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Pancreatitis

Pancreatitis: diagnosis and management

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Full guideline

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1 Guideline summary

1.1 Full list of recommendations

INFORMATION AND SUPPORT

Patient information

1. Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following, where relevant, as soon as possible after diagnosis:
   - pancreatitis and any proposed investigations and procedures, using diagrams
   - hereditary pancreatitis, and pancreatitis in children, including specific information on genetic counselling, genetic testing, risk to other family members and advice on life insurance and travel
   - the long-term effects of pancreatitis, including effects on the person's quality of life
   - the harm caused to the pancreas by smoking or alcohol.
2. Advise people with pancreatitis where they might find reliable high-quality information and support after consultations, from sources such as national and local support groups, networks and information services.
3. Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following about management of pancreatitis when applicable:
   - why a person may be going through a phase where no treatment is given
   - that pancreatitis is managed by a multidisciplinary team
   - the multidisciplinary treatment of pain, including how to access the local pain team and types of pain relief
   - nutrition advice, including advice on how to take enzyme replacement therapy if needed
   - follow-up and who to contact for relevant advice, including advice needed during episodes of acute illness
   - psychological care if needed, where available (see the NICE guideline on depression in adults)
   - pancreatitis services, including the role of specialist centres, for people with acute, chronic or hereditary pancreatitis
   - welfare benefits, education and employment support, and disability services
4. For more guidance on giving information, including providing an individualised approach, see the NICE guideline on patient experience in adult NHS services).
5. Explain to people with severe acute pancreatitis, and their family members and carers (as appropriate), that:

- a hospital stay lasting several months is relatively common, including time in critical care
- people who have started to make a recovery may have a relapse
- although children rarely die from acute pancreatitis, approximately 15-20% of adults with severe acute pancreatitis die in hospital.

6. Ensure that people with pancreatitis have the opportunity to record or take notes at clinic appointments and ward rounds.
7. Tell adults with pancreatitis that NICE has published a guideline on patient experience in adult NHS services that will show them what they can expect about their care.

Lifestyle interventions: stopping or reducing alcohol consumption

8. Advise people with pancreatitis caused by alcohol to stop drinking alcohol.
9. Advise people with recurrent acute or chronic pancreatitis that is not alcohol-related that alcohol might exacerbate their pancreatitis.
10. For guidance on alcohol use disorders, see the NICE guideline on the diagnosis and management of alcohol use disorders.

Lifestyle interventions: stopping or reducing smoking

11. For guidance on stopping smoking, see the NICE guideline on stop smoking services.

IDENTIFYING THE CAUSE

Aetiology of acute pancreatitis

12. Do not assume that a person's acute pancreatitis is alcohol-related just because they drink alcohol.
13. If gallstones and alcohol have been excluded as potential causes of a person's acute pancreatitis, investigate other possible causes such as:
    - metabolic causes (such as hypercalcaemia or hyperlipidaemia)
    - prescription drugs
    - microlithiasis
    - hereditary causes
    - autoimmune pancreatitis
    - ampullary or pancreatic tumours
    - anatomical anomalies (pancreas divisum).

Aetiology of chronic pancreatitis

14. Do not assume that a person's chronic pancreatitis is alcohol-related just because they drink alcohol. Other causes include:
    - genetic factors
    - autoimmune disease, in particular IgG4 disease
    - metabolic
    - structural or anatomical.

MANAGING PANCREATITIS

Fluid resuscitation

15. For guidance on fluid resuscitation see the NICE guidelines on intravenous fluid therapy in adults in hospital and in children and young people in hospital.

Nutrition support for acute pancreatitis

16. Ensure that people with acute pancreatitis are not made 'nil-by-mouth' and do not have food withheld unless there is a clear reason for this (for example, vomiting).

17. Offer enteral nutrition to anyone with severe or moderately severe acute pancreatitis. Start within 72 hours of presentation and aim to meet their nutritional requirements as soon as possible.

18. Offer anyone with severe or moderately severe acute pancreatitis parenteral nutrition only if enteral nutrition has failed or is contraindicated.

Nutrition support for chronic pancreatitis

19. Be aware that all people with chronic pancreatitis are at high risk of malabsorption, malnutrition and a deterioration in their quality of life.

20. Use protocols agreed with the specialist pancreatic centre to identify when advice from a specialist dietitian is needed, including advice on food, supplements and long-term pancreatic enzyme replacement therapy, and when to start these interventions.

21. Consider assessment by a dietitian for anyone diagnosed with chronic pancreatitis.

22. For guidance on nutrition support for people with chronic alcohol-related pancreatitis, see alcohol-related pancreatitis in the NICE guideline on alcohol-use disorders.

Nutrition support

23. For guidance on nutrition support see the NICE guidelines on nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition

Antimicrobial prophylaxis

24. Do not offer prophylactic antimicrobials to people with acute pancreatitis.

MANAGING COMPLICATIONS

Necrosis

25. Offer people with acute pancreatitis an endoscopic approach for managing infected or suspected infected pancreatic necrosis when anatomically possible .

26. Offer a percutaneous approach when an endoscopic approach is not anatomically possible.

27. Balance the need to debride infected pancreatic necrosis promptly against the advantages of delaying intervention.

Management of pain in people with chronic pancreatitis

28. For adults with neuropathic pain related to chronic pancreatitis, follow the recommendations in the NICE guideline on neuropathic pain in adults.

Pancreatic duct obstruction

29. Consider surgery (open or minimally invasive) as first line treatment in adults with painful chronic pancreatitis that is causing obstruction of the main pancreatic duct.

30. Consider extracorporeal shock wave lithotripsy for adults with pancreatic duct obstruction caused by a dominant stone if surgery is unsuitable.

Pseudocysts

31. Offer endoscopic ultrasound (EUS)-guided drainage, or endoscopic transpapillary drainage for pancreatic head pseudocysts, to people with symptomatic pseudocysts (for example those with pain, vomiting or weight loss).

32. Consider EUS-guided drainage, or endoscopic transpapillary drainage for pancreatic head pseudocysts, for people with non-symptomatic pseudocysts that meet 1 or more of the following criteria:

- are associated with pancreatic duct disruption
- are creating pressure on large vessels or the diaphragm
- are at risk of rupture
- there is suspicion of infection.

33. Consider surgical (laparoscopic or open) drainage of pseudocysts that need intervention if endoscopic therapy is unsuitable or has failed.

Pancreatic ascites and pleural effusion

34. Consider referring a person with pancreatic ascites and pleural effusion for management in a specialist pancreatic centre.

REFERRAL FOR SPECIALIST TREATMENT

Receiving specialist input in people with acute pancreatitis

35. If a person develops necrotic, infective, haemorrhagic or other local complications of acute pancreatitis:

- seek advice from a specialist pancreatic centre within the referral network and
- discuss whether to move the person to the specialist centre for treatment of the complications.

36. When managing acute pancreatitis in children:

- seek advice from a paediatric gastroenterology or hepatology unit and a specialist pancreatic centre and
- discuss whether to move the child to the specialist centre.

FOLLOW UP INVESTIGATIONS

Follow-up of pancreatic exocrine function in people with chronic pancreatitis

37. Offer people with chronic pancreatitis monitoring by clinical and biochemical assessment for pancreatic exocrine insufficiency and malnutrition every 12 months (every 6 months in under 16s), and adjust treatment of vitamin and mineral deficiencies accordingly.

38. Offer adults with chronic pancreatitis a bone density assessment every 24 months.

Follow-up to identify pancreatic cancer in people with chronic pancreatitis

39. Be aware that people with chronic pancreatitis have an increased risk of developing pancreatic cancer. The lifetime risk is highest, around 40%, in those with hereditary pancreatitis.

40. Consider annual monitoring for pancreatic cancer in people with hereditary pancreatitis.

Follow-up to identify diabetes in people with chronic pancreatitis

41. Be aware that people with chronic pancreatitis have a greatly increased risk of developing diabetes, with a lifetime risk as high as 80%. The risk increases with duration of pancreatitis and presence of calcific pancreatitis.

42. Offer people with chronic pancreatitis monitoring of HbA1c for diabetes at least every 6 months.

TYPE 3C DIABETES

Management of Type 3C Diabetes

43. People with type 3c diabetes should be assessed every 6 months for potential benefit of insulin therapy.

44. For guidance on managing type 3c diabetes for people who are not using insulin therapy see the NICE guidelines on type 2 diabetes in adults and diagnosing and managing diabetes in children and young people.

45. For people with type 3c diabetes who require insulin, see the:

- recommendations on insulin therapy and insulin delivery in the NICE guideline on type 1 diabetes in adults
- recommendations on insulin therapy in the NICE guideline on diagnosing and managing diabetes in children and young people
- NICE technology appraisal on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus.

46. For guidance on education and information for people with pancreatitis and type 3c diabetes requiring insulin, see the recommendations on education and information in the NICE guideline on diagnosing and managing type 1 diabetes in adults and education and information in the NICE guideline on diagnosing and managing diabetes in children and young people.

47. For guidance on self-monitoring blood glucose for people with pancreatitis and type 3c diabetes requiring insulin, see the recommendations on blood glucose management in the NICE guideline on diagnosing and managing type 1 diabetes in adults and blood glucose monitoring in the NICE guideline on diagnosing and managing diabetes in children and young people.

1.2 Research recommendations

1. In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by the use of ‘first-line’ tests (for example, CT scan, ultrasound scan, upper gastrointestinal (GI) endoscopy or combinations of these), what is the most accurate diagnostic test to identify whether chronic pancreatitis is present?

2. What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?
3. What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?
4. Is the long-term use of opioids more clinically effective and cost effective than non-opioid analgesia (including non-pharmacological analgesia) in people with chronic pain due to chronic pancreatitis?
5. What is the most clinically effective and cost-effective intervention for managing pancreatic duct obstruction, with or without an inflammatory mass, in children with chronic pancreatitis presenting with pain?
6. What is the most clinically effective and cost-effective intervention for managing small duct disease (in the absence of pancreatic duct obstruction, inflammatory mass or pseudocyst) in people with chronic pancreatitis presenting with pain?
7. What is the clinical and cost effectiveness of metal stents compared to surgery for treating biliary obstruction in adults with chronic pancreatitis?
8. What is the most clinically effective and cost-effective insulin regimen for type 3c diabetes secondary to pancreatitis?

2 Introduction

Pancreatitis is inflammation of the pancreas and may be acute or chronic. Acute pancreatitis is acute inflammation of the pancreas and a common cause of acute abdominal pain causing hospitalisation. In the majority of patients, the illness settles over a few days but in 25% of cases it is more severe and associated with organ failure or pancreatic necrosis, requiring critical care and a prolonged hospital stay. The incidence in the UK is approximately 56 cases per 100,000 people per year and the overall mortality rate around 5%. In some cases acute pancreatitis may progress to chronic pancreatitis, particularly after recurrent attacks. Chronic pancreatitis is an inflammatory process of the pancreas that results in fibrosis, cyst formation and stricturing of the pancreatic duct. It usually presents with chronic abdominal pain but the clinical course is variable. The annual incidence in Western Europe is about 5 new cases per 100,000 people, although this is probably an underestimate. Most people with chronic pancreatitis have had 1 or more attacks of acute pancreatitis. In others, chronic pancreatitis has a more insidious onset and delay in diagnosis is common.

In the UK approximately 50% of cases of acute pancreatitis are caused by gallstones, 25% by alcohol and 25% by other factors. Alcohol is responsible for 70–80% of cases of chronic pancreatitis and cigarette smoking is strongly associated with chronic pancreatitis; and is thought to exacerbate the condition. Acute and chronic pancreatitis may be idiopathic or, in about 5% of cases, caused by hereditary factors (in these cases there is usually a positive family history). Other causes include hypercalcaemia, hyperlipidaemia or autoimmune disease. In acute and chronic pancreatitis identifying the cause may not be straightforward and specialist investigations may be necessary.

Management of acute pancreatitis in the early stages is supportive. Intravenous fluid replacement has an important role but the type and rate of administration of the fluid is unclear. The role of antibiotics in preventing infection is hotly debated. It is recognised that patients who develop infected pancreatic necrosis should undergo a form of drainage or necrosectomy to treat this but the type of intervention for each patient is unclear. Indications for referral to a specialist pancreatic centre are variable and require clarification.

Chronic pancreatitis causes a significant reduction in pancreatic function and a majority of people have reduced exocrine (digestive) function and reduced endocrine function (causing diabetes). They may need expert dietary advice and medication. Chronic pancreatitis can also give rise to specific complications including painful inflammatory mass and obstructed pancreatic duct, biliary or duodenal obstruction and haemorrhage.

Some complications are common to acute and chronic pancreatitis such as malnutrition caused by digestive problems, diabetes, which occurs in up to 80% of those with chronic pancreatitis, and accumulation of fluid within local collections (pseudocysts), in the abdomen (ascites) or chest (pleural effusion). Managing all these complications may be difficult because of ongoing comorbidities and social problems, such as alcohol or opiate dependence.

People with pancreatitis are at long-term risk of nutritional problems and diabetes, and also have an increased risk of pancreatic cancer, which is even higher in people with hereditary pancreatitis. It is necessary to identify those who need to be followed up and what tests are required.

Pancreatitis is a serious and complex condition. It causes immense suffering, can have a severe effect on quality of life and may result in reduced life expectancy. In the past, there has been lack of knowledge on how to manage pancreatitis and this has resulted in clinicians avoiding those with the disease and conflicting advice being offered. With this guideline it is hoped that sound advice will be provided to enable people with pancreatitis to receive appropriate care to improve the outcomes from this difficult condition.

3 Development of the guideline

3.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a guideline committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'NICE guideline' lists the recommendations.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline. The remit for this guideline is to develop a clinical guideline on the Diagnosis and management of pancreatitis.

3.3 Who developed this guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Richard Charnley in accordance with guidance from NICE.

The group met approximately every 5 – 6 weeks during the development of the guideline. At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix B.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

Children, young people and adults with acute or chronic pancreatitis, including hereditary pancreatitis will be included. Consideration will be given to aetiology assessments; diagnosis of chronic pancreatitis; management of the condition, including fluid resuscitation, antibiotics, pain and complications (such as necrosis in acute pancreatitis, and malnutrition in chronic pancreatitis); follow-up; and information and support. For further details please refer to the scope in appendix A and the review questions in section 4.1.

3.3.2 What this guideline does not cover

This guideline does not cover people with pancreatic cancer, the diagnosis of acute pancreatitis, the management of gallstones, duodenal obstruction or the management of haemorrhage secondary to pancreatitis.

3.3.3 Relationships between the guideline and other NICE guidance

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to the diagnosis and management of pancreatitis.

Patient experience in adult NHS services (2012) NICE guideline CG138

Medicines adherence (2009) NICE guideline CG76

Medicines optimisation (2015) NICE guideline NG5

Antimicrobial stewardship (2015) NICE guideline NG15

NICE guidance that is closely related to this guideline

Published: NICE has published the following guidance that is closely related to this guideline:

Type 1 diabetes in adults: diagnosis and management (2015) NICE guideline NG17

Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015) NICE guideline NG18

Intravenous fluid therapy in children and young people in hospital (2015) NICE guideline NG29

Gallstone disease: diagnosis and initial management (2014) NICE guideline CG188

Intravenous fluid therapy in adults in hospital (2013) NICE guideline CG174

Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (2011) NICE guideline CG115

Alcohol-use disorders: diagnosis and management of physical complications (2010) NICE guideline CG100

Alcohol-use disorders: prevention (2010) NICE guideline PH24

Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition (2006) NICE guideline CG32

Endoscopic transluminal pancreatic necrosectomy (2016) NICE interventional procedure guidance IPG567

Percutaneous retroperitoneal endoscopic necrosectomy (2011) NICE interventional procedure guidance IPG384

Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy (2008) NICE interventional procedure guidance IPG274

Laparoscopic distal pancreatectomy (2007) NICE interventional procedure guidance IPG204

Pancreatic cancer (2018) NICE guideline NG858

In development: NICE is currently developing the following guidance that is closely related to this guideline:

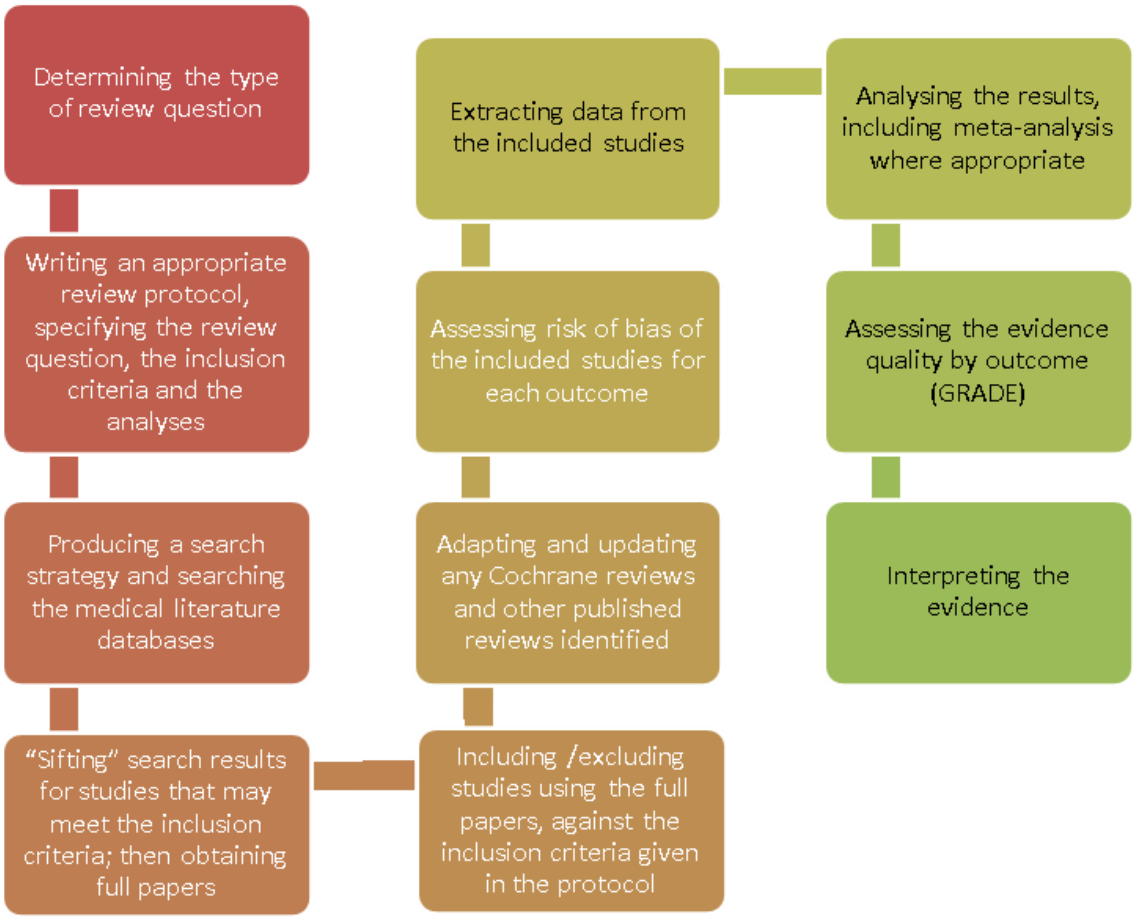
Stop smoking interventions and services. NICE guideline. Publication expected March 2018

4 Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014 version.[75]

Sections 4.1 to 4.3 describe the process used to identify and review clinical evidence (summarised in Figure 1), sections 4.2 and 4.4 describe the process used to identify and review the health economic evidence, and section 4.5 describes the process used to develop recommendations.

Figure 1: Step-by-step process of review of evidence in the guideline



4.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using a framework of population, setting and context for qualitative reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the guideline committee. The review questions were drafted by the NGC technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (appendix A).

A total of 24 review questions were developed to cover all areas of the guideline scope. Please see full review protocols in appendix C..

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5	Qualitative	What information and support should people with acute or chronic pancreatitis, their family and carers receive after diagnosis?	Any type of information and support of people with acute or chronic pancreatitis, their family or carers after diagnosis described by studies. For example: • Content of information and support required • How the information and support is delivered (for example, face-to-face, telephone, electronic, paper, television) • Information and support to include pain relief, dietary advice • Timing of information and support • Information for family and carers
6	Intervention	What is the clinical effectiveness and cost effectiveness of stopping or reducing alcohol consumption in reducing recurrent episodes of acute pancreatitis and improving quality of life in people with both chronic and acute pancreatitis?	Critical • Quality of life • Mortality • Recurrent episodes of pancreatitis • Alcohol consumption Important • Nutritional status • Admissions to hospital • Morbidity (for example, pancreatic function, pain)
8	Intervention	What is the clinical effectiveness and cost effectiveness of assessing the aetiology of acute pancreatitis to prevent recurrent attacks in people in whom the aetiology is unconfirmed by first-line test results within normal ranges?	Critical outcomes • Quality of life • Pancreatitis-related mortality • Number of repeated tests Important outcomes • Any pancreatitis-related admissions (including recurrent attacks) • Confirmation of aetiology or identification of a cause • Adverse events following investigations
9	Intervention	What is the clinical effectiveness and cost effectiveness of performing genetic marker and autoantibody tests for identifying the aetiology of chronic pancreatitis in people with no	Critical outcomes • Quality of life • Mortality • Number of repeated tests or any pancreatitis-related admissions Important outcomes • Early detection of cancer (for hereditary

Chapter	Type of review	Review questions	Outcomes
		known family history of pancreatitis, no significant alcohol history, and normal serum calcium and lipid levels?	pancreatitis) • Early detection of extra-pancreatic involvement (for IgG4 related pancreatitis) • Confirmation of aetiology or identification of a cause
10a	Diagnostic	In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by any of CT scan, ultrasound scan or upper GI endoscopy, what is the most accurate diagnostic test to identify whether chronic pancreatitis is present (as indicated by the reference standards: biopsy, clinical follow-up or subsequent CT scan)?	Statistical measures • Specificity • Sensitivity • Positive or negative predictive value (influenced by prevalence of a condition) • Positive or negative likelihood ratio (less dependent on the prevalence of the condition) • ROC curve or area under curve The committee agreed that sensitivity would be the primary measure for decision-making.
10b		In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by any of CT scan, ultrasound scan or upper GI endoscopy, what is the most clinically effective and cost effective test to identify whether chronic pancreatitis is present, when each is followed by the appropriate treatment, in order to improve patient outcomes?	Critical • Quality of life • Mortality • Adverse events related to test (endoscopic complications) • Adverse events related to treatment Important • Hospital admission • Number of people receiving treatment (including people who may not have needed it, such as those with false positive results) • Patient or physician confidence in test • Repeat testing or additional testing
11	Intervention	What is the most clinically effective and cost-effective type of intravenous fluid for	Critical outcomes • Quality of life • Length of stay (in CCU or hospital) • Length of stay (in CCU or hospital)

Chapter	Type of review	Review questions	Outcomes
		resuscitation in people with acute pancreatitis?	• Mortality • Serious adverse events Important outcomes • Local complications (fluid collection; cystic collection; pancreas necrosis; peri-pancreatic necrosis; local infection) • Systemic complications (persistent organ failure; fluid overload)
12	Intervention	What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?	Critical outcomes • Quality of life • Mortality • Length of stay (in critical care unit [CCU] or hospital) • Achievement of pre-specified target for resuscitation (for example, target central venous pressure, urine output, lactate levels, PiCCO measurement) Important outcomes • Local complications (fluid collection; cystic collection; pancreas necrosis; peri-pancreatic necrosis; local infection) • Systemic complications (persistent organ failure; fluid overload) • Serious adverse events
13	Intervention	What is the most clinically effective and cost-effective route of feeding at time of admission to the hospital in people with severe acute pancreatitis?	Critical outcomes • Mortality • Quality of life • Length of stay (in CCU or hospital) • Achieving nutrition (meeting nutritional requirements; at least 20–25 kcal/kg • Requiring total parenteral nutrition Important outcomes • Infections • Serious adverse events • Adverse events (for example, tube displacements, aspirational pneumonia, ischaemic gut and central-line infections – in PN group) • Weight loss
14	Intervention	What is the clinical effectiveness and cost effectiveness of early compared with late nutritional intervention (for example, food supplements, enzyme supplements) in people with chronic	Critical outcomes • Quality of life • Mortality • Weight loss or BMI Important outcomes • Signs of vitamin and mineral deficiency (for example, skin problems, swollen tongue, poor vision at night, breathlessness, bone and joint pain)

Chapter	Type of review	Review questions	Outcomes
		pancreatitis and signs of malnutrition or malabsorption?	
15	Intervention	What is the clinical effectiveness and cost effectiveness of a specialist nutritional assessment compared with a non-specialist assessment for managing malabsorption or malnutrition in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality • Weight loss or BMI • Osteoporosis or biochemical deficiencies • Hospital admissions • Unnecessary dietary restriction (low fat diets) Important outcomes • Signs of vitamin and mineral deficiency (for example, skin problems, swollen tongue, poor vision at night, breathlessness, bone and joint pain)
16	Intervention	What is the clinical and cost effectiveness of prophylactic antimicrobial agents to prevent infection in people with acute pancreatitis?	Critical outcomes • Quality of life • Mortality • Length of stay (in CCU or hospital) • Infected necrosis Important outcomes • Extra-pancreatic infection • Colonisation of resistant organisms • Serious adverse events
17	Intervention	What is the most clinically effective and cost-effective method for managing (suspected) infected necrosis in people with acute pancreatitis?	Critical • Quality of life • Mortality • Length of stay (in CCU or hospital) Important • Complications (for example, bleeding, fistulae) • Number of procedures (repeated procedures) • Recurrence of infection • Pancreatic function (for example, development of diabetes)
18	Intervention	What is the most clinically effective and cost-effective timing of intervention for managing (suspected) infected necrosis in people with acute pancreatitis?	Critical outcomes • Quality of life • Mortality • Length of stay (in CCU or hospital) Important outcomes • Number of procedures (repeated procedures) • Recurrence of infection • Complication (for example, bleeding, fistulae) • Pancreatic function (for example, development of diabetes)

Chapter	Type of review	Review questions	Outcomes
19	Intervention	What is the most clinically effective and cost-effective intervention for managing chronic pain in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) Important outcomes • Serious adverse events • Adverse events • Return to usual activities • Pancreatic function (endocrine and exocrine)
20	Intervention	What is the most clinically effective and cost-effective intervention for managing pancreatic duct obstruction, with or without an inflammatory mass, in people with chronic pancreatitis presenting with chronic pain?	Critical outcomes • Quality of life • Mortality • Complications • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) Important outcomes • Length of stay (in CCU or hospital) • Repeated procedures • Pancreatic function (endocrine and exocrine)
21	Intervention	What is the most clinically effective and cost-effective intervention for managing small-duct disease (in the absence of pancreatic duct obstruction, inflammatory mass or pseudocyst) in people with chronic pancreatitis presenting with chronic pain?	Critical outcomes • Quality of life • Mortality • Complications • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) Important outcomes • Length of stay (in CCU or hospital) • Repeated procedures • Pancreatic function (endocrine and exocrine)
22	Intervention	What is the most clinically effective and cost-effective intervention for managing pseudocysts in people with pancreatitis presenting with or without pain?	Critical outcomes • Quality of life • Mortality • Complications – bleeding, perforation and infection or overall rate of complications • Resolution of presenting symptoms (for example, pain, nutritional status, gastric outlet obstruction) • Resolution or recurrence of pseudocysts Important outcomes • Length of stay (in CCU or hospital) • Repeated procedures
23	Intervention	What are the most	Critical outcomes

Chapter	Type of review	Review questions	Outcomes
		clinically effective and cost-effective interventions for treating pancreatic ascites and pleural effusion secondary to acute or chronic pancreatitis?	• Quality of life • Mortality • Length of stay (in CCU or hospital) • Resolution (for example, resolution of fluid collection, resolution of fistulae) Important outcomes • Number of procedures (repeated procedures) • Recurrence • Complications
24	Intervention	What is the most clinically effective and cost-effective intervention for treating biliary obstruction in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality • Recurrence of biliary obstruction (including failed stent, both removal and additional stents) • Biliary infections Important outcomes • Number of procedures (repeated procedures) • Length of stay (in CCU or hospital) • Complications (for example, bleeding, fistulae)
25	Intervention	What is the most clinically effective and cost-effective insulin regimen strategy specifically for type 3c diabetes secondary to pancreatitis?	Critical outcomes: • Quality of life • HbA1c levels • Hospital admissions (for example related to diabetic ketoacidosis or decompensated high glucose levels • Severe hypoglycaemia (as defined by the American Diabetes association: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration) Important outcomes: • Mortality • Hyperglycaemic hyperosmolar non-ketotic coma (HONK) • Fear of hypoglycaemia according to known validated scoring systems (for example, hypoglycaemia fear survey) • Impaired awareness of hypoglycaemia according to known validated scoring systems (for example, Gold score, Clarke score, Ryan score (hypoglycaemia burden score) , Pedersen–Bjergaard score)
26	Intervention	What is the clinical effectiveness and cost effectiveness	Critical outcomes • Quality of life • Mortality

Chapter	Type of review	Review questions	Outcomes
		of receiving specialist input in people with acute pancreatitis?	• Length of stay Important outcomes • Hospital admissions
27	Intervention	How often should follow-up to assess pancreatic exocrine function and any secondary health issues, if any, be carried out in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality • Exocrine function (as measured by for example faecal elastase) • Low impact fractures • Changes in nutritional status Important outcomes • Hospital admissions • Return to usual activities
28	Intervention	How often should follow-up to identify the development of diabetes be carried out in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality Important outcomes • People requiring insulin • Diabetic complications (for example, retinopathy, peripheral neuropathy, chronic kidney disease) • Diagnosis of diabetes
29	Intervention	How often should follow-up to identify development of pancreatic cancer be carried out in people with chronic pancreatitis?	Critical outcomes • Quality of life • Mortality • Cancer-related mortality Important outcomes • Stage of cancer at diagnosis • Serious adverse events

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[75] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline, Embase, The Cochrane Library and PsycINFO. Additional subject specific databases were used for some questions: Current Nursing and Allied Health Literature (CINAHL) for information and support. All searches were updated on 28 September 2017. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight

any additional studies. Searches were quality assured by a second information specialist before being run. The questions, the study types applied, the databases searched and the years covered can be found in appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- NHS Evidence Search (www.evidence.nhs.uk).

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to pancreatitis in the: the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database with no date restrictions (NHS EED ceased to be updated after March 2015).

Additionally, the search was run on Medline and Embase using a health economic filter to ensure recent publications that had not yet been indexed by the economic databases were identified. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in appendix G. All searches were updated on 28 September 2017. No papers published after this date were considered.

4.3 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in appendix C).
- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[75] Qualitative studies were critically appraised using the GRADE CERQual approach for rating confidence in the body of evidence as a whole and using an NGC checklist for the methodological limitations section of the quality assessment.
- Extracted key information about interventional study methods and results using 'Evibase', NGC's purpose-built software. Evibase produces summary evidence tables, including critical appraisal

ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in appendix H).

- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Data from non-randomised studies were presented separately in GRADE profile tables, and meta-analysis was not appropriate for any of the non-randomised evidence identified.
  - Diagnostic data studies presented as a range of values in adapted GRADE profile tables, and no meta-analysis was appropriate
  - Qualitative data were synthesised across studies and presented as summary statements with accompanying GRADE CERQual ratings for each review finding.
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix L. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Children, young people and adults with acute or chronic pancreatitis.

The key population exclusion criterion was:

- Children, young people and adults with pancreatic cancer.

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. No relevant conference abstracts were identified for this guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.3.1.1 Saturation of qualitative studies

Data extraction in qualitative reviews is a thorough process and may require more time compared with intervention reviews. It is common practice to stop extracting data once saturation has been reached. This is the point when no new information emerges from studies that match the review protocol. The remaining identified studies are, however, not directly excluded from the review as they nevertheless fit the criteria defined in the review protocol. Any studies for which data were not extracted due to saturation having been reached, but that fit the inclusion criteria of the protocol,

were listed in the table for studies 'identified but not included due to saturation' in the appendix for the qualitative evidence review.

4.3.2 Type of studies

Randomised trials, non-randomised intervention studies, and other observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If non-randomised intervention studies were considered appropriate for inclusion (for example, where no randomised evidence was available for critical outcomes) the committee stated a priori in the protocol the most important variables that should be equivalent at baseline or controlled for within the analysis. In this guideline the committee did not exclude studies if these variables were not considered. This is because of the general paucity of evidence available for this condition. However, the limitations of uncontrolled data were captured in the study quality assessment and highlighted during committee discussions of the relevant evidence. Please refer to the review protocols in appendix C for full details on the study design of studies selected for each review question.

For diagnostic review questions, diagnostic RCTs, cross-sectional studies and retrospective studies were included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

4.3.3 Methods of combining clinical studies

4.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[92] software to combine the data given in all studies for each of the outcomes of interest for the review question.

Most analyses were stratified for age (under 16 years and 16 years or over), which meant that different studies with predominant age-groups in different age strata were not combined and analysed together. The exceptions were the reviews on the aetiology of acute pancreatitis and interventions to reduce alcohol consumption. For some questions additional stratification was used, and this is documented in the individual review question protocols (see appendix C). When additional strata were used this led to substrata (for example, 2 stratification criteria leads to 4 substrata, 3 stratification criteria leads to 9 substrata) which were analysed separately.

4.3.3.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- mortality
- local complications
- adverse events.

The absolute risk difference was also calculated using GRADEpro[43] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- heath-related quality of life (HRQoL)
- length of stay in hospital.

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5)[92] software. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

4.3.3.1.2 Generic inverse variance

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[92] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[43] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

4.3.3.1.3 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out. If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup). Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

For some questions additional subgrouping was applied, and this is documented in the individual review question protocols (see appendix C). These additional subgrouping strategies were applied independently, so subunits of subgroups were not created, unlike the situation with strata. Other subgrouping strategies were only used if the age category subgroup was unable to explain heterogeneity, then these further subgrouping strategies were applied in order of priority. Again, once a subgrouping strategy was found to explain heterogeneity from all derived subgroups, further subgrouping strategies were not used.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

4.3.3.1.4 Complex analysis

Network meta-analysis was considered for the comparison of interventional treatments, but was not pursued because of insufficient data available for the relevant outcomes.

Where studies had used a crossover design, paired continuous data were extracted where possible, and forest plots were generated in RevMan5[92] with the generic inverse variance function. When a crossover study had categorical data and the number of subjects with an event in both interventions was known, the standard error (of the log of the risk ratio) was calculated using the simplified Mantel-Haenszel method for paired outcomes. Forest plots were also generated in RevMan5[92] with the generic inverse variance function. If paired continuous or categorical data were not available from the crossover studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that this approach would overestimate the confidence intervals and thus artificially reduce study weighting resulting in a conservative effect. Where a meta-analysis included a mixture of studies using both paired and parallel group approaches, all data were entered into RevMan5[92] using the generic inverse variance function.

4.3.3.2 Data synthesis for diagnostic test accuracy reviews

Two separate review protocols were produced to reflect the 2 different diagnostic study designs.

4.3.3.2.1 Diagnostic RCTs

Diagnostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods for intervention reviews (see section 4.3.3.1.1 above).

4.3.3.2.2 Diagnostic accuracy studies

For diagnostic test accuracy studies, a positive result on the index test was found if the patient had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were prespecified by the committee including whether or not data could be pooled across a range of thresholds. Diagnostic test accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this varies amongst studies. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a

specificity of 97% will only incorrectly diagnose 3% of people who do not have the condition as positive. For this guideline, sensitivity was considered more important than specificity due to the consequences of a missed diagnosis (false negative result). Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5.[92] In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Diagnostic meta-analysis was not possible as in no case were 3 or more studies were available per threshold. Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots.

4.3.3.3 Data synthesis for qualitative study reviews

The main findings for each included paper were identified and thematic analysis methods were used to synthesise this information into broad overarching themes, which were summarised into the main review findings. The evidence was presented in the form of a narrative summary detailing the evidence from the relevant papers and how this informed the overall review finding plus a statement on the level of confidence for that review finding. Considerable limitations and issues around relevance were listed. A summary evidence table with the succinct summary statements for each review finding was produced including the associated quality assessment.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[43]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.

Quality element	Description
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

4.3.4.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and detection bias (lack of blinding of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence

Limitation	Explanation
	of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at high risk of selection bias. For this reason, GRADE requires that non-randomised evidence is initially downgraded on the basis of study design, starting with a rating of −2. This accounts for selection bias and so non-randomised intervention studies are not downgraded any further on that domain. Non-randomised evidence was assessed against the remaining domains used for RCTs in Table 3, and downgraded further as appropriate.

4.3.4.1.2 Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

4.3.4.1.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on prespecified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the committee took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

4.3.4.1.4 Imprecision

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was

consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 2. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

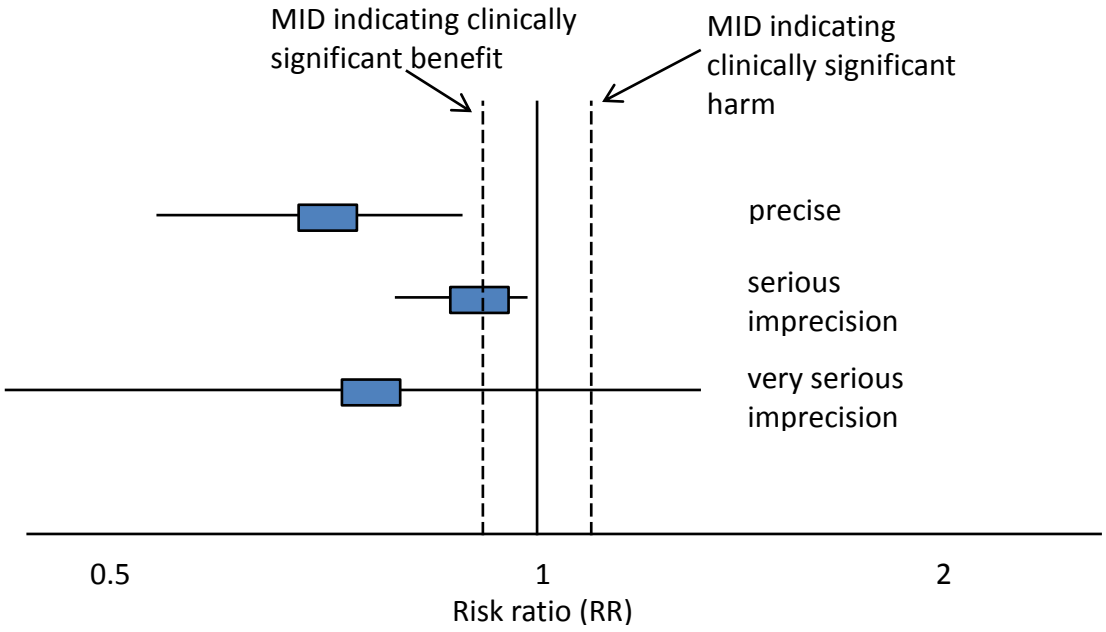
In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

- For categorical outcomes the MIDs were taken to be RRs of 0.8 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.8 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.8 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect, that is whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.
- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted.

Figure 2: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)



4.3.4.1.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.4.2 Diagnostic studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see appendix H in the NICE guidelines manual 2014[75]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 3):

- patient selection
- index test
- reference standard
- flow and timing.

Figure 3: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/ unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case–control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/ unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/ unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.3.4.2.1 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the sensitivity value using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold above which it would be acceptable to recommend a test of 90%. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (0–50%, 50–90% and 90–100%).

4.3.4.2.2 Imprecision

As diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only 1 study contributed to the evidence, the 95% CI around the single study. As a general rule (after discussion with the committee) a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.3.4.2.3 Overall grading

Quality rating started at High for prospective and retrospective cross-sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of Very Low, as explained for intervention reviews.

4.3.4.3 Qualitative reviews

Review findings from the included qualitative studies were evaluated and presented using the 'Confidence in the Evidence from Reviews of Qualitative Research' (CERQual) Approach developed by the GRADE-CERQual Project Group, a subgroup of the GRADE Working Group.

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 5.

Table 5: Description of quality elements in GRADE-CERQual for qualitative studies

Quality element	Description
Methodological limitations	The extent of problems in the design or conduct of the included studies that could decrease the confidence that the review finding is a reasonable representation of the phenomenon of interest. Assessed at the study level using an NGC checklist.
Coherence	The extent to which the reviewer is able to identify a clear pattern across the studies included in the review.
Relevance	The extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol.
Adequacy	The degree of the confidence that the review finding is being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme.

Details of how the 4 quality elements (methodological limitations, coherence, relevance and adequacy) were appraised for each review finding are given below.

4.3.4.3.1 Methodological limitations

Each review finding had its methodological limitations assessed within each study first using an NGC checklist. Based on the degree of methodological limitations studies were evaluated as having minor, moderate or severe limitations. The questions to be answered in the checklist below included:

- Was qualitative design an appropriate approach?
- Was the study approved by an ethics committee?
- Was the study clear in what it sought to do?
- Is the context clearly described?
- Is the role of the researcher clearly described?
- Are the research design and methods rigorous?
- Was the data collection rigorous?
- Was the data analysis rigorous?
- Are the data rich?
- Are the findings relevant to the aims of the study?
- Are the findings and conclusions convincing?

The overall assessment of the methodological limitations of the evidence was based on the primary studies contributing to the review finding. The relative contribution of each study to the overall review finding and of the type of methodological limitation(s) were taken into account when giving an overall rating.

4.3.4.3.2 Coherence

Coherence is the extent to which the reviewer is able to identify a clear pattern across the studies included in the review, and if there is variation present (contrasting or disconfirming data) whether this variation is explained by the contributing study authors. If a review finding in 1 study does not support the main finding and there is no plausible explanation for this variation, then the confidence that the main finding reasonably reflects the phenomenon of interest is decreased. Each review finding was given a rating of minor, moderate or major concerns about coherence.

4.3.4.3.3 Relevance

Relevance is the extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol. As such, relevance is dependent on the individual review and discussed with the guideline committee. Relevance is categorised in 3 ways: partial relevance, indirect relevance and no concerns about relevance.

4.3.4.3.4 Adequacy

The judgement of adequacy is based on the confidence of the finding being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme. Rich data provide sufficient detail to gain an understanding of the theme or review finding, whereas thin data do not provide enough detail for an adequate understanding. Quantity of data is the second pillar of the assessment of adequacy. For review findings that are only supported by 1 study or data from only a small number of participants, the confidence that the review finding reasonable represents the phenomenon of interest might be decreased. As with richness of data, quantity of data is review dependent. Based on the overall judgement of adequacy, a rating of no concerns, minor concerns, or substantial concerns about adequacy was given.

4.3.4.3.5 Overall judgement of the level of confidence for a review finding

GRADE-CERQual is used to assess the body of evidence as a whole through a confidence rating representing the extent to which a review finding is a reasonable representation of the phenomenon of interest. The 4 components (methodological limitations, coherence, relevance and adequacy) are used in combination to form an overall judgement. GRADE-CERQual uses 4 levels of confidence: high,

moderate, low and very low confidence. The significance of these overall ratings is explained in Table 6. Each review finding starts at a high level of confidence and is downgraded based on the concerns identified in any 1 or more of the 4 components. Quality assessment of qualitative reviews is a subjective judgement by the reviewer based on the concerns that have been noted. A detailed explanation of how such a judgement had been made was included in the narrative summary.

Table 6: Overall level of confidence for a review finding in GRADE-CERQual

Level	Description
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

4.3.5 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[43] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared with the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For the critical outcome of mortality any reduction represented a potential clinical benefit and this outcome was discussed each time it was available. For adverse events 50 events or more per 1000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.6 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared with the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

4.4 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.[75]

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Considered undertaking new cost-effectiveness analysis in priority areas.

4.4.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.[75]
- Extracted key information about the studies' methods and results into health economic evidence tables (included in appendix I).
- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality see Table 7 below and the economic evaluation checklist (appendix H of the NICE guidelines manual[75]) and the health economics review protocol in appendix D.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.4.1.2 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[75] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[82]

Table 7: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[(a)] • Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[(a)] • Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with a strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with a strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).

Item	Description
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in appendix H of the NICE guidelines manual[75]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was considered for selected areas. Priority areas for new analysis were discussed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified no high priority areas for original health economic modelling. Diagnosis of chronic pancreatitis and treating biliary obstruction in people with chronic pancreatitis were both considered for original analysis, but the lack of clinical evidence meant that economic modelling was not possible for either question, and so the committee instead made research recommendations in both cases. Management of necrosis in acute pancreatitis was also considered for original economic analysis, but the identification of 2 existing health economic studies along with clinical evidence meant that the committee was able to draw conclusions without any additional analysis.

4.4.3 [75, 77]Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[76] In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[76]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in appendices H and I.
- Summaries of clinical and health economic evidence and quality (as presented in chapters 5–29).
- Forest plots (appendix K).

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 4.5.1 below).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual[75]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

1 # INFORMATION AND SUPPORT

5 Patient information

5.1 Introduction

Pancreatitis is a disease with a wide spectrum of severity; those affected can have complex physical, psychological and social issues requiring individualised care from a multidisciplinary team of surgeons, gastroenterologists, radiologists, critical care specialists and therapists. Reliable information regarding symptoms, complications, treatment options, lifestyle modifications and the socio-economic support required is not consistent or widely available in the UK. A lack of credible resources and care standards mean people diagnosed with acute and chronic pancreatitis, their families and carers, are often left without the specific information and support they need to make choices about their health, and as such may go untreated, suffering worsening disease and its effects. For people requiring longer term care it is not always clear to them or their care providers when, where or how to access specialist services or advice. This is important because, when people are provided with the correct information and support, they can share decision-making in line with their needs and wishes, enabling them to actively participate in their own care and improve their health outcomes. This review attempts to address what information or support people with pancreatitis, their families and carers should receive after diagnosis.

5.2 Review question: What information and support should people with acute or chronic pancreatitis, their family and carers receive after diagnosis?

For full details see review protocol in appendix C.

Table 8: Characteristics of review question

Objective	To determine what type of information and support should be provided to people with acute or chronic pancreatitis, their family and carers after diagnosis. Patient support refers here to direct patient or carer interaction or engagement designed to help management of medication or disease outcomes (for example, adherence, awareness and education), or to provide healthcare professionals with support for their patients.
Population and setting	People with acute or chronic pancreatitis, including hereditary forms.
Context	Any type of information and support of people with acute or chronic pancreatitis, their family or carers after diagnosis described by studies. For example: • Content of information and support required • How the information and support is delivered (for example, face-to-face, telephone, electronic, paper, television). • Information and support to include pain relief and dietary advice. • Timing of information and support. • Information for family and carers.
Review strategy	Synthesis of qualitative research: thematic analysis – information synthesised into main review findings. Results presented in a detailed narrative with accompanying diagrams and in table format with summary statements of main review findings. The methodological quality of each study will be assessed using NGC-modified NICE checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CERQual approach for each review finding.

5.3 Qualitative evidence

5.3.1 Methods

One qualitative study related to people with chronic pancreatitis was included in the review[24] and is summarised in Table 9 below. Key findings from this study are summarised in section 5.3.2 below. No studies were included relating to people with acute pancreatitis. See also the study selection flow chart in appendix E, study evidence table in appendix H, and excluded studies lists in appendix L.

5.3.2 Summary of included studies

Table 9: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Cronin 2012[24]	Qualitative study using multiple unstructured interviews	14 people with chronic pancreatitis and 5 relatives	To develop an understanding of what it means to live with chronic pancreatitis	Partial applicability as there is a large section of the paper on suffering and enduring physiological and social disruption

5.3.3 Qualitative evidence synthesis

Table 10: Review findings

Main findings	Statement of finding
Information provision	Inadequate information provision to manage their condition.
	Differences in information provision. Most sought information from other sources such as the internet and family and friends.
	Adjusting or self-management. All participants made lifestyle modifications and performed 'self-monitoring' to contribute to how they make decisions.
Support	Relationships with healthcare professionals were a perceived barrier.
	Coping strategies were used, including 'emotional coping' and 'drawing on social resources' such as family, friends and professional agencies.

5.3.3.1 Narrative summary of review findings

The included study, Cronin and Begley 2012,[24] details findings based across 2 main themes: information provision and support.

5.3.3.1.1 Information provision

The information provided was thought to be inadequate to manage their condition and it was only by living with chronic pancreatitis that its implications became evident, described as 'coming to know'. Participants reported differences in information provision and most sought information from other sources such as the internet and family and friends: *"I'm still caught between what I've read and what the specialists have told me".*

All participants made lifestyle modifications which included abstaining from alcohol, adjusting diet, 'prioritising demands' and 'struggling to live well'. Continuous 'self-monitoring' provides participants with feedback on their body's response to illness and contributes to how they make decisions.

5.3.3.1.2 Support

Relationships with healthcare professionals were important mediators in facilitating or constraining their coping and were a perceived barrier: *"You go to casualty, you've got this triage battle… having to fight your case like a barrister for admittance into the hospital", "No matter what I said about he doesn't drink […] I always thought they didn't believe me"* – family member (wife).

Participants also used coping strategies including 'emotional coping' and 'drawing on social resources' such as family, friends and professional agencies: "*When I go to [Alcoholics Anonymous] meeting, I don't think I am going because I'm an alcoholic. I'm thinking of them as part and parcel of my daily routine of keeping well", "We're both very much in tune with how each other is feeling […] she'll know when something is wrong'.*

5.3.3.1.3 Quality assessment

The quality of each theme was rated as low as it is unclear how many participants reported each theme finding. Unstructured interviews were performed, and it is unknown what questions were asked or if all interviews were conducted in the same manner, therefore minor concerns were recorded about methodological limitations. There are minor concerns about adequacy of each theme as only 1 study was identified; therefore theme saturation was not met. Although some quotations are given in the paper, the study was not assessed as data rich.

5.3.4 Qualitative evidence summary

Table 11: Summary of evidence

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Information provision					
1	Interviews	Inadequate information provision to manage their condition. It was only by living with chronic pancreatitis that its implications became evident.	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	
1	Interviews	Participants reported differences in information provision. Most sought information from other sources such as the internet and family and friends. Most did not appear to have any knowledge of long-term complications associated with chronic pancreatitis.	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	Minor concerns about adequacy	
1	Interviews	Adjusting or self-management. All participants made lifestyle modifications which included abstaining from alcohol, adjusting diet and 'prioritising demands' and 'struggling to live well'. Continuous 'self-monitoring' provides participants with feedback on their body's response to illness and contributes to how they make decisions.	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	
Support					
1	Interviews	Relationships with healthcare professionals were a perceived barrier both in being admitted to hospital and being believed whether they had consumed alcohol.	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	Minor concerns about adequacy	
1	Interviews	Participants also used coping strategies including 'emotional coping' and 'drawing on social resources' such as family, friends and professional agencies.	Limitations	Minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	

5.4 Economic evidence

5.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.5 Evidence statements

5.5.1 Qualitative

- One qualitative study suggested the following about the information and support people with acute or chronic pancreatitis, their family and carers after diagnosis may want:
  - Low quality evidence suggested that the information provided was thought to be inadequate to manage their condition, and that the information that was received differed between different sources. Most sought information from sources such as the internet and family and friends.
  - Low quality evidence suggested that the relationship with the healthcare professional can act as a barrier to coping, and that people with pancreatitis use strategies including 'emotional coping' and 'drawing on social resources' for support and to cope with their pancreatitis.

5.5.2 Economic

- No relevant economic evaluations were identified.

5.6 Recommendations and link to evidence

Recommendations	**1. Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following, where relevant, as soon as possible after diagnosis:** • **pancreatitis and any proposed investigations and procedures, using diagrams** • **hereditary pancreatitis, and pancreatitis in children, including specific information on genetic counselling, genetic testing, risk to other family members and advice on life insurance and travel** • **the long-term effects of pancreatitis, including effects on the person's quality of life** • **the harm caused to the pancreas by smoking or alcohol.** **2. Advise people with pancreatitis where they might find reliable high-quality information and support after consultations, from sources such as national and local support groups, networks and information services.** **3. Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following about management of pancreatitis when applicable:** • **why a person may be going through a phase where no treatment is**

	given • **that pancreatitis is managed by a multidisciplinary team** • **the multidisciplinary treatment of pain, including how to access the local pain team and types of pain relief** • **nutrition advice, including advice on how to take enzyme replacement therapy if needed** • **follow-up and who to contact for relevant advice, including advice needed during episodes of acute illness** • **psychological care if needed, where available (see the NICE guideline on depression in adults)** • **pancreatitis services, including the role of specialist centres, for people with acute, chronic or hereditary pancreatitis** • **welfare benefits, education and employment support, and disability services** **4. For more guidance on giving information, including providing an individualised approach, see the NICE guideline on patient experience in adult NHS services).** **5. Explain to people with severe acute pancreatitis, and their family members and carers (as appropriate), that:** • **a hospital stay lasting several months is relatively common, including time in critical care** • **people who have started to make a recovery may have a relapse** • **although children rarely die from acute pancreatitis, approximately 15-20% of adults with severe acute pancreatitis die in hospital.** **6. Ensure that people with pancreatitis have the opportunity to record or take notes at clinic appointments and ward rounds.** **7. Tell adults with pancreatitis that NICE has published a guideline on patient experience in adult NHS services that will show them what they can expect about their care.**
Findings identified in the evidence synthesis	Evidence was identified about the impact of information provision and support. Patients identified inadequate information provision to manage their condition and differences in information provision from different practitioners. Most patients sought information from other sources such as the internet and family and friends. All participants made lifestyle modifications and performed 'self-monitoring' to contribute to how they made decisions. Regarding support, relationships with healthcare professionals were an important factor in their ability to cope, and coping strategies were also used, including 'emotional coping' and 'drawing on social resources' such as family, friends and professional agencies. The benefit for patients, in terms of managing their condition successfully and coping with their condition, receiving more information and more accurate information was considered to outweigh the increase in time invested by healthcare professionals to deliver this information. The guideline committee also noted that investing more time in providing adequate information may lead to a reduction in time spent with patients presenting to the emergency department as a result of insufficient understanding and information.

	The committee noted that all the evidence in the review came from a single study, and therefore agreed that it was difficult to make meaningful conclusions based on this study. The committee also noted that the study was conducted in a specialist pancreatic centre, and therefore the issues raised may be even more prevalent in non-specialist environments. Additionally, the evidence was consistent with the views and experiences of the patient representatives in the committee. It was therefore agreed it was important to include recommendations that promote increased information provision, as this was perceived to be inadequate, and to promote relationships with healthcare professionals as a facilitator of coping rather than as a barrier. The committee used its own experience and opinion to determine the specific recommendations that would enable these goals. Specifically, key information should be delivered soon after diagnosis to avoid unnecessary uncertainty that can lead to anxiety and depression, and to manage expectations better. Thus applies to both in- and out-patients. The committee noted that the NICE guideline on patient experience provides useful recommendations about patient information that clinicians should be aware of when treating people with pancreatitis, and which the patient themselves should be aware of in order to know what level of care they should expect. The committee wanted to specifically highlight the importance of giving patients the opportunity to record audio or take written notes during appointments or clinical discussions. The committee agreed that this would allow patients time to revisit the advice, information and discussion in a less pressurised environment, and give patients the opportunity to assimilate and comprehend the information given, as well as formulate any questions. This also gives family members the opportunity to review the clinical advice and information, and to be involved in the patients care. Clinic letters and discharge notes do not provide the level of detail required by patients to successfully manage their condition, and the committee noted the need for a detailed, personalised follow-up plan, with accurate and comprehensive information. In the case of severe acute pancreatitis, it was agreed that expectations are often not managed well regarding the likely disease course, and length of hospital stay, which again has the potential to contribute towards the development of depression in these individuals. Therefore, it was recommended that these patients and their family members or carers should be advised that a prolonged stay in hospital is common, relapse can follow an initial recovery and that the in-hospital mortality rate is approximately 15-20% in adults. This was based on the expert knowledge of the committee.
Quality of the evidence	The quality of each theme was rated as low as it was unclear how many participants reported each theme finding. Unstructured interviews were performed, and it is unknown what questions were asked or if all interviews were conducted in the same manner, therefore minor concerns were recorded about methodological limitations. There are minor concerns about adequacy of each theme as only 1 study was identified; therefore theme saturation was not met. Although some quotations are given in the paper, the study was not assessed as data rich. However, the findings were aligned with the experience of the committee and so the committee members were confident in using these results.
Trade-off between net effects and costs	No relevant health economic evidence was identified for this question. The resource implications of patient information and support strategies will vary depending on the specific strategies adopted. Short-term resource use and costs will be those associated with implementing the strategy, for example, those associated with staff time to give information and support, and the production costs of information leaflets. The committee identified the most important issue as the content of the information, as described in the recommendations. Initial design of information will have minor costs, whilst printing leaflets is very cheap. Information will be explained

	by staff, and leaflets distributed, in the course of consultations with the patients (and, where relevant, with family members). To inform patients fully, as recommended by the committee, may require longer - or a greater number - of appointments, which would incur a modest upfront cost per patient. There will, however, be downstream resource implications. These will depend on how effective the information strategy is in affecting a patient's quality of life. For example, if better informed patients then present to appropriate healthcare facilities urgently they need care, then that will lead to treatment being more successful, and often cheaper with better outcomes. Whilst if patients also do not present when they do not require care, that will reduce costs. The committee also discussed the need to give patients an opportunity to record or take notes during appointments or clinical discussions. This may reduce the number of repeat or extended healthcare appointments and so reduce later costs. In the absence of available data, the committee agreed that the small potential resources and costs involved in a patient information and support strategy were more than likely to be smaller than the savings to treatment costs, due to patients being enabled to engage with the health service more appropriately. Ensuring that the content and delivery of information is appropriate and effective is likely to reduce downstream costs whilst also improving health benefits, and therefore, is likely to be cost saving or highly cost effective.
Other considerations	The patient members of the committee noted that they often do not feel well looked after by their GPs, and that healthcare professionals, in general, seem to act as a barrier to adequate care until the patient is referred to the correct consultant. In this regard it was discussed that more work could be done by specialist pancreatic centres to disseminate their expertise more effectively. When referring to severity in acute pancreatitis the committee used the Revised Atlanta Classification.[11]

1

6 Lifestyle interventions: stopping or reducing alcohol consumption

6.1 Introduction

Pancreatitis may present with acute inflammatory attacks which can progress to a chronic fibrotic illness affecting sufferers physically, emotionally and socially, reducing their quality of life. Alcohol consumption is recognised as a common cause. Whilst research and previous guidance has identified a need to establish if alcohol is a cause of pancreatitis, the measures required to reduce alcohol consumption and the impact this can have on quality of life have yet to be fully explored. The NCEPOD report 'Measuring the Units' (2013)[73] recommended all people with a history of potentially harmful drinking should be referred to alcohol support services. Despite this, the subsequent NCEPOD report 'Treat the Cause' (2016),[74] which examined the quality of care delivered to patients with acute pancreatitis in the UK, observed disparity in almost half of all cases, with only 54% of patients being referred to alcohol support services. This potentially leaves people exposed to further attacks of pancreatitis and progression to chronic disease.

It is also important to note that for people in whom alcohol is considered not to be the cause of pancreatitis, information and advice regarding the risks of occasional alcohol consumption is not widely available. This review aims to highlight the importance of complete abstinence or reduced alcohol consumption in decreasing attacks of pancreatitis, and improving quality of life.

6.2 Review question: What is the clinical effectiveness and cost effectiveness of stopping or reducing alcohol consumption in reducing recurrent episodes of acute pancreatitis and improving quality of life in people with either chronic or acute pancreatitis?

For full details see review protocol in appendix C.

Table 12: PICO characteristics of review question

Population	People with acute or chronic pancreatitis
Intervention	Structured programme to support people with both chronic and acute pancreatitis in stopping or reducing alcohol consumption
Comparison	No structured programme or usual care (for example, general advice)
Outcomes	Critical • Quality of life (no time cut-off) (continuous) • Mortality (no time cut-off) (dichotomous) • Recurrent episodes of pancreatitis (no time cut-off) (dichotomous) • Alcohol consumption (no time cut-off) (dichotomous or continuous) Important • Nutritional status (no time cut-off) (continuous or dichotomous) • Admissions to hospital (no time cut-off) (dichotomous) • Morbidity (for example, pancreatic function, pain) (no time cut-off) (continuous or dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a

recommendation is found, non-randomised comparative studies will be included.

6.3 Clinical evidence

A search was conducted for randomised trials and systematic reviews comparing the effectiveness of structured programmes to support people with both chronic and acute pancreatitis in stopping or reducing alcohol consumption compared with no structured programmes or usual care.

One study was included in the review; [78] this is summarised in Table 13 below. Evidence from this study is summarised in the clinical evidence summary below (Table 15) and data not suitable for meta-analysis are presented in Table 14. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

An additional search for non-randomised comparative studies was conducted, but no relevant clinical studies were identified.

Table 13: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Nordback 2009[78]	• Structured programme to support people with both chronic and acute pancreatitis in stopping or reducing alcohol consumption: initial in-hospital structured 30-minute conversation (on the toxic effect of alcohol on the pancreas, on the need for a change in drinking habits, on social problems), plus repeated similar conversations at 6-months intervals in the gastrointestinal outpatient clinic. (n=59) • No structured programme or usual care (for example, general advice): initial in-hospital structured 30-minute conversation. (n=61)	Patients who had been admitted to the hospital for their first alcohol-associated acute pancreatitis n=120 Mean age (range): Control group 47 (18-73) years Intervention group 46 (25-71) years Finland	• Recurrent episodes of pancreatitis (3 years) • Alcohol consumption (2 years) • Admissions to hospital (2 years)	RCT Concurrent care: not stated

Table 14: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Nordback 2009[78]	Dependency on alcohol (SADD scale, 0-45) at 2 years	Median (range): 3 (0–28)	59	Median (range): 5 (0–26)	61	Very high
	Self-reported alcohol consumption (grams of absolute alcohol during past week) at 2 years	Median (range): 0 (0–1126)	59	Median (range): 0 (0–912)	61	Very high
	Self-reported alcohol consumption (grams of absolute alcohol during past 2 months) at 2 years	Median (range): 168 (0–9408)	59	Median (range): 324 (0–5880)	61	Very high
	Alcohol consumption (AUDIT scale, 0-40) at 2 years	Median (range): 12 (0–35)	59	Median (range): 11 (0–33)	61	Very high

Table 15: Clinical evidence summary: Structured programme to support people with acute pancreatitis in stopping or reducing alcohol consumption versus usual care

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Structured programme to stop alcohol (95% CI)
N of episodes of recurrent AP at 36 months	84 (1 study) 36 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.58 (0.26 to 1.28)	311 per 1000	131 fewer per 1000 (from 230 fewer to 87 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Structured programme to stop alcohol (95% CI)
Admissions to hospital (n of patients admitted for abdominal complaints fulfilling criteria of recurrent AP) at 2 years	84 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.38 (0.11 to 1.32)	200 per 1000	124 fewer per 1000 (from 178 fewer to 64 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

6.4 Economic evidence

6.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

6.5 Evidence statements

6.5.1 Clinical

- The randomised evidence in adults suggested a clinical benefit of using a structured programme to reduce alcohol intake for recurrent episodes and hospital admissions (1 study; n=84; very low quality). There was also evidence from the same study to suggest there may be no clinical difference in alcohol consumption or dependence after 2 years (1 study; n=120; very low quality).

6.5.2 Economic

- No relevant economic evaluations were identified.

6.6 Recommendations and link to evidence

Recommendations	**8. Advise people with pancreatitis caused by alcohol to stop drinking alcohol.** **9. Advise people with recurrent acute or chronic pancreatitis that is not alcohol-related that alcohol might exacerbate their pancreatitis.** **10. For guidance on alcohol use disorders, see the NICE guideline on the diagnosis and management of alcohol use disorders.**
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, recurrent episodes of pancreatitis and alcohol consumption). The committee also noted the following outcomes to be important: Nutritional status (continuous or dichotomous), admissions to hospital, morbidity (for example, pancreatic function and pain). There was no evidence found for the following outcomes: quality of life, mortality, nutritional status, admission to hospital and morbidity. No evidence was identified for children.
Quality of the clinical evidence	One randomised controlled trial was identified for inclusion in the review. The quality of evidence for all outcomes was graded as very low, due to risk of bias and imprecision for recurrent episodes of pancreatitis and admissions to hospital, and because data were unable to be meta-analysed for alcohol consumption.
Trade-off between clinical benefits and harms	The evidence identified was limited. A clinical benefit was found for the structured programme to stop alcohol for reducing the number of episodes of recurrent acute alcohol-associated pancreatitis at 36 months and for fewer admissions to hospital for abdominal complaints at 2 years. The data, reported as medians which could not be further analysed, showed slightly higher rates of dependency on alcohol and higher rates of self-reported consumption in the past 2 months in the control group. A very small increase was

	shown for alcohol consumption overall (at 2 years) in the intervention group and no difference for self-reported alcohol consumption in the last week. The committee noted that all patients were, or had recently been, high-level-dependent. The committee commented that it was very important to make people aware of the harm caused by alcohol consumption when they have acute or chronic pancreatitis, but that ultimately it is their own choice how to act on that information. Specifically, for people with acute or chronic pancreatitis that is caused by alcohol, clear advice should be given to stop their alcohol consumption. Amongst people with recurrent acute or chronic pancreatitis, due to causes other than alcohol, the committee agreed that it is important to make them aware that alcohol might exacerbate their pancreatitis. The committee further commented on the danger for those with hereditary pancreatitis and alcohol use.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. Although there is limited clinical evidence the committee agreed to make consensus recommendations reflecting the harms of alcohol consumption in people with pancreatitis. The committee discussed the effects of this advice on quality of life for patients. It noted that there may be a reduction in quality of life for some patients due to the loss of the social aspect of alcohol consumption or in some cases due to dependency on alcohol. This was weighed against the negative impact on quality of life due to exacerbations of pancreatitis and required hospitalisations and subsequent downstream effects. Therefore, the committee considered that advice to stop alcohol consumption would result in a better quality of life overall. Such advice would be given during regular existing consultations and so would not require any additional resources. The committee discussed that, if adhered to, this would result in significant cost savings to the health service due to reduced acute episodes and hospitalisations. In people who have pancreatitis due to the misuse of alcohol the committee agreed that a structured programme to aid in the stopping of alcohol consumption is appropriate in accordance with the guidance from NICE's alcohol-use disorders guideline (CG115). It was noted that the cost of buying alcoholic drinks falls upon the person with pancreatitis, and so a reduction or cessation of alcohol consumption would benefit their personal finances.
Other considerations	None.

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7 Lifestyle interventions: stopping or reducing smoking

7.1 Introduction

Cigarette smoking is recognised as a risk factor for pancreatitis. Exposure to tobacco smoking is associated with an earlier diagnosis of chronic alcoholic pancreatitis and predisposes to the development of both calcification and diabetes. Recent evidence also suggests that cigarette smoking may be an independent risk factor for acute pancreatitis. Stopping smoking is considered beneficial for all people, not just those with pancreatitis. Rather than conduct a review in this guideline other guidance has been cross referred to.

7.2 Recommendation

Recommendation	**11.For guidance on stopping smoking, see the NICE guideline on stop smoking services.**

1 # IDENTIFYING THE CAUSE

8 Aetiology of acute pancreatitis

8.1 Introduction

Acute pancreatitis has many and varied underlying causes. The most frequent cause in the western world includes biliary tract disease and alcohol consumption which account for about 80 – 90% of all cases.

Other causes that are responsible for the remaining 10 – 20% of cases include medications, metabolic causes, autoimmune, mechanical (blunt abdominal trauma, postoperative or endoscopic), anatomic or functional lesions (pancreatic divisum, pancreatic duct strictures/tumours, ampullary stenosis or sphincter of Oddi dysfunction), infection and toxins. Other rare causes include ischaemia (cardiac surgery or secondary to severe systemic hypotension). A small number of cases will continue to be labelled as idiopathic, that is, have no specific aetiology and one should suspect the possibility of a hereditary cause in this group, even in the absence of a family history.

Finding the cause for the acute pancreatitis requires a systematic approach with a national standard to prevent further attacks, alleviate suffering and improve quality of life. The aim of this review is to determine what diagnostic tests will help identify the cause of acute pancreatitis in people whose aetiology is unconfirmed by first-line tests within normal range (that is, patient enquiry for alcohol and genetic causes, ultrasound for gallstones and blood tests for metabolic causes).

8.2 Review question: What is the clinical effectiveness and cost effectiveness of assessing the aetiology of acute pancreatitis to prevent recurrent attacks in people in whom the aetiology is unconfirmed by first-line test results within normal ranges?

For full details see review protocol in appendix C.

Table 16: PICO characteristics of review question

Population	People with a diagnosis of acute pancreatitis and aetiology unconfirmed by first-line tests within normal range (that is, patient enquiry for alcohol and genetic causes, ultrasound for gallstones and blood tests for metabolic causes).
Interventions	Testing for aetiology of acute pancreatitis with any of the following tests: • History: drug history, specific questioning for Sphincter of Oddi dysfunction • Blood tests: autoantibodies, antibodies, serological tests, tests for hypercalcaemia and hyperlipidaemia • DNA test • Endoscopic ultrasound (EUS) of gall bladder and bile duct, EUS with duodenoscopy • MRCP, secretin-MRCP • Combinations of tests
Comparison	No test
Outcomes	Critical outcomes • Quality of life (continuous) • Pancreatitis-related mortality (dichotomous) • Number of repeated tests (dichotomous) Important outcomes • Any pancreatitis-related admissions (including recurrent attacks) (dichotomous)

	• Confirmation of aetiology or identification of a cause (dichotomous) • Adverse events following investigations (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled studies will be included.

8.3 Clinical evidence

A search was conducted for randomised trials or non-randomised controlled studies to evaluate the effectiveness of conducting tests to identify the aetiology of acute pancreatitis in people with no known alcoholic or genetic causes, no gallstones and no metabolic causes. No relevant studies were identified.

8.4 Economic evidence

8.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

8.5 Evidence statements

8.5.1 Clinical

- No relevant clinical evidence was identified.

8.5.2 Economic

- No relevant economic evaluations were identified.

8.6 Recommendations and link to evidence

Recommendations	**12. Do not assume that a person's acute pancreatitis is alcohol-related just because they drink alcohol.** **13. If gallstones and alcohol have been excluded as potential causes of a person's acute pancreatitis, investigate other possible causes such as:** • **metabolic causes (such as hypercalcaemia or hyperlipidaemia)** • **prescription drugs** • **microlithiasis** • **hereditary causes** • **autoimmune pancreatitis** • **ampullary or pancreatic tumours** • **anatomical anomalies (pancreas divisum).**
Relative values of different outcomes	The guideline committee considered the following outcomes to be critical: quality of life, pancreatitis-related mortality and number of repeated tests. The committee also considered the following outcomes to be important: any pancreatitis-related admissions (including recurrent attacks, confirmation of aetiology/identification of a cause and adverse events following investigations).

	No relevant clinical studies were identified therefore no evidence was available for any of these outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess the clinical effectiveness of testing for the aetiology of acute pancreatitis versus not testing in people in whom the aetiology is unconfirmed by normal first-line test results (that is, patient enquiry for alcohol and genetic causes, US for gallstones and blood tests for metabolic causes). However, the committee felt that a good practice statement on the aetiology of acute pancreatitis would be justified, as this would be likely to improve awareness of potential different diagnoses across care settings. The committee therefore agreed on a consensus recommendation for clinicians to be aware that in patients in whom gallstones and alcohol have been excluded as potential causes of acute pancreatitis, other important causes include hypercalcaemia, hyperlipidaemia, drugs, microlithiasis, hereditary causes, autoimmune pancreatitis, ampullary or pancreatic tumours, anatomical anomalies (pancreas divisum), infections and metabolic causes. The committee also agreed it was important to stress that if a person drinks alcohol, this does not necessarily mean that their acute pancreatitis is alcohol-related, and that clinicians should be aware of other potential causes.
Trade-off between net clinical effects and costs	No health economic evidence was identified for this question. Due to the absence of clinical evidence the committee could not assess the cost effectiveness of testing for the aetiology of acute pancreatitis, but agreed it was important to make a good practice recommendation to make clinicians aware of the various possible aetiologies. As no tests have been recommended there are no specific costs associated with these recommendations. To the extent that awareness of the various possible causes of acute pancreatitis may be improved by these recommendations, this may potentially improve the correct diagnosis and hence treatment of acute pancreatitis, leading to better clinical results, fewer cases diagnosed late or misdiagnosed and fewer adverse effects. This would be expected to improve clinical and economic outcomes, although there are no data available to quantify the degree of possible benefit. When investigating the cause of acute pancreatitis clinicians will need to consider the costs of the tests available to them and the likelihood of each cause before undertaking any particular tests.
Other considerations	The committee noted that the incidence of acute pancreatitis in the UK is approximately 56 cases per 100,000 people per year. Approximately 50% of cases are caused by gallstones, 25% by alcohol and 25% by other factors. The committee agreed that studies in this area would be helpful but were concerned that if they do not write a recommendation, people with pancreatitis could potentially go undetected for years. Therefore, a recommendation was drafted to highlight that investigative tests can identify, for example, those with hereditary or auto-immune causes.

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9 Aetiology of chronic pancreatitis

9.1 Introduction

There are several factors that cause chronic pancreatitis. Chronic alcoholism is the most frequent cause of chronic pancreatitis in adults whilst in children cystic fibrosis is the major cause. Other causes include hypertriglyceridaemia, autoimmune conditions including IgG4 related disease or following a severe attack of acute pancreatitis from any cause. In a small number of patients genetic factors may be important and several genetic mutations of the CFTR (cystic fibrosis, transmembrane-conductance regulator) and PRSS1 (cationic trypsinogen) genes have been identified. Idiopathic chronic pancreatitis may account for up to 30% of cases. Obstruction of the pancreatic duct either due to malignant (tumours) or benign causes (pancreas divisum, post trauma or duodenal wall cysts) can also lead to chronic pancreatitis. Smoking is also increasingly being recognised as a cause. Providing people with a cause of their pancreatitis can reassure a patient and may improve the subsequent management of their condition. This review attempts to address the value of trying to detect autoimmune chronic pancreatitis and hereditary pancreatitis.

9.2 Review question: What is the clinical effectiveness and cost effectiveness of performing genetic marker and autoantibody tests for identifying the aetiology of chronic pancreatitis in people with no known family history of pancreatitis, no significant alcohol history, and normal serum calcium and lipid levels?

For full details see review protocol in appendix C.

Table 17: PICO characteristics of review question

Population	People with a diagnosis of chronic pancreatitis and no known family history of pancreatitis, no significant alcohol history, and normal serum calcium and lipids
Interventions	• For the identification of autoimmune chronic pancreatitis: autoantibodies (for example IgG4, ANA) • For the identification of hereditary chronic pancreatitis (including CFTR): genetic markers (PRSS1, SPINK1, CFTR)
Comparison	No test
Outcomes	Critical outcomes • Quality of life (continuous) • Mortality (dichotomous) • Number of repeated tests or any pancreatitis-related admissions (dichotomous) Important outcomes • Early detection of cancer (for hereditary pancreatitis) (dichotomous) • Early detection of extra-pancreatic involvement (for IgG4 related pancreatitis) (dichotomous) • Confirmation of aetiology or identification of a cause (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled studies will be included.

9.3 Clinical evidence

A search was conducted for randomised trials or non-randomised controlled studies to evaluate the effectiveness of conducting tests to identify the aetiology of chronic pancreatitis in people with no known family history of pancreatitis, no significant alcohol history and normal serum calcium and lipids.

No relevant clinical studies comparing testing for the identification of autoimmune chronic pancreatitis or hereditary chronic pancreatitis with no test were identified.

9.4 Economic evidence

9.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

9.5 Evidence statements

9.5.1 Clinical

- No relevant clinical evidence was identified.

9.5.2 Economic

- No relevant economic evaluations were identified.

9.6 Recommendations and link to evidence

Recommendation	**14. Do not assume that a person's chronic pancreatitis is alcohol-related just because they drink alcohol. Other causes include:** • **genetic factors** • **autoimmune disease, in particular IgG4 disease** • **metabolic** • **structural or anatomical.**
Relative values of different outcomes	The guideline committee considered the following outcomes to be critical: quality of life, mortality and number of repeated tests/any pancreatitis-related admissions. The committee also considered the following outcomes to be important: early detection of cancer (for hereditary pancreatitis), early detection of extra-pancreatic involvement (for IgG4 related pancreatitis), confirmation of aetiology/identification of a cause. No relevant clinical studies were identified therefore no evidence was available for any of these outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess the clinical and cost effectiveness of testing for the aetiology of chronic pancreatitis versus not testing in people with no known family history of pancreatitis, no significant alcohol history and normal serum calcium and lipids. However, the committee felt that a good practice statement on the aetiology of

	chronic pancreatitis would be justified, as this would be likely to improve awareness of potential different diagnoses across care settings. The committee therefore agreed on a consensus recommendation for clinicians to be aware that if a person drinks alcohol, this does not necessarily mean that their chronic pancreatitis is alcohol-related, and that clinicians should be aware of other potential causes. These include hereditary factors, even in people without a known family history of pancreatitis, and autoimmune disease, in particular IgG4 disease, as well as metabolic, structural or anatomical causes.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. Due to the absence of clinical evidence the committee could not assess the cost effectiveness of testing for the aetiology of chronic pancreatitis. Instead the committee agreed it was important to make a good practice recommendation to make clinicians aware of the various possible aetiologies. As no tests have been recommended there are no costs associated with these recommendations. To the extent that awareness of the various possible causes of chronic pancreatitis may be improved by these recommendations, this may potentially improve the correct diagnosis and hence treatment of chronic pancreatitis, leading to better clinical results, fewer cases diagnosed late or misdiagnosed and fewer adverse effects. This would be expected to improve clinical and economic outcomes, although there are no data available to quantify the degree of possible benefit.
Other considerations	None.

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10 Diagnosing chronic pancreatitis

10.1 Introduction

Chronic Pancreatitis is a chronic inflammatory condition of the pancreas which leads to irreversible damage that may result in abdominal pain, exocrine and endocrine dysfunction. The commonest cause is long term alcohol usage. Other causes include metabolic conditions, autoimmune and genetic disorders such as defects in the CFTR gene or PRSS1 gene. Patients may present with mild symptoms of abdominal pain but as the disease progresses there may be signs of exocrine deficiency such as fat malabsorption or endocrine deficiency with the development of diabetes. Some patients develop severe disabling pain requiring strong long term analgesics which may lead to dependence and other related issues.

The diagnosis should be prompted by the history of intermittent upper abdominal pain, loss of weight and diarrhoea suggesting deficiency in exocrine function. Patients may show signs of malnutrition with low body mass and may develop diabetes due to loss of endocrine function. The diagnosis can usually be confirmed with cross-sectional imaging, CT or MRI. Initial investigations also include ultrasound or upper gastrointestinal endoscopy. However, there are a group of patients who are still suspected of having chronic pancreatitis with normal or uncertain results from imaging or the initial investigations. This review attempts to address the value of performing further tests to diagnose and treat chronic pancreatitis.

10.2 Review question 1: In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by any of CT scan, ultrasound scan or upper gastrointestinal (GI) endoscopy, what is the most accurate diagnostic test to identify whether chronic pancreatitis is present (as indicated by the reference standards: biopsy, clinical follow-up or subsequent CT scan)?

For full details see review protocol in appendix C.

Table 18: Characteristics of review question – diagnostic test accuracy

Population	All people with suspected (or under investigation for) chronic pancreatitis whose diagnosis has not been confirmed by the use of CT scan, ultrasound scan or upper GI endoscopy • Adults and young people (>16 years) • Children (<16 years)
Target condition	Chronic pancreatitis in people presenting with chronic abdominal pain, and normal or uncertain CT or ultrasound scan or upper GI endoscopy
Index tests	• Breath tests (C13 mixed tryglicerides test) • Endoscopic-based pancreatic function tests • Faecal tests (stool tests): Faecal elastase (monoclonal or polyclonal tests) (<200 micrograms per gram) • Faecal tests (stool tests): Faecal fat/coefficient of fat absorption (>7 gr per day, when people are on a 100 gr fat intake) • Radiological imaging: MRI

	• Radiological imaging: MRCP (= magnetic resonance cholangiopancreatography) • Radiological imaging: secretin-MRCP • Endoscopic imaging: ERCP (= endoscopic retrograde cholangiopancreatography) • Endoscopic imaging: endoscopic ultrasound (cut-off: Rosemont criteria: presence of chronic pancreatitis if >5) (including elastography) • Combinations of the above tests
Reference standards	Any of the following: • Biopsy • Clinical follow-up • Subsequent CT scan
Statistical measures	• Specificity • Sensitivity • Positive or negative predictive value (influenced by prevalence of a condition) • Positive or negative likelihood ratio (less dependent on the prevalence of the condition) • ROC curve or area under curve The committee agreed that sensitivity would be the primary measure for decision-making.
Study design	Prospective and retrospective cohort studies, in which the index tests and the reference standard test are applied to the same patients in a cross-sectional design

10.3 Review question 2: In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by any of CT scan, ultrasound scan or upper GI endoscopy, what is the most clinically effective and cost effective test to identify whether chronic pancreatitis is present, when each is followed by the appropriate treatment, in order to improve patient outcomes?

Table 19: Characteristics of review question – diagnostic RCTs

Population	All people with suspected (or under investigation for) chronic pancreatitis whose diagnosis has not been confirmed by the use of CT scan, ultrasound scan or upper GI endoscopy • Adults and young people (>16 years) • Children (< 16 years)
Target condition	Chronic pancreatitis in people presenting with chronic abdominal pain, and normal or uncertain CT or ultrasound scan or upper GI endoscopy
Index tests and treatment	Index tests: • Breath tests (C13 mixed tryglicerides test) • Endoscopic-based pancreatic function tests • Faecal tests (stool tests): Faecal elastase (monoclonal or polyclonal tests) (<200 micrograms per gram) • Faecal tests (stool tests): Faecal fat/coefficient of fat absorption (>7 gr per day, when people are on a 100 gr fat intake) • Radiological imaging: MRI • Radiological imaging: MRCP (= magnetic resonance cholangiopancreatography) • Radiological imaging: Secretin-MRCP • Endoscopic imaging: ERCP (= endoscopic retrograde cholangiopancreatography)

	• Endoscopic imaging: Endoscopic ultrasound (cut-off: Rosemont criteria: presence of chronic pancreatitis if >5) (including elastography) Treatment: Pancreatic enzyme replacement (PERT) or insulin; pain control; management of complications
Reference standards and treatment	Reference standards: any of the following: • Biopsy • Clinical follow-up • Subsequent CT scan Treatment: Pancreatic enzyme replacement (PERT) or insulin; pain control; management of complications
Outcomes	Critical • Quality of life • Mortality • Adverse events related to test (endoscopic complications) • Adverse events related to treatment Important • Hospital admission • Number of people receiving treatment (including people who may not have needed it, such as those with false positive results) • Patient or physician confidence in test • Repeat testing or additional testing
Study design	Diagnostic RCTs Systematic reviews of diagnostic RCTs

10.4 Clinical evidence

A search was conducted for cohort studies (including both retrospective and prospective analyses) assessing the diagnostic test accuracy of a range of tests including pancreatic function tests, faecal tests, and imaging to identify whether chronic pancreatitis is present (as indicated by the reference standard biopsy, or clinical follow-up, or subsequent CT scan) in people under investigation for chronic pancreatitis presenting with chronic abdominal pain, and normal or uncertain CT or ultrasound scan or upper GI endoscopy.

One study was included in the review;[57] this is summarised in Table 20 below. Evidence from this is summarised in the clinical evidence profile below (Table 21). See also the study selection flow chart in appendix E, study evidence tables in appendix H, sensitivity and specificity forest plots in appendix K, and exclusion list in appendix L.

A search was also conducted for diagnostic randomised controlled trials to evaluate the clinical effectiveness of different tests in improving patients' outcomes when followed up by appropriate treatment for chronic pancreatitis, in people with suspected (or under investigation for) chronic pancreatitis whose diagnosis has not been confirmed by CT scan, ultrasound scan or upper GI endoscopy. No relevant diagnostic RCTs were identified.

Table 20: Summary of studies included in the review for review question 1 – Diagnostic accuracy

Study	Intervention and comparison	Population	Diagnosis of interest	Comments
Ketwaroo 2013[57]	Endoscopic-based pancreatic function tests (Secretin	People with a clinical history highly suggestive of chronic pancreatitis and a prior work-up including	Chronic pancreatitis	

Study	Intervention and comparison	Population	Diagnosis of interest	Comments
	Pancreatic Function Test, SPFT) Clinical follow-up (including imaging or pathology)	negative esophagogastroduodenoscopy, gastric emptying study, abdominal ultrasound and laboratory testing, normal cross-sectional or endoscopic pancreatic imaging (n=116) Mean (SD) age SPTF positive: 45.5 (13.3) years SPTF negative: 45.5 (11.1) years USA		

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Table 21: Clinical evidence summary: diagnostic test accuracy for Secretin Pancreatic Function test (SPFT) for chronic pancreatitis in people with suspected chronic pancreatitis whose diagnosis has not been confirmed by any of CT scan, ultrasound scan or upper GI endoscopy

Index test (Threshold)	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (median/ range/ 95% CI)	Specificity % (median/ range/ 95% CI)	Quality
Secretin pancreatic function test (SPFT): cut-off peak bicarbonate level of < 75 mEq/L	1	116	Very serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness[c]	Very serious imprecision[d]	0.82 (0.48, 0.98)	0.86 (0.76, 0.93)[e]	VERY LOW

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making. The committee set the sensitivity threshold at 90% as the acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity forest plots, using the point estimates and confidence intervals. Particular attention was placed on sensitivity values above or below 50% (diagnosis based on chance alone) and the threshold above which would be acceptable to recommend a test of 90%. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (0–50%, 50–90% and 90–100%).

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

(d) Imprecision was assessed according to the confidence intervals of the included study for sensitivity. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate was 20–40%, and downgraded by 2 increments when there was a range of >40%

(e) The quoted specificity value is the value associated with the median sensitivity (the primary measure) in order to maintain paired values; sensitivity was the primary measure discussed in decision-making.

10.5 Economic evidence

10.5.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

10.6 Evidence statements

10.6.1 Clinical

- One study that evaluated 1 diagnostic test was included in the review. The very low quality evidence in 116 participants showed that at a cut-off peak bicarbonate level of <75 mEq/litre the secretin pancreatic function test has a specificity of 82% and a sensitivity of 86% for identifying chronic pancreatitis.

10.6.2 Economic

- No relevant economic evaluations were identified.

10.7 Recommendations and link to evidence

Research recommendation	**1. In people with suspected (or under investigation for) chronic pancreatitis, whose diagnosis has not been confirmed by the use of 'first-line' tests (for example, CT scan, ultrasound scan, upper gastrointestinal (GI) endoscopy or combinations of these), what is the most accurate diagnostic test to identify whether chronic pancreatitis is present?**
Relative values of different diagnostic measures	The aim of the review was to assess the performance of diagnostic tests for use in people in whom the diagnosis of chronic pancreatitis is 'difficult'. Therefore, the guideline committee was interested in the performance of diagnostic tests for chronic pancreatitis in people in whom other causes have not been excluded by the use of CT scan, US scan and/or upper GI endoscopy. The committee acknowledged these tests are commonly used as first line tests when patients present with chronic abdominal pain to exclude more common causes, for example, peptic ulcer disease, gallstone disease or gastro-oesophageal reflux disease. Consequently, the committee was interested in the performance of the following tests for the diagnosis of chronic pancreatitis: breath tests (C13 mixed triglycerides test), endoscopic-based pancreatic function tests, faecal tests (monoclonal or polyclonal tests faecal elastase test; faecal fat/coefficient of fat absorption), radiological imaging (MRI, MRCP, secretin-MRCP), endoscopic imaging (ERCP, endoscopic US) and combinations of tests. **Diagnostic test accuracy** Diagnostic accuracy for chronic pancreatitis in people whose diagnosis has not been confirmed by any of CT scan, US scan and/or upper GI endoscopy was the outcome prioritised for this review. Sensitivity was considered the most important measure by the committee for this review question because a clinical decision rule should select all patients with suspected chronic pancreatitis. The consequences of missing a patient with chronic pancreatitis would have serious implications, including the missed opportunity to treat or prevent chronic pain or pancreatic insufficiency. **Diagnostic RCTs** The committee considered the following outcomes to be critical: quality of life,

	mortality, adverse events related to test (endoscopic complications), and adverse events related to treatment. The committee also considered the following outcomes to be important: hospital admission, number of people receiving treatment (including people who may not have needed it, such as those with false positive results), patient/physician confidence in test, repeat testing/additional testing. No evidence was identified for this review question.
Quality of the clinical evidence	The study included in the review was graded very low quality by GRADE criteria. This was due to very serious risk of bias, as assessed using the QUADAS-2 checklist, as well as very serious inconsistency and imprecision.
Trade-off between clinical benefits and harms	One study reported the sensitivity and specificity of secreting pancreatic function test (SPFT) (cut-off peak bicarbonate level of, 75 mEq/l) in people with a clinical history highly suggestive of chronic pancreatitis and a prior work-up including negative esophagogastroduodenoscopy, abdominal US and/or endoscopic pancreatic imaging. The evidence from this study was very low quality and showed the test to have higher specificity than sensitivity. No relevant diagnostic RCTs were identified. The committee considered there was insufficient clinical evidence to recommend any tests to be performed in people in whom chronic pancreatitis is suspected, but in whom other causes have not been excluded by the use of CT scan, US scan and/or upper GI endoscopy. They therefore agreed that a research recommendation was warranted in this area.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee noted that failing to detect cases of chronic disease can have significant cost and benefit implications since patients are not put on an appropriate management pathway that caters for their needs (chronic pain, exocrine and endocrine deficiency, risk of cancer and reduced bone density). However, the committee opted to not make a recommendation over the use of a specific diagnostic test in people with an inconclusive first-line test result due to the absence of adequate comparative clinical and cost-effectiveness evidence. Instead, the committee opted to recommend that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee highlighted the importance of suspecting and diagnosing chronic pancreatitis in all settings of care, including primary care, as missing cases could have unfavourable health outcomes. The committee was keen on raising awareness of chronic pancreatitis as possible differential diagnosis in people who present with chronic abdominal pain. The committee acknowledged that patients presenting with symptoms of chronic pancreatitis (the most prominent of which is usually chronic abdominal pain) would normally have been investigated by CT scan, US scan and/or upper GI endoscopy as 'first-line' tests. The committee could not comment on the performance of these 'first-line' tests in the diagnosis of chronic pancreatitis, as this was out of the scope of the present review, and stressed that other tests might be equally or more appropriate, depending on the clinical context. In drafting the research recommendation, the committee recognised the possibility that MRI is used as first-line test in children to exclude more common causes of chronic abdominal pain, which was not originally included in the wording of the review question.

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1 # MANAGING PANCREATITIS

1 # FLUID RESUSCITATION

11 Type of intravenous fluid for resuscitation in people with acute pancreatitis

11.1 Introduction

Acute pancreatitis is an inflammatory condition, which results in depletion of body fluids (hypovolaemia) due to vomiting, poor oral fluid intake, pooling of fluid in and around the pancreas, and leaking of fluid from the blood vessels into the body tissues. Fluid resuscitation, especially early in the disease process, aims to restore the volume of fluid sufficient to perfuse the vital organs and avoid organ failure.

There are many different intravenous fluids available, the main 2 classes being crystalloids and colloids. Absence of clear guidance on the optimal resuscitative fluid leads to wide variations in practice. Existing guidelines give conflicting advice on which fluid type to administer for initial resuscitation The British Society of Gastroenterology Guidelines makes no specific recommendation on fluid type but the American College of Gastroenterology expert recommendations suggest giving Ringer's Lactate (Hartmann's) solution as the fluid of choice for initial resuscitation.

This review attempts to address the optimal fluid type for use in the initial resuscitation of people with acute pancreatitis.

11.2 Review question: What is the most clinically effective and cost-effective type of intravenous fluid for resuscitation in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 22: PICO characteristics of review question

Population	People admitted to hospital (secondary care, tertiary care) with acute pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Albumin • Synthetic colloids • Balanced crystalloids • Saline
Comparisons	• To each other
Outcomes	Critical outcomes • Quality of life at <1 year (continuous) • Length of stay (in CCU or hospital) at <1 year (continuous, dichotomous) • Length of stay (in CCU or hospital) at <1 year (continuous) • Mortality at <1 year (dichotomous) • Serious adverse events at during admission (dichotomous) Important outcomes • Local complications (fluid collection; cystic collection; pancreas necrosis; peri-pancreatic necrosis; local infection) at <6 months (dichotomous) • Systemic complications (persistent organ failure; fluid overload) at during admission (dichotomous)

Key confounders	• Severity of acute pancreatitis • Aetiology • Age
Study design	Systematic Review RCT Non-randomised comparative study

11.3 Clinical evidence

A search for randomised trials comparing types of intravenous fluids for resuscitation in acute pancreatitis was undertaken. Two studies were included[26, 101], comparing balanced crystalloids (Ringer's lactate) to normal saline. The search was extended to non-randomised comparative studies due to insufficient evidence and 1 additional study was identified that met the inclusion criteria.[1] This study compared balanced crystalloids (Ringer's lactate) to normal saline. No studies were identified relating to children.

Included studies are summarised in Table 23 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 25 and Table 26) and data not suitable for meta-analysis are presented in Table 98. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 23: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Aboelsoud 2016[1]	Intervention: Balanced crystalloids: Ringer's lactate solution (duration: 72h) (n=68) Comparison: Isotonic saline (duration: 72h) (n=130)	People with acute pancreatitis (n=198) Follow-up: unclear Age < 75 years USA	• Length of stay (critical care unit [CCU]) (time-point unclear) • Mortality (time-point unclear)	Non-randomised comparative study Multivariable analysis done for mortality adjusting for age, amount of fluid in 72 h and BISAP score but full results not reported. If a patient received both Ringer's lactate and Isotonic saline, they were assigned to the group of predominant fluid amount Concurrent medication/care: Not reported
de-Madaria 2017[26]	Intervention: Balanced crystalloids: 10 ml/kg in 60 minutes following	People with acute pancreatitis (n=40) Follow-up: unclear	• Mortality (time-point unclear) • Serious adverse events (transfer to	RCT Concurrent medication/care:

Study	Intervention and comparison	Population	Outcomes	Comments
	randomisation, and then 1 ml/kg/hour of Ringer's lactate solution (duration: 3 days) (n=19) Comparison: Normal saline (duration: unclear) (n=21)	Age (mean, SD): intervention group: 63.8 (19.1), control group 61.4 (15.5) Spain	CCU) (time-point unclear) • Local complications (peri-pancreatic necrosis) (time-point unclear) • Systemic complications (persistent organ failure) (time-point unclear)	All patients received 1000 ml of 10% dextrose solution in addition to the study fluid Patients with hematocrit >44% or 2 or more SIRS criteria or blood urea nitrogen >20 mg/dl or signs of dehydration or hypovolaemia received more vigorous resuscitation: 15 ml/kg of the study fluid in 60 minutes immediately after randomization, and then 1.2 litre/kg/hour of the study fluid for 3 days.
Wu 2011[101]	Intervention: Balanced crystalloids: either 20 mL/kg or standard resuscitation of Ringer's lactate solution (duration: unclear) (n=19) Comparison: Normal saline: either 20 mL/kg or standard resuscitation of normal saline (duration: unclear) (n=21)	People with acute pancreatitis (n=40) Follow-up: unclear Age (median, IQR): intervention group: 50 (40, 73), control group: 54 (40, 60) USA	• Length of stay (CCU) (time-point unclear) • Mortality (time-point unclear) • Serious adverse events (transfer to CCU) (time-point unclear) • Local complications (necrosis; infection) (time-point unclear) • Systemic complications (respiratory organ failure; shock; renal failure) (time-point unclear)	RCT Concurrent medication/care: Not reported

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Table 24: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Wu 2011[101]	Length of stay (in CCU), days, < 1 year	Median (IQR) 5.0 (3.0, 6.0) days	19	Mean (IQR): 5.5 (5.0, 8.0)) days	21	Very high

Table 25: Clinical evidence summary: Balanced crystalloid (Ringer's lactate) versus normal saline (RCT)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Normal saline (RCT)	Risk difference with Balanced crystalloid (Ringer's lactate) (95% CI)
Mortality	80 (2 studies) time-point unclear	⨁⊖⊖⊖ LOW[a] due to imprecision	Peto OR 0.15 (0.00 to 7.54)	24 per 1000	48 fewer per 1000 (from 173 fewer to 78 more)1
Serious adverse events (transfer to CCU)	61 (2 studies) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.37 (0.06 to 2.20)	143 per 1000	90 fewer per 1000 (from 134 fewer to 172 more)
Local complications (infection)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.15 (0 to 7.54)	48 per 1000	40 fewer per 1000 (from 48 fewer to 226 more)
Local complications (necrosis)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.36)	95 per 1000	81 fewer per 1000 (from 94 fewer to 104 more)
Local complications (peri-pancreatic necrosis)	24 (1 study) time-point	⨁⨁⊖⊖ LOW[a] imprecision	RR 0.56 (0.24 to 1.28)	714 per 1000	314 fewer per 1000 (from 543 fewer to 200 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Normal saline (RCT)	Risk difference with Balanced crystalloid (Ringer's lactate) (95% CI)
	unclear				
Systemic complications (renal failure)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.55 (0.05 to 5.62)	95 per 1000	43 fewer per 1000 (from 90 fewer to 440 more)
Systemic complications (respiratory organ failure)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.15 (0 to 7.54)	48 per 1000	40 fewer per 1000 (from 48 fewer to 226 more)
Systemic complications (shock)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.15 (0 to 7.54)	48 per 1000	40 fewer per 1000 (from 48 fewer to 226 more)
Systemic complications (persistent organ failure)	40 (1 study) time-point unclear	⨁⨁⊖⊖ LOW[a] imprecision	Peto OR 0.15 (0 to 7.54)	48 per 1000	48 fewer per 1000 (from 173 fewer to 78 more)1

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(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 26: Clinical evidence summary: Balanced crystalloid (Ringer's lactate) versus normal saline (observational studies)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Normal saline	Risk difference with Balanced crystalloid (Ringer's lactate) (95% CI)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Normal saline	Risk difference with Balanced crystalloid (Ringer's lactate) (95% CI)
Mortality	198 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.36 (0.13 to 1.02)	162 per 1000	104 fewer per 1000 (from 141 fewer more to 3 more)
Length of stay (in CCU), days	198 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of stay (in CCU) in the control groups was 4.2 days	The mean length of stay (in CCU) in the intervention groups was 2 days higher (0.19 to 3.81 higher)

(a) Downgraded by 2 increments if the majority of the evidence was from studies with observational/non-randomised study design. Further downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

11.4 Economic evidence

11.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

11.4.2 Unit costs

See appendix N.6.

11.5 Evidence statements

11.5.1.1 Clinical

All evidence was in adults or young people over 16 years.

Balanced crystalloid (Ringer's lactate) versus normal saline

- Evidence from randomised trials suggested a clinical benefit of a balanced crystalloid over normal saline for the outcome of local complications (peri-pancreatic necrosis) (1 study, n=24, very low quality), and for mortality (2 studies; n=80; low quality). Evidence from 2 randomised trials suggested no clinically important difference between the 2 groups in terms of local complications (infection; necrosis) or systemic complications (renal failure; respiratory organ failure; shock; persistent organ failure) (1–2 studies, n=40–80, very low quality).
- Evidence from a non-randomised study suggested a clinical benefit of normal saline compared with a balanced crystalloid in terms of mortality, but no clinically important difference in terms of length of stay in CCU (n=198, very low quality).

11.5.2 Economic

- No relevant economic evaluations were identified.

11.6 Recommendations and link to evidence

Recommendation	**15. For guidance on fluid resuscitation see the NICE guidelines on intravenous fluid therapy in adults in hospital and in children and young people in hospital.**
Research recommendation	**2. What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?**
Relative values of different outcomes	The guideline committee considered the following outcomes to be critical: quality of life, length of stay (in hospital or CCU), mortality and serious adverse events. The committee also considered the following outcomes to be important: local complications (fluid collection, cystic collection, pancreas necrosis, peri-pancreatic necrosis, local infection) and systemic complications (persistent organ failure, fluid overload). No evidence was identified for quality of life. No evidence was identified for the paediatric population.

Quality of the clinical evidence	The included studies provided evidence that compared balanced crystalloids (Ringer's lactate) with normal saline. The quality of evidence for this comparison was very low; the evidence was made up of 1 RCT and 1 non-randomised study. The evidence was graded as low or very low due to risk of bias and imprecision. There was no evidence comparing albumin and synthetic colloids with any of the other interventions.
Trade-off between clinical benefits and harms	When compared with normal saline, balanced crystalloids showed evidence of clinically important benefit for serious adverse events. There was also evidence of clinically important benefit favouring balanced crystalloids for mortality, however, the event rate was low and the uncertainty around the estimate reduced the committee's confidence in this finding. For the outcomes, length of stay, local complications and systemic complications, the evidence demonstrated no clinical difference between normal saline and balanced crystalloids. Overall, the committee noted that the body of evidence was of very low quality and that there was no clear evidence to suggest balanced crystalloids or normal saline would improve patient outcomes. The studies included had small participant numbers, which further added to the committee's uncertainty regarding the results of the outcomes in the review. The committee considered the evidence included in this chapter alongside the review on speed of IV fluid resuscitation therapy. The poor quality of the limited evidence available led the committee to agree that more research needs to be done in order to recommend the type of IV fluid that should be used and at the speed at which it should be used. The committee also agreed that it would be useful to identify studies that begin fluid administration within 3–6 hours of admission as there is evidence to suggest that patients admitted to hospital with acute pancreatitis are under-hydrated.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee noted the relative expense of saline in comparison to crystalloids. It also noted the points raised above regarding the potential benefit in terms of serious adverse events and mortality associated with balanced crystalloids. On balance, given the lack of clear evidence regarding comparative clinical effectiveness or cost effectiveness, the committee was not able to recommend any specific volume replacer, but instead recommended that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee was aware of guidance on IV fluid resuscitation therapy in the NICE guideline CG174, recommending that patients who require resuscitation should be given crystalloid fluid over 15 minutes, and to consider using human albumin solution in patients with sepsis. The rationale for this review however, was that from a critical care perspective, patients with severe pancreatitis are not necessarily patients with severe sepsis. Despite some similarities in the pathophysiology of their fluid deficit and hypotension, the level of shock and hypotension caused by fluid shifts in pancreatitis is severe and caused by severe inflammation in the abdomen, but also lung damage and compromise to renal function. This makes pancreatitis a specific case with regards to fluid management. Furthermore, the guideline CG174 was published in 2013, and the committee was aware of the unclear and mixed evidence over what is the appropriate rate of fluid resuscitation administered to critically ill patients over the past few years. It was therefore considered appropriate to make a research recommendation to promote the investigation of the clinical and cost effectiveness of the type and speed of fluid resuscitation therapy in the people with pancreatitis.

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12 Speed of intravenous fluid for resuscitation in people with acute pancreatitis

12.1 Introduction

Acute pancreatitis, even in its mildest form, leads to dehydration that mandates timely correction by adequate fluid resuscitation. In severe acute pancreatitis the depletion of body fluids and reduction of the intravascular volume can be severe enough to cause hypotension, acute renal failure and pancreatic hypoperfusion aggravating the damage to the pancreas.

There is evidence from other conditions similar in pathophysiology to acute severe pancreatitis that delayed fluid resuscitation causes increased mortality. Evidence also suggests, however, that overly aggressive fluid administration can also cause increased mortality due to fluid overload, particularly affecting the lungs.

The current guidelines advocate giving aggressive fluid therapy to people with acute pancreatitis during the first 24 hours of hospital admission guided by central venous pressure monitoring or the intrathoracic blood volume index. However, there is uncertainty over the use of central venous pressure monitoring to guide fluid resuscitation and the most beneficial time of hydration.

This review attempts to address the optimal speed of fluid resuscitation for people with acute pancreatitis.

12.2 Review question: What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 27: PICO characteristics of review question

Population	Those admitted to hospital and receiving treatment for acute pancreatitis who require fluid resuscitation • Adults and young people (>16 years) • Children (≤16 years)
Interventions and comparators	• '**Aggressive' fluid administration** (as defined by studies, including goal-directed therapies; for example: 15 ml/kg body weight per hour, ≥33% of total volume in 72 hours of infusion performed in the first 24 hours, >3.1 litres given in first 24 hours) • '**Conservative' fluid administration** (as defined by studies, including goal-directed therapies; for example, 5–10 ml/kg body weight per hour) Studies in the following fluids will be considered: albumin, synthetic colloids, balanced crystalloids (for example, Ringer's lactate), saline. Only studies where both arms use the same type of fluid will be included.
Outcomes	Critical outcomes • Quality of life (<1 year) (continuous) • Mortality (<1 year) (dichotomous) • Length of stay (in CCU or hospital) (continuous or dichotomous) • Achievement of pre-specified target for resuscitation (for example, target central

	venous pressure, urine output, lactate levels, PiCCO measurement) (dichotomous) Important outcomes • Local complications (fluid collection; cystic collection; pancreas necrosis; peri-pancreatic necrosis; local infection) (<6 months) (dichotomous) • Systemic complications (persistent organ failure; fluid overload) (during admission) (dichotomous) • Serious adverse events (during admission) (dichotomous)
Key confounders	• Severity of acute pancreatitis • Aetiology • Age
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled studies will be included.

12.3 Clinical evidence

A search was conducted for randomised trials and non-randomised comparative studies comparing aggressive fluid resuscitation to conservative fluid resuscitation (as defined by studies).

Nine studies[20, 27, 36, 40, 99, 102, 115, 116, 118] were included in the review. These are summarised in Table 28, and Table 29 below. One study was identified in the children and young people population and 8 studies were identified in the adult population. As there was insufficient RCT evidence, non-randomised studies were also included in the review; 3 randomised controlled trials and 6 non-randomised comparative studies were included. The aim of all studies was to assess whether aggressive fluid resuscitation improves outcomes in people with acute pancreatitis compared with conservative fluid management.

Evidence from these studies is summarised in the clinical evidence summaries below (Table 31 to Table 33) and data not suitable for meta-analysis are presented in Table 30. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 28: Summary of studies in adults included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Buxbaum 2017[20]	Intervention: 'Aggressive' fluid administration – Participants were given a 20ml/kg bolus followed by infusion at 3ml/kg/hour (n=27) Comparison: 'Conservative' fluid administration – Participants were given a 10ml/kg bolus followed by infusion at 1.5ml/kg/hour (n=33) Fluid type: Lactated Ringer's solution	Adults with acute pancreatitis (n=60) Follow-up during admission Age (mean, SD): Aggressive group 44.4 (13.7); standard group 45.3 (12.3) USA	• Mortality (3 days) • Systemic complications (development of SIRS, persistent SIRS) (36 hours) • Serious adverse events (development of severe acute pancreatitis) (36 hours)	RCT Concurrent medication/care : not reported

Study	Intervention and comparison	Population	Outcomes	Comments
De Madaria 2011[27]	Intervention: 'Aggressive' fluid administration - Participants were given > 4.1 L during the initial 24 hours of admission (n=61) Intervention: 'Aggressive' fluid administration - Participants were given 3.1-4.1 L during the initial 24 hours of admission (n=123) Comparison: 'Conservative' fluid administration - Participants were given < 3.1 L during the initial 24 hours of admission (n=63) Fluid type: 0.9% sodium chloride plus 5-10% dextrose	Adults aged 42-81 with acute pancreatitis (n=247) Intervention time: 2.5 years Age (range): 50-81 Spain	• Local complications (necrosis; acute collections) (time-point unclear) • Systemic complications (persistent organ failure) (time-point unclear)	Non-randomised comparative study Multivariable analysis adjusting for age, Charlson score, hemacrit >44%, previous haemodialysis Concurrent medication/care: all other treatment followed the local protocol for general management of AP.
Eckerwall 2006[36]	Intervention: 'Aggressive' fluid administration - Patients received 4000 mL or more during the first 24 hours of admission (n=32) Comparison: 'Conservative' fluid administration - Patients received less than 4000 mL of fluid during the first 24 hours of admission (n=67) Fluid type: mainly crystalloids during the first 24 hours but within the first 72 hours 56% of patients received a combination of crystalloids and colloids. Albumin was the most commonly used colloid.	Adults with severe acute pancreatitis (n=99) Follow-up: during admission Age (mean, SD): 60 (18) Sweden	• Systemic complications (respiratory complications; pulmonary oedema) (during admission)	Non-randomised comparative study No adjusting for confounders Concurrent medication/care: 69/95 of the patients received TPN
Gardner 2009[40]	Intervention: 'Aggressive' fluid administration. Participants received ≥33% of their cumulative 72-hour intravenous fluid within the first 24 hours after presentation to the emergency room. Total volume in the first 72 hours: 12, 190 ml. The mean rate of IV fluid resuscitation in	Adults with acute pancreatitis (n=45) Follow-up during admission Age (mean, SD): aggressive group 53 (13); conservative group: 57 (17)	• Mortality (during admission) • Length of stay in hospital (during admission) • Local complications (necrosis, development of	Non-randomised comparative study Regression analysis revealed no evidence of confounding when adjusted for age,

Study	Intervention and comparison	Population	Outcomes	Comments
	the first 24 hours was 203 mL/h (n=17) Comparison: 'Conservative' fluid administration. Participants received <33% of their cumulative 72-hour intravenous fluid within the first 24 hours after presentation to the emergency room. Total volume in the first 72 hours: 7, 664 mL. The mean rate of IV fluid resuscitation in the first 24 hours was 71 mL/h (n=28) Fluid type: All patients received crystalloid solutions; 32 received 0.9% NaCl, 9 received 5% dextrose with 0.45% NaCl, and 4 received lactated Ringer's solution.	USA	a pseudocyst or abscess) (during admission) • Systemic complications (persistent organ failure, SIRS) (during admission)	Charlson score, BMI, aetiology, and hematocrit). Full findings not reported. Concurrent medication/care : there was no difference between groups in the types of fluid received.
Singh 2017[99]	Intervention: 'Aggressive' fluid administration – Participants received >1000ml between the time of arrival at the ER to 4 hours after diagnosis (n=314) Intervention: 'Aggressive' fluid administration – Participants received 500-1000ml (n=427) Comparison: 'Conservative' fluid administration – Participants received <500ml (n=269) Fluid type: not stated, but varied between centres.	Adults with first or recurrent acute pancreatitis (n=1010) The study period included the index hospital admission and further hospital admissions due to symptomatic local complications Age (mean, SD): 53.6 (19.6) Four institutions in Spain and USA	• Mortality (time-point unclear) • Local complications (not listed) (time-point unclear) • Systemic complications (persistent organ failure) (time-point unclear)	Non-randomised comparative study using retrospectively and prospectively recorded databases Multivariable analysis controlling for: age>60, alcoholic aetiology, haematocrit >44%, blood urea nitrogen >25 mg/dl, presence of systemic inflammatory response syndrome and centre of origin. Not adjusted for type of fluid used. Concurrent medication/

Study	Intervention and comparison	Population	Outcomes	Comments
				care: not reported
Wall 2011[115]	Intervention: 'Aggressive' fluid administration - Hydration was provided at 284 mL/h during the first 6 hours and 221 mL/h during the first 12 hours (n=113) Comparison: 'Conservative' fluid administration - Hydration was provided at 113 (80) mL/h during the first 6 hours and 152 (67) mL/h during the first 12 hours (n=173) Fluid type: not stated	Adults over the age of 18 with acute pancreatitis (n=286) Age < 75 years USA	• Mortality (during admission) • Length of stay (in CCU or hospital) (during admission) • Local complications (pancreatic necrosis) (during admission) • Systemic complications (renal failure; pulmonary failure; cardiovascular failure; multi-organ failure) (during admission)	Non-randomised comparative study (historical control) No adjusting for confounders Concurrent medication/care: Not reported
Wang 2013[116]	Intervention: 'Aggressive' fluid administration - During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following: central venous pressure 8-12 mmHg, mean arterial pressure ≥65 mmHg, urine output ≥0.5 mL/kg/h and central venous or mixed venous oxygen saturation ≥70% (n=64) Comparison: 'Conservative' fluid administration - Patients fluid resuscitation was in line with the Practice Guidelines in Acute Pancreatitis (n=68) Fluid type: crystalloids (Ringer's lactate and normal saline) plus 6% hydroxyethyl starch 130/0.42.	Adults with severe acute pancreatitis (n=200) Age (range): 18-70 China	• Mortality (during admission) • Length of stay (CCU) (during admission) • Systemic complications (abdominal compartment syndrome, multiple organ dysfunction syndrome) (during admission) • Serious adverse events (days on ventilation) (during admission)	RCT Concurrent medication/care: All patients were managed and cared for in the same manner according to Practice Guideline in Acute Pancreatitis, including supportive care, enteral feeding, treatment of sterile pancreatic necrosis, treatment of associated pancreatic duct disruptions, and use of antibiotics. Hydroxyethyl

Study	Intervention and comparison	Population	Outcomes	Comments
				starch has now been recommended for withdrawal.
Wu 2011[118]	Intervention: 'Aggressive' fluid administration - Each patient received an initial fluid challenge with 20 mL/kg of either LR solution or NS during a period of 30 minutes. Participants then received continuous infusion of 3 mL/kg/h of intravenous hydration for volume maintenance. After 8-12 hours, study physicians reassessed patients with a bedside clinical examination as well as a BUN measurement. If refractory to initial volume challenge, participants received a second fluid challenge of 20 mL/kg to be administered during 30 minutes. They then continued to receive volume replacement at a rate of 3 mL/kg/h. An additional bolus of 20 mL/kg during a period of 30 minutes was initiated at 16-20 hours for patients who remained refractory to volume resuscitation (n=19) Comparison: 'Conservative' fluid administration - Patients randomised to standard fluid resuscitation had fluid adjustments managed by their treating physician (n=21) Fluid type: lactated Ringer's solution or normal saline	Adults with acute pancreatitis (n=40) Age < 75 years USA	• Mortality (time-point unclear) • Length of stay (time-point unclear) • Local complications (necrosis; infection) (time-point unclear) • Systemic complications (respiratory organ failure; shock; renal failure) (time-point unclear) • Serious events during admission (transfer to CCU) (time-point unclear)	RCT Concurrent medication/care : Not reported

Table 29: Summary of studies in children included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Szabo 2015[102]	Intervention: 'Aggressive' fluid administration - Intravenous fluid was	Children and young people aged 0-21 with acute	• Serious adverse events (readmission rate; CCU transfer	Non-randomised comparative

Study	Intervention and comparison	Population	Outcomes	Comments
	initiated at 1.5-2 times the maintenance rate of dextrose 5% normal saline on admission. Intravenous fluid was administered within 24 hours of admission. (n=126) Comparison: 'Conservative' fluid administration - Intravenous fluid was initiated at the normal maintenance rate of dextrose 5% normal saline on admission. Intravenous fluid was administered within 24 hours of admission (n=75)	pancreatitis and severe acute pancreatitis (n=201) Age (range): 1-21 USA	rate; severe acute pancreatitis rate) (during admission)	study Concurrent medication/ care: 30 participants received enteral nutrition and 96 did not.

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Table 30: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Wall 2011[115]	Length of stay (in hospital)	Median: 5.5	113	Median: 7.7	173	Very high
Wu 2011[118]	Length of stay (in CCU), days, < 1 year	Median (IQR) 5.0 (4.0, 8.0)	19	Mean (IQR): 5.0 (3.5, 6.5)	21	Very high
Szabo 2015[102]	Length of stay (in hospital), days, < 1 year (NPO group)	Mean (SE): 5 (0.58)	30	Mean (SE): 7.1 (1.01)	20	Very high
Szabo 2015[102]	Length of stay (in hospital), days, < 1 year (PO group)	Mean (SE): 3.2 (0.22)	96	Mean (SE): 2.8 (0.24)	55	Very high

Table 31: Clinical evidence summary: Aggressive intravenous fluid resuscitation therapy versus conservative intravenous fluid resuscitation therapy in adults with acute pancreatitis (RCTs)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Mortality	232 (3 studies) 3 days/ during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.90 (0.49 to 1.67)	118 per 1000	12 fewer per 1000 (from 60 fewer to 79 more)
Length of time in CCU (days)	132 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of time in CCU (days) in the control groups was 20.6	The mean length of time in CCU (days) in the intervention groups was 2 lower (4.23 lower to 0.23 higher)
Local complications (infection)	40 (1 study) time-point	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias,	Peto OR 8.68 (0.52 to 144.35)		105 more per 1000 (from 52 fewer to 263 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
	unclear	imprecision			
Local complications (necrosis)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.21 (0.16 to 415.76)		52 more per 1000 (from 78 fewer to 183 more)
Systemic complications (development of SIRS)	60 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.54 (0.19 to 1.57)	273 per 1000	125 fewer per 1000 (from 221 fewer to 155 more)
Systemic complications (persistent SIRS)	60 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.35 (0.08 to 1.54)	212 per 1000	138 fewer per 1000 (from 195 fewer to 115 more)
Systemic complications (Multiple organ dysfunction syndrome)	132 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.96 (0.56 to 1.64)	294 per 1000	12 fewer per 1000 (from 129 fewer to 188 more)
Systemic complications (Sepsis)	76 (1 study) during admission	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 3 (1.93 to 4.64)	325 per 1000	650 more per 1000 (from 302 more to 1000 more)
Systemic complications (Abdominal compartment syndrome)	132 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias,	RR 0.83 (0.45 to 1.52)	265 per 1000	45 fewer per 1000 (from 146 fewer to 138 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
		imprecision			
Systemic complications (renal failure)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.21 (0.22 to 22.47)	48 per 1000	58 more per 1000 (from 37 fewer to 1000 more)
Systemic complications (respiratory failure)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.21 (0.16 to 415.76)		52 more per 1000 (from 78 fewer to 183 more)
Systemic complications (shock)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.21 (0.16 to 415.76)		52 more per 1000 (from 78 fewer to 183 more)
Serious adverse events (Days using ventilation)	132 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean serious adverse events (days using ventilation) in the control groups was 15.3	The mean serious adverse events (days using ventilation) in the intervention groups was 3 lower (4.61 to 1.39 lower)
Serious adverse events (transfer to CCU)	40 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 9.78 (1.27 to 75.43)		210 more per 1000 (from 17 more to 403 more)
Serious adverse events (development of	60	⨁⊖⊖⊖ VERY LOW[a,b]	Peto OR		25 fewer per 1000

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
severe acute pancreatitis)	(1 study) 36 hours	due to risk of bias, imprecision	0.16 (0 to 8.34)		(from 30 fewer to 222 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 32: Clinical evidence summary: Aggressive intravenous fluid resuscitation therapy versus conservative intravenous fluid resuscitation therapy in adults with acute pancreatitis (non-randomised comparative studies)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Mortality	45 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.17 (0.03 to 1.14)	179 per 1000	148 fewer per 1000 (from 173 fewer to 25 more)
Mortality	286 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.38 (0.13 to 1.12)	92 per 1000	57 fewer per 1000 (from 80 fewer to 11 more)
Mortality - 500-1000ml versus <500ml	696 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.46 (0.15 to 1.41)	Not estimable[c]	Not estimable[c]
Mortality - >1000ml versus <500ml	583	⊕⊖⊖⊖	OR 0.64	Not estimable[c]	Not estimable[c]

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
	(1 study) time-point unclear	VERY LOW[a,b] due to risk of bias, imprecision	(0.20 to 2.05)		
Length of hospital stay	45 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 37 days	The mean length of hospital stay in the intervention groups was 3 higher (37.7 lower to 43.7 higher)
Local complications (Acute collection) - 3100-4100 ml versus >4100 ml	186 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	OR 1.90 (1.00 to 3.61)	Not estimable[c]	Not estimable[c]
Local complications (Acute collection) - <3100 ml versus 3100-4100 ml	184 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	OR 0.60 (0.30 to 1.20)	Not estimable[c]	Not estimable[c]
Local complications (Pancreatic necrosis)	45 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.20 (0.61 to 2.37)	393 per 1000	79 more per 1000 (from 153 fewer to 538 more)
Local complications (Pancreatic necrosis)	286 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.12 (1.00 to 4.52)	71 per 1000	79 more per 1000 (from 0 more to 249 more)
Local complications (Pancreatic necrosis) – <3100 ml versus 3100-4100 ml	186 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 1.80 (0.60 to 5.40)	Not estimable[c]	Not estimable[c]

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Local complications (Pancreatic necrosis) – 3100-4100 versus >4100 ml	184 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 1.50 (0.60 to 3.75)	Not estimable[c]	Not estimable[c]
Local complications (Pseudocysts)	45 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.91 (0.59 to 1.38)	714 per 1000	64 fewer per 1000 (from 293 fewer to 271 more)
Local complications (acute peripancreatic fluid collections and/or pancreatic necrosis and/or peripancreatic necrosis)) - 500-1000 ml versus <500 ml	696 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.67 (0.43 to 1.04)	Not estimable[c]	Not estimable[c]
Local complications (acute peripancreatic fluid collections and/or pancreatic necrosis and/or peripancreatic necrosis)) - >1000 ml versus <500 ml	583 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 1.15 (0.71 to 1.86)	Not estimable[c]	Not estimable[c]
Systemic complications (Cardiovascular failure)	286 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.87 (0.26 to 2.92)	41 per 1000	5 fewer per 1000 (from 30 fewer to 79 more)
Systemic complications (Pulmonary failure)	286 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.68 (0.21 to 2.16)	52 per 1000	17 fewer per 1000 (from 41 fewer to 60 more)
Systemic complications (Multisystem organ failure)	286 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.43 (0.16 to 1.11)	104 per 1000	59 fewer per 1000 (from 87 fewer to 11 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Systemic complications (Respiratory complications)	69 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.67 (0.52 to 0.87)	973 per 1000	321 fewer per 1000 (from 126 fewer to 467 fewer)
Systemic complications (Fluid overload)	99 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[d]	No events	
Systemic complications (Persistent organ failure)	45 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.82 (0.38 to 1.78)	429 per 1000	77 fewer per 1000 (from 266 fewer to 334 more)
Systemic complications (persistent organ failure) - 3100-4100 ml versus <3100 ml	186 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 2.10 (0.30 to 14.70)	Not estimable[c]	Not estimable[c]
Systemic complications (persistent organ failure) - >4100 ml versus 3100-4100 ml	184 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 7.70 (1.50 to 39.53)	Not estimable[c]	Not estimable[c]
Systemic complications (persistent organ failure) - 500-1000 ml versus <500 ml	696 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.56 (0.28 to 1.12)	Not estimable[c]	Not estimable[c]
Systemic complications (persistent organ failure) - >1000 ml versus <500 ml	583 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.50 (0.22 to 1.14)	Not estimable[c]	Not estimable[c]

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Systemic complications (Renal failure)	286 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.85 (0.29 to 2.47)	52 per 1000	8 fewer per 1000 (from 37 fewer to 76 more)
Systemic complications (SIRS)	45 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.24 (0.92 to 1.65)	714 per 1000	171 more per 1000 (from 57 fewer to 464 more)
Serious adverse events (pulmonary oedema)	99 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable [d]	No events	

(a) Downgraded by 2 increments if the majority of the evidence was from studies with observational/non-randomised study design. Further downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Could not be calculated as only adjusted OR were reported.
(d) Could not be calculated as there were no events in the intervention or control arms.

Table 33: Clinical evidence summary: Aggressive intravenous fluid resuscitation therapy versus conservative intravenous fluid resuscitation therapy in children with acute pancreatitis (non-randomised comparative studies)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
Serious adverse events (CCU transfer rate)	201 (1 study)	⨁⊖⊖⊖ VERY LOW[a]	RR 0.21 (0.08 to	187 per 1000	147 fewer per 1000 (from 80 fewer to 172 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conservative fluid therapy	Risk difference with Aggressive fluid therapy (95% CI)
	during admission	due to risk of bias	0.57)		
Serious adverse events (Readmission rate)	201 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.6 (0.18 to 1.99)	67 per 1000	27 fewer per 1000 (from 55 fewer to 66 more)
Serious adverse events (SAP rate)	201 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.45 (0.2 to 1.01)	160 per 1000	88 fewer per 1000 (from 128 fewer to 2 more)

(a) Downgraded by 2 increments if the majority of the evidence was from studies with observational/non-randomised study design. Further downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

12.4 Economic evidence

12.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

12.5 Evidence statements

12.5.1 Clinical

12.5.1.1 Aggressive intravenous fluid resuscitation therapy versus conservative intravenous fluid resuscitation therapy

Adults with acute pancreatitis

- There was evidence from randomised trials to suggest a possible clinically important benefit of aggressive IV fluid resuscitation for mortality, but there was a high degree of uncertainty in this effect estimate (3 studies; n=232; very low quality), but no clinically important difference in terms of length of stay in CCU between the 2 group (1 study; n=132; very low quality). Evidence for local complications was mixed, with a possible clinically important benefit of conservative IV therapy for the outcome of infection, but evidence to suggest no clinically important difference in terms of necrosis between the 2 groups (1 study; n=40; very low quality). There was a clinically important benefit of conservative IV therapy for the outcome of sepsis (1 study; n=76; low quality), and a possible clinically important benefit of aggressive IV therapy for the outcomes of development of SIRS and for persistent SIRS (1 study; n=60; very low quality). There was evidence to suggest no clinically important difference for any of the other outcomes related to systemic complications (multiple organ dysfunction syndrome, abdominal compartment syndrome, renal failure, respiratory failure, shock). In terms of serious adverse events, the evidence suggested a clinically important benefit of conservative IV therapy for the outcome of transfer to CCU (1 study; n=40; very low quality) but no clinically important difference for the use of ventilation (1 study; n=132; very low quality) or development of severe acute pancreatitis (1 study; n=60; very low quality).
- Evidence from observational studies showed a clinically important benefit of aggressive IV fluid resuscitation for the mortality outcome (1 study; n=45; very low quality and 1 study; n=286; very low quality). Evidence from studies that reported adjusted odds ratios also favoured aggressive IV fluid resuscitation (1 study; n=696; very low quality and 1 study; n=583; very low quality). However, there was a clinically important benefit of conservative fluid therapy for the outcome of length of stay in hospital (1 study; n=45; very low quality).
- In terms of local complications, evidence from studies that reported adjusted odds ratios suggested a potential benefit of conservative fluid resuscitation in terms of local complications (acute collection) (1 study; n=186; very low quality and 1 study; n=184; very low quality). The evidence also suggested no clinically important difference between the 2 groups in terms of local complications (pseudocysts, pancreatic necrosis). Evidence from studies that reported adjusted odds ratios suggested a potential benefit of conservative IV fluid resuscitation for local complications (pancreatic necrosis) when conservative was defined as 3,100–4,100 ml and aggressive was defined as >4,100 ml (1 study; 186; very low quality). However, when conservative was defined as <3,100 ml and aggressive was defined as 3,100–4,100 ml, the results suggested that aggressive IV fluid resuscitation was favoured (1 study; n=184; very low quality). For the local complications outcome of acute peripancreatric fluid collection or pancreatic necrosis or

peripancreatic necrosis, evidence from studies that reported adjusted odds ratios suggested a potential benefit of aggressive IV fluid resuscitation when comparing 500–1,000 ml to <500 ml, but a benefit of conservative when comparing >1,000 ml to <500 ml (1 study; n=583–696; very low quality).

- In terms of systemic complications, there was evidence to suggest a clinically important benefit of aggressive IV fluid resuscitation for the outcome of respiratory complications (1 study; n=696; very low quality) and of conservative IV fluid therapy for the outcome of SIRS (1 study; n=45; very low quality), but no clinically important difference between the 2 groups in terms of systemic complications (cardiovascular failure, pulmonary failure, multisystem organ failure, fluid overload or renal failure) or persistent organ failure. Evidence from studies that reported adjusted odds ratios suggested a potential benefit of aggressive IV fluid resuscitation in terms of persistent organ failure for 3 of the 4 comparisons, but a potential benefit of conservative IV fluid resuscitation in 1 study when aggressive was defined as >4,100 ml and conservative was defined as 3,100–4,100 ml (n=184; very low quality).
- One study reported serious adverse events (pulmonary oedema), and the evidence suggested no clinically important difference between the 2 groups (n=99; very low quality).

Children with acute pancreatitis

- For the outcome of serious adverse events, a single study showed clinical benefit of aggressive IV resuscitation therapy in terms of CCU transfer rate and a possible clinical benefit for SAP rate, but suggested no clinically important difference in terms of readmission rate (1 study; n=201; very low quality).

12.5.2 Economic

- No relevant economic evaluations were identified.

12.6 Recommendations and link to evidence

Research recommendation	3. What is the most clinically effective and cost-effective speed of administration of intravenous fluid for resuscitation in people with acute pancreatitis?
Relative values of different outcomes	The guideline committee considered the following outcomes to be critical: quality of life, length of stay (in hospital or CCU), mortality and achievement of pre-specified target for resuscitation. The committee also considered the following outcomes to be important: local complications (fluid collection; cystic collection; pancreas necrosis; peri-pancreatic necrosis; local infection), systemic complications (persistent organ failure; fluid overload) and serious adverse events. There was no evidence identified for quality of life in all populations. No critical outcomes were reported in children.
Quality of the clinical evidence	The included studies provided evidence that compared aggressive versus conservative fluid administration. The quality of evidence for this comparison ranged from low to very low; the evidence was made up of 3 RCT and 6 non-randomised studies. The evidence was graded as low or very low due to risk of bias and imprecision. One of the included studies used a fluid type containing 6% hydroxyethyl starch, which has now been recommended for withdrawal from the market.
Trade-off between clinical benefits and harms	The committee noted that there was evidence to suggest a possible benefit of aggressive fluid therapy in terms of mortality, but this was very imprecise and of very low quality; therefore, the committee were not confident that the effect estimate was likely to be true. There was also evidence of benefit of aggressive fluid therapy

	in terms of systemic complications, and some evidence of benefit of conservative fluid therapy for the outcomes of local and systemic complications, and severe adverse events. In all cases the evidence was limited and of very low quality. Most evidence pointed to no clinically important difference between the 2 resuscitation strategies. In children, the committee noted that no critical outcomes were available, and the only outcome of serious adverse events was reported by a single study. The committee noted that the interpretation of the results was complicated by the heterogeneity in defining 'aggressive' and 'conservative' fluid therapies across studies. Similarly, there was wide variation in the timing of fluid resuscitation initiation across the body of evidence, which could have influenced the results. Overall, the committee commented that the body of evidence was limited, with small studies of low to very low quality and no clear evidence of benefit of aggressive or conservative fluid resuscitation strategies. The committee considered this evidence alongside the evidence from the type of fluid therapy review and agreed that more research needs to be done in order to recommend the rate at which IV fluid resuscitation therapy should be used. The committee noted that it would be important to define what aggressive fluid therapy is, as opposed to using the definitions available in studies. They also felt that it would be useful to identify studies that begin fluid administration within 3-6 hours of admission as there is evidence to suggest that patients admitted to hospital with acute pancreatitis are under-hydrated.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee noted the points raised above regarding the potentially greater effectiveness associated with the aggressive strategy of administration. However, it also noted that although aggressive fluid therapy was loosely defined in the studies it was associated with a slightly higher volume of fluids in the first 72 hours of administration (on average 1–2 litres). On balance, given the lack of clear evidence regarding comparative clinical effectiveness or cost effectiveness, the committee was not able to recommend any specific speed of administration strategy, but instead recommended that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee was aware of guidance on IV fluid resuscitation therapy in the NICE guideline CG174, recommending to give patients who require resuscitation crystalloid fluid over 15 mins, and to consider using human albumin solution in patients with sepsis. The rationale for this review however was that from a critical care perspective, patients with severe pancreatitis are not necessarily patients with severe sepsis. Despite some similarities in the pathophysiology of their fluid deficit and hypotension, the level of shock and hypotension caused by fluid shifts in pancreatitis is severe and caused by severe inflammation in the abdomen, but also lung damage and compromise to renal function. This makes pancreatitis a specific case with regards to fluid management. Furthermore, the guideline CG174 was published in 2013, and the committee was aware of the unclear and mixed evidence over what is the appropriate rate of fluid resuscitation administered to critically ill patients over the past few years. It was therefore considered appropriate to investigate the clinical and cost effectiveness of type and speed of fluid resuscitation therapy in the people with pancreatitis.

NUTRITION SUPPORT FOR ACUTE PANCREATITIS

13 Route of feeding in people with severe acute pancreatitis

13.1 Introduction

Most people with severe acute pancreatitis require nutritional support. Historically parenteral nutrition was routinely used, but over the last 20 years there has been a shift towards enteral feeding. Research has focused on the route of feeding used at the time of admission, where the use of the gut is thought to reduce systemic infectious complications due to a reduction in bacterial translocation. However, gastric stasis due to extrinsic duodenal compression and impairment of gastric motility due to the use of opiates can reduce tolerance of oral and gastric feeding. The presence of paralytic ileus, haemodynamic instability and the need for inotrope support often results in inadequate enteral feeding, and the need for supplemental parenteral nutrition. Nasogastric feeding tube placement is easy to achieve in all environments, whereas jejunal feeding requires access to endoscopy or radiology services, but may be more effective than nasogastric feeding in patients with gastric outlet obstruction. Parenteral nutrition carries an increased risk of infection and is more costly than enteral nutrition.

A recent NCEPOD report (2016) identified that a wide range of nutritional interventions are still used in the initial management of acute pancreatitis[80], suggesting that there is still uncertainty over which route of feeding is most effective, and patients report prolonged periods of starvation. This review attempts to address both the clinical and cost-effectiveness of different routes of providing nutrition at the time of admission in people with severe acute pancreatitis.

13.2 Review question: What is the most clinically effective and cost-effective route of feeding at time of admission to the hospital in people with severe acute pancreatitis?

For full details see review protocol in appendix C.

Table 34: PICO characteristics of review question

Population	People with severe or moderately severe acute pancreatitis admitted to hospital • Adults and young people (>16 years) • Children (≤16 years)
Interventions	The following routes of administration will be considered: • Oral feeding • Enteral feeding (with or without oral feeding), where separate data are available this will be stratified as: ○ gastric ○ jejunal or duodenal • Parenteral feeding (with or without oral feeding)
Comparisons	• Compared with each other • Early versus late
Outcomes	Critical outcomes • Mortality (dichotomous) (≤1 year) • Quality of life (continuous) (≤ 1 year) • Length of stay (in CCU or hospital) (continuous or dichotomous) (≤1 year)

	• Achieving nutrition (meeting nutritional requirements; at least 20–25 kcal/kg (dichotomous) (≤1 year) • Requiring total parenteral nutrition (dichotomous) (≤1 year) Important outcomes • Infections (dichotomous) (≤1 year) • Serious adverse events (dichotomous) (≤1 year) • Adverse events (dichotomous) (for example, tube displacements, aspirational pneumonia, ischaemic gut and central-line infections – in PN group) (≤1 year) • Weight loss (continuous or dichotomous) (≤1 year)
Key confounders	• Predicted severity on admission • Presence of organ failure • Vomiting
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled studies will be included.

13.3 Clinical evidence

13.3.1 Summary of included studies

A search was conducted for randomised trials comparing the safety and effectiveness of different routes of feeding for patients with acute pancreatitis admitted to hospital. Patients with mild pancreatitis do not normally require any nutritional support, and it is not considered best practice to provide enteral nutrition to patients with mild pancreatitis. Therefore, this group of patients were excluded from the review. As insufficient randomised evidence was found for the comparison of early versus late enteral or parenteral nutrition, observational data were sought for this part of the question.

Seventeen studies reported in 19 papers were included in the review;[2, 6, 8-10, 23, 32, 35, 37, 46, 54, 56, 59, 62, 84, 98, 117, 119, 121] these are summarised in Table 35 below. No studies in children were identified. A published Cochrane review[6] that was examined for inclusion. Owing to differences in the population inclusion criteria, additional outcomes in our protocol and a lack of risk of bias information per outcome this was modified for use in our review as follows:

- Studies in mild and moderate acute pancreatitis were excluded.
- Risk of bias was reassessed by outcome.
- Data for infection, serious adverse events and adverse events were re-extracted or reclassified according to our protocol.
- Data for mortality and length of hospital stay were taken directly from the published review.
- Study characteristics for the evidence tables were taken directly from the published review, although additional relevant details were added for the summary of studies table.
- Outcomes that did not match our protocol were removed and additional outcomes meeting our protocol were extracted.
- Studies for additional comparisons in our protocol were added.

Evidence from these studies is summarised in the clinical evidence summaries below (Table 37–Table 41) and data not suitable for meta-analysis are presented in Table 36. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

The aim of all of the included studies was to determine the safest and most effective method of nutritional support in people with acute pancreatitis. The available comparisons were enteral (jejunal or duodenal) versus parenteral, enteral (gastric) versus parenteral, gastric versus jejunal or duodenal, early versus conventional (delayed) oral feeding, early versus on-demand enteral feeding, and early versus delayed enteral nutrition.

13.3.2 Heterogeneity

For the comparison of enteral (jejunal or duodenal) versus parenteral nutrition, there was substantial heterogeneity between the studies when they were meta-analysed for the outcomes of serious adverse events and adverse events. Pre-specified subgroup analyses did not explain such heterogeneity. A random effects meta-analysis was therefore applied to these outcomes, and the evidence was downgraded for inconsistency in GRADE.

Table 35: Summary of studies included in the review

Study		Intervention and comparison	Population	Outcomes	Comments
Enteral (jejunal or duodenal) versus parenteral					
From Al-Omran, 2010[6]	Abou-Assi 2002[2]	Intervention: Jejunal tubes were placed by fluoroscopy or endoscopy. Tube feeding was commenced at 20 ml/hour and increased progressively to goal rates over 48h. (n=28) Control group: Total parenteral nutrition (TPN) was delivered via central vein catheters in patients in the CCUs and by peripheral catheter in floor patients, electrolytes were first corrected before full nutritional infusions were given. (n=27) Both groups: initially nil by mouth (IV fluids and electrolytes plus analgesics), then started nutritional support **after 48 hours**; weaning from nutritional support to an oral diet attempted when abdominal pain and distension had settled and enzyme levels had consistently decreased towards normal levels over 3 days. Goal nutrition rates: 1.5–2 g protein/kg/day and 25–30 kcal/kg/day.	All patients admitted with acute pancreatitis requiring nutritional support (did not improve after 48-hour bowel rest). (n=53) **Severity:** Patients who failed to show improvement were graded by Ransons criteria and approximately 50% had RC >3. Intervention group: mean Ranson's score: 3.1 (0.5), Control group: mean Ranson's score: 2.5 (0.4). Mean (SD) age: Enteral: 48 (3) years Parenteral: 50 (3) years USA	• Mortality (time point unclear) • Length of hospital stay (with subgroup analysis for those with Ranson's criteria >3) (time point unclear) • Infections (time point unclear) • Serious adverse events (time point unclear) • Adverse events (time point unclear)	Not all severe by Ranson's criteria but 15% in CCU Unclear where the jejunal tubes were placed to

Study		Intervention and comparison	Population	Outcomes	Comments
	Casas 2007[23]	Intervention: Total enteral nutrition (TEN) through a single-lumen, 114-cm long naso-jejunal 10 F feeding tube whose tip was placed, under fluoroscopic screening, close to Treitz's ligament. The initial infusion rate was 25 ml/hour with increases of 25 ml/4 hours until requirements were reached. (n=11) Control: 24-hour continuous infusion of TPN through a central venous catheter (subclavian/ jugular). Venous infusion was started at a rate of 40 ml/hour and increased 20 ml/hour every 4 hours until the required needs were met. (n=11) Both groups: started nutritional support **within 72 hour,** prior to this they had intensive control to maintain water and electrolyte balance; weaning to an oral diet not stated. Goal nutrition rates: 1.5–2 g protein/kg/day and 30–35 kcal/kg/day	Adults with severe acute pancreatitis (n=22) Severity: diagnosis made within 48 hours when 2 or more of the following criteria were evident: • Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥8, • C-reactive protein (CRP) level in excess of 150 mg/litre • Balthazar D or E grade in the abdominal CT scan. Mean (SD) age: Enteral: 61.2 (16.6) years Parenteral: 55.6 (15.6) years Spain	• Mortality (during admission) • Length of hospital stay (during admission) • Achieving nutrition (5 days) • Infections (during admission) • Serious adverse events (during admission) • Adverse events (during admission)	Tube placement likely to be duodenal, but this is unclear.

Study		Intervention and comparison	Population	Outcomes	Comments
	Gupta 2003[46]	Intervention: TEN delivered by nasojejunal dual lumen tubes. The weighted nasojejunal tube was passed into the stomach, the patient was encouraged to sit up, or roll onto the right side, and subsequently a radiograph was taken to confirm the placement of the tube. Enteral support commenced **within 6 hours of diagnosis**. (n=8) Control: TPN delivered by a central intravenous line placed by a standard sterile technique. Parenteral support commenced **as soon as possible after diagnosis (maximum delay would be 45 hours if diagnosed on a Saturday pm)**. (n=9) Both groups: weaning to an oral diet not stated but time to full oral diet ranged from 0 to 9 days. Goal caloric intake 36 kcal/kg/day based on admission weight.	Age >15 years (range: 38–89 years) admitted with severe acute pancreatitis. (n=22) Severity: presence of an acute physiology, APACHE II ≥6. Mean (range) age: Enteral: 65 (56-89) years Parenteral: 57 (38-86) years UK	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Infections (time point unclear) • Serious adverse events (time point unclear) • Adverse events (time point unclear)	Precise tube placement not specified, but likely to be duodenal.

Study		Intervention and comparison	Population	Outcomes	Comments
	Kalfarentzos 1997[56]	Intervention: enteral nutrition through a nasoenteric feeding tube, placed fluoroscopically distal to the ligament of Treitz within the **first 48 hours** after admission. Reabilan HM caloric density 1.33 kcal/ml (58 g protein; 158 g carbohydrate; 52 g fat per litre (61% long-chain triglycerides, 39% medium chain triglycerides)); non-protein kcal per g nitrogen 152:1. Full strength formula started at 25 ml/hour and increased by 25 ml/hour every 4 hours until target reached. (n=18) Control: Patients received parenteral nutrition containing; crystalline L-amino acid, carbohydrates in the form of dextrose, fat emulsion (lipofudin long- or medium-chain triglycerides), vitamins, and minerals through a subclavian central venous line. Unclear when parenteral nutrition was initiated. Infusion initially 40 ml/hour increased by 20 ml/hour every 4 hours until target reached. (n=20) Target in both groups: 1.5–2 g protein/kg/day and 30–35 kcal/kg/day Both groups: during the acute phase treatment was adequate fluid replacement, with haemodynamic monitoring and assistance of respiratory or renal function when needed. Prophylactic imipenem was given. Weaning to an oral diet not stated	Severe acute pancreatitis in CCU (n=40) Severity: • 3 or more criteria according to the Imrie classification, • or APACHEII score of 8 or more, C-reactive protein concentration greater than 120 mg/litre within 48 hours of admission, and grade D or E by computed tomography (CT) according to the Balthazar criteria. Mean (SD) age: Enteral: 63 (10.7) years Parenteral: 67.2 (8.9) years Greece	• Mortality (during admission) • Length of hospital stay (during admission) • Infections (during admission) • Adverse events (during admission)	Nasojeunal tube placement Not all included participants were assessed for severity (8% had severity data missing) but all in CCU

Study		Intervention and comparison	Population	Outcomes	Comments
	Louie 2005[62]	Intervention: Nasojejunal (NJ) feeding tubes were placed distal to ligament of Treitz via gastroscopy and confirmed radiographically. Peptamen, a semi-elemental product with low fat content, was infused at 25 ml/hour and increased by 10 ml/hour every 6 hours, until the target rate was achieved. (n=10) Control: In the PN group, long-term vascular catheters were placed percutaneously and confirmed radiographically. PN was initially infused with a 10% dextrose solution and Intralipid at half of the calculated energy requirements; then increased over 2 days to achieve 100% of the target energy rate. (n=18) Both groups: daily nutritional support was provided as 105 kJ/kg, and 1.5 g protein/kg and started **within 24 hours** of enrolment. Weaning to an oral diet gradually instituted as the clinical condition permitted.	Adults with severe acute pancreatitis (n=28) Severity: A Ransons score (calculated by counting 1 point for each of the criteria met over the 48- hour period) of 3 or greater, and inability to tolerate oral fluids after a maximum time from admission of 96 hours. Mean (SD) age: Enteral: 65.3 (18.3) years Parenteral: 59 (15.3) years Canada	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Achieving nutrition (time point unclear) • Infections (time point unclear) • Serious adverse events (time point unclear) • Adverse events (time point unclear)	Nasojeunal tube placement

Study		Intervention and comparison	Population	Outcomes	Comments
	Petrov 2006[84]	Intervention: Enteral feeding was through a radiologically placed nasojejunal feeding tube, distal to the ligament of Treitz. The position of a tube was confirmed by X-ray. The standard enteral feed used was a semi-elemental nutrition (Peptamen), which is low in fat and higher in predigested protein than regular tube feeding formulas. Enteral feeding was commenced at a rate of 25 ml/hour and increased by 10 ml/hour every 6 hours, until the desired caloric intake was reached. (n=35) Control: TPN was delivered through a central venous catheter, it was initially infused with a 10% dextrose solution, 10% amino acid solution and 10% fat emulsion at half of the calculated energy requirements; then increased over 48 hours to achieve 100% of the target energy rate. (n=34) Both groups: Nutritional support, supplying daily 30 kcal/kg and 1.5 g/kg of protein, based on ideal body weight, was commenced **within 24 hours** of enrolment, patients received full supportive therapy as required; all patients received analgesia, antibiotic prophylaxis (ofloxacin plus metronidazole) and intravenous fluids. Weaning to an oral diet not stated.	Severe acute pancreatitis within 72 hours of the onset of symptoms. (n=70) Severity: APACHEII score of 8 or more, and/or a C-reactive protein (CRP) level in excess of 150 mg/litre. Median (IQR) age: Enteral: 51 (42-67) years Parenteral: 52 (41-70) years Russia	• Mortality (time point unclear) • Infections (during admission) • Serious adverse events (time point unclear) • Adverse events (time point unclear)	Nasojeunal tube placement Note that this is a fast rate of feeding for severe acute pancreatitis patients and the use of ionotropes was not mentioned.

Study	Intervention and comparison	Population	Outcomes	Comments
Doley 2009[32]	Intervention: Enteral nutrition delivered distal to the ligament of Treitz using fluoroscopic control. Jejunal feeding was started at low flow rates - an initial rate of 20–30 ml/hour until achievement of the full regime of EN. Feed composition not stated. (n=25) Control: TPN using a central venous catheter inserted through the subclavian or internal jugular vein. The position was subsequently checked by chest x-ray. Parenteral nutrition formula was administered. (n=25) Both groups: managed routinely by GI decompression, prophylactic antibiotics, IV fluids and organ system support. Nutritional support was **initiated within 72 hours of admission** and continued for a minimum of 14 days. Weaning to an oral diet not stated. The targeted requirements were 2,500–2,700 kcal/day, and 120–130 g/day of protein.	Admitted with severe acute pancreatitis (n=50) Severity: defined using the Atlanta criteria Mean (SD) age: Enteral: 38.4 (13.8) years Parenteral: 41.1 (11.3) years. India	• Mortality (14 days) • Length of hospital stay (14 days) • Length of CCU stay (14 days) • Infections (14 days) • Adverse events (14 days)	Nasojeunal tube placement Quasi-randomised

Study	Intervention and comparison	Population	Outcomes	Comments
Wu 2010[119]	Intervention: Total enteral nutrition. An 8F or 12F nasojejunal-gastric feeding tube was placed by endoscopy, which confirmed the feeding port position to be distal to the ligament of Treitz. Enteral feeding with an elemental formula TEN, peptide enteral nutritional formulae was given at 20 ml/hour for 20 hours with feeding rates that provided 1.5 g of protein per kilogram per day and 105 to 126 kJ of energy intake per kilogram per day. The feeding was gradually increased in volume according to patient's condition. (n=54) Control: Total parenteral nutrition solution, containing nitrogen, glucose, calcium, magnesium, potassium, trace elements, and multiple vitamins in a volume of 2000 ml, was continuously infused within 24 hours, along with 250 ml of 20% introlipid, with infusion rates that provided 1.2 g of protein per kilogram per day and 105 to 126 kJ of energy intake per kilogram per day. Total parenteral nutrition was infused by single lumen polyurethane catheters through the anterior chests. (n=53) Both groups: nutritional support attempted **within 7 days** of hospitalisation; weaning to oral diet not stated.	Severe acute pancreatitis in CCU with pancreatic necrosis and sufficient prophylactic antibiotics (n=107) Severity: determined by APACHE II criteria Mean APACHE II score = 15 Mean (SD) age: Parenteral: 54 (11.2); Enteral: 52 (12.1) China	• Mortality (time point unclear) • Infections(time point unclear) • Serious adverse events(time point unclear) • Adverse events (time point unclear)	Nasojeunal tube placement All in CCU
Enteral (gastric) versus parenteral				

Study	Intervention and comparison	Population	Outcomes	Comments
Eckerwall 2006[37]	Intervention: Early nasogastric enteral nutrition infused at an initial rate of 25 ml/hour and gradually increased up to 100 ml/hour as tolerated and as needed. Control: TPN infused via central or peripheral venous catheter Both groups: energy target of 25 kcal/kg/day using standard formulas; aimed to be isocaloric and started **within 24 hours from admission**. Oral feeding was reintroduced when amylase and CRP levels had decreased and abdominal pain resolved.	Severe acute pancreatitis (n=50) Severity: • APACHE II score ≥8 or • CRP ≥150 mg/litre or • peripancreatic liquid shown on CT. Median (IQR) age: Parenteral: 68 (60-80) years Enteral: 71 (58-80) years Sweden	• Mortality (3 months) • Length of hospital stay (3 months) • Achieving nutrition (10 days) • Infections (3 months) • Serious adverse events (3 months) • Adverse events (3 months)	Unconventional feed type Despite predicted severity, 54% of the randomised patients were **'mild'** according to the Atlanta classification system
Enteral (gastric) versus enteral (jejunal or duodenal)				
Eatock 2005[35]	Intervention: Nasogastric tubes placed on the ward with position checked by aspiration and pH check or chest X-ray. (n=26) Control: Nasojejunal tubes placed under endoscopic guidance into the proximal jejunum. (n=24) Both groups: Feeds were commenced at a full strength and rate of 30ml/h increasing to 100 ml/h over 24-48 h. The caloric target was 2000kcal/day. Low fat semi-elemental feed was used (Pepti 2000 LF), which contains 1 kcal/ml and 40g protein/l (5.9g nitrogen/l). Carbohydrate provides 75% of energy, protein 16% and fat 9%. Time to starting nutritional support and weaning to oral diet not stated	Adults with severe acute pancreatitis (n=50) Severity: • Glasgow score >3 or • APACHE II score ≥6 or • CRP >150 mg/litre Median (IQR) age: Nasogastric: 63 (47-74) years Nasojejunal: 58 (48-64) years UK	• Mortality (during admission) • Length of hospital stay (during admission) • Achieving nutrition (within 48 and 60 hours) • Requiring total parenteral nutrition (during admission) • Adverse events (during admission)	Nasojeunal tube placement

Study	Intervention and comparison	Population	Outcomes	Comments
Kumar 2006[59]	Intervention: Nasogastric tubes placed under endoscopic guidance by the nasal route into the stomach. (n=14) Control: Nasojejunal tubes with endoscopic placement into the third part of the duodenum. (n=16) Both groups: 'Re-feeding' (nutritional support) started **48 hours after admission** and used a semi-elemental formula given at a slow infusion rate of 1-1.5 ml/min through an enteral tube. Oral feeding was attempted after 7 days of enteral feeding. Standard care of antibiotics, IV fluids, electrolytes and organ system support given as indicated.	Severe acute pancreatitis (n=31) Severity: defined according to Atlanta criteria Mean (SD) age: Nasojejunal: 33.57 (12.53) years Nasogastric: 43.25 (12.76) years India	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Infections (7 days) • Serious adverse events (7 days) • Adverse events (7 days)	Nasogastric versus nasoduodenal

Study	Intervention and comparison	Population	Outcomes	Comments
Singh 2012[98]	Intervention: Nasogastric tube placed in the ward with the position being confirmed at the bedside by air test and aspirating gastric contents. (n=39) Control: Nasojejunal tube placed under endoscopic guidance. A commercially available single-port tube, 200 cm long was placed in the jejunum beyond the ligament of Trietz and confirmed radiologically. (n=39) Both groups: 'Re-feeding' (nutritional support) attempted **48 hours after admission**. Novasource, a commercially available semielemental enteral formula, was used to reach the nutrient goal (25 kcal/kg per day) in 3 to 4 days. The composition of feed was similar in both groups and was aimed to be of equal energy value in both groups. If the elemental feed was tolerated well, with no postfeeding pain, distension, and vomiting for 7 days, it was switched to a polymeric feed and then from oral soft to solid hospital diet reintroduced gradually. All patients were treated in an critical care unit initially with nil by mouth, analgesics, aggressive fluid resuscitation, and supportive treatment. Antibiotics were prescribed if patients had infected pancreatic necrosis or if there was documented infection at the extra-pancreatic sites.	Severe acute pancreatitis admitted within 7 days of onset of pain (n=78) Severity: at least 1 of the following criteria: • Presence of 1 or more organ failure as defined by the Atlanta classification. • An APACHE II score of 8 or higher. • CT severity index greater than 7. Mean (SD) age: Nasogastric: 39.1 (16.70) years Nasojejunal: 39.7 (12.3) years India	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Achieving nutrition (within 3 days) • Infections (time point unclear) • Adverse events (time point unclear)	Nasojeunal tube placement All in CCU initially
Early versus conventional (delayed) oral 're-feeding'				

Study	Intervention and comparison	Population	Outcomes	Comments
Zhao 2015[121]	Intervention: Early oral feeding based on hunger. (n=70) Control: Conventional (delayed) oral feeding (recommenced oral feeding once their abdominal pain resolved and biochemical markers had normalised). (n=76) Both groups: All patients received limited PN if they were in malnutrition and EN was contraindicated or not feasible, prophylactic antibiotics if they were at risk for infection, glucose control if they were at risk for hyperglycaemia, treatment to maintain the homeostasis, appropriate fluid resuscitation therapy, and Traditional Chinese Medicine formulation. Adequate protein delivery (1.2–2.0 g/kg daily) and calories (15–30 kcal/kg daily) were given to patients according to their individual condition. The volume of PN was gradually reduced after oral feeding (usually 12–24 h after the first oral intake). The diet was gradually progressed from clear liquid to a low-fat solid diet that comprised foods such as porridge and vegetables in the early stage, then steamed bread and rice, and finally an ordinary diet.	Adults with severe acute pancreatitis (n=146) Severity: according to the 2012 revision of the Atlanta classification Median (range) age: Early group: 51 (24-72) years Conventional group: 48 (21-74) years China	• Length of hospital stay (time point unclear) • Requiring parenteral nutrition (time point unclear) • Adverse events (time point unclear)	Moderate and severe acute pancreatitis
Early versus on-demand enteral feeding				

Study	Intervention and comparison	Population	Outcomes	Comments
Bakker 2011[10] and 2014[9]	Intervention: Nasoenteric tube feeding **within 24 hours**. Feeding tubes were placed endoscopically or radiologically, according to local practice to ensure the tip was beyond Treitz' ligament. Nasoenteric feeding was administered as Nutrison Protein Plus (Nutricia). After tube placement, feeding was started at 20 ml per hour during the first 24 hours and was gradually increased. (n=104) Control: oral diet **72 hours after presentation**, with tube feeding if oral diet not tolerated. Did not receive nutrition by any means other than that provided by standard intravenous fluids during the first 72 hours unless requested. If an oral diet was not tolerated, it was offered again after 24 hours. If an oral diet still was not tolerated after 96 hours from the time of presentation, nasoenteric feeding was started after the placement of a nasojejunal tube, and the same procedure was followed as in the early group. (n=104) Both groups: full nutrition was defined as an energy target of 25 kcal/kg/day for patients in the critical care unit and 30 kcal/kg/day for patients in the ward	Severe acute pancreatitis (n=208) Severity: • APACHE II ≥8 or • Imrie or modified Glasgow score ≥3 or • Serum CRP >150 mg/litre Mean (SD) age: 65 (15) years The Netherlands	• Mortality (6 months) • Requiring parenteral nutrition (6 months) • Infections (6 months) • Serious adverse events (6 months) • Adverse events (6 months)	Nasojeunal tube placement Early versus on-demand Unconventional feed type for this group of patients
Early versus delayed enteral nutrition (observational)				

Study	Intervention and comparison	Population	Outcomes	Comments
Bakker 2014[8] [individual patient data meta-analysis based on data from the early enteral nutrition group of 8 randomised trials: 5 included above[3, 23, 46, 56, 62, 85] and 3 others [81, 85, 86]]	Intervention: Early (within 24 h of admission) enteral nutrition. (n=47) Control: Late (after 24 h from admission) enteral nutrition. (n=48) Both groups: the feed types included elemental, semi-elemental, and polymeric amongst the included trials	Acute pancreatitis (n=165) Median (IQR) age: Early: 53 (42-66) years Late: 55 (45-70) years Greece, UK, USA, Hungary, Canada, Spain and New Zealand	• Mortality (time point unclear) • Infections (time point unclear) • Serious adverse events (time point unclear)	Nasojejunal tube placement in 7 trials, nasogastric in 1 Data used for this report were from only those patients with predicted severe pancreatitis (n=95) Adjusted in multivariable analysis for: age, gender, etiology, presence of necrosis, and predicted severity based on APACHE-II, Imrie or modified Glasgow score, Ranson score, or CRP

Study		Intervention and comparison	Population	Outcomes	Comments
From Bakker 2014[8]	Olah 2002[81]	Intervention: Early enteral nutrition (admitted within 24-72 h of onset of symptoms and treated within 24 hours of admission). A nasojejunal feeding tube was inserted and position was confirmed by x ray to be in the second jejunal loop. An elemental feed was used; 1 cal/ml, protein 22.5 g/500 ml. The dose was increased gradually and the maximum daily intake was reached within 2-3 days with a goal of 30 kcal.kg. (n=41) Control: Conventional parenteral nutrition (not included in analysis). Both groups: adjuvant therapy with spasmolytic drugs and H_2-blockers.	Acute pancreatitis (n=89) Hungary	• N/A – individual patient data sought by review author	Not all of the included patients were analysed in the predicted severe pancreatitis cohort in the systematic review
	Petrov 2013[85]	Intervention: Early nasogastric tube feeding (within 24 h of admission). A semielemental feed (Peptisorb) was used and enteral nutrition was started at a rate of 25 ml/h and increased stepwise until 100 ml/h was reached over 24-48 h. It was continued until the treating teams decided to introduce oral feeding. (n=29) Control: Nil per os (not included in analysis) Both groups: Patients were managed by standard medical treatment in AP: intravenous fluid and analgesia	Adults with acute pancreatitis, with symptoms for <96 hours at enrolment (n=78) New Zealand	• N/A – individual patient data sought by review author	Not all of the included patients were analysed in the predicted severe pancreatitis cohort in the systematic review

Study		Intervention and comparison	Population	Outcomes	Comments
	Powell 2000[86]	Intervention: Enteral feeding. Nasojejunal feeding tubes were placed under fluoroscopic screening such that the tip of the tube was distal to the ligament of Treitz. Commenced at a rate of 25 ml/h, increasing daily by 25 ml/h until the desired caloric intake was reached. An isotonic polymeric formula containing fibre was used; 500 ml contains 4 g protein, 3.5 g fat, 13.1 g carbohydrate and 1.4 g dietary fibre, providing 2105 kJ. (n=28) Control: conventional therapy (not included in analysis)	Severe acute pancreatitis within 72 hours of onset (n=27) Severity: Glasgow score of 3 or more; and/or APACHE II score ≥7 UK	• N/A – individual patient data sought by review author	

Study	Intervention and comparison	Population	Outcomes	Comments
Wereszczynska-Siemiatkowska 2013 [117]	Intervention: Early (within 48 h of admission) enteral feeding. (n=97) Control: Late (after 48 h from admission). (n=100) Both groups: Patients were managed by standard medical treatment in AP: intravenous fluid and electrolytes, analgesia, prophylactic antibiotics, and other supportive therapies for organ failure, as indicated. Emergency endoscopic retrograde cholangiopancreatography was performed within 24 to 72 hours on patients with suspected choledocholithiasis.	Severe AP within the first 48 hours of admission to hospital and treatment with total enteral feeding (n=197) Severity, 1 or more from: • SIRS; • Acute Physiology and Chronic Health Evaluation (APACHE) II score, 8 or greater; • Bedside Index of Severity in AP (BISAP), 3 or greater; • Panc 3 score; • Ranson score, 3 or greater; • Balthazar score C-E; • Organ failure assessed using Sequential Organ Failure Assessment (SOFA) score Median (IQR) age: Early: 49 (39-56) years Delayed: 50 (41-62.5) years Poland	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Infections (time point unclear) • Serious adverse events (time point unclear) • Adverse events (time point unclear)	Most outcomes did not adjust for any confounders Nasojejunal tube placement

Study	Intervention and comparison	Population	Outcomes	Comments
Jin 2017 [54]	Intervention: Early (within 3 days of hospital admission) enteral feeding. (n=35) Control: Late (starting after 3 days from hospital admission) enteral. (n=52) Both groups: nasojejunal feeding tube placed under X ray guidance, with peptide formulation. Enteral nutrition was given continuously using an infusion pump at 20 ml/h in the first 24 h, 40 ml/h from 24 to 48 h, 60-80 ml/h between 48 and 72 h to reach 25 kcal/kg/d based on ideal weight at 72 h. PN was initiated if full nutrition could not be achieved using the enteral route after 3 attempts Rehydration, correction of electrolyte disorders and organ function support as required	Moderately severe or severe acute pancreatitis based on the Revised Atlanta classification 42% severe; 58% moderately severe. 100% had abdominal pain (n=104) Mean (SD) age: Early: 43.9 (15.9) years Late: 45.2 (13.5) years China	• Mortality (time point unclear) • Length of hospital stay (time point unclear) • Infections (time point unclear) • Adverse events (time point unclear)	Propensity-matched cohort: matched for age, sex, etiology, disease severity, abdominal pain, VAS of abdominal pain, abdominal distension, AGI grade and serum albumin level at admission Nasojejunal tube placement

Table 36: Data not suitable for meta-analysis

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Eatock 2005[35]	Gastric versus jejunal or duodenal	Length of hospital stay	Median (IQR): 16 (10–22)	27	Median (IQR) 15 (10–42) days	22	High
Singh 2012[98]	Gastric versus jejunal or duodenal	Length of hospital stay	Median (range): 17 (1–73)	39	Median (range): 18 (4–54) p=0.4383	39	Low
Eckerwall 2006[37]	Gastric versus parenteral	Length of hospital stay	Median (IQR): 9 (7–14)	23	Median (IQR): 7 (6–14)	25	High
Doley 2009[32]	Jejunal versus parenteral	Length of hospital stay	Median (range): 42 (15–108)	25	Median (range): TPN - 36 (20–77) days	16	High
Doley 2009[32]	Jejunal versus parenteral	Length of CCU stay	Median (range): EN - 10 (0–44)	25	Median (range): TPN - 15 (0–60) days	16	High

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Gupta 2003	Jejunal or duodenal versus parenteral	Length of hospital stay	Median (range): 7 (4–14) days	8	Median (range): 10 (7–26) days	9	Very high
Wereszczynska-Siemiatkowska 2013 [117]	Early versus delayed enteral feeding	Length of hospital stay	Median (IQR): 18.0 (14.0-26.0) days	97	Median (IQR): 18.5 (14.0-30.0) days	100	High

Table 37: Clinical evidence summary: Enteral (jejunal or duodenal) versus parenteral nutrition for acute pancreatitis

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral	Risk difference enteral (95% CI)
Mortality	375 (8 studies) during hospitalisation	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 0.36 (0.22 to 0.59)	174 per 1000	111 fewer per 1000 (from 71 fewer to 136 fewer)
Length of hospital stay – Overall	113 (3 studies) hospitalisation	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control groups ranged from 18.4 to 39 days	The mean length of hospital stay in the intervention groups was 2.46 lower (8.45 lower to 3.53 higher)
Length of hospital stay - Severe (Ranson's criteria >3)	26 (1 study) hospitalisation	⨁⨁⨁⨀ MODERATE[a] due to risk of bias		The mean length of hospital stay in the control group ranged was 20.1 days	The mean length of hospital stay - severe (Ranson's criteria >3) in the intervention groups was 7.3 lower (9.24 to 5.36 lower)
Achieving nutrition - kcal/kg/day (day 5)	22 (1 study) hospitalisation	⨁⨁⨀⨀ LOW[b] due to		The mean kcal/kg/day in the control group was	The mean kcal/kg/day (day 5) in the intervention groups was 0.71 higher

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral	Risk difference enteral (95% CI)
		imprecision		20.09	(0.76 lower to 2.18 higher)
Achieving nutrition - Days to goal	28 (1 study) hospitalisation	⨁⨁⨁⨀ MODERATE[b] due to imprecision		The mean days to goal in the control group was 1.9 days	The mean days to goal in the intervention groups was 1.4 higher (0.56 lower to 3.36 higher)
Infections - Pancreatic (for example, infected necrosis, abscess)	264 (5 studies) hospitalisation	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 0.36 (0.24 to 0.54)	222 per 1000	142 fewer per 1000 (from 102 fewer to 169 fewer)
Infections - Extra-pancreatic (for example, UTI, pneumonia)	146 (4 studies) hospitalisation	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.73 (0.34 to 1.57)	144 per 1000	39 fewer per 1000 (from 95 fewer to 82 more)
Infections - Systemic (for example, central-line infection, blood culture)	227 (6 studies) hospitalisation	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 0.15 (0.06 to 0.41)	199 per 1000	169 fewer per 1000 (from 117 fewer to 187 fewer)
Infections – not specified	50 (1 study) hospitalisation	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.69 to 1.65)	600 per 1000	42 more per 1000 (from 186 fewer to 390 more)
Serious adverse events	296 (6 studies) hospitalisation	⨁⨀⨀⨀ VERY LOW[b,c] due to inconsistency, imprecision	RR 0.51 (0.29 to 0.92)	694 per 1000	340 fewer per 1000 (from 56 fewer to 493 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral	Risk difference enteral (95% CI)
Adverse events - Operative intervention	384 (8 studies) hospitalisation	⨁⨁⊖⊖ LOW[a,c] due to risk of bias, inconsistency	RR 0.5 (0.27 to 0.92)	411 per 1000	205 fewer per 1000 (from 33 fewer to 300 fewer)
Adverse events - Non-infective pancreatic complications (for example, necrosis, pseudocyst, fistulae)	298 (6 studies) hospitalisation	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.09 (0.53 to 2.24)	214 per 1000	19 more per 1000 (from 101 fewer to 265 more)
Adverse events - Feeding complications (for example, tube displacement, hyperglycaemia, diabetes)	205 (5 studies) hospitalisation	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.03 (0.27 to 3.85)	147 per 1000	4 more per 1000 (from 107 fewer to 419 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Downgraded by 1 or 2 increments because of heterogeneity, I^2>50%, p<0.04, unexplained by subgroup analysis.

Table 38: Clinical evidence summary: Enteral (gastric) versus parenteral nutrition for acute pancreatitis

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral nutrition	Risk difference with enteral (gastric) (95% CI)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral nutrition	Risk difference with enteral (gastric) (95% CI)
Mortality	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	Peto OR 8.06 (0.16 to 407.6)	0 per 1000	40 more per 1000 (from 70 fewer to 150 more)
Achieving nutrition (25 kcal/kg/day)	50 (1 study) 10 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	RR 1.02 (0.68 to 1.52)	654 per 1000	13 more per 1000 (from 209 fewer to 340 more)
Infections - Pancreatic (for example, infected necrosis, abscess)	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	Peto OR 8.06 (0.16 to 407.6)	0 per 1000	40 more per 1000 (from 70 fewer to 150 more)
Infections - Systemic (for example, central-line infection, blood culture)	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	Peto OR 8.43 (0.51 to 139.29)	0 per 1000	90 more per 1000 (from 50 fewer to 220 more)
Serious adverse events - Multiple or single organ failure	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	RR 1.09 (0.17 to 7.1)	80 per 1000	7 more per 1000 (from 66 fewer to 488 more)
Adverse events - General (for example, pleural effusion)	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	RR 1.86 (0.89 to 3.91)	280 per 1000	241 more per 1000 (from 31 fewer to 815 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parenteral nutrition	Risk difference with enteral (gastric) (95% CI)
Adverse events - Non-infective pancreatic complications (for example, necrosis, pseudocyst, fistulae)	48 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	RR 2.45 (0.87 to 6.87)	160 per 1000	232 more per 1000 (from 21 fewer to 939 more)
Adverse events - Surgical intervention	50 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, indirectness	RR 1.08 (0.07 to 16.38)	39 per 1000	3 more per 1000 (from 36 fewer to 592 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment because the majority of evidence was from an indirect population.

(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 39: Clinical evidence summary: Gastric versus jejunal or duodenal nutrition for acute pancreatitis

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Jejunal or duodenal	Risk difference with gastric (95% CI)
Mortality	157 (3 studies) unclear	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.69 (0.37 to 1.29)	286 per 1000	89 fewer per 1000 (from 180 fewer to 83 more)
Length of hospital stay	30 (1 study)	⨁⨁⨁⊖ MODERATE[a] due to		The mean length of hospital stay in the control group was	The mean length of hospital stay in the intervention group was 5.87 days lower

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Jejunal or duodenal	Risk difference with gastric (95% CI)
	unclear	imprecision		29.93 days	(20.98 lower to 9.24 higher)
Achieving nutrition - Tolerating administration of at least 75% of target within 48 h	49 (1 study) 48 h	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.91 (0.65 to 1.27)	773 per 1000	70 fewer per 1000 (from 270 fewer to 209 more)
Achieving nutrition - Tolerating administration of at least 75% of target within 60 h	49 (1 study) 60 h	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.74 to 1.36)	773 per 1000	8 more per 1000 (from 201 fewer to 278 more)
Achieving nutrition - Achieving goal nutrient requirement within 3 days	78 (1 study) 3 days	⨁⨁⨁⨁ HIGH	RR 1 (0.95 to 1.05)	1000 per 1000	0 fewer per 1000 (from 50 fewer to 50 more)
Requiring total parenteral nutrition	49 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.11 (0 to 5.55)	46 per 1000	40 fewer per 1000 (from 45 fewer to 164 more)
Infections - Pancreatic (for example, infected necrosis, abscess)	108 (2 studies) unclear	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.59 (0.21 to 1.67)	171 per 1000	70 fewer per 1000 (from 135 fewer to 115 more)
Infections – Extra-pancreatic	108 (2 studies) unclear	⨁⨁⨁⊖ MODERATE[a] due to imprecision	RR 0.36 (0.12 to 1.05)	164 per 1000	105 fewer per 1000 (from 144 fewer to 8 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Jejunal or duodenal	Risk difference with gastric (95% CI)
Infections - Systemic (for example, central-line infection, blood culture)	108 (2 studies) unclear	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.97 (0.46 to 2.05)	187 per 1000	6 fewer per 1000 (from 101 fewer to 196 more)
Serious complications requiring tube removal	30 (1 study) unclear	⨁⨁⨁⨁ HIGH	Not estimable[c]	No events	No events
Adverse events - Tube displacement Eatock 2005, Kumar 2006	79 (2 studies) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.84 (0.13 to 5.68)	58 per 1000	9 fewer per 1000 (from 50 fewer to 271 more)
Adverse events - Surgical intervention	108 (2 studies) unclear	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 1.19 (0.34 to 4.17)	97 per 1000	18 more per 1000 (from 64 fewer to 307 more)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Could not be calculated as there were no events in the intervention or comparison group

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(c) Could not be calculated as there were no events in the intervention or comparison group.

Table 40: Clinical evidence summary: Early oral 're-feeding' versus conventional (delayed) oral 're-feeding' for acute pancreatitis

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conventional oral 're-feeding'	Risk difference with early oral 're-feeding' (95% CI)
Length of hospital stay	138 (1 study) unclear	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control group was 15.7 days	The mean length of hospital stay in the intervention group was 2 days lower (3.94 to 0.06 lower)
Requiring parenteral nutrition	138 (1 study) unclear	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 1 (0.94 to 1.06)	972 per 1000	0 fewer per 1000 (from 58 fewer to 58 more)
Adverse events (abdominal pain relapse)	138 (1 study) unclear	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.74 (0.3 to 1.84)	141 per 1000	37 fewer per 1000 (from 99 fewer to 118 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 41: Clinical evidence summary: Early enteral nutrition versus on-demand enteral nutrition for acute pancreatitis

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with on-demand enteral feeding	Risk difference with early enteral nutrition (95% CI)
Mortality	205 (1 study) 6 months	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.62 (0.65 to 4.01)	67 per 1000	42 more per 1000 (from 24 fewer to 203 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with on-demand enteral feeding	Risk difference with early enteral nutrition (95% CI)
Requiring parenteral nutrition	204 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.51 (0.18 to 1.44)	97 per 1000	48 fewer per 1000 (from 80 fewer to 43 more)
Infection - Pancreatic (for example, infected necrosis, abscess)	205 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.62 (0.28 to 1.35)	144 per 1000	55 fewer per 1000 (from 104 fewer to 50 more)
Infection - Extra-pancreatic (for example, UTI, pneumonia)	205 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.95 (0.46 to 1.98)	125 per 1000	6 fewer per 1000 (from 67 fewer to 123 more)
Infection - Systemic (for example, central-line infection, blood culture)	205 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.97 (0.53 to 1.78)	173 per 1000	5 fewer per 1000 (from 81 fewer to 135 more)
Serious adverse events - Necrosis	208 (1 study) 6 months	⨁⨁⨁⨁ HIGH	RR 0.98 (0.8 to 1.22)	625 per 1000	12 fewer per 1000 (from 125 fewer to 138 more)
Serious adverse events - Multiple or single organ failure	140 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.97 (0.7 to 1.35)	507 per 1000	15 fewer per 1000 (from 152 fewer to 177 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with on-demand enteral feeding	Risk difference with early enteral nutrition (95% CI)
Adverse events - Tube displacement	131 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.88 (0.55 to 1.4)	438 per 1000	53 fewer per 1000 (from 197 fewer to 175 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 42: Clinical evidence summary: Early versus delayed enteral nutrition for acute pancreatitis (Observational data)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with delayed enteral feeding	Risk difference with early enteral nutrition (95% CI)
Mortality - adjusted Early = within 24 h of admission	95 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.46 (0.11 to 1.92)	146 per 1000	73 fewer per 1000 (from 127 fewer to 101 more)
Mortality Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	Peto OR 0.19 (0 to 10.22)	19 per 1000	15 fewer per 1000 (from 19 fewer to 146 more)
Mortality Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	OR 0.13 (0.03 to 0.49)	90 per 1000	77 fewer per 1000 (from 44 fewer to 87 fewer)
Additional parenteral nutrition Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.4 (0.15 to 1.07)	130 per 1000	78 fewer per 1000 (from 110 fewer to 9 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with delayed enteral feeding	Risk difference with early enteral nutrition (95% CI)
Infections - Infected pancreatic necrosis - adjusted Early = within 24 h of admission	95 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.66 (0.22 to 1.95)	188 per 1000	55 fewer per 1000 (from 139 fewer to 123 more)
Infections - Infected pancreatic necrosis or infected fluid collection - adjusted Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.24 (0.07 to 0.86)	Not estimable[c]	Not estimable[c]
Infections - Pancreatic infections Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.25 (0.03 to 1.97)	115 per 1000	87 fewer per 1000 (from 112 fewer to 112 more)
Infections - Extra-pancreatic infections Early = within 48 h of admission	197 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.46 to 1.04)	390 per 1000	121 fewer per 1000 (from 211 fewer to 16 more)
Infections - Systemic infections Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.52 (0.1 to 2.75)	40 per 1000	19 fewer per 1000 (from 36 fewer to 70 more)
Infections - Extra-pancreatic or systemic infections Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.2 (0.05 to 0.81)	289 per 1000	231 fewer per 1000 (from 55 fewer to 274 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with delayed enteral feeding	Risk difference with early enteral nutrition (95% CI)
Serious adverse events - Organ failure - adjusted Early = within 24 h of admission	95 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 0.51 (0.22 to 1.18)	500 per 1000	162 fewer per 1000 (from 320 fewer to 41 more)
Serious adverse events -Multi-organ failure Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.58 (0.27 to 1.25)	160 per 1000	67 fewer per 1000 (from 117 fewer to 40 more)
Adverse events - Pancreatic complications (necrosis, pseudocyst, ascites, hemorrhage, fistula) Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.92 (0.81 to 1.05)	962 per 1000	77 fewer per 1000 (from 183 fewer to 48 more)
Adverse events - Pancreatic complications (necrosis, pseudocyst, ascites, hemorrhage, fistula) Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.76 (0.64 to 0.89)	860 per 1000	206 fewer per 1000 (from 95 fewer to 310 fewer)
Adverse events - Operative intervention Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.27 (0.06 to 1.15)	212 per 1000	155 fewer per 1000 (from 199 fewer to 32 more)
Adverse events - Operative intervention Early = within 48 h of admission	197 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.66 (0.27 to 1.62)	110 per 1000	37 fewer per 1000 (from 80 fewer to 68 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with delayed enteral feeding	Risk difference with early enteral nutrition (95% CI)
Adverse events - Feeding complications (abnormal glucose metabolism) Early = within 3 days of hospital admission	87 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.05 (0.75 to 1.48)	596 per 1000	30 more per 1000 (from 149 fewer to 286 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Absolute risk could not be estimated as only the adjusted odds ratio was reported.

13.4 Economic evidence

13.4.1 Published literature

One health economic study was identified with the relevant comparison and has been included in this review.[62] This is summarised in the health economic evidence profile below (Table 43) and the health economic evidence table in appendix I.

See also the health economic study selection flow chart in appendix F.

Table 43: Health economic evidence profile: enteral versus parenteral nutrition

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
Louie 2005[62] (Canada)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Cost–consequences analysis (within RCT economic evaluation, n=28) • Outcomes: morbidity secondary to pancreatitis (infected fluid collection), morbidity secondary to nutritional practices (infected central line) and dislodged or removal of nasojejunal tube.	−£633 (enteral nutrition is cheaper)	Infected fluid collections −0.12 infections per person (favours enteral) Infected central lines −0.11 infections per person (favours enteral)	Enteral nutrition was dominant for these 2 outcomes	Enteral costs were explored, and it was suggested that these could be lowered by improved clinical protocols. However no sensitivity analysis was conducted on any important parameters.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Canadian health service perspective; outcomes were not valued using QALYs.

(b) Data taken from a single study of 28 patients; currency and cost year not stated, costs taken from the Canadian health system; sensitivity analysis not undertaken.

(c) Results assumed to be in 2004 Canadian dollars, presented as 2004 UK pounds, converted using 2004 purchasing power parities[82]

13.5 Evidence statements

All evidence was in adults or young people over 16 years.

13.5.1 Clinical

13.5.1.1 Enteral (jejunal or duodenal) versus parenteral nutrition for acute pancreatitis

- The randomised evidence showed a clinical benefit of enteral nutrition for mortality (8 studies; n=375; moderate quality), pancreatic infections (5 studies; n=254; moderate quality), systemic infections (6 studies; n=227; moderate quality), and operative intervention (8 studies; n=384; low quality); and a possible clinical benefit for length of hospital stay (3 studies; n=113; low quality), and severe adverse events (6 studies; n=296; very low quality). However, the evidence also suggested no clinical difference for achieving nutrition (2 studies; n=50; moderate and low quality), extra-pancreatic infections (4 studies, n=146, very low quality), unspecified infections (1 study; n=50; very low quality), non-infective pancreatic complications (6 studies; n=298; very low quality) and feeding complications (5 studies; n=205; very low quality).

13.5.1.2 Enteral (gastric) versus parenteral nutrition for acute pancreatitis

- The randomised evidence suggested a clinical benefit of parenteral nutrition for general adverse events and non-infective pancreatic complications (1 study; n=48; very low quality). However, there was also randomised evidence suggesting no clinical difference for mortality (1 study; n=48; very low quality), achieving nutrition (1 study; n=50; very low quality), pancreatic or systemic infections (1 study; n=48; very low quality), severe adverse events (1 study; n=48; very low quality) and surgical intervention (1 study; n=50; very low quality).

13.5.1.3 Enteral (gastric) versus enteral (jejunal or duodenal) nutrition for acute pancreatitis

- The randomised evidence suggested a clinical benefit of gastric nutrition for mortality (3 studies; n=157; low quality) and extra-pancreatic infections (2 studies; n=108; moderate quality). However, the randomised evidence also demonstrated no clinical difference for serious complications requiring tube removal (1 study; n=30; high quality), and suggested no clinical difference for length of hospital stay (1 study; n=30; moderate quality), achieving nutrition (2 studies; n=127; very low and high quality), requiring total parenteral nutrition (1 study; n=49; very low quality), pancreatic infections (2 studies; n=108; low quality), systemic infections (2 studies; n=108; low quality), tube displacement (2 studies; n=79; very low quality) and surgical intervention (2 studies; n=108; low quality).

13.5.1.4 Early oral ‘re-feeding’ versus conventional (delayed) oral ‘re-feeding’ for acute pancreatitis

- The randomised evidence suggested a clinical benefit of early oral feeding for length of hospital stay (1 study; n=138; low quality). However, there was no clinical difference for requiring parenteral nutrition (1 study; n=138; moderate quality) or adverse events (1 study; n=138; very low quality).

13.5.1.5 Early enteral nutrition versus on-demand enteral nutrition for acute pancreatitis

- The randomised evidence suggested no clinical difference for any of the reported outcomes (1 study; n=208; high and low quality).

13.5.1.6 Early enteral nutrition versus delayed enteral nutrition for acute pancreatitis

- The non-randomised evidence suggested a clinical benefit of early enteral nutrition (within 24 or 48 hours of admission) for mortality (2 studies; n=292; very low quality), but no clinical difference in 1 further study, defining early as within 3 days of admission (1 study; n=87; very low quality).
- There was also inconsistency between the non-randomised studies for the outcome of infections, although all outcomes favoured early enteral nutrition this did not always reach clinical significance. There was a possible clinical benefit of early enteral nutrition for infected pancreatic necrosis or infected fluid collection (if enteral nutrition was within 48 hours of admission; 1 study; n=197; very low quality), extra-pancreatic infections (if enteral nutrition was within 48 hours of admission; 1 study; n=197; very low quality), extra-pancreatic or systemic infections (if enteral nutrition was within 3 days of admission; 1 study; n=87; very low quality). However, there was no clinical difference for infected pancreatic necrosis (if enteral nutrition was within 24 hours of admission; 1 study; n=95; very low quality), pancreatic infections (if enteral nutrition was within 3 days of admission; 1 study; n=87; very low quality) or systemic infections (if enteral nutrition was within 48 hours of admission; 1 study; n=197; very low quality).
- The non-randomised evidence for adverse events and serious adverse events was inconsistent between studies, suggesting a clinical benefit of early enteral nutrition for organ failure (1 study; n=95; very low quality), pancreatic complications (1 study; n=197; very low quality) and operative intervention (1 study; n=87; very low quality), but also no clinical difference for multiple organ failure (1 study; n=197; very low quality), requiring additional parenteral nutrition (1 study; n=197; very low quality), feeding complications (1 study; n=87; very low quality), pancreatic complications (1 study; n=87; very low quality), and operative intervention (1 study; n=197; very low quality).

13.5.2 Economic

- One cost–consequences analysis found that enteral nutrition dominated parenteral nutrition as a route of feeding for patients with acute pancreatitis admitted to hospital with respect to infections (costing £633 less per patient and being associated with 0.12 fewer infected fluid collections and 0.11 fewer infected central lines per patient). This analysis was assessed as partially applicable with potentially serious interventions.

13.6 Recommendations and link to evidence

Recommendations	**16. Ensure that people with acute pancreatitis are not made 'nil-by-mouth' and do not have food withheld unless there is a clear reason for this (for example, vomiting).** **17. Offer enteral nutrition to anyone with severe or moderately severe acute pancreatitis. Start within 72 hours of presentation and aim to meet their nutritional requirements as soon as possible.** **18. Offer anyone with severe or moderately severe acute pancreatitis parenteral nutrition only if enteral nutrition has failed or is contraindicated.**
Relative values of different outcomes	The guideline committee agreed the following outcomes to be critical: mortality, quality of life, length of stay (in hospital or CCU), achieving nutrition and requiring parenteral nutrition. The committee also chose the following outcomes as important outcomes: infections, adverse events, weight loss and serious adverse events.
Quality of the clinical evidence	Seventeen studies reported in 19 papers were included; these were 13 RCTs, 1 quasi-RCT, and 3 observational studies. The majority of the evidence compared enteral

	versus parenteral nutrition and there were no comparisons of parenteral versus oral feeding or anything that matches current UK practice in terms of early versus late nutritional support. The evidence ranged from very low to high quality, but the majority was of low or very low quality. The most common reasons for downgrading the evidence were imprecision and risk of bias. Imprecision was a particular concern for some outcomes with low event rates, leading the committee to lack confidence in the estimated clinical difference. This made it difficult for the committee to make a specific recommendation about where an enteral feeding tube should be placed. However, as more studies were available for the comparison of enteral versus parenteral nutrition and the findings reflect what is seen in clinical practice the committee were confident in basing recommendations on the findings of this comparison. The evidence comparing gastric with parenteral nutrition was based on an indirect population, as the majority had mild pancreatitis, and all of the outcomes were very imprecise. Also, the feed type used is unlikely to be well absorbed. Therefore, the committee did not rely on evidence from this comparison as a basis for any recommendations. The committee highlighted that in 2 studies conducted in India comparing gastric and jejunal or duodenal nutrition, the delay from disease onset to admission to hospital was 5–7 days, which is longer than would be expected in UK practice. The observational evidence comparing early and delayed enteral feeding was all of very low quality owing to risk of bias and imprecision. Two studies adequately accounted for confounders using either propensity matching or multivariable analysis.
Trade-off between clinical benefits and harms	There was consistent evidence for a clinical benefit of enteral nutrition (delivered to the duodenum or jejunum) over parenteral nutrition for mortality, length of hospital stay, pancreatic infections, systemic infections, severe adverse events and requirement for operative interventions. There was no evidence of clinical harm, but no clinical difference for achieving nutrition, extra-pancreatic infections, non-infective pancreatic complications or feeding complications. Based on the clear evidence for enteral nutrition being safer and not less effective than parenteral nutrition the committee recommended that enteral nutrition should be the first route offered to people with severe or moderately severe acute pancreatitis requiring nutritional support unless it is contraindicated, for example in the presence of ileus, or high ionotrope requirements, in which case parenteral nutrition may be considered. The committee agreed that it was important to specify that the aim should be to meet nutritional requirements as soon as possible, to avoid underfeeding in this population which is known to occur in current practice. It was acknowledged that it is unlikely to be possible to meet requirements within 72 hours of diagnosis of acute pancreatitis. Comparing enteral nutrition delivered into the stomach with parenteral nutrition, there was a potential clinical harm of gastric nutrition for increased length of hospital stay and increased rate of general and non-infective pancreatic adverse events. However, no clinical difference was seen for mortality, achieving nutrition, infections, severe adverse events or surgical intervention. Given the uncertainty around the estimate of clinical harm, inconsistency with other comparisons and concerns about indirectness relating to this evidence the committee did not put much weight on this evidence in their overall decision-making. Comparing enteral feeding delivered to the jejunum or duodenum versus the stomach there was a potential clinical harm of the jejunal or duodenal route for increased mortality and extra-pancreatic infections, although there was considerable uncertainty associated with these estimates. All other outcomes showed no clinical difference and the committee therefore believed it would be appropriate not to specify where the enteral tube should be placed and to leave this to clinical judgement on a case-by-case basis. For example, gastric feeding is suitable for

	patients with no duodenal stenosis or oedema. The committee noted that there is a common belief that gastric feeding, although simpler to achieve in practice, is not usually appropriate in this setting. However, it was clear that there is no evidence to support this view. Comparing early versus conventional re-institution of oral feeding there was a clinical benefit of early oral feeding for reduced length of hospital stay and no clinical difference for requiring parenteral nutrition or adverse events. Overall the committee agreed that the limited available evidence demonstrated that there is no evidence to support delayed feeding. There is also consensus in clinical opinion and an ethical basis for not routinely managing patients with acute pancreatitis as 'nil by mouth' initially, as pancreatic rest is no longer believed to be beneficial. This is also supported indirectly by the evidence in this review that enteral nutrition is clinically beneficial compared with parenteral nutrition, which is similar to 'nil by mouth'. Therefore, based on the clinical evidence and their expert opinion the committee agreed to include recommendations to raise awareness that patients with acute pancreatitis do not benefit from withholding nutrition and therefore should not be kept 'nil by mouth'. The comparison of 'early' versus 'on-demand' enteral feeding showed no convincing clinical difference for any of the reported outcomes. It was also noted that initiating nutrition at either of the time points used within the published evidence would classify as 'early' in UK practice and that the 'early' group received a higher amount of nutrition over the study period. However, the evidence from this comparison further supports the recommendation that there is no benefit of delayed nutrition. Additionally, the observational data comparing early (within 24–72 hours of admission) with late enteral feeding showed a clinical benefit of early feeding across all studies for mortality, and in individual studies for some infection and complication outcomes. Although there was inconsistency and other studies did not show a clinical benefit for infections or complications, all showed a direction of effect favouring early intervention, and so there was no harm associated with early enteral nutrition. Furthermore 8 out of 9 studies comparing enteral and parenteral nutrition, where a benefit of the enteral route was found, initiated nutrition support within 72 hours of admission. Therefore, the committee agreed that nutritional support should be initiated within 72 hours of presentation in order to achieve the benefits of nutritional support demonstrated in the studies. The committee stated that it was important to highlight this as it is aware that people with acute pancreatitis can wait more than 5–7 days before any form of nutritional support is established. The committee noted that pancreatic complications and the need for surgery were not adverse events of the intervention, but were complications important to consider in assessing the evidence for these interventions and so they were taken into account when weighing up the benefits and harms. Overall, there is evidence that there is no benefit of delayed nutrition in severe or moderately severe acute pancreatitis and that the safest first-line route of administration is enteral nutrition, which is not less effective than the parenteral route.
Trade-off between net clinical effects and costs	One health economic evaluation was identified, set in Canada. This compared parenteral nutrition and enteral nutrition. The evaluation found enteral nutrition to be both cheaper and more effective in terms of fewer infections secondary to pancreatitis or secondary to nutrition practices, which was consistent with the clinical evidence. The committee agreed that parenteral nutrition is more expensive compared with enteral nutrition, as it requires regular blood tests, more nursing time and supervision from a consultant, whereas enteral nutrition, although needing the initial insertion of tubes by specialists, can be supervised by a dietitian. The committee therefore agreed that enteral nutrition should be recommended as the first-line treatment to people with severe or moderately severe acute

	pancreatitis requiring nutritional support, as it is both cheaper and likely to lead to better health outcomes, and so will be cost saving compared with current practice, which is to use parenteral nutrition in a majority of cases. Parenteral feeding should only be recommended where enteral nutrition has failed (and hence the only alternative is no feeding, which would lead to much worse health outcomes). The committee also agreed that it is important that professionals, patients and families are aware that patients with acute pancreatitis should not routinely be made nil-by-mouth. Where oral feeding is possible that is cost effective compared with artificial feeding as oral feeding is cheaper than either enteral nutrition or parenteral nutrition; the committee also agreed that it would be preferred by patients as it is more convenient and more pleasant. However the committee noted that oral diet alone is unlikely to be sufficient to meet nutritional requirements. Deliberately withholding all forms of feeding is likely to be counterproductive both clinically and economically, as this could seriously affect a person's overall health and increase complications and comorbidities, leading to greater treatment costs later on. The committee therefore agreed that this recommendation will be cost effective or cost saving.
Other considerations	Lay members of the committee noted their experience that enteral feeding was critical for improving energy levels to allow mobilisation and recovery sufficient for discharge from hospital. They emphasised that earlier initiation of nutritional support would have been beneficial in many cases. This is different to the recommendations in the NICE guideline on nutrition support in adults (CG32) which suggests a nutrition intervention only if a patient shows signs of malnutrition. The committee emphasised the importance of early intervention for people with acute pancreatitis to avoid a person's nutritional status deteriorating. The committee agreed that oral feeding should be re-instituted as quickly as possible. Lay members also noted that oral intake is difficult when a feeding tube is still in place. When referring to severity in acute pancreatitis the committee used the Revised Atlanta Classification.[11]

1

NUTRITION SUPPORT FOR CHRONIC PANCREATITIS

14 Early compared with late nutritional intervention in people with chronic pancreatitis

14.1 Introduction

People with chronic pancreatitis can experience significant malnutrition with reported cases of micronutrient deficiencies and poor bone health. Patients voice strong concerns regarding the availability of dietary advice. Nutritional screening in hospitals will trigger a formal nutritional review once 5% weight loss has occurred, but will not detect more subtle symptoms of exocrine insufficiency or sarcopenia. Some clinicians support earlier routine intervention to try and prevent nutritional deterioration and its subsequent impact on quality of life.

Routine outpatient nutritional assessment is not available in the UK. It is unknown whether earlier intervention will reduce long term healthcare costs, improve quality of life and reduce malnutrition related complications. This review attempts to answer this question, and identify any aspects of nutritional intervention that may prove most beneficial.

14.2 Review question: What is the clinical effectiveness and cost effectiveness of early compared with late nutritional intervention (for example, food supplements, enzyme supplements) in people with chronic pancreatitis and signs of malnutrition or malabsorption?

For full details see review protocol in appendix C.

Table 44: PICO characteristics of review question

Population	Individuals with chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Intervention	Early intervention (as defined by studies, for example, <5% weight loss) The following interventions will be considered: • Nutrition advice • Food supplements • Enzyme supplements
Comparison	• Late intervention (as defined by studies, for example, ≥5% weight loss)
Outcomes	Critical outcomes • Quality of life (≤1 year) (continuous) • Mortality (≤1 year) (dichotomous) • Weight loss or BMI (≤1 year) (continuous or dichotomous) Important outcomes • Signs of vitamin and mineral deficiency (for example, skin problems, swollen tongue, poor vision at night, breathlessness, bone and joint pain) (≤1 year) (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a

recommendation is found, non-randomised controlled studies will be included.

14.3 Clinical evidence

No relevant clinical studies were identified comparing early versus late nutritional intervention in people with chronic pancreatitis.

14.4 Economic evidence

14.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

14.5 Evidence statements

14.5.1 Clinical

- No relevant published evidence was identified.

14.5.2 Economic

- No relevant economic evaluations were identified.

14.6 Recommendations and link to evidence

Recommendations and the committee's discussion of the evidence can be found in section 15.6.

15 Specialist compared with non-specialist nutritional assessment in people with chronic pancreatitis

15.1 Introduction

Pancreatology is increasingly recognised as a specialist area in dietetics, but lack of access to specialist services is highlighted as a significant concern by patient groups. Patient information is scarce, and leads to frustration and lack of appropriate nutritional intervention. A Dutch study highlighted that those patients who were seen by non-specialist dietitians did not experience any difference in nutritional management to those who had not received any nutritional advice[97], thus calling into question the benefit of patients being assessed by non-specialist dietitians.

It is hypothesised that nutritional assessment carried out by a specialist could result in improved outcome in terms of improved abdominal symptoms, nutritional status, quality of life and patient satisfaction. This review attempts to identify if access to specialist services improves outcome in people with chronic pancreatitis compared with non-specialist services.

15.2 Review question: What is the clinical effectiveness and cost effectiveness of a specialist nutritional assessment compared with a non-specialist assessment for managing malabsorption or malnutrition in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 45: PICO characteristics of review question

Population	Individuals with chronic pancreatitis • Adults and young people (≥16 years) • Children (<16 years)
Intervention	Specialist nutritional assessment
Comparison	Non-specialist nutritional assessment
Outcomes	Critical outcomes • Quality of life (≤ 1 year) (continuous) • Mortality (≤1 year) (dichotomous) • Weight loss or BMI (≤1 year) (change from baseline or final score; continuous or dichotomous) • Osteoporosis or biochemical deficiencies (≤1 year) (dichotomous) • Hospital admissions (≤1 year) (dichotomous) • Unnecessary dietary restriction (low fat diets) (≤1 year) (dichotomous) Important outcomes • Signs of vitamin and mineral deficiency (for example, skin problems, swollen tongue, poor vision at night, breathlessness, bone and joint pain) (≤1 year) (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence is found to form a recommendation, non-randomised comparative studies will be included.

15.3 Clinical evidence

No relevant clinical studies were identified comparing specialist nutritional assessment with non-specialist nutritional assessment in people with chronic pancreatitis.

15.4 Economic evidence

15.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

15.5 Evidence statements

15.5.1 Clinical

- No relevant published evidence was identified.

15.5.2 Economic

- No relevant economic evaluations were identified.

15.6 Recommendations and link to evidence

Recommendations	**<u>Nutrition support for chronic pancreatitis</u>** **19. Be aware that all people with chronic pancreatitis are at high risk of malabsorption, malnutrition and a deterioration in their quality of life.** **20. Use protocols agreed with the specialist pancreatic centre to identify when advice from a specialist dietitian is needed, including advice on food, supplements and long-term pancreatic enzyme replacement therapy, and when to start these interventions.** **21. Consider assessment by a dietitian for anyone diagnosed with chronic pancreatitis.** **22. For guidance on nutrition support for people with chronic alcohol-related pancreatitis, see alcohol-related pancreatitis in the NICE guideline on alcohol-use disorders.** **<u>Nutrition support for pancreatitis</u>** **23. For guidance on nutrition support see the NICE guidelines on nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition**
Relative values of different outcomes	The guideline committee agreed the following outcomes to be critical: quality of life, mortality, weight loss or BMI, osteoporosis or biochemical deficiencies, hospital admissions and unnecessary dietary restriction. The committee also agreed the following outcome to be important: signs of vitamin and mineral deficiency.

Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess the effectiveness of specialist nutritional assessment for chronic pancreatitis, or early versus late timing of nutritional intervention for chronic pancreatitis. The committee noted that currently many people with chronic pancreatitis are not seen by a dietitian. It was noted that chronic pancreatitis is a complex condition, and the potential consequences of not receiving involvement from a dietitian specialising in pancreatitis includes a deterioration in quality of life, due to: • pain when eating • weight loss because of lack of pancreatic enzymes • possible development of diabetes (and hence the need for a diabetic diet) • the potential for nausea and vomiting • duodenal narrowing, which may mean food does not pass through the duodenum effectively exacerbating weight loss and vomiting • prior malnutrition may increase the likelihood of comorbidities such as bone disease • the use of analgesics can prevent good nutrition and smoking may reduce appetite. Therefore, the committee recommended that physicians should be aware that people with chronic pancreatitis are at high risk of deterioration in health and quality of life. The committee also discussed nutritional assessment in people with chronic pancreatitis, and the role of specialist and non-specialist dietitians. Non-specialist dietitians were defined as dietitians who are able to identify malnutrition, but may not be able to recognise malabsorption, those that do not have specialist training in understanding indications of malabsorption, and those that are not permitted to manage pancreatic exocrine insufficiency. A non-specialist will look at oral intake, anthropometry and work with food fortification and nutritional supplements. A specialist dietitian, on the other hand, is able to identify malabsorption and treat it, as well as advising on the prevention of micronutrient deficiencies, long term screening and biochemical and anthropometric assessments. A specialist dietitian will also look at oral intake, anthropometry, advise on food fortification, nutritional supplements and enteral/parenteral nutrition if necessary. In addition they should assess for exocrine insufficiency, endocrine dysfunction, micronutrient deficiencies and abdominal symptoms that will contribute to malnutrition. It was agreed that nutritional assessment should include a dietary history, anthropometry assessment, and micronutrients (magnesium, zinc) and should be performed at least annually, and more often in symptomatic patients. The committee discussed that although assessment by a specialist dietitian would be beneficial, this may not always be possible, as there are only a small number of specialist dietitians in England. Therefore, the committee discussed the use of protocols disseminated by specialist dietitians and specialist pancreatic centres to non-specialist centres. The committee discussed the importance of a network of dietitians and specialist dietitians to support the production and dissemination of such protocols. The committee discussed that the triggers for referral could include: • unexplained weight loss • uncontrolled hypoglycaemia • uncontrolled bowel symptoms The committee noted that receiving such specialist nutritional input to inform assessment and intervention at an early stage (that is, routinely, rather than only on request, and not only once deterioration is advanced) may prevent deterioration of

	quality of life through detection of the early signs and symptoms of deteriorating health, which can occur with little prior indication. This may lead to a reduction in: • length of hospital stay • need for hospital admission, as it is easier to get nutrition on board if complications are identified early • need for nutritional support and intervention such as feeding tube • risk of osteopenia, osteoporosis, infection and premature death It was also noted that early assessment will also lead to the ability to identify patients who are eligible for or may benefit from pancreatic enzyme replacement therapy. Therefore, the committee decided to recommend that early assessment by a dietitian should be considered for all people with chronic pancreatitis using agreed protocols. The committee discussed the strength of the recommendation, and unanimously agreed that all people should get specialist dietary input, and that it would want this to be a strong recommendation. However, due to the lack of evidence and potential cost and resource impact, a strong recommendation was not possible.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee agreed that it was important that clinicians are aware that people with chronic pancreatitis are at high risk of deterioration in health and quality of life. The committee noted that seeing a dietitian (whether a generalist or one specialising in pancreatitis) would lead to an additional cost of that dietitian's time, but highlighted that specialist advice would be expected to reduce the costs of potential consequences of pancreatitis such as pain management, weight loss issues, development of diabetes and malnutrition which can lead to bone diseases. The committee noted that the best advice would come from dietitians specialising in pancreatitis, but that the small number of these mean that it would not be possible for every person with chronic pancreatitis to see a dietitian specialising in pancreatitis. There was a strong consensus that routine specialist input, either by the use of protocols or through a network of dietitians, would be expected to lead to reductions in length of hospital stays, need for hospital admission, need for nutritional support and nutritional interventions, and the risk of developing further complications such as osteoporosis, neutropenia and infections Reductions in any of these outcomes would also be expected to decrease costs. Seeking dietary advice early in a person's treatment could therefore lead to decreased overall costs, with shorter treatment times and better health outcomes. The committee therefore expect assessment by a dietitian to be cost saving or cost effective. However, given the lack of clinical or health economic studies to base this recommendation on, the committee have recommended that this be considered rather than a stronger recommendation.
Other considerations	The committee was aware that many chronic pancreatitis patients are currently receiving no advice or inappropriate advice from non-specialist dietitians (for example, to maintain a 'low fat' diet), and many are also not well informed about how best to take pancreatic enzymes to control their symptoms. The committee also discussed nutritional assessment and intervention in children, noting that all paediatric cases are seen in a specialist centre but that no paediatric pancreatitis dietitians are available. The committee also noted the potential growth implications for children if they are taken off enzyme replacement therapy.

1

16 Prophylactic antimicrobial agents to prevent infection in people with acute pancreatitis

16.1 Introduction

Acute pancreatitis is caused by inflammation of the pancreas, an organ with both digestive and endocrine functions. Sometimes the pancreatitis becomes so severe that part of the pancreas dies, and this pancreatic necrosis can often become infected. Infected pancreatic necrosis has a higher morbidity and mortality than non-infected (sterile) necrotic pancreatitis. For this reason it is common for people with non-infected acute severe pancreatitis with necrosis to be given antimicrobial drugs as prophylaxis with the intention of trying to prevent the development of infected pancreatic necrosis. However, the use of antimicrobial prophylaxis may have important negative outcomes including the selection of multidrug resistant microorganisms. Subsequent infection with these multidrug resistant organisms may be harder to treat effectively, leading to higher mortality.

There is conflicting evidence that the use of antimicrobial prophylaxis is effective in reducing mortality from acute pancreatitis, as reflected in the current guidelines. The British Society of Gastroenterology Guidelines state that there is no consensus on this issue and they do not have sufficient evidence to make a recommendation. The American College of Gastroenterology Guidelines on management of acute pancreatitis do not recommend routinely using antimicrobial prophylaxis in patients with acute severe pancreatitis or sterile necrosis. The recent NCEPOD report on acute pancreatitis showed that 61% of the people with acute pancreatitis received antimicrobials, and in a-fifth of cases, they were inappropriately prescribed. This review attempts to address the clinical and cost effectiveness of using antimicrobials to prevent infection in people presenting with acute pancreatitis.

16.2 Review question: What is the clinical effectiveness and cost-effectiveness of prophylactic antimicrobial agents to prevent infection in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 46: PICO characteristics of review question

Population	People admitted to hospital with acute pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Intervention	Any antimicrobial therapy administered prophylactically, including antifungals
Comparison	• Any prophylactic antimicrobial therapy • No prophylactic antimicrobial therapy • Placebo
Outcomes	Critical outcomes • Quality of life (≤1 year) (continuous) • Mortality (≤1 year) (dichotomous) • Length of stay (in CCU or hospital) (continuous or dichotomous) • Infected necrosis (≤1 year) (dichotomous)

	Important outcomes • Extra-pancreatic infection (≤1 year) (dichotomous) • Colonisation of resistant organisms (≤6 months, >6 months) • Serious adverse events (≤ 6 months, >6 months)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included for the children and young people strata only.

16.3 Clinical evidence

16.3.1 Summary of included studies

A search was conducted for randomised trials comparing the effectiveness of antimicrobials with no antimicrobial treatment, placebo or with each other as prophylactic treatment for patients with acute pancreatitis.

Thirteen studies (reported in 15 papers) were included in the review;[14, 28, 29, 38, 39, 49, 52, 64, 65, 68, 79, 83, 93, 94, 120] these are summarised in Table 47, Table 48, Table 49 and Table 50 below. All studies were conducted in adult populations. As no randomised trials included a paediatric population, we also searched for non-randomised comparative studies for this stratum but no studies were found.

Eight studies compared antimicrobials to no antimicrobial treatment; 3 studies compared antimicrobials to placebo; 1 study compared antimicrobials of different classes; and 1 study compared antimicrobials of the same class. A variety of antimicrobials was used. Most studies used antibiotics, and 2 studies used antifungals. The aim of all studies was to assess whether antimicrobials are effective at preventing infections in people with acute pancreatitis.

One Cochrane review was identified [114] but was excluded as it did not match our protocol because the population was limited to those with acute pancreatitis complicated by CT proven necrosis and the control group combined no prophylactic antimicrobial therapy and placebo. The studies included in this review were individually assessed and included if they matched the review protocol, and relevant unpublished data from the published review were included.

Evidence from the included studies is summarised in the clinical evidence summaries below (Table 52 to Table 55) and data not suitable for meta-analysis are presented in Table 51. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

16.3.2 Heterogeneity

For the comparison of prophylactic antimicrobial treatment versus no prophylactic antimicrobial treatment, there was substantial heterogeneity between the studies when they were meta-analysed for the outcome of extra-pancreatic infections and infected necrosis (peri-pancreatic infections) at under 1 year. Pre-specified subgroup analyses did not explain such heterogeneity. A random effects meta-analysis was therefore applied to these outcomes, and the evidence was downgraded for inconsistency in GRADE.

Table 47: Summary of studies included in the review: Prophylactic antimicrobial therapy versus no prophylactic antimicrobial therapy

Study	Intervention and comparison	Population	Outcomes	Comments
Delcenserie 1996 [28]	Intervention: Prophylactic antimicrobial therapy – Combination of antimicrobials: cephalosporin plus aminoglycoside plus nitroimidazole derivative (intravenous ceftazidime, 2 g every 8 hours; intravenous amikacin, 7.5 mg/kg every 12 hours; and intravenous metronidazole, 0.5 g every 8 hours) (n=11) Comparison: No prophylactic antimicrobial treatment (n=12)	People with severe acute pancreatitis (n=23) Intervention duration: 10 days Age (range): 21-74 years France	• Mortality (10 days) • Length of hospitalisation (10 days) • Infected necrosis (10 days) • Extra-pancreatic infection (10 days) • Serious adverse events (multi-organ failure) (10 days)	Concurrent treatment: all patients received medical treatment
He 2003[49]	Intervention: Prophylactic antimicrobial therapy - Imidazole antifungal (venous instillation of 100 mg fluconazole once a day) (n=22) Comparison: No prophylactic antimicrobial treatment (n=23)	People with severe acute pancreatitis (n=45) Intervention duration: unclear (until relief of predisposing factors) Age not reported China	• Extra-pancreatic infection (time-point unclear)	Concurrent care: routine treatment
Luiten 1995[64] (Luiten 1997[65])	Intervention: Prophylactic antimicrobial therapy - Combination of antimicrobials: polymixin plus polyene antifungal plus quinolone plus cephalosporin	People with severe acute pancreatitis (n=109) Intervention duration: unclear (selective	• Mortality (time-point unclear) • Length of stay (time-point unclear) • Infected necrosis (time-point unclear)	Concurrent medication: a nasogastric tube was always inserted. Intravenous crystalloid solutions were given according to clinical requirements. Oxygen

Study	Intervention and comparison	Population	Outcomes	Comments
	(Selective decontamination: colistin sulfate (200 mg), amphotericin (500 mg) and norfloxacin (50 mg) every 6 hours. A sticky paste containing 2% of the 3 selective decontamination drugs was smeared along the upper and lower gums every 6 hours and at the tracheostomy, if present. The aforementioned daily dose was also given in a rectal enema every day. A short-term systemic prophylaxis of cefotaxime sodium (500 mg) was given every 8 hours until gram-negative bacteria were eliminated from the oral cavity and rectum) (n=50) Comparison: No prophylactic antimicrobial therapy (n=52)	decontamination was done until the risk of acquiring a new infection was absent and follow-up was continued till discharge or death) Age (range): 20-91 years Netherlands		therapy, based on arterial blood gas analysis, was administered by face mask and was replaced by assisted ventilation if the patient developed respiratory insufficiency. Mean duration of decontamination in the intervention group: 7.4 days
Nordback 2001[79]	Intervention: Prophylactic antimicrobial therapy – Carbapenem (imipenem 1.0 g plus cilastatin, IV 3 times a day) (n=25) Comparison: No prophylactic antimicrobial therapy (n=33)	People with severe acute pancreatitis (n=58) Intervention duration: unclear Age (mean, SD): intervention group 47 (8); control group 46 (7) years Finland	• Mortality (time-point unclear) • Length of stay (time-point unclear) • Serious adverse events (major organ complications) (time-point unclear) • Infected necrosis (data from published review[114]) • Extra-pancreatic infection (data from published review[114])	Concurrent medication: non-operative conservative treatment was always attempted first. Three patients with gallstone pancreatitis underwent early ERCP. Patients with infected necrosis in the intervention group received surgery; in the control group, they first received imipenem at a dosage similar to that used in the early imipenem group for 5 days and if indication to surgery persisted or patient

Study	Intervention and comparison	Population	Outcomes	Comments
				deteriorated surgery was performed.
Pederzoli 1993[83]	Intervention: Prophylactic antimicrobial therapy – Carbapenem (500 mg imipenem given intravenously every 8 hours for 14 days) (n=41) Comparison: No prophylactic antimicrobial therapy (n=33)	Severe necrotising acute pancreatitis (n=74) Intervention duration: 14 days Age (range): 20-84 years Italy	• Mortality (14 days) • Infected necrosis (14 days) • Extra-pancreatic infection (14 days) • Serious adverse events (multi-organ failure) (14 days)	Concurrent care: all patients received the same medical treatment
Rokke 2007[93]	Intervention: Prophylactic antimicrobial therapy – Carbapenem (early therapy with imipenem, 500 mg 3 times daily) (n=36) Comparison: No prophylactic antimicrobial therapy (n=37)	People with severe acute pancreatitis (n=73) Intervention duration: 5-7 days Age (range): 19-84 years Norway	• Mortality (4 weeks) • Length of stay (4 weeks) • Extra-pancreatic infection (4 weeks) • Serious adverse events (organ failure) (4 weeks)	Concurrent care: patients in both groups were given antibiotics on demand when infection was diagnosed
Sainio 1995[94]	Intervention: Prophylactic antimicrobial therapy – Cephalosporin (3 doses of 1.5 g cefuroxime per day intravenously until clinical recovery and fall to normal of CRP concentrations. In cases of full recovery but moderately raised CRP concentrations, antibiotic treatment was continued with cefuroxime by mouth, 2 doses of 250 mg per day) (n=30)	People with severe alcohol-induced acute pancreatitis (n=60) Intervention duration: up to 14 days Age (mean, SD): intervention group 43 (11.3); control group 38.7 (8.4) years	• Mortality (14 days) • Length of stay (14 days) • Infected necrosis (Including peri-pancreatic infection) (14 days) • Extra-pancreatic infection (Blood culture positive sepsis, urinary tract infection, pneumonia/ARDS) (14 days)	Concurrent care: Adequate fluid replacement by central venous catheter, with monitoring of central venous pressure, and assistance of respiratory or renal function when needed Control group: No antibiotic treatment was given before infection had been clinically, microbiologically, or radiologically

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: No prophylactic antimicrobial therapy (n=30)	Finland		verified, or until there was a secondary rise in CRP of more than 20% after the acute phase
Xue 2009[120]	Intervention: Prophylactic antimicrobial therapy – Carbapenem. 500 mg imipenem-cilastatin every 8 hours by 30 mins IV drip within 72 h of onset of symptoms. All 500mg doses were diluted in 100 ml normal saline solution (n=30) Comparison: No prophylactic antimicrobial therapy (n=29)	People with severe acute necrotising pancreatitis (n=59) Intervention duration: 7–14 days plus 1 month follow-up Age (mean, SD): intervention group 48.4 (15.1); control group 47.5 (12.3) years China	• Mortality (6 weeks) • Length of stay (6 weeks) • Infected necrosis (6 weeks) • Extra-pancreatic infection (6 weeks) • Serious adverse events (organ complication) (6 weeks)	Concurrent medication/care: The use of non-study antibiotics in the study group or any antibiotics in the control group was not encouraged until progressive pancreatitis was manifested by clinical deterioration, and/or infection was microbiologically verified or strongly suspected, or after an initial SIRS, a secondary rise in serum C-reactive protein (CRP) was measured. During the hospital stay, all patients received daily critical care (monitoring of temperature, oxygen saturation, central venous pressure vis central venous catheter, liquid intake and output, and were given supportive care and nutritive administration)

Table 48: Summary of studies included in the review: Prophylactic antimicrobial therapy versus placebo

Study	Intervention and comparison	Population	Outcomes	Comments
Garcia Barrasa 2010[39]	Intervention: Prophylactic antimicrobial therapy – Quinolone (300 mg ciprofloxacin every 12 hours) (n=22) Comparison: Placebo (n=19)	People with severe necrotising acute pancreatitis (n=41) Intervention duration: 10 days	• Mortality (10 days) • Length of stay (10 days) • Infected necrosis (10 days) • Extra-pancreatic infection (10 days) • Serious adverse events (organ	Concurrent care: all patients were treated medically on admission (aggressive fluid resuscitation along with electrolyte imbalance, complete avoidance of oral intake, pain control and total parenteral nutrition)

Study	Intervention and comparison	Population	Outcomes	Comments
		Age (range): 31-84 years Spain	failure) (10 days)	Intervention group: in 7 patients, medication had to be discontinued and open antibiotic treatment had to be started after a mean of 7 days (range 3-9). Control group: In 8 patients placebo had to be discontinued and open antibiotic treatment had to be started instead after a mean of 6 days (range 4-8 days)
Dellinger 2007[29]	Intervention: Prophylactic antimicrobial therapy – Carbapenem (meropenem 1 g powder reconstituted in fluid administered by intravenous infusion over 15 to 30 minutes every 8 hours) (n=50) Comparison: Placebo (dose- and administration-matched placebo) (n=50)	People with severe acute necrotising pancreatitis (n=100) Intervention duration: 7-21 days (follow-up at least 35 days) Age: 18-64 years, n=68; 65-74 years, n=18; >75 years, n=14 Austria, Belgium, Canada, Estonia, Germany, Latvia, Lithuania, Portugal, Spain, United Kingdom, USA	• Mortality (42 days) • Infected necrosis (42 days) • Extra-pancreatic infection (42 days) • Colonisation by resistant organisms (42 days) • Serious adverse events (42 days)	Concurrent care: The use of non-protocol antibiotics during this time was discouraged but could not be prohibited in these seriously ill patients. Most patients received nutritional support and the incidence of support was not different between the meropenem and placebo arms 31 patients in the intervention group and 32 patients in the control group received drug for a duration <14 days: 11 and 10 stopped as they were diagnosed an infection and started non-study antibiotic or received surgery; 5 and 2 recovered; 2 and 4 died in the intervention and control groups, respectively. 25 and 27 patients received additional antibiotics other than study drug for clinical indications in the intervention and control groups, respectively.

Study	Intervention and comparison	Population	Outcomes	Comments
Isenmann 2004[52] (Forsmark 2005[38])	Intervention: Prophylactic antimicrobial therapy - Combination of antimicrobials: quinolone plus nitroimidazole derivative (Ciprofloxacin 2x400 mg/day intravenously in combination with metronidazole 2x500 mg/day) (n=58) Comparison: Placebo (n=56)	People with severe acute pancreatitis (n=114) Intervention plus follow-up: 21 days Age (median, range): Ciprofloxacin/metronidazole group: 47.9 (25.1-72.5); control group: 45.6 (21.9-78.4) years. Germany	• Mortality (21 days) • Length of stay (21 days) • Infected necrosis (21 days) • Extra-pancreatic infection (21 days) • Serious adverse events (pulmonary insufficiency, renal insufficiency, shock, SIRS) (21 days)	Concurrent medication: not stated Intervention group: study medication was given for 3-23 days (median 14 days) after the onset of symptoms. 16 people discontinued study medication and switched to open antibiotic treatment. Control group: study medication was given for 2-19 days (median 12 days) after onset of symptoms. 26 people discontinued placebo and switched over to antibiotic open treatment

Table 49: Summary of studies included in the review: Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (same class)

Study	Intervention and comparison	Population	Outcomes	Comments
Manes 2003[68]	Intervention: Prophylactic antimicrobial therapy – Carbapenem (500 mg meropenem intravenously every 8 hours) (n=88) Comparison: Prophylactic antimicrobial therapy – Carbapenem (500 mg imipenem intravenously every 6 hours) (n=88)	People with necrotising severe acute pancreatitis (n=176) Intervention duration: 14 days Age (range): 19-91 years Italy	• Mortality (14 days) • Length of stay (14 days) • Infected necrosis (14 days) • Extra-pancreatic infections (14 days) • Serious adverse events (multi-organ failure) (14 days)	Concurrent medication: all patients received the usual supportive medical treatment; endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy was performed in 96 patients with biliary forms

Table 50: Summary of studies included in the review: Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (different class)

Study	Intervention and comparison	Population	Outcomes	Comments

Study	Intervention and comparison	Population	Outcomes	Comments
Bassi 1998[14]	Intervention: Prophylactic antimicrobial therapy – Quinolone (400 mg Pefloxacin IV, 2 times daily) (n=30) Comparison: Prophylactic antimicrobial therapy – Carbapenem (500 mg Imipenem IV, 3 times daily) (n=30)	People with severe acute necrotising pancreatitis (n=60) Intervention duration: 2 weeks Age (range): 34-70 years Italy, Greece	• Mortality (2 weeks) • Length of stay (2 weeks) • Infected necrosis (2 weeks) • Extra-pancreatic infection (2 weeks)	Concurrent care: Patients with pancreatitis of biliary etiology underwent endoscopic sphincterotomy within 72 hours of admission.

Table 51: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Manes 2003[68] (Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy: same class - Meropenem versus imipenem)	Length of stay (in hospital) < 1 year	Mean (range): 24 (7-90)	88	Mean (range): 23.3 (6-80)	88	High
Røkke 2007[93] (Prophylactic antimicrobial therapy - Imipenem versus no prophylactic antimicrobial therapy)	Length of stay (in hospital) < 1 year	Mean (range): 18 (6-71)	36	Mean (range): 22 (1-95)	37	High
Xue 2009[120] (Prophylactic antimicrobial therapy - Imipenem versus no prophylactic antimicrobial therapy)	Length of stay (in hospital) < 1 year	Median (range): 28.3 (23-71)	30	Median (range): 30.7(25-60)	29	Low
Sainio 1995[94] (Prophylactic antimicrobial therapy - Cefuroxime versus no prophylactic antimicrobial therapy)	Length of stay (in hospital) < 1 year	MD 10.6, p=0.24				High
	Length of stay (in CCU) < 1 year	MD 10.9, p=0.06				High

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Luiten 1995[64] (Prophylactic antimicrobial therapy – Combination of antimicrobials (selective decontamination) versus no prophylactic antimicrobial therapy)	Length of stay (in hospital) < 1 year	Median (range): 30 (10-106)	50	Median (range): 32(6-241)	52	Low
Isenmann 2004[52] (Prophylactic antimicrobial therapy – Combination of antimicrobials versus placebo)	Length of stay (in hospital) < 1 year	Median (min-max): 21(7-237)	58	Median (min-max): 18(3-129)	56	High
	Length of stay (in CCU) < 1 year	Median (min-max): 8(0-103)	58	Median (min-max): 6(0-80)	55	High

Table 52: Clinical evidence summary: Prophylactic antimicrobial therapy versus no prophylactic antimicrobial therapy

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No therapy	Risk difference with Antibiotic therapy (95% CI)
Mortality < 1 year	344 (6 studies) 1-6 weeks	⊕⊕⊕⊕ HIGH	RR 0.48 (0.26 to 0.91)	150 per 1000	78 fewer per 1000 (from 13 fewer to 111 fewer)
Mortality (Selective decontamination) < 1 year	102 (1 study) time-point unclear	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.64 (0.33 to 1.21)	346 per 1000	125 fewer per 1000 (from 232 fewer to 73 more)
Length of hospital stay < 1 year	74 (2 studies) 10 days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 22.4	The mean length of hospital stay in the intervention groups was 1.67 higher (4.3 lower to 7.64 higher)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No therapy	Risk difference with Antibiotic therapy (95% CI)
Infected necrosis < 1 year	301 (5 studies) 1-6 weeks	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 0.54 (0.35 to 0.84)	303 per 1000	139 fewer per 1000 (from 48 fewer to 197 fewer)
Infected necrosis (Selective decontamination) < 1 year	102 (1 study) time-point unclear	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 0.47 (0.24 to 0.93)	385 per 1000	204 fewer per 1000 (from 27 fewer to 292 fewer)
Infected necrosis (Peri-pancreatic infection) < 1 year	133 (2 studies) 5-14 days	⨁⨀⨀⨀ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.97 (0.66 to 1.41)	395 per 1000	12 fewer per 1000 (from 134 fewer to 162 more)
Extra-pancreatic infection < 1 year	340 (6 studies) 1-6 weeks	⨁⨀⨀⨀ VERY LOW [a,d] due to inconsistency, imprecision	RR 0.47 (0.17 to 1.26)	405 per 1000	215 fewer per 1000 (from 336 fewer to 105 more)
Extra-pancreatic infection (Blood culture positive sepsis) < 1 year	60 (1 study) 14 days	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.17 to 1.48)	267 per 1000	133 fewer per 1000 (from 221 fewer to 128 more)
Extra-pancreatic infection (Pneumonia/ARDS) < 1 year	60 (1 study) 14 days	⨁⨁⨀⨀ LOW [a,b] due to risk of bias, imprecision	RR 0.65 (0.37 to 1.14)	567 per 1000	198 fewer per 1000 (from 357 fewer to 79 more)
Extra-pancreatic infection (Urinary tract infection) < 1 year	60 (1 study) 14 days	⨁⨁⨀⨀ LOW [a,b] due to risk of bias,	RR 0.35 (0.16 to 0.77)	567 per 1000	368 fewer per 1000 (from 130 fewer to 476 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No therapy	Risk difference with Antibiotic therapy (95% CI)
		imprecision			
Serious adverse events (Multiorgan failure) < 1 year	267 (4 studies) 1-6 weeks	⊕⊕⊕⊖ MODERATE [a] due to imprecision	RR 0.93 (0.73 to 1.20)	394 per 1000	28 fewer per 1000 (from 106 fewer to 79 more)
Serious adverse events (major organ complications) < 6 months	58 (1 study) time-point unclear	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.6 (0.24 to 1.51)	333 per 1000	133 fewer per 1000 (from 253 fewer to 170 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(c) Downgraded by 1 or 2 increments because heterogeneity, I2=59%, p=0.12, unexplained by subgroup analysis
(d) Downgraded by 1 or 2 increments because heterogeneity, I2=78%, p=0.0003, unexplained by subgroup analysis

Table 53: Clinical evidence summary: Prophylactic antimicrobial therapy versus placebo

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Antibiotic therapy (95% CI)
Mortality < 1 year	255 (3 studies) 10-42 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.09 (0.58 to 2.08)	105 per 1000	9 more per 1000 (from 44 fewer to 113 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Antibiotic therapy (95% CI)
Infected necrosis < 1 year	235 (3 studies) 10-42 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.18 (0.7 to 2)	150 per 1000	27 more per 1000 (from 45 fewer to 150 more)
Extra-pancreatic infection < 1 year	258 (3 studies) 10-42 days	⊕⊕⊕⊖ MODERATE [b] due to imprecision	RR 0.77 (0.53 to 1.11)	364 per 1000	84 fewer per 1000 (from 171 fewer to 40 more)
Serious adverse events < 6 months	100 (1 study) 42 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.67 (0.26 to 1.73)	180 per 1000	59 fewer per 1000 (from 133 fewer to 131 more)
Serious adverse events (Pulmonary insufficiency) < 6 months	113 (1 study) 21 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.99 (0.66 to 1.48)	455 per 1000	5 fewer per 1000 (from 155 fewer to 218 more)
Serious adverse events (Renal insufficiency) < 6 months	113 (1 study) 21 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.11 (0.4 to 3.09)	109 per 1000	12 more per 1000 (from 65 fewer to 228 more)
Serious adverse events (Shock) < 6 months	113 (1 study) 21 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.68 (0.23 to 2.01)	127 per 1000	41 fewer per 1000 (from 98 fewer to 129 more)
Serious adverse events (SIRS) < 6 months	113 (1 study) 21 days	⊕⊕⊖⊖ LOW [a,b] due to risk of bias, imprecision	RR 1.22 (0.83 to 1.8)	436 per 1000	96 more per 1000 (from 74 fewer to 349 more)
Serious adverse events (multi-organ failure) < 6	41	⊕⊖⊖⊖	RR 1.12	526 per	63 more per 1000

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Antibiotic therapy (95% CI)
months	(1 study) 10 days	VERY LOW [a,b] due to risk of bias, imprecision	(0.65 to 1.95)	1000	(from 184 fewer to 500 more)
Colonisation by resistant organism < 6 months	80 (1 study) 42 days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 2.5 (0.51 to 12.14)	50 per 1000	75 more per 1000 (from 25 fewer to 557 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 54: Clinical evidence summary: Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (same class)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Imipenem	Risk difference with Meropenem (95% CI)
Mortality < 1 year	176 (1 study) 14 days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.2 (0.55 to 2.63)	114 per 1000	23 more per 1000 (from 51 fewer to 185 more)
Infected necrosis < 1 year	176 (1 study) 14 days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.38 to 1.83)	136 per 1000	23 fewer per 1000 (from 85 fewer to 113 more)
Extra-pancreatic infection < 1 year	176	⊕⊖⊖⊖	RR 0.9	239 per	24 fewer per 1000

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Imipenem	Risk difference with Meropenem (95% CI)
	(1 study) 14 days	VERY LOW[a,b] due to risk of bias, imprecision	(0.52 to 1.56)	1000	(from 115 fewer to 134 more)
Serious adverse event (Multiorgan failure) < 6 months	176 (1 study) 14 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.75 (0.27 to 2.07)	91 per 1000	23 fewer per 1000 (from 66 fewer to 97 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 55: Clinical evidence summary: Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (different class)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Imipenem	Risk difference with Pefloxacin (95% CI)
Mortality < 1 year	60 (1 study) 2 weeks	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.67 (0.44 to 6.36)	100 per 1000	67 more per 1000 (from 56 fewer to 536 more)
Infected necrosis < 1 year	60 (1 study) 2 weeks	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, imprecision	RR 3.33 (1.02 to 10.92)	100 per 1000	233 more per 1000 (from 2 more to 992 more)
Extra-pancreatic infection < 1 year	60 (1 study) 2 weeks	⨁⨁⊖⊖ LOW[a,b] due to risk of bias,	RR 2.17 (0.95 to 4.94)	200 per 1000	234 more per 1000 (from 10 fewer to 788 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Imipenem	Risk difference with Pefloxacin (95% CI)
		imprecision			

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

16.4 Economic evidence

16.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

16.4.2 Unit costs

See appendix N.11.

16.5 Evidence statements

16.5.1 Clinical

All evidence was from randomised trials in adults or young people over 16 years.

16.5.1.1 Prophylactic antimicrobial therapy versus no prophylaxis

- Evidence from 5 studies comparing prophylactic antimicrobial therapy versus no prophylaxis suggested a clinically important benefit for extra-pancreatic infections (6 studies; n=340; very low quality). There was also evidence to suggest a clinically important benefit specifically for sepsis, pneumonia or ARDS and urinary tract infections (1 study; n=60; very low quality), but not for peri-pancreatic infections (2 studies; n=133; very low quality). There was evidence to suggest a clinically important benefit of prophylactic antimicrobial therapy for infected necrosis (5 studies; n=301; moderate quality), and for the same outcome when the therapy was administered as selected decontamination (1 study; n=102; moderate quality). A clinically important benefit of prophylactic antimicrobial therapy was also shown for mortality (6 studies; n=344; high quality), and in a further study for the same outcome when the therapy was administered as selected decontamination (1 study; n=102; moderate quality). There was mixed evidence for the outcome of serious adverse events, with a possible clinical benefit of prophylactic antimicrobial therapy for multi-organ failure (4 studies; n=267; moderate quality), but evidence to suggest a benefit of the intervention for major organ complications (1 study; n=58; very low quality). Two studies suggested no clinically important difference in terms of length of hospital stay (2 studies; n=74; very low quality).

16.5.1.2 Prophylactic antimicrobial therapy versus placebo

- When prophylactic antimicrobial therapy was compared with placebo, 3 studies suggested no clinically important difference between groups for the outcome of extra-pancreatic infections (3 studies; n=258; moderate quality) or the number of people with infected necrosis (3 studies; n=235; very low quality). However, the evidence also suggested a clinically important benefit of placebo in terms of mortality (3 studies; n=255; very low quality). There was mixed evidence for the outcome of serious adverse events with evidence to suggest a benefit of prophylactic antimicrobial therapy (1 study; n=100; very low quality), but also to suggest a benefit of placebo specifically for multiple-organ failure (1 study; n=41; very low quality), and evidence to suggest no clinically important difference in terms of pulmonary insufficiency, renal insufficiency, shock, and SIRS (1 study; n=113; low to very low quality). The evidence suggested no clinically important difference between groups in terms of colonisation by resistant organisms (1 study; n=80; very low quality).

16.5.1.3 Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (same class)

- A single study comparing the use of meropenem versus imipenem as prophylactic antimicrobial therapy suggested a clinically important benefit of imipenem for mortality (1 study; n=176; very low quality), but no clinical difference between groups for infected necrosis, extra-pancreatic infection and serious adverse events (1 study; n=176; very low quality.

16.5.1.4 Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (different class)

- A single study comparing quinolones (pefloxacin) with carbapenem (imipenem) suggested a clinically important benefit of imipenem for extra-pancreatic infections, infected necrosis and mortality (1 study; n=60; low quality).

16.5.2 Economic

- No relevant economic evaluations were identified.

16.6 Recommendations and link to evidence

Recommendation	24. Do not offer prophylactic antimicrobials to people with acute pancreatitis.
Relative values of different outcomes	The committee considered the following outcomes to be critical for decision-making: quality of life, mortality, length of stay (in CCU or hospital) and infected necrosis. The committee also considered the following outcomes to be important for decision-making: extra-pancreatic infection, colonisation of resistant organisms and serious adverse events. There was no evidence identified for quality of life.
Quality of the clinical evidence	The included studies provided evidence that compared prophylactic antimicrobials with no treatment, placebo and other antimicrobial therapy. The evidence for the prophylactic antimicrobial therapy versus no antimicrobial therapy comparison ranged from very low to high quality. The studies included in this comparison were unblinded RCTs, however, where the outcomes were objective the evidence was not downgraded for this reason under the risk of bias domain. The committee noted the inconsistencies between the blinded and unblinded trials, suggesting the unblinded nature of the earlier RCTs may have overestimated the efficacy of prophylactic antimicrobials and therefore more weight should be given to the placebo-controlled trials. The evidence for the prophylactic antimicrobial therapy versus placebo comparison was predominantly of very low quality, with 1 outcome being of moderate quality and 1 outcome of low quality. The evidence in this comparison is of lower quality as there was consistent evidence of imprecision. The inconsistent results between comparisons and high levels of imprecision demonstrate a great amount of uncertainty surrounding the effectiveness of prophylactic antimicrobials. The evidence for meropenem versus imipenem was graded as very low due to risk of bias and imprecision. The evidence for pefloxacin versus imipenem was graded as low to very low due to risk of bias and imprecision. The committee commented on 1 study comparing prophylactic antimicrobial therapy in the form of selective decontamination versus no therapy. They commented that the use of additional parenteral antibiotic was unclear and possibly related to poor patient performance.
Trade-off between clinical benefits and harms	**Prophylactic antimicrobial therapy versus no prophylactic antimicrobial therapy** When compared with no prophylaxis, prophylactic antimicrobial therapy showed clinically important benefit for the outcomes of mortality and infected necrosis. There was also some evidence of clinically important benefit for the outcomes of extra-pancreatic infections and serious events. There was no evidence of a clinically

important difference between the 2 groups in terms of length of hospital stay.

Prophylactic antimicrobial therapy versus placebo

For the outcome of mortality, there was evidence of clinically important benefit of placebo over prophylactic antimicrobial therapy. There was mixed evidence in terms of serious events, with both evidence of clinical benefit favouring antimicrobial prophylaxis and placebo, and evidence of no difference between interventions. There was also no clinically important difference in colonisation by resistant organisms and extra-pancreatic infections between groups.

Prophylactic antimicrobial therapy versus prophylactic antimicrobial therapy (same class; different class)

There was evidence of clinically important benefit of imipenem over both meropenem and pefloxin in terms of mortality. Imipenem also showed clinical benefit over pefloxin for the outcomes of infected necrosis and extra-pancreatic infection. There was no clinically important difference between imipenem and meropenem in terms of infected necrosis, extra-pancreatic infections and serious adverse events.

Summary

The committee found the evidence for prophylactic antimicrobial therapy in people with acute pancreatitis to be mixed, with no clear demonstration of benefit or harm. The committee noted that there was evidence of clinically important benefit in terms of mortality when antimicrobial therapy was compared with no treatment; however, this was not confirmed when antimicrobial therapy was compared with placebo. The committee agreed that placebo studies are more reliable. When antimicrobial prophylaxis was compared with no prophylactic therapy, there was no difference in length of stay in hospital between the 2 groups. Furthermore, the demonstration of clinical benefit or harm of prophylactic antimicrobial therapy was unclear in infected necrosis, extra-pancreatic infection and serious adverse events across comparisons to no prophylactic treatment, placebo or other antimicrobial therapy. There was also no difference in colonisation between the intervention and control groups when antimicrobial therapy was compared with placebo.

The committee observed that the majority of evidence was of low to very low quality and came from a small number of studies, which were all conducted in a specific population of people with severe acute pancreatitis. They noted that studies did not make a distinction between predicted severe and proven severe acute pancreatitis. The committee also acknowledged that all studies administered antibiotics to people with pancreatitis >72 hours from admission, which could have underestimated the potential efficacy of prophylaxis. The committee noted that only 1 study had reported the outcome of colonisation by resistant organisms, while they were aware that fungal colonisation is an important issue in this population.

The committee noted the absence of evidence in children. They discussed that there was a parallelism in the treatment of adults and children and that the recommendation should apply to all people with acute pancreatitis. This reflects current clinical practice in paediatric units across the country. Paediatric patients are assessed on an individual basis for other co-morbidities such as chemotherapy, immunodeficiency and immunosuppression, but as the pathogenesis of acute pancreatitis is more of inflammatory nature than an infectious one, prophylactic antibiotics have no clear role.

Overall, the committee agreed there was limited evidence of clinical benefit of prophylactic antimicrobial therapy, but also a lack of clear evidence of harm. Nevertheless, there was consensus that the deleterious effect of opportunistic fungal infection in those patients treated with broad spectrum antimicrobial prophylaxis should be taken into account when making a recommendation. Additionally, without strong evidence to support the use of prophylactic antimicrobials in this group it was agreed that it would be appropriate to align practice with the general principle of antimicrobial stewardship to avoid the risk of encouraging antibacterial resistance.

	For these reasons, the committee concluded that the risks outweigh any benefits of antimicrobial prophylaxis and, therefore, antimicrobial prophylaxis should not be routinely used in people admitted to hospital with acute pancreatitis.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. Unit costs were presented to the committee for consideration alongside the clinical evidence. These showed that a course of antimicrobials would cost between £1 and £322 per week depending on the agent and regimen chosen. The committee agreed that prophylactic antimicrobials should not be used for patients with acute episodes of pancreatitis based on the uncertain clinical effectiveness and potential adverse effects. Compared with current practice, where antimicrobials may sometimes be given to people with acute pancreatitis, the only difference caused by this recommendation would be a reduction in spending on antimicrobial drugs. However, any saving would be very small.
Other considerations	The committee noted that there is currently is a large amount of variation in practice with some patients receiving prophylaxis and others not. The NCEPOD report notes that the antibiotic prophylaxis remains a common practice in acute pancreatitis. The committee highlighted the difference between antimicrobial prophylaxis and the use of antimicrobials when the presence of an infection has been identified. They noted that participants in the studies switched to open antimicrobial therapy when there was evidence of infection.

1

1 # MANAGING COMPLICATIONS

17 Methods of management of infected necrosis in people with acute pancreatitis

17.1 Introduction

Acute pancreatitis (AP) accounts for over 50% of all admissions to hospital for pancreatic digestive disease, with an annual incidence of 30-50/100,000, accounting for around 20,000 annual hospital admissions in England. In 20% of patients with AP pancreatic and/or peri-pancreatic necrosis develops, which in the majority of cases occurs in association with transient (<48 h) or persistent (>48 h) organ failure (moderately severe or severe AP respectively in the revised Atlanta classification). Infection may develop in pancreatic necrosis, which is particularly hazardous for the patient if associated with organ failure. Drainage and/or debridement is an established strategy for the management of proven or suspected infected pancreatic necrosis, or for sterile necrosis that is causing pressure symptoms such as gastric outlet obstruction. Drainage and/or debridement of infected necrosis reduces the potential for systemic sepsis, exacerbation of organ failure and development of multi-resistant organisms through prolonged treatment with antibiotics. There are a range of different techniques that can be used for the drainage and/or debridement of pancreatic and peri-pancreatic necrosis from conservative approaches with antibiotics alone, percutaneous drainage, minimal access debridement (percutaneous or endoscopic necrosectomy) and open surgical necrosectomy.

This review attempts to address the relative benefits and risks of different types of intervention for infected or suspected infected pancreatic necrosis.

17.2 Review question: What is the most clinically effective and cost-effective method for managing (suspected) infected necrosis in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 56: PICO characteristics of review question

Population	People admitted to hospital (secondary care, tertiary care) with acute pancreatitis and (suspected) infected necrosis • Adults and young people (>16 years) • Children (≤16 years)
Interventions and comparators	• No treatment • Minimally invasive surgery: percutaneous • Minimally invasive surgery: endoscopic • Open surgery • Percutaneous drainage (radiological) • Antibiotic treatment • Combination of intervention techniques: combined approach upfront • Combination of intervention techniques: step-up approach
Outcomes	Critical • Quality of life at <1 year (continuous) • Mortality at <1 year (dichotomous) • Length of stay (in CCU or hospital) at <1 year (continuous) Important

	• Complications (for example, bleeding, fistulae) at <1 year (dichotomous) • Number of procedures (repeated procedures) at <1 year (dichotomous) • Recurrence of infection at <1 year (dichotomous) • Pancreatic function (for example, development of diabetes) at <1 year (dichotomous)
Key confounders for non-randomised studies	• Percentage necrosis • Positive bacteriology • Presence of organ failure
Study design	Systematic review RCT Non-randomised comparative study

17.3 Clinical evidence

Twelve studies (reported in 13 papers) were included in the review;[15, 16, 41, 42, 48, 60, 87, 89, 103, 107-110] these are summarised in Table 57 below. The aim of all studies was to assess what therapeutic method is most effective in treating (suspected) infected pancreatic necrosis. Two randomised controlled trials, 9 non-randomised studies, and 1 individual patient data meta-analysis of non-randomised cohorts were identified for inclusion in the review and none of the studies included children. One RCT compared minimally invasive surgery (percutaneous or endoscopic) with open surgery. The second RCT compared an endoscopic step-up approach with a minimally-invasive surgical step-up approach. The non-randomised studies assessed the following comparisons: endoscopic step-up approach to percutaneous drainage with step-up to open surgery; minimally invasive surgery (dual modality drainage) to percutaneous drainage; minimally invasive surgery to 3 different types of open surgery; minimally invasive surgery (endoscopic necrosectomy) to open surgery; minimally invasive surgery (endoscopic necrosectomy) to a step-up approach; a step-up approach to open surgery; percutaneous drainage to open surgery; a combination of techniques (percutaneous drainage and video assisted retroperitoneal debridement (VARD)) to open surgery; and a combination of techniques (percutaneous drainage and VARD) to percutaneous drainage. Evidence from these studies is summarised in the clinical evidence summaries below (Table 59 to Table 73) and data not suitable for meta-analysis are presented in Table 58. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 57: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Van Santvoort 2010[109] (Besselink 2006[16])	Intervention: Minimally invasive surgery - Percutaneous. The first step in the step-up approach was percutaneous or endoscopic transgastric drainage. 92% underwent retroperitoneal percutaneous drainage, 2% underwent transabdominal percutaneous drainage and 5% underwent endoscopic transgastric drainage. If there was no clinical improvement after 72 hours and if the position of the drain was inadequate or other fluid collections could be drained, a second drainage procedure was performed. If this was not possible, or if there was no clinical improvement after an	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=88) Mean (SD) age: Percutaneous group: 57.6 (2.1) years Open group: 57.4 (2) years The	• Mortality (during admission) • Length of stay (during admission) • Number of procedures (during admission) • Complications (during admission) • Pancreatic function (during admission)	Randomised controlled trial Postoperative management included the following: Continuous postoperative lavage with normal saline or peritoneal dialysis fluid was started. On the third postoperative day, the

Study	Intervention and comparison	Population	Outcomes	Comments
	additional 72 hours, the second step, video -assisted retroperitoneal debridement with postoperative lavage was performed. (n=43) Comparator: Open surgery. Laparotomy through a bilateral subcostal incision. After blunt removal of all necrotic tissue, 2 large-bore drains for post-operative lavage were inserted, and the abdomen was closed. (n=45)	Netherlands		lavage amounted to at least 10 L per 24 hours. CECT was performed 1 week after every drain placement and surgical intervention. Catheters were removed if collapse of the cavity was shown through CECT.
Besselink 2006[15]	Intervention 1: Open surgery. Open abdomen strategy (OAS): the abdomen was left open following the first laparotomy for debridement; planned relaparotomy or relaparotomy on demand were both possible after the first laparotomy. (n=23) Intervention 2: Open surgery. Continuous postoperative lavage (CPL): rinsing of the necrosectomy areas after debridement for infected pancreatic necrosis (IPN), followed by closure of the abdomen and continuous postoperative local or locoregional lavage with liberal amounts of fluids. (n=53) Intervention 3: Minimally invasive procedures (MIP): open or videoscopically assisted retroperitoneal debridement, followed by closure of the abdomen and continuous local or locoregional lavage with liberal amounts of fluids. The preferred route was straight into the retroperitoneum through a small left-sided lumbar incision. If this was not possible, an anterior transabdominal laparoscopic approach was used. (n=18) Intervention 4: Open surgery. Laparotomy with primary abdominal closure (PAC): laparotomy and blunt debridement of necrotic tissue, followed by abdominal closure with	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=106) Median (range) age: 59 (20-81) years The Netherlands	• Mortality (time-point unclear) • Length of stay (time-point unclear) • Number of procedures (time-point unclear) • Complications (time-point unclear)	Non-randomised study No confounders accounted for Concurrent care not reported. Data for the open surgery groups has been considered together as comparator group.

Study	Intervention and comparison	Population	Outcomes	Comments
	no postoperative lavage system in place. (n=12)			
Garg 2010[41]	Intervention: Combination of interventions, step-up approach. Primary conservative medical treatment: aggressive medical management that included combination antibiotics, organ support, intensive nutritional support and percutaneous drainage if required (for IPN that had become organised and walled off, under US or CT guidance). If clinical improvement was noted, the patient was continued on conservative treatment and antibiotics were given for 4 weeks. If no improvement, the patient was subjected to surgery. (n=50) Comparator: Open surgery. Open surgical necrosectomy, lavage and drainage. Initial surgical treatment included debridement (necrosectomy) and if required (for example, intraoperative bleeding necessitating packing or inadequate necrosectomy), planned re-explorations after 48 hours. When intraoperative assessment was considered satisfactory regarding hemostasis/necrosectomy, the abdomen was closed, multiple drains were placed, and perioperative lavage was carried out. (n=30)	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=80) Mean age: not stated India	• Length of stay in hospital (during admission)	Non-randomised study No confounders accounted for Concurrent care not reported.
Gluck 2012[42]	Intervention: Minimally invasive procedure - endoscopic. CT-guided percutaneous drains were placed, but only 10 mL of fluid was aspirated. The patient was then rapidly transferred to a fluoroscopically equipped endoscopy suite at which time the WOPN was accessed either transgastrically or transduodenally. Endoscopic ultrasound was used if there was an inconclusive luminal bulge. (n=50) Comparator: Percutaneous drainage. Symptomatic SAP patients had percutaneous drainage catheters placed into areas of WOPN. (n=52)	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=102) Mean (SD) age: endoscopic: 55.9 years percutaneous: 53.5 years USA	• Mortality (during admission) • Length of stay (during admission) • Complications (during admission)	Non-randomised study No confounders accounted for All patients received culture directed antibiotics, and all patients were managed by critical care specialists or hospitalists.
He 2017[48]	Intervention: Minimally invasive	Adults admitted	• Mortality (1	Non-

Study	Intervention and comparison	Population	Outcomes	Comments
	procedure – endoscopic step-up approach. Initial session of endoscopic transluminal drainage consisted of an EUS-guided puncture and placement of 2 double-pigtail plastic stents and a nasocystic catheter in the necrotic collection. If a patient did not have clinical improvement or changes in pancreatic necrosis after 3-5 days, the patient proceeded to endoscopic transluminal necrosectomy (ETN). Patients with clinical improvement would be observed to see if symptoms would appear again or the necrotic cavity hadn't decreased after 2 weeks, in which case they would also receive ETN. (n=13) Comparator: Minimally invasive procedure – percutaneous step-up approach to open surgery. Percutaneous drainage consisted of CT or ultrasound-guided placement of 12-16 Fr catheters in the pancreatic or peripancreatic collection using the Seldinger technique. Drains were flushed with 0.9% saline solution every 8 hours. Clinical improvement was observed 3-5 days after the procedure. If there is no clinical improvement or changes in pancreatic necrosis, 1 or more catheters were changed to double-catheterisation cannulas. Open surgical debridement of necrotic tissue with placement of 2 large bore drains for post-operative lavage was performed if necessary. (n=13)	or transferred to hospital with suspected infected pancreatic necrosis (n=26) Median (IQR) age: endoscopic group: 48 (27-55) years percutaneous group 48 (43-59) years China	year) • Length of stay (hospital and CCU; during admission) • Complications (upper gastrointestinal bleeding, intra-abdominal bleeding requiring intervention, enterocutaneous fistula or perforation, pancreatic fistula, new-onset organ failure, multiple organ failure) (1 year)	randomised study No confounders accounted for All patients received enteral nutrition, and an oral diet was restored if oral feeding was tolerated. If the required caloric intake would not be reached, the patient would receive additional parenteral nutrition. All patients received intravenous antibiotics which were stopped if there was clinical improvement
Kumar 2014[60]	Intervention 1: Minimally invasive surgery - Endoscopic. All procedures were performed by a single endoscopist using a standardised technique. Linear endoscopic ultrasound was employed to localise the site of WOPN entry and avoid vascular injury. Walled off pancreatic necrosis contents were aspirated and sent for Gram stain and culture. (n=12) Comparator: Combination of intervention techniques - Step-up approach. With the use of cross-	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=24) Mean (SD) age: endoscopic: 58.9 (3.9) years step-up: 53.3 (3) years	• Mortality (during admission) • Length of stay (during admission) • Complications (during admission) • Number of procedures (during admission) • Pancreatic function	Non-randomised study Matched cohorts for collection size and Charlson comorbidity index

Study	Intervention and comparison	Population	Outcomes	Comments
	sectional imaging to avoid injury to vasculature and organs, a percutaneous needle was placed into the necrotic collection. Fluid was aspirated and sent for Gram stain and culture. The collection was followed with repeat cross-sectional imaging. If the collection size was no longer decreasing with irrigation, the drains were repositioned or additional drains were placed at the discretion of the radiologist. Those patients with lack of response to drainage or with clinical signs or symptoms of infection or abdominal pain were taken to surgery at the discretion of the surgical team. Surgical technique was at the discretion of the attending surgeon and included both open and minimally invasive approaches. (n=12)	USA	(during admission)	
Pupelis 2015[87]	Intervention: Minimally invasive procedure. Ultrasound-guided percutaneous acute necrotic collections (ANC) drainage was performed under local anaesthesia. Ultrasound-guided surgery included a provision of intraoperative ultrasound and ultrasound-guided minimally invasive interventions. The main intraoperative ultrasound steps were as follows: stereotypical diagnostics ensuring the recognition of anatomical structures and its relation to ANC and necrotic tissue; intraoperative navigation - precise definition of the surgical access; intraoperative monitoring - ultrasonography in real time during the surgical manipulation in reaching deep collections through the avascular zone; controlled drain provision; precise definition of necroses and assistance in focused necrosectomy. (n=31) Comparator: Open surgery. Conventional open necrosectomy was performed using the longitudinal midline or bilateral subcostal trand-peritoneal approach, adhering to the semi-opened or closed drainage principles. The laparotomy was executed providing examination of the abdominal cavity, peripancreatic	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=70) Median (IQR) age: Minimally-invasive: 52 (46-64) years Open: 47 (41-62) years Latvia	• Mortality (during admission) • Length of stay (during admission) • Number of procedures (during admission) • Complications (during admission)	Non-randomised study No confounders accounted for All patients received conservative treatment during the early phase of the disease.

Study	Intervention and comparison	Population	Outcomes	Comments
	and paracolic spaces and providing proper necrosectomy using blunt finger dissection combined with a suction and drainage. Once the necrosectomy was finished, 2 large bore drains for postoperative lavage were inserted, and the abdomen was closed in cases when completeness of necrosectomy was achieved. (n=39)			
Rasch 2016[89]	Intervention: Combination of interventions, step-up approach. 190/220 patients were treated according to a step-up approach. (n=190) Comparator: Open surgery. Primary open surgical necrosectomy was performed in 30/220. 36/190 patients in the step-up group needed open surgical intervention later in the course of disease. (n=30)	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=220) Age range: 18-88 Germany	• Mortality (during admission or within 4 weeks of discharge) • Length of stay (during admission) • Complications (during admission) • Pancreatic function (during admission)	Non-randomised study No confounders accounted for Concurrent care not reported.
Szeliga 2014[103]	Intervention 1: Combination of interventions. Type 1: laparotomy plus necrosectomy plus passive drainage (scheduled repeated laparotomies) plus targeted antibiotic therapy. (n=7) Intervention 2: Combination of interventions. Type 2: laparotomy plus necrosectomy plus active drainage plus targeted antibiotic therapy. (n=5) Intervention 3: Combination of interventions. Type 3: video-assisted retroperitoneal debridement. For patients in whom an attempt of percutaneous drainage to collect fluid or foci of pancreatic necrosis had been made, but no satisfactory clinical outcomes were observed after such a procedure. Approx. 5-cm incision in the left lumbar area was made at the site of a drain to be introduced, or after determination during an ultrasound examination so that it would not interfere with significant anatomical structures (for example, large vessels) and would be	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=34) Mean (range) age: 52 (28-78) years Poland	• Mortality (perioperative) • Length of stay (during admission) • Complications (perioperative)	Non-randomised study No confounders accounted for Concurrent care not reported.

Study	Intervention and comparison	Population	Outcomes	Comments
	at the lowest distance in relation to the target space indicated for drainage. After integuments were dissected, the peri-pancreatic space was reached bluntly, most frequently with a finger and under ultrasound supervision, so to achieve free flow of infected, necrotic tissues. Then a laparoscopic camera was introduced and under video supervision necrotic tissues were flushed out using a suction-flushing device. No attempt was undertaken to remove fragments of necrotic pancreas that were not demarcated; they were left for subsequently placed active flushing gravitational drainage covering the bed after necrosectomy. (n=12) Intervention 4: Percutaneous drainage. Type 4: Percutaneous drainage (12 to 20 F drains) of necrotic and suppurative cisterns from the pancreatic area. (n=10)			
Van Brunschot 2017 (B)[108]	Intervention: Minimally invasive procedure – endoscopic step-up approach. Endoscopic ultrasound-guided transluminal (transgastric or transduodenal) drainage with placement of 2 double-pigtail stents and 1 nasocystic catheter. If drainage alone did not lead to considerable clinical improvement endoscopic transluminal necrosectomy was performed. (n=51) Comparator: Minimally invasive procedure – percutaneous step-up approach to video-assisted retroperitoneal debridement. Radiological CT-guided or ultrasound-guided percutaneous catheter drainage, preferably through the left retroperitoneum with the catheter as guidance for video-assisted retroperitoneal debridement (VARD) if needed. If drainage was not successful a VARD procedure was performed. (n=47)	Adults with acute pancreatitis and a high suspicion or evidence of infected necrosis with an indication for invasive intervention and for whom both the endoscopic and surgical step-up approach were deemed feasible. (n=98) Mean (SD) age: Endoscopic: 63 (14) years Surgical: 60 (11) years The Netherlands	• Mortality (6 months) • Complications (6 months) • Pancreatic function (6 months) • Length of hospital stay (6 months) • Number of procedures (6 months)	Randomised controlled trial Additional endoscopic/percutaneous drainage and endoscopic or surgical necrosectomies were allowed
Van Brunschot 2017 (A)[107]	Intervention: Minimally invasive procedure – endoscopic. Endoscopic pancreatic necrosectomy following endoscopic ultrasound-guided	Adults undergoing surgical necrosectomy	• Mortality (during admission)	Non-randomised study - individual

Study	Intervention and comparison	Population	Outcomes	Comments
	transgastric or transduodenal drainage of the pancreatic necrotic cavity. Usually, the drainage canal is created using electrocautery and balloon dilation. For endoscopic necrosectomy, further balloon dilation is needed in order to allow entrance of necrosectomy instruments (for example, snares, baskets, grasping forceps). (n=127) Intervention: Minimally invasive procedure. Minimally invasive surgical pancreatic necrosectomy is usually preceded by radiologic catheter drainage, the drain being preferably placed in the left retroperitoneum. A small incision close to the drain entrance allows the surgeon to follow the drain tract into the necrotic cavity. Subsequent pancreatic necrosectomy can be performed under direct vision or videoscopic guidance using basic surgical instruments. (n=335) Comparator: Open surgery. Pancreatic necrosectomy performed through a bilateral subcostal incision with blunt and/or surgical removal of necrotic tissue. (n=462) All groups: Postprocedural lavage and re-necrosectomy was performed at the treating physician's discretion.	or endoscopic necrosectomy for pancreatic and/or peripancreatic necrosis. (n=1485; 924 in infected necrosis subgroup) Mean (SD) age: Minimally invasive: 45 (11); open (MI matched): 46 (14); endoscopic: 41 (14); open (endoscopic matched): 42 (10) years Brazil, Canada, Germany, Hungary, India, Netherlands, United Kingdom, USA		patient data meta-analysis using propensity matching Unclear if literature search was adequate; none of the other studies included in this report were identified
Van Santvoort 2007[110]	Intervention: Percutaneous drainage. As the first step, a 12F to 14F percutaneous drain is placed in the collection through the left retroperitoneum. If drainage does not lead to clinical improvement (combined normalisation of body temperature and decreased WBC count and CRP level) within the next days, the patient is operated on. (n=15) Comparator: Open surgery. Open necrosectomy. After a bilateral subcostal or median incision, the lesser sac is entered through the gastrocolic omentum. Blunt debridement of all necrotic tissue is performed. Two double-lumen catheters are inserted through	Adults admitted to hospital with acute pancreatitis with infected or suspected infected necrosis. (n=30) Median (range) age: Percutaneous: 52 (34-66) years Open: 53 (39-75) years The Netherlands	• Mortality (during admission) • Length of stay (during admission) • Number of procedures (during admission) • Complications (during admission)	Non-randomised study Matched for organ failure prior to necrosectomy, infection of pancreatic or peripancreatic necrosis, timing of surgery, age, and CTSI score. Concurrent care not

Study	Intervention and comparison	Population	Outcomes	Comments
	separate incisions and positioned in the retroperitoneal space. Six patients received pre-operative PCD. (n=15)			reported.

1

Table 58: Data not suitable for meta-analysis

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Van Santvoort 2010 [109](Besselink 2006 [16])	Minimally invasive procedure versus open surgery	Length of stay in hospital	Median (Range): **50 (1–287)**	43	Median (Range): **60 (1–247)**	45	High
Van Santvoort 2010 [109](Besselink 2006 [16])	Minimally invasive procedure versus open surgery	Length of stay in CCU	Median (Range): **9 (0–281)**	43	Median (Range): **11 (0–111)**	45	High
Besselink 2006 [15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in hospital)	Median (Range): **35 (18–162)**	18	Median (Range): **13 (1–62)**	12	Very high
Besselink 2006[15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in hospital)	Median (Range): **35 (18–162)**	18	Median (Range): **87 (8–236)**	53	Very high
Besselink 2006[15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in hospital)	Median (Range): **35 (18–162)**	18	Median (Range): **70 (45–139)**	23	Very high
Besselink 2006[15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in CCU)	Median (Range): **2 (0–83)**	18	Median (Range): **2 (0–17)**	12	Very high
Besselink 2006[15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in CCU)	Median (Range): **2 (0–83)**	18	Median (Range): **10 (0–206)**	53	Very high
Besselink 2006[15]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in CCU)	Median (Range): **2 (0–83)**	18	Median (Range): **16 (0–68)**	23	Very high
Garg 2010 [41]	Step-up approach versus open surgery	Length of stay in hospital	Median (Range): **26.5 (2–80)**	50	Median (Range): **32 (6–90)**	30	Very high

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Pupelis 2015 [87]	Minimally invasive procedure versus open surgery	Length of stay in hospital	Median (IQR): **61 (53-71)**	31	Median (IQR): **68 (48–97)**	39	Very high
Pupelis 2015 [87]	Minimally invasive procedure versus open surgery	Length of stay in CCU	Median (IQR): **12.5 (8-29)**	31	Median (IQR): **29 (18–37)**	39	Very high
Rasch 2016 [89]	Step-up approach versus open surgery	Length of stay in hospital	Median (Range): **42 (16-367)**	190	Median (Range): **74 (21–239)**	30	Very high
Szeliga 2014 [103]	Minimally invasive procedure versus open surgery	Length of stay in hospital	Mean: **41**	10	Mean: **145**	7	Very high
Szeliga 2014 [103]	Minimally invasive procedure versus open surgery	Length of stay in hospital	Mean: **41**	10	Mean: **85**	5	Very high
Szeliga 2014 [103]	Combination approach versus minimally invasive procedure	Length of stay in hospital	Mean: **66**	12	Mean: **41**	10	Very high
Van Brunschot 2017 (B)[108] - RCT	Endoscopic step-up versus percutaneous drainage with step-up to minimally invasive surgery	Number of drainage procedures	Median (IQR): **3 (2-6)**	51	Median (IQR): **4 (2–6)**	47	Low
Van Brunschot 2017 (B)[108]- RCT	Endoscopic step-up versus percutaneous drainage with step-up to minimally invasive surgery	Length of stay in hospital	Median (IQR): **35 (19-85)**	51	Median (IQR): **65 (40–90)**	47	Low
Van Santvoort 2007 [110]	Minimally invasive procedure versus open surgery	Postoperative length of stay (in hospital)	Median (Range): **57 (18-162)**	15	Median (Range): **54 (20–150)**	15	Very high

Table 59: Clinical evidence summary: Minimally invasive surgery compared with open surgery (Randomised controlled trial)

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgery	Risk difference with Minimally invasive surgery (95% CI)
Mortality	88 (1 study) during admission	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.2 (0.47 to 3.01)	156 per 1000	31 more per 1000 (from 82 fewer to 313 more)
Complications (Enterocutaneous fistula or perforation of a visceral organ requiring intervention)	88 (1 study) during admission	⨁⨁⨀⨀ LOW [a] due to imprecision	RR 0.63 (0.25 to 1.58)	222 per 1000	82 fewer per 1000 (from 167 fewer to 129 more)
Complications (Intra-abdominal bleeding)	88 (1 study) during admission	⨁⨁⨀⨀ LOW [a] due to imprecision	RR 0.73 (0.31 to 1.75)	222 per 1000	60 fewer per 1000 (from 153 fewer to 167 more)
Complications (Multiple organ failure)	88 (1 study) during admission	⨁⨁⨁⨁ HIGH	RR 0.29 (0.12 to 0.71)	400 per 1000	284 fewer per 1000 (from 116 fewer to 352 fewer)
Complications (Multiple systemic complications)	88 (1 study) during admission	⨁⨁⨁⨀ MODERATE [a] due to imprecision	RR 0.35 (0.01 to 8.33)	22 per 1000	14 fewer per 1000 (from 22 fewer to 163 more)
Complications (New-onset multiple organ failure)	88 (1 study) during admission	⨁⨁⨁⨁ HIGH	RR 0.28 (0.11 to 0.67)	422 per 1000	304 fewer per 1000 (from 139 fewer to 376 fewer)
Pancreatic function (New-onset diabetes)	88 (1 study) during admission	⨁⨁⨁⨀ MODERATE [a] due to imprecision	RR 0.43 (0.2 to 0.93)	378 per 1000	215 fewer per 1000 (from 26 fewer to 302 fewer)

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgery	Risk difference with Minimally invasive surgery (95% CI)
Pancreatic function (Use of pancreatic enzymes)	88 (1 study) during admission	⨁⨁⨁⨁ HIGH	RR 0.21 (0.07 to 0.67)	333 per 1000	263 fewer per 1000 (from 110 fewer to 310 fewer)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 60: Clinical evidence summary: Minimally invasive surgery (endoscopic) compared with open surgery

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgery	Risk difference with Minimally invasive surgery versus open surgery (95% CI)
Mortality	254 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.32 (0.18 to 0.58)	268 per 1000	182 fewer per 1000 (from 112 fewer to 220 fewer) [b]

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Absolute risk not adjusted for paired data

Table 61: Clinical evidence summary: Endoscopic step-up compared with percutaneous drainage, with step-up to open surgery

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Endoscopic versus percutaneous (95% CI)
Mortality	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.18 (0.3 to 4.72)	231 per 1000	42 more per 1000 (from 162 fewer to 858 more)
Length of stay (hospital)	24 (1 study) during	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of		The mean length of stay (hospital) in the control groups was	The mean length of stay (hospital) in the intervention groups was 26 lower

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Endoscopic versus percutaneous (95% CI)
	admission	bias, imprecision		66 days	(50.96 to 1.04 lower)
Length of stay (CCU)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of stay (CCU) in the control groups was 25 days	The mean length of stay (CCU) in the intervention groups was 8 lower (20.44 lower to 4.44 higher)
Complications (new-onset organ failure)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.18 (0.2 to 7.06)	154 per 1000	28 more per 1000 (from 123 fewer to 932 more)
Complications (multiple organ failure)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.86 (0.17 to 452.79)	0 per 1000	91 more per 1000 (from 120 fewer to 302 more)[c]
Complications (upper gastrointestinal bleeding)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[b] due to risk of bias, imprecision	Peto OR 8.86 (0.17 to 452.79)	0 per 1000	91 more per 1000 (from 120 fewer to 302 more)[c]
Complications (intra-abdominal bleeding requiring intervention)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.59 (0.06 to 5.68)	154 per 1000	63 fewer per 1000 (from 145 fewer to 720 more)
Complications (enterocutaneous fistula or perforation)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.24 (0.03 to 1.73)	385 per 1000	292 fewer per 1000 (from 373 fewer to 281 more)
Complications (Pancreatic fistula)	24 (1 study) during admission	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.16 (0 to 8.06)	77 per 1000	64 fewer per 1000 (from 77 fewer to 325 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Risk difference calculated in Review Manager

Table 62: Clinical evidence summary: Endoscopic step-up compared with minimally-invasive surgical step-up approach

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Endoscopic step-up versus surgical step-up (95% CI)
Mortality	98 (1 study) 6 months	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.38 (0.53 to 3.59)	128 per 1000	49 more per 1000 (from 60 fewer to 332 more)
Length of hospital stay	98 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to imprecision		Mean 69 days	The mean length of hospital stay in the intervention groups was 16 days lower (32.86 lower to 0.86 higher)
Complications - Bleeding requiring reintervention	98 (1 study) 6 months	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.01 (0.47 to 2.17)	213 per 1000	2 more per 1000 (from 113 fewer to 249 more)
Complications – New-onset multiple organ failure	98 (1 study) 6 months	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 0.31 (0.07 to 1.45)	128 per 1000	88 fewer per 1000 (from 119 fewer to 58 more)
Complications – New-onset single organ failure	98 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 0.5 (0.22 to 1.14)	277 per 1000	139 fewer per 1000 (from 216 fewer to 39 more)
Complications - Pancreatic fistula	83 (1 study) 6 months	⨁⨁⨁⨁ HIGH	RR 0.15 (0.04 to 0.62)	317 per 1000	269 fewer per 1000 (from 120 fewer to 304 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Endoscopic step-up versus surgical step-up (95% CI)
Complications - Perforation of visceral organ or enterocutaneous fistula requiring intervention	98 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 0.46 (0.15 to 1.43)	170 per 1000	92 fewer per 1000 (from 145 fewer to 73 more)
Pancreatic function - Endocrine insufficiency	83 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 1.08 (0.49 to 2.39)	220 per 1000	18 more per 1000 (from 112 fewer to 306 more)
Pancreatic function - Exocrine insufficiency	83 (1 study) 6 months	⨁⨁⊖⊖ LOW[a] due to imprecision	RR 1.13 (0.73 to 1.75)	463 per 1000	60 more per 1000 (from 125 fewer to 347 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 63: Clinical evidence summary: Minimally invasive procedure (dual modality drainage) versus percutaneous drainage

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Percutaneous drainage	Risk difference with Dual modality drainage (95% CI)
Mortality	94 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.61 (0.11 to 3.5)	67 per 1000	26 fewer per 1000 (from 59 fewer to 167 more)
Length of stay in hospital	94 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias		The mean length of stay in the control group was 24 days	The mean length of stay in hospital in the intervention groups was 30 lower (43.6 to 16.4 lower)
Complications (Pseudoaneurysm)	94 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	OR 0.11 (0.02 to 0.68)	111 per 1000	98 fewer per 1000 (from 33 fewer to 109 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 64: Clinical evidence summary: Minimally invasive surgery (open or videoscopically-assisted tretroperitoneal debridement/necrosectomy) versus open surgery (open abdomen strategy, or continuous postoperative lavage, or laparotomy with primary abdominal closure)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgery	Risk difference with Minimally invasive surgery versus open surgery (95% CI)
Mortality	106 (1 study) unclear	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.29 (0.08 to 1.09)	386 per 1000	274 fewer per 1000 (from 355 fewer to 35 more)
Mortality	669 (1 study) during admission	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.75 (0.57 to 0.98)	239 per 1000	60 fewer per 1000 (from 5 fewer to 103 fewer)[c]
Complications (Bleeding)	106 (1 study) unclear	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.49 (0.17 to 1.43)	341 per 1000	174 fewer per 1000 (from 283 fewer to 147 more)
Complications (Bowel perforation)	106 (1 study) unclear	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.81 (0.27 to 2.48)	205 per 1000	39 fewer per 1000 (from 149 fewer to 303 more)
Number of procedures (Reintervention)	106 (1 study) unclear	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.92 (0.65 to 1.3)	727 per 1000	58 fewer per 1000 (from 255 fewer to 218 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Absolute risk not adjusted for paired data

Table 65: Clinical evidence summary: Combination of interventions (Step-up approach) versus open surgery (open necrosectomy)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgery	Risk difference with Step-up approach (95% CI)
Mortality	220 (1 study) during admission or within 4 weeks of discharge	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	RR 0.32 (0.16 to 0.61)	333 per 1000	227 fewer per 1000 (from 130 fewer to 280 fewer)
Severe complication (Sepsis, persistent MODS or erosion bleeding)	220 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	RR 0.54 (0.43 to 0.67)	833 per 1000	383 fewer per 1000 (from 275 fewer to 475 fewer)
Pancreatic function (Emergence of type 3c diabetes)	220 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	RR 0.14 (0.06 to 0.32)	333 per 1000	287 fewer per 1000 (from 227 fewer to 313 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 66: Clinical evidence summary: Minimally invasive surgery (Focused open necrosectomy) versus open surgery (conventional open surgery)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional open necrosectomy	Risk difference with Focused open necrosectomy (95% CI)
Mortality	70 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.5 (0.1 to 2.42)	128 per 1000	64 fewer per 1000 (from 115 fewer to 182 more)
Complications (Intestinal fistulae)	70 (1 study) during	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias,	RR 1.68 (0.41 to 6.94)	77 per 1000	52 more per 1000 (from 45 fewer to 457 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional open necrosectomy	Risk difference with Focused open necrosectomy (95% CI)
	admission	imprecision			
Complications (Pancreatic fistulae)	70 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.01 (0.29 to 3.43)	128 per 1000	1 more per 1000 (from 91 fewer to 312 more)
Number of repeated procedures (Repeat necrosectomy)	70 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.56 (0.28 to 1.11)	462 per 1000	203 fewer per 1000 (from 332 fewer to 51 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 67: Clinical evidence summary: Percutaneous drainage versus combination of interventions (laparotomy plus necrosectomy plus active drainage)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lap plus Nec plus Active drainage	Risk difference with PCD (95% CI)
Mortality	15 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.5 (0.04 to 6.44)	200 per 1000	100 fewer per 1000 (from 192 fewer to 1000 more)
Complications (Wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula)	15 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.25 (0.08 to 0.76)	1000 per 1000	750 fewer per 1000 (from 240 fewer to 920 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 68: Clinical evidence summary: Percutaneous drainage versus combination of interventions (laparotomy plus necrosectomy plus passive drainage)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lap plus Nec plus Passive drainage	Risk difference with PCD (95% CI)
Mortality	17 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.14 (0.02 to 0.95)	714 per 1000	614 fewer per 1000 (from 36 fewer to 700 fewer)
Complications (Wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula)	17 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.24 (0.08 to 0.73)	1000 per 1000	760 fewer per 1000 (from 270 fewer to 920 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 69: Clinical evidence summary: Combination of interventions (percutaneous drainage plus VARD) versus combination of interventions (laparotomy plus necrosectomy plus active drainage)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lap plus Nec plus AD	Risk difference with PCD plus VARD (95% CI)
Mortality	17 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.83 (0.1 to 7.24)	200 per 1000	34 fewer per 1000 (from 180 fewer to 1000 more)
Complications (Wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula)	17 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.55 (0.3 to 0.99)	1000 per 1000	450 fewer per 1000 (from 10 fewer to 700 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 70: Clinical evidence summary: Combination of interventions (Percutaneous drainage plus VARD) versus combination of interventions (laparotomy plus necrosectomy plus passive drainage)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lap plus Nec plus PD	Risk difference with PCD plus VARD (95% CI)
Mortality	19 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.23 (0.06 to 0.9)	714 per 1000	550 fewer per 1000 (from 71 fewer to 671 fewer)
Complications (Wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula)	19 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.53 (0.3 to 0.95)	1000 per 1000	470 fewer per 1000 (from 50 fewer to 700 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 71: Clinical evidence summary: Combination of interventions (percutaneous drainage plus VARD) versus percutaneous drainage

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PCD	Risk difference with PCD plus VARD (95% CI)
Mortality	22 (1 study) perioperative	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.67 (0.18 to 15.8)	100 per 1000	67 more per 1000 (from 82 fewer to 1000 more)
Complications (Wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula)	22 (1 study) perioperativ	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias,	RR 2.5 (0.64 to 9.77)	200 per 1000	300 more per 1000 (from 72 fewer to 1000 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PCD	Risk difference with PCD plus VARD (95% CI)
	e	imprecision			

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 72: Clinical evidence summary: Percutaneous drainage versus open surgery (laparotomy)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laparotomy	Risk difference with Percutaneous drainage (95% CI)
Mortality	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.17 (0.02 to 1.22)	400 per 1000	332 fewer per 1000 (from 392 fewer to 88 more)
Complications (Bleeding)	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 4 (0.5 to 31.74)	67 per 1000	200 more per 1000 (from 33 fewer to 1000 more)
Complications (Bowel perforation)	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.5 (0.05 to 4.94)	133 per 1000	67 fewer per 1000 (from 127 fewer to 525 more)
Complications (GI fistulas)	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.33 (0.04 to 2.85)	200 per 1000	134 fewer per 1000 (from 192 fewer to 370 more)
Complications (Pancreatic fistulas)	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias,	Peto OR 7.94 (0.47 to 133.26)	0 per 1000	133 more per 1000 (from 64 fewer to 330 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laparotomy	Risk difference with Percutaneous drainage (95% CI)
		imprecision			
Number of repeated procedures (Further necrosectomy)	30 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.85 (0.59 to 1.22)	867 per 1000	130 fewer per 1000 (from 355 fewer to 191 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 73: Clinical evidence summary: Minimally invasive procedure (direct endoscopic necrosectomy) versus combination of interventions (step-up approach, drainage and surgery)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Step-up approach	Risk difference with Minimally invasive surgery (95% CI)
Mortality	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	Not estimable [c]	No events	
Length of stay	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias		The mean floor length of stay in the control groups was 23.6	The mean floor length of stay in the intervention groups was 18.3 lower (22.07 to 14.53 lower)
Complications	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.13 (0.02 to 0.85)	667 per 1000	580 fewer per 1000 (from 100 fewer to 653 fewer)
Number of procedures	24 (1 study)	⨁⊖⊖⊖ VERY LOW [a]		The mean number of procedures in the control groups was	The mean number of procedures in the intervention groups was

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Step-up approach	Risk difference with Minimally invasive surgery (95% CI)
	during admission	due to risk of bias		2.8	1.3 lower (1.5 to 1.1 lower)
Pancreatic function (new exocrine insufficiency)	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.6 (0.18 to 1.97)	417 per 1000	167 fewer per 1000 (from 342 fewer to 404 more)
Pancreatic function (new endocrine insufficiency)	24 (1 study) during admission	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	Peto OR 0.07 (0.01 to 0.37)	583 per 1000	494 fewer per 1000 (from 242 fewer to 570 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Could not be calculated as there were no events in the intervention or comparison group

17.4 Economic evidence

17.4.1 Published literature

Two health economic studies were identified with relevant comparisons and have been included in this review.[108, 109] These are summarised in the health economic evidence profiles below (Table 74 and Table 75) and the health economic evidence tables in appendix I.

See also the health economic study selection flow chart in appendix F.

Table 74: Health economic evidence profile: minimally invasive (endoscopic or percutaneous) step-up approach versus open surgery

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
Van Santvoort	Partially	Potentially	• Cost–consequences	−£4,977	Death: +3%	Death	No sensitivity analysis was

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
2010 [109] (Netherlands)	applicable[(a)]	serious limitations[(b)]	analysis (within RCT economic evaluation) • 6-month follow-up • Patients were randomly assigned to either primary open necrosectomy or a minimally invasive step-up approach	(favouring the minimally invasive approach)	(favours open surgery) Length of stay: −2 days in CCU, −10 days in hospital (favours the minimally invasive step-up approach) Major complications: −0.45 per person (favours the minimally invasive step-up approach)	ICER: £163,000 per death averted with open surgery Length of stay and major complications: Minimally invasive step-up approach dominated open surgery (cheaper and more effective)	conducted. Differences in the outcomes of death (1 fewer death) and lengths of stay were not statistically significant at a level of p=0.05

Abbreviations: CCU: critical care unit; ICER: incremental cost-effectiveness ratio; RCT: randomised controlled trial
(a) Dutch cohort of patients, the study did not collect quality of life data
(b) The study had a short, 6-month time horizon, unit costs are representable of the Dutch healthcare system
(c) 2008 Euros, presented as 2008 UK pounds, converted using 2008 purchasing power parities[82]

Table 75: Health economic evidence profile: minimally invasive endoscopic step-up approach versus minimally invasive percutaneous step-up approach

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
Van Brunschot 2017 (B)[108]	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Cost–utility analysis (within RCT economic evaluation, n=98) • 6-month follow-up • Patients randomly assigned to either	−£11,725 (favouring endoscopic step-up approach)	−0.0161 QALYs gained (favouring percutaneous step-up approach)	**ICER:** £728,000 per QALY gained (percutaneous versus endoscopic approach)	The endoscopic step-up approach was both cheaper and very slightly less effective. The probability of the endoscopic step-up approach being cost effective compared with the

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
			endoscopic step-up approach or percutaneous step-up approach.				percutaneous step-up approach was 89% at a cost-effectiveness threshold of £43,000 per QALY gained. But no sensitivity analysis was conducted, and only surviving patients were included in the results.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; RCT: randomised controlled trial

(a) The majority (77%) of patients were excluded from the study, so may have limited applicability. The interventions differ in some respects from current UK practice (such as using plastic stents). The study had a short, 6-month, time horizon.

(b) Quality of life was measured 3 months and 6 months after treatment. Quality of life was compared only for surviving patients over the first 6 months; mortality and life expectancy were not included in QALY calculations. Costs are based on the Dutch healthcare system.

(c) 2014 Euros, presented as 2014 UK pounds, converted using 2014 purchasing power parities[82]

17.5 Evidence statements

All evidence was in adults or young people over 16 years.

17.5.1 Clinical

17.5.1.1 Minimally invasive procedure (percutaneous or endoscopic transgastric drainage) versus open surgery

- When a minimally invasive procedure was compared with open surgery a single randomised trial, the findings suggested a clinically important benefit of the comparator for the outcome of mortality (1 study; n=88; low quality). The study showed mixed evidence in terms of complications following interventions. There was evidence to suggest no clinical difference between groups in terms of enterocutaneous fistula or perforation of a visceral organ requiring intervention, intraabdominal bleeding and multiple systemic complications (1 study; n=88; low to moderate quality). However, there was evidence of a clinically important benefit of minimally invasive procedure in terms of (new-onset) multiple organ failure (1 study; n=88; moderate to high quality). There was also evidence of clinically important benefit of the intervention for pancreatic function (new-onset diabetes and use of pancreatic enzymes) (1 study; n=88; moderate to high quality).

17.5.1.2 Minimally invasive surgery (endoscopic) versus open surgery

- Evidence from a single non-randomised study comparing endoscopic intervention with open surgery suggested a clinically important benefit of endoscopic necrosectomy for the outcome of mortality (1 study; n=254; very low quality).

17.5.1.3 Endoscopic step-up approach versus percutaneous drainage with step-up to open surgery

- A single non-randomised study comparing an endoscopic step-up approach with a surgical step-up approach suggested a clinically important benefit of percutaneous drainage for the outcome of mortality (1 study; n=24; very low quality). There was no difference between the interventions in terms of complications, including new-onset organ failure, multiple organ failure, upper gastrointestinal bleeding, intra-abdominal bleeding, and pancreatic fistula, however there was a clinically important benefit of endoscopic surgery in terms of the complication enterocutaneous fistula or perforation (1 study; n=24; very low quality). There was also evidence to suggest a clinically important benefit of the endoscopic approach for the length of stay outcomes, for both hospital and CCU (1 study; n=24; very low quality).

17.5.1.4 Endoscopic step-up compared with minimally invasive surgical step-up approach

- Evidence from a single randomised trial comparing endoscopic step-up approach to a minimally-invasive surgical step-up approach showed a clinically important benefit of the endoscopic step-up approach for pancreatic fistula (1 study; n=98; high quality), with a possible clinical benefit for length of hospital stay and new-onset organ failure (1 study; n=98; moderate quality). However, there was a possible clinical harm of the endoscopic approach for increased mortality, although there was a great deal of uncertainty around this estimate (1 study; n=98; low quality). No clinical difference was seen between the 2 groups for other complications (bleeding, new-onset multiple organ failure, or perforation of visceral organ or enterocutaneous fistula) or pancreatic function (endocrine or exocrine insufficiency) (1 study; n=98; low quality).

17.5.1.5 Minimally invasive procedure (endoscopic dual modality drainage) versus percutaneous drainage

- One non-randomised study showed a clinically important benefit of minimally invasive procedure for length of stay in hospital and a possible clinical benefit for mortality (1 study; n=94; very low quality). There was no clinical difference between the 2 groups in terms of complications (pseudoaneurysms) (1 study; n=94; very low quality).

17.5.1.6 Minimally invasive procedure (open or videoscopically assisted retroperitoneal debridement) versus open surgery (open abdomen strategy continuous postoperative lavage; laparotomy with primary abdominal closure)

- There was evidence from 1 non-randomised study of a possible clinically important benefit of a minimally invasive procedure for mortality (2 studies; n=360; very low quality) and complications (bleeding) (1 study; n=106; very low quality), but no clinically important difference was reported between groups for complications (bowel perforation) and number of procedures (reintervention) (1 study; n=106; very low quality).

17.5.1.7 Combination of interventions (step-up approach) versus open surgery (open necrosectomy)

- One non-randomised study demonstrated a clinically important benefit of a combination of interventions for mortality, severe complications (sepsis, persistent MODS or erosion bleeding) and pancreatic function (emergence of type 3c diabetes) (1 study; n=220; very low quality)

17.5.1.8 Minimally invasive procedure (focused open necrosectomy) versus open surgery (open necrosectomy)

- There was evidence from 1 non-randomised study to suggest a benefit of minimally invasive procedure for mortality and number of repeated procedures, but no clinically important difference between the 2 groups in terms of complications (internal fistulae and pancreatic fistulae) (1 study; n=70; very low quality).

17.5.1.9 Percutaneous drainage versus combination of interventions (laparotomy plus necrosectomy plus active or passive drainage)

- There was evidence from 1 non-randomised study to suggest a clinically important benefit of percutaneous drainage compared with a combination of interventions for the outcomes of mortality and complications (wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula) (1 study; n=17–19; very low quality).

17.5.1.10 Combination of interventions (percutaneous drainage plus VARD) versus combination of interventions (laparotomy plus necrosectomy plus active or passive drainage)

- There was evidence from 1 non-randomised study to suggest a clinically important benefit of a combination of interventions (percutaneous drainage plus VARD) compared with a different combination of interventions for mortality and complications (wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula) (1 study; n=17–22; very low quality).

17.5.1.11 Combination of interventions (percutaneous drainage plus VARD) versus percutaneous drainage

- There was evidence from 1 non-randomised study to suggest a clinically important benefit of percutaneous drainage over a combination of interventions (percutaneous drainage plus VARD) for the outcomes of mortality and complications (wound infection, haemorrhage at surgical site, pancreatic fistula, intestinal fistula) (1 study; n=22; very low quality)

17.5.1.12 Percutaneous drainage versus open surgery (open necrosectomy)

- There was evidence from 1 non-randomised study to suggest a clinically important benefit of percutaneous drainage for the outcomes of mortality and number of repeated procedures

(further necrosectomy) (1 study; n=30; very low quality). There was mixed evidence reported for the outcome of complications: the study showed a possible clinical benefit of percutaneous drainage for gastrointestinal fistulae; a clinical benefit of open surgery for pancreatic fistulae and bleeding; and suggested no clinical difference between groups for bowel perforation (1 study; n=30; very low quality).

17.5.1.13 Minimally invasive procedure (endoscopy) versus combination of interventions (step-up approach, drainage plus surgery)

- There was evidence from 1 non-randomised study of no clinically important difference between the 2 groups for the outcome of mortality (1 study; n=24; very low quality). There was evidence of clinical benefit of minimally invasive procedure for the outcomes of length of stay, pancreatic function (new endocrine insufficiency), and number of procedures; and a possible clinically important benefit for pancreatic function (new exocrine insufficiency) and complications (1 study; n=24; very low quality).

17.5.2 Economic

- One cost–consequences analysis that compared a minimally invasive step-up approach with open surgery in people with infected or suspected infected necrosis found that:
  - Open surgery was associated with an additional death averted for an additional cost of £163,000.
  - The step-up approach dominated open surgery in relation to major complications; costing £4,977 less per person and with 0.45 fewer major complications per person.

  This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis that compared a minimally invasive endoscopic step-up approach with a minimally invasive percutaneous step-up approach found that the percutaneous approach was not cost-effective compared to the endoscopic approach (ICER: £728,000 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

17.6 Recommendations and link to evidence

Recommendations and the committee's discussion of the evidence can be found in section 18.6.

18 Timing of management of infected necrosis in people with acute pancreatitis

18.1 Introduction

The timing of intervention is another important factor to consider. Infection of necrosis is not usually identified until the fourth week or later, such as by the presence of gas within necrosis detected on CT scanning. After 4 or more weeks necrosis is more likely to become walled off, and after a further period liquefaction of the necrotic tissue occurs, making drainage or debridement easier to achieve. Nevertheless once necrosis is infected there is a risk of spreading sepsis that may induce or worsen organ failure. There is a balance to be struck between early drainage and/or debridement to avoid further deterioration of the patient versus delay to ensure localization and liquefaction of the necrosis with greater likelihood of efficient success of drainage/debridement.

This review attempts to address the optimal timing of interventions to manage infected necrosis.

18.2 Review question: What is the most clinically effective and cost-effective timing of intervention for managing (suspected) infected necrosis in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 76: PICO characteristics of review question

Population	Individuals with infected necrosis in acute pancreatitis. • Adults and young people (>16 years) • Children (≤16 years)
Interventions and comparators	• Early intervention (as defined by studies) • Late interventions (as defined by studies) ≥6 weeks after onset of attack The following interventions will be considered: • Minimally invasive surgery (percutaneous, endoscopic or both) • Open surgery • Percutaneous drainage (radiological) • Antibiotic treatment • No treatment • Combination of interventions
Outcomes	Critical outcomes • Quality of life (≤1 year) (continuous) • Mortality (≤1 year) (dichotomous) • Length of stay (in CCU or hospital) (≤1 year) (continuous or dichotomous) Important outcomes • Number of procedures (repeated procedures) (≤1 year) • Recurrence of infection (≤1 year) • Complication (for example, bleeding, fistulae) (≤1 year) • Pancreatic function (for example, development of diabetes) (≤1 year)
Key confounders	• Percentage necrosis

	• Positive bacteriology • Presence of organ failure
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled comparative studies will be included.

18.3 Clinical evidence

One study was included in the review;[45] this is summarised in Table 77 below. The aim of the study was to assess when management of infected or suspected infected necrosis is most clinically effective in adults. The study is a non-randomised comparative trial that looks at late intervention versus early intervention; it includes a number of different management techniques.

Evidence from this study is summarised in the clinical evidence summary below (Table 78). See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 77: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Guo 2014[45]	Intervention 1: Late combination of interventions. Intervention was postponed until approximately 4 weeks after the onset of disease, whenever possible (n=87) Intervention 2: Early combination of interventions. Intervention was postponed until approximately 4 weeks after the onset of disease, whenever possible. However, when severe clinical deterioration persisted, a prompt intervention was performed (n=136)	Adults with acute pancreatitis and infected or suspected infected necrosis. Including (n=223): • People with persistent early organ failure • People without persistent early organ failure Age (median, range): 47 (22-74) years China	• Mortality (≤1 year) • Number of procedures (≤1 year) • Complications (≤1 year)	Non-randomised study No confounders accounted for Open pancreatic necrosectomy, retroperitoneal pancreatic necrosectomy, or primary percutaneous catheter drainage with pigtail plastic stents were the possible types of intervention. Cultures were taken during all primary procedures to confirm the diagnosis of infected necrosis.

Table 78: Clinical evidence summary: late intervention versus early intervention

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Early intervention	Risk difference with Late intervention (95% CI)
Organ failure stratum					
Mortality	82 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.38 (0.13 to 1.13)	377 per 1000	234 fewer per 1000 (from 328 fewer to 49 more)
Number of procedures (Re-intervention)	82 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.34 (0.09 to 1.36)	279 per 1000	184 fewer per 1000 (from 254 fewer to 100 more)
Complications (Intra-abdominal bleeding)	82 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.61 (0.26 to 1.38)	393 per 1000	153 fewer per 1000 (from 291 fewer to 150 more)
Complications (Enterocutaneous fistula)	82 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.45 (0.40 to 5.30)	98 per 1000	44 more per 1000 (from 59 fewer to 423 more)
Complications (New-onset organ failure)	82 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.09 (0.49 to 2.42)	262 per 1000	24 more per 1000 (from 134 fewer to 372 more)
No organ failure stratum					
Mortality	141 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.36 (0.44 to 4.26)	67 per 1000	24 more per 1000 (from 37 fewer to 217 more)
Number of procedures (Re-intervention)	141	⨁⊖⊖⊖	RR 0.49	93 per 1000	48 fewer per 1000

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Early intervention	Risk difference with Late intervention (95% CI)
	(1 study) ≤1 year	VERY LOW[a,b] due to risk of bias, imprecision	(0.13 to 1.81)		(from 81 fewer to 76 more)
Complications (Intra-abdominal bleeding)	141 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.14 (0.24 to 5.44)	40 per 1000	6 more per 1000 (from 30 fewer to 178 more)
Complications (Enterocutaneous fistula)	141 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.7 (0.64 to 4.54)	80 per 1000	56 more per 1000 (from 29 fewer to 283 more)
Complications (New-onset organ failure)	141 (1 study) ≤1 year	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.28 (0.03 to 2.48)	53 per 1000	38 fewer per 1000 (from 52 fewer to 79 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

18.4 Economic evidence

18.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

18.5 Evidence statements

18.5.1 Clinical

18.5.1.1 Late intervention versus early intervention in people with organ failure

- One non-randomised study compared late intervention to early intervention in adults with organ failure. The evidence suggested a clinically important benefit of late intervention in terms of mortality, intra-abdominal bleeding complications, and number of procedures (n=82; very low quality). However, the evidence also suggested no clinically important difference between late and early intervention in terms of enterocutaneous fistula complications, and new-onset organ failure (n=82; very low quality).

18.5.1.2 Later intervention versus early intervention in people with no organ failure

- One non-randomised study compared late intervention to early intervention in adults with no organ failure. There was a possible clinically important benefit of early intervention in terms of mortality, and a suggestion of no clinically important difference between the interventions in terms of number of procedures, intra-abdominal bleeding, enterocutaneous fistula, or new-onset organ failure complications (n=141; very low quality).

18.5.2 Economic

- No relevant economic evaluations were identified.

18.6 Recommendations and link to evidence

Recommendations	**25. Offer people with acute pancreatitis an endoscopic approach for managing infected or suspected infected pancreatic necrosis when anatomically possible .** **26. Offer a percutaneous approach when an endoscopic approach is not anatomically possible.** **27. Balance the need to debride infected pancreatic necrosis promptly against the advantages of delaying intervention.**
Relative values of different outcomes	The guideline committee agreed the following outcomes to be critical: mortality, length of stay (in hospital or CCU) and quality of life. The committee also agreed the following outcomes to be important: number of interventional procedures, recurrence of infection, complications (for example, bleeding and fistulae) and pancreatic function (for example, pancreatic exocrine insufficiency or diabetes). There was no evidence found for the following outcomes: quality of life and recurrence of infection. No evidence was identified for children.

Quality of the clinical evidence	Two randomised controlled trials and 10 non-randomised studies were identified for inclusion in the review. The quality of randomised evidence in the minimally invasive surgery (percutaneous or endoscopic) versus open surgery comparison was graded from low to high, with the critical outcome being graded as low due to imprecision. The quality of the randomised evidence in endoscopic step-up versus minimally-invasive surgical step-up approach comparison was graded as low to high, with the limitation being imprecision. The evidence for the comparison of minimally invasive surgery (endoscopic) versus open surgery was graded as very low due to risk of bias. The evidence for the comparison of endoscopic step-up approach versus percutaneous drainage with step-up to open surgery was graded as very low for all outcomes due to risk of bias and imprecision. The evidence for the comparison of minimally invasive surgery versus percutaneous drainage was graded as very low due to risk of bias and imprecision. The evidence for the comparison of minimally invasive surgery versus different types of open surgery was also graded as very low due to risk of bias and imprecision. The evidence for the comparisons of step-up approach versus open surgery, percutaneous drainage versus open surgery, combination of techniques (percutaneous drainage and video assisted retroperitoneal debridement (VARD)) versus open surgery, and combination of techniques (percutaneous drainage and VARD) versus percutaneous drainage obtained from the non-randomised studies was graded as very low due to risk of bias and imprecision. The evidence for the comparison of minimally invasive surgery (endoscopic necrosectomy) versus a step-up approach was graded as very low due to risk of bias. The committee considered meta-analysing studies according to the prespecified intervention categories agreed at protocol stage, but concluded that this was not possible, as there was little overlap of comparison. Where comparisons were similar, the minimally invasive interventions used in the studies were too heterogeneous to be analysed together.
Trade-off between clinical benefits and harms	**Type of intervention** <u>Minimally invasive surgery compared with open surgery (randomised evidence)</u> The committee noted that the evidence from 1 randomised trial provided moderate to high quality evidence of clinically important benefit of minimally invasive procedures over open surgery for complications (multiple organ failure), which is an important outcome that impacts on mortality, diabetes and incisional hernia. Mortality was marginally higher among patients treated by the step-up approach, however because this evidence was of low quality the committee did not think it was appropriate to base their recommendation on this outcome. Overall, the committee considered the evidence from this study as showing a benefit of minimally invasive procedures. <u>Endoscopic step-up approach compared with minimally invasive surgical step-up approach (randomised evidence)</u> The second randomised trial provided moderate and high quality evidence of a clinically important benefit of the endoscopic step-up approach over the minimally invasive surgical approach for length of hospital stay, new-onset organ failure and pancreatic fistula. However, there was an apparent clinical harm of the endoscopic approach for increased mortality. The committee discussed this finding and was not concerned by the slightly higher mortality rate because there was a great deal of uncertainty around the estimate because of the low event rate in a small sample. The committee did not believe that this finding translated to a true clinical difference. All other outcomes showed no clinical difference between the endoscopic and minimally-invasive surgical step-up approaches. The committee

	noted that this study only compared those patients who were suitable for both percutaneous and endoscopic necrosectomy. Patients who had necrosis which could not be accessed by both techniques were excluded from or not considered for the study. The conclusions, therefore, refer to those patients in whom both percutaneous and endoscopic necrosectomy were possible, which represents around 30% of all patients who would require a necrosectomy. Observational evidence The committee noted that several of the non-randomised studies had small sample sizes, which was also reflected in the downgrading of their quality due to imprecision. The committee agreed that it was difficult to generalise any results from these studies. However, the individual patient data meta-analysis did provide evidence supporting the RCT data by finding that there is a clinically important benefit of minimally invasive procedures (either endoscopic or percutaneous) for mortality, especially in individuals at high baseline risk of death. **Timing of intervention** One non-randomised study compared late intervention to early intervention in subgroups of people with and without organ failure. This gave very low quality evidence suggesting a clinical benefit of late intervention in terms of mortality, intra-abdominal bleeding and number of procedures in the subgroup with organ failure but not in the subgroup with no organ failure. No clinical difference was seen for enterocutaneous fistulas and new-onset organ failure in either subgroup. The committee discussed significant risks related to either early or late timings for intervention. For example, early intervention may induce or exacerbate critical illness and carry a higher risk of complications such as death or bleeding. Delayed intervention reduces these risks, but may have a higher risk of complications due to infection. The committee agreed that it is important to raise awareness that there are both advantages and disadvantages of delaying intervention and that these should be carefully considered on a case-by-case basis. **Summary** The committee agreed that there was sufficient evidence to support the use of minimally invasive approaches to the management of necrosis, and that where possible the first choice should be endoscopic owing to the larger reduction in length of hospital stay, reduction in complications and greater acceptability to patients. Therefore, a recommendation for the use of minimally invasive procedures using an endoscopic approach where anatomically feasible was made. The guideline committee agreed that approximately 60-70% of patients with infected pancreatic necrosis are more suitable for either percutaneous necrosectomy or endoscopic necrosectomy but not for both and that this suitability for one or the other technique is governed by the anatomy of the necrosis and its relationship to the posterior wall of the stomach (for the endoscopic approach) or postero-lateral abdominal wall (for the percutaneous approach). This recommendation was noted to apply to children as well as adults. The committee agreed that all hospitals offering minimally invasive procedures for the management of necrosis should be set up to offer both endoscopic and percutaneous procedures as appropriate to each person. Regarding the timing of intervention the committee highlighted the need to consider the potential benefits and harms of early versus delayed intervention on an individual basis.
Trade-off between net clinical effects and costs	**Type of intervention** Two health economic evaluations were identified comparing alternative approaches. One health economic evaluation compared a minimally invasive step-up approach with open surgery in a cohort of adults with acute pancreatitis and signs of pancreatic necrosis, peri-pancreatic necrosis or both, as detected by CT scan. This evaluation used the same clinical effectiveness data comparing these interventions

	as the RCT included in the clinical review. Analysis within this study identified that the minimally invasive approach was less costly by £4,977 and was associated with fewer major complications and shorter length of stay. As noted above, mortality was 3% greater (1 additional death) in the minimally invasive arm, but this was not believed to be a meaningful difference. Given the committee's view that the clinical evidence on balance shows a benefit for minimally invasive procedures, this approach dominates (that is, it is both cheaper and more clinically effective than) open surgery. It would therefore be cost saving as well as clinically beneficial to adopt minimally invasive surgery in preference to open surgery. The committee noted that the published evaluation only included costs incurred within 6 months of surgery. With a lower rate of major complications the committee would expect future costs later than 6 months to also be lower in the minimally invasive group due to fewer adverse events and fewer additional later procedures, and thus the cost savings from using minimally invasive surgery could be even greater over a longer time horizon than those measured within the first 6 months. The second health economic evaluation compared an endoscopic step-up approach with a percutaneous step-up approach. Analysis within the study identified that the percutaneous step-up approach was fractionally more effective but considerably more expensive (£11,725 per patient) and so was not cost effective at a threshold of £20,000 per QALY gained, with an ICER of £782,268 per QALY gained. The committee noted that the estimate of effectiveness used in the study was limited as it only studied the effect on the quality of life of surviving patients in the first 6 months following surgery, and thus left out any effects due to differing short-term or long-term survival. As such, the small benefit suggested for percutaneous step-up could not be relied upon. The cost difference favouring endoscopic step-up was mainly driven by a difference of £9,247 for hospital stay, along with the cost of treating complications, with the costs of the initial procedures themselves (slightly cheaper for percutaneous step-up) having relatively little impact. The committee agreed that by offering the minimally invasive approach patients had a quicker recovery leading to shorter length of hospital stay and fewer complications which would reduce total costs as well as leading to better health, quality of life and a better patient experience. Taking the evidence together, the committee agreed that whichever approach gave rise to better patient health outcomes in each case – in particular reducing complications and length of hospital stay – would be very likely to also be the cheapest option in that case and so would be more effective and cost saving compared with all other approaches. Therefore, the committee agreed that a minimally invasive approach should be offered for the management of infected or suspected infected necrosis in acute pancreatitis, with an endoscopic approach used where possible. **Timing of intervention** No relevant health economic evidence was identified relating to the timing of intervention. Due to the uncertainty of the clinical evidence the committee could not assess the cost effectiveness of early or late intervention. As discussed in the clinical trade-off above, this should be considered on a case-by-case basis. Whichever approach is believed to be likely to minimise the risks of complications for a particular person is likely also to be cost saving or cost effective compared with alternative approaches for that person, due to reduced costs from complications and length of hospital stay.
Other considerations	The committee noted that few patients would be suitable for both endoscopic and percutaneous interventions and that there is variation in current practice in the UK, with what is 'anatomically possible' varying between centres depending on local confidence in the techniques. The committee also agreed that endoscopic procedures for the management of infected or suspected infected necrosis should

	only be undertaken by an experienced clinician in, or supported by, a specialist pancreatic centre, as it is the highest risk endoscopic procedure. The committee noted that the randomised study comparing endoscopic and percutaneous step-up approaches used pigtail stents and a nasocystic drain, which is a technique that has been superseded in current UK practice by self-expanding metal stents. Therefore, the endoscopic approach based on current UK techniques is likely to be more effective than that seen in this study, whilst also being more expensive. An important factor in the decision to recommend endoscopic interventions as the first choice was related to patient experience. The committee agreed that percutaneous drainage leads to a poor patient experience due to the ongoing drainage, which can leak and cause pain and require regular flushing, as well as resulting in a much longer hospital stay.

1

19 Management of pain in people with chronic pancreatitis

19.1 Introduction

Abdominal pain is the predominant symptom in patients with chronic pancreatitis. The pain is varied in nature, intensity, duration and severity along with acute exacerbations. Chronic pancreatitis related pain is also multifactorial, making it difficult to have a set standard regime of pain control that can work for every patient. This is further complicated by the long-term effects of pain at the spinal and central nervous system such as wind up and central sensitisation.

Pain is not the only symptom people affected also develop gastro-intestinal symptoms and other psycho-social factors causing a reduction in quality of life such as unemployment, relationship issues, addiction to pain killers and financial difficulties. With time, they may develop a neuropathic component of pain in the form of viscero-somatic hyperalgesia. It's important to consider all these factors in managing the pain.

Pain secondary to pancreatic duct obstruction or small-duct disease may need to be investigated and treated with appropriate intervention such as endoscopy or surgery. Pain may continue, however after treatment.

Pain management starts with education on alcohol and smoking cessation and other life style changes. Opioids are commonly used in treating both chronic pancreatitis and acute exacerbation of chronic pancreatitis. The dose used in pancreatitis pain can be varied from "on demand" use to very high doses on a regular basis. There is strong emerging evidence that the long term use of opioids may cause harm. The Faculty of Pain Medicine has launched a campaign on opioid awareness. This is an online resource on appropriate use of opioids for patients, carers and healthcare professionals.

The following reviews attempt to address the management of pain for people with chronic pancreatitis. The NICE guideline on neuropathic pain management (CG173) and spinal cord stimulation for chronic pain of neuropathic origin (TA159) helps in managing the neuropathic component of pancreatitis pain. Other interventions such as coeliac plexus blocks, splanchnic nerve blocks and radiofrequency denervation are currently utilised in managing this complex pain. Therefore, this aspect of pain management in chronic pancreatitis has not been addressed in this guideline.

19.2 Review question: What is the most clinically effective and cost-effective intervention for managing chronic pain in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 79: PICO characteristics of review question

Population	People with chronic pancreatitis presenting with chronic pain • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Nerve blocks • Opioids • Pharmacological therapies (excluding opioids, including antioxidants) • Psychological interventions, for example, psychotherapy • Enzyme replacement therapy

	• Surgery • Endoscopic treatment • Combinations of the above
Comparisons	• Standard treatment • Placebo • To each other • No pain relief
Outcomes	Critical outcomes • Quality of life (no time cut-off) (continuous) • Mortality (no time cut-off) (dichotomous) • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) (no time cut-off) (continuous or dichotomous) Important outcomes • Serious adverse events (≤1 year) (dichotomous) • Adverse events (≤1 year) (dichotomous) • Return to usual activities (no time cut-off) (continuous or dichotomous) • Pancreatic function (endocrine and exocrine) (no time cut-off)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

19.3 Clinical evidence

A search was conducted for randomised trials comparing the clinical effectiveness of different interventions for managing pain in people with chronic pancreatitis.

Ten studies reported in 11 papers were included in the review;[4, 12, 17, 34, 53, 58, 66, 71, 100, 105, 106] these are summarised in Table 80 below. No evidence was identified in children. This included a published Cochrane review that was identified and examined for inclusion. Due to additional outcomes in our protocol, differences in populations and a lack of risk of bias per outcome it was not possible to include this directly in the review. However, the review was included and modified for use in our review as follows:

- studies in which less than 80% of the population had chronic pancreatitis were excluded
- studies that were conference abstracts only, where the data are based solely on the abstracts were excluded
- studies that were in foreign languages but had been translated were included
- crossover studies were included and data were adjusted to allow for pooling with parallel data
- study characteristics for the evidence tables were taken directly from the published review, although additional relevant details were added for the summary of studies table
- data for pain, serious adverse events and adverse events were taken directly from the published review
- outcomes that do not match our protocol were removed and additional outcomes meeting our protocol were extracted
- risk of bias was reassessed by outcome, except for the non-English language study where this was not possible.

Two outcomes that were reported in the Cochrane review were not included in this review as it was unclear how these data were obtained (pain VAS[105, 106]; pain-free participants[100]). Further, 2 studies

were excluded as they included patients with acute pancreatitis,[19, 95] and 2 studies were excluded as they were conference abstracts only and additional information had not been sought from the authors.[30, 72]

The available comparisons were enzyme replacement therapy versus placebo and antioxidants versus placebo. Evidence from these studies is summarised in the clinical evidence summaries below (Table 82 and Table 83) and data not suitable for meta-analysis are presented in Table 81. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

No relevant clinical studies assessing the clinical effectiveness of nerve blocks, opioids, psychological interventions, surgery or endoscopic treatment were identified.

19.3.1 Heterogeneity

For the comparison of pharmacological therapy versus no placebo, there was substantial heterogeneity between the studies when they were meta-analysed for the outcome of pain (pain free participants) at 6 months. Pre-specified subgroup analyses did not explain such heterogeneity. A random effects meta-analysis was therefore applied to these outcomes, and the evidence was downgraded for inconsistency in GRADE.

Table 80: Summary of studies included in the review

Study		Intervention and comparison	Population	Outcomes	Comments
Ahmed 2014[4] Cochrane systematic review	Banks 1997[12]	(n=16) Intervention: pharmacological therapy (antioxidants). Participants were given allopurinol 300 mg/day (n=16) Control: Placebo	Adults with continuous or intermittent episodes of pain due to chronic pancreatitis (n=16) Age (median, range): 42 (31–51) years USA	• Quality of life (10 weeks): activities of daily living questionnaire, 0-120, high score is good outcome • Pain (10 weeks): visual analogue scale (VAS), 0-10, high score is poor outcome • Pain (10 weeks): descriptive pain scale, 0-6, high score is poor outcome • Pain (10 weeks): numerical rating scale, 0-10, high is poor outcome • Adverse events (10 weeks)	Crossover trial. Antioxidant or placebo for 4 weeks, followed by a wash-out period of 2 weeks, and then a second treatment period of 4 weeks
	Bhardwaj 2009[17]	(n=76) Intervention: pharmacological therapy (antioxidants). Participants were given antioxidant supplementation including daily doses of 0.6 mg organic selenium, 0.54 g ascorbic acid, 5.4 mg β-carotene, 270 IU α-tocopherol and 2 g methionine, for 6 months. (n=71) Control: Placebo	Adults with chronic pancreatitis and significant abdominal pain of pancreatic origin (n=147) Age (mean, SD): antioxidant 31.3 (11.4); placebo 29.6 (9.3) years India	• Pain (6 months): reduction in analgesic medication • Pain (6 months): number of pain free patients • Pain (6 months): reduction in painful days • Mortality (6 months) • Adverse events (6 months)	
	Durgaprasad 2005[34]	(n=10) Intervention: pharmacological therapy (antioxidants). Participants were given pure extract of curcumin 0.5 g with 5 mg piperine, to be taken 3 times a day after food for 6 weeks.	Adults with tropical chronic pancreatitis (n=20) Age (mean, SD): antioxidant 23.6 (12.8);	• Pain (6 weeks): visual analogue scale, 0-10, high score is poor outcome • Adverse events (6 weeks)	

Study		Intervention and comparison	Population	Outcomes	Comments
		(n=10) Control: placebo, 3 times a day after food for 6 weeks.	placebo 27.8 (16.8) years India		
	Kirk 2006[58]	(n=36) Intervention: pharmacological therapy (antioxidants). Participants were given Antox (75 microgram selenium, 3 mg betacarotene, 47 mg d-alpha-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C) and 400 mg methionine), 1 tablet, 4 times a day. (n=36) Control: Identical placebo tablets, 4 times a day	Adults with chronic pancreatitis and chronic abdominal pain (n=36) Age not reported Northern Ireland	• Adverse events (20 weeks)	Crossover trial. Antioxidant or placebo was given for 10 weeks, followed by a crossover treatment period of 10 weeks. No washout period was used.
	Jarosz 2010[53]	(n=46) Intervention: Combination antioxidants (vitamin C and vitamin E) (n=45) Control: standard treatment (no alcohol consumption, high energy frequent diet and painkillers [buskopan, paracetamol] if needed)	Adults with proven alcoholic chronic pancreatitis and abdominal pain (n=91) Age not reported Poland	• Pain (time-point not reported): number of pain free patients	
	Siriwardena 2012[100]	(n=45) Intervention: pharmacological therapy (antioxidants). Participants received antioxidant supplementation (38.5 mg selenium yeast of which 50 microgram was l-selenomethionine, 113.4 mg d-α-tocopherol acetate, 126.3 mg absorbic acid, and 480 mg l-	Adults with painful chronic pancreatitis (n=92) Participants had a baseline daily pain score of ≥5 on a 0–10 numerical rating scale for at least 7 days Age (mean, SD):	• Quality of life (6 months): EQ-5D, 0-1, high score is good outcome • Pain (6 months): numerical rating scale, 0-10, high score is poor outcome • Adverse events (6 months)	

Study		Intervention and comparison	Population	Outcomes	Comments
		methionine, together with 285.6 mg microcrystalline cellulose, 14 mg croscarmellose sodium, 7.0 mg colloidal anhydrous silica, and 3.0 mg magnesium stearate). The coating contained 4.2 mg β carotene. Two tablets were taken 3 times daily with an 8 week supply. (n=47) Control: Placebo supplementation contained 657.9 mg microcrystalline cellulose, 73.3 mg croscarmellose sodium and 3.7 mg magnesium stearate. Two tablets were taken 3 times daily with an 8 week supply.	antioxidant 49.8 (12.7); placebo 50 (9) years UK		
	Uden 1990[105, 106]	(n=23) Intervention: pharmacological therapy (antioxidants). Participants received daily doses of 0.6 mg organic selenium, 9000 IU β carotene, 0.54 g vitamin C, 270 IU vitamin E and 2 g methionine (n=23) Control: Identical placebo	Adults with recurrent attacks of pancreatitis or with constant pain suggestive of pancreatic origin (n=23) Age (mean, SD not reported): 39.17 years UK	• Pain (10 weeks): not suitable for meta-analysis • Adverse events (time-point not reported)	Crossover trial. Antioxidant or placebo was given for 10 weeks, followed by crossover treatment period for 10 weeks. There was no washout period. 17.9% of participants had recurrent acute pancreatitis
Malesci 1995[66]		(n=24) Intervention: Enzyme replacement therapy. Participants were given pancreatic extract (Pancrex-Duo, Samil-Sandoz, Italy) as capsules of enteric-coated microspheres, each capsule containing 34,376 United Stated	Adults with pain due to chronic pancreatitis (n=24) Age (range): 21-70 years Denmark	• Pain (4 months): number of people experiencing long-lasting (>12 hour) pain attacks • Pain (4 months): use of analgesics	Strict alcohol abstinence was strongly recommended to all the recruited patients at least 1 year before the entered the study. Patients were allowed to consume analgesics: the drug and manner of

Study	Intervention and comparison	Population	Outcomes	Comments
	Pharmacopeia (USP) units of protease, 13,000 USP units of lipase, and 43, 570 USP units of amylase. The dose given was 4 times daily (at meals and bedtime). (n=24) Control: Participants were given placebo 4 times daily (at meals and bedtime).			administration were the patients' choice in accordance with pre-study habits.
Mossner 1992[71]	(n=47) Intervention: Enzyme replacement therapy, A new preparation of acid-protected commercially available porcine pancreatic enzymes was applied together with meals in a higher dosage that commonly used for treatment of pancreatic insufficiency (5×2 capsules a day; Panzytrat 20,000, Nordmark Arzneimittel, Uetersen, FRG; capsules with microtablets, containing per capsule according to the information provided by the manufacturer, triaglycerol lipase 20,000 Pharmacopoea europaea units, (Ph Eur U), amylase 20,000 Ph Eur U, proteases 1000 Ph Eur U). This dosage ensured the application of 10,000 Ph Eur U of proteases per day. (n=47) Control: Placebo extracts	Adults with pain due to chronic pancreatitis (n=94) Age not reported Germany	• Pain (2 weeks): pain score (0-3), high score is poor outcome	

Table 81: Data not suitable for meta-analysis

Study	Intervention versus comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Other results	Risk of bias
Uden 1990[105, 106]	Antioxidant versus placebo	Pain at 10 weeks	Not reported	20	Not reported	20	Median difference (CI): 0.26 (-0.06, 0.84) p=0.10	High

Table 82: Clinical evidence summary: Pharmacological therapy (antioxidants) versus placebo

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antioxidant versus control intervention (95% CI)
Quality of life (activities of daily living) Scale from: 0 to 120.	26 (1 study) 10 weeks	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, imprecision			The mean quality of life (activities of daily living) in the intervention groups was 3.3 lower (10.3 lower to 3.7 higher)
Quality of life (EQ-5D) Scale from: 0 to 1.	70 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		The mean quality of life (EQ-5D) in the control groups was 0.51	The mean quality of life (EQ-5D) in the intervention groups was 0.04 higher (0.1 lower to 0.18 higher)
Quality of life (EQ-5D VAS) Scale from: 0 to 100.	70 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		The mean quality of life (EQ-5D VAS) in the control groups was 56.6	The mean quality of life (EQ-5D VAS) in the intervention groups was 2.3 higher (6.5 lower to 11.1 higher)
Mortality	147 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	Not estimable[d]	No events[d]	
Pain (VAS score)	111	⨁⨁⨁⊖			The mean pain (VAS score) in the

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antioxidant versus control intervention (95% CI)
Scale from: 0 to 10.	(3 studies) 6 weeks - 6 months	MODERATE[a] due to risk of bias			intervention groups was 0.27 lower (0.69 lower to 0.15 higher)
Pain (descriptive scale) Scale from: 0 to 5.	26 (1 study) 10 weeks	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision			The mean pain (descriptive scale) in the intervention groups was 0.09 lower (0.29 lower to 0.11 higher)
Pain (numeric scale) Scale from: 0 to 10.	26 (1 study) 10 weeks	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision			The mean pain (VAS score) in the intervention groups was 0.25 lower (0.72 lower to 0.22 higher)
Pain (reduction in pain medication) - Oral analgesic tablets per month	127 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias		The mean reduction in pain medication – (oral analgesic tablets per month) in the control groups was 4.36	The mean reduction in pain medication – (oral analgesic tablets per month) in the intervention groups was 6.15 higher (3.02 to 9.28 higher)
Pain (reduction in pain medication) - Parenteral analgesic injections per month	127 (1 study) 6 months	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision		The mean reduction in pain medication – (parenteral analgesic injections per month) in the control groups was 1.89	The mean reduction in pain medication – (parenteral analgesic injections per month) in the intervention groups was 0.7 higher (0.5 lower to 1.9 higher)
Pain (reduction in number of painful days per month)	119 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias		The mean reduction in number of painful days per month in the control groups was 3.21	The mean reduction in number of painful days per month in the intervention groups was 4.16 higher (2.21 to 6.11 higher)
Pain (number of free participants)	264 (3 studies) 1 day - 6 months	⨁⨀⨀⨀ VERY LOW[a,b,e] due to risk of bias, inconsistency,	RR 1.73 (0.95 to 3.15)	427 per 1000	229 more per 1000 (from 16 fewer to 675 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antioxidant versus control intervention (95% CI)
		imprecision			
Adverse events	223 (3 studies) 10 weeks - 6 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 3.44 (1.30 to 9.09)	54 per 1000	132 more per 1000 (from 16 more to 437 more)
Adverse events	93 (3 studies) 6 - 20 weeks	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	Peto OR 8.28 (0.81 to 84.88)	54 per 1000	132 more per 1000 (from 16 more to 437 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Could not be calculated as there were no events in the control arm.

(d) Could not be calculated as there were no events in the intervention or comparison group.

(e) Downgraded by 1 or 2 increments because heterogeneity, I^2=71%, p= > 0.1, unexplained by subgroup analysis

Table 83: Clinical evidence summary: Enzyme replacement therapy versus placebo

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Enzyme replacement therapy (95% CI)
Pain (People experiencing long-lasting (>12 hours) pain attacks)	44 (1 study) 4 months	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.27 (0.75 to 2.15)	500 per 1000	135 more per 1000 (from 125 fewer to 575 more)
Pain (Use of analgesics)	44 (1 study) 4 months	⨁⨁⨀⨀ LOW[,a,b] due to risk of	RR 2 (0.82 to 4.9)	227 per 1000	227 more per 1000 (from 41 fewer to 886 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Enzyme replacement therapy (95% CI)
		bias, imprecision			
Pain (Pain score)	94 (1 study) 2 weeks	⨁⨁⨀⨀ LOW[a] due to risk of bias		The mean pain (pain score) in the control groups was 1.26	The mean pain (pain score) in the intervention groups was 0.18 lower (25.63 lower to 25.27 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

19.4 Economic evidence

19.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

19.5 Evidence statements

19.5.1 Clinical

All evidence was from randomised trials in adults and young people over 16 years.

19.5.1.1 Antioxidants versus placebo

- Evidence from 1 study comparing antioxidants to placebo suggested no clinical difference between the interventions in terms of quality of life as measured by the Activities of Daily Living Questionnaire (n=26; low quality), and 1 study found no clinical difference between the interventions when quality of life was measured in terms of the EQ-5D and EQ-5D VAS (n=70; moderate quality). There was no clinical difference between the interventions in terms of mortality (1 study; n=147; very low quality). There was also no clinical difference in terms of pain when measured as a VAS scale, descriptive scale or numeric scale (1 study; n=26; low quality). There was a clinically important benefit of antioxidants when pain was measured in terms of the reduction in oral analgesic pain medication, but no clinically important difference in terms of the reduction in parenteral analgesic injections (1 study; n=127; low-moderate quality). There was a clinically important benefit of antioxidants when pain was measured in terms of the reduction in the number of painful days per month (1 study; n=119; moderate quality), and a possible clinical benefit for the number of pain free participants (3 studies; n=264; very low quality). There was a clinically important benefit of placebo in terms of adverse events (3 studies; n=93–223; low tomoderate quality).

19.5.1.2 Enzyme replacement therapy versus placebo

- Evidence from 1 study comparing enzyme replacement therapy to placebo showed a possible clinically important benefit of placebo for pain when measured as people experiencing long lasting (>12 hours) pain attacks (1 study; n=44; low quality) and a possible clinically important benefit of placebo when pain was measured as the use of analgesics (1 study; n=44; low quality). However, there was also a clinically important benefit of enzyme replacement therapy when pain was measured in terms of a pain score (1 study; n=94; low quality).

19.5.2 Economic

- No relevant economic evaluations were identified.

19.6 Recommendations and link to evidence

Recommendation	**28. For adults with neuropathic pain related to chronic pancreatitis, follow the recommendations in the NICE guideline on neuropathic pain in adults.**
Research	**4. Is the long-term use of opioids more clinically effective and cost**

recommendation	effective than non-opioid analgesia (including non-pharmacological analgesia) in people with chronic pain due to chronic pancreatitis?
Relative values of different outcomes	The guideline committee agreed the following outcomes to be critical: quality of life, mortality and pain. The committee also chose the following outcomes as important outcomes: serious adverse events, adverse events, return to usual activities and pancreatic function. There was no evidence found for the following outcomes: serious adverse events, return to usual activities and pancreatic function.
Quality of the clinical evidence	One Cochrane review including 7 randomised controlled trials comparing antioxidants to placebo was identified for inclusion in this review. The evidence was of very low to moderate quality, due to risk of bias, imprecision and inconsistency. Two randomised controlled trials comparing enzyme replacement therapy to placebo were also identified for inclusion in this review. The evidence provided by the randomised controlled trials was of low quality due to risk of bias and imprecision. No studies were identified investigating any other drugs or alternative interventions for managing pain.
Trade-off between clinical benefits and harms	**Antioxidants** The committee noted that there was no difference between the interventions in terms of quality of life and mortality. Whilst many of the pain outcomes showed no clinical difference, the committee noted that there was a clinically important benefit of antioxidants in terms of the number of pain-free participants. However, it was noted that the evidence for this outcome was very low quality and came from very small studies. The committee discussed concerns about generalisability of the evidence for this outcome due to the fact that only 1 of the studies was conducted in the UK, and 1 was conducted in India. The committee discussed that features of pancreatitis may be different in India compared with the UK and therefore the evidence from that study may not be relevant to UK practice. The committee further noted that the UK study showed no difference between antioxidants and placebo. The committee also considered the outcomes of reduction in pain medication and number of painful days and noted that the data were difficult to interpret due to a lack of information about the type of pain medication being used, and differences between the placebo and antioxidant groups at baseline. The committee also discussed issues with the design of the studies such as inadequate length of follow-up and a lack of double blinding. The committee agreed that there was a lack of substantial evidence demonstrating a clinically important benefit of antioxidants, and therefore agreed that antioxidants should not be recommended. The committee discussed the potential benefit of a research recommendation, however it noted that a UK study had already been carried out, and agreed that further research is unlikely to have additional benefit. **Enzyme replacement therapy** The committee noted that the studies included in the review had conflicting results and highlighted the vast difference in the dose of enzyme replacement therapy used in the 2 studies. It was noted that in the study with a much larger dose, there was evidence of a larger absolute effect. The committee also discussed the issues surrounding studies that are currently conducted in people with painful chronic pancreatitis: most studies are likely to be conducted over a short period of time; however people with chronic pancreatitis are treated with pharmacological interventions over very long periods of time. Currently, there is a lack of RCT evidence investigating long-term pain relief and there is a chance that people are receiving inappropriate treatment. Given the lack of evidence specific to pancreatitis the committee decided a recommendation could not be made but a research recommendation was

	appropriate. **Opioids** One issue was highlighted as worthy of further research. The rates of opioid-induced death are recognised as being high due to over-prescription of opioids and the high doses of opioids that are being prescribed. This is particularly important in people with chronic pancreatitis, as misuse of opioids may lead to a change in the perception of pain and as a result of this people with painful chronic pancreatitis may begin to fear oncoming pain and increase their opiate use. The committee also discussed the risk of increased tolerance and addiction, particularly in people who may have a history of alcohol misuse. The committee believed that further research into the appropriate treatment of chronic pain in chronic pancreatitis is necessary. Because some people may suffer from chronic pain that is not necessarily caused by their pancreatitis, the committee wanted to include those with pancreatitis and chronic pain as opposed to chronic pain caused by pancreatitis. The committee wished to address the issues surrounding opioid use and felt that a randomised controlled trial comparing the use of opioid to non-opioid treatments in people with chronic pancreatitis, of at least 1 year's duration, would provide good quality evidence for clinical practice in the future.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee did not make any recommendations for a change in practice due to a shortage of clinical evidence, but instead recommended that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee discussed what other considerations were important to highlight to clinicians; it agreed that people with hereditary pancreatitis and children with pancreatitis need to be looked at with special consideration and believe they should be discussed at a multidisciplinary meeting. The committee agreed that adults presenting with neuropathic pain in chronic pancreatitis could be managed using the NICE guideline on neuropathic pain in adults.

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20 Management of pancreatic duct obstruction in people with chronic pancreatitis

20.1 Introduction

Abdominal pain is the predominant symptom in patients with chronic pancreatitis. The pain is varied in nature, intensity, duration and severity along with acute exacerbations. Chronic pancreatitis related pain is also multifactorial, making it difficult to have a set standard regime of pain control that can work for every patient. This is further complicated by the long-term effects of pain at the spinal and central nervous system such as wind up and central sensitisation.

Pain is not the only symptom people affected also develop gastro-intestinal symptoms and other psycho-social factors causing a reduction in quality of life such as unemployment, relationship issues, addiction to pain killers and financial difficulties. With time, they may develop a neuropathic component of pain in the form of viscero-somatic hyperalgesia. It's important to consider all these factors in managing the pain.

Pain secondary to pancreatic duct obstruction or small-duct disease may need to be investigated and treated with appropriate intervention such as endoscopy or surgery. Pain may continue, however after treatment.

Pain management starts with education on alcohol and smoking cessation and other life style changes. Opioids are commonly used in treating both chronic pancreatitis and acute exacerbation of chronic pancreatitis. The dose used in pancreatitis pain can be varied from "on demand" use to very high doses on a regular basis. There is strong emerging evidence that the long term use of opioids may cause harm. The Faculty of Pain Medicine has launched a campaign on opioid awareness. This is an online resource on appropriate use of opioids for patients, carers and healthcare professionals.

The following reviews attempt to address the management of pain for people with chronic pancreatitis. The NICE guideline on neuropathic pain management (CG173) and spinal cord stimulation for chronic pain of neuropathic origin (TA159) helps in managing the neuropathic component of pancreatitis pain. Other interventions such as coeliac plexus blocks, splanchnic nerve blocks and radiofrequency denervation are currently utilised in managing this complex pain. Therefore, this aspect of pain management in chronic pancreatitis has not been addressed in this guideline.

20.2 Review question: What is the most clinically effective and cost-effective intervention for managing pancreatic duct obstruction, with or without an inflammatory mass, in people with chronic pancreatitis presenting with chronic pain?

For full details see review protocol in appendix C.

Table 84: PICO characteristics of review question

Population	People with chronic pancreatitis and pancreatic duct obstruction, with or without an inflammatory mass, presenting with chronic pain • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Pancreatic endotherapy (endoscopic techniques – pancreatic stent (plastic or metal), pancreatic sphincterotomy, drainage)

	• Pancreatic extracorporeal shock wave lithotripsy (ESWL) – with or without endoscopic retrograde cholangiopancreatography (ERCP) • Surgery (resection or surgical drainage procedure) • Combination of techniques (for example, ESWL plus pancreatic endotherapy)
Comparisons	• Standard treatment or no treatment • To each other
Outcomes	Critical outcomes • Quality of life (no time cut-off) (continuous) • Mortality (no time cut-off) (dichotomous) • Complications (≤1 year) (dichotomous) • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) (no time cut-off) (continuous or dichotomous) Important outcomes • Length of stay (in CCU or hospital) (≤1 year) (continuous) • Repeated procedures (no time cut-off) (dichotomous) • Pancreatic function (endocrine and exocrine) (no time cut-off)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

20.3 Clinical evidence

Three studies, reported in 4 papers, were included in the review;[22(21),31,33] these are summarised in Table 85 below. The aim of the studies was to identify the most clinically effective way to treat pancreatic duct obstruction in people with chronic pancreatitis and painful symptoms. The studies included were randomised controlled trials that assessed the following comparisons: extracorporeal shockwave lithotripsy (ESWL) and pancreatic endotherapy to surgery, pancreatic endotherapy to surgery and ESWL alone to ESWL combined with pancreatic endotherapy. Evidence from these studies is summarised in the clinical evidence summaries below (Table 87 to Table 89) and data not suitable for meta-analysis are presented in Table 86. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

No relevant clinical studies comparing ESWL alone with surgery were identified and no studies in children were found.

Table 85: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Cahen 2007[22] (Cahen 2011[21])	(n=19) Intervention 1: ESWL plus pancreatic endotherapy; Endoscopic treatment was performed by experienced endoscopists who had each performed more than 1000 ERCPs. If 1 or more intraductal stones more than 7 mm in diameter were identified by imaging studies, the patient was referred for lithotripsy. After lithotripsy, stone fragments were removed during a consecutive endoscopic transampullary drainage procedure. If obstruction of the main	Adults with chronic pancreatitis and obstruction of the pancreatic duct due to stenosis, intraductal stones, or both located left of the spine, with	• Quality of life (2 and 7 years) • Mortality (2 years) • Pain (2 and 7 years) • Length of stay (2 and 7 years) • Repeated procedure (2	In patients with persistent or recurrent pain, imaging studies were repeated and evaluated by a multidisciplinary team. If a recurrent pancreatic duct

Study	Intervention and comparison	Population	Outcomes	Comments
	duct could not be completely resolved, 1 or 2 endoprostheses were placed during the last endoscopic procedure. If an endoprosthesis had been inserted, an elective endoscopic pancreatogram was scheduled for every 3 months. (n=20) Intervention 2: Surgery, Surgery was performed 4 weeks after randomisation by experienced hepatobiliary surgeons. A pancreaticojejunostomy was performed by the method of Partington and Rochelle.	dilation of the duct by at least 5 mm proximal to the obstruction. Mean (SD) age: Endoscopic: 52 (9); surgery: 46 (12) years. (n=39) The Netherlands	and 7 years) • Pancreatic function (2 and 7 years)	obstruction was seen in a patient who had completed endoscopic treatment, stent therapy was resumed.
Dite 2003[31]	(n=36) Intervention 1: Pancreatic endotherapy, Endotherapy was carried out by 2 experienced therapeutic endoscopists (who had each performed over 200 therapeutic ERCPs prior to the start of the study). Endotherapy consisted of pancreatic sphincterotomy, dilatation or, stenting and/or stone extraction, extracorporeal shock-wave lithotripsy (ESWL) was not included in the treatment protocol. Stenting was planned for 12–24 months, with stent exchanges being performed every 2–4 months. (n=36) Intervention 2: Surgery was carried out by 1 experienced abdominal surgeon (who had performed 90 pancreatic operations before the start of the study). The surgical therapy was tailored to the individual's situation and included resection procedures for localised disease and drainage procedures for diffuse disease with ductal dilation.	Adults over 18 with an obstructive form of chronic pancreatitis and a pain score of more than 3 on Melzack's score. Age range: 26-53 years (n=72) Czech Republic	• Pain (2 years) • Pancreatic function (2 years)	
Dumonceau 2007[33]	(n=26) Intervention 1: One or more sessions of ESWL were performed in all patients using the Lithostar Plus until the obstructive stones were broken into fragments <2 mm, as measured by x-ray. (n=29) Intervention 2: Combination of techniques: ESWL versus ESWL plus endotherapy. One or more sessions of	Adults over 18 with painful chronic pancreatitis with at least 1 calcification >4 mm in the pancreatic head or body with upstream dilation of the	• Pain (2 years) • Length of stay (2 years) • Complications (1 month)	

Study	Intervention and comparison	Population	Outcomes	Comments
	ESWL were performed in all patients using the Lithostar Plus until the obstructive stones were broken into fragments <2 mm, as measured by x-ray. In addition to this, the patients in the ESWL combined with endoscopy group underwent an endoscopic retrograde pancreatography immediately after the last ESWL session with attempted extraction of stone fragments and insertion of 10-French plastic pancreatic stents if pancreatic strictures were identified.	main pancreatic duct. Mean (SD) age: ESWL alone: 51.8 (12.3); ESWL with endoscopy: 49 (10.1) years (n=51) Switzerland		

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Table 86: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Cahen 2007[22] (Cahen 2011[21])	Length of hospital stay	Median (range): 8 (0-128)	19	Median (range): 11 (5-59)	20	High
Cahen 2007[22] (Cahen 2011[21])	Number of procedures	Median (range): 8 (1-21)	19	Median (range): 3 (1-9)	20	High

Table 87: Clinical evidence summary: ESWL and endotherapy versus surgery

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with ESWL plus endotherapy (95% CI)
QoL (SF-36; Mental health component at 2 years)	39 (1 study) 2 years	⨁⨁◯◯ LOW[a,b] due to risk of bias, imprecision		The mean QoL (SF-36; mental health component at 2 years) in the control groups was 45	The mean QoL (SF-36; mental health component at 2 years) in the intervention groups was 5 lower (10.65 lower to 0.65 higher)
QoL (SF-36; Mental health component at 7 years)	30 (1 study) 7 years	⨁◯◯◯ VERY LOW [a,b] due to risk of bias, imprecision		The mean QoL (SF-36; mental health component at 7 years) in the control groups was 48	The mean QoL (SF-36; mental health component at 7 years) in the intervention groups was 2 lower (8.81 lower to 4.81 higher)
QoL (SF-36; Physical health component at 2 years)	39 (1 study) 2 years	⨁⨁◯◯ LOW [a,b] due to risk of bias, imprecision		The mean QoL (SF-36; physical health component at 2 years) in the control groups was 47	The mean QoL (SF-36; physical health component at 2 years) in the intervention groups was 9 lower (14.08 to 3.92 lower)
QoL (SF-36; Physical health component at	31	⨁◯◯◯ VERY LOW [a,b]		The mean QoL (SF-36; physical	The mean QoL (SF-36; physical health

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with ESWL plus endotherapy (95% CI)
7 years)	(1 study) 7 years	due to risk of bias, imprecision		health component at 7 years) in the control groups was 48	component at 7 years) in the intervention groups was 5 lower (12.06 lower to 2.06 higher)
Mortality	39 (1 study) 2 years	⨁⨁⨀⨀ LOW [a] due to imprecision	Peto OR 7.79 (0.15 to 393.02)	0 per 1000	52 more per 1000 (from 80 fewer to 185 more)
Pain (Pain relief at 2 years)	39 (1 study) 2 years	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 0.42 (0.21 to 0.86)	750 per 1000	435 fewer per 1000 (from 105 fewer to 593 fewer)
Pain (Pain relief at 7 years)	31 (1 study) 7 years	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.47 (0.24 to 0.93)	800 per 1000	424 fewer per 1000 (from 56 fewer to 608 fewer)
Pain (Izbicki pain score at 2 years)	39 (1 study) 2 years	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision		The mean pain (Izbicki pain score at 2 years) in the control groups was 25	The mean pain (Izbicki pain score at 2 years) in the intervention groups was 26 higher (13.75 to 38.25 higher)
Pain (Izbicki pain score at 7 years)	31 (1 study) 7 years	⨁⨀⨀⨀ VERY LOW[a] due to risk of bias, imprecision		The mean pain (Izbicki pain score at 7 years) in the control groups was 22	The mean pain (Izbicki pain score at 7 years) in the intervention groups was 17 higher (3.84 lower to 37.84 higher)
Pancreatic function (Endocrine	39	⨁⨁⨀⨀	RR 3.16	50 per 1000	108 more per 1000

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with ESWL plus endotherapy (95% CI)
insufficiency developed at 2 years)	(1 study) 2 years	LOW[a] due to imprecision	(0.36 to 27.78)		(from 32 fewer to 1000 more)
Pancreatic function (Endocrine insufficiency developed at 7 years)	31 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.19 (0.69 to 6.94)	200 per 1000	238 more per 1000 (from 62 fewer to 1000 more)
Pancreatic function (Endocrine insufficiency persisted at 2 years)	39 (1 study) 2 years	⨁⨁⊖⊖ LOW[b] due to imprecision	RR 0.79 (0.2 to 3.07)	200 per 1000	42 fewer per 1000 (from 160 fewer to 414 more)
Pancreatic function (Endocrine insufficiency persisted at 7 years)	31 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.94 (0.28 to 3.09)	267 per 1000	16 fewer per 1000 (from 192 fewer to 557 more)
Pancreatic function (Exocrine insufficiency developed at 2 years)	39 (1 study) 2 years	⨁⨁⨁⊖ MODERATE[b] due to imprecision	RR 6.32 (0.84 to 47.69)	50 per 1000	266 more per 1000 (from 8 fewer to 1000 more)
Pancreatic function (Exocrine insufficiency developed at 7 years)	31 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.81 (0.67 to 11.83)	133 per 1000	241 more per 1000 (from 44 fewer to 1000 more)
Pancreatic function (Exocrine insufficiency persisted at 2 years)	39 (1 study) 2 years	⨁⨁⊖⊖ LOW[a] due to	RR 0.89 (0.54 to 1.47)	650 per 1000	72 fewer per 1000 (from 299 fewer to 306 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with ESWL plus endotherapy (95% CI)
		imprecision			
Pancreatic function (Exocrine insufficiency persisted at 7 years)	31 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.85 (0.52 to 1.39)	733 per 1000	110 fewer per 1000 (from 352 fewer to 286 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 88: Clinical evidence summary: Endotherapy versus surgery

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with Endotherapy (95% CI)
Pain (Complete absence of abdominal pain)	72 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.42 (0.16 to 1.06)	333 per 1000	193 fewer per 1000 (from 280 fewer to 20 more)
Pain (Partial relief of abdominal pain)	72 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.56 to 1.42)	528 per 1000	58 fewer per 1000 (from 232 fewer to 222 more)
Pancreatic function (New-onset diabetes)	72 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias,	RR 0.86 (0.46 to 1.59)	389 per 1000	54 fewer per 1000 (from 210 fewer to 229 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with Endotherapy (95% CI)
		imprecision			

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 89: Clinical evidence summary: ESWL versus ESWL and endotherapy

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ESWL plus endotherapy	Risk difference with ESWL (95% CI)
Pain (Pain relapse at 2 years)	48 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.77 (0.42 to 1.4)	542 per 1000	125 fewer per 1000 (from 314 fewer to 217 more)
Pain (Pain intensity; VAS score)	48 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean pain (pain intensity; vas score) in the control groups was 5.7	The mean pain (pain intensity; vas score) in the intervention groups was 0 higher (0.99 lower to 0.99 higher)
Length of hospital stay	48 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 8.6	The mean length of hospital stay in the intervention groups was 5.5 lower (12.43 lower to 1.43 higher)
Procedure related complications	48 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	42 per 1000	36 fewer per 1000 (from 42 fewer to 187 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

20.4 Economic evidence

20.4.1 Published literature

One health economic study was identified comparing ESWL alone to ESWL in combination with endotherapy and has been included in this review.[33] This is summarised in the health economic evidence profile below (Table 90) and the health economic evidence table in appendix I.

See also the health economic study selection flow chart in appendix F.

20.4.2 Unit costs

See appendix N.15.

Table 90: Health economic evidence profile: ESWL versus ESWL plus endotherapy

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
Dumonceau 2007[33] (Belgium)	Partially applicable[(a)]	Potentially serious limitations [(b)]	• Cost–consequences analysis (within trial economic evaluation, n=55) • Mean 21.5 month follow-up • Interventions: ○ ESWL combined with endotherapy ○ ESWL	−£5,932 (ESWL is cheaper)	Pain relapse: −7% of patients (favouring ESWL alone) Intensity of pain: No difference Complications: −3% of patients (favouring ESWL alone) Length of hospital stay: −5.5 days (favouring ESWL alone)	ESWL dominates (is cheaper and more effective than) ESWL in combination with endotherapy for these outcomes	No sensitivity analysis was conducted.

Abbreviations: ESWL: extracorporeal shock wave lithotripsy

(a) Belgian public healthcare insurance perspective. The study did not collect quality of life data. Costs were not discounted.

(b) Short follow-up time that may not capture all costs and benefits. Sensitivity analysis not undertaken.

(c) 2003 Euros, presented as 2003 UK pounds, converted using 2003 purchasing power parities[82]

20.5 Evidence statements

20.5.1 Clinical

All evidence was from randomised trials in adults or young people over 16 years.

20.5.1.1 ESWL and endotherapy versus surgery

- There was evidence of to suggest a clinical harm of ESWL and endotherapy compared with surgery for mortality, pain and pancreatic function (development of endocrine or exocrine insufficiency) (1 study; n=31; moderate to very low quality). However, the evidence also suggested no clinical difference for persistence of endocrine insufficiency at 2 years and a clinical benefit of ESWL and endotherapy compared with surgery for persistence of endocrine insufficiency at 7 years (1 study; n=31; low to very low quality). Additionally, there was a possible clinical harm of ESWL and endotherapy compared with surgery for quality of life at 2 and 7 years for the physical component of the SF-36 and at 2 years for the mental component, with no clinical difference suggested at the 7 year time point on this component (1 study; n=31; low to very low quality).

20.5.1.2 Endotherapy versus surgery

- There was evidence of a possible clinical harm of endotherapy compared with surgery for the complete absence of abdominal pain; however, no clinical difference was suggested for partial relief of abdominal pain (1 study; n=72; very low quality). Furthermore, the evidence suggested no clinical difference for new-onset diabetes (1 study; n=72; very low quality).

20.5.1.3 ESWL versus ESWL and endotherapy

- There was evidence of a possible clinical benefit of ESWL compared with ESWL and endotherapy for pain relapse at 2 years and length of hospital stay (1 study; n=48; very low quality). However, the evidence also suggested no clinical difference for pain intensity or procedure-related complications (1 study; n=48; very low quality).

20.5.2 Economic

- One cost–consequences analysis found that ESWL was dominant compared with ESWL and endotherapy for treating pancreatic duct obstruction in people with chronic pancreatitis and painful symptoms (costing £5,932 less per patient, and associated with pain relapses in 7% fewer patients, complications in 3% fewer patients and 5.5 days fewer in hospital per patient). This analysis was assessed as partially applicable with potentially serious limitations.

20.6 Recommendations and link to evidence

Recommendations	**29. Consider surgery (open or minimally invasive) as first line treatment in adults with painful chronic pancreatitis that is causing obstruction of the main pancreatic duct.** **30. Consider extracorporeal shock wave lithotripsy for adults with pancreatic duct obstruction caused by a dominant stone if surgery is unsuitable.**
Research recommendation	**5. What is the most clinically effective and cost-effective intervention for managing pancreatic duct obstruction, with or without an inflammatory**

	mass, in children with chronic pancreatitis presenting with pain?
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, complications and pain. The also noted the following outcomes to be important: length of stay, repeated procedures and pancreatic function.
Quality of the clinical evidence	**Adults** Three randomised controlled trials were identified for inclusion in the review. The comparisons included in the review were ESWL and endotherapy versus surgery, endotherapy versus surgery, and ESWL versus ESWL and endotherapy. The quality of evidence provided by the ESWL and endotherapy versus surgery comparison was graded as very low to moderate due to risk of bias and/or imprecision, the quality of evidence provided by the endotherapy versus surgery comparison was graded as very low due to risk of bias and imprecision and the quality of evidence provided by the ESWL plus endotherapy versus ESWL comparison was graded as very low due to risk of bias. **Children** There was no evidence identified for inclusion in this review.
Trade-off between clinical benefits and harms	**Adults** The committee noted that the evidence provided by the ESWL and endotherapy versus the surgery comparison showed there was evidence of clinical benefits of surgery over ESWL and endotherapy. Additionally, where there was no evidence of a clinical benefit of surgery, the outcomes demonstrated no clinically important difference between the 2 interventions. This was corroborated by the evidence provided by the endotherapy versus surgery comparison in which there was either a clinical benefit demonstrated by surgery or no clinical difference between the 2 interventions. Although the evidence presented was in favour of surgery, the committee discussed the merits of using endotherapy as a bridge to surgery as is sometimes done in current practice. It was noted that clinicians may try to offer less invasive therapies to people who are fit for surgery but want to delay when they have surgery. Conversely, it was also highlighted that people who are fit for surgery should go for surgery sooner rather than later to prevent potential complications further down the line when they may be more seriously unwell. An example of when surgery may be the best first-line intervention is in people with hereditary pancreatitis, due to the increased risk of pancreatic cancer. The final comparison, between ESWL and endotherapy and ESWL alone, demonstrated either a clinically important benefit of ESWL alone or no clinical difference when combined with endotherapy. The committee discussed the variations in current practice across the UK and highlighted that some clinicians may refer people with pancreatic duct obstructions for surgery but also that there are some clinicians who prefer to attempt endotherapy as a first-line treatment. The committee also noted that 1 of the studies which provides evidence for ESWL only includes people with stones larger than 4 mm; as such there is no evidence to suggest that ESWL would be effective in stones smaller than 4 mm. The committee believe it is important to note that there is no evidence to support the use of endotherapy as a first-line treatment in people with pancreatic duct obstruction. The committee noted that people with an inflammatory mass and a large duct obstruction were not included in the studies in the review. They believed that this would be due to the nature of the condition, which is most appropriately treated with a resection and drainage procedure, therefore treatment with ESWL and/or endotherapy would not be indicated. **Children**

	No relevant studies were identified for this review and the committee was therefore not able to assess the most clinical and cost effective intervention for the management of pancreatic duct obstructions in children. As there were no clinical studies identified for inclusion in the review the committee felt it was necessary for further research into how pancreatic duct obstructions should be treated in children. Whilst there was evidence that surgery was clinically beneficial in adults, the committee did not feel it was appropriate to extrapolate these results to children and recommend its use without clinical evidence. The committee decided that the same question should be asked as a research recommendation; however it decided not to include ESWL as one of the interventions as it is not appropriate for use in children.
Trade-off between net clinical effects and costs	**Adults** One health economic evaluation was identified comparing ESWL with ESWL combined with endotherapy in adults. This was a cost–consequences analysis which demonstrated that ESWL dominated ESWL and endotherapy (less costly and better outcomes) for the outcomes of pain relapse, complication and length of hospital stay. For the outcome intensity of pain, ESWL was less costly and equally effective. No health economic evaluations were identified including surgery as a comparator. Unit costs were also presented to the committee. The committee noted that a surgical procedure (average £7,547) is more expensive than an ESWL procedure (£470 – cost not specific to the pancreas) or endotherapy (£1,840), however it also noted than in the clinical study comparing surgery with ESWL and endotherapy, the patients given surgery had fewer repeat procedures (3) than in the SEWL and endotherapy group (8). In addition, the committee expect that the better clinical outcomes demonstrated by surgery would be likely to lead to lower downstream medical costs due to better health and fewer complications. Therefore, the committee concluded that the additional costs of conducting surgery as the first-line treatment would be either partly or wholly compensated for by reductions in other costs, and any net increase in costs compared with current practice would be expected to be cost effective due to the better clinical outcomes for people undergoing surgery. **Children** No health economic evidence was identified relating to children. Given the lack of clinical or economic evidence relating to children, the committee agreed to make a recommendation that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee discussed what other considerations were important to highlight to clinicians; it agreed that people with hereditary pancreatitis and children with pancreatitis need to be looked at with special consideration and believe they should be discussed at a multidisciplinary meeting. The committee also wanted to highlight that it is important to discuss the use of endotherapy in a multidisciplinary meeting before using it as a treatment. The committee agreed that people with chronic pancreatitis being considered for intervention should be discussed and managed by a specialist pancreatic multidisciplinary team. Those with hereditary pancreatitis and children with pancreatitis present clinicians with a particular challenge.

1

21 Management of small-duct disease in people with chronic pancreatitis

21.1 Introduction

Abdominal pain is the predominant symptom in patients with chronic pancreatitis. The pain is varied in nature, intensity, duration and severity along with acute exacerbations. Chronic pancreatitis related pain is also multifactorial, making it difficult to have a set standard regime of pain control that can work for every patient. This is further complicated by the long-term effects of pain at the spinal and central nervous system such as wind up and central sensitisation.

Pain is not the only symptom people affected also develop gastro-intestinal symptoms and other psycho-social factors causing a reduction in quality of life such as unemployment, relationship issues, addiction to pain killers and financial difficulties. With time, they may develop a neuropathic component of pain in the form of viscero-somatic hyperalgesia. It's important to consider all these factors in managing the pain.

Pain secondary to pancreatic duct obstruction or small-duct disease may need to be investigated and treated with appropriate intervention such as endoscopy or surgery. Pain may continue, however after treatment.

Pain management starts with education on alcohol and smoking cessation and other life style changes. Opioids are commonly used in treating both chronic pancreatitis and acute exacerbation of chronic pancreatitis. The dose used in pancreatitis pain can be varied from "on demand" use to very high doses on a regular basis. There is strong emerging evidence that the long term use of opioids may cause harm. The Faculty of Pain Medicine has launched a campaign on opioid awareness. This is an online resource on appropriate use of opioids for patients, carers and healthcare professionals.

The following reviews attempt to address the management of pain for people with chronic pancreatitis. The NICE guideline on neuropathic pain management (CG173) and spinal cord stimulation for chronic pain of neuropathic origin (TA159) helps in managing the neuropathic component of pancreatitis pain. Other interventions such as coeliac plexus blocks, splanchnic nerve blocks and radiofrequency denervation are currently utilised in managing this complex pain. Therefore, this aspect of pain management in chronic pancreatitis has not been addressed in this guideline.

21.2 Review question: What is the most clinically effective and cost-effective intervention for managing small-duct disease (in the absence of pancreatic duct obstruction, inflammatory mass or pseudocyst) in people with chronic pancreatitis presenting with chronic pain?

For full details see review protocol in appendix C.

Table 91: PICO characteristics of review question

Population	People with chronic pancreatitis and small-duct disease presenting with chronic pain • Adults and young people (>16 years) • Children (≤16 years)

Interventions	• Surgery (partial or total resection, resection and drainage operation,) • Endoscopic treatment
Comparisons	• Standard care treatment (for example, pharmacological treatment only, enzyme replacement therapy, nerve blocks) or no treatment • To each other
Outcomes	Critical outcomes • Quality of life (no time cut-off) (continuous) • Mortality (no time cut-off) (dichotomous) • Complications (≤ 1 year) (dichotomous) • Pain – acute or chronic (duration of pain, reduction in pain, medication reduction) (no time cut-off) (continuous or dichotomous) Important outcomes • Length of stay (in CCU or hospital) (≤ 1 year) (continuous) • Repeated procedures (no time cut-off) (dichotomous) • Pancreatic function (endocrine and exocrine) (no time cut-off)
Key confounders	• Presence of diabetes • Opiates for pain • Presence of pancreatic calcification • Continued alcohol consumption • Continued smoking
Study design	RCTs, systematic reviews of RCTs If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

21.3 Clinical evidence

One study in adults was included in the review;[13] this is summarised in Table 92 below. Evidence from this study is summarised in the clinical evidence summary below (Table 94) and data not suitable for meta-analysis are presented in Table 93. The aim of the study was to assess which intervention most effectively reduced pain and improved quality of life. The study was a non-randomised comparative study that compared the intervention arms of 2 different case–controlled studies. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 92: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Basinski 2005[13]	Intervention 1: (n=18) Videoscopic splanchnicectomy (VSPL), all patients were given a left-sided intervention. Intervention 2: (n=30) Neurolytic celiac plexus block (NCPB)	Adults with small-duct chronic pancreatitis and chronic pain Mean (SD) age: NCPB: 49.9 (7.8) VSPL: 47.3 years (n=48)	• Pain (timepoint unclear) • Quality of life (timepoint unclear)	Non-randomised study No confounders controlled for

Study	Intervention and comparison	Population	Outcomes	Comments
		Poland		

Table 93: Data not suitable for meta-analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Basinski 2005[13]	Pain	Median (95% CI): 15.82 (14.68-16.96)	18	Median (95% CI): 8.89 (8.3-9.48)	30	Very high
Basinski 2005[13]	Physical wellbeing	Median (95% CI): 1.81 (1.57-2.06)	18	Median (95% CI): 2.19 (1.96-2.42)	30	Very high
Basinski 2005[13]	Emotional wellbeing	Median (95% CI): 1.12 (0.91-1.34)	18	Median (95% CI): 4.40 (4.07-4.73)	30	Very high

Table 94: Clinical evidence summary: VSPL versus NCPB

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NCPB	Risk difference with VSPL (95% CI)
Pain (Use of opioids)	48 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.08 (0.67 to 1.75)	567 per 1000	45 more per 1000 (from 187 fewer to 425 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

21.4 Economic evidence

21.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

21.5 Evidence statements

21.5.1 Clinical

- There was non-randomised evidence in adults to suggest no clinical difference between videoscopic splanchnicectomy and neurolytic celiac plexus block for the use of opioids or quality of life (1 study; n=48; very low quality).

21.5.2 Economic

- No relevant economic evaluations were identified.

21.6 Recommendations and link to evidence

Research recommendation	6. What is the most clinically effective and cost-effective intervention for managing small duct disease (in the absence of pancreatic duct obstruction, inflammatory mass or pseudocyst) in people with chronic pancreatitis presenting with pain?
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, complications and pain. The committee also chose the following outcomes as important outcomes: length of stay, repeated procedures and pancreatic function. There was no evidence found for the following outcomes: mortality, serious adverse events, adverse events, return to usual activities and pancreatic function.
Quality of the clinical evidence	One non-randomised controlled trial was identified for inclusion in this review. The study compared videoscopic splanchnicectomy to neurolytic coeliac plexus block for the management of small-duct disease in people with chronic pancreatitis. The evidence provided by the non-randomised trial was graded as very low quality due to risk of bias and imprecision.
Trade-off between clinical benefits and harms	The evidence provided by the study showed no important clinical difference between the 2 interventions, but this was based on a small study with very low quality evidence that did not report all of the critical outcomes. Therefore, the committee felt it would be most appropriate to recommend further research into the most clinical and cost-effective method of managing small-duct disease in people with chronic pancreatitis.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee did not make any recommendations for a change in practice due to a shortage of clinical evidence, but instead recommended that further research be conducted. There are therefore no economic implications from this review.
Other considerations	The committee discussed how difficult it would be to define the population included in the review for a clinical study, it noted that many people with small-duct disease may not be known to have chronic pancreatitis and this might be reflected by the lack of studies identified for inclusion in this review.

	The committee discussed what other considerations were important to highlight to clinicians; it agreed that people with hereditary pancreatitis and children with pancreatitis need to be looked at with special consideration and believe they should be discussed at a multidisciplinary meeting.

1

22 Management of pseudocysts

22.1 Introduction

Pseudocysts develop as a frequent complication of acute or chronic pancreatitis with the prevalence in chronic pancreatitis lying between 20 and 40%. Within the first 6 weeks after an acute attack of pancreatitis, 40% of pseudocysts resolve spontaneously, but the spontaneous remission of pseudocysts after 12 weeks is very rare. The management of symptomatic pancreatic pseudocyst has been controversial, in terms of patient selection, timing and technique. There are many therapeutic options including trans-papillary drainage, EUS-guided endoscopic drainage, laparoscopic surgical drainage and open surgical drainage. Whilst it is widely accepted that percutaneous drainage should not be performed in chronic pseudocyst, except in patients who are not candidates for other procedures, the choice of other techniques in symptomatic patients tends to vary.

Surgical procedures for treating pseudo- cysts may have higher initial success rates, but have the potential to be associated with somewhat higher mortality than endoscopic pseudocyst drainage into the duodenum or stomach. This review attempts to address the most effective method for managing pseudocysts.

22.2 Review question: What is the most clinically effective and cost-effective intervention for managing pseudocysts in people with pancreatitis presenting with or without pain?

For full details see review protocol in appendix C.

Table 95: PICO characteristics of review question

Population	People with acute or chronic pancreatitis and pseudocysts presenting with or without pain • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Pancreatic endoscopic stent • Endoscopic drainage • Laparoscopic drainage • Percutaneous drainage • Open surgery (resection or drainage) • Combination of techniques
Comparisons	• Standard treatment or no treatment • To each other
Outcomes	Critical outcomes • Quality of life (no time cut-off) (continuous) • Mortality (≤1 year) (dichotomous) • Complications – bleeding, perforation and infection or overall rate of complications (no time cut-off) (dichotomous) • Resolution of presenting symptoms (for example, pain, nutritional status, gastric outlet obstruction) (no time cut-off) (continuous or dichotomous) • Resolution or recurrence of pseudocysts (no time cut-off) (dichotomous) Important outcomes

	• Length of stay (in CCU or hospital) (≤ 1 year) (continuous or dichotomous) • Repeated procedures (no time cut-off) (dichotomous)
Key confounders	• Acute or chronic pancreatitis • Presence of necrosis • Pancreatic duct disruption
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

22.3 Clinical evidence

Thirteen studies were included in the review;[5, 7, 18, 25, 50, 55, 69, 70, 88, 96, 104, 111, 112] these are summarised in **Error! Reference source not found.** below. The aim of all studies was to assess what therapeutic ethod is most effective in treating pancreatic pseudocysts. One randomised controlled trial[111] and 12 non-randomised studies were identified for inclusion in the review. The available comparisons are summarised in Table 97 below. It was not appropriate to combine studies in a meta-analysis owing to differences in the populations and procedures and because the observational studies did not control for key confounding variables. No relevant studies in children were identified.

Evidence from these studies is summarised in the clinical evidence summaries below (Table 99 to Table 109) and data not suitable for meta-analysis are presented in Table 98. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 96: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Akshintala 2014 [5]	Intervention: **percutaneous drainage.** Performed under CT guidance and/or US and fluoroscopic guidance. The pseudocyst was identified, and a suitable route for **catheter drainage** was chosen. The skin and subcutaneous tissue were anaesthetised with a subcutaneous injection of 1% lidocaine solution. The pseudocyst was first punctured under CT/US guidance with an 18 gauge single-wall needle. Cyst fluid was aspirated and the drain was flushed with saline twice a day. (n=40) Comparator: **endoscopic drainage (with [71%] or without [29%] EUS guidance).** Performed using monitored sedation after appropriate antibiotic prophylaxis. The conventional transmural approach using a duodenoscope or therapeutic upper GI endoscope was performed only if a visible **gastric or duodenal bulge** from a pseudocyst was appreciated by the endopscopist. The transmural drainage approach of using **EUS guidance** was performed using linear array echo endoscopes. In both approaches 1-3 double-pigtail stents were inserted across the tract. (n=41)	Adults with symptomatic pseudocysts within 1 cm of the gastric or duodenal wall and acute or chronic pancreatitis (n=81) Mean (SD) age: Endoscopic: 47.1 (14.9) years; Percutaneous: 52.7 (12.68) years USA	• Mortality (time-point unclear) • Procedural adverse events (time-point unclear) • Length of hospital stay (time-point unclear) • Re-intervention (time-point unclear)	Non-randomised study (retrospective) Not all key confounders accounted for. Baseline comparability for acute/chronic pancreatitis
Andersson 2006 [7]	Intervention: **percutaneous puncture and drainage.** Performed under US or CT guidance. (n=20) Intervention: **open surgery.** Included internal drainage with cystogastrostomy or external drainage. (n=3) Comparator: **conservative treatment (observation)** (n=21)	Adults with pancreatic pseudocysts; 77% acute pancreatitis and 23% chronic pancreatitis (n=44) Mean (SD) age: 55 (14) years Sweden	• Complications (26 months) • Recurrence of pseudocysts (26 months) • Length of hospital stay (26 months)	Non-randomised study (retrospective) No key confounders accounted for. Only 3 people had open surgery
Bhasin 2011 [18]	Intervention: **Endoscopic transpapillary nasopancreatic**	Patients with	• Resolution of	Non-randomised study

Study	Intervention and comparison	Population	Outcomes	Comments
	drainage. Endoscopic retrograde cholangiopancreatography (ERCP) under conscious sedation by intravenous midazolam and hyoscine butylbromide to inhibit duodenal contractions. Once cannulated, minimal contrast was injected to confirm pancreatic duct (PD) disruption. A 5-Fr **nasopancreatic drain** was placed across the papilla in to the PD. An attempt was made to place the NPD across the area of the disruption and if that was not possible, it was placed as close as possible to the disruption. The drain may be kept in place for up to 8 weeks. (n=6) Comparison: **Pancreatic endoscopic stent.** ERCP under conscious sedation by intravenous midazolam and hyoscine butylbromide to inhibit duodenal contractions. Once cannulated, minimal contrast was injected to confirm PD disruption. A 5-Fr **stent** was placed across the papilla in to the PD. (n=5) Both groups had IV ciprofloxacin for prophylaxis and in all patients ERCP demonstrated **disruption of the pancreatic duct**.	symptomatic large (>6cm) pseudocysts of pancreas located at tail region of pancreas and PD disruption. Acute or chronic pancreatitis (n=11) Mean (SD) age: 41 (9) years India	pseudocyst (4-8 weeks) • Complications (3-10 days after stent insertion) • Recurrence of pseudocyst (follow-up 16.4± 11.4 months)	(prospective) No key confounders accounted for.
Davila Cervantes 2004 [25]	Intervention: **laparoscopic drainage**. Type of drainage chosen according to the size and location of the pseudocyst (4 Roux-en-Y cystojejunostomy, 4 extraluminal cystogastrostomy and 2 intraluminal cystogastrostomy). Closed drains used in all cases. (n=10) Comparator: **open surgery (drainage)**. Conventional open drainage (3 people had cystojejunostomy and 3 had cystogastrostomy) (n=6)	Patients with mature pseudocysts developed after a documented episode of acute pancreatitis. (n=16) Indication for drainage was abdominal pain in 44%. Mean (range) age: Laparoscopic 42 (17-68) years; open surgery 36 (18-54) years Mexico	• Mortality (22 months) • Treatment success (22 months) • Complications (22 months) • Length of hospital stay (22 months)	Non-randomised study (retrospective) No key confounders accounted for. Laparoscopic drainage was used as the first option in the absence of contraindications
Heider 1999 [50]	Intervention: **percutaneous drainage.** Non-operative with US- or	Well-documented	• Mortality (time-	Non-randomised study

Study	Intervention and comparison	Population	Outcomes	Comments
	CT-guided percutaneous placement of a catheter for pseudocyst drainage. (n=66) Intervention: **open surgery (drainage or resection).** Included internal or external drainage, longitudinal pancreaticojejunostomy, or distal pancreatectomy. (n=66) Comparator: **conservative treatment (observation).** Lack of intervention other than fluid management and pain control. (n=41)	pancreatic pseudocyst secondary to pancreatitis (Atlantic International Symposium definition of pseudocyst applied retrospectively to CT and US reports for a consistency). 46% had pain as indication for treatment; **71% presented with abdominal pain**. 27% had documented chronic pancreatitis. (n=173) Mean (SD) age: 45 (1) USA	point unclear) • Treatment success or failure (time-point unclear) • Complications (time-point unclear) • Length of hospital stay (time-point unclear)	(retrospective; collection of data from between December 1984 and May 1995). Not all key confounders accounted for (proportion with chronic pancreatitis said to be balanced).
Johnson 2009 [55]	Intervention: **Combination of endoscopic drainage and pancreatic endoscopic stent.** Performed using monitored sedation and consisted of transmural drainage through the gastric wall with or without transpapillary drainage. Transmural drainage was performed if a **visible bulge** was appreciated by the endoscopist. **EUS not routinely used.** Using Seldinger technique, the tract was balloon-dilated and stented with either 1 or 2 double pigtail stents. A pancreatic duct sphincterotomy was performed and **pancreatic duct stent** was placed unless technical reasons prevented access to the pancreatic duct. 50% had cystogastrostomy alone, 25% transpapillary drainage alone and 25% combined transmural and transpapillary drainage. (n=24)	Patients who had undergone an intervention for a diagnosed pancreatic pseudocyst. (n=54) Mean age: Surgery: 49 years Endoscopy: 52 years USA	• Mortality (time-point unclear) • Complications (time-point unclear) • Resolution of pseudocyst (time-point unclear)	Non-randomised study (retrospective) Not all key confounders accounted for. Surgical and endoscopic patients said to be similar for age (49 versus 52 years); chronic pancreatitis (50 versus 32%); and complicated pancreatobiliary disease, including pancreatic duct disruption or obstruction, pancreatic necrosis and common bile duct obstruction

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparator: **Open surgery (drainage).** Pseudocyst **drainage** plus additional pancreatobiliary procedures as deemed necessary by the surgeon. Cholecystectomy was performed when there was a question of gallstones either contributing to, or potentially complicating pancreatitis. Longitudinal pancreaticojejunostomy was performed when feasible in the presence of chronic pancreatitis. Splenectomy and gastric drainage procedures were selectively performed in the presence of splenic vein thrombosis and gastric outlet obstruction, respectively. (n=30) 47% had cystogastrostomy, 17% Roux-en-Y cystojejunostomy and 13% cystoduodenostomy.			(69 versus 60%) Unclear if children were included
Melman 2009 [69]	Intervention: **endoscopic drainage (with or without EUS).** Procedural sedation by an anesthetist was used and all cases were managed using a transmural approach. **Endoscopic retrograde cholangiopancreatography (ERCP)** was performed before endoscopic pancreatic cystgastrostomy. The pancreatic cystgastrostomy was created by puncturing the cyst through the posterior gastric wall, introducing a guidewire through the needle into the pancreatic cyst, and dilating the tract with a balloon. Double pigtail catheters were exchanged over the wire. (n=45) Intervention: **laparoscopic drainage.** The laparoscopic transgastric technique was similar to the open surgery technique (see below), except that the pancreatic cystgastrostomy was accomplished using a linear endoscopic stapler to create the cystenteric anastomosis. (n=16) Comparator: **open surgery.** Open cyst gastrostomy was usually achieved through a midline or bilateral subcostal incision. An anterior gastrostomy was performed at the position overlying the area in which the cyst was adherent to the posterior wall of	Patients who underwent transgastric pancreatic pseudocyst drainage. (n=83) Mean (SD) age: Endoscopic: 51.8 (1.9) years Laparoscopic: 46.5 (3.6) years Open: 52 (3.8) years USA	• Resolution (primary success rate and overall success rate) (16 months) • Complications (16 months)	Non-randomised study (retrospective) No key confounders accounted for. Unclear if all cases had pancreatitis. Although ERCP was performed, pancreatic duct stents are not stated to have been placed

Study	Intervention and comparison	Population	Outcomes	Comments
	the stomach. An 8- to 10-cm posterior **gastrostomy** was extended through the cyst wall, and the pancreatic pseudocyst was **aspirated and debrided** of its contents. A biopsy of the cyst wall was performed. The cystogastrostomy was performed with a running suture between the gastric and cyst walls to complete the anastomosis. The anterior gastrostomy then was closed. (n=22)			
Morton 2005 [70]	Intervention: **percutaneous drainage.** No further details reported. (n=8121) Comparator: **open surgery drainage.** No further details reported. (n=6409)	Adults and young people (>17 years) with pseudocysts identified from the National Inpatient Sample reference codes (n=14530) Mean (SD) age: Percutaneous: 53 (16); Open: 51 (15) years USA	• Mortality (4 years) • Complications (4 years) • Length of hospital stay (4 years)	Non-randomised study (retrospective) Confounding variables (ERCP use, emergency admission, acute pancreatitis, biliary diagnosis, Charlson Comorbidity Index score, CT scan use and teaching hospital status) controlled for by regression models for length of stay and mortality outcomes. Not all key confounders accounted for.
Rasch 2017 [88]	Intervention: **endoscopic drainage.** Performed under endosonographic guidance by a linear scanner. (n=41) Intervention: **percutaneous drainage.** Pig tail catheters were placed by Seldinger's technique under sonographic or computer tomographic guidance. (n=8) Intervention: **open surgical drainage or resection.** A gastro- or duodenocystostomy was carried out with a cystostome, fluid specimen were obtained by aspiration and 1–3 double pig tails were placed via a guide wire. All surgical drainage procedures were cystojejunostomies with a Roux-en-Y reconstruction. (n=21)	Patients with pancreatic pseudocysts larger than 10 mm who presented more than once; 63.6% presented with abdominal pain; 65.1% chronic pancreatitis; 14.7% acute pancreatitis; 16.3% idiopathic; 3.9% iatrogenic or trauma (n=129) Mean (SD) age: 52 (14.9) years	• Mortality(time-point unclear) • Complications (time-point unclear) • Reintervention (time-point unclear) • Length of hospital stay (time-point unclear)	Non-randomised study (retrospective) No key confounders accounted for.

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparator: **conservative management.** (n=44)	Germany		
Saul 2016 [96]	Intervention: **Pancreatic endoscopic drainage (EUS guided).** Intubated and received 1g I.V. of ceftazidime 30 minutes before the procedure. A convex linear-array echoendoscope with fluoroscopic guidance was used to access the pseudocysts. A needle knife was inserted over a guidewire to create a bigger fistula. The gastric wall was dilated up to 15mm using a wire-guided balloon and 2 double pigtail plastic stents (7F and 4cm) were deployed for drainage. Transgastric in 16/21 and transduodenal in 5/21. (n=21) Comparison: **Combination of open and laparoscopic drainage and resection approaches**. Open drainage (laparotomy approach), cystogastrostomy (90% open), cystojejunostomy (62.5% laparoscopic), distal pancreatectomy, pancreatic pseudocyst resection and pancreato-jejunostomy. In patients with open drainage due to inflammation, a second surgery (distal pancreatectomy or PPC resection) was performed months later. They were considered as different procedures and they were analysed separately. (n=43)	People with pancreatic pseudocysts treated with endoscopic or surgical treatment (n=61) (64 procedures in 61 patients) Mean (SD) age: 41.5 (13.8) years Mexico	• Mortality • Treatment success • Recurrence • Complications • Length of ITU stay Median follow-up 270 and 580 days for endoscopic and combination groups, respectively	Non-randomised study (retrospective) No key confounders accounted for.
Talar-Wojnarowska 2010 [104]	Intervention: **Endoscopic drainage**. No further details reported. (n=10) Intervention: **Percutaneous drainage**. No further details reported. (n=4) Comparator: **Open surgery**. No further details reported. (n=7)	Adults with chronic pancreatitis and pancreatic pseudocysts requiring intervention Mean (SD) age: 47.2 (7.3) years (n=21) Poland	• Complications (time-point unclear) • Recurrence of pseudocysts (26 months) • Length of hospital stay (time-point unclear)	Non-randomised study (retrospective) No key confounders accounted for. Treatment modality mostly determined by cyst location and associated pathologies in the pancreatic duct.

Study	Intervention and comparison	Population	Outcomes	Comments
Varadarajulu 2008 [112]	Intervention: **endoscopic drainage (EUS-guided; ±pancreatic endoscopic stent)**. After administration of 1 dose of IV ciprofloxacin (400 mg), an EUS-guided **cyst-gastrostomy** was performed, with the patient under conscious sedation with a combination of midazolam, meperidine, and ketamine administered by the endoscopist. An **ERCP** was routinely attempted in all patients. If PD was completely disrupted and proximal duct was accessible, or if ductal stricture was present, a transpapilliary bridging **PD stent** was placed. (n=20) Comparator: **open surgery (drainage)**. IV cefaxolin was administered before incision. Cautery was used to create an approximate 5-cm longitudinal **gastrostomy** near the greater curvature of the fundus. Cautery was used to incise an approximate 2 cm opening in the posterior gastric wall. The pseudocysts were aspirated and irrigated. A **nasogastric tube** was left in the stomach. (n=10)	Adults who had undergone surgical cyst-gastrostomy and EUS-guided cyst-gastrostomy at a tertiary referral centre for uncomplicated pseudocysts. All had pancreatitis; 60% idiopathic (n=30) Mean age: Surgery: 42.3 years EUS: 43.1 years USA	• Complications (during admission) • Resolution of pseudocysts (4-6 weeks) • Length of hospital stay (during admission) • Repeated procedures (during admission)	Non-randomised study (retrospective case–controlled; matched for age, aetiology of pancreatitis and size of pseudocyst). Management option determined by the clinical service the patient was admitted to. Not all key confounders accounted for. Patients with pancreatic necrosis excluded. **16/20 endoscopic patients had ERCP, and 12/16 had successful pancreatic stenting**
Varadarajulu 2013 [111]	Intervention: **endoscopic drainage (EUS-guided; ±pancreatic endoscopic stent). Cystogastrostomy** performed with EUS guidance and fluoroscopy under conscious sedation after administration of IV ciprofloxacin. Two plastic **stents** deployed to facilitate the drainage of pseudocyst contents into the stomach. If the pseudocyst was persistent, additional drainage performed by placement of more stents. If the patient failed 1 additional intervention by endoscopy they were converted to surgery. An **ERCP** was routinely attempted in all patients. If PD leak was seen a 5F **pancreatic duct stent** was placed to bridge the site of the leak or stricture. (n=20) Comparator: **open surgery (drainage). Cystogastrostomy** performed by 1 pancreatic surgeon after administration of IV cefazolin. The anterior stomach was exposed and a 2-cm gastrostomy was created with cautery. The pseudocyst was **aspirated** and entered with cautery and at least a 6-cm	Adults with chronic or acute pancreatitis and a pseudocyst measuring ≥6 cm located adjacent to the stomach. (n=40) **All had persistent pancreatic pain** requiring narcotics or analgesics. Mean (SD) age: Endoscopy: 48 (14) years Surgery 51 (17) years USA	• Treatment success (8 and 4 weeks for endoscopic and surgery groups, respectively) • Recurrence (24 months) • Complications (24 months) • Length of hospital stay (24 months) • Re-intervention (24 months) • SF36 (24 months)	**Randomised controlled trial** Persistent or recurrent pseudocysts were treated by either a repeat intervention or the patient was crossed over to the alternate treatment arm. **18/20 endoscopic patients had successful ERCP, and 10/18 required pancreatic stenting**

Study	Intervention and comparison	Population	Outcomes	Comments
	cystogastrostomy was created. A **nasogastric tube** then was left in the stomach and passed into the pseudocyst cavity to allow for intermittent irrigation until postoperative day 1. The anterior gastrostomy was then closed. (n=20)			

Table 97: Summary matrix of study comparisons

	Pancreatic endoscopic stent	Endoscopic drainage (±EUS-guided)	Endoscopic drainage (±PD stent)	Laparoscopic drainage	Percutaneous drainage	Open surgery (resection/ drainage)	Observation
Pancreatic endoscopic stent		Bhasin 2011					
Endoscopic drainage (±EUS)				Melman 2009 (±EUS) Saul 2016 (+EUS; combines laparoscopic and open surgery)	Akshintala 2014 (±EUS) Rasch 2017 (+EUS) Talar-Wojnarowska 2010	Melman 2009 (±EUS) Rasch 2017 (+EUS) Talar-Wojnarowska 2010	Rasch 2017 (+EUS)
Endoscopic drainage (±PD stent)						Johnson 2009 (+PD stent) Varadarajulu 2008 (+EUS) (±PD stent) **Varadarajulu 2013 (+EUS) (±PD stent) (RCT)**	
Laparoscopic drainage						Davila Cervantes 2004 Melman 2009	
Percutaneous drainage						Andersson 2006 Heider 1999 Morton 2005 Rasch 2017 (+EUS) Talar-Wojnarowska 2010	Heider 1999 Rasch 2017 (+EUS)
Open surgery (resection/drainage)							Heider 1999 Rasch 2017 (+EUS)

Table 98: Data not suitable for meta-analysis

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Varadarajulu 2008[112]	EUS-guided endoscopic drainage (± pancreatic endoscopic stent) versus open surgery drainage	Length of post-procedure hospital stay	Median (range): 2.6 (1–11)	20	Median (range): 6.5 (4–20)	10	High
Varadarajulu 2013[111] RCT	EUS-guided endoscopic drainage (± pancreatic endoscopic stent) versus open surgery drainage	Length of hospital stay	Median (IQR): 2 (1–4) days	20	Median (IQR): 6 (5–9) days *Difference in medians (95% CI) −4 (−5, −3) days*	20	Low
		SF36 mental component score (high score better)	NA	20	Mean (95% CI): 4.41 (8.26 to 0.55) lower than intervention	20	Low
		SF36 physical component score (high score better)	NA	20	Mean (95% CI): 4.48 (8.23 to 0.73) lower than intervention	20	Low
Saul 2016[96]	EUS-guided endoscopic drainage versus laparoscopic or open surgery	Length of hospital stay	Median (range): 0 (0–10)	21	Median (range): 7 (2–42)	43	Very high
Davila-Cervantes 2004[25]	Laparoscopic drainage versus open surgery drainage	Length of hospital stay	Median (range): 7 (4–15)	10	Median (range): 14 (8–21)	6	Very high
Rasch 2017[88]	Endoscopic, percutaneous, surgical drainage and surgical resection versus conservative management	Length of hospital stay	Median endoscopic : 16 days percutaneous 21 days surgical drainage 19.5 days	 41 8 6	Median 3 days	44	High

Study	Intervention versus Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
			surgical resection 27 days	15			

Table 99: Clinical evidence summary: endoscopic drainage versus open surgical drainage or resection

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with open surgical drainage or resection	Risk difference with Endoscopic drainage (95% CI)
Mortality	62 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable [b]	No events	
Complications - Grade 2 or greater	67 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.68 (0.24 to 1.91)	227 per 1000	73 fewer per 1000 (from 173 fewer to 207 more)
Complications – bleeding infection or leakage	17 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.35 (0.04 to 3.15)	286 per 1000	186 fewer per 1000 (from 274 fewer to 614 more)
Complications	62 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.77 (0.32 to 1.87)	286 per 1000	66 fewer per 1000 (from 209 fewer to 100 more)
Resolution of presenting symptoms or pseudocysts - Overall success rate	67 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.93 (0.77 to 1.11)	909 per 1000	64 fewer per 1000 (from 209 fewer to 100 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with open surgical drainage or resection	Risk difference with Endoscopic drainage (95% CI)
Resolution of presenting symptoms or pseudocysts - Primary success rate	67 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.43 (0.28 to 0.67)	818 per 1000	466 fewer per 1000 (from 270 fewer to 589 fewer)
Recurrence of pseudocysts	17 (1 study) 26 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 2.8 (0.39 to 20.02)	143 per 1000	257 more per 1000 (from 87 fewer to 1000 more)
Length of hospital stay (days)	17 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias		The mean length of hospital stay (days) in the control group was 15.4 days	The mean length of hospital stay (days) in the intervention group was 8.2 lower (12.87 to 3.53 lower)
Repeated procedure (reintervention)	62 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 5.7 (1.3 to 25.06)	0 per 1000	220 more per 1000 (from 80 more to 360 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as there were no events in the intervention or comparison group
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 100: Clinical evidence summary: combined endoscopic drainage and pancreatic endoscopic stent versus open surgical drainage

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with open surgical drainage or resection	Risk difference with combined endoscopic drainage and stent (95% CI)
Mortality	54 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with open surgical drainage or resection	Risk difference with combined endoscopic drainage and stent (95% CI)
Complications – Overall (including technical failure, bleeding, wound infection, deep vein thrombosis, fistulae and incisional hernia)	54 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1.04 (0.36 to 3)	200 per 1000	8 more per 1000 (from 128 fewer to 400 more)
Complications – Overall (not defined)	30 (1 study4) During admission	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	Not estimable[b]	No events	
Complications - Overall (including wound infection, and haematemesis) **(RCT)**	40 (1 study) 24 months	⨁⨁⊖⊖ LOW[c] due to imprecision	RR 0.2 (0.01 to 3.92)	100 per 1000	80 fewer per 1000 (from 99 fewer to 292 more)
Resolution of pseudocysts	54 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.94 (0.78 to 1.12)	933 per 1000	56 fewer per 1000 (from 205 fewer to 112 more)
Resolution of pseudocysts	30 (1 study4) 4-6 weeks	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.97 (0.82 to 1.16)	1000 per 1000	30 fewer per 1000 (from 180 fewer to 160 more)
Resolution of presenting symptoms - Treatment success (resolution of symptoms at 4 weeks for surgery group; resolution or a decrease in the size of the fluid collection to 2 cm or smaller on CT with resolution of symptoms at 8 weeks)	40 (1 study) 4–8 weeks	⨁⨁⨁⨁ HIGH	RR 0.95 (0.83 to 1.09)	1000 per 1000	50 fewer per 1000 (from 170 fewer to 90 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with open surgical drainage or resection	Risk difference with combined endoscopic drainage and stent (95% CI)
(RCT)					
Recurrence (new-onset abdominal pain in the presence of a pancreatic fluid collection on CT after resolution of the initial presentation) **(RCT)**	40 (1 study) 24 months	⨁⨁⨀⨀ LOW[c] due to imprecision	RR 0.33 (0.01 to 7.72)	50 per 1000	34 fewer per 1000 (from 49 fewer to 336 more)
Repeated procedures (reintervention)	30 (1 study[d]) during admission	⨁⨀⨀⨀ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.17 (0.01 to 3.94)	100 per 1000	83 fewer per 1000 (from 99 fewer to 294 more)
Repeated procedures (reintervention) **(RCT)**	40 (1 study) 24 months	⨁⨁⨀⨀ LOW[c] due to imprecision	RR 1 (0.07 to 14.9)	50 per 1000	0 fewer per 1000 (from 47 fewer to 695 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as there were no events in the intervention or comparison group
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(d) Case–control

Table 101: Clinical evidence summary: endoscopic drainage versus open or laparoscopic surgery

Outcomes	No of Participants	Quality of the	Relative	Anticipated absolute effects

	(studies) Follow-up	evidence (GRADE)	effect (95% CI)	Risk with Combination of open and laparoscopic surgical techniques	Risk difference with Endoscopic drainage (95% CI)
Mortality	64 (1 study) Median (IQR) follow-up: endoscopic 270 (30-1915); combination 580 (0-4320) days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.67 (0.03 to 15.7)	23 per 1000	8 fewer per 1000 (from 23 fewer to 342 more)
Overall complications (including bleeding, infection, stent migration)	64 (1 study) Median (IQR) follow-up: endoscopic 270 (30-1915); combination 580 (0-4320) days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 0.93 (0.37 to 2.33)	256 per 1000	18 fewer per 1000 (from 161 fewer to 340 more)
Clinical success (complete resolution or decrease in the size of pseudocysts to 2cm or smaller on CT with associated resolution of symptoms).	64 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 1 (0.84 to 1.18)	907 per 1000	0 fewer per 1000 (from 145 fewer to 163 more)
Recurrence (pancreatic pseudocyst found on CT in association with symptoms after initial resolution)	64 (1 study) Median (IQR) follow-up: endoscopic 270 (30-1915); combination 580 (0-4320) days	⊕⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 2.05 (0.31 to 13.54)	47 per 1000	49 more per 1000 (from 32 fewer to 583 more)
Length of CCU stay (days)	64 (1 study) Median (IQR) follow-up: endoscopic 270 (30-1915); combination 580 (0-4320) days	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias		The mean length of CCU stay (days) in the control group was 1.4 days	The mean length of CCU stay (days) in the intervention group was 1.21 lower (1.43 to 0.99 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 102: Clinical evidence summary: endoscopic drainage versus laparoscopic drainage

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laparoscopic drainage	Risk difference with Endoscopic (95% CI)
Complications (Grade 2 or greater)	61 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.62 (0.21 to 1.85)	250 per 1000	95 fewer per 1000 (from 198 fewer to 213 more)
Resolution of presenting symptoms or pseudocysts - Overall success rate	61 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.9 (0.75 to 1.08)	938 per 1000	94 fewer per 1000 (from 234 fewer to 75 more)
Resolution of presenting symptoms or pseudocysts - Primary success rate	61 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 0.41 (0.26 to 0.63)	875 per 1000	516 fewer per 1000 (from 324 fewer to 648 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 103: Clinical evidence summary: endoscopic drainage versus endoscopic pancreatic stent

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Pancreatic endoscopic stent	Risk difference with Endoscopic drainage (95% CI)
Significant complications (including infection)	10 (1 study) 3-10 days after stent insertion	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.16 (0.01 to 2.28)	667 per 1000	560 fewer per 1000 (from 660 fewer to 853 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Pancreatic endoscopic stent	Risk difference with Endoscopic drainage (95% CI)
Resolution of pseudocysts	10 (1 study) 4-8 weeks	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 2.52 (0.89 to 7.1)	333 per 1000	507 more per 1000 (from 37 fewer to 1000 more)
Recurrence of pseudocysts	6 (1 study) 16.4 ±11.4 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[c]	No events	

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Could not be calculated as there were no events in the intervention or comparison group

Table 104: Clinical evidence summary: endoscopic drainage versus standard treatment (observation)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Endoscopic drainage (95% CI)
Mortality	85 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	
Complications	85 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	Peto OR 9.89 (2.5 to 39.09)	0 per 1000	220 more per 1000 (from 90 more to 350 more)
Repeated procedure (reintervention)	85 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW [a] due to risk of bias	Peto OR 9.89 (2.5 to 39.09)	0 per 1000	220 more per 1000 (from 90 more to 350 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as there were no events in the intervention or comparison group

Table 105: Clinical evidence summary: percutaneous drainage versus open surgical drainage or resection

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgical drainage	Risk difference with Percutaneous (95% CI)
Mortality	132 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 8 (1.56 to 40.90)	0 per 1000	90 more per 1000 (from 20 more to 160 more)
Mortality	14530 (1 study) 4 years	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 2.11 (1.78 to 2.5)	28 per 1000	31 more per 1000 (from 22 more to 42 more)
Mortality	29 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[c]	No events	
Complications – bleeding, infection or leakage	11 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.75 (0.38 to 8.06)	286 per 1000	214 more per 1000 (from 177 fewer to 1000 more)
Complications - Intra-abdominal abscess and bleeding requiring transfusion	14530 (1 study) 4 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.22 (1.13 to 1.32)	135 per 1000	30 more per 1000 (from 18 more to 43 more)
Complications - Post-operative bleeding, infection or fistula	23 (1 study) 10 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.3 (0.09 to 0.98)	667 per 1000	467 fewer per 1000 (from 13 fewer to 607 fewer)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgical drainage	Risk difference with Percutaneous (95% CI)
Complications - Post-operative bleeding, infection or fistula	132 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 2.41 (1.54 to 3.79)	258 per 1000	363 more per 1000 (139 more to 719 more)
Complications	29 (1 study) Median 4.7 months	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.44 (0.06 to 3.09)	286 per 1000	160 fewer per 1000 (from 269 fewer to 597 more)
Resolution of pseudocyst or symptoms	132 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.73 (0.55 to 0.98)	682 per 1000	184 fewer per 1000 (from 14 fewer to 307 fewer)
Recurrence of pseudocyst - Failure: radiographic persistence of a symptomatic pseudocyst in the observed group and a persistent symptomatic pseudocyst requiring a further procedure in the intervention groups	132 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 4.75 (2.4 to 9.39)	121 per 1000	455 more per 1000 (from 170 more to 1000 more)
Recurrence of pseudocyst	23 (1 study) 10 years	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.25 (0.45 to 11.37)	333 per 1000	417 more per 1000 (from 183 fewer to 1000 more)
Recurrence of pseudocyst	11 (1 study) 26 months	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 5.25 (0.78 to 35.13)	143 per 1000	607 more per 1000 (from 31 fewer to 1000 more)
Length of hospital stay	132 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias		The mean length of hospital stay in the control group was 18 days	The mean length of hospital stay in the intervention groups was 27 higher (25.7 to 28.3 higher)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Open surgical drainage	Risk difference with Percutaneous (95% CI)
Length of hospital stay	14530 (1 study) 4 years	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias		The mean length of hospital stay in the control group was 15 days	The mean length of hospital stay in the intervention groups was 6 higher (5.4 to 6.6 higher)
Length of hospital stay	11 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control group was 15.4 days	The mean length of hospital stay in the intervention groups was 2.2 lower (6.95 lower to 2.55 higher)
Repeated procedure (reintervention)	29 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 57.97 (5.69 to 590.19)	0 per 1000	500 more per 1000 (from 170 more to 830 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Could not be calculated as there were no events in the intervention or comparison group

Table 106: Clinical evidence summary: percutaneous drainage versus endoscopic drainage

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Endoscopic drainage	Risk difference with Percutaneous drainage (95% CI)
Mortality	81 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Endoscopic drainage	Risk difference with Percutaneous drainage (95% CI)
Mortality	49 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable [b]	No events	
Complications – bleeding infection or leakage	14 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 5 (0.61 to 40.91)	100 per 1000	400 more per 1000 (from 39 fewer to 1000 more)
Complications	49 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.57 (0.08 to 3.89)	220 per 1000	94 fewer per 1000 (from 202 fewer to 634 more)
Procedural adverse events	81 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1.02 (0.36 to 2.91)	146 per 1000	3 more per 1000 (from 94 fewer to 280 more)
Recurrence of pseudocysts	14 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1.88 (0.73 to 4.83)	400 per 1000	352 more per 1000 (from 108 fewer to 1000 more)
Length of hospital stay	81 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias		The mean length of hospital stay in the control group was 6.5 days	The mean length of hospital stay in the intervention group was 8.3 higher (3.39 to 13.21 higher)
Length of hospital stay	14 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision		The mean length of hospital stay in the control group was 7.2 days	The mean length of hospital stay in the intervention group was 6 higher (1.43 to 10.57 higher)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Endoscopic drainage	Risk difference with Percutaneous drainage (95% CI)
Repeated procedures (re-intervention)	81 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 4.36 (1.61 to 11.82)	98 per 1000	329 more per 1000 (from 60 more to 1000 more)
Repeated procedures (re-intervention)	49 (1 study) Median 4.7 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 2.28 (0.92 to 5.61)	220 per 1000	281 more per 1000 (from 18 fewer to 1000 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as there were no events in the intervention or comparison group
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 107: Clinical evidence summary: percutaneous drainage versus standard treatment (observation)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Percutaneous drainage (95% CI)
Mortality	107 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 5.48 (1.02 to 29.59)	0 per 1000	90 more per 1000 (from 10 fewer to 170 more)
Mortality	52 (1 study) Median 4.7 months	⊕⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[c]	No events	
Complications - Post-operative bleeding, infection or fistula	41 (1 study) 10 years	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 9.17 (1.19 to 70.44)	0 per 1000	200 more per 1000 (from 10 more to 390 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Percutaneous drainage (95% CI)
Complications - Post-operative bleeding, infection or fistula	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 5.09 (2.19 to 11.83)	122 per 1000	499 more per 1000 (from 233 more to 1000 more)
Complications	52 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 665.14 (2.91 to 152094.1)	0 per 1000	130 more per 1000 (from 120 fewer to 370 more)
Resolution of pseudocyst or symptoms	107 (1 study) after discharge	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias, imprecision	RR 0.73 (0.53 to 1.01)	683 per 1000	184 fewer per 1000 (from 321 fewer to 7 more)
Failure (defined as radiographic persistence of a symptomatic pseudocyst in the observed group and a persistent symptomatic pseudocyst requiring a further procedure in the intervention groups)	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 7.87 (2.6 to 23.85)	73 per 1000	503 more per 1000 (from 117 more to 1000 more)
Recurrence of pseudocyst	41 (1 study) 10 years	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 1.34 (0.81 to 2.2)	524 per 1000	178 more per 1000 (from 100 fewer to 629 more)
Repeated procedures (re-intervention)	52 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 998.5 (60.74 to 16415.31)	0 per 1000	500 more per 1000 (from 170 more to 830 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Could not be calculated as there were no events in the intervention or comparison group

Table 108: Clinical evidence summary: laparoscopic drainage versus open surgical drainage or resection

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgical drainage or resection	Risk difference with Laparoscopic drainage (95% CI)
Mortality (all-cause)	16 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.95 (0.09 to 283.86)	0 per 1000	100 more per 1000 (from 180 fewer to 380 more)
Complications - Overall (including pneumonia, post-operative abscess, small bowel obstruction secondary to an internal hernia, upper gastrointestinal bleeding)	16 (1 study) Median 22 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.6 (0.11 to 3.21)	333 per 1000	133 fewer per 1000 (from 297 fewer to 737 more)
Complications - Grade 2 or greater	38 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.1 (0.35 to 3.46)	227 per 1000	23 more per 1000 (from 148 fewer to 559 more)
Resolution of presenting symptoms - Asymptomatic with no evidence of recurrent disease by CT scan	16 (1 study) Median 22 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.78 to 1.27)	1000 per 1000	0 fewer per 1000 (from 220 fewer to 270 more)
Resolution of presenting symptoms or pseudocysts - Overall success rate	38 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	RR 1.03 (0.86 to 1.24)	909 per 1000	27 more per 1000 (from 127 fewer to 218 more)
Resolution of presenting symptoms or pseudocysts - Primary success rate	38 (1 study) 16 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.82 to 1.4)	818 per 1000	57 more per 1000 (from 147 fewer to 327 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgical drainage or resection	Risk difference with Laparoscopic drainage (95% CI)
Residual pseudocyst	16 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.6 (0.05 to 7.92)	167 per 1000	67 fewer per 1000 (from 158 fewer to 1000 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 109: Clinical evidence summary: open surgical drainage or resection versus standard treatment (observation)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Open surgical drainage/resection (95% CI)
Mortality	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	
Mortality	65 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	
Complications - Post-operative bleeding, infection or fistula	24 (1 study) 10 years	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 4288.26 (59.08 to 311264.	0 per 1000	670 more per 1000 (from 190 more to 1000 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Open surgical drainage/resection (95% CI)
			31)		
Complications - Post-operative bleeding, infection or fistula	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 2.11 (0.84 to 5.29)	122 per 1000	135 more per 1000 (from 20 fewer to 523 more)
Complications	65 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Peto OR 28.72 (4.83 to 170.64)	0 per 1000	290 more per 1000 (from 90 more to 480 more)
Resolution of pseudocyst and symptoms (after hospital discharge; defined as recurrent cyst, recurrent pancreatitis, fistula, infection)	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1 (0.77 to 1.3)	683 per 1000	0 fewer per 1000 (from 157 fewer to 205 more)
Failure (radiographic persistence of a symptomatic pseudocyst)	107 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1.66 (0.47 to 5.89)	73 per 1000	48 more per 1000 (from 39 fewer to 358 more)
Recurrence of pseudocyst	24 (1 study) 10 years	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.64 (0.12 to 3.32)	524 per 1000	189 fewer per 1000 (from 461 fewer to 1000 more)

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment (observation)	Risk difference with Open surgical drainage/resection (95% CI)
Repeated procedure (reintervention)	65 (1 study) Median 4.7 months	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as there were no events in the intervention or comparison group
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

22.4 Economic evidence

22.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

22.4.2 Unit costs

See appendix N.17.

22.5 Evidence statements

All evidence was in adults or young people over 16 years.

22.5.1 Clinical

22.5.1.1 Endoscopic drainage versus open surgical drainage or resection

- There was non-randomised evidence of a clinical benefit of endoscopic drainage for length of hospital stay (1 study; n=17; very low quality) and a possible clinical benefit for complications (3 studies; n=146; very low quality). However, there was also evidence of a clinical benefit of open surgery for primary success rate and a possible clinical benefit for recurrence of pseudocysts (1 study; n=17; very low quality). Furthermore, the evidence suggested no clinical difference for mortality (1 study; n=17; very low quality), overall success rate (1 study; n=67; very low quality) and re-intervention (1 study; n=62; very low quality).

22.5.1.2 Combined endoscopic drainage and pancreatic endoscopic stent versus open surgical drainage

- There was evidence from 1 randomised controlled trial to suggest a clinical benefit of endoscopic drainage for complications (1 study; n=40; low quality). However, there was no clinical difference for mortality (1 study; n=54; very low quality), resolution of pseudocysts (2 studies; n=84; very low quality), and resolution of symptoms (1 study; n=40; high quality); and a suggestion of no clinical difference for complications (2 studies; n=84; very low quality), , recurrence (1 study; n=40; low quality) or re-intervention (2 studies; n=70; low to very low quality).

22.5.1.3 Endoscopic drainage versus open or laparoscopic surgery

- There was non-randomised evidence of a clinical benefit of endoscopic drainage for length of CCU stay (1 study; n=64; very low quality). However, the evidence also suggested no clinical difference for mortality, complications, clinical success or recurrence (1 study; n=64; very low quality).

22.5.1.4 Endoscopic drainage versus laparoscopic drainage

- There was non-randomised evidence to suggest a clinical benefit of endoscopic drainage for grade 2 or greater complications, but a clinical benefit of laparoscopic drainage for primary success rate. Furthermore, the evidence suggested no clinical difference for overall success rate (1 study; n=61; very low quality).

22.5.1.5 Endoscopic drainage versus endoscopic pancreatic stent

- There was non-randomised evidence to suggest a clinical benefit of endoscopic drainage for significant complications and resolution of pseudocysts (1 study; n=10; very low quality). However, there was no clinical difference for recurrence of pseudocysts (1 study; n=6; very low quality).

22.5.1.6 Endoscopic drainage versus standard treatment (observation)

- There was non-randomised evidence of a clinical benefit of observation for complications and re-intervention (1 study; n=85; very low quality), but no clinical difference for mortality (1 study; n=85; very low quality).

22.5.1.7 Percutaneous drainage versus open surgical drainage or resection

- There was non-randomised evidence of a clinical benefit of open surgical drainage or resection for mortality (2 studies; n=14,662; very low quality), but no deaths in 1 further non-randomised study (1 study; n=29; very low quality). There was also non-randomised evidence to suggest a clinical benefit of open surgical drainage or resection for complications (2 studies; n=133; very low quality). However, 2 further non-randomised studies suggested a clinical benefit of percutaneous drainage for complications (2 studies; n=52; very low quality), and 1 study showed no clinical difference for the same outcome (1 study; n=14530; very low quality). The non-randomised evidence for length of hospital stay was also inconsistent with 2 studies showing a clinical benefit of open surgical drainage or resection (2 studies; n=14662; very low quality) and 1 study suggesting a clinical benefit of percutaneous drainage (1 study; n=11; very low quality).
- The non-randomised evidence also showed a clinical benefit of open surgical drainage or resection for re-intervention (1 study; n=29; very low quality) and a possible clinical benefit for resolution of pseudocyst or symptoms (1 study; n=132; very low quality), and recurrence of pseudocyst (3 studies; n=165; very low quality).

22.5.1.8 Percutaneous drainage versus endoscopic drainage

- There was non-randomised evidence to suggest a clinical benefit of endoscopic drainage for complications from 1 study (1 study; n=14; very low quality), but another study suggested a clinical benefit of percutaneous drainage for the same outcome (1 study; n=49; very low quality). The evidence also demonstrated of a clinical benefit of endoscopic drainage for length of hospital stay (2 studies; n=95; very low quality), and repeated procedures (2 studies; n=130; very low quality), and a possible clinical benefit for recurrence of pseudocysts (1 study; n=14; very low quality). However, the evidence suggested no clinical difference for procedural adverse events (1 study; n=81; very low quality).

22.5.1.9 Percutaneous drainage versus standard treatment (observation)

- There was non-randomised evidence of a clinical benefit of observation for mortality (1 study; n=107; very low quality; 1 further study reported no deaths), complications (3 studies; n=200; very low quality), failure (1 study; n=107; very low quality), recurrence of pseudocyst (1 study; n=41; very low quality) and repeated procedures (1 study; n=52; very low quality), and a possible clinical benefit for resolution of pseudocyst or symptoms (1 study; n=107; very low quality).

22.5.1.10 Laparoscopic drainage versus open surgical drainage or resection

- There was non-randomised evidence to suggest a clinical benefit of open surgical drainage or resection for mortality (1 study; n=16; very low quality). However, there was also non-randomised evidence to suggest a clinical benefit of laparoscopic drainage for overall complications (1 study; n=16; very low quality). However, the eveidenc also suggestde no clinical difference for grade 2 or

greater complications (1 study; n=38; very low quality), resolution of pseudocyst or symptoms (2 studies; n=54; very low quality) and residual pseudocysts (1 study; n=16; very low quality).

22.5.1.11 Open surgical drainage or resection versus standard treatment (observation)

- No deaths were reported in 2 studies (n=172; very low quality) and no repeated procedures reported in 1 study (n=65; very low quality). However, there was non-randomised evidence of a clinical benefit of observation for complications (3 studies; n=196; very low quality) but consverely a clinical benefit of open surgical drainage or resection for recurrence of pseudocysts (1 study; n=24; very low quality). Furthermore, the evidence suggested no clinical difference for resolution of pseudocysts and symptoms or failure (1 study; n=107; very low quality).

22.5.2 Economic

- No relevant economic evaluations were identified.

22.6 Recommendations and link to evidence

Recommendations	**31. Offer endoscopic ultrasound (EUS)-guided drainage, or endoscopic transpapillary drainage for pancreatic head pseudocysts, to people with symptomatic pseudocysts (for example those with pain, vomiting or weight loss).** **32. Consider EUS-guided drainage, or endoscopic transpapillary drainage for pancreatic head pseudocysts, for people with non-symptomatic pseudocysts that meet 1 or more of the following criteria:** • **are associated with pancreatic duct disruption** • **are creating pressure on large vessels or the diaphragm** • **are at risk of rupture** • **there is suspicion of infection.** **33. Consider surgical (laparoscopic or open) drainage of pseudocysts that need intervention if endoscopic therapy is unsuitable or has failed.**
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, complications, resolution of presenting symptoms and resolution or recurrence of pseudocysts. The committee also chose the following outcomes as important outcomes: length of stay in hospital or CCU and repeated procedures.
Quality of the clinical evidence	One randomised controlled trial (RCT) and 12 non-randomised, comparative studies were included in this review. The majority of the data included either open surgery or endoscopic drainage as one of the comparators and there were few comparisons with observation, laparoscopic or endoscopic drainage, or pancreatic endoscopic stent. The quality of the evidence for all observational study outcomes was graded as very low due to risk of bias and also, in most cases, imprecision. None of the observational studies adequately controlled for confounding and many had different sample sizes in each of the intervention groups. The way people were allocated to different treatment options was often unclear and likely to be based on clinical indication, which creates a high risk of bias. The quality of evidence for the RCT ranged from high to low, with the limitation of imprecision being present for some critical outcomes. The committee considered meta-analysing studies according to the pre-specified intervention categories agreed at protocol stage, but concluded that this was not

	possible, as the interventions used and populations included in the studies were too heterogeneous to be analysed together, as well as the lack of controlling for confounders.
Trade-off between clinical benefits and harms	The committee noted that the evidence from the randomised trial provided high quality evidence that endoscopic drainage (with or without placement of a pancreatic duct stent) was not inferior to open surgical drainage for resolution and low quality evidence to show no clinical difference for recurrence or re-intervention. There were also fewer complications with endoscopic drainage, but the low event rate and small sample size produced a large degree of uncertainty in this estimate. This was in people with symptomatic, large pseudocysts. The committee reviewed the observational evidence for all comparisons with endoscopic drainage and noted that there was a clinical benefit of endoscopic drainage compared with all other active interventions for reducing complications and length of hospital stay. In addition, there was some inconsistency in findings regarding resolution and recurrence of endoscopic drainage compared with open or laparoscopic drainage, with some evidence suggesting a clinical benefit of the surgical approach for these outcomes. However, the committee noted that the endoscopic approach used in the studies was outdated and the current procedures, for example using large-bore metal stents, would be more successful, particularly in the presence of necrosis and therefore compare more favourably with the surgical approach. Consequently, considering the increased risk of complications with open or laparoscopic surgery, the equivocal findings regarding the relative success of the treatments and the fact that more interventional procedures can be attempted if endoscopic drainage fails, the committee recommended endoscopic drainage as the first-line option in people with symptomatic pseudocysts. The symptoms experienced are pain, vomiting and weight loss. This is not a departure from current practice in most centres. The current method for this is to use EUS guidance in most cases, and this was used in the majority of studies, therefore the committee included this within the recommendation to ensure that appropriate guidance of the endoscope will be used in (or under the supervision of) a specialist pancreatic centre. The committee also noted that in some cases where the pseudocyst is in the head of the pancreas, as seen in the RCT and observational evidence, pancreatic duct stents placed using ERCP may be more appropriate and so the transpapillary route was also included in the recommendation. The committee highlighted that if the pseudocysts is not located close to the stomach endoscopic drainage can be more complicated and specialist review is needed. Regarding the population, the committee discussed that symptomatic pseudocysts would always require intervention (and 10 out of 13 studies, including the RCT, included all or a majority of people with symptomatic pseudocysts), but that in some circumstances non-symptomatic pseudocyst would also require intervention. These non-symptomatic pseudocysts may be identified on an incidental scan and would require action if large, causing pancreatic duct disruption, creating pressure on large vessels or the diaphragm, or at risk of rupture. This is to prevent symptoms occurring and to prevent serious complications such as fluid leaking into the chest cavity. The pseudocyst characteristics that would prompt action were based on the committee's expertise and included those at risk of rupture, which can be indicated by rapid expansion, or radiological features. The committee discussed the most appropriate second-line approach for managing pseudocysts when endoscopic drainage is not appropriate, for example if open surgery is required for a co-morbid condition such as gallstones, or has not been successful. The committee noted that open and laparoscopic surgery can be effective and safe where there are local expertise to perform them and the evidence did not show a clear clinical difference between these 2 treatment options across all outcomes. Although there was 1 case of mortality with laparoscopic drainage and 0 with open surgery in 1 study, the sample size was too small to draw any conclusions from this. Therefore, it was agreed that surgical drainage (either open or

	laparoscopic) should be recommended as a second-line option. However, the committee highlighted than open surgery is rarely performed in current practice. The committee noted that the evidence for percutaneous drainage is not favourable for any comparison. However, the committee did not wish to make a recommendation that percutaneous drainage should not be performed due to the very low quality of the evidence and their clinical knowledge that the percutaneous route can be useful, safe and effective in some cases and in some centres where there is expertise in this practice. The committee specifically highlighted that for the comparison with open surgery it may have been that those unfit for surgery were offered percutaneous drainage, which may explain the higher mortality in the percutaneous group. The committee discussed the evidence suggesting that observation can be appropriate in some cases as no clinical difference was seen between open drainage or resection and conservative treatment (observation) for mortality or resolution of symptoms in 1 study, and a clinical benefit for fewer complications with observation from 2 studies. However, 1 study did show a clinical benefit of open surgery for fewer recurrences. The committee highlighted the risk of bias associated with 1 study regarding the indication for treatment confounding the results, but noted that the findings still indicate that observation can be appropriate in some cases. For example, in elderly people with low risk pseudocysts it may not be worth the risk of complications associated with intervention. Also, small pseudocysts often do not need to be drained and pseudocysts of the pancreas commonly resolve spontaneously.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. Unit costs were presented to the committee for consideration alongside the clinical evidence. The committee recommended that EUS-guided endoscopic drainage (or endoscopic stent by ERCP where the pseudocyst is in the head of the pancreas) should be offered as first-line treatment to people with symptomatic pseudocysts, which is current practice. The average cost of EUS-guided pseudocyst drainage was estimated to be £4,903 (NHS reference cost codes GA05C, GA05D, GB09D, GB09E, GB09F), which is a cheaper procedure compared with laparoscopic and pseudocyst drainage, which both cost approximately £6,560 (NHS reference cost codes GA05C, GA05D, GA06C, GA06D) and percutaneous drainage which costs £5,431 (NHS reference cost codes GA06C,GA06D). However, the committee noted that due to a low number of procedures, these reference costs cover a range of interventions, not all related to the pancreas or pseudocysts, and so may not fully reflect the true difference in the costs of carrying out these procedures. It was also found from clinical studies that EUS-guided endoscopic drainage reduces complications and length of hospital stay compared with open or laparoscopic surgery, both of which are likely to decrease long-term total healthcare costs considerably, as well as improving the patient's health and quality of life. Percutaneous drainage, on the contrary, is expected to lead to high rates of complications, leading to significant additional downstream costs (as well as worse health outcomes). The committee therefore agreed that EUS-guided endoscopic drainage is likely to be cost saving or cost effective compared with the alternative approaches. The average cost of an endoscopic stenting procedure was found to be £1,996 (NHS reference cost codes GB06E, GB06F, GB06G, GB06H). The committee discussed that although pancreatic stenting is a less costly initial procedure than other alternatives, repeat procedures are required in 30% of people, increasing overall costs and decreasing quality of life due to additional procedures. Therefore, the committee considered that the overall long-term cost of using a stent is likely to be similar to the other options, such as EUS-guided drainage. Pancreatic stents were therefore only recommended for cases where this approach is more clinically appropriate.

Other considerations	The committee noted that it takes at least 4 weeks for a pseudocyst to form in acute pancreatitis and sometimes much longer. In 1 study that reported both a primary and overall success rate, the committee noted that the overall success rate reflected resolution following multiple attempts at or methods of intervention (for example, in those initially managed endoscopically this could be repeated endoscopic drainage or salvage using open or percutaneous methods). Therefore, the committee was most interested in the primary success rate. The committee anticipates that drainage will be done by experienced EUS practitioners after discussion with a specialist pancreatic centre.

1

23 Management of pancreatic ascites and pleural effusion secondary of pancreatitis

23.1 Introduction

Pancreatic ascites is defined by high amylase concentration in ascitic fluid (usually over 1000 IU/L) The term encompasses people with ascites and pleural effusion, including fistulae and intra-abdominal collections, secondary to acute or chronic pancreatitis. It is a rare complication of acute and chronic pancreatitis (<5%) but should be suspected in patients with pancreatitis presenting with ascites particularly with a history of alcohol abuse. Leakage from a pancreatic pseudocyst or disruption of the pancreatic duct is usually the underlying cause. Patients may present with pain and symptoms caused by irritant abdominal ascites, or shortness of breath due to amylase rich pleural effusion.

Therapy for pancreatic ascites is controversial. Historically treatment has focussed on total parenteral nutrition or naso-jejunal feeding and somatostatin analogues to reduce secretion; paracentesis and diuretics with escalation to surgery in those that fail to respond with patients suffering a 10-15% mortality. However, with the advances in endoscopic techniques and MRCP (for ductal anatomy and disruption), the last 20 years has seen an increase in transpapillary stenting and other endotherapies within specialist pancreatic centres.

It is still unclear whether conservative, medical, endoscopic or surgical management or a combination of these provides the most clinically and cost effective treatment. This review attempts to answer this question.

23.2 Review question: What are the most clinically effective and cost-effective interventions for treating pancreatic ascites and pleural effusion secondary to acute or chronic pancreatitis?

For full details see review protocol in appendix C.

Table 110: PICO characteristics of review question

Population	People with ascites and pleural effusion, including fistulae and intra-abdominal collections, secondary to acute or chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Percutaneous intervention (for example, aspiration or drainage) • Surgery (for example, resection or drainage procedure) • Pharmacological treatment (including, somatostatin analogues, for example octreotide, lanreotide; diuretics, for example, spironolactone) • Nutritional supplements (enteral or parenteral) • Pancreatic endotherapy • Combinations
Comparisons	• To each other • No treatment • Usual care
Outcomes	Critical outcomes

	• Quality of life (no time cut-off) (continuous) • Mortality (no time cut-off) (dichotomous) • Length of stay (in CCU or hospital) (no time cut-off) (continuous or dichotomous) • Resolution (for example, resolution of fluid collection, resolution of fistulae) (no time cut-off) Important outcomes • Number of procedures (repeated procedures) (no time cut-off) • Recurrence (no time cut-off) • Complications (no time cut-off)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

23.3 Clinical evidence

No relevant clinical studies comparing any of the above interventions with each other, no treatment or usual care were identified.

23.4 Economic evidence

23.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

23.5 Evidence statements

23.5.1 Clinical

- No relevant published evidence was identified.

23.5.2 Economic

- No relevant economic evaluations were identified.

23.6 Recommendations and link to evidence

Recommendation	34.Consider referring a person with pancreatic ascites and pleural effusion for management in a specialist pancreatic centre.
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, length of stay and resolution. The also noted the following outcomes to be important: repeated procedures, recurrence and complications.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess what are the most clinically and cost-effective interventions for treating pancreatic ascites and pleural effusion secondary to acute or chronic pancreatitis. However, the committee noted this was to be expected given the low number of cases that occur, which would also make future research in the area difficult. Given the severity of the clinical presentation when pancreatic ascites and pleural effusion does occur, often associated with pancreatic duct disruption, the committee believed it to be important to raise awareness and provide some level of advice for management. As the condition is difficult to manage, the committee agreed that there is a benefit of management in a specialist pancreatic centre, with regard to prevention of ineffective interventions and re-interventions, and reduction in mortality and length of hospital stay. Additionally, early recognition and intervention are required, which is likely to include: specialist nutritional advice (distal jejunal feeding or parenteral nutrition), somatostatin analogue, and endoscopic, radiological or surgical treatment. This effective specialist management can prevent malnutrition, infection, and intra-abdominal organ damage.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee was therefore not able to assess the most cost-effective interventions for treating pancreatic ascites and pleural effusion secondary to acute or chronic pancreatitis. The committee agreed it was important to make a good practice recommendation to make clinicians aware of the complex and unusual nature of pancreatic ascites and pleural effusion which would require specialist advice. The committee noted that

	this condition occurs in a very small population and would not have a large resource implication; however the committee agreed that by intervening early, including giving specialist neutralist advice, there should be a reduction in the need for either endoscopic or surgical treatment, and a reduction in adverse effects of the condition, which may also lead to a shortening of hospital inpatient stays. This would result in savings from reduced later treatment as well as improvements in health. Therefore, even if this recommendation leads to a small increase in the number of people being referred to specialist pancreatic centres, the overall effect is likely to be either cost saving or highly cost effective compared with fewer people being referred.
Other considerations	The committee noted that this occurs in acute and chronic pancreatitis and is associated with pancreatic duct disruption.

1

24 Management of biliary obstruction in people with chronic pancreatitis

24.1 Introduction

Biliary obstruction in adults with chronic pancreatitis is a significant cause of morbidity and recurrent hospital admission. Relief of obstruction is therefore indicated in symptomatic or persistent cholestasis. Practice has included single plastic stents, multiple plastic stents, self-expanding metal stents (covered, partially covered and fully uncovered) and surgery (for example, hepaticojejunostomy or choledocho-jejunostomy). Temporary stenting of common bile duct strictures with multiple plastic stents or covered self-expanding metal stents is also an option. This review attempts to address the most effective way of treating biliary obstruction.

24.2 Review question: What is the most clinically effective and cost-effective intervention for treating biliary obstruction in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 111: PICO characteristics of review question

Population	People with biliary obstruction and chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Plastic stents (single, multiple) • Metal stents (uncovered, partially covered, fully covered) • Surgery (for example, hepatojejunostomy, choledocho-jejunostomy, biliary-enteric anastomosis) • Combination stent plus surgery (for example, step-up approach as defined by studies)
Comparison	To each other
Outcomes	Critical outcomes • Quality of life (continuous) • Mortality (≤1 year) (dichotomous) • Recurrence of biliary obstruction (including failed stent, both removal and additional stents) (dichotomous) • Biliary infections (dichotomous) Important outcomes • Number of procedures (repeated procedures) (dichotomous) • Length of stay (in CCU or hospital) (continuous or dichotomous) • Complications (for example, bleeding, fistulae) (dichotomous)
Key confounders	• Presence of pancreatic head mass • Portal hypertension or portal vein thrombosis • Previous biliary stent
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised controlled studies will be included.

24.3 Clinical evidence

Two studies were included in the review: Haapamäki 2017, [47] Regimbeau 2012; [91] these are summarised in Table 112 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 113 and Table 114). No studies looking at biliary obstruction in children have been identified. One of the included studies compares covered metal stents to multiple plastic stents while the other included study compares metal and plastic stents to surgery. See also the study selection flow chart in appendix E, study evidence tables in appendix H, GRADE tables in appendix J, forest plots in appendix K, and excluded studies list in appendix L.

Table 112: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Haapamäki 2017[47]	Intervention 1: Metal stent - Fully covered metal stent. Dilation was performed with an 8-mm balloon in both groups. The original plastic stent was replaced with a cSEMS. At 3 months, the position and function of the stent were checked by ERCP. In case of stent migration, the stent was replaced with a new cSEMS. At 6 months after randomisation, all stents were removed (n=30) Intervention 2: Plastic stent - Multiple plastic stents. Dilation was performed with an 8-mm balloon in both groups. The original plastic stent was replaced with 3 plastic stents. At 3 months, balloon dilation was performed and the number of plastic stents was increased to a maximum of six 10-Fr stents when possible. At 6 months after randomisation, all stents were removed (n=30)	Adults with chronic pancreatitis and biliary obstruction (n=60) Age (median, range): 53 (33-78) years Finland	• Mortality (2 years) • Recurrence of biliary obstruction or stricture resolution (2 years) • Complications (2 years)	All patients were prepared and sedated for ERCP according to the standard medical practice at the hospital. At the initial ERCP, an endoscopic sphincterotomy was performed and one 10-Fr plastic stent was inserted for the treatment of cholestasis. CBD dilation was performed only if deemed necessary. Any existing CBD stones above the stricture were removed. Pancreatic stents were inserted if indicated Randomised controlled trial
Regimbeau 2012[91]	Intervention 1: Plastic or metal stent. A flexible guidewire was passed through the stricture followed by a guiding catheter. The choice of stent was left to the endoscopist. In the event of an associated, symptomatic pancreatic duct stricture, a plastic pancreatic stent was	Adults with chronic pancreatitis and biliary obstruction (n=39) Age (median, range): stent group 52 (49-55); surgery group 52 (38-66) years	• Mortality (time-point unclear) • Recurrence of biliary obstruction (time-point unclear) • Length of stay (time-point unclear) • Complications	Non-randomised comparative study No confounders accounted for Before biliary drainage all the patients underwent a

Study	Intervention and comparison	Population	Outcomes	Comments
	inserted concomitantly. Oral ciprofloxacin therapy (500 mg twice daily) was started before ERCP and continued 3 days thereafter. The minimum defined time for stent therapy was 12 months (with multiple plastic or metallic stents). Patients with plastic stents had a routine stent exchange in 3 months, whereas patients with metallic stents had a routine stent exchange in 6 months to improve the calibration of the CBD and to decrease the number procedures. At the end of the period defined for ET therapy, the stents were removed (n=33) Intervention 2: Open surgery - Surgical treatment consisted of choledochoduodenostomy or choledochojejunostomy. For patients with a symptomatic inflammatory cephalic mass (diameter >4 cm), surgical biliary drainage consisted of a duodenum-preserving pancreatic head resection (the Frey procedure) with concomitant decompression of the CBD within the head of the pancreas to avoid a biliary bypass. 17 people who were originally in the endoscopy group went on to have surgery (n=6)	France	(time-point unclear)	comprehensive imagine workup (including pancreatic MRI or contrast-enhanced, triple phase CT scan) and a nutritional status evaluation, then received appropriate therapy for diabetes or exocrine pancreatic insufficiency. The outcome reporting number of procedures was not extracted as data was unclear.

Abbreviations: CBD: common bile duct; cSEMS: covered self-expandable metallic stent; ERCP: endoscopic retrograde cholangiopancreatography; ET: endoscopic treatment

Table 113: Clinical evidence summary: metal stents versus plastic stents

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Multiple plastic stents	Risk difference with Covered metal stents (95% CI)
Mortality	58 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 3.21 (0.35 to 29.12)	33 per 1000	74 more per 1000 (from 22 fewer to 937 more)
Recurrence of biliary obstruction (Recurrent strictures)	58 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.71 (0.13 to 3.96)	100 per 1000	29 fewer per 1000 (from 87 fewer to 296 more)
Complications (Adverse events)	58 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.22 (0.51 to 2.93)	233 per 1000	51 more per 1000 (from 114 fewer to 450 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 114: Clinical evidence summary: stenting versus surgery

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with Stenting (95% CI)
Mortality	39 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a] due to risk of bias	Not estimable[b]	No events	

Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with Stenting (95% CI)
Recurrence of biliary obstruction (Successful treatment)	39 (1 study) time-point unclear	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.72 (0.48 to 1.08)	870 per 1000	243 fewer per 1000 (from 452 fewer to 70 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Could not be calculated as no events in the intervention or control arms
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

24.4 Economic evidence

24.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

24.4.2 Unit costs

See appendix N.19.

24.5 Evidence statements

24.5.1 Clinical

24.5.1.1 Metal stents versus plastic stents

- One randomised trial in adults suggested a clinical benefit of plastic stents over metal stents for the outcome of mortality at 2 years (1 study; n=58; very low quality). The evidence suggested no clinically important difference between the 2 groups in terms of recurrence of biliary obstruction (recurrent strictures) and complications (adverse events) at 2 years (1 study; n=58; Very Low quality).

24.5.1.2 Stenting versus surgery

- One non-randomised study in adults showed no clinical difference between groups in terms of mortality (1 study; n=39; very low quality) but a possible benefit of surgery over stenting for the outcome of recurrence of biliary obstruction (successful treatment) (1 study; n=39; Very low quality).

24.5.2 Economic

- No relevant economic evaluations were identified.

24.6 Recommendations and link to evidence

Research recommendation	7. What is the clinical and cost effectiveness of metal stents compared to surgery for treating biliary obstruction in adults with chronic pancreatitis?
Relative values of different outcomes	The guideline committee considered the following to be critical outcomes: quality of life, mortality, recurrence of biliary obstruction and biliary infections. The committee also considered the following were important outcomes: number of procedures, length of stay and complications. No evidence was found for children. For the adult population, 2 studies reported data on mortality, complications and recurrence of biliary obstruction. One study also reported evidence on length of stay. There were no outcomes reported for quality of life, biliary infections and number of procedures.
Quality of the clinical evidence	The studies included provided evidence for metal stents versus plastic stents, and stenting versus surgery. The evidence for the metal stents versus plastic stents comparison was provided by a randomised controlled trial and the quality was graded as very low due to risk of bias and imprecision. The evidence for the stenting

	versus surgery comparison was provided by a non-randomised comparative study and was graded as very low due to risk of bias and imprecision.
Trade-off between clinical benefits and harms	The committee considered the body of evidence for this review. For the comparison of metal stents versus plastic stents, the committee noted that there was a clinically important benefit of plastic stents in terms of mortality, but no difference between groups for the outcomes of recurrence of obstruction and complications. The committee was concerned that in the paper reporting on this comparison, all stents were removed at 6 months which is quite early compared with clinical practice in the UK. For the comparison of stenting versus surgery, the committee noted that there was no clinically important difference between the 2 groups in terms of mortality, and that surgery was shown to have clinically important benefit over stenting in terms of recurrence of biliary obstruction. The committee noted that people in whom stenting was not successful and who later received surgery were analysed in the surgery group in this study. Overall, the committee found that the evidence was insufficient to support a recommendation on the most clinically and cost effective intervention to treat biliary obstruction in people with chronic pancreatitis. However, the committee discussed the importance of further research into how to effectively treat biliary strictures in chronic pancreatitis and therefore agreed to draft a research recommendation in this area. The committee discussed the differences between each of the interventions and noted that when plastic stents are used to treat biliary obstruction, patients are more likely to require multiple stents as well as multiple procedures before the biliary stricture is resolved, the usage of plastic stents also requires stricture dilatation for endoscopic procedures which increases morbidity. As such, the committee did not want further research to be done to assess the effectiveness of both plastic and metal stents, but rather wanted to recommend that future research focus on comparing metal stents to surgery.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. Unit costs were presented to the committee for consideration alongside the clinical evidence. The average cost of open surgery was estimated to be around £7,120 (NHS reference cost codes GA04C–GA06D), whereas endoscopic stenting to treat biliary obstruction was found to be around £2,177 (NHS reference cost codes GB05F–GB09F). Unfortunately, the cost of a stenting procedure does not differentiate between the uses of plastic or metal stents. Therefore the stent costs were sought from the NHS supply chain catalogue. The unit cost of a plastic stent is £21, whereas a metal stent is £688. The committee discussed that although plastic stents are less costly than metal stents, multiple plastic stents are often required to treat the obstruction whereas usually only 1 metal stent is required. More importantly, plastic stents often have to be replaced more frequently than metal stents, requiring a greater number of repeat procedures. Therefore, overall the committee considered that using plastic stents is likely to be more costly than using metal stents, and is also likely to have a negative impact on the patient's quality of life due to the number of procedures required. The committee noted that as stenting procedures are often repeated, the overall costs of treating biliary obstruction through open surgery or stenting are likely to be similar. Taking these economic factors into consideration alongside the absence of high quality clinical evidence the committee decided to recommend that further research be conducted to assess the clinical and cost effectiveness of metal stenting versus open surgery. There are therefore no economic implications from this review from this review.

Other considerations	The committee were aware that there are studies looking at biliary obstruction in chronic pancreatitis, however the vast majority of these were non-comparative studies. The committee were also aware of studies that included mixed populations of patients with benign biliary obstruction due to a number of causes including chronic pancreatitis; however these studies did not have separate analyses specifically for people with chronic pancreatitis. The committee discussed the discrepancies in treating biliary obstruction within the NHS. It was highlighted that in some cases, people with benign biliary strictures are treated with stents as permanent solutions which can lead to recurrent infections, secondary biliary cirrhosis and increased levels of mortality. The committee agreed that it would be clinically beneficial to have clear guidance on how biliary obstruction should be managed. The committee noted that plastic stents rather than metal stents are usually used in children. The committee felt that research in this area for children was a lower priority than for the adult population. The committee discussed what other considerations were important to highlight to clinicians; it agreed that people with hereditary pancreatitis and children with pancreatitis need to be looked at with special consideration and believe they should be discussed at a multidisciplinary meeting.

1

1 # REFERRAL FOR SPECIALIST TREATMENT

25 Receiving specialist input in people with acute pancreatitis

25.1 Introduction

Acute pancreatitis (AP) accounts for over 50% of all admissions to hospital for pancreatic digestive disease, with an annual incidence of 30-50/100,000, accounting for around 20,000 annual hospital admissions in England. The severity of acute pancreatitis is classified according to the revised Atlanta criteria as mild, moderate or severe. In 70% of patients AP results in pain and nutritional deficit requiring pain relief and modest nutritional support but the disease is of short duration with no complications (mild acute pancreatitis). Appropriate management of gallstones (cholecystectomy with or without endoscopic sphincterotomy), alcohol excess (counselling/support) or other causes is important.). In 20% of patients AP results in either transient (<48 h) organ dysfunction and/or pancreatic fluid collections with or without necrosis that cause more prolonged pain, nutritional deficit and longer hospital stays. (moderately severe AP). In 10% of patients AP results in persistent organ failure (>48 h) and necrosis, causing more prolonged pain, prolonged nutritional deficit and hospital stays over 4 weeks. Critical care is required, usually with percutaneous, endoscopic or surgical intervention for pancreatic necrosis. Death is likely in up to half of this group (severe AP), resulting in an overall likelihood of death in all cases of AP of 3-5%.

The full range of interventions for AP are provided by some 30 of the 150 acute NHS Trusts in England, almost all co-located with the provision of specialist services for pancreatic cancer. Specialist service provision for AP, however, is less well defined than for pancreatic cancer. The 2016 NCEPOD audit[74] of the management of AP in England showed substantial variation in the interaction between Trusts providing secondary and tertiary level care for AP throughout the country. Only some Trusts providing specialist pancreatic services have established networks and frequent interaction with surrounding acute Trusts providing secondary level care for AP. The management of patients with AP may be appropriately conducted in any acute NHS Trust, but are likely to be some patients whose condition may be better managed by a specialist pancreatic centre. This review attempts to address the roles of specialist (tertiary) versus non-specialist (secondary) level care and expertise in the management of AP, assessing which patients should be considered for discussion and potential transfer, the priority necessary, and mechanisms to ensure appropriate use of specialist services.

25.2 Review question: What is the clinical effectiveness and cost effectiveness of receiving specialist input in people with acute pancreatitis?

For full details see review protocol in appendix C.

Table 115: PICO characteristics of review question

Population	People with acute pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Intervention	Specialist input in the diagnosis, management or follow-up of acute pancreatitis (regardless of setting)
Comparison	No specialist input in the diagnosis, management or follow-up of acute pancreatitis
Outcomes	Critical outcomes

	• Quality of life (continuous) • Mortality (dichotomous) • Length of stay (continuous) Important outcomes • Hospital admissions (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

25.3 Clinical evidence

No relevant clinical studies comparing specialist input in the diagnosis, management or follow-up of acute pancreatitis with no specialist input were identified.

25.4 Economic evidence

25.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

25.5 Evidence statements

25.5.1 Clinical

- No relevant published evidence was identified.

25.5.2 Economic

- No relevant economic evaluations were identified.

25.6 Recommendations and link to evidence

Recommendations	**35.If a person develops necrotic, infective, haemorrhagic or other local complications of acute pancreatitis:** • **seek advice from a specialist pancreatic centre within the referral network and** • **discuss whether to move the person to the specialist centre for treatment of the complications.** **36.When managing acute pancreatitis in children:** • **seek advice from a paediatric gastroenterology or hepatology unit and a specialist pancreatic centre and** • **discuss whether to move the child to the specialist centre.**
Relative values of different outcomes	The guideline committee noted the following outcomes to be critical: quality of life, mortality, and length of stay. The also noted the following outcome to be important: hospital admission.

Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess the effectiveness of specialist input for acute pancreatitis. The committee was aware of historical lack of appropriate referral to specialist centres for acute pancreatitis and current variation in practice in the UK, as well as models of practice for specialist input that have been successful in some localities. In line with the NCEPOD report 'A review of the quality of care provided to patients treated for acute pancreatitis' a specialist pancreatic centre is defined as a high volume centre with critical care facilities, daily access to radiological intervention, interventional endoscopy including EUS and ERCP and surgical expertise in managing necrotising pancreatitis. Similarly, a formal referral network is defined as a linked group of health professionals and organisations from primary, secondary and tertiary care and social care and other services working together in a coordinated manner with clear governance and accountability arrangements. The committee acknowledged that a comparative trial in this area may not be ethical and therefore believed it to be appropriate to make a recommendation based on its expert opinion as this is a critical part of the care pathway. The committee noted that the benefits of appropriate specialist input and intervention at a specialist centre included: • Improved patient outcomes (for example, reduction of septic complications, reduction in hospital stay, removal of necrosis). • Patients stay in their local hospital for longer in consultation with the specialist team. • Preventing inappropriate delay in referral and intervention, which can result in prolonged CCU stay in the pancreatic centre or death. This will reduce resource use by appropriate management being achieved earlier. • Some patients can be managed in the local hospital with remote specialist care by the use of electronic communication with image transfer and ongoing monitoring • Use of minimally invasive treatments. • Specialist nutritional input. However, the committee also noted the following possible risks: • Communication between the specialist and local hospitals must be effective for patient-management to be optimal. • Specialist pancreatic centres may not have access to specialist advice needed (for example, specialist dietitians), as they are often funded for cancer rather than pancreatitis. • The local hospital may develop an over-dependence on the specialist centre and not provide appropriate day-to-day care as they await specialist advice. Therefore, the committee recommended that when local complications of severe acute pancreatitis occur, management options should be discussed with a specialist pancreatic centre, including whether transfer to the specialist centre for intervention is appropriate. Transfer is only likely to be necessary in patients who require radiological, endoscopic or operative intervention. The committee also recommended that all children with acute pancreatitis should be discussed with a paediatric gastroenterology or hepatology unit and a specialist pancreatic centre, including whether to move the child to the specialist centre. The committee noted that as there are no specialist paediatric centres for pancreatitis in the UK, adult units provide support and advice and that acute pancreatitis is a rare condition in children. However, the complexity of the disease may require a multidisciplinary approach including specialised paediatric gastroenterology or hepatology, nutrition, chronic pain, endoscopic, genetic and laboratory, interventional radiology and paediatric surgical services which are available only in a

	limited number of specialist centres in the UK. Early discussion and referral to a specialist centre can enhance diagnosis and optimise management in complicated cases of acute pancreatitis in children where local expertise are limited.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee noted that a recommendation was required to improve clinicians' understanding about liaising with specialist centres and transferring people who require interventions, given current variations in practice including both over-referral and under-referral to specialist centres. The committee was not able to predict the exact effect that these recommendations will have on the total number of people with acute pancreatitis who will be referred to specialist pancreatic centres in future, not least because current practice varies across the country and does not follow consistent principles. The committee judged that this recommendation will lead to a reduction in current unnecessary referrals, and an increase in appropriate referrals. Only a minority of people with acute pancreatitis (those with particularly complex complications) needs to be referred to specialist pancreatic centres, and the committee believes that most people who need to be treated in a specialist centre already are treated there. On balance, therefore, the committee believes that these recommendations are likely to increase the total number of referred patients by a small amount, and perhaps also lead some people who are currently referred to specialist care to be referred at an earlier stage. The committee emphasised the importance of discussing patients' cases with a specialist pancreatic centre before taking the decision to refer, to reduce unnecessary referrals. Referring those patients who need specialist care to a specialist centre should lead to better health outcomes for them. There will also be an increase in staff costs due to increased contact time with consultants and specialist nurses. But there is also likely to be a reduction in some of the treatment costs in the medium term. Complications can be expensive to treat, and treating them well at the earliest opportunity can decrease total treatment costs over the course of a hospital stay. Prompt and accurate referral can reduce both total length of stay in hospital and in particular length of stay in CCU. One CCU bed day costs £2,119 compared with £680 for an inpatient general bed day, and so effective treatment which reduces time spent in CCU can be cost saving. Discussing patients with colleagues at a specialist centre at the earliest opportunity could lead some patients who will currently receive specialist care at a later point to be referred at an earlier stage. Receiving the most suitable treatment at an earlier point is more efficient, will improve outcomes and reduce length of stay and costs. For example, earlier treatment can help to reduce the risks of septic complications or necrosis. For other patients, a discussion with staff at a specialist centre will lead to a decision that the patient can stay in their current hospital, but their doctors will receive high quality advice on the best course of treatment for them. This will increase costs in respect of the time taken to consider the case and give advice, but is expected to significantly increase the quality of care and health outcomes for the patient, and may again lead to decreases in downstream costs due to reductions in complications and length of stay. As a result, the committee expects these recommendations to be cost saving or highly cost effective compared with current practice. An increase in total costs, if any, would not be substantial due to the low number of patients involved.
Other considerations	The committee discussed that only a subset of patients with severe acute pancreatitis need and will benefit from specialist intervention. Therefore, it is unnecessary (as well as not possible) to transfer all people with severe acute pancreatitis to a specialist centre, as CCU can appropriately manage most cases. However, those who require an intervention will likely benefit from referral. It has

	been demonstrated in some UK centres that a model where local centres interact with a regional specialist centre can be successful. This involves sending patient clinical details and imaging and seeking advice from the specialist centre when a new case is received, then ongoing collaborative review with regular clinical updates. People are transferred in discussion with the specialist centre only if intervention is required. The committee was aware that specialist centres may not always have access to the same range of specialist skills. There is an existing discrepancy across the UK in the specialist centres. The centres were set up for pancreatic cancer, not for acute or chronic pancreatitis, and this has resulted in a lack of available resources for benign disease (both in tertiary and secondary care). For example, some centres may have 'access to' specialist dietitians and nurse specialists and not have a dedicated team for this purpose. By making it 'access only', teams will have access to a 'generalist' with no specialist training. The committee was aware that this is a service delivery issue and difficult to address in a clinical guideline.

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FOLLOW-UP INVESTIGATIONS

26 Follow-up of pancreatic exocrine function in people with chronic pancreatitis

26.1 Introduction

Patients with chronic pancreatitis are at risk of ongoing complications of the disease including progression of the local effects of the disease, including worsening of nutritional debilation, and pancreatic exocrine insufficiency (PEI). PEI is associated with fat malabsorption (steatorrhoea) and malnutrition and can be confirmed with physiological tests such as estimation of faecal fat or measurement of faecal elastase. Deficiencies of fat soluble vitamins A, D, E and K may occur over time. Osteoporosis and osteopenia is common and can be identified by bone density testing. This review attempts to address how often to people with chronic pancreatitis should be followed up to assess their pancreatic exocrine function and secondary health issues.

26.2 Review question: How often should follow-up to assess pancreatic exocrine function and any secondary health issues, if any, be carried out in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 116: PICO characteristics of review question

Population	People with a diagnosis of chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Follow-up with any of the following tests, alone or in combination: ○ faecal elastase ○ assessment of nutritional status (for example, measurement of fat-soluble vitamins ADEK; iron; body weight; anthropometrics [for example Z scores]; parathyroid hormone [PTH]) ○ bone density (dual energy X-ray absorptiometry [DEXA] scan) At frequencies of: ○ 6-monthly (or at intervals of ≤6 months) ○ Yearly (or at intervals of 6 months–1 year) ○ At intervals >1 year • No follow-up
Comparisons	• Follow-up versus no follow-up (or follow-up on demand) • Different frequency of same follow-up investigation
Outcomes	Critical outcomes • Quality of life (continuous) • Mortality (dichotomous) • Exocrine function (as measured by for example faecal elastase) • Low impact fractures (dichotomous) • Changes in nutritional status Important outcomes • Hospital admissions (dichotomous)

	• Return to usual activities (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

26.3 Clinical evidence

A search was conducted for randomised trials or non-randomised comparative studies to evaluate how often people with chronic pancreatitis should be followed-up to assess pancreatic function and secondary health issues. There were no relevant clinical studies found for inclusion in this review.

26.4 Economic evidence

26.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

26.5 Evidence statements

26.5.1 Clinical

- No relevant published evidence was identified.

26.5.2 Economic

- No relevant economic evaluations were identified.

26.6 Recommendations and link to evidence

Recommendations	**37. Offer people with chronic pancreatitis monitoring by clinical and biochemical assessment for pancreatic exocrine insufficiency and malnutrition every 12 months (every 6 months in under 16s), and adjust treatment of vitamin and mineral deficiencies accordingly.** **38. Offer adults with chronic pancreatitis a bone density assessment every 24 months.**
Relative values of different outcomes	The guideline committee considered the following to be critical outcomes: quality of life, mortality, exocrine function, low impact fractures and changes in nutritional status. The committee also considered the following outcomes to be important: hospital admissions and return to usual activities. No relevant clinical studies were identified; therefore no evidence was available for any of these outcomes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess how often people with chronic pancreatitis should be followed up to assess their pancreatic exocrine function and any secondary health issues that they may have.

	Nevertheless, the committee agreed it was important to raise awareness of the potential health issues that people with chronic pancreatitis may face. The committee believed that clinicians should see their patients at least once a year, as this will give them an opportunity to assess the patient's pancreatic function, whether formally or informally, as symptoms can worsen over time. They agreed that the specific tests for each individual will vary, and discussed what tests should be included during follow-up. The committeefelt that due to the lack of evidence, it was best to leave this to the clinician's discretion, while noting that more than just body mass index (BMI) should be considered when assessing indications for nutrition support (see recommendations on indications for nutrition support in the NICE guideline on nutrition support (CG32) available at https://www.nice.org.uk/guidance/cg32/). The committee also discussed the holistic nature of follow-up and agreed that when deciding on who should follow a patient up, protocols should be developed in conjunction with pain management specialists, addiction specialists, psychologists, and specialist dietitians. It was agreed that this follow-up should be offered in secondary and tertiary care settings. The committee highlighted that there is good evidence for increased fracture risk and reduced bone density in chronic pancreatitis, and therefore the committee recommended that everyone with chronic pancreatitis should be offered a bone density assessment every 24 months. Twenty four months was picked as the appropriate follow-up period in line with the recommendations in the NICE guideline 'Osteoporosis: assessing the risk of fragility fracture' (available from https://www.nice.org.uk/guidance/cg146/).
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee agreed that it is important that clinicians are aware of the increased risk of problems associated with malabsorption and vitamin and mineral deficiencies including osteoporosis. The committee agreed that these recommendations would help clinicians initiate annual follow-up meetings with patients to discuss any health issues, and to carry out inexpensive routine blood tests depending on patients' concerns at the clinician's discretion. The committee members also noted that, in their experience, there is an increased need to carry out a bone density assessment (DEXA scan) in patients with chronic pancreatitis every 24 months. The committee agreed that follow-up appointments for patients with chronic pancreatitis are currently best practice, but noted that many patients do not currently receive routine follow-up, and therefore deterioration of pancreatic function is currently not always identified in a timely fashion. This can lead to malnutrition, readmission to hospital and increased fracture rate. These will all lead to significant additional costs which could be prevented or reduced by monitoring. The committee therefore agreed that routine monitoring is likely to be cost saving or cost effective compared to no monitoring. The committee also noted that the NICE guidance on nutrition support and osteoporosis referred to above has already been assessed and found to be cost effective for the relevant populations, and agreed that these are also relevant for people with chronic pancreatitis, who have similar risks of malnutrition and fracture.
Other considerations	The committee noted that DEXA scanning is not routinely used in children but that due to the potential growth implications follow-up needs to be undertaken more often, every 6 months.

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27 Follow-up to identify pancreatic cancer in people with chronic pancreatitis

27.1 Introduction

Patients with chronic pancreatitis are at increased risk of pancreatic cancer. In those with a hereditary cause the lifetime risk is particularly high. . This review attempts to address how often to people with chronic pancreatitis should be followed up to investigate the presence of pancreatic cancer.

27.2 Review question: How often should follow-up to identify the development of pancreatic cancer be carried out in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 117: PICO characteristics of review question

Population	People with a diagnosis of chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Interventions	• Surveillance (with any of the following tests, alone or in combination: tumour markers (for example, CA19.9); MRI; EUS; CT) ○ 6-monthly (or at intervals of ≤ 6 months) ○ Yearly (or at intervals of 6 months–1 year) ○ At intervals >1 year • No surveillance
Comparisons	• Follow-up versus no follow-up (or follow-up on demand) • Different frequency of same follow-up investigation
Outcomes	Critical outcomes • Quality of life (continuous) • Mortality (dichotomous) • Cancer-related mortality (dichotomous) Important outcomes • Stage of cancer at diagnosis • Serious adverse events (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

27.3 Clinical evidence

A search was conducted for randomised controlled trials and non-randomised comparative studies to evaluate how often people with chronic pancreatitis should be followed-up to check for pancreatic cancer. There were no relevant clinical studies found for inclusion in this review.

27.4 Economic evidence

27.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

27.5 Evidence statements

27.5.1 Clinical

- No relevant published evidence was identified.

27.5.2 Economic

- No relevant economic evaluations were identified.

27.6 Recommendations and link to evidence

Recommendations	**39. Be aware that people with chronic pancreatitis have an increased risk of developing pancreatic cancer. The lifetime risk is highest, around 40%, in those with hereditary pancreatitis.** **40. Consider annual monitoring for pancreatic cancer in people with hereditary pancreatitis.**
Relative values of different outcomes	The guideline committee agreed the following were critical outcomes: quality of life, mortality, cancer-related mortality. The committee also agreed the following outcomes were important: stage of cancer at diagnosis and serious adverse events.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess how often people with chronic pancreatitis should be followed up to identify development of pancreatic cancer. The committee felt it was important to address this question nonetheless, as many people with pancreatitis are also concerned about their risk of developing pancreatic cancer but are not invited for monitoring for its development. The committee agreed that it was important to discuss the risk of developing cancer with patients and take their wishes into consideration. The discussion should also include the risk of high cumulative exposure to radiation with repeated testing over a lifetime, and consideration that the likelihood of developing pancreatic cancer increases over a certain age, however, no evidence was available to recommend a specific age cut-off for monitoring. Additionally, early identification of pancreatic cancer can increase the survival time and so early identification is important. The committee discussed good practice measures that should be put into place; for example, when people with chronic pancreatitis suddenly deteriorate, they should be investigated for the development of pancreatic cancer. Most importantly, the committee want to increase awareness of the risk of pancreatic cancer in people with chronic pancreatitis, particularly in those who have been diagnosed with hereditary pancreatitis as this is a particularly high risk group. Epidemiological studies have found a cumulative lifetime risk of at least 40% in people with hereditary pancreatitis.[51, 63, 90] The committee made a recommendation to consider monitoring people with hereditary pancreatitis for the development of pancreatic

	cancer annually owing to the high incidence in this group and the benefits of identifying the condition early. However, a stronger recommendation was not possible as the diagnostic accuracy of the tests is not known. The committee discussed the possibility of making a research recommendation. However, there were concerns that this could downgrade some of the research already happening and may prevent patients being monitored whilst the research data are being gathered.
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee agreed that it was important to make a good practice recommendation to alert clinicians to the increased risk of developing pancreatic cancer, particularly in people with hereditary pancreatitis. There was a strong consensus that awareness of the increased risk and annual monitoring for pancreatitis cancer in patients with hereditary pancreatitis may potentially improve early diagnosis, and hence increase survival time and quality of life. Pancreatic cancer is an extremely serious condition, which people with chronic pancreatitis are at high risk of developing, and therefore patients have a reasonable desire to be monitored for pancreatic cancer. However, the lack of data on the accuracy of diagnostic testing for pancreatic cancer, and the lack of data regarding the impact of early diagnosis of pancreatic cancer on outcomes, mean that the committee was not able to assess the cost effectiveness of alternative frequencies of monitoring for development of pancreatic cancer in people with chronic pancreatitis. Therefore the committee made a recommendation that monitoring should be considered in the group at highest risk – those with hereditary pancreatitis – rather than a stronger recommendation that monitoring is essential, as the committee could not be sure that such testing would be cost effective. People with hereditary pancreatitis are a small group, thought to comprise around 3–5% of those with chronic pancreatitis (around 600 to 1250 people in England), and hence if these people were to receive annual monitoring this would not be expected to give rise to a substantial increase in NHS costs.
Other considerations	The committee noted that there is a lot of support for a screening programme to check people with hereditary pancreatitis for pancreatic cancer. However, the committee noted that there is little evidence to show that a screening programme, with supportive interventions during follow-up, demonstrates an improvement on mortality. Therefore, it is hard to make a recommendation. The committee discussed the possibility of recommending that people be immediately screened if their symptoms deteriorate and that pancreatic cancer symptoms that are particularly distinct from pancreatitis symptoms would be jaundice, diabetes, onset of weight loss or increase in pain. It was noted that patients have a lot of concern that they are at risk of pancreatic cancer yet there is no screening programme offered. The lay members on the committee agreed strongly that patients are given the choice to be screened for pancreatic cancer. The committee noted that lifestyle factors such as smoking, alcohol intake further increase the risk of developing pancreatic cancer in this patient group. It was noted that families of patients also need appropriate support.

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28 Follow-up to identify diabetes in people with chronic pancreatitis

28.1 Introduction

Patients with chronic pancreatitis are at risk of ongoing complications of the disease including progression of the local effects of the disease and the development of diabetes. Endocrine insufficiency leads to diabetes due to deficiency of insulin production. Diabetes is diagnosed with routine blood testing. Type 3c diabetes needs to be considered as many patients with chronic pancreatitis are diagnosed with type 2 diabetes wrongly and are not treated adequately with insulin. This review attempts to address how often to people with chronic pancreatitis should be followed up to assess if they have developed diabetes.

28.2 Review question: How often should follow-up to identify the development of diabetes be carried out in people with chronic pancreatitis?

For full details see review protocol in appendix C.

Table 118: PICO characteristics of review question

Population	People with a diagnosis of chronic pancreatitis • Adults and young people (>16 years) • Children (≤16 years)
Intervention	• Surveillance (with HbA1c; fasting glucose; oral glucose tolerance test (OGTT)) ○ 6-monthly (or at intervals of ≤6 months) ○ Yearly (or at intervals of 6 months–1 year) ○ At intervals >1 year • No surveillance
Comparisons	• Follow-up versus no follow-up (or follow-up on demand) • Different frequency of same follow-up investigation
Outcomes	Critical outcomes • Quality of life (continuous) • Mortality (dichotomous) Important outcomes • People requiring insulin (dichotomous) • Diabetic complications (for example, retinopathy, peripheral neuropathy, chronic kidney disease) (dichotomous) • Diagnosis of diabetes (dichotomous)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

28.3 Clinical evidence

No relevant clinical studies comparing follow-up with no follow-up or different frequencies of investigations were identified.

28.4 Economic evidence

28.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

28.5 Evidence statements

28.5.1 Clinical

- No relevant published evidence was identified.

28.5.2 Economic

- No relevant economic evaluations were identified.

28.6 Recommendations and link to evidence

Recommendations	**41. Be aware that people with chronic pancreatitis have a greatly increased risk of developing diabetes, with a lifetime risk as high as 80%. The risk increases with duration of pancreatitis and presence of calcific pancreatitis.** **42. Offer people with chronic pancreatitis monitoring of HbA1c for diabetes at least every 6 months.**
Relative values of different outcomes	The guideline committee selected the following outcomes as critical outcomes: quality of life and mortality. The committee also considered the following to be important outcomes: people requiring insulin, diabetic complications and diagnosis of diabetes.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	No relevant studies were identified for this review and the committee was therefore not able to assess how often people with chronic pancreatitis should be assessed for the development of diabetes. Diabetes secondary to chronic pancreatitis is associated with risk of acute metabolic decompensation including life-threatening severe hypoglycaemia and diabetic ketoacidosis. Concomitant diabetes is an independent risk factor for mortality in chronic pancreatitis, with epidemiological studies suggesting a cumulative risk of up to 80%.[67] Additionally, the risk of diabetes-specific microvascular complications is likely equivalent to type 1 and type 2 diabetes.[44, 61] Given the potential for absence of classical symptoms and for diabetes contributing to nutritional insufficiency, the committee agreed that screening should be undertaken through HbA1c testing with or without fasting plasma glucose according to the NICE guidance on type 2 diabetes: prevention in people at high risk; however, the committee acknowledges that the risk of developing diabetes in patients with chronic pancreatitis is not dependent of

	obesity.[44] Because of the high rate of progression to diabetes, monitoring more frequently than annually, every 3–6 months may be appropriate to allow prompt diagnosis and timely initiation of appropriate management. For those whose HbA1c levels have previously been high or in whom there is another reason an increased risk for development of diabetes a check more often than every 6 months would be appropriate. Additionally, any deterioration in symptoms should prompt reassessment, including glucose levels. Therefore, a recommendation was made allowing some flexibility in frequency of monitoring, stating at least every 6 months. The committee though it very unlikely that on this basis monitoring would be undertaken too often, for example, every month without good reason. The committee agreed that primary osmotic symptoms (thirst, polyuria, weight loss) should prompt additional random plasma glucose testing or HbA1c and blood or urine testing for ketones and that clinicians should assess the need for immediate insulin commencement where there is non-fasting ketosis. Diagnosis of diabetes requires initial and then annual screening for microvascular and macrovascular complications in line with those with type 1 and type 2 diabetes (link to NICE type 2 management guidance).
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee agreed that it was important to make a good practice recommendation to alert clinicians to the increased risk of developing diabetes with chronic pancreatitis. The committee also agreed that annual screening using HbA1c testing would be beneficial for all people with chronic pancreatitis, in accordance with the NICE guidance on managing type 2 diabetes. The cost of HbA1c is approximately £6 per patient (NHS reference costs 2015/16), this includes medical and staffing cost involved in analysing the results and staff time and equipment required to take the blood sample. Furthermore, the committee felt that additional screening should be carried out every 6 months. The committee recognised that diabetes screening blood tests could be carried out as part of a patient's regular check-up visits to their GP and therefore would not incur large additional costs. The committee recognised that carrying out this test could improve diabetes detection and reduce diabetes complications which can be expensive to treat as well as causing significant ill health and decreasing quality of life. As a result, the committee agreed that such low-cost tests were very likely to be either cost effective or cost saving to the NHS.
Other considerations	The lay members noted that it was important for patients with chronic pancreatitis to be tested for diabetes if they request. The Committee anticipates that if the patient is being seen in a specialist pancreatic centre their follow-up will be delivered by the specialist team. If they are still under the care of their GP their follow-up will be covered by the practice and the HBA1c result will then be available for the hospital consultants to check the result when reviewed in secondary or specialist care.

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1 # TYPE 3C DIABETES MANAGEMENT

29 Management of type 3c diabetes secondary to pancreatitis

29.1 Introduction

Chronic pancreatitis is associated with diabetes in up to 80% of cases, with prevalence even higher in individuals who have long duration disease, pancreatic calcification or previous partial pancreatectomy. Pancreatitis-associated diabetes is characterised by progressive insulin deficiency. This can lead to a catabolic state, worsening nutritional deficiency and ultimately risk of ketoacidosis. Insulin therapy is thus often instituted.

Pancreatic endocrine insulin insufficiency is associated with loss of normal glucagon counter-regulatory response to hypoglycaemia. Glucose instability can be further exacerbated by variable appetite and carbohydrate absorption in addition to nausea, vomiting, pain and alcohol intake. This is associated with risk of impaired hypoglycaemia awareness, severe hypoglycaemia requiring assistance from others and decompensated high glucose levels (ketoacidosis, hyperosmolar hyperglycaemic state).

This has led to use of a wide range of insulin regimens including insulin pump therapy without any currently agreed national standard. This review attempts to address the best insulin regimen strategy for type 3c diabetes.

29.2 Review question: What is the most clinically effective and cost-effective insulin regimen strategy specifically for type 3c diabetes secondary to pancreatitis?

For full details see review protocol in appendix C.

Table 119: PICO characteristics of review question

Population	Individuals diagnosed with type 3c diabetes secondary to pancreatitis • C peptide-positive people only • Includes chronic pancreatitis in people with cystic fibrosis mutations
Intervention	• Multiple daily injection therapy (basal-bolus) • Twice daily insulin regimen • Insulin pump
Comparisons	To each other
Outcomes	Critical outcomes: • Quality of life (≤1 year) (continuous) • HbA1c levels (no time cut-off) • Hospital admissions (for example related to diabetic ketoacidosis or decompensated high glucose levels (no time cut-off) • Severe hypoglycaemia (as defined by the American Diabetes association: an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration) (no time cut-off) Important outcomes:

	• Mortality (dichotomous) (≤1 year) • Hyperglycaemic hyperosmolar non-ketotic coma (HONK) (≤1 year) (dichotomous) • Fear of hypoglycaemia according to known validated scoring systems (for example, hypoglycaemia fear survey) (no time cut-off) • Impaired awareness of hypoglycaemia according to known validated scoring systems (for example, Gold score, Clarke score, Ryan score (hypoglycaemia burden score) , Pedersen–Bjergaard score) (no time cut-off)
Study design	RCTs, systematic reviews of RCTs. If insufficient RCT evidence to form a recommendation is found, non-randomised comparative studies will be included.

29.3 Clinical evidence

No relevant clinical studies comparing multiple daily injection therapy with twice daily insulin regimen or insulin pump were identified.

29.4 Economic evidence

29.4.1 Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

29.5 Evidence statements

29.5.1 Clinical

- No relevant published evidence was identified.

29.5.2 Economic

- No relevant economic evaluations were identified.

29.6 Recommendations and link to evidence

Recommendations	**43. People with type 3c diabetes should be assessed every 6 months for potential benefit of insulin therapy.** **44. For guidance on managing type 3c diabetes for people who are not using insulin therapy see the NICE guidelines on type 2 diabetes in adults and diagnosing and managing diabetes in children and young people.** **45. For people with type 3c diabetes who require insulin, see the:** • **recommendations on insulin therapy and insulin delivery in the NICE guideline on type 1 diabetes in adults** • **recommendations on insulin therapy in the NICE guideline on diagnosing and managing diabetes in children and young people** • **NICE technology appraisal on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus.** **46. For guidance on education and information for people with pancreatitis**

	and type 3c diabetes requiring insulin, see the recommendations on education and information in the NICE guideline on diagnosing and managing type 1 diabetes in adults and education and information in the NICE guideline on diagnosing and managing diabetes in children and young people. **47. For guidance on self-monitoring blood glucose for people with pancreatitis and type 3c diabetes requiring insulin, see the recommendations on blood glucose management in the NICE guideline on diagnosing and managing type 1 diabetes in adults and blood glucose monitoring in the NICE guideline on diagnosing and managing diabetes in children and young people.**
Research recommendation	**8. What is the most clinically effective and cost-effective insulin regimen for type 3c diabetes secondary to pancreatitis?**
Relative values of different outcomes	The guideline committee chose the following outcomes as critical outcomes: quality of life, HbA1c levels, hospital admissions and severe hypoglycaemia. The committee also chose the following as important outcomes: mortality, hyperglycaemic hyperosmolar non-ketotic coma.
Quality of the clinical evidence	No relevant clinical studies were identified.
Trade-off between clinical benefits and harms	Type 3c diabetes is defined as diabetes mellitus secondary to pancreatic disease. When this is associated with pancreatitis, the primary endocrine defect is insufficient insulin secretion (the abnormality in type 1 diabetes) rather than insulin resistance (characteristic of type 2 diabetes). No relevant studies were identified for this review and the committee was therefore not able to assess what is the most clinically effective insulin strategy for type 3c diabetes secondary to pancreatitis. The committee agreed that the recommendations regarding the use of insulin in people with type 1 diabetes are also relevant to those with type 3c diabetes, and in the absence of any evidence assessing insulin therapy in those with type 3c diabetes, that it was most appropriate to cross-refer to existing NICE guidance regarding insulin therapy and self-monitoring of blood glucose. Additionally, the committee agreed that it is important for further research to be done to provide evidence for future recommendations specific to type 3c diabetes. The committee agreed that it is important that clinicians are aware that type 3c diabetes secondary to chronic pancreatitis is difficult to control in terms of fluctuating blood glucose levels with associated risk of life-threatening severe hypoglycaemia, hyperglycaemic hyperosmolar non-ketotic coma and diabetic ketoacidosis; this may be particularly pronounced in people who have had total pancreatectomy. However, the committee also noted that while it is important to manage insulin effectively it is not known how appropriate a type 1 diabetes regimen is for those with type 3 c diabetes. Therefore, the committee agreed that it is important for further research to be done to provide evidence for future recommendations specific to type 3c diabetes. The committee also discussed the importance of considering insulin therapy early on in the treatment pathway for type 3c diabetes given the potential predominance of insulin deficiency over insulin resistance. However, it was also noted that insulin only becomes necessary if there is sufficient pancreatic endocrine impairment, as degradation occurs and that each patient should be assessed on a case by case basis. In the absence of ketosis, management using oral glucose lowering agents should be undertaken by an experienced care team according to guidelines for type 2 diabetes.

	The committee discussed the difficulty in controlling type 3c diabetes secondary to chronic pancreatitis and the need for considering insulin therapy early on in the pathway. Early introduction of insulin therapy is likely to improve wellbeing and nutritional status through prevention of uncontrolled diabetes. Education and support is important in optimal insulin self-management and glucose monitoring to prevent potentially life-threatening decompensated high glucose levels and severe hypoglycaemia. Attainment of better overall glucose control is likely to lead to better long-term outcomes through reduced risk of microvascular (eye, renal, foot) and macrovascular complications that are associated with chronic high glucose levels in all types of diabetes including type 3c. It was estimated by the committee that insulin therapy may be required for 50% of those with type 3c diabetes. In the absence of further evidence, the committee recommended that in those requiring insulin for type 3c diabetes, NICE guidelines on type 1 diabetes management should be followed including guidance on insulin pump therapy or continuous glucose monitoring (for those who fulfil existing restricted criteria for these interventions).
Trade-off between net clinical effects and costs	No relevant health economic evidence was identified for this question. The committee agreed that it is important that clinicians are aware of existing NICE guidance on managing type 1 diabetes and type 2 diabetes, which are also relevant for the management of type 3c diabetes. The recommendations in those guidelines have already been found to be cost effective for people in the relevant populations according to NICE's cost-effectiveness policies. The committee considered that the recommendations relating to type 2 diabetes should also be appropriate for people with type 3c diabetes who do not yet require insulin, and recommendations relating to insulin use for people with type 1 diabetes are appropriate for people with type 3c diabetes who do require insulin, due to clinical similarities between the conditions. The committee agreed that although there is considerable uncertainty as to the best insulin regimen strategy for people with type 3c diabetes, this is the best advice that can currently be provided given the lack of alternative strategies specific to type 3c diabetes. Consequently the committee also recommended that further research be conducted. If not carefully managed, diabetes can give rise to complications (such as in the eyes, feet and kidneys) that can be expensive to treat as well as causing significant ill health and decreasing quality of life. As a result, the committee agreed that these recommendations should be either cost effective or cost saving to the NHS.
Other considerations	The committee noted that the incidence of children with chronic pancreatitis and type 3c diabetes is very low. The committee discussed that in the early stages some people with type 3c diabetes may not need insulin, but the likelihood of progression to insulin-dependence is more likely than in type 2 diabetes.

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31 Acronyms and abbreviations

Acronym or abbreviation	Description
ACA	Available case analysis
ADL	Activities of daily living
ANC	Acute necrotic collections
AP	Acute pancreatitis
APACHE	Acute physiology and chronic health evaluation
AUDIT	Alcohol use disorder identification test
CBD	Common bile duct
CCU	Critical care unit
CEA	Cost-effectiveness analysis
CECT	Contrast-enhanced CT
CI	Confidence interval
CPL	Continuous postoperative lavage
CRP	C-reactive protein
cSEMS	Covered self-expandable metallic stent
CUA	Cost-utility analysis
DEXA	Dual energy X-ray absorptiometry
ED	Endoscopic drainage
EQ5D	EuroQol-5D
ERCP	Endoscopic retrograde cholangiopancreatography
ESWL	Extracorporeal shock wave lithotripsy
ET	Endoscopic treatment
ETN	Endoscopic transluminal necrosectomy
EUS	Endoscopic ultrasound
GI	Gastrointestinal
GRADE	Grading of recommendations assessment, development and evaluation
ICER	Incremental cost-effectiveness ratio
IPN	Infected pancreatic necrosis
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
MD	Mean difference
MID	Minimally important difference
MIP	Minimally invasive procedures
MOD	Multiple organ dysfunction
MODS	Multiple organ dysfunction syndrome
MRCP	Magnetic resonance cholangiopancreatography
NCPB	Neurolytic celiac plexus block
NGC	National Guideline Centre

Acronym or abbreviation	Description
NICE	National Institute For Health And Care Excellence
NR	Not reported
OAS	Open abdomen strategy
OECD	Organisation for Economic Co-operation and Development
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAC	Primary abdominal closure
PD	Percutaneous drainage
PD	Pancreatic duct
PTH	Parathyroid hormone
QALY	Quality-adjusted life years
QoL	Quality of life
RR	Relative risk
SADD	Short alcohol dependence data
SAP	Severe acute pancreatitis
SD	Standard deviation
SF-36	36-item short form survey
SIRS	Systemic inflammatory response syndrome
SPFT	Secretin pancreatic function test
TEN	Total enteral nutrition
TPN	Total parenteral nutrition
VARD	Video-assisted retroperitoneal debridement
VAS	Visual analogue scale
VSPL	Videoscopic splanchnicectomy
WOPN	Walled-off pancreatic necrosis

32 Glossary and Acronyms

The NICE Glossary can be found at www.nice.org.uk/glossary.

32.1 Clinical acronyms and abbreviations

Acronym or abbreviation	Description
AGI	Acute Gastrointestinal Injury
ANC	Acute Necrotic Collections
AP	Acute Pancreatitis
BISAP	Bedside Index of Severity in Acute Pancreatitis
CBD	Common Bile Duct
CECT	Contrast Enhanced Computed Tomography
CFTR gene	Cystic Fibrosis Transmembrane Conductance Regulator gene
CP	Chronic Pancreatitis
CPL	Continuous Postoperative Lavage
CRP	C-reactive protein
cSEMS	Covered self-expandable metal stent
CT	Computerised Tomography
CTSI	Computerised Tomography Severity index
DEXA	Dual Energy X-ray absorptiometry
DNA	Deoxyribonucleic acid
EQ-5D	EuroQol five dimension scale
EQ-5D VAS	EuroQol five dimension Visual Analogue Scale
ERCP	Endoscopic Retrograde Choloangiopancreatography
ESWL	Extracorporeal shock wave lithotripsy
ETN	Endoscopic Transluminal Necrosectomy
EUS	Endoscopic Ultrasound
GI	Gastrointestinal
HONK	Hyperglycaemic hyperosmolar non-ketotic coma
IgG4	immunoglobulin G4-related disease
IPN	Infected Pancreatic Necrosis
MHRA	The Medicines and Healthcare products Regulatory Agency
MID	Minimally important differences
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NCEPOD	The National Confidential Enquiry into Patient Outcome and Death
NCPB	Neurolytic Celia Plexus Block
NHS EED	National Health Service Economic Evaluation Database
OAS	Open Abdomen Strategy
OECD	Organisation for Economic Co-operation and Development
OGTT	Oral Glucose Tolerance Test

Acronym or abbreviation	Description
PAC	Primary Abdominal Closure
PCD	Percutaneous drainage
PEI	Pancreatic Exocrine insufficiency
PERT	Pancreatic enzyme replacement
PPC	Primary Pancreatic Cancers
PTH	Parathyroid hormone
SOFA	Sequential Organ Failure Assessment
SPINK1	Serine protease inhibitor Kazal-type 1 (SPINK1)
TEN	Total enteral nutrition
TPN	Total Parenteral Nutrition
VARD	Video assisted retroperitoneal debridement
VAS	Visual Analogue Scale
VSPL	Videoscopic Splanchnicectomy
WBC	White Blood Cell count
WOPN	Walled Off Pancreatic Necrosis

32.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive a particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at

Term	Definition
	different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).

Term	Definition
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical

Term	Definition
	decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.

Term	Definition
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a

Term	Definition
	given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN)
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold

Term	Definition
	is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Non-randomised intervention study	A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments. Non-randomised intervention studies can use a number of different study designs, and include cohort studies, case–control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant.

Term	Definition
	For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient

Term	Definition
	or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain

Term	Definition
	conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).

Term	Definition
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

32.1 Clinical terms

Term	Definition
Acute Necrotic Collections	Acute necrotic collections develop within the first four weeks and contain a variable amount of fluid/non-liquid necrotic material. They may be pancreatic or peripancreatic in location and can be sterile or infected.
Acute Pancreatitis	Acute pancreatitis is sudden inflammation of the pancreas that may be mild or life threatening but usually subsides.
Acute Peri-pancreatic fluid collections	Acute peripancreatic fluid collections (APFC) are an early complication of acute pancreatitis that usually develop in the first four weeks. After four weeks, the term pseudocysts is used.
Aetiology	The cause, set of causes, or manner of causation of a disease or condition.
Aetiology	The cause, set of causes, or manner of causation of a disease or condition.
Ampullary stenosis	The Ampulla Vater is where the bile and pancreatic ducts meet and empty into the small intestine. Ampullary stenosis means the abnormal narrowing of this area.
Atlanta Classification [11]	Classification system for the severity of acute pancreatitis derived by international consensus. It defines three grades of severity for acute

Term	Definition
	pancreatitis as follows: Mild acute pancreatitis No organ failure No local or systemic complications Moderately severe acute pancreatitis Organ failure that resolves within 48 h (transient organ failure) and/or Local or systemic complications without persistent organ failure Severe acute pancreatitis Persistent organ failure (>48 h) Single organ failure Multiple organ failure
Bedside Index of Severity in Acute Pancreatitis	Score used to predict the mortality in patients with acute pancreatitis.
Billary-enteric anastomosis	A common surgical procedure performed for the management of biliary obstruction or leakage that results from a variety of benign and malignant diseases. Complications following BEA are not rare.
Choledochoduodenostomy	Surgical creation of a passage uniting the common bile duct and the duodenum.
Choledochojejunostomy	A procedure for creating an anastomosis of the common bile duct (CBD) to the jejunum, performed to relieve symptoms of biliary obstruction and restore continuity to the biliary tract.
Chronic Pancreatitis	A progressive inflammatory disease of the pancreas, characterized by irreversible morphologic changes and gradual fibrotic replacement of the gland. Loss of exocrine and endocrine function results from parenchymal fibrosis. The primary symptoms of CP are abdominal pain and maldigestion.
Clark score	Clark's level is a staging system, used in conjunction with Breslow's depth, which describes the level of anatomical invasion of the melanoma in the skin.
Common Bile Duct	A small, tube-like structure formed where the common hepatic duct and the cystic duct join. Its physiological role is to carry bile from the gallbladder and empty it into the upper part of the small intestine (the duodenum).
Computerised Tomography	Radiography in which a three-dimensional image of a body structure is constructed by computer from a series of plane cross-sectional images made along an axis — called also computed axial tomography, computerized axial tomography, computerized tomography.
Computerised Tomography Severity index	Based on findings from a CT scan with intravenous contrast to assess the severity of acute pancreatitis. The severity of computed tomography findings have been found to correlate well with clinical indices of severity.
Continuous Postoperative Lavage	Several large bore drains are inserted into the abdomen for continuous postoperative irrigation. This offers the advantages of the non-surgical removal of necrotic tissue and bacterially and biologically active compounds.
Contrast Enhanced Computed Tomography	Involves the administration of intravenous contrast agents containing microbubbles of perfluorocarbon or nitrogen gas. The bubbles greatly affect ultrasound backscatter and increase vascular contrast in a similar manner to intravenous contrast agents used in CT and MRI scanning.

Term	Definition
Convex linear-array echoendoscope	Convex (sequential) arrays, also known as curvilinear or curved linear arrays, are similar to linear arrays but with piezoelectric elements arranged along a curved transducer head. Ultrasound beams are emitted at 90 degrees to the transducer head. Echoendoscopes are able to image both intramural structures and structures adja- cent to the GI tract and fall into 2 broad categories: radial ("sector") or linear ("convex array").
Covered self-expandable metal stent	A metallic tube, or stent, used in order to hold open a structure in the gastrointestinal tract in order to allow the passage of food, chyme, stool, or other secretions required for digestion.
C-reactive protein	One of the plasma proteins known as acute-phase proteins: proteins whose plasma concentrations increase (or decrease) by 25% or more during inflammatory disorders. CRP can rise as high as 1000-fold with inflammation.
Crystalloid fluid	The most commonly used crystalloid fluid is normal saline, a solution of sodium chloride at 0.9% concentration, which is close to the concentration in the blood (isotonic).
Cystic collection	A loculated fluid collection due to infection, i.e. abscess or as a result of pancreatitis, perforation or bile peritonitis.
Cystic Fibrosis Transmembrane Conductance Regulator gene	This gene provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes.
Cystogastrostomy	Surgery to create an opening between a pancreatic pseudocyst and the stomach when the cyst is in a suitable position to be drained into the stomach.
Cystojejunostomy	Surgical creation of a passage from the jejunum to a nearby cyst for drainage.
Dextrose	A form of glucose derived from starches.
Distal pancreatectomy	The removal of the bottom half of the pancreas by a surgical procedure.
Dual Energy X-ray absorptiometry	A means of measuring bone mineral density (BMD).
Duodenoscope	Flexible, lighted tubes that are threaded through the mouth, throat, and stomach into the top of the small intestine (duodenum).
Elastography	A medical imaging modality that maps the elastic properties and stiffness of soft tissue.
Endocrine	Glands of the endocrine system that secrete their products, hormones, directly into the blood rather than through a duct.
Endoprostheses	An internal prosthesis.
Endosconographic	A procedure in which an endoscope is inserted into the body.
Endoscopic Retrograde Choloangiopancreatography	A technique that combines the use of endoscopy and fluoroscopy to diagnose and treat certain problems of the biliary or pancreatic ductal systems.
Endoscopic sphincterotomy	Endoscopic sphincterotomy: An operation to cut the muscle between the common bile duct and the pancreatic duct. The operation uses a catheter and a wire to remove gallstones or other blockages. Also called endoscopic papillotomy.
Endoscopic Transluminal Necrosectomy	A minimally invasive procedure involving the endoscopic passage of an inflatable catheter along the lumen of a blood vessel to surgically excise necrotic tissue.
Endoscopic Ultrasound	Also known as echo-endoscopy, is a medical procedure in which endoscopy (insertion of a probe into a hollow organ) is combined with ultrasound to

Term	Definition
	obtain images of the internal organs in the chest, abdomen and colon.
Enteral nutrition	Enteral nutrition generally refers to any method of feeding that uses the gastrointestinal (GI) tract to deliver part or all of a person's caloric requirements. It can include a normal oral diet, the use of liquid supplements or delivery of part or all of the daily requirements by use of a tube (tube feeding).
Enterocutaneous fistula (ECF)	An abnormal connection that develops between the intestinal tract or stomach and the skin. As a result, contents of the stomach or intestines leak through to the skin. Most ECFs occur after bowel surgery.
EuroQol five dimension scale (EQ-5D)	The health status measured with EQ-5D is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year (QALY) can be computed.
EuroQol five dimension Visual Analogue Scale (EQ-5D VAS)	The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.
Extracorporeal shock wave lithotripsy	A procedure that uses sound waves (also called shock waves) to break a kidney stone into small pieces that can more easily travel through the urinary tract and pass from the body.
Fat emulsion	Used as dietary supplements for patients who are unable to get enough fat in their diet, usually because of certain illnesses or recent surgery.
Fluoroscopic guidance, Fluoroscopic	A type of medical imaging that shows a continuous X-ray image on a monitor, much like an X-ray movie. During a fluoroscopy procedure, an X-ray beam is passed through the body.
Gastorcolic omentum	A large apron-like fold of visceral peritoneum that hangs down from the stomach.
Gold score	This Modified Clark and Gold score is an example used in the NICE diagnostic guidance adoption support resource for Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) , and was not produced, commissioned or sanctioned by NICE.
Haematemesis	The vomiting of blood.
Haematocrit	The ratio of the volume of red blood cells to the total volume of blood.
Haemodialysis	Kidney dialysis.
Hemostasis	A process which causes bleeding to stop, meaning to keep blood within a damaged blood vessel (the opposite of hemostasis is hemorrhage). It is the first stage of wound healing. This involves coagulation, blood changing from a liquid to a gel.
Hepaticojejunostomy or choledocho-jejunostomy	A connection of the hepatic duct to the jejunum. This is usually performed to correct iatrogenic bile duct injuries.
Hepatobillary	Having to do with the liver plus the gallbladder, bile ducts, or bile.
Hereditary pancreatitis	A genetic condition characterized by recurrent episodes of inflammation of the pancreas (pancreatitis).
Hyperglycaemic hyperosmolar non-ketotic coma	Coma resulting from very high blood glucose levels in a patient with normal ketone levels. If very high blood glucose levels are combined with high ketone levels, the state is likely to be ketoacidosis.
Hypertriglyceridaemia	Severe hypertriglyceridaemia occurs when there is an increased VLDL production from the liver (familial or secondary (e.g. diabetes, alcohol, alcohol, oestrogen administration)) in conjunction with reduced triglyceride clearance (e.g. familial or secondary (hypothyroidism, beta-blocker treatment, diabetes))

Term	Definition
Hypoperfusion	The inadequate perfusion of body tissues, resulting inadequate supply of oxygen and nutrients to the.
IgG4	IgG4-related disease (IgG4-RD), formerly known as IgG4-related systemic disease, is a chronic inflammatory condition characterized by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, various degrees of fibrosis (scarring) and a usually prompt response to oral steroids.
Intraductal stones	Abdominal pain, one of the major symptoms of chronic pancreatitis, is believed to be caused in part by obstruction of the pancreatic duct system (by stones or strictures) resulting in increasing intraductal pressure and parenchymal ischemia.
Ionotropes	A group of drugs that alter the contractility of the heart. Positive inotropes increase the force of contraction of the heart, whereas negative inotropes weaken it.
Isocaloric	Having similar caloric values.
Jejunal feeding	The method of feeding directly into the small bowel.
Jejunum	The part of the small intestine between the duodenum and ileum.
Laparatomy	A surgical incision into the abdominal cavity, for diagnosis or in preparation for major surgery.
Laparotomy approach	A surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity. It is also known as a celiotomy.
Lavage	Washing out of a body cavity, such as the colon or stomach, with water or a medicated solution.
Locoregional lavage	Washing out of a body cavity, such as the colon or stomach, with water or a medicated solution.
lymphocytes	A form of small leucocyte (white blood cell) with a single round nucleus, occurring especially in the lymphatic system.
Magnetic resonance cholangiopancreatographyspecial	Type of magnetic resonance imaging (MRI) exam that produces detailed images of the hepatobiliary and pancreatic systems, including the liver, gallbladder, bile ducts, pancreas and pancreatic duct.
Magnetic resonance imaging	A medical imaging technique used in radiology to form pictures of the anatomy and the physiological processes of the body in both health and disease. MRI scanners use strong magnetic fields, electric field gradients, and radio waves to generate images of the organs in the body.
Microlithiasis	The formation of minute concretions (a hard solid mass formed by the local accumulation of matter) in an organ.
Moderately severe acute pancreatitis	Moderately severe acute pancreatitis is characterised by organ failure is failure that resolves within forty eight hours (transient organ failure) or local or systemic complications in the absence of persistent organ failure.[11]
Nasocystic catheter	Sometimes it is necessary to leave a long tube into the cyst that comes out of the nose. This is known as a nasocystic catheter. This tube can be used to wash out the cyst contents and improve drainage of infected material from the cyst.
Nasoenteric	Flexible, double or single lumen tubes that are passed proximally from the nose distally into the stomach or small bowel.
Nasojejunal	A nasojejunal or NJ-tube is threaded through the stomach and into the jejunum, the middle section of the small intestine. In some cases, a nasoduodenal or ND-tube may be placed into the duodenum, the first part of the small intestine.
Necrosectomy	Excision of necrotic tissue; generally, debridement

Term	Definition
Necroses	To cause necrosis. To become the site of necrosis.
Neurolytic Celia Plexus Block	A celiac plexus block procedure is an injection performed to reduce abdominal pain caused by cancer, chronic pancreatitis or adhesions. An injection of local anesthetic is used to block the celiac plexus nerves that transmit pain signals from your abdomen to your brain.
Neutropeania	An abnormally low level of neutrophils. Neutrophils are a common type of white blood cell important to fighting off infections.
Non ketotic	Not related to ketosis (the accumulation in the body of the ketone bodies: acetone, beta-hydroxybutyric acid and acetoacetic acid. Ketosis usually results from the incomplete metabolism of fatty acids, generally from carbohydrate deficiency or inadequate utilization and is commonly observed in starvation, high-fat diets, pregnancy, following either anesthesia, and most significantly I inadequately controlled diabetes mellitus.)
Osteoporosis	A disease where increased bone weakness increases the risk of a broken bone.
Pancreatic divisum	A congenital anomaly in the anatomy of the ducts of the pancreas in which a single pancreatic duct is not formed, but rather remains as two distinct dorsal and ventral ducts.
Pancreatic endotherapy	A therapeutic procedure that involves the use of an endoscope to localize the intervention to the pancreas.
Pancreatic enzyme replacement therapy.	Involves taking the digestive enzymes you need in the form of a tablet (capsule). All enzyme supplements contain Pancreatin – a mixture of pancreatic enzymes, lipase, amylase and protease. These assist the digestion of fat, carbohydrates and proteins.
Pancreatic Exocrine insufficiency	The inability to properly digest food due to a lack of digestive enzymes made by the pancreas.
Pancreatic extracorporeal shock wave lithotripsy	A procedure that uses high-energy shock waves to break down kidney stones into small crystals. You can then pass them out of your body in your urine.
Pancreatic necrosis	A permanent condition in which a portion of the pancreas loses its blood supply.
Pancreatic Sphincterotomy	The cutting of the biliary sphincter and is typically carried out during endoscopic retrograde cholangiopancreatography (ERCP). Sphincterotomy is a technically complex procedure that is performed under visual and fluoroscopic guidance.
Pancreaticojejunostomy	A surgical technique used in the treatment of chronic pancreatitis. It involves a side-to-side anastomosis of the pancreatic duct and the jejunum.
Pancreatobillary procedures	Procedures of, relating to, or affecting the pancreas and the bile ducts and gallbladder.
Pancreatogram	An x-ray film produced by pancreatography.
Paracolic spaces	The paracolic gutters (paracolic sulci, paracolic recesses) are spaces between the colon and the abdominal wall.
Parathyroid hormone	An ongoing process in which bone tissue is alternately resorbed and rebuilt over time
Parenteral nutrition	Parenteral nutrition refers to the delivery of calories and nutrients into a vein. This could be as simple as carbohydrate calories delivered as simple sugar in an intravenous solution or all of the required nutrients could be delivered including carbohydrate, protein, fat, electrolytes (for example sodium and potassium), vitamins and trace elements (for example copper and zinc).

Term	Definition
Partington and Rochelle method	Laparoscopic side-to-side pancreaticojejunostomy for chronic pancreatitis.
Pedersen-Bjergaard score	A scoring system that requires the patient to respond to the question “can you feel when you are low?” requiring the selection of one response from “always,” ”usually,” “sometimes,” or. “never”.
Percutaneous drainage	In percutaneous abscess drainage, an interventional radiologist uses imaging guidance (CT, ultrasound or fluoroscopy) to place a thin needle into the abscess to obtain a sample of the infected fluid from an area of the body such as the chest, abdomen or pelvis.
Postero-lateral abdominal wall	The abdominal wall represents the boundaries of the abdominal cavity. The abdominal wall is split into the posterior (back), lateral (sides) and anterior (front) walls.
PRSS1 gene	PRSS1-related hereditary pancreatitis (HP) is characterized by inflammation of the pancreas that progresses from acute (sudden onset; duration <6 months) to recurrent acute (>1 episode of acute pancreatitis) to chronic (duration >6 months).
Pseudoaneurysm	A pseudoaneurysm, sometimes called a false aneurysm, occurs when a blood vessel wall is injured, and the blood is contained by the surrounding tissues.
Ranson score	Estimates mortality of patients with pancreatitis, based on initial and 48-hour lab values.
Relaparatomy	An abdominal operation performed after an initial surgery within 60 days, and the decision is made upon criteria of general reaction to surgical stress.
Retroperitoneum	The retroperitoneal space (retroperitoneum) is the anatomical space (sometimes a potential space) in the abdominal cavity behind (retro) the peritoneum. It has no specific delineating anatomical structures. Organs are retroperitoneal if they have peritoneum on their anterior side only.
Ringer’s lactate	Also known as sodium lactate solution and Hartmann's solution, is a mixture of sodium chloride, sodium lactate, potassium chloride, and calcium chloride in water. It is used for replacing fluids and electrolytes in those who have low blood volume or low blood pressure.
Ryan score	Hypoglycaemia burden score
Secretin-MRCP	Secretin increases bicarbonate and pancreatic fluid secretion by the exocrine cells. Secretin relaxes the sphincter of Oddi and opens pancreatic duct orifices. Secretin is injected intravenously at the time of the MRCP.
Secretin-MRCP	noninvasive magnetic resonance (MR) imaging technique for the evaluation of the pancreaticobiliary ductal system.
Semielemental enteral	Elemental diet formulas are used to provide liquid nutrients in a form that is easily and readily assimilated. Such diets provide protein in the form of individual amino acids and may provide a portion of the fat calories as medium chain triglycerides (MCT).
Sequential Organ Failure Assessment	Also known as Sepsis-related organ failure assessment score, (SOFA score), is used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure.
Severe acute pancreatitis	Severe acute pancreatitis is characterised by single or multiple organ failure that persists for more than forty eight hours (persistent organ failure)
Sphincter of Oddi dysfunction	Bile is a digestive juice, made by the liver. It is stored in the gallbladder. It then flows into the upper part of the small intestine to aid digestion. At the same time, the pancreas makes juices that are important for digestion. Both bile and pancreatic juices flow to the small intestine through a common duct that is opened and closed by a round valve. The valve is a muscle called the sphincter of Oddi. In rare cases, the sphincter of Oddi

Term	Definition
	goes into spasm. It clamps shut and cannot relax. Other times it may be narrowed from previous inflammation. This is called sphincter of Oddi dysfunction (SOD).
SPINK1	Serine protease inhibitor Kazal-type 1 (SPINK1) or tumor-associated trypsin inhibitor (TATI) is a protein that in humans is encoded by the SPINK1 gene. Mutations in SPINK1 has been associated with hereditary pancreatitis.
Steatorrhoea	The excretion of abnormal quantities of fat with the faeces owing to reduced absorption of fat by the intestine.
Stricturing (of the pancreatic duct)	A narrowing of the pancreatic duct.
Subcostal	Beneath a rib; below the ribs.
Suppurative cisterns	A closed space serving as a reservoir for pus.
TEN	Total enteral nutrition (TEN) is indicated for patients who have a functional GI tract, but are not able to nourish themselves by mouth.
Therapeutic Upper GI endoscope	Equipment used to carry out endoscopic treatment in the upper gastrointestinal tract.
Total Parenteral Nutrition	The feeding of a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formulae that contain nutrients such as glucose, salts, amino acids, lipids and added vitamins and dietary minerals. This is usually used in patients who do not have an intact Gastro Intestinal Tract.
Transabdominal lapararoscopic approach	Keyhole surgery, through or across the abdomen.
Transduodenal	Surgery performed by cutting across or through the duodenum.
Transgastric drainage	Drainage done through or across the stomach.
Transgastric jejunal	Transgastric jejunal feeding devices are a combination of a gastrostomy device (placed into the stomach) and a jejunostomy device (placed into the jejunum, the first part of the intestines). The feeding device allows your child to be fed directly into the jejunum, bypassing the mouth, throat and stomach.
Transpapillary nasopancreatic	Nasopancreatic: endoscopic method in which naso pancreatic drain placed into pancreatic duct beyond the site of obstruction.
transperitoneal	Through the peritoneum. The peritoneum is the serous membrane that forms the lining of the abdominal cavity or coelom in amniotes and some invertebrates, such as annelids. It covers most of the intra-abdominal (or coelomic) organs, and is composed of a layer of mesothelium supported by a thin layer of connective tissue.
Tryglicerides	Triglycerides are fat in the blood, and a high triglyceride level can increase the risk of heart disease.
Type 3c diabetes	Diabetes mellitus secondary to pancreatic disease. When this is associated with pancreatitis, the primary endocrine defect is insufficient insulin secretion (the abnormality in type 1 diabetes) rather than insulin resistance (characteristic of type 2 diabetes).
Video assisted retroperitoneal debridement	A hybrid between endoscopic and open retroperitoneal necrosectomy.
Videoscopic Splanchnicectomy	A method of pain relief in chronic pancreatitis patients. It's a minimally invasive surgical procedure to dissect splanchnic nerves through a thoracoscopic approach.
Viscero-somatic hyperalgesia	Each segment in the spinal cord receives afferent fibres from visceral as well as somatic structures. viscero-somatic hyperalgesia or referred pain originates because of this convergence of spinal afferents.

Term	Definition
Visual analogue scale	A psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured.
WOPN	Walled Off Pancreatic Necrosis consists of necrosis and subsequent liquefaction of pancreatic and/or peripancreatic tissue. It may be intrapancreatic or parapancreatic. It is a late complication of acute pancreatitis, although it can occur in chronic pancreatitis or as a result of pancreatic trauma.