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1. Title of the project

Clinical and cost effectiveness of cholecystectomy versus observation/conservative therapy for preventing recurrent symptoms and complications in adults presenting with first episode of symptomatic gallstones (biliary colic or cholecystitis) in secondary care.

2. Name of TAR team and project 'lead'

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3. Plain English summary

Gallstones are common, especially in women, but in many people they do not cause any symptoms. Gallstones usually contain solid lumps of cholesterol-like (fatty) material and sometimes bile pigments. The risk of gallstones increases with age and with certain medical conditions such as obesity and diabetes.

About one out of three people with gallstones develop symptoms or problems. Symptoms usually include a severe pain in the upper right hand side of the abdomen (known as biliary colic), sometimes nausea and vomit and the impulse to walk. Some people may feel the pain below the right shoulder. Pain from biliary colic can last just for few minutes but, more frequently, lasts several hours. Sometimes the biliary pain is accompanied by inflammation of the gallbladder (cholecystitis).

Once gallstones start giving symptoms, painkillers, anti-inflammatory medicines, and antibiotics are usually prescribed. The treatments of gallstones include drugs, non-drug methods, and surgery. Gallstones can sometimes be treated using bile acids (in particular ursodeoxycholic acid), which dissolve gallstones. The use of bile acids in clinical practice is limited to a minority of people for whom surgery is not recommended.

Lithotripsy is a method of concentrating ultrasonic shock waves onto the gallstones in order to break them up into tiny pieces and reduce the occurrence of symptoms. However, the chance of symptoms returning after lithotripsy is high and therefore this procedure is rarely used in clinical practice.

Surgery to remove the gallbladder, known as cholecystectomy, is the most common way to treat symptomatic gallstones. There are two types of cholecystectomy: open cholecystectomy and laparoscopic cholecystectomy.

An open cholecystectomy is an effective method of treating gallstones, but it is now being widely replaced by laparoscopic cholecystectomy, which is a type of minimally invasive ‘keyhole’ surgery. The advantage of having a laparoscopic cholecystectomy is that the recovery is quicker and the length of stay shorter than open cholecystectomy.

A considerable number of cholecystectomies are performed every year in the UK with significant costs for the NHS.

Surgery is commonly offered to people with complicated and uncomplicated gallstone disease. However, the available evidence suggests that some people with mild, uncomplicated

symptoms do not experience a recurrence at least in the short/medium period. In these cases a policy of 'observation' or 'conservative treatment' (painkillers and lifestyle advice) could, therefore, be appropriate.

The purpose of the present study is to bring together the existing evidence on the risks of 'observation/conservative treatment' as an alternative to surgery, and to model the costs and benefits of cholecystectomy compared to conservative management.

4. Decision problem

Gallstones disease (cholelithiasis) is one of the most common and costly gastrointestinal disorders in Western countries.[1-3] Approximately, 15% of the adult western population suffer from gallstones.[4-9] Gallstones are more common in women and people over the age of 40.[10]

About 75 to 80% of gallstones are cholesterol gallstones (i.e. cholesterol monohydrate crystals) whilst the remaining 20 to 25% are pigment stones containing mainly insoluble bilirubin or calcium bilirubinate. Cholesterol gallstones can be divided into two further categories: cholesterol stones, which contain 90 to 100% cholesterol, and mixed gallstones which contain 50 to 90% cholesterol. The risk of cholesterol gallstones is higher in the elderly and in people with type 2 diabetes, obesity, dyslipidaemia, and hyperinsulinemia.[11-12] Treatment options are usually the same irrespective of the type of gallstone.

Gallstones may be 'silent', even for years, and not requiring treatment. However, between 1% and 4% of gallstones become symptomatic within a year.[6-9, 13] Symptoms of gallstones are usually characterised by intense pain in the right upper quadrant of the abdomen, often accompanied by nausea and vomiting and the urge to walk, that can last from a few minutes to several hours (i.e. biliary colic). The pain may radiate to the angle of the right scapula or below the right shoulder. The biliary pain is normally caused by the stone obstruction in the cystic duct or the sphincter of Oddi and can be relieved if the stone moves back into the gallbladder lumen, passes through the sphincter into the duodenum, or migrates back to the common bile duct.[14-15] Analgesic and anti-inflammatory drugs are commonly administered to alleviate the biliary pain and prevent acute cholecystistis, and anticholinergic agents may be used to reduce the gallbladder contraction. In some patients gallstones may lead to acute cholecystitis (i.e. acute inflammation of the gallbladder). Typical complications of cholecystitis may include infection, cholangitis (inflammation of a bile duct), acute pancreatitis, gallbladder perforation and abscess formation. These conditions require further medical interventions with antibiotics, radiological, endoscopic or surgical procedures.

Management of gallstone disease may include pharmacological, non-pharmacological and surgical interventions. Medical therapy for gallstones disease using bile acids (e.g. ursodeoxycholic acid - UDCA) to dissolve stones (especially cholesterol stones) is presently restricted to a small, highly-selected group of symptomatic patients for whom a surgical intervention is not recommended and recurrence is likely to have particularly adverse consequences.[16] Novel experimental animal models and preliminary clinical findings indicate that future research should focus on the mechanisms of intestinal absorption of cholesterol, on the hepatic cholesterol biosynthesis as well as on the role of gallstones genes (LITH).[15-16]

Other non-pharmacological, non-surgical treatments include dissolution/fragmentation of gallstones using the cholesterol solvent methyl tert butylether (MTBE) and extracorporeal shock wave lithotripsy (ESWL). These treatment options, however, are very rarely used in clinical practice due to their potential side effects (MTBE), high recurrence rate in patients with multiple stones (ESWL) and occurrence of transient biliary pain after successful stones fragmentation (ESWL).[6-7,17-18]

Surgery remains the treatment of choice for symptomatic gallstones with 63,915 surgical removals of the gallbladder performed in England and Wales during 2010-2011 and 53,700 patients waiting for surgery (NHS Information Centre, Hospital Episode Statistics for England; *http://www.hesonline.nhs.uk*). Until the introduction of laparoscopic cholecystectomy in 1987, open cholecystectomy was the definitive treatment of choice in clinical practice but is now increasingly being replaced by the minimal access surgery in the UK. Laparoscopic cholecystectomy is currently an ambulatory procedure with a low risk of major complications which is commonly offered to patients with symptomatic gallstone disease. Findings from a recent meta-analysis have provided evidence that laparoscopic cholecystectomy is safe and cost-effective compared with open cholecystectomy.[19] Both procedures are comparable in terms of mortality, complications rates, and operating time, but the convalescence period is quicker and the length of hospital stay shorter (and total cost lower) for laparoscopic cholecystectomy.[19] The outcome of laparoscopic surgery relies greatly on the training, experience and manual skills of the surgeon performing the procedure. There is evidence that early rather than delayed laparoscopic cholecystectomy has also greater clinical and economic benefits (e.g. reduced length of hospital stay and risk of recurrence).[20-24] Laparoscopic cholecystectomy has become the therapy of choice for patients with symptomatic gallstones with or without cholecystitis and the rate of surgical procedures has increased over time.[25-26]

In the UK, (early) cholecystectomy is commonly offered to symptomatic patients suffering from biliary colic or cholecystitis, with a significant cost to the NHS.[27] However, a proportion of these patients do not show up for elective surgery or opt for conservative treatment.[28-29] On the other hand, a certain number of patients continue to suffer from biliary type pain or develop new symptoms after cholecystectomy (e.g. postcholecystectomy syndrome).[30-31] Whilst many studies have concentrated on the best timing of performing surgery and on operative outcomes and complications the question whether cholecystectomy is always required in patients with mild, uncomplicated symptomatic gallstones has not been rigorously evaluated in a UK setting. The annual rates of developing or persisting symptoms in patients with symptomatic gallstones may range from 1% to 50% in the current literature.[32-34] In a recent population-based cohort study, 58% of the patients who initially presented with mild, uncomplicated symptoms and 52% of those who had severe, uncomplicated symptoms at presentation did not experience further episodes of biliary pain at medium follow up.[35] These findings indicate that symptomatic uncomplicated patients may be treated expectantly. A recent randomised controlled trial comparing cholecystectomy with 'observation' (including pain management and dietary advice) has concluded that expectant management is a safe alternative to surgery in mild uncomplicated patients, as the risk of developing complications is low and quality of life and pain measurements are not significantly affected.[36-37]

The aim of the current study is to assess the clinical and cost effectiveness of cholecystectomy versus observation/conservative therapy for preventing recurrent symptoms and complications in adults presenting with first episode of symptomatic gallstones (biliary colic or cholecystitis) in secondary care.

The specific objectives of the study are the following:

i) Develop clinical care pathways for treatment of symptomatic gallstones in a UK NHS context;
ii) Summarise evidence of the clinical effectiveness and safety of each observation /conservative treatment alternative to surgery;
iii) Determine which management options are most likely to be efficient for implementation into the UK NHS;
iv) Identify and prioritise future research.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for the clinical and cost effectiveness of cholecystectomy compared with non surgical interventions (i.e. observation/conservative treatment) for preventing recurrent symptoms and complications in patients with symptomatic gallstones

(biliary colic or cholecystitis) will be undertaken following the general principles of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[36] and reported in accordance with the PRISMA statement.[37]

5.1 Population

The population considered will be adults (18 years and older or as defined by the trialists) with first episode of symptomatic gallstones (biliary colic or cholecystitis) being considered for cholecystectomy in a secondary care setting. For the purpose of this review, 'first episode of symptomatic gallstones' is defined as the first instance in which the patient presents to secondary care attention (with the possibility of receiving surgical treatment) even though the clinical history may document previous clinical symptoms or pain attacks. The gallstones disease will be confirmed by ultrasonography.

An accepted definition of 'acute cholecystitis' is based on a combination of relevant clinical symptoms (e.g. pain localised to the right upper quadrant of the abdomen; temperature exceeding 37.5°C, leukocytosis greater than 10 x 10^9/1, increased C-reactive protein level) and ultrasonographic evidence of gallstones. It is likely that many reports will not provide a definition of 'acute cholecystitis' within their methods. We will consider suitable for inclusion any study population presenting with acute mild, uncomplicated, cholecystitis.

Patients with acute severe cholecystitis (e.g. obstruction of the cystic duct or neck of the gallbladder by gallstones) and/or cholangitis (inflammation of a bile duct) or pancreatitis will not be considered suitable for inclusion as they normally require urgent or emergency intervention. Similarly, patients with symptomatic gallstones complicated by severe concomitant diseases, critically ill patients, i.e. patients who are judged to be unfit or unsuitable for surgery will not be considered within the scope of this review.

5.2 Intervention(s)

The intervention considered will be surgical removal of the gallbladder (open or laparoscopic).

5.3 Comparator

The comparator intervention will be observation (watchful waiting) and/or conservative treatment. 'Conservative treatment' refers here to the course of analgesics/ anti-inflammatory drugs accompanied by lifestyle advice. Patients with cholecystitis and signs of inflammation may also be prescribed antibiotics.

'Delayed surgery' will not be considered a suitable comparator. The focus of current RCTs and meta-analyses looking at early versus delayed cholecystectomy (open and laparoscopic) has been on the optimal timing of surgical intervention as well as operative outcomes (in a patient population scheduled to receive surgery) rather than on the necessity of cholecystectomy in uncomplicated patients with symptomatic gallstones presenting to secondary care.

5.4 Outcomes

The following outcomes will be considered:

1. Disease-related morbidity
    a. Recurrence of symptoms
    b. Complications (e.g. pancreatitis)
    c. Number of visits to primary care settings or hospital emergency department
    d. Analgesic requirements
2. Need for surgical, endoscopic or radiological intervention
3. Need for further medical intervention
4. Surgery-related morbidity (e.g. bile duct injury, infection, bleeding, reoperation rate, recurrent pain, diarrhoea)
5. Quality of life (as defined by the studies' authors)
6. Cost of initial and any subsequent treatments
7. Mortality

5.5 Search strategy

Comprehensive literature searches will be conducted to identify reports of published, ongoing, and unpublished studies on the clinical and/or cost-effectiveness of cholecystectomy versus non-surgical interventions for the management of patients with symptomatic gallstones and cholecystitis. Highly sensitive search strategies will be designed, including appropriate subject headings and text word terms, interventions under consideration and relevant study designs. Searches will be run from 1980 to date, to mirror the use of surgical techniques currently available in clinical practice as well as the introduction of novel interventions for the management of symptomatic gallstones. A draft MEDLINE search is reported in Appendix 1. Databases to be searched will include MEDLINE, MEDLINE in process, Embase, Science Citation Index, Biosis and the Cochrane Controlled Trials Register. Reports of relevant evidence syntheses will also be sought from the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effects (DARE).

Ongoing studies will be identified through searching the WHO International Clinical Trials Registry, Current Controlled Trials, Clinical Trials and the NIHR Portfolio. Recent conference proceedings of key organisations such as the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the Association of Laparoscopic Surgeons of Great Britain and Ireland and the British Society of Gastroenterology will be screened for further relevant reports. The websites of regulatory bodies and HTA agencies will also be checked to identify relevant unpublished reports.

Reference lists of all included studies will be perused to identify additional potentially relevant reports. Clinical experts in the field will be contacted to provide details of any further potentially relevant reports they are aware of.

5.6 Inclusion criteria

Evidence from randomised controlled trials (RCTs) which compare cholecystectomy (open or laparoscopic) with non-surgical interventions (i.e. observation/conservative treatments) will be deemed suitable for inclusion irrespective of language, blinding, and publication status. Where insufficient evidence from RCTs is available to answer the review question, data from non-randomised comparative studies will be considered.

5.7 Exclusion criteria

The following types of report will be excluded:

- Reviews, editorials and opinions;
- Case series and case reports;
- Reports published in non-English languages for which a translation cannot be organised.

5.8 Data extraction strategy

One reviewer will screen the titles and, when available, abstracts of all reports identified by the search strategies. All potentially relevant reports will be retrieved in full and assessed independently by two reviewers. Any disagreement that cannot be resolved by consensus will be referred to a third party.

A data extraction form will be specifically designed to collect data from included studies. Two independent reviewers will extract the following information from each individual study (without concealing the study authorship or other publication details): journal name, year of publication, study design and method of patients recruitment, setting, number and characteristics of participants (e.g. gender, age, clinical history, risk factors, previous

'gallstones attacks', concomitant disease), characteristics of interventions (e.g. type, duration, cost) and outcome measures. Any disagreements will be resolved by consensus or arbitration by a third party.

5.9 Quality assessment strategy

The methodological quality of included RCTs will be assessed by means of The Cochrane Collaboration's tool for assessing risk of bias.[38] Two reviewers will independently assess the risk of bias within each included trial based on the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

A modified version of the Cochrane risk of bias tool,[38] which the Cochrane Non-Randomised Methods Group has adapted to include potential topic-specific confounders, will be used for assessing risk of bias in non-randomised comparative studies. The project group will identify *a priori* the main confounders (by outcome) for non-randomised comparative studies and imbalance in any of the confounders (e.g. age and gender differences between comparative groups) will affect study quality. Individual outcomes will be scored as High risk of bias, Low risk of bias or Unclear. Any disagreements between reviewers will be resolved by consensus or arbitration by a third party.

5.10 Methods of analysis

Where the same outcome is assessed by more than one included study, a quantitative synthesis of results will be carried out. Results of each study will be tabulated and summarised according to type of study design for each outcome and plotted as point estimates with corresponding 95% confidence intervals. Mean differences will be reported for continuous outcomes (e.g. number of visits to GP or hospital, quality of life measures), and risk ratios for dichotomous outcomes (e.g. morbidity event rates, need for further treatment, mortality). Heterogeneity between studies will be assessed by visual inspection of forest plots and from Cochran-Mantel-Haenszel chi-square test and I-squared statistict. If there is no evidence of heterogeneity, then pooled summary estimates will be derived from fixed-effects meta-analyses. Where significant heterogeneity exists, random effects meta-analyses will be used and potential sources of heterogeneity will be assessed e.g. by checking the appropriateness of the choice of effect measures or by exploratory analyses of subgroups. If multiple interventions are identified, then network meta-analysis methods (in which the research team is experienced) may be considered to derive summary estimates that would not be possible to obtain from traditional pairwise meta-analyses. If a quantitative synthesis is considered to be inappropriate or not feasible for any outcome, then a narrative synthesis of the findings will be provided for the included studies.

6. Report methods for synthesising evidence of cost-effectiveness

An economic model will be developed to compare alternative treatment strategies for patients with gallstone disease, in terms of health and social care costs, and health outcomes. The model will be populated using i) data obtained from the systematic review of clinical effectiveness as well as ii) data obtained from a review of evidence-based guidelines for the management of gallstone disease relevant to the UK. Costs of treatment will be estimated by combining estimates of resource use with appropriate unit costs.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

A formal systematic review of existing economic evaluations on gallstone disease will be performed. Major bibliographic databases will be searched including MEDLINE, MEDLINE in process, Embase, Science Citation Index, Health Management Information Consortium (HMIC), Research Papers in Economics (RePec), NHS Economic Evaluations Database (NEED) and the HTA Database.

A health economist will assess the title and abstract of all citations identified by the search for economic evaluations. Full-text papers will be obtained for those studies that appear to be potentially relevant and will be formally assessed for inclusion.

The quality of included studies will be assessed against the BMJ checklist for referees of economic analyses[39] and, where appropriate, the criteria for the review of economic models set out by Phillips and colleagues.[40] Costs and cost-effectiveness will be assessed, where possible, from the perspective of the NHS and personal social services.

6.2 Evaluation of costs and cost-effectiveness

Economic modelling will be performed to estimate the costs and consequences of the alternative management strategies. This model will reflect the care pathways that individuals may follow under alternative management strategies over time, covering the costs and consequences of the initial intervention and any subsequent events experienced - including treatment of recurrent symptoms and/or complications.

The model is likely to be a Markov state transition model that will be developed to capture the consequences of each strategy in terms of symptom remission and recurrence rates, and associated costs to the health service. The model will be based on a hypothetical cohort of patients presenting with symptomatic gallstones (biliary colic or cholecystitis). This cohort will be followed up in the model over the identified relevant time horizon allowing

cumulative costs and consequences to be tracked (e.g. extrapolated remission and recurrence rates, symptom free years, surgical complications, subsequent surgery). Where sufficient data are available, sub-group analyses will be performed.

The perspective will be that of the NHS and Personal Social Services. Data will include the direct health service costs associated with each initial treatment and subsequent management. Surgical procedures will be mapped to their appropriate HRG, and costed using NHS reference costs or the payment by results national tariff. Resource use associated with watchful waiting or conservative management will be estimated based on existing guidelines and clinical opinion, and valued using appropriate units costs (e.g. British National Formulary, Unit Costs of Health and Social Care, NHS reference costs). Further resource use events following initial treatment will be modelled using available literature and valued using the same approach as described above.

Cumulative costs and consequences will be presented using a balance sheet approach and where appropriate, costs and outcomes will be discounted at 3.5% per annum. Cost-effectiveness will be expressed in terms of the incremental cost per additional unit of effect, depending on the availability of data (e.g. incremental cost per symptom free year). An attempt will be made to identify quality of life weights associated with the different outcomes of treatment in order to extend the economic evaluation into a cost-utility analysis. A focused search of the literature and other relevant sources (e.g. the Harvard Database of Cost-utility Analyses) will be performed to ascertain whether any health state utility weights relevant to a UK setting exist. If sufficient data are available, different outcomes will be ascribed utility values and quality adjusted life years (QALYs) will be estimated.

Probabilistic and deterministic sensitivity analyses will be applied to the model in order to assess the robustness of the results to realistic variations in the values attached to model parameters. Uncertainty surrounding the cost-effectiveness of the alternative approaches to management will be presented in the form of cost-effectiveness acceptability curves (CEACs). Where the overall results are sensitive to a particular variable or assumption, deterministic sensitivity analysis will be reported. Such analyses may involve changes to the structure of the model or the parameter inputs (resource use, unit costs, utilities) used in the model. The results of the evaluation will be used to estimate the cost implications to the NHS of changing management practice for symptomatic gallstones. Finally, if sufficient data are identified to allow the assignment of appropriate distributions to all model parameters, a value of information analysis will be performed in order to identify priority areas for future research.[41]

7. Expertise in this TAR team

The TAR team are experienced in conducting reviews of this nature in both the clinical and technical aspects required to address the commissioning brief. Miriam Brazzelli, Craig Ramsay, Paul McNamee and Cynthia Fraser have been involved in a number of similar projects and the remaining TAR team members are familiar with the methods of systematic reviewing and economic modelling.

7.1 TAR centre

The Aberdeen Technology Assessment Group has a track record of producing these types of focused reports whilst keeping to tight timescales for various policy customers such as the National Institute for Health and Clinical Excellence (NICE), the National Screening Committee and the NHS R&D HTA programme. In recent years the following similar types of systematic reviews have been completed:

- Robotic prostatectomy;
- 64-slice computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease;
- Detection and treatment of staphylococcus aureus infection for patients on peritoneal dialysis for end stage renal disease;
- Rapid point of care tests for the detection of genital Chlamydia;
- Photodynamic diagnosis, urine biomarkers and cytology for the detection and follow-up of bladder cancer.

7.2 Team members' contributions

Moira Cruickshank, Research Fellow at the Health Services Research Unit (HSRU), University of Aberdeen, will be technical lead on this project and will be responsible for the day-to-day running of the review, as well as undertaking the reviews of effectiveness, and will be supervised by Miriam Brazzelli, Senior Research Fellow at the HSRU, and Craig Ramsay, lead of the Aberdeen Health Technology Assessment Group. Mary Kilonzo, Research Fellow at the Health Economics Research Unit, University of Aberdeen, will undertake the economic evaluation. Paul McNamee and Graham Scotland will provide health economics advice and support. Fiona Stewart, Information Specialist at the HSRU, will develop and run the search strategies and will be responsible for obtaining papers and managing references, and will be supervised by Cynthia Fraser, senior Information Specialist at the HSRU. Andrew Elders, Statistician at the HSRU, will provide statistical advice and support and will be overseen by the senior statistician, Jonathan Cook. Heather Peace will provide service user insights. Irfan Ahmed, Consultant Surgeon NHS Grampian & Senior

Lecturer, University of Aberdeen; John Leeds, Consultant Gastroenterologist & Honorary Senior Lecturer NHS Grampian; and Alison Avenell, Clinical Senior Lecturer, HSRU, will provide clinical support and advice to the review team.

8. Competing interests of authors

None.

9. Timetable/milestones

2012:

28 May 2012	Submit draft protocol

Following protocol approval:

Aug-Oct 2012	Develop care pathways, design data extraction and quality assessment forms, develop and run searches, assess studies for inclusion
Oct- Nov	Data extraction and quality assessment, develop economic model
Nov-Dec	Data analysis
2013:	
Jan-Feb	Prepare draft report
Feb-March	Submit report

(This review will be carried out over a six- month period, with the main work starting in August 2012)

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Appendix 1 Draft MEDLINE search strategy

Ovid MEDLINE 1946 to 24 May 2012

1. cholecystitis/
2. cholecystitis, acute/
3. cholecystolithiasis/
4. gallstones/
5. (gall?bladder adj3 (empyema or inflam$)).tw.
6. ("biliary colic" or gall?stone$ or cholecystitis or cholecystolithiasis).tw.
7. or/1-6
8. exp Cholecystectomy/
9. cholecystectom$.tw.
10. ((excis$ or remov$) adj4 gallbladder).tw.
11. Aspirin/
12. Ibuprofen/
13. Acetaminophen/
14. (aspirin$ or paracetamol$ or ibuprofen$).tw.
15. watchful waiting.tw.
16. ((observ$ or conserv$ or expectant$) adj2 (treat$ or manage$)).tw.
17. Watchful Waiting/
18. or/8-17
19. exp clinical trial/
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomi?ed.ab.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/20-25
27. comparative study/ use prmz
28. follow-up studies/ use prmz
29. time factors/ use prmz
30. (preoperat$ or pre operat$).tw.
31. (chang$ or evaluat$ or reviewed or baseline).tw.
32. (prospective$ or retrospective$).tw.
33. (compare$ or compara$).tw.
34. or/27-33
35. 7 and 18 and 26
36. 7 and 18 and 34
37. 35 or 36
38. (review or editorial or case reports or letter).pt.
39. exp animals/ not humans/
40. 37 not (38 or 39)
41. limit 40 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
42. 40 not 41