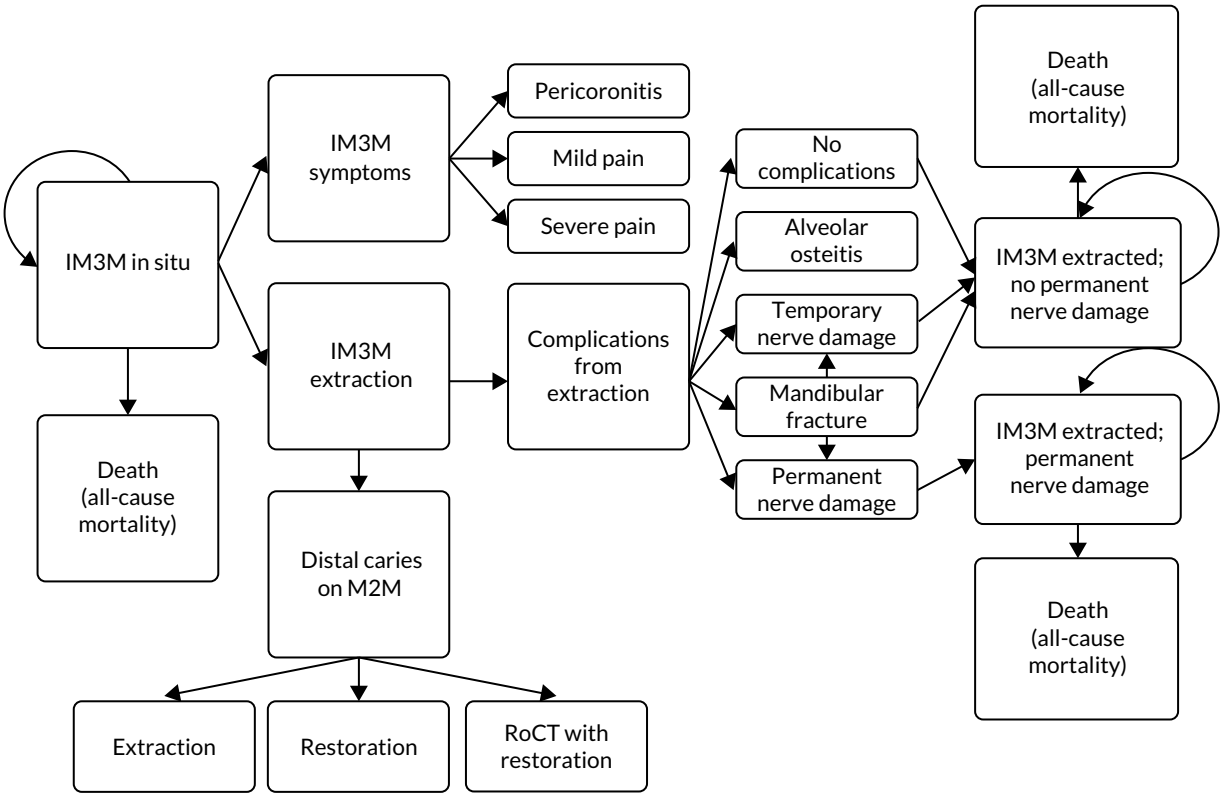

FIGURE 3 Prophylactic removal of the IM3M model pathway. M2M, mandibular second molar; RoCT, root canal treatment.

either 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.

Based on the pathway, a model was constructed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) that captured the cost and benefits of 1000 patients transitioning through the intervention and comparator pathways.

Model transition probabilities

The transition probabilities used in the AG's model have been drawn from published studies identified in the clinical evidence review and from evidence identified by clinical experts.

Evidence presented by Fernandes *et al.*[48] 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[34] 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.*,[48] the annual rate of extraction (5.47%) was found to be independent of age. The inclusion criterion in terms of the age of the cohort studied by Fernandes *et al.*[48] was 18–70 years, but only those aged 20–63 years were actually recruited to the study. This determined the model start age of 20 years. It was assumed that the annual rate of extraction continued at 5.47% after the age of 63 years. A scenario analysis explored a scenario in which no extractions were undertaken after the age of 63 years.

Although the Fernandes *et al.*[48] study is a prospective cohort study, the AG considered that it was well designed with a large sample and provided a satisfactory evidence base to estimate the annual rate of extraction of IM3Ms in a UK NHS setting. The annual rate of extraction of 5.47% that was reported by Fernandes *et al.*[48] gives a 5-year extraction rate of 24.5%, which is lower than, but of a similar order to, that reported by Hill and Walker[47] (31.4%). Given that Hill and Walker[47] report on extraction from a different part of the UK to Fernandes *et al.*[48] and the two studies suggest similar annual extraction rates, this supports the generalisability of the findings from Fernandes *et al.*[48] to the wider NHS. To check the effect of varying the annual rate of extraction, the upper (7.39% per annum, equivalent to a 5-year extraction rate of 32.0%) and lower (3.94% per annum) bounds of the 95% CI quoted in the paper by Fernandes *et al*[48] 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.*[48] 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[34] 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 45.9% of patients who could not recall why their IM3M was extracted had their tooth extracted when the IM3M was asymptomatic. However, it could also be an underestimate if future guidelines were to suggest that prophylactic removal is recommended. Owing 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.*[48] study suggest that symptom development is age dependent (at least up to 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 the ages of 53 to 63 years, and that 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 6*.

The probability of a person who, on having an IM3M extracted, is found to have 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.*[104] In this study, the investigators undertook a retrospective review of 339 people in England, across two cohorts from 2006 to 2014, who had IM3Ms removed as a result of having M2M DCC.

The probabilities of specific complications that are associated with tooth extraction were derived from Chuang *et al.*[80] Chuang *et al.*[80] also reported an odds ratio (OR) for all complications (OR 1.46) for patients aged $\geq$ 25 years compared with those aged < 25 years. The AG has adjusted the individual complication rates reported by Chuang *et al.*[80] using this OR to estimate the probability of specific complications for those aged < 25 years and for those aged $\geq$ 25 years.

One complication for which there is no evidence available in the study by Chuang *et al.*[80] is the rate of permanent nerve damage. The AG has used a value reported by Valmaseda-Castellón *et al.*[105] This value has been adjusted for age (aged < 25 years and aged $\geq$ 25 years) using the OR reported by Chuang *et al.*[80]

Table 14 shows a full list of probabilities used in the AG's model. Rates for death from any cause have been taken from the Office for National Statistics' life tables.[106]

TABLE 14 Probabilities of symptom, extraction complication and DCC of the M2M used in the base case of the AG's model

Parameters	Probability (%)	Study
Symptoms		
Pericoronitis	13.16	Fernandes *et al.* 2010[48]
Severe pain	14.04	
Mild pain	19.30	
DCC of M2M on extraction of IM3M		
DCC of M2M	15.00	McArdle *et al.* 2018[104]
M2M extracted	42.00	
M2M restored	42.00	
M2M root canal treatment and restored	16	
IM3M extraction complications		
Mandibular fracture (aged < 25 years)	0.019	Chuang *et al.* 2007[80]
Mandibular fracture (aged ≥ 25 years)	0.03	
Permanent nerve damage (< 25 years)	0.22	Valmaseda-Castellón *et al.* 2001[105]
Permanent nerve damage (≥ 25 years)	0.33	Chuang *et al.* 2007[80]
Temporary nerve damage (< 25 years)	2.89	Chuang *et al.* 2007[80]
Temporary nerve damage (≥ 25 years)	4.16	
Alveolar osteitis (< 25 years)	5.61	
Alveolar osteitis (≥ 25 years)	7.98	

The use of annual transition probabilities for symptom development in the AG's model results in a person being able to experience IM3M symptoms only once per year for each tooth. Given that people may develop symptoms more than once per year in each IM3M, the model may underestimate the actual annual symptom burden for people with IM3Ms. This will result in the AG's 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 does, the results of the AG's 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 the 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 IM3M left in situ, pericoronitis can develop into a severe infection that can spread to the throat and lead to severe cellulitis, which causes 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 reported treating one person per month who had been admitted to the

intensive care unit with life-threatening cellulitis that was 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's model, if such a complication were to be included, it would result in a reduction in QALYs and an increase in costs for the watchful waiting strategy.

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.*[104] have estimated that, in 2014/15, there were 152,000 people with IM3M extractions: 67,000 (44.1%) extractions 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. The unit costs of extraction in an acute setting have been taken from the *NHS Reference Costs 2015 to 2016*.[107] The cost of an extraction in primary care is a band 2 treatment and is charged to the NHS as 3 units of dental activity (UDAs).

The AG has assumed that 75% of M2Ms with DCC are extracted at the same time as the IM3M, at 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 extractions 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 or 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% of people who require treatment, dental care will be required. Based on clinical advice, this dental care would comprise 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 an analgesic (codeine, which incurs 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.[108] The AG has undertaken sensitivity analyses to explore the impact of lower and higher UDA costs on model results. 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, England 2015* data.[109] 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 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. For more serious complications following extraction, the AG has assumed that everyone with permanent nerve damage will receive surgery to try to correct the damage and that no one with temporary nerve damage will receive 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 be only 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. For mandibular fracture, the NHS Reference Cost[107] for fixation of jaw following fracture was used.

With the exception of the costs of antibiotics and analgesia, the AG has undertaken sensitivity analyses to explore the impact of varying these costs on model results. For those costs based on the *NHS Reference Costs 2015 to 2016*,[107] upper and lower quartile figures have been used in these analyses.

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

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 (see search strategy in *Appendix 7*). Therefore, the AG used values from a working paper by Ara and Brazier[110] to populate these parameters in the model. It is reported in this paper[110] that people with teeth, mouth or tongue conditions in the UK have a EuroQol-5 Dimensions utility score that is 0.345 less than those who do not report having any

TABLE 15 Base-case costs included in the model

Cost element	Value (£)	Calculation details and source
UDA	25.00	BDA[108]
Tooth extraction: hospital admission	801.81	*NHS Reference Costs 2015 to 2016*[107] HRG code: major surgical removal of tooth CD04 A (weighted by activity of day case/elective inpatient/non-elective inpatient)
Tooth extraction: outpatient	148.00	*NHS Reference Costs 2015 to 2016*[107] HRG code: major surgical removal of tooth CD04 A (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: used for IM3M extraction)	413.62	McArdle *et al.* 2018[104]
Average cost of extraction of M2M with DCC	103.41	£413.62 divided by 4, as 75% of extractions undertaken concurrently with IM3M extraction (see source above[104])
Pericoronitis treatment	70.31	3.75 UDAs (see source above[104]) × 75% seeking treatment (assumption)
Antibiotics (for pericoronitis)	2.25	*Prescription Cost Analysis 2015*: erythrocin_B-Pack 10 Filmtab 500 mg[109]
Severe dental pain treatment	36.56	1.95 UDAs (see source above) × 75% seeking treatment (assumption)
Analgesic (for severe dental pain)	3.56	*Prescription Cost Analysis 2015*: codeine Phos_Tab 30 mg[109]
Fixation of jaw following fracture (for mandibular fracture)	2854.00	*NHS Reference Costs 2015 to 2016*[107] HRG code: reduction or fixation of jaw CA96Z (inpatient)
Surgery for permanent nerve damage	5507.00	*NHS Reference Costs 2015 to 2016*[107] HRG code: complex maxillofacial procedures CA91B (inpatient)
Restoration of M2M	75.00	Band 2 treatment (3 UDAs) (assumption)
M2M endodontically treated and restored	300.00	Band 3 treatment (12 UDAs) (assumption)

HRG, Healthcare Resource Group; PCA, Prescription Cost Analysis.

teeth, mouth or tongue conditions. This is comparable to a utility decrement for level 3 pain based on the EuroQol-5 Dimensions, three-level version, questionnaire ('I have extreme pain or discomfort') of 0.386.[110]

The AG's 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.[110] The AG has assumed that M2M restoration is not associated with any loss of utility and that extraction of the M2M would result in a loss of utility only 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 that described the duration of symptoms associated 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 the 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.[110]

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

Analysis of uncertainty

The AG explored the uncertainty surrounding the 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 as a result of the lack of data (e.g. the actual utility values associated with symptoms or the duration of symptoms).

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

Furthermore, a probabilistic sensitivity analysis could potentially lead to confounding results, as the uncertainty around most of the assumptions used in the AG's model is not known; therefore, from a statistical perspective, this cannot be confidently modelled.

The parameter ranges explored in the deterministic sensitivity analyses 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	Ara and Brazier[110] (95% CI)
Severe pain	0.345	0.102 to 0.549	
Mild pain	0.1725	0.051 to 0.275[a]	
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 (days)			
Pericoronitis	9	4.5 to 13.5	Assumption (base case ± 50%)
Severe pain	30	15 to 45	
Mild pain	30	15 to 45	
Alveolar osteitis	9	4.5 to 13.5	
Tooth extraction	7	3.5 to 10.5	
Mandibular fracture	42	21 to 63	
Temporary nerve damage	30	15 to 45	
Unit costs (£)			
UDA	25.00	11.08 to 105.58	BDA[108]
Discount rate (%)			
Annual rate	3.5	1.5 to 5.0	NICE Reference Case[103]
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.*[48] (95% CI)
Extraction of M2M (%)			
Percentage of patients having M2M with DCC extracted at same time as IM3M	75	0 to 100	McArdle *et al.*[104]

a Automatically varied between these values when the severe pain utility was varied as it is set in the model to 50% of the severe pain value.

TABLE 18 Scenario analyses

Scenario variant	Base-case value	Value(s) used in scenario(s)
Vary model start age	20 years	30, 40 and 50 years
Vary model time horizon	Lifetime	10, 20, 30, 40 and 50 years
No IM3M symptoms after 63 years of age	Same rate of symptoms as for those aged 53–63 years	0
No extractions after 63 years of age	5.47% per annum	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)

Base-case results

Costs

For the modelled population, the AG's 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 than the watchful waiting strategy.

The AG's model results show that a prophylactic removal strategy leads to lower rates of permanent nerve damage and jaw fracture following extraction than a watchful waiting strategy. However, the actual discounted cost of treating these extraction complications will be higher for 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 a prophylactic removal strategy results in lower IM3M symptom treatment costs than a watchful waiting strategy. These cost savings lead to the total cost of a prophylactic removal strategy being £55.71 higher per person than a watchful waiting strategy.

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

Health-related quality-of-life results

More people have an IM3M extracted under a prophylactic removal strategy and more extractions happen earlier than with a watchful waiting strategy. The AG's 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.

TABLE 19 Base-case cost results for 1000 people with symptomatic IM3Ms

	Strategy					
	Watchful waiting		Prophylactic removal		Difference (prophylactic removal – watchful waiting)	
Complication or symptom	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	9874	2.6	10,979	−0.3	1106
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	4064	32.5	2196	−27.7	−1867
M2Ms restored	60.2	2947	32.5	1593	−27.7	−1354
M2Ms RoCT and restoration	22.9	4491	12.4	2427	−10.5	−2064
Pericoronitis	295.9	15,946	160.0	8620	−135.9	−7326
Severe pain	315.7	9408	170.7	5085	−145.0	−4322

RoCT, root canal treatment.

However, the QALY loss from IM3M symptoms is lower when using a prophylactic removal strategy than 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's model for a cohort of 1000 people with asymptomatic IM3Ms are shown in *Table 20*.

Cost-effectiveness results

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

TABLE 20 Base-case QALY results for 1000 people with symptomatic IM3Ms

	Strategy					
	Watchful waiting		Prophylactic removal		Difference (prophylactic removal – watchful waiting)	
Complication or symptom	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

TABLE 21 Base-case ICERs for 1000 people with asymptomatic IM3Ms

Total costs (£)		Total QALYs				
Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Incremental cost (£)	Incremental QALYs	Incremental ICER per QALY gained (£)
305,173	360,885	22,615	22,620	55,713	4.74	11,741

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 costs 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 £3377 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's 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 of > £20,000 per QALY gained for prophylactic removal (£21,469 per QALY gained).

As stated previously, there is evidence from Hill and Walker[47] that the annual rate of extraction of IM3Ms is closer to the upper bound of 7.39% per annum reported by Fernandes *et al.*,[48] rather than the 5.47% per annum used in the base case. If the annual rate of extraction was 7.39% per annum, the ICER would be £9944 per QALY gained. However, even if the annual rate of extraction was at the lower bound, suggested by Fernandes *et al.*,[48] 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's base case (£25) is at the lower end of the potential range used in England (i.e. from £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's model results are insensitive to several parameters for which no information was available and assumptions had to be made, for example the duration of symptoms of complications from extraction, the percentage of patients seeking treatment for pericoronitis and the percentage of patients having a M2M extraction at the same time as an IM3M extraction. This finding suggests that the lack of robust information on these parameters does not affect on the conclusions that can be drawn from the AG's model.

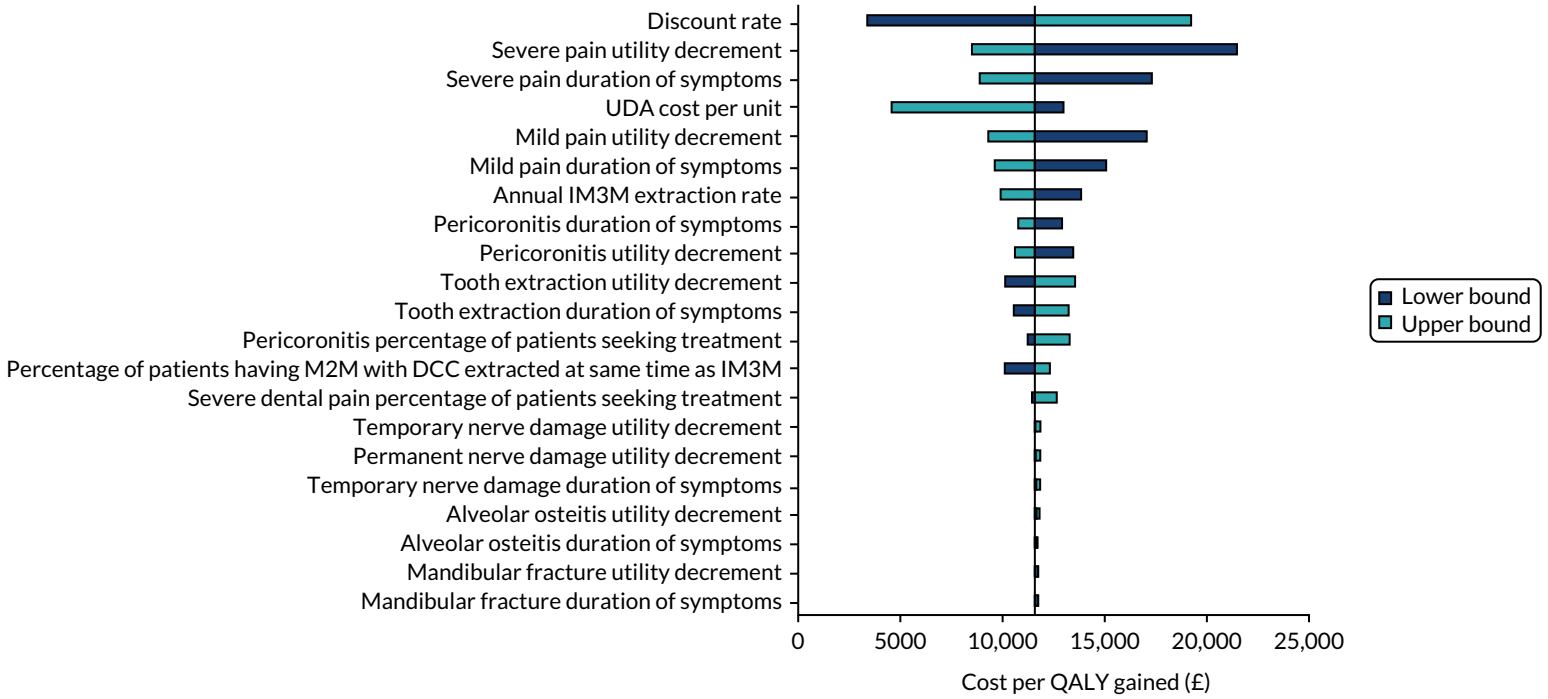

FIGURE 4 Deterministic sensitivity analyses results.

Scenario analyses

The total number of patients with IM3M extractions each year in the NHS is unknown. However, McArdle *et al.*[104] have estimated that, in 2014/15, 152,000 people underwent IM3M extractions: 67,000 (44.1%) extractions 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 of IM3M extractions to the NHS. Unit costs of extraction in an acute setting have been taken from the *NHS Reference Costs 2015 to 2016*.[107] The cost of an extraction in primary care is a band 2 treatment and is charged to the NHS as 3 UDAs. Although the number of extractions in an acute setting was derived from published statistics, McArdle *et al.*[104] estimated the number of extractions in primary care from a historical data source, as primary care IM3M extractions have not been recorded since 2004/5. McArdle *et al.*[104] 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 in which (1) no extractions occurred in primary care and (2) all extractions occurred in primary care.

Proportion of extractions occurring in primary care

Increasing the proportion of people having extractions in primary care reduced 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 with 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*.

Model start age

The age at which people entered the model varied between 30 years 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*.

Time horizon

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

TABLE 22 Impact on cost-effectiveness results from assuming 100% and 0% of IM3M extractions occur in primary care

	Total costs (£)		Total QALYs				
IM3M extractions	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Incremental cost (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	305,173	360,885	22,615	22,620	55,713	4.74	11,741
100% of extractions in primary care	90,616	89,331	22,615	22,620	−1285	4.74	Dominates
0% of extractions in primary care	401,173	482,388	22,615	22,620	81,215	4.74	17,116

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

Model start age	Total costs (£)		Total QALYs		Incremental cost (£)	Incremental QALYs	ICER per QALY gained (£)
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy			
Base case (20 years)	305,173	360,885	22,615	22,620	55,713	4.74	11,741
30 years	303,175	362,483	20,616	20,620	59,308	4.36	13,609
40 years	296,341	358,764	18,190	18,194	62,423	4.22	14,787
50 years	283,219	351,611	15,335	15,339	68,392	3.94	17,348

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

Model time horizon	Total costs (£)		Total QALYs		Incremental cost (£)	Incremental QALYs	ICER per QALY gained (£)
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy			
Base case (lifetime)	305,173	360,885	22,615	22,620	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	13,102	13,106	76,758	3.72	20,620
30 years	288,021	351,613	16,987	16,992	63,593	4.42	14,401
40 years	299,141	357,625	19,538	19,543	58,484	4.64	12,598
50 years	303,325	359,886	21,184	21,188	56,562	4.72	11,994

As the prophylactic removal strategy 'front loads' the costs of extraction compared with a watchful waiting strategy, the ICER per QALY gained is sensitive to the time horizon employed in the model. The shorter the time horizon, the fewer people in the watchful waiting strategy who have an extraction and develop symptoms as a result of 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.

No impacted mandibular third molar 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 years increases the ICER per QALY gained by £51. The results of this scenario analysis are shown in *Table 25*.

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 value 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 years increases the ICER per QALY gained by £437. The results of this scenario analysis are shown in *Table 26*.

TABLE 25 Impact on cost-effectiveness results from assuming that there are no symptoms from IM3Ms after the age of 63 years

IM3M symptoms	Total costs (£)		Total QALYs		Incremental cost (£)	Incremental QALYs	ICER per QALY gained (£)
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy			
Base case	305,173	360,885	22,615	22,620	55,713	4.74	11,741
No IM3M symptoms after the age of 63 years	305,097	360,844	22,615	22,620	55,747	4.73	11,793

TABLE 26 Impact on cost-effectiveness results from assuming that there are no extractions of IM3Ms after the age of 63 years

IM3M extractions	Total costs (£)		Total QALYs		Incremental cost (£)	Incremental QALYs	ICER per QALY gained (£)
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy			
Base case	305,173	360,885	22,615	22,620	55,713	4.74	11,741
No IM3M extractions after the age of 63 years	301,435	358,865	22,615	22,620	57,430	4.71	12,180

Proportion of people accepting prophylactic removal of impacted mandibular third molars

Varying the proportion of people who accept 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. Therefore, 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.

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 with a watchful waiting strategy is £11,741 for people aged 20 years 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.

Discussion of cost-effectiveness results

The AG's review of cost-effectiveness evidence identified only two published cost-effectiveness studies[17,20] that directly consider the decision problem. The authors of both studies[17,20] concluded 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; therefore, the relevance of the reported results to the decision problem is limited.

The results generated by the AG's economic model indicated that the ICER per QALY gained for the comparison of the cost-effectiveness of a prophylactic removal strategy with a watchful waiting strategy is markedly lower 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 through the 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's model results. However, the AG's notes that a central model assumption is that symptoms can develop only once per year, which will probably 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 probably be an underestimate by the authors of the study (McArdle *et al.*[104]) from which the proportions of location of extraction were derived. The greater the percentage of people who can have their IM3Ms extracted in a primary care setting, the more cost-effective prophylactic removal becomes.

In addition to the limit of developing symptoms only once per year, seven other model assumptions also suggested 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.
7. 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 inherently more prone to symptom development or that prior symptoms and treatment increase the likelihood of developing future symptoms.

The AG's 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.*[48] In this sense, a watchful waiting strategy may be more accurately described as 'putting off the inevitable'. The findings reported by Fernandes *et al.*[48] on the rate of extraction of IM3Ms are supported by the results of Hill and Walker.[47] Importantly, even if the annual rates of extraction are substantially lower than that used in the model base case, the ICER per QALY gained remains below £20,000.

Chapter 5 Discussion

Statement of principal 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[58,59] that investigated the rate of surgical complications concluded that no serious complications were reported. The three longitudinal studies[47,48,58] that assessed the outcomes of retained IM3Ms reported varying extraction rates owing to the different lengths of follow-up. No studies reported the impact of retention on the status of the 2Ms.

As there is very limited clinical effectiveness evidence comparing the prophylactic removal of I3Ms with a watchful waiting strategy, it is unsurprising that the 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 with that of a watchful waiting strategy is £11,741 for people aged 20 years 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.

Although 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 consider only 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[47,48] 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[104] are also now available on, for example, the rate of M2Ms with DCC as a result of 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 from 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]

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 of the 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 dated 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) or on whether or not teeth were impacted, 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.

Although the quality of the four cohort studies[47,48,58,59] was generally good, it should be noted that no RCTs were identified limiting the ability of the review to draw firm conclusions.

The findings of this review were in line with those from the other nine identified SRs,[20,40,42–46,50,56] 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[48] 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 with 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.

Uncertainties

The AG's model results are driven by figures reported by Fernandes *et al.*[48] and McArdle *et al.*[104] Although the results reported by Fernandes *et al.*[48] on the rate of extraction of IM3Ms are supported by the results reported by Hill and Walker,[47] the results reported by McArdle *et al.*[104] 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 of the extractions were carried out in the acute setting, the size of the ICER for prophylactic removal compared with watchful waiting would still remain below £20,000 per QALY gained.

The Fernandes *et al.*[48] study from which IM3M symptom development and extraction rates were derived was not a clinical trial but an analysis of real-world data. As such, the study provides estimates of symptom development and extraction in a real-world setting when watchful waiting has been recommended, rather than to a strictly defined and monitored policy of watchful waiting, as would be the case in a clinical trial. Although this is a limitation of the economic model, it can also be seen as a strength, as the model findings are based on a change in potential recommendation and its impact on actual practice, rather than any specific watchful waiting strategy itself. The results of the modelling in this respect are clear – that under current extraction and symptom development rates for IM3Ms, any change in recommendations that increased the proportion of patients opting for prophylactic extraction would most likely be cost-effective.

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.*[48] (this study included people with both bony IM3Ms and partially erupted IM3Ms) would be underestimates 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.

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 the study by Ara and Brazier.[110] The utility values reported in Ara and Brazier[110] were not sourced directly from patients with IM3Ms, and this is a limitation of the findings. However, the model results were insensitive to a wide range of utility values considered. This suggests that, unless the values chosen for the model were substantially different from reality, the use of the values from Ara and Brazier[110] will not have influenced the conclusions drawn from the model. The limitation of the source of the utility values also has to be interpreted against the range of assumptions made by the AG as QALY gains from the model are potentially lower than would be expected in reality, for example applying no disutility M2M decay, the assumption of no serious complications arising from pericoronitis and that extraction of an IM3M does not increase in difficulty as people age.

Chapter 6 Conclusions

The findings from the clinical evidence review are consistent with previous SRs,[20,40,42–46,50,56] 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 that demonstrated what happens when asymptomatic IM3Ms are left in situ.

Only two published cost-effectiveness studies[17,20] 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's economic model indicate that the ICER per QALY gained for the comparison of the cost-effectiveness of a prophylactic removal strategy with a watchful waiting strategy is markedly lower than the £20,000 per QALY gained threshold widely accepted by NICE Appraisal Committees.

Implications for service provision

The results from the clinical studies and those generated by the economic model show that most people with IM3Ms will have their impacted teeth removed at some point and that, although prophylactic removal is probably more costly than a watchful waiting strategy (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.

The reintroduction of the prophylactic removal of pathology-free/trouble-free IM3Ms will have resource implications in both primary and secondary care settings, with the rate of pathology-free IM3M 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.[80]

Suggested research priorities

The AG was able to produce a robust economic model, despite the limited clinical evidence relating to the prophylactic removal of pathology-free/trouble-free IM3Ms by using IM3M extraction, symptom development and extraction complication rates from the literature. Utility valuation studies of patients with symptomatic IM3Ms and following extraction (with and without complications) would strengthen the economic modelling that can be undertaken in the future. However, there remains a lack of head-to-head trial evidence comparing a prophylactic removal strategy with a watchful waiting strategy. The practical difficulties (e.g. time, cost and the need for extended follow-up) associated with undertaking such studies mean that it is unlikely that this type of study will be conducted.

Future longitudinal studies on the pathology of retained I3Ms could be designed to record the impaction status and health of the retained I3M, with the results being presented separately for maxillary and mandibular teeth. Ideally these studies would include longer follow-up periods and include subgroup analyses of adults based on age to help identify the outcomes of retained IM3Ms and the pattern of extraction rate over the years. If such studies are not possible, the systematic collection of routine data collected across different countries may be beneficial; however, for further studies to be meaningful, common definitions and outcome reporting methods need to be agreed.

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Data-sharing statement

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

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Appendix 1 Literature search strategies

The Cochrane Library

Cochrane Database of Systematic Reviews/Cochrane Central Register Of Controlled Trials/Database of Abstracts of Reviews of Effects (DARE)/Health Technology Assessments

Date range searched: 1999 to 29 April 2016.

Date searched: 29 April 2016.

Search strategy

#	Search	Hits (*n*)
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*	39,875
10	MeSH descriptor: [Age Determination by Teeth] explode all trees	5
11	#9 or #10	39,875
12	#8 not #11	1206

MEDLINE

Date range searched: 1999 to 29 April 2016.

Date searched: 29 April 2016.

Search strategy

#	Search	Hits (*n*)
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

#	Search	Hits (*n*)
6	(itm or itms).tw.	491
7	1 or 2 or 3 or 4 or 5 or 6	12,952
8	M3.tw.	17,929
9	(tooth or teeth).tw.	114,879
10	8 and 9	147
11	7 or 10	13,039
12	limit 11 to yr = "1999 -Current"	7043
13	animal/not human/	4,178,280
14	12 not 13	6746
15	limit 14 to english language	6312
16	comment/or editorial/or letter/or news/	1,532,370
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

Date range searched: 1999 to 29 April 2016.

Date searched: 29 April 2016.

Search strategy

#	Search	Hits (*n*)
1	Molar, Third/	24,449
2	((third or three) adj1 molar*).tw.	7130
3	(wisdom adj1 (tooth or teeth)).tw.	1068
4	Tooth, Impacted/	16,122
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	42,489
8	M3.tw.	34,492
9	(tooth or teeth).tw.	123,929
10	8 and 9	231
11	7 or 10	42,616
12	limit 11 to yr = "1999 -Current"	20,887
13	animal/not human/	1,297,895

#	Search	Hits (*n*)
14	12 not 13	19,854
15	limit 14 to english language	18,383
16	comment/or editorial/or letter/or news/	1,398,219
17	15 not 16	17,982
18	Age Determination by Teeth/	5092
19	(age adj2 (determin* or estimat*)).tw.	15,389
20	18 or 19	18,641
21	17 not 20	17,719
22	limit 21 to embase	6238

EconLit

Search strategy

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

NHS Economic Evaluation Database

Date searched: 29 April 2016.

Search strategy

#	Search	Hits (*n*)
1	mandibular wisdom teeth	3

Appendix 2 Excluded studies

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

Reason for exclusion	Number of studies
Wrong design	61
Non-SR	24
Non-English language	8
Wrong setting	87
No relevant outcomes	20
Not M3M	24
Not impacted	13
Not pathology free 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

Reason for exclusion	Number of studies
Ahmad *et al.* 2008[10]	Not impacted
Al-Belasy *et al.* 2009[111]	Not pathology free or trouble free
Allen *et al.* 2009[112]	No data for impacted pathology free/trouble free
The Centre for Review on Dissemination 1999[113]	Reprint of an article based on Song *et al.* 1997[64]
Baykul *et al.* 2005[114]	Not pathology free or trouble free
Blakey *et al.* 2010[115]	Not all impacted, not all M3Ms, no relevant outcomes reported for IM3Ms
Blakey *et al.* 2009[116]	
Blakey *et al.* 2007[117]	
Blakey *et al.* 2006[118]	
Blakey *et al.* 2002[119]	
Blakey *et al.* 2009[120]	
Divaris *et al.* 2012[121]	
Phillips *et al.* 2007[122]	
Shugars *et al.* 2005[123]	
Shugars *et al.* 2004[124]	
Bloomer 2000[125]	Not pathology free or trouble free
Brann *et al.* 1999[126]	Not pathology free or trouble free
Chaparro-Avendaño *et al.* 2005[127]	No results for impacted pathology free or trouble free

Reason for exclusion	Number of studies
Cunha-Cruz *et al.* 2014[128]	Not all impacted pathology-free or trouble-free M3Ms
Huang *et al.* 2014[129]	
Dicus *et al.* 2010[130]	Not results for impacted, mandibular pathology-free or trouble-free teeth
Faria *et al.* 2012[131]	No relevant outcomes
Faria *et al.* 2013[132]	
Figueiredo *et al.* 2005[133]	Not pathology free or trouble free
Güven *et al.* 2000[134]	No results for impacted pathology free or trouble free
Hanson *et al.* 2004[135]	Not impacted
Juhl *et al.* 2006[136]	Not pathology free or trouble free
Juhl *et al.* 2008[137]	Not pathology free or trouble free
Kucukkolbasi *et al.* 2014[138]	No relevant outcomes
Monaco *et al.* 2009[139]	Not pathology free or trouble free
Montevecchi *et al.* 2014[140]	Not pathology free or trouble free
Naghipur *et al.* 2013[141]	Not pathology free or trouble free
Naghipur *et al.* 2014[142]	Not pathology free or trouble free
Nunn *et al.* 2013[12]	No results for impacted pathology-free or trouble-free M3Ms
Ozeç *et al.* 2009[143]	No results for impacted pathology free or trouble free
Pepper *et al.* 2012[144]	Not pathology free or trouble free
Phillips *et al.* 2003[92]	No relevant outcomes
Phillips *et al.* 2012[145]	No relevant outcomes
Poeschl *et al.* 2004[146]	94% impacted but not pathology free/trouble free
Polat *et al.* 2008[147]	Not pathology free or trouble free
Sarikov and Juodzbalys 2014[148]	Not pathology free or trouble free
Şimşek-Kaya *et al.* 2011[149]	Premolars
Ventä *et al.* 1999[150]	No relevant outcomes reported by impacted M3Ms
Ventä *et al.* 2001[151]	
Ventä *et al.* 2000[152]	
Ventä *et al.* 2004[65]	
Vondeling *et al.* 1999[153]	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 subsequently excluded

Study	Country	3Ms or I3Ms	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon	Cost year
Inverso *et al.* 2014[71]	USA	3Ms	Microcosting analysis	S1: extraction of four symptom-free, disease-free 3Ms. S2: active surveillance of four symptom-free, disease free 3Ms	S1: average time and cost by visit type (consultation, operative and post-operative) for extraction of four 3Ms; 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 2012[72]	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 3Ms 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.* 2006[74] Kunkel *et al.* 2007[73]	Germany	3Ms	Prospective cohort study of patients who were 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	2004–5 NA
Liedholm *et al.* 2005[75]	Sweden and Wales (UK)	3Ms	Comparison of patient preferences using the multiattribute utility method	Patients referred (1997/8) for removal of one or both of their M3Ms	Home and social life; general health and well-being; job and studies; health and comfort of mouth, teeth and gums; appearance	Patient interviews	Interviews took place in the clinic immediately after consultation	NA

NA, not applicable; S1, scenario 1; S2, scenario 2.

Appendix 3 Quality assessment

Quality assessment of systematic reviews

Study question	Study								
	Bouloux *et al.* 2015[44]	Clinical evidence[56]	CADTH 2010[42]	Costa *et al.* 2013[45]	Mettes *et al.* 2012[46]	[a]Senter for Medisinsk Metodevurdering[50]	Song *et al.* 2000[20]	Stordeur and Eyssen 2012[40]	Suska *et al.* 2010[43]
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	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

NA, not applicable; NS, not stated.
a English summary only.

Appendix 4 Data abstraction tables

Characteristics of the study comparing prophylactic removal with retention and standard care

Characteristic	Study Vares and Kyyak 2014[58]
Aim	*The aim of our investigation was to systematize a scheme of objective preoperative clinical and roentgenological assessment of mandibular impacted symptom-free 'wisdom teeth' to create a rationale for their prophylactic removal*
Conclusion	*The low-to-no percentage of intra- and postoperative 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 postoperative period*
Design	Prospective cohort study
Setting	Department of Surgical Dentistry and Maxillofacial Surgery of Lviv Danylo Halytsky National Medical University, Ukraine
Recruitment period/follow-up	2009–13/annual follow-up, 5 years
Sponsorship/conflict of interests	NR/NR
Power	NR
Description of IM3Ms, total	84 patients with 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 and 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, $n = 52$ patients [subgroups by ages 18–25 years ($n = 41$), 25–45 years ($n = 10$), 68 years ($n = 1$)] • Group 2: identified as requiring removal of IM3Ms but refused removal of IM3Ms, $n = 7$ patients • Group 3: identified as not requiring removal of IM3Ms, $n = 25$ 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.

Outcomes of prophylactic removal versus retention and 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, 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 teeth
Retention ($n = 25$)	Removed during follow-up because of the appearance of indications	0/25 teeth

NR, not reported.

Study characteristics of retention and standard care studies

	Characteristic							
Study	Aim	Conclusion	Design	Setting	Recruitment period; follow-up	Sponsorship; conflict of interests	Power	Outcomes
Fernandes *et al.* 2010[48]	• 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	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

Study	Characteristic							
	Aim	Conclusion	Design	Setting	Recruitment period; follow-up	Sponsorship; conflict of interests	Power	Outcomes
Hill and Walker 2006[47]	Find out what happened over a period of 5 years to fully or partially impacted M3Ms that were left alone	• None of the examined factors (smoking, extent of eruption, depth of periodontal pocket, and history of pericoronitis) predicted which teeth would subsequently require removal • Although one-third of the teeth did require removal in the 5-year period. • 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	Prospective cohort study	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 needed to complete the study	• Extraction rates • Reasons for extraction • Clinical factors: ○ Visible plaque ○ Depth of pocket distal to the 2M ○ Bleeding on probing ○ Intrabony defect ○ Evaluation of the position of the upper 3M ○ Any evidence of resorption ○ Radiographic measurement of the follicular space

NR, not reported.

Participant characteristics of retention and standard care studies

Study	Characteristic			
	Description of I3Ms (*n*)	Inclusion/exclusion criteria	Demographics	Baseline assessments
Fernandes *et al.* 2010[48]	*n* = 421 (69% of 613 assessed at baseline); lower I3Ms examined, *n* = 676	Inclusion: • Be a registered patient in the dental primary care system of one of the three regions involved • Aged 18–70 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 (years): ○ 18–34.9, *n* = 400 ○ 35–49.9, *n* = 149 ○ 50–70, *n* = 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 2006[68]	• Lower I3M and no criterion for its immediate removal • 228 patients analysed out of 250 recruited • 427 3Ms (19 fully erupted) • 153 patients had no history of pericoronitis	Inclusion: • Aged 16–30 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 • Patients outside the declared age range • Patients with fully erupted 3Ms • Patients who were unwilling to be followed up for 5 years or who moved away from the geographical area were withdrawn	• Males: 34% • Median age: 23 years • Age range: 16–30 years	• Clinical and radiographic examination • Eruption state • Pericoronitis 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 ○ Bleeding on probing ○ Intrabony defect ○ Evaluation of the position of the upper 3M ○ Any evidence of resorption ○ Radiographic measurement of the follicular space

NIH, National Institutes of Health.

Outcomes of retention and standard care studies

Study	Outcomes assessed	Rate, *n* (%) (unless otherwise stated)	*p*-value	How it was measured; timing; analysis
Fernandes *et al.* 2010[48]	Teeth extracted	37 (5.47)		Questions and assessed by research dentist; 1 year; NA
	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, *n/N* (%)	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)		
	Extracted with symptoms (non-SIGN)	5 (0.7)		
	Some form of symptoms			
	18–34.9 years of age	83 (22.6)	$p = 0.0028$	Questioned and assessed by research dentist; 1 year; Pearson chi-squared test
	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)	$p \leq 0.001$	
	Mesial angulation	43 (13.15)		
	Distal angulation	31 (30.7)		
	Horizontal angulation	6 (6.5)		
	Unerupted (%)	10.49	$p \leq 0.001$	
	Partially erupted (%)	23.05		
	Average number of teeth	NR	$p > 0.05$	

Study	Outcomes assessed	Rate, *n* (%) (unless otherwise stated)	*p*-value	How it was measured; timing; analysis
	Maximum BPE scores	NR	$p > 0.05$	Questioned and assessed by research dentist; 1 year; NR
	Average GI	NR	$p > 0.05$	
	Average mean plaque	NR	$p > 0.05$	
	Reason for last visit to the general dental practitioner	NR	$p = 0.041$	Questioned and assessed by research dentist; 1 year; *t*-test
	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	$p = 0.291$	
	Drinking > 14 units of alcohol per week	NR	$p = 0.447$	
	Deprivation category	NR	$p = 0.058$	
	Symptoms as SIGN symptoms only (infection, severe pain and caries) (%)			
	Vertical angulation	10.29	$p \leq 0.001$	Questioned and assessed by research dentist; 1 year; Pearson χ^2 test
	Mesial angulation	5.48		
	Distal angulation	24.69		
	Horizontal angulation	3.34		
	Unerupted	NR	$p = 0.004$	
	Partially erupted	NR		
Hill 2006[68]	Extraction rates (per patient)	No history of pericoronitis: 48/153; history of pericoronitis: 23/66		Questionnaire/telephone (every 6 months); clinical examination (or telephone)
	Reasons for extraction, *n/N* (%)			
	Pericoronitis after start of study	30/48 (62.5)		Every year; NA
	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			
	Visible plaque	NR		Clinical examination (or telephone call); every year; NA
	Depth of pocket distal to the 2M	NR		
	Bleeding on probing	NR		
	Intrabony defect	NR		

Study	Outcomes assessed	Rate, *n* (%) (unless otherwise stated)	*p*-value	How it was measured; timing; analysis
	Evaluation of the position of the upper 3M	NR		
	Any evidence of resorption	0		
	Radiographic measurement of the follicular space	NR		
	Remained symptomless (*n*/*N*)	150/228		

BPE, Basic Periodontal Examination; NA, not applicable; NR, not reported; TMJ, temporomandibular joint.

Study and participant characteristics of the prophylactic removal study

Characteristic	Study Petsos *et al.* 2016[59]
Aim	*To investigate the effect of M3M removal on the 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	2 June to 31 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, $n = 58$, fully impacted, $n = 20$
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	• Male: 37% • Mean age: 16.0 ± 2.0 years • Non-smokers = 74 participants
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 cementoenamel 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 and mesiolingual)

Characteristic	Study Petsos *et al.* 2016[59]
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 tooth was horizontally dissected with rotary instruments using continuous sterile saline irrigation, and removed • Local or general anaesthesia • Oral surgeon • All patients received oral hygiene instruction and were prescribed 300 mg of clindamycin every 8 hours for 5 days, 400 mg of ibuprofen every 8 hours for 3 days, 4 mg of dexamethasone every 8 hours for 3 days (tapering off on the fourth day) and a rinsing solution (chlorhexidine digluconate 0.1%) twice daily for 10 days

NR, not reported; PII, plaque index.

Outcomes for the prophylactic removal study

Outcomes assessed by Pestos *et al.* 2016[59]	Rate	*p*-value
PII		
Baseline	NR	> 0.5
6 months	NR	
GI		
Baseline	NR	> 0.05
6 months	NR	
PPD (mm) of 3 sites,[a] mean ± SD (range)		
Baseline	3.25 ± 0.65 (2–5.7)	< 0.05
6 months	2.57 ± 0.5 (1.3–3.7)	
PAL (mm) of 3 sites,[a] mean ± SD (range)		
Baseline	2.96 ± 0.53 (2.0–5.0)	< 0.05
6 months	2.55 ± 0.5 (1.3–3.7)	
Any complication, *n*/*N*	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	

NR, not reported; PII, plaque index; SD, standard deviation.
a Three sites located closest to the distovestibular incision (buccal, distobuccal and distolingual).

Systematic reviews

Systematic review characteristics

Study	Characteristic: Publication type; date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
Bouloux *et al.* 2015[44] AAOMS M3Taskforce	SR; NR	*To determine clinically whether or not 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 number of 3Ms requiring extraction during study period • Follow-up duration of ≥ 1 year • Aged ≥ 18 years • More than one 3M present at enrolment • Only asymptomatic 3Ms at enrolment • Assumption that the teeth had been retained because they were asymptomatic and disease-free 3Ms	• Number of 3Ms removed during the follow-up period • Number of patients who required one or more 3Ms removed during that period	• Patient age • Number of 3Ms or patients present at the baseline examination • Predictor variable: follow-up duration, recorded in years
CADTH 2010[42]	Rapid review; 9 July 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?* *Reproduced with permission from CADTH[42]* *Note: 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 that underwent prophylactic surgery for 3M removal with the other group that retained their asymptomatic teeth	Clinical outcomes summarised narratively	Each study was summarised narratively
Clinical evidence[41,51–56]	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

Study	Characteristic				
	Publication type; date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
Costa *et al.* 2013[45]	SR; up to 30 August 2012	*To investigate whether or not there is evidence justifying the prophylactic extraction of 3Ms*	• Study design: ○ RCT ○ SR ○ 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[46]	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	Characteristic				
	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	
Senter for Medisinsk Metodevurdering 2003[50]	SR (English summary only); 1999–2003	To evaluate the evidence on the incidence of surgical complications following the prophylactic removal of I3Ms, and the morbidity, quality-of-life and economic aspects associated with retention of I3Ms	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

Study	Characteristic				
	Publication type; date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
Song *et al.* 2000[20]	Clinical guidance/ SR; 1984–99	*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 • Undergoing surgical removal of 3Ms either as prophylaxis or due to associated pathological changes Outcomes: • Pathological changes associated with retention of 3Ms • Post-operative complications following extraction	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 • 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 and Eyssen 2012[40]	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*	English, French, German and Dutch languages Study design: • SRs with or without meta-analyses • RCT • Non-randomised clinical trials • HTA • CPGs	NR	SRs and HTAs: • Search date • Publication year • Searched databases • Availability of evidence tables • Included studies • Main results

Study	Characteristic				
	Publication type; date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
		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?* *Reproduced with permission from the Belgian Health Care Knowledge Centre. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nd/4.0/), which permits reproduction, provided the original author and source are credited*	• Comparing the effect of prophylactic removal of pathology-free wisdom teeth with no-treatment • Existing guidelines of high quality		CPGs: • Search date • Publication year • Searched databases • Availability of evidence tables • Recommendations and referenced evidence • The recommendations from the identified SRs • 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[43]	May 2003 to December 2009; based on the Norwegian HTA so searches conducted after 2003 only	*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?* *Reproduced with permission from HTA-centrum*	• 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

AAOMS, American Association of Oral and Maxillofacial Surgeons; CPG, clinical practice guideline; HTA, Health Technology Assessment; NR, not reported.

Systematic review results

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Bouloux *et al.* 2015[44] AAOMS M3Taskforce	Cohort studies: $n = 7$ • von Wowern *et al.* 1989[154] • Garcia and Chauncey 1989[155] • Ventä *et al.* 2000[152] • Kruger *et al.* 2001[62] • Ventä *et al.* 2004[65] • Hill and Walker 2006[47] • Fernandes *et al.* 2010[48]	• Mandibular only: $n = 3$ • Both maxillary and mandibular: $n = 4$ • 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 cohort studies were included with follow-up periods ranging from 1 to 18 years and samples sizes ranging from 70 to 821 participants • The mean incidence rate for extraction of previously asymptomatic 3Ms was 3.0% annually (range 1–9%) • The cumulative incidence rate for 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[42]	SRs: $n = 4$ • Song *et al.* 2000[20] • Senter for Medisinsk Metodevurdering 2003[50] • Mettes *et al.* 2005[49] • Dodson and Susarla 2010[41] Non-RCTs: $n = 1$ • Kunkel *et al.* 2007[73] Guidelines, $n = 2$ • NICE 2000[2] • Agency for Quality in Dentistry 2006[28]	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 two CPGs. 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 towards a potentially unnecessary surgical procedure* *Reproduced with permission from CADTH[42]*

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Clinical evidence[41,51–56]	• Extraction of asymptomatic impacted wisdom teeth. SR, $n = 5$: • Song *et al.* 1997[64] • Song *et al.* 2000[20] • Senter for Medisinsk Metodevurdering 2003[50] • Mettes *et al.* 2005[49] • Costa *et al.* 2013[45] Between them one RCT was identified: • Harradine *et al.* 1998[61] An RCT on incisor crowding was excluded in latest update: • Lindqvist and Thilander 1982[63] Active surveillance of asymptomatic impacted wisdom teeth: • No studies	Extraction: • Mandibular only, $n = 1$ 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*

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Costa *et al* 2013[45]	SR, $n = 1$: • Mettes *et al.* 2005[49] RCT, $n = 3$: • Van der Sanden *et al.* 2005[156] • Harradine *et al.* 1998[61] • Lindqvist and Thilander 1982[63]	• Mandibular only: $n = 3$ • Not specified: $n = 1$ • Range of sample sizes: 36 (simulated patient cases) to 164 • Range of mean ages: NR for simulated patients, mean age 14 years 10 months, 13–19 years and 19–60 • Range of % male: 44–45 (NR for simulated cases) • Follow-up: 36–66 months	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*
Mettes *et al.* 2012[46]	RCT, $n = 1$: • Harradine *et al.* 1998[61] Note: the original version review had found two RCTs (Harradine *et al.* 1998,[61] Lindqvist and Thilander 1982[63]) and one ongoing study (van de Waal 1999[157])	Maxillary only Sample size: $n = 164$ Completed trial: $n = 77$ Mean length of follow-up: 66 months ± 12.6 months Mean age: 14 years and 10 months % male: 45	One RCT was identified that compared removal with retention of asymptomatic impacted wisdom teeth. This study was restricted to adolescents and the only relevant outcome measured was 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	Insufficient evidence was found to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults The single RCT compared removal with retention of asymptomatic impacted wisdom teeth and reported only one relevant outcome (late lower incisor crowding at 5 years). No difference was found Watchful monitoring of asymptomatic third molar teeth may be a more prudent strategy

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Senter for Medisinsk Metodevurdering 2003[50]	Patient series, $n = 13$ (11 reported in summary): • Berge 2002[158] • Blakey *et al.* 2002[119] • Conrad *et al.* 1999[83] • Gülicher and Gerlach 2001[159] • Hill *et al.* 2001[160] • Rakprasitkul 2001[161] • Renton and McGurk 2001[162] • Tay 2000[163] • Valmaseda-Castellón *et al.* 2000[164] • Valmaseda-Castellón *et al.* 2001[105] • White *et al.* 2002[165] • Yamaoka *et al.* 1999[166] • Yoshii *et al.* 2001[167] Cohort studies, $n = 3$ (five reported in summary): • Kruger *et al.* 2001[62] • Ventä *et al.* 1999[150] • Ventä *et al.* 2001[151] Case–controlled studies, $n = 2$: • Güngörmüs 2002[168] • Shafer *et al.* 1999[169]		Studies on complications related to prophylactic removal report low incidences of: • pain • permanent nerve damage (more than 6 months) on inferior alveolar and lingual nerve • fractures or serious infection But 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 Studies on complications related to retention report low incidence of: • root resorption of 2M teeth • cysts • tumours But report a relatively high incidence of pericoronitis and caries, with higher incidence of pericoronitis related to partially erupted third molars compared to fully retained	Removal of asymptomatic fully retained wisdom teeth is not recommended. However, Norwegian dentists recommend prophylactic removal of 3Ms when the likelihood of 3Ms causing problems in the future is high and the incidence of post-operative complications is low (including partially erupted wisdom teeth). As this report is based on studies that are not optimal, the patient's preferences need to be decisive

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
	Cross-sectional studies, $n = 6$: • Güven *et al.* 2000[134] • Kan *et al.* 2002[170] • Libersa *et al.* 2002[171] • Ma'aita and Alwrikat 2000[172] • Perry and Goldberg 2000[173] • Punwutikorn *et al.* 1999[174] Decision analysis, $n = 1$ • Edwards *et al.* 1999[60]			
Song *et al.* 2000[20]	RCT, $n = 2$ • Harradine *et al.* 1998[61] • Vondeling *et al.* 1999[153] Decision analysis studies, $n = 4$ Brickley *et al.* 1995[175] Edwards *et al.* 1999[60] Tulloch and Antczack-Bouckoms 1987[176] Tulloch *et al.* 1990[177] Literature reviews, $n = 34$ • Toth 1993[178] • Stephens *et al.* 1989[179] • Mercier and Precious 1992[180]	Only available for Harradine 1998.[61] • Sample size: $n = 164$ • Completed trial. $n = 77$ • 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 ongoing 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*	*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	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
	• Daley 1996[181] • Vasir and Robinson 1991[182] • Anderson 1998[183] • Bertrand 1989[184] • Bishara 1999[185] • Bonetti *et al.* 1988[186] • Bramante 1990[187] • Brokaw 1991[188] • Cade 1992[189] • Chikhani *et al.* 1994[190] • Dénes *et al.* 1993[191] • ECRI 1993[192] • Flick 1999[4] • Forssel and Miettinen 1988[193] • Garattini *et al.* 1990[194] • Goia *et al.* 1990[195] • Pajarola 1994[196] • Kugelberg 1992[197] • Lechien 1995[198] • Mommaerts and Jacobs 1991[199] • Peterson 1992[200] • Robinson and Vasir 1993[201] • Robinson 1994[202] • Sands *et al.* 1993[203,204] • Southard 1992[205] • Tate 1994[206] • Tealdi and Domini 1986[207] • Torres 1997[208] • van der Linden *et al.* 1993[209] • Waite and Reynolds 1998[210] • Weisenfeld and Kondis 1991[211]		*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. Twelve 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 rated as being 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 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 than prophylactic removal of I3Ms*	

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Stordeur and Eyssen 2012[40]	SRs, $n = 2$: • Mettes *et al.* 2005[49] • Song *et al.* 2000[20] HTAs, $n = 2$: • CADTH 2010[42] • Suska *et al.* 2010[43] CPG, $n = 1$: • NICE 2000[2]	NA	*Evidence of good quality in this domain is sparse. The methodological quality of the primary studies is rated as being low to very low. The three RTCs 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* *Reproduced with permission from the Belgian Health Care Knowledge Centre. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nd/4.0/), which permits reproduction, provided the original author and source are credited* *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 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*	*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. Preventative 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* *Reproduced with permission from the Belgian Health Care Knowledge Centre. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nd/4.0/), which permits reproduction, provided the original author and source are credited*

Study	Characteristic			
	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
			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[43]	HTA/SRs, *n* = 2: • Mettes *et al.* 2005[49] • Norwegian Knowledge centre 2003[50] Case series, *n* = 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* *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* *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* *Reproduced with permission from HTA-centrum*	*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* *Reproduced with permission from HTA-centrum*

AAOMS, American Association of Oral and Maxillofacial Surgeons; AMSTAR, Assessment of Multiple Systematic Reviews; CPG, clinical practice guideline; HTA, Health Technology Assessment; NA, not applicable; NR, not reported.

Appendix 5 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, as a result of the paucity of information available, the AG feels that 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 reviews[2,20,41,43,45,47–50] met the inclusion criteria for this review, meaning that 75 references, previously included in SRs, were excluded. For 41 of these references,[61,63,64,154,155,175–184,186–211] 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 27*. Nine of these references did not meet our specific inclusion criteria but warrant further discussion as they are papers often cited in the debate. The details of the study aims, the results and conclusions are summarised narratively and in *Table 28*.

TABLE 27 Reasons for exclusion of studies included in previous SRs

Study	Design and reason for exclusion
Agency for Quality in Dentistry (ZZQ) 2006[28]	• 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[158]	• Retrospective single cohort • IM3Ms no mention of prophylactic removal • Outcome is pain
Bishara 1999[185]	• Literature review • Some of the pertinent studies related to the management of 3Ms in an orthodontic context
Blakey *et al.* 2002[119]	• Longitudinal single cohort • Not all impacted • Not all M3Ms
Conrad *et al.* 1999[83]	• Prospective patient series • No details of impaction • All 3Ms were removed in 175/201 patients, and at least both lower 3Ms were removed in 182/201 patients • Teeth were symptomatic
Edwards *et al.* 1999[60]	• Decision analysis • Impaction status not mentioned
Flick 1999[4]	Literature review
Gülicher and Gerlach 2001[159]	• 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
Güngörmüs 2002[168]	• Retrospective case–control study • Evaluate the changes in M3M position and pathological status associated with 3Ms after extraction of four first premolars

continued

TABLE 27 Reasons for exclusion of studies included in previous SRs (*continued*)

Study	Design and reason for exclusion
Güven *et al.* 2000[134]	• Retrospective cross-sectional study • 3 : 1 ratio of mandibular : maxillary • 3621/7582 teeth removed prophylactically but outcomes assess how many had pathology
Hill *et al.* 2001[160]	• Prospective patient series • Comparing general with local anaesthesia for unilateral or bilateral removal of IM3Ms
Kan *et al.* 2002[170]	• Retrospective cross-sectional study • Not asymptomatic • Pathology of 2Ms after removal of 3Ms
Kruger *et al.* 2001[62]	• Prospective single cohort • Change in eruption status from 18 to 26 years • No data on asymptomatic or symptomatic wisdom teeth
Kunkel *et al.* 2007[73]	• 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[171]	• Retrospective cross-sectional study • Patients with immediate or late fracture after removal of IM3Ms • No details on whether or not they are removed prophylactically
Ma'aita and Alwrikat 2000[172]	• 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 and Goldberg 2000[173]	• 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[174]	• Retrospective cross-sectional study • Unerupted though eruption status and angle are reported • 62% asymptomatic • Thailand
Rakprasitkul 2001[161]	• 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 and McGurk 2001[162]	• Prospective patient series • 90% impacted • 87% had therapeutic indications for operation
Shafer *et al.* 1999[169]	• Prospective case–control study • All four 3Ms were removed • Outcome taste change
Tay 2000[163]	• Retrospective patient series • Both mandibular and maxillary • 56.2% were removed prophylactically • Singapore
Valmaseda-Castellón *et al.* 2000[164] and Valmaseda-Castellón *et al.* 2001[105]	• Prospective patient series • 5% erupted no details on impaction? Angulation? 36% vertical • No mention of prophylactic removal or retention
van de Waal 1999[157]	• No results • Excluded in Mettes *et al.*[46] update
van der Sanden *et al.* 2005[156]	Decision-making tool

TABLE 27 Reasons for exclusion of studies included in previous SRs (*continued*)

Study	Design and reason for exclusion
Ventä *et al.* 1999[150]	• Not all impacted or mandibular or pathology free or trouble free • No relevant outcomes reported
Ventä *et al.* 2000[152]	• Not all impacted and mandibular • No relevant outcomes reported • However, details on symptoms are reported
Ventä *et al.* 2001[151]	• All impacted and many results reported for mandibular subgroup • 74% of the whole group were asymptomatic • No relevant outcomes
Ventä *et al.* 2004[65]	• Not all impacted and mandibular or pathology free or trouble free • No relevant outcomes reported
Vondeling *et al.* 1999[153]	• Not all impacted • Cannot get hold of paper • Originally included in Song *et al.*[20]
White *et al.* 2002[165]	• Longitudinal single cohort study • Not all impacted • Not all M3Ms
Yamaoka *et al.* 1999[166]	• Retrospective patient series • Not all impacted • Both 2Ms and 3Ms removed • No mention of prophylactic removal or retention
Yoshii *et al.* 2001[167]	• Retrospective patient series • Data available for impacted subgroup • Not prophylactic removal

TABLE 28 Summary characteristics of nine often cited studies that were excluded from this review

Study	Reason for exclusion	Aims	Conclusions
Blakey *et al.* 2002[119]	• Not all impacted • Not all M3Ms	*To 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*
White *et al.* 2002[165]	• 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*
Ventä *et al.* 1999[150]	• Not all impacted or mandibular or pathology free or trouble free • No relevant outcomes reported	*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*

continued

TABLE 28 Summary characteristics of nine often cited studies that were excluded from this review (*continued*)

Study	Reason for exclusion	Aims	Conclusions
Ventä *et al.* 2000[152]	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*
Ventä *et al.* 2001[151]	• All impacted and many results reported for mandibular subgroup • 74% of the whole group were asymptomatic • No relevant outcomes	*To examine radiographic changes in I3Ms in adults from 20 to 32 years, with special interest on sagittal changes in inclination*	*Considerable radiographic changes, without notable symptoms, may occur involving inclination of the tooth and state of impaction in I3Ms after the usual age of eruption*
Ventä *et al.* 2004[65]	• 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*
Edwards *et al.* 1999[60]	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*
van de Waal 1999[157]	• 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
Vondeling *et al.* 1999[153]	An ongoing trial identified by Song *et al.*[20] No further results have been published and we have not been able to access the conference abstract identified by Song *et al.*[20]	NR	NR

NR, not reported; PD, periodontol probing depth.

Blakey *et al.*[119] 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.*[119] paper assessed the periodontal probing depth (PD) of these molars at enrolment and found that 64 out of the 329 patients had a PD of $\geq$ 5 mm on any 3M, 35 of which were on the M3M only. 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.*[165] 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[165] 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 Ventä *et al.*[65,150–152] are based on a longitudinal study that followed 181 first-year students at the University of Helsinki. Participants' 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 of the teeth were impacted and both mandibular and maxillary 3Ms were included. Not all were pathology free or trouble free, although 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 I3Ms after the usual age of eruption'. One paper[152] reporting the results of the need for removal reported that 33 out of 54 3Ms that were 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'.

The study by Edwards *et al.*[60] is a decision analysis that was identified by two SRs.[20,50] The study aimed to identify the 'least costly, most effective and most cost-effective management strategy for asymptomatic, disease free mandibular third molars'. Although 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 *Chapter 4*.

It was not possible to access any published data on either the van de Waal[157] or the Vondeling *et al.*[153] papers. However, both reported on discontinued trials, according to the SRs citing them. The van de Waal[157] citation was a reference to an ongoing trial and was identified in the original Cochrane review by Mettes *et al.*,[49] but van de Waal[157] is also listed as an author of the Vondeling *et al.*[153] abstract. 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,[49,202] neither of the studies was restricted to I3Ms.

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 29*.

There were five references[13,112,143,212,213] included in the submissions that partially met the inclusion criteria for this SR and that 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[65,80,81,118,122,147,150,152,214] were identified, which also fell into this category. The AG has therefore summarised these 14 studies[13,65,80,81,112,118,122,143,147,150,152,212–214] in *Table 30*.

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

Study	Design and reason for exclusion
AAOMS 2016[31]	Wrong study design
Allen *et al.* 2009[112]	• Retrospective review of patient records • Not all patients pathology free/trouble free and no results for specific population of pathology-free/trouble-free IM3Ms
Chang *et al.* 2009[215]	• Retrospective cohort • M3Ms • Not all impacted, not all pathology free or trouble free • Wrong setting (South Korea)
Devine *et al.* 2016[35]	Wrong study design
Falci *et al.* 2012[212]	• Retrospective review of patient records • All M3Ms • Unclear whether or not all 3Ms were pathology free or trouble free
Draft FDS RCS M3M Guidance[a]	Wrong study design
Finnish Guidelines 2014[70]	Wrong study design
Hospital Episode Statistics[216]	Wrong study design
Internal Audit GSTT Dept of Oral Surgery, 2016[b]	Wrong study design
Kang *et al.* 2016[217]	• Wrong setting (China) • Not all patients pathology free/trouble free and no results for specific population of pathology-free/trouble-free IM3M
McArdle and Renton 2006[213]	• Retrospective review of patient records • All IM3Ms • Unclear whether or not all patients pathology free/trouble free
McArdle and Renton 2012[19]	Wrong study design
McArdle 2013[218]	Wrong study design
McArdle *et al.* 2014[13]	• Retrospective cohort • All IM3Ms • Unclear whether or not all 3Ms were pathology free/trouble free
McArdle *et al.* 2018[104]	Retrospective cohort All IM3Ms Unclear whether or not all 3Ms were pathology free/trouble free
McArdle PhD data	No access to reference
Oderinu *et al.* 2012[219]	• Wrong setting (Nigeria) • Withdrawn from publication
National Life Tables, UK: 2013 to 2015[106]	Wrong study design
Ozeç *et al.* 2009[143]	• Retrospective review of patient records • All M3Ms • Unclear whether or not all 3Ms were pathology free/trouble free
Ozgun *et al.*[220]	• AIC data • Wrong study design
SIGN 2000[34]	Wrong study design
World Health Organization 2010[221]	Wrong study design
Worrall *et al.* 1998[8]	Pre 1999

AAOMS, American Association of Oral and Maxillofacial Surgeons; AIC, academic in confidence; GSST, Guy's and St Thomas'.
a Renton T, FGDP, 2016, NICE submission.
b Internal audit, 2016.

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

Study	Reason for exclusion	Aims	Conclusions
Allen *et al.* 2009[112]	• Not all patients pathology free/ trouble free • 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*
Blakey *et al.* 2006[118]	• Not all mandibular and impacted • Results unclear	*To assess the change in periodontal status over time by PD in the 3M region*	*Increased PDs of ≥ 2 mm were often found in the 3M region for asymptomatic patients with at least one PD of ≥ 4 mm at enrolment, clinical measures that indicated increased periodontal pathology, and a deteriorating periodontal condition*
Blondeau and Daniel 2007[214]	• All IM3Ms • Not pathology free or trouble free	*To evaluate the incidence of various complications, including alveolitis, infection and paraesthesia 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*
Chuang *et al.* 2008[81]	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*
Chuang *et al.* 2007[80]	• 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*
Falci *et al.* 2012[212]	Unclear whether or not all patients pathology 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*
McArdle and Renton 2006[213]	Unclear whether or not all patients pathology free/trouble free	*DCC in M2M 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*

continued

TABLE 30 Studies identified in the submissions and excluded from this review (*continued*)

Study	Reason for exclusion	Aims	Conclusions
McArdle *et al.* 2014[13]	Unclear whether or not 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*
Ozeç *et al.* 2009[143]	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*
Phillips *et al.* 2007[122]	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 one 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*
Polat *et al.* 2008[147]	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*
Ventä *et al.* 1999[150]	• 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*
Ventä *et al.* 2000[152]	• Not all impacted and mandibular • No relevant outcomes reported • 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*
Ventä *et al.* 2004[65]	• 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*

Six studies[13,112,143,147,212,213] were retrospective in design, five publications[65,118,122,150,152] reported the outcomes of longitudinal studies and three publications[80,81,214] reported outcomes of prospective cohort studies. Six of the studies[13,112,143,147,212,213] reported outcomes relating to DCC in the 2M. The position of 3Ms and probing depth or clinical changes were reported in three publications.[118,122,150] Clinical complications of 3M surgery were reported by three studies[80,81,214] and one study[152] reported the estimation of the need for removal of 3Ms.

The publications by Blakey *et al.*[118] and Phillips *et al.*[122] report on different outcomes from the same longitudinal study conducted in the USA at the University of Kentucky and the University of North Carolina. Two other linked publications[119,165] from the same longitudinal study were discussed in the previous section and are not repeated here. Blakey *et al.*[118] assessed the changes in periodontal health over time and it was concluded that, for asymptomatic patients with at least one PD of ≥ 4 mm at enrolment, there were increased PDs of ≥ 2 mm often found in the 3M region. Phillips *et al.*[122] reported on the changes over time in the position of 3Ms relative to the occlusal plane and concluded that the anatomical 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.*[65,150,152] that 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, Ventä *et al.*[150] followed the clinical changes in 3M status in patients aged 20–32 years and, similar to Phillips *et al.*,[122] 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,[152] it was reported that 67% of patients had one or more 3Ms removed during the follow-up period.

The publications by Chuang *et al.*[80,81] are linked to a series of publications[78,79,222] that report the outcomes of the American Association of Oral and Maxillofacial Surgeons Age-Related Third Molar Study,[222] a prospective cohort study. Chuang *et al.*[80] 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 25–35 years were statistically significantly more likely to have a complication than patients aged < 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.*[81] 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. Fully 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 than erupted teeth. Blondeau and Daniel[214] 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; $\chi^2 = 13$; $p = 0.0003$).

Six studies[13,112,143,147,212,213] reported outcomes relating to DCC in the 2M; all of the studies reported a relationship between I3Ms, in particular mesioangular I3Ms, and the presence of 2M DCC. Allen *et al.*[112] concluded that, if 3Ms are left in situ, there is a need for close monitoring and regular bitewing radiographs. McArdle *et al.*[13,213] and Ozeç *et al.*[143] recommend prophylactic removal of the 3M to prevent DDC of the 2M.

Appendix 6 Transition probabilities used in the model

Age (years)	Mortality rate active	Probability of symptoms
20	0.0003165	0.196694
21	0.000328486	0.19048
22	0.000324472	0.184418
23	0.000372943	0.178507
24	0.000357425	0.172744
25	0.000375412	0.16713
26	0.000414361	0.161663
27	0.000424342	0.156341
28	0.00046136	0.151162
29	0.000475787	0.146125
30	0.000525243	0.141229
31	0.000569221	0.13647
32	0.000572207	0.131847
33	0.000626161	0.127357
34	0.000677156	0.122999
35	0.00074904	0.118769
36	0.000776518	0.114666
37	0.000864864	0.110687
38	0.00097521	0.106829
39	0.001062676	0.10309
40	0.00116042	0.099467
41	0.001236812	0.095958
42	0.0013093	0.092561
43	0.001457008	0.089271
44	0.001580834	0.086088
45	0.00175737	0.083007
46	0.001809657	0.080027
47	0.002005622	0.077145
48	0.002094736	0.074359
49	0.002342629	0.071665
50	0.002514115	0.069062
51	0.002791667	0.066546
52	0.003009129	0.064116
53	0.003313748	0.061769

Age (years)	Mortality rate active	Probability of symptoms
54	0.003623468	0.059502
55	0.003987477	0.057313
56	0.004297595	0.0552
57	0.004825849	0.05316
58	0.005308646	0.051192
59	0.005923238	0.049293
60	0.006400301	0.047461
61	0.007057382	0.045694
62	0.007728454	0.043989
63	0.008281076	0.042345
64	0.009066209	0.040778235
65	0.009661762	0.03926944
66	0.010460394	0.037816471
67	0.011719073	0.036417262
68	0.012927631	0.035069823
69	0.014311085	0.033772239
70	0.015800852	0.032522667
71	0.017563933	0.031319328
72	0.02002717	0.030160513
73	0.02188925	0.029044574
74	0.024206902	0.027969925
75	0.026799934	0.026935037
76	0.029680244	0.025938441
77	0.032715119	0.024978719
78	0.03680341	0.024054506
79	0.041100184	0.023164489
80	0.046894523	0.022307403
81	0.05270411	0.021482029
82	0.059299519	0.020687194
83	0.066956709	0.019921768
84	0.075685636	0.019184663
85	0.084829623	0.01847483
86	0.095257973	0.017791261
87	0.106315742	0.017132985
88	0.118288053	0.016499064
89	0.1331211	0.015888599
90	0.146901404	0.015300721
91	0.161803302	0.014734594
92	0.184076189	0.014189414

Age (years)	Mortality rate active	Probability of symptoms
93	0.197660796	0.013664406
94	0.210945629	0.013158823
95	0.230126836	0.012671946
96	0.260778283	0.012203084
97	0.279505262	0.01175157
98	0.301488605	0.011316762
99	0.324712845	0.010898042
100	0.335866615	0.010494814

Appendix 7 Search strategy (impacted mandibular third molar-specific utilities)

MEDLINE

Date searched: 10 March 2016.

Search strategy

#	Search term
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

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HTA
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