Appendix C: Review protocols

C.1 Protocol for review question 1: risk factors for gallstone disease

	Details
Question 1	**What signs, symptoms, and risk factors should prompt a clinician to suspect gallstone disease in adults presenting to healthcare services?**
Objectives	To identify if there are any specific signs, symptoms and risk factors that can predict patients who have gallstone disease.
Study design	RCT, cross sectional, cohort
Language	English
Population	Adults presenting to healthcare services
Prognostic factor	- Right upper quadrant pain - Upper abdomen pain - Dyspepsia - Upper epigastric pain - Biliary colic - Pancreatitis - Cholecystitis - Obstructive jaundice - Cholangitis - Cardiac pain All terms will be combined with the term 'gallstones' to improve relevance.
Comparator	No comparator
Outcomes	• Event rates • Diagnostic accuracy • Any other predictive measurements • Resource use and cost
Inclusion criteria	• Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Studies conducted with children • Acalculous cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Any study that analyses using simple correlation only • Editorials/letters/studies available in abstract only
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Sub-group analysis will be undertaken where appropriate

C.2 Protocol for review question 2: Diagnosing gallstone disease

	Details
Question 2	**What is the most accurate strategy for diagnosing symptomatic gallstone disease in adults suspected of the condition?**
Objectives	To investigate whether there is an accurate method for diagnosing gallstone disease. To determine whether different diagnostic methods have differing acceptability within the population.
Study design	RCT, cross sectional, cohort
Language	English
Population	Adults with gallbladder stones (including biliary colic), acute cholecystitis or common bile duct stones (including the following gallstone related conditions cholangitis, obstructive jaundice, pancreatitis)
Diagnostic method	• Murphy's test (sign) • Local inflammation (Right upper quadrant abdominal pain and tenderness, fever and systemic inflammatory reaction • Blood tests • X-ray • Ultrasonography (transabdominal, endoscopic) • Computer tomography • Hepatobiliary iminodiacetic acid (HIDA) scan • Magnetic resonance imaging (MRI) • Magnetic resonance cholangiopancreatography (MRCP), • Endoscopic retrograde cholangiopancreatography (ERCP). Sequencing of diagnostic methods will also be addressed
Comparator	Surgery for evaluating the gallbladder ERCP for evaluating the biliary tree
Outcomes	• Diagnostic accuracy/clinical utility • Adverse events associated with diagnostic methods • Health related quality of life associated with diagnostic methods • Resource use and costs
Inclusion criteria	• Studies published after 1993 (for radiologic/endoscopic tests only, since significant progress has been made in the last 20 years and studies published before this date will have limited relevance on clinical practice today. Murphy's sign, Local inflammation and blood tests will not have this restriction applied. All studies on these diagnostic methods will be included regardless of their publication date) • Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Studies conducted with children • Studies published from 1 • Acalculous cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Any study that analyses using simple correlation only • Editorials/letters/studies available in abstract only
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables

	• Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Sub-group analysis will be undertaken where appropriate

C.3 Protocol for review question 3: complications of asymptomatic gallbladder stones

	Details
Question 3	**What factors predict which patients with asymptomatic gallbladder stones will develop acute complications?**
Objectives	To establish whether different management strategies should be offered for subgroups of people with asymptomatic gallbladder stones.
Language	English only
Study design	RCT, cross sectional, cohort
Status	Full text only
Population	• Adults with symptomatic gallstone disease (for retrospective studies, where people with symptomatic gallstone disease had their prior medical history examined to identify whether asymptomatic gallbladder stones had been previously diagnosed) • Adults with asymptomatic gallbladder stones (for prospective studies as people with asymptomatic gallbladder stones can be followed up to establish if symptoms develop in future)
Prognostic factors	• Any prognostic factor • Stone size • Stone type • Co-morbidity • Location of stone • Liver function tests • Polyps in gall bladder • Calcification of gallbladder • Thickening of gallbladder wall • Bariatric surgery
Comparator	N/A
Outcomes	• Event rates • Any other predictive measurements • Resource use and cost
Inclusion criteria	• Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Studies conducted with children • Editorials/letters/studies available in abstract only
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate

C.4 Protocols for review question 4: managing gallstone disease

C.4.1 4a- managing asymptomatic gallbladder stones

	Details
Question 4a	**Which strategies should be used for managing asymptomatic gallbladder stones?**
Objectives	To establish if some patients with asymptomatic gallbladder stones should be offered prophylactic interventions.
Language	English only
Study design	Randomised controlled trials
Population	Adults with asymptomatic gallbladder stones
Intervention	• Laparoscopic cholecystectomy • Lithotripsy • Dissolution therapy • Watch and wait/routine care
Comparator	Interventional management strategies will be compared with each other.
Outcomes	• Development of symptomatic stones • Post-cholecystectomy symptoms (continuation of existing symptoms or onset of new symptoms after gallbladder removal such as diarrhoea). • Mortality. • Complications of intervention (such as conversion rates from laparoscopic to open surgery, injury to ducts, perforation, pancreatitis, bleeding, sepsis). • Health-related quality of life. • Resource-use and costs.
Inclusion criteria	• Any healthcare setting • Gallbladder stones
Exclusion criteria	• Studies conducted with children • Acalculous cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Editorials/letters/studies available in abstract only • Non comparative studies • Comparisons to open surgery
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate

C.4.2 4b- Managing symptomatic gallbladder stones

	Details
Question 4b	**Which strategies should be used for managing symptomatic gallbladder stones?**
Objectives	To establish which management strategies should be used for managing patients with symptomatic gallbladder stones and whether different management strategies should be used for different subgroups of patients (e.g. high surgical risk).
Language	English only
Study design	Randomised controlled trials
Population	Adults with biliary colic or acute cholecystitis
Comparisons and outcomes	**Q4b.1** Laparoscopic cholecystectomy alone vs laparoscopic cholecystectomy+ intraoperative cholangiography • Bile leak • Bile injury • Length of stay • Missed common bile duct stones **Q4b.2** Laparoscopic cholecystectomy vs conservative management • Disease progression/requirement for additional intervention • Readmission • Length of stay • Mortality **Q4b.3** Cholecystostomy vs laparoscopic cholecystectomy • Mortality • Readmission • Progression to cholecystectomy • Length of stay • Disease progression/requirement for additional intervention **Q4b.5** Day-case laparoscopic cholecystectomy vs inpatient laparoscopic cholecystectomy for acute cholecystitis • Failed day case discharge • Readmission • Length of stay • Mortality • Quality of life
Inclusion criteria	• Any healthcare setting • Gallbladder stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Studies conducted with children • Acalcuolus cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Editorials/letters/studies available in abstract only • Non comparative studies • Comparisons to open surgery • Comparisons to dissolution therapy

	• Comparisons to lithotripsy • Sub types of laparoscopic surgery (e.g. single incision, Videolaparocholecystectomy, Laparoscopic subtotal cholecystectomy, mini-laparoscopic cholecystectomy, Telerobotic laparoscopic cholecystectomy)
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate

C.4.3 4c- Managing common bile duct stones

	Details
Question 4c	**Which strategies should be used for managing common bile duct stones?**
Objectives	To establish which management strategies should be used for managing patients with common bile duct stones and whether different management strategies should be used for different subgroups of patients (e.g. high surgical risk).
Language	English only
Study design	Randomised controlled trials
Population	Adults with or suspected of common bile duct stones (including the following gallstone related conditions cholangitis, obstructive jaundice, pancreatitis)
Comparisons and outcomes	**4c.1** Laparoscopic cholecystectomy + pre/intra/post op ERCP vs Laparoscopic cholecystectomy + surgical bile duct exploration • Length of stay • Number of ERCP's taken to clear duct • Mortality • Retained stones • Failed procedure • Conversion to open surgery • Quality of life **4c.2** ERCP + laparoscopic cholecystectomy vs ERCP + gallbladder in situ • Quality of life • Recurrence/disease progression • Requirement for additional intervention **4c.3** ERCP vs conservative management • Mortality • Disease progression • Requirement for additional intervention **4c.4** Uncleared bile duct + biliary stent vs cleared bile duct (surgery or ERCP) • Mortality • Disease progression • Requirement for additional intervention **4c.5** Day case ERCP vs inpatient ERCP for common bile duct stones

	• Failed day case discharge • Bile leak • Length of • Readmission • Mortality • Quality of life
Inclusion criteria	• Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Studies conducted with children • Acalcuolus cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Editorials/letters/studies available in abstract only • Non comparative studies • Comparisons to open surgery • Comparison of ERCP 'add ons' e.g. balloon dilation, sphincterotomy, lithotripsy • Rendezvous technique • Sub types of laparoscopic surgery (e.g. single incision, Videolaparocholecystectomy, Laparoscopic subtotal cholecystectomy, mini-laparoscopic cholecystectomy, Telerobotic laparoscopic cholecystectomy)
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate

C.5 Protocol for review question 5: timing of cholecystectomy

	Details
Question 5	**In adults with acute cholecystitis or symptomatic common bile duct stones, should cholecystectomy be performed during the acute episode (early) or should intervention be delayed until the acute episode has subsided (delayed)?**
Objectives	To determine the most appropriate time for intervention
Language	English only
Study design	Randomised controlled trials for cholecystectomy in adults with acute cholecystitis. Prospective cohort studies and quasi randomised controlled trials where there is insufficient RCT evidence for adults with common bile duct stones
Population	Adults with acute cholecystitis or common bile duct stones (including the following gallstone related conditions: cholangitis, obstructive jaundice, pancreatitis)
Comparisons and outcomes	**Q5.1** Early laparoscopic cholecystectomy vs delayed laparoscopic cholecystectomy for acute cholecystitis • Readmission due to symptoms • Readmission due to surgical complications • Length of stay • Mortality • Quality of life **Q5.2** ERCP + early laparoscopic cholecystectomy vs ERCP + delayed laparoscopic cholecystectomy for common bile duct stones • Readmission due to symptoms • Readmission due to surgical complications • Length of stay • Mortality • Quality of life
Inclusion criteria	• Studies comparing early versus delayed intervention • Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Acalculous cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Comparisons to open surgery • Sub types of laparoscopic surgery (e.g. single incision, Videolaparocholecystectomy, Laparoscopic subtotal cholecystectomy, mini-laparoscopic cholecystectomy, Telerobotic laparoscopic cholecystectomy) • Cholecystectomy for other conditions such as cancer or gallbladder injury • Studies conducted with children • Non comparative studies • Editorials/letters/studies available in abstract only

Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate

C.6 Review question 6

	Details
Question 6	**What are the information and education needs of patients and carers of people with gallstone disease?**
Objectives	To identify areas for which information and education should be provided
Language	English only
Study design	Any
Population	Adults with gallbladder stones, acute cholecystitis or common bile duct stones (including the following gallstone related conditions cholangitis, obstructive jaundice, pancreatitis)
Intervention	Not applicable
Comparator	Not applicable
Outcomes	• Patient and carer information and support needs • Health-related quality of life • Satisfaction
Inclusion criteria	• Any healthcare setting • Gallbladder stones • Common bile duct stones • Acute cholecystitis presumed to be caused by gallstones regardless of whether gallstones can be found during investigations
Exclusion criteria	• Acalculous cholecystitis (cholecystitis that is secondary to another condition such as critical/traumatic illness) • Studies conducted with children • Editorials/letters/studies available in abstract only
Review strategy	• The appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Where possible all key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. • Sub-group analysis will be undertaken where appropriate