Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of Scheduled Procedures

Referral thresholds for adult patients suspected of having gallstone disease

November 2014

Safer Better Care

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1 Gallstone disease

1.1 Scope of this health technology assessment

This health technology assessment (HTA) evaluates the appropriateness and potential impact of introducing clinical referral or treatment thresholds for people suspected of requiring a cholecystectomy for management of gallstone disease in Ireland. The effectiveness of this surgery may be limited unless undertaken within strict clinical criteria. This report is one of a series of HTAs of scheduled procedures. Details of the background to the request and general methodology are provided in the separate 'Background and Methods' document.[1]

The scope of this HTA is to investigate clinical referral and diagnostic thresholds that can be used in the assessment, referral and diagnosis of adults who potentially require a cholecystectomy in Ireland. Inputs from an Expert Advisory Group along with a review of the clinical and cost-effectiveness literature were used to inform the criteria. Additionally, the budget impact and resource implications were assessed, as appropriate.

1.2 Background

Biliary calculi (that is, gallstones) are one of the most common surgical problems in the western world. Gallstone disease is the most common abdominal condition for which patients are admitted to hospital in developed countries.[2] An estimated 20 million Americans, 6.3 million men and 14.2 million women, have gallbladder disease and between 500,000 and 750,000 cholecystectomies are performed in the US each year.[3-5] Analysis of UK autopsy reports, meanwhile, has estimated that 12% of men and 24% of women of all ages have gallstones present.[6]

Two main categories of gallstones can be identified according to their predominant chemical composition: cholesterol and pigment stones.[7] Cholesterol stones (greater than [>] 50% cholesterol content) are the most common type in the western world and account for approximately 70% of all stones.[4]

The most important factors influencing the formation of gallstones are age, gender and body weight. An estimated 20% of adults over 40 years of age and 30% of those over age 70 have biliary calculi.[5] Gallstones are at least twice as common in women.[8] The increased risk in females begins at puberty and is increased further with the use of the oral contraceptive pill.[9] Patients with a body mass index (BMI) greater than 40 Kg/m^2 have been shown to have a risk of having gallstones eight

times higher than those with a lower BMI.[10] Other risk factors include, but are not limited to, terminal ileal disease, diabetes mellitus, long-term parenteral nutrition, haemolytic anaemia, liver cirrhosis, cystic fibrosis, and recurrent use of very low fat diets.

Most patients with gallstones are asymptomatic. Biliary colic describes the symptom complex arising from sudden and complete obstruction of the cystic duct or the common bile duct by a stone.[11] The Rome Group for the Epidemiology and Prevention of Cholelithiasis defines symptomatic gallstone disease as pain in the epigastrium and or hypochondrium lasting more than one half hour.[12] A variety of other gastrointestinal complaints have been associated with uncomplicated gallstone disease, such as bloating, belching, nausea, and fatty food intolerance, but these other factors do not consistently discriminate between gallstone disease and other causes.[4] Acute inflammation of the gallbladder is known as acute cholecystitis.

Stones may be found in the gallbladder (cholelithiasis), the cystic duct, common bile duct (choledocholithiasis), pancreatic duct or ileum. The clinical picture can depend on their location in the hepatobiliary tract (Table 1.1).

Table 1.1. Location of gallstones and typical associated symptoms and signs

Gallstone location	Symptoms and Signs
Gallbladder neck/cystic duct (Cholelithiasis)	Biliary colic, flatulence, dyspepsia, cholecystitis
Common bile duct (Choledocholithiasis)	Jaundice (progressive or intermittent), fevers, cholangitis (pain, swinging fevers and jaundice)
Pancreatic duct	Pancreatitis
Ileum	Gallstone ileus

1.3 Surgical procedure, potential complications and alternative treatments

Investigations will usually include blood tests for liver function, inflammatory markers and imaging. Ultrasound is the most widely used modality for confirming the diagnosis of gallstones; approximately 95% of gallstones will be detected by ultrasound.[4] Its reliability in diagnosing common bile duct stones can vary from 23% to 80%, and is influenced by body habitus and the experience of the ultrasonographer;[13] hence, computed tomography (CT) or magnetic resonance imaging (MRI) may be required to better characterise the common bile duct in some cases. The iREFER guidelines, published by the Royal College of Radiologists in the

UK, should be available on all hospital intranet systems in Ireland, and may be employed by those who work in this setting to assess the need or otherwise for radiological investigation of those suspected of suffering from gallstone disease.[14]

Cholecystectomy is the preferred option in the treatment of gallstones. This procedure can be performed by a keyhole operation (laparoscopic cholecystectomy), by a small-incision cholecystectomy (incision less than [<] 8cm in length), or by traditional open operation (incision >8cm in length).[15] While there was interest previously in non-operative treatment of gallstones including dissolution therapy and lithotripsy (the use of shock waves to break up the stones) the advent of laparoscopic cholecystectomy has superseded both of these techniques.

Laparoscopic cholecystectomy is associated with less pain, shorter hospital stay, faster return to activities of daily living and less abdominal scarring than open surgery, and it is therefore the treatment of choice in symptomatic gallstone disease. It can be offered to the majority of patients requiring cholecystectomy, although contraindications include previous abdominal surgery(s) and or cardiorespiratory comorbidity. In addition, the laparoscopic approach is amenable to use in the day case setting with appropriate patient selection, improved operative techniques and postoperative control of pain, nausea and vomiting.[16]

The mortality rate for a low risk patient undergoing laparoscopic cholecystectomy is <1%; operative risks usually arise from comorbid disease. The most serious complication of cholecystectomy (open and laparoscopic) is damage to the common bile duct; the overall incidence of bile duct injuries requiring corrective surgery varies between 0.1% and 0.3%.[15] Other complications of cholecystectomy include bile leak treated conservatively (0.1% to 0.2%), radiologically (0% to 0.1%), endoscopically (0.05% to 0.1%) or by operation (0% to 0.05%); peritonitis requiring re-operation (0.2%); postoperative bleeding requiring operation (0.1% to 0.5%); and intra-abdominal abscesses requiring operation (0.1%). The laparoscopic approach is associated with a lower rate of surgical site infection when compared with the open procedure.[17] A 2014 review of 1,382 obese patients who underwent laparoscopic cholecystectomy between 2008 and 2011, found no association between obesity and risk of postoperative complications, although previous studies have demonstrated that those who are obese are at higher risk of requiring intra-operative conversion from laparoscopic to open surgery.[18;19] A 2005 study by Hawn et al. examined the impact of obesity on operating theatre workload, in the context of cholecystectomy; there was a mean increase of 7% in time taken to perform this procedure in those who were obese (BMI >30 Kg/m^2).[20]

Up to 30% of patients still complain of some symptoms following surgery. Studies have reported that biliary colic remained in only 8% to 9% of patients, in contrast to

non-colicky pain in 18% to 32%. It has been suggested that persistent functional gastrointestinal disorder (characterised by abnormal motility, sensation and perception of gut processes) causes post-cholecystectomy symptoms, especially in those who are operated on for atypical symptoms.[21]

Between 10% and 18% of patients undergoing surgery for symptomatic gallstones will also have stones in their common bile duct (choledocholithiasis).[22] Choledocholithiasis may be suspected pre-operatively by symptoms or signs of jaundice, pancreatitis, or cholangitis, or by derangement in liver function tests, or on imaging showing duct dilatation or actual ductal stones. Management options include pre-cholecystectomy endoscopic retrograde cholangiopancreatography (ERCP), intra-operative ERCP, or post-operative ERCP and laparoscopic common bile duct exploration. The ideal treatment approach remains controversial.[22;23]

1.4 Current practice in Ireland

Potential candidates for cholecystectomy are generally referred by their general practitioner (GP) or by another hospital specialist to a general surgeon. Referral or treatment thresholds (similar to those discussed in Section 2 below) may be used by GPs and surgeons in Ireland to identify eligible candidates for referral or treatment. However, it is unclear if such thresholds are being used, or how consistently they are being applied.

Cholecystectomy is a routine scheduled surgical procedure within the publicly-funded healthcare system in Ireland. The Hospital In-Patient Enquiry (HIPE) system was employed in this HTA to assess activity levels in relation to cholecystectomy. This procedure may be coded as the principal procedure or as a secondary procedure. For consistency and completeness, data are reported to include the principal and secondary procedures (that is 'all procedures') with all data presented on this basis. The International Classification of Diseases (ICD) intervention codes used to retrieve this data are listed in Appendix 1.1.

The HIPE system reports that there were approximately 5,154 patients who underwent cholecystectomy in 2012. Of these, 3,960 (76.8%) patients were admitted for their procedure on an elective (planned surgery) basis.

This data captures procedures provided as hospital day case and inpatient procedures, as in the other HTA reports in this series. Of the 3,960 procedures carried out in the pure elective setting, 967 (24.4%) were reported as being done on a day case basis. A total of 2,993 procedures were undertaken on an inpatient basis, with an average length of stay of 3.1 days. The National Clinical Programme in Surgery has established targets for the percentage of procedures which should be

performed as day cases in its document, 'model of care in elective surgery'.[24] This identifies a day case target of 40% for patients undergoing laparoscopic cholecystectomy (no target is set for open cholecystectomy); analysis of HIPE data suggests that 26.6% (hospital range 0%-67.4%) of elective laparoscopic cholecystectomies performed in Irish public hospitals in 2012 were day cases.

It is noted that the average length of stay for patients undergoing elective cholecystectomy in public hospitals decreased from 4.4 days in 2005 to 3.1 days in 2012 (Figure 1.1). Given the variation in day case rates noted above, it may be that those institutions with shorter average lengths of stay have concomitantly lower day case rates. The average age of patients undergoing cholecystectomy in 2012 was 48.4 years.

The 3,960 elective cholecystectomies recorded within the HIPE system in 2012 were performed across 36 different hospital sites (range 5-249 procedures per hospital). These institutions are categorised according to their hospital groups in Table 1.2 on the following page. Any variation in practice may be explained by differing catchment sizes or the availability of a particular surgical service, hospital size or specialisation.

Table 1.2 HIPE data for elective cholecystectomy per HSE hospital group* (2012)[25]

Hospital group	Number (%) (Range)	ALOS (days)	% day cases (Hospital range)	Average age (years)
Dublin North East	573 (14.5%) (39-145)	2.1	13.3 (0-31.2)	47.1
Dublin Midlands	815 (20.6%) (103-223)	3.2	48.2 (0-62.9)	47.5
Dublin East	786 (19.8%) (50-155)	4.6	34.2 (7.8-63.2)	49.6
South/South West	849 (21.4%) (22-219)	3.5	17.7 (0-63)	48.3
West/North West	666 (16.8%) (18-213)	2.5	11.7 (0.9-51.5)	49.6
Midwest	266 (6.7%) (17-249)	2.0	0.4 (0-0.4)	48.9
Total	**3,960 (100)**	**3.1**	**24.4**	**48.4**

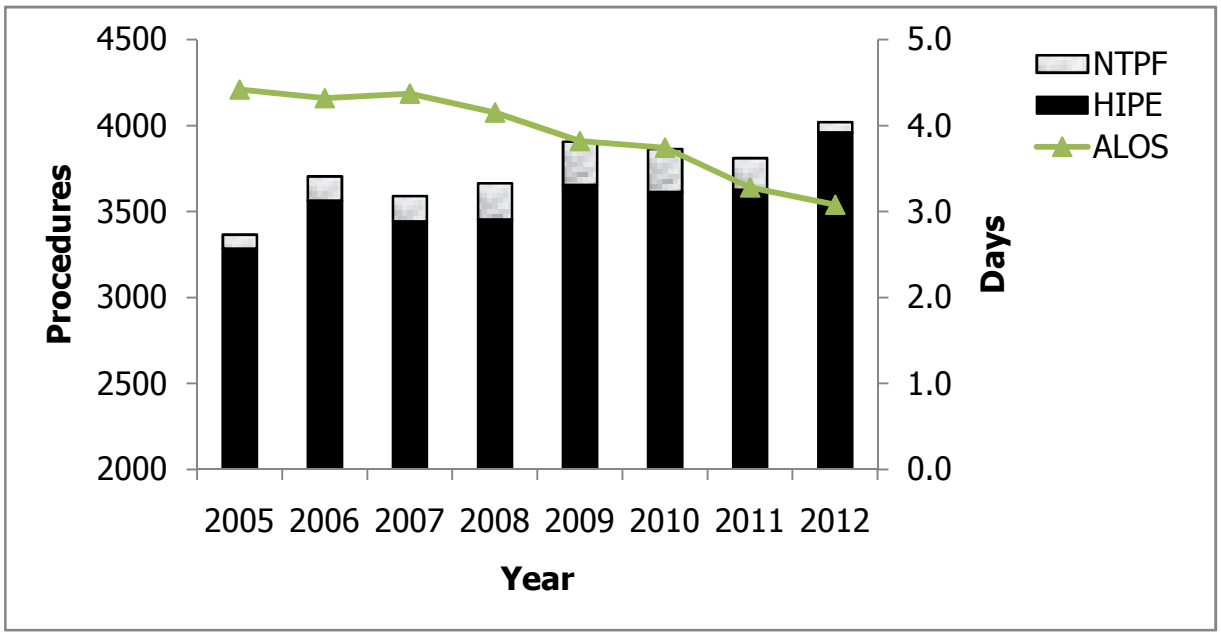
*Key: Range – the range in terms of number of procedures performed in individual institutions within the hospital group; ALOS – average length of stay; * See Appendix 1.1 for HIPE codes; HIPE data include all activity in publicly-funded hospitals, including procedures in patients that used private health insurance.*

All patients who undergo a surgical procedure in Irish public hospitals have an operative diagnosis coded as part of the HIPE coding process. This is recorded as the principal diagnosis at the time of procedure, and may not be synonymous with the pre-operative diagnosis. In 2012, the principal diagnosis – at the time of cholecystectomy – was coded as 'calculus of gallbladder with other cholecystitis' (46.1%). The next most frequently coded diagnoses were as 'chronic cholecystitis' (18.0%), 'calculus of gallbladder without cholecystitis' (15.2%), 'calculus of gallbladder with acute cholecystitis' (4.0%), and 'acute cholecystitis'(2.8%).

In addition to the activity levels in public hospitals, there were 1,325 procedures procured by the public healthcare system via the National Treatment Purchase Fund (NTPF), from private hospitals, between 2005 and 2012. Data on the total number of

procedures undertaken in the publicly-funded system, including the additional procedures funded by the NTPF are shown in Figure 1.1. The number of elective cholecystectomies undertaken in the publicly-funded healthcare system increased by 19.5% between 2005 (number of procedures 3,366) and 2012 (4,021).

Figure 1.1 Number and average length of stay (days) for elective cholecystectomies provided through the publicly-funded healthcare system in Ireland, 2005-2012[25]



Key: HIPE (Hospital In-Patient Enquiry Scheme) data; NTPF (National Treatment Purchase Fund) funded procedures in private hospitals. HIPE data include all activity in publicly funded hospitals, including procedures in patients that used private health insurance. ALOS – average length of stay.

The length of time a patient must wait to be reviewed varies according to the referral pathway and the individual hospital and consultant to which a patient is referred. At the end of July 2014, it was reported that there were 360,753 patients on the Outpatient Waiting List database collated by the NTPF, 34.7% of whom were waiting longer than six months, with 10.5% on the list for longer than 12 months.[26] Speciality-specific figures were published at the end of July 2014. Referrals to general surgery, (including 'gastrointestinal surgery'), constituted 10.3% (37,080) of the total outpatient waiting list at that time.[27] Delays in access to routine radiological services from primary care have also been noted. In a report published by the Irish College of General Practitioners in 2013, it was noted that more than 20% of GPs do not have direct access to either abdominal or pelvic ultrasound in the public system. Where access is available, public patients were noted to have an average waiting period of 14 weeks (range one day to 42 weeks, depending on geographical location).[28]

Initiatives are underway by the HSE to standardise the management of outpatient services and to ensure that there are consistent management processes across all publicly-funded healthcare facilities that provide outpatient services. This includes the publication of a protocol for the management of these services by the NTPF in January 2013 which provides the core guidance of the Outpatient Services Performance Improvement Programme.[29] The protocol specifies that patients should be treated based on clinical urgency, with urgent referrals seen and treated first. It is intended that the definition of clinical urgency and associated maximum wait times will be developed at speciality or condition-level and agreed by the clinical programmes.

In January 2013, the NTPF published a national waiting list management policy that outlines the standardised approach to managing scheduled care treatment for inpatient, day case and planned procedures in all publicly-funded hospitals.[29;30] It outlines a consistent structured approach that must be adopted in the management of the waiting list. Monitoring of the implementation of the policy will be routinely undertaken by the NTPF in the form of annual quality assurance reviews.

2 Clinical referral/treatment threshold

2.1 Review of the literature

A comprehensive review of the literature was conducted during May 2014 to identify international clinical guidelines and health policy documents describing treatment thresholds that are in place in other healthcare systems. It also considered systematic reviews and economic evaluations examining the effect of the introduction of those thresholds. The approach and general search terms are described in Appendix 1 in the 'Background and Methods' document, and a summary of the results is included in Table 2.1. A summary of the clinical guidelines identified from the search and thresholds in use elsewhere are provided in Appendix 1.5 and 1.6, respectively.

Table 2.1. Summary of literature search results

Publication Type	Number	References
Clinical guidelines	6	(31-36)
Reviews	6	(36-41)
Health technology assessment	1	(42)
Cost-effectiveness studies	5	(43-46)

2.2 Clinical evidence

Gurusamy and colleagues have published a number of Cochrane reviews[39-41] which are of relevance to this HTA. Unfortunately, these reviews have primarily served to highlight the dearth of randomised controlled trials (RCTs) within this subject area, so the authors were unable to come to any firm conclusions. In 2007, they examined the use of cholecystectomy for patients with 'silent' or asymptomatic gallstones; no RCTs were found that compared cholecystectomy versus no cholecystectomy in asymptomatic patients with gallstones.[41] The same authors published their Cochrane review entitled 'early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic' in 2013.[40] Just one trial was found that could contribute information to the review. This had randomised just 75 patients, and the review authors regarded it as being at high risk of bias. The authors concluded that – the results of this trial notwithstanding (the trial had favoured early laparoscopic cholecystectomy) – further trials were needed prior to making any firm recommendations.[40] Finally, Gurusamy et al.[39] also performed a Cochrane review which examined outcomes in early (less than seven days) versus delayed (more than six weeks) laparoscopic cholecystectomy for patients with acute cholecystitis. In this instance, seven trials met the inclusion criteria, with data from six included for meta-analysis (244 patients in each group). No significant differences were seen in relation to primary outcomes: mortality, bile duct injury, other serious adverse events, and quality of life.[39]

In 2013, a national commissioning guide for gallstones in the UK was jointly published by the Association of Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), and the Royal College of Surgeons (RCS), with the National Institute for Health and Care Excellence (NICE) accrediting the process.[33] Noting that the majority of people with gallbladder stones remain asymptomatic and require no treatment, the guideline went on to state that the definitive treatment of symptomatic gallbladder stones is surgical removal of the gallbladder. It further

suggested that all patients with stones in their common bile duct should be referred for treatment because of the risk of potential severe complications. Their guidelines in relation to management in primary care are included in Appendix 1.2 of this report. Of note, the guideline suggests that most patients with symptomatic gallstones present with a self-limiting attack of pain that lasts for hours only, and that further episodes of biliary pain can be prevented in around 30% of patients by adopting a low fat diet. Specifically in relation to referral, the guidelines suggested that:

- Patients with an incidental finding of stones in an otherwise normal gallbladder require no further investigation or referral.
- Epigastric or right upper quadrant pain, frequently radiating to the back, lasting for several minutes to hours (often occurring at night) suggests symptomatic gallstones. These patients should have liver function tests checked and be referred for ultrasonography.
- Confirmation of symptomatic gallstones should result in a discussion of the merits of a referral to a surgical service regularly performing cholecystectomies.
- Following treatment for common bile duct stones with endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, removal of the gallbladder should be considered in all patients. However, in patients with significant comorbidities, the risks of surgery may outweigh the benefits.
- Patients with known gallstones with a history of acute pancreatitis should be referred for a cholecystectomy to a surgical service regularly performing the procedure.
- Patients with known gallstones and jaundice or clinical suspicion of biliary obstruction (for example, significantly abnormal liver function tests) should be referred urgently to a gastroenterology or surgical service with expertise in managing biliary diseases.[33]

In 2014, meanwhile, a national commissioning guide for emergency general surgery and acute abdominal pain in the UK was jointly published by the Association of Surgeons of Great Britain and Ireland (ASGBI) and the Royal College of Surgeons (RCS), with NICE again accrediting the process.[32] Although much of this guidance lay outside the scope of this present work, a number of relevant points were made regarding patients who present with right upper quadrant pain. This guide noted that an ultrasound scan together with liver function tests can facilitate initial triage of acute biliary patients into one of four categories: biliary colic, acute cholecystitis, complex biliary disease, and gallstone pancreatitis (Appendix 1.3). Of relevance to this HTA, the guideline noted that patients with biliary colic could either:

- Be discharged to have an early outpatient ultrasound with follow-up in either a 'hot' biliary or acute general surgical clinic. Most patients who are medically fit will be offered an elective laparoscopic cholecystectomy (within six weeks ideally) after one severe attack of biliary colic, as the likelihood of symptomatic recurrence is high.
- Proceed after ultrasound to acute inpatient cholecystectomy. A reliable service requires dedicated theatre access.

Of note, the guideline also recommended that those with acute cholecystitis should have a cholecystectomy, either electively following conservative management in the first instance (ideally about six weeks after the acute episode), or with an early cholecystectomy during the first admission, particularly if the pain is of less than five days' duration.[32]

The Society for Surgery of the Alimentary Tract (SSAT) published its most recent patient care guideline regarding management of gallstones and gallbladder disease in 2007.[35] This guideline noted that most patients with gallstones do not have symptoms, but that approximately 20% of these will eventually become symptomatic. It did not discuss referral guidelines specifically, but did suggest that a surgeon should see the patient within a few weeks of an attack if the acute episode has resolved or symptoms are mild. It went on to suggest that the presence of gallstones without abdominal symptoms is not an indication for cholecystectomy unless the patient is immunosuppressed or there is a predisposition for malignancy (for example, the gallbladder wall is calcified or there is a family history of gallbladder cancer). The guideline noted that once a patient with gallstones becomes symptomatic, elective cholecystectomy is indicated. Finally, it suggested that patients with recurrent symptoms typical of biliary pain, but without gallstones on ultrasound, should be referred for surgical evaluation.

In 2010, the Association for Gastrointestinal Endoscopy (ASGE) published its guideline regarding the role of endoscopy in the evaluation of suspected choledocholithiasis.[34] This made no recommendations in relation to referral from primary care. It did note that although there is no single accepted scoring system to predict the presence of stones in the common bile duct (choledocholithiasis), by using factors such as age, liver test results, and ultrasound findings, patients can generally be categorised into low (<10%), intermediate (10%-50%), and high (>50%) probability of having stones in the common bile duct (Appendix 1.4). A common bile duct stone seen on ultrasound was taken to be the most reliable predictor of choledocholithiasis at subsequent endoscopic retrograde cholangiography (ERC) or surgery. The guideline's treatment algorithm was based on the premise that all patients with symptoms require some form of operative

intervention, with that intervention dependent upon the likelihood or otherwise of a stone being present in the common bile duct.

In 2008, Williams et al.[36] published guidelines in relation to the management of common bile duct stones on behalf of the British Society of Gastroenterology. These were endorsed by the Clinical Standards and Services Committee (CSSC) of the Society and its Endoscopy Committee, in addition to the ERCP stakeholder group, the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), Association of Laparoscopic Surgeons (ALS), and the Royal College of Radiologists (RCR).[36] Although much of this report related to management in secondary care, a number of recommendations were of relevance to this current report. The guidelines suggested that although the majority of people with gallstones are unaware of their presence and that over a 10-year period of follow-up only 15%-26% of initially asymptomatic individuals will develop biliary colic, the onset of pain heralds the beginning of recurrent symptoms in the majority of patients. In addition, these patients are at risk of serious complications including pancreatitis, cholecystitis and biliary obstruction; over a 10-year period such complications can be expected to occur in 2%-3% of patients with initially silent gallbladder stones and hence cholecystectomy should be offered to all patients with symptomatic gallstones, with the exception of those in whom surgical risk is considered prohibitive. Similarly, in relation to patients with symptomatic common bile duct stones, the consequences are often serious and can include pain, partial or complete biliary obstruction, cholangitis, hepatic abscesses or pancreatitis. Chronic obstruction may also cause secondary biliary cirrhosis and portal hypertension. Based on these risks, the guidelines recommend that whenever patients have symptoms, and investigation suggests ductal stones, extraction should be performed if possible. Trans-abdominal ultrasound scanning (USS) was recommended as the preliminary investigation for common bile duct stones and the guidelines noted that it can help identify patients who have a high likelihood of ductal stones. However, it cautioned that clinicians should not consider it a sensitive test for this condition.[36]

In 2000, the Danish Institute for Health Technology Assessment (DIHTA), in collaboration with the National Institute of Public Health, published their HTA regarding management of patients with gallstones.[42] This report concluded that secondary prevention in the form of prophylactic cholecystectomy for people with asymptomatic gallstones could not be recommended. It did not make specific recommendations for symptomatic gallbladder or common bile duct stones, but instead suggested the need for national guidelines to be drawn up.

In keeping with the consensus outlined thus far, the World Gastroenterology Association has also suggested that cholecystectomy confers no benefit in those who

are asymptomatic; it went on to suggest that this also applies to patients who have had one attack of uncomplicated gallstone pain.[31] The guideline did outline a number of exceptions to this rule, however, and these are included in Appendix 1.5 of this report. Similarly, a review by Duncan and Riall, published in 2012, highlighted a number of instances in which those with asymptomatic gallstones should be considered for cholecystectomy (Appendix 1.5).[38]

In 2000, Berger et al. published a systematic review which examined the use of abdominal symptoms as predictors of gallstones.[37] The analysis was based on results from 24 included studies. Noting that although biliary colic was specific for gallstones, 80% of the referred patients with gallstones presented with other abdominal symptoms, the authors concluded that there is no evidence to justify the use of single abdominal symptoms, other than biliary colic, in the diagnosis of symptomatic gallstones.[37]

The use of referral thresholds by primary care trusts (PCTs) in the English NHS has been common practice for several years. As part of the changes to the NHS brought about by the Health and Social Care Act 2012, PCTs and strategic health authorities (SHAs) ceased to exist on 31 March 2013. Their responsibilities were taken over by clinical commissioning groups (CCG) and the NHS Trust Development Authority. However, the thresholds that were previously developed by these trusts are likely to represent ongoing practice at a local level while new commissioning guides are being established. A summary of specific thresholds from a sample of two NHS PCTs and one CCG area is provided in Appendix 1.6.

To summarise, all guidelines agree that surgery is not indicated for those with asymptomatic gallstones, except in specific circumstances. For those who become symptomatic, the consensus suggests that a combination of ultrasound scanning and liver function testing should be employed to confirm the diagnosis and inform the need for, and nature of, the onward referral. Patients who suffer acute biliary colic or cholecystitis requiring hospitalisation should either have immediate or delayed cholecystectomy. Although a discussion around the merits of one strategy over the other is beyond the scope of this HTA, it is clear that this patient pathway should be managed by secondary care.

2.3 Cost-effectiveness evidence

No studies were found that directly compared the cost-effectiveness of watchful waiting versus operative intervention in the management of cholelithiasis. A number of studies were identified that analysed the costs associated with varying the timing to cholecystectomy surgery, for example, the costs associated with complications due

to emergency admittance while waiting for surgery or delayed surgery compared with immediate surgery. These are discussed here to provide context. An evidence table summarising the data extracted is included in Appendix 1.7. For ease of review, all costs presented have been inflated to 2013 values using the local consumer price index for health and then converted to Irish Euro using the latest Purchasing Power Parities.

A 2010 study by Borowski et al. reported the costs associated with cholecystectomy over a three-month period (May-July 2007) in one UK surgical unit.[46] Over this time, 114 patients were admitted for the treatment of confirmed gallstone-related diseases; only 40 patients (35.1%) followed an entirely elective referral and admission pathway. The total cost of cholecystectomy and the management of gallstone disease and its complications over a three-month period was €445,642, equivalent to a potential annual cost of €1.69 million. Delay in referral of symptomatic patients had substantial cost implications; more than half of the patients (11/21 [52.4 %]) already diagnosed with gallstone-related symptoms in primary care or non-surgical secondary care had not been referred for a surgical opinion. It was estimated that earlier referral and avoidance of complications could have resulted in savings of €21,876 over the three months.[46]

A 2002 UK study by Somasekar et al. examined the costs for patients who were admitted with acute exacerbations of symptoms while waiting for elective cholecystectomy.[45] A total of 156 patients underwent cholecystectomy, after a mean duration of 12 months on the waiting list. Indications for surgery were biliary colic in 127 patients (81%), acute cholecystitis in 24 patients (15%), obstructive jaundice in four patients (3%), and acute pancreatitis in one patient (0.6%). Of these, 37 patients (23.7%) were admitted (47 admission episodes) as an emergency with recurrent gallstone-related symptoms while on the waiting list; 32 for biliary colic, 13 for acute cholecystitis, and two for acute pancreatitis. The cost per episode of admission was €1,631 and the total costs of treating these 37 patients was €76,654. The authors concluded that there is a potential to reduce costs through identification and prioritisation of those on the waiting list at an increased risk of recurrent symptoms and complications.

A similar study by Lawrentschuk et al. in 2003 reported on their retrospective analysis of 322 patients who underwent laparoscopic cholecystectomy between 1999 and 2001.[44] While awaiting surgery, 44 of 322 patients (14%) re-presented to the emergency department with biliary symptoms (89 separate presentations); 21 patients (6%) were admitted (28 admissions), of whom 18 (86%) were on the waiting list for biliary colic symptoms only. Reasons for emergency admission included pancreatitis (one), cholangitis (three), choledocholithiasis (seven),

cholecystitis (seven), and exacerbation of symptoms (ten). The median waiting time for cholecystectomy was 130 days (1 to 1,481 days) (mean 188 days).The authors estimated a total cost for these 28 admissions of €133,485; this did not include the cost of 13 endoscopic retrograde cholangiopancreatography (ERCP) procedures for 11 patients, nor did it include the cost of attendance at the emergency department.[44]

In 2013, Gutt et al. published the results of their randomised controlled multicentre trial which examined primary (morbidity) and secondary outcomes (rate of conversion from laparoscopic to open surgery, costs and cost-effectiveness, overall length of hospital stay) in 618 patients with acute cholecystitis who were randomised to either immediate cholecystectomy within 24 hours of hospital admission or initial antibiotic treatment, followed by delayed laparoscopic cholecystectomy between days 7 and 45.[43] Costs were calculated on the basis of Germany's DRG classification, using cost data from 2010. Both complications and costs were significantly less in the immediate surgery group – €3,071 (95% confidence interval €2,958–€3,183) versus €4,484 (95% CI €4,239–€4,728) for patients who had delayed surgery.[43]

In 2014, Morris et al.[47] published their model-based cost-utility analysis of laparoscopic cholecystectomy performed within: a) three days of admission, b) during the same admission, but after more than three days, or c) electively in a subsequent admission, for patients with mild acute gallstone pancreatitis. A payer (NHS) perspective was taken, mean costs were calculated in 2011 to 2012 UK pounds sterling and presented in 2011 to 2012 euro using an exchange rate of GBP £1 = €1.19. As this method of exchange does not align with the Guidelines for the Economic Evaluation of Health Technologies in Ireland,[48], these costs are converted here using the methods detailed in the first paragraph. A one-year time horizon was taken for costs and outcomes. The costs for the aforementioned three strategies were €2,854, €3,679 and €3,896, respectively, while the quality-adjusted life years (QALYs) were 0.888, 0.888 and 0.884, respectively. In other words, laparoscopic cholecystectomy within three days of index admission dominates (is less costly and as, or more efficacious than) the alternatives of delayed surgery during the same or a future admission. The authors concluded that early laparoscopic cholecystectomy for patients with mild acute gallstone pancreatitis is cost-effective, but may not be feasible in all settings given resource limitations (particularly at weekends for endoscopic retrograde cholangiopancreatography and MR cholangiopancreatography). After three days, surgery during the same admission conferred little advantage over elective admission at a later date.[47]

In summary, no literature was retrieved that directly examined the cost-effectiveness of watchful waiting with operative management of cholelithiasis. For a small subset of patients with mild acute gallstone pancreatitis, early surgery within three days was

found to be the most cost-effective strategy in the UK. A limited number of international cost studies and economic evaluations were also identified in relation to operative management of gallstone disease. Conclusions included that early prioritisation and surgery for those at risk of complications has the potential to reduce costs and complications compared with delayed care. Given the described epidemiology, clinical management and methodologies used, it is likely that these findings are transferable to the current Irish healthcare setting.

2.4 Budget impact and resource implications

As noted in Section 1.4, the number of elective cholecystectomies provided through the publicly-funded healthcare system has increased by over 19.5% since 2005. The current estimated annual national cost of elective cholecystectomies is €23.6 million, with an average weighted cost per patient case of €5,973; the average weighted cost per inpatient case was €7,040, while that for day cases was €2,669, based on the latest Casemix costs (see Table 2.3).

Table 2.3. HSE inpatient and day case acute hospital activity and costs for elective cholecystectomy summarised by diagnosis-related group (based on 2011 costs and 2012 activity)[49]

DRG code	Description	Number carried out (Principal Procedure)	Cost/ inpatient (€)	Cost/ day case (€)
H08B	Laparoscopic Cholecystectomy W/O Closed CDE W/O Cat or Sev CC	3,389	4,922	2,691
H07B	Open Cholecystectomy W/O Closed CDE W/O Catastrophic CC	198	10,127	1,446
H08A	Laparoscopic Cholecystectomy W Closed CDE or W (Cat or Sev CC)	139	8,135	2,691
H07A	Open Cholecystectomy W Closed CDE or W Catastrophic CC	14	16,577	1,446
H05B	Hepatobiliary Diagnostic Procedures W/O Catastrophic CC	12	8,995	1,631
H02C	Major Biliary Tract Procedures W/O Catastrophic or Severe CC	11	10,118	2,500
H02B	Major Biliary Tract Procedures W Severe CC	8	13,987	2,500

Key: DRG – diagnostic-related group; W – with; W/O –without; CC – complication or comorbidity. Data summary from HSE National Casemix Programme Ready Reckoner, 2013 based on the 2011 inpatient and day case costs reported by 38 hospitals participating in the programme that year. Activity is based on the latest 2012 HIPE data. Note the remaining diagnosis-related groups accounted for five or fewer of the procedures each.

Assuming the DRG code for uncomplicated laparoscopic cholecystectomy (H08B), it is estimated that, were the target day case rate for laparoscopic cholecystectomy of 40% (as set out by the National Clinical Programme in Surgery) to be achieved, there

would be a potential for a saving in opportunity costs versus the present situation (in which 28% of cholecystectomies when undertaken as the principal procedure are completed as day cases) of up to approximately €0.93 million per annum (see Table 2.4) allowing therefore more efficient use of available resources.

Table 2.4 Potential cost saving through achievement of National Clinical Programme target of 40% of laparoscopic cholecystectomies performed as day cases

DRG code	Description	Cost/ inpatient (€)	Cost/ day case (€)
H08B	Laparoscopic Cholecystectomy W/O Closed CDE W/O Cat or Sev CC	4,922	2,691
H07B	Open Cholecystectomy W/O Closed CDE W/O Catastrophic CC	10,127	1,446
	Laparoscopic Cholecystectomy as Principal Procedure		
Present	Day Cases (no. procedures)	27.7% (938)	€2,524,158
	Inpatient (no. procedures)	72.3% (2,451)	€12,063,822
	Total	467	€14,587,980
Target	Day Cases (no. procedures)	40% (1356)	€3,647,920
	Inpatient (no. procedures)	60% (2033)	€10,008,395
	Total	467	€13,656,314

Key: DRG- Diagnostic-related group; W-with; W/O-without; CC-complication or comorbidity. Data summary from HSE National Casemix Programme Ready Reckoner, 2013 based on the 2011 inpatient and day case costs reported by 38 hospitals participating in the programme that year. Activity is based on the latest 2012 HIPE data.

2.5 Advice on clinical referral/treatment threshold

Taking account of the available evidence that exists in relation to gallbladder disease, and the role of cholecystectomy in its management, the following threshold criteria are advised for referral and treatment within the publicly-funded healthcare system in Ireland:

Patients in whom acute cholecystitis, cholangitis or acute pancreatitis is suspected should be referred to secondary care as an emergency.

Patients who suffer acute biliary colic or cholecystitis requiring hospitalisation should either have immediate or delayed cholecystectomy. This patient pathway should be managed by the secondary care team (including gastroenterology, general surgery and interventional radiology services, as appropriate). Repeat referral from primary care should not be required.

Where symptoms are suggestive of gallstone disease, all patients should have timely access to necessary radiological investigations via primary care services. An ultrasound scan and liver function testing should form the basis for decision making regarding the need for, and urgency of, referral to secondary care.

Patients with symptomatic gallstones should be referred for review in secondary care if:

- they express a desire to proceed to surgery following discussion of the implications of undergoing cholecystectomy
  AND
- they are considered likely surgical candidates based on assessment of patient comorbidities.

Referral of patients for review in secondary care should be considered for patients with known gallstone disease (incidentally picked up through radiological investigation for other reasons), that present to primary care with any of the following features, even if asymptomatic:

- suspicion of stones in the common bile duct
- asymptomatic gallstones, but deranged liver function tests
- gallbladder polyps reported on ultrasound – if greater than or equal to [≥] 1cm in size or if demonstrating growth on annual surveillance ultrasound
- patients with a 'porcelain gallbladder' (calcification of gallbladder wall) – because of the association with malignancy

- patients who are due to undergo organ transplantation
- patients with insulin-dependent diabetes.

Patients who do not meet these criteria should remain under the care of the general practitioner (GP) who will manage conservative treatment of the patient in the community.

Where surgery is indicated, it should be made available at a time when the patient is most likely to derive maximum potential benefit, with due consideration given to their associated risk factors and risk of disease progression.

3 Discussion

Referral thresholds have been developed based on a comprehensive review of the literature and international referral guidelines. The aim of these thresholds is to ensure that the right patients receive referral and treatment at the right time, and to avoid unnecessary interventions, particularly in those who are unlikely to derive additional benefit from surgery over conservative management. This applies to the majority of patients with asymptomatic gallstones. While referral thresholds may currently be used on an informal basis within the Irish system, this has not been done consistently. Therefore, the thresholds developed here aim to provide primary care practitioners, surgeons and other clinicians involved in the care of these patients with a template upon which decision-making can be standardised.

This requirement for standardisation is increasingly relevant, both in the context of an increase of 19.5% in the number of cholecystectomies performed annually since 2005, but also as changing demographics and the increasing prevalence of chronic disease place additional strain on the publicly-funded healthcare system. In particular, it is noted that in Ireland at present, 39% of adults are overweight and 18% are obese. As noted in Section 1, obesity has been identified as a key risk factor for the development of gallstone disease. While the evidence regarding resource utilisation and post-operative outcomes may be equivocal at present, the likely continued increased demand within the obese population places an onus on the healthcare system to develop thresholds that will aid in defining which patients are suitable candidates for surgery.

This threshold recognises the role of radiology, and ultrasound in particular, in contributing to the diagnosis of gallstone disease, and hence a caveat to implementation of these thresholds is that mechanisms are in place to ensure timely

access to these services via primary care. As noted in Section 1.4, however, for the 80% of GPs that have reported having direct access to abdominal or pelvic ultrasound in the public system, the average waiting period is 14 weeks with substantial variation (range one day to 42 weeks) depending on geographical location.

A further key point is that the extent to which patients must wait, both for their appointment in secondary care, and later for their cholecystectomy once they have been listed for this procedure, is unclear at the time of this report. It is noted that 23.2% of cholecystectomies undertaken in 2012 were performed in the emergency setting. While a breakdown of the indications for these procedures is not available, it is likely that a significant number of these patients had previously been diagnosed with gallstone disease and could potentially have been managed in the scheduled-care setting.

While beyond the immediate scope of this HTA, it has been noted that day case rates remain significantly below the target of 40% set out by the National Clinical Programme for Surgery for patients undergoing laparoscopic cholecystectomy. Analysis of HIPE data suggests that just 26.6% (hospital range 0%-67.4%) of elective laparoscopic cholecystectomies performed in Irish public hospitals in 2012 were day cases, with evidence of significant local and regional variation in practice.[24] As demonstrated in Table 2.3, potential for a saving in opportunity costs of approximately €0.93 million per annum could be attained through achievement of this target. The reasons for the regional and local variation are currently unclear and therefore an analysis of the underlying causative factors would be useful in identifying how existing resources might be better utilised.

While efficiencies have also been achieved in terms of length of stay and the total number of procedures undertaken, it is likely that waiting lists for surgical intervention will remain substantial. These delays are clearly not desirable for patients; in addition, the evidence suggests that earlier referral and surgical intervention, prior to the onset of complications, has significant cost benefits, and thus implementation of the threshold as part of an overall process of streamlining services could have significant impact on budget and resource allocation.

It is noted that while development of this threshold should aid in defining who should be referred for urgent review, the mechanisms around its practical implementation remain to be fully clarified. It is clear that the National Healthlink Project, which permits the secure transmission of clinical patient information between GPs and hospitals, has facilitated improved communication of referrals between primary and secondary care. It is thus suggested that one mechanism through which this referral

threshold might be implemented would be through its integration in the form of a standardised referral form into this project.

In conclusion, the thresholds outlined above are consistent with well established clinical guidelines and published evidence. Hence, they are unlikely to represent a major change from current practice, but rather a standardisation of referral and treatment criteria across all areas of the publicly-funded healthcare system. As with all thresholds, it is imperative that there are opportunities for appeal mechanisms to ensure good governance. In addition, while these thresholds represent best practice, their implementation will depend on timely access to radiology services at the primary care level.

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Appendices

Appendix 1.1 – HIPE ICD-10AM/ACHI list of intervention codes for cholecystectomy procedures

Intervention code	Description
3044500	Laparoscopic cholecystectomy
3044600	Laparoscopic cholecystectomy proceeding to open cholecystectomy
3044800	Laparoscopic cholecystectomy removal of common bile duct calculus via cystic duct
3044900	Laparoscopic cholecystectomy removal of common bile duct calculus via laparoscopic choledochotomy
3044300	Cholecystectomy
3045401	Cholecystectomy with choledochotomy
3045500	Cholecystectomy; choledochotomy and biliary intestinal anastomosis

Appendix 1.2 – Management of gallstone disease in primary care – AUGIS and RCS, 2013[33]

- Most patients with symptomatic gallstones present with a self-limiting attack of pain that lasts for hours only. This can often be controlled successfully in primary care with appropriate analgesia, avoiding the requirement for emergency admission. When pain cannot be managed or if the patient is otherwise unwell (e.g. sepsis), he or she should be referred to hospital as an emergency.
- Further episodes of biliary pain can be prevented in around 30% of patients by adopting a low fat diet. Fat in the stomach releases cholecystokinin, which precipitates gallbladder contraction and might result in biliary pain.
- Patients with suspicion of acute cholecystitis, cholangitis or acute pancreatitis should be referred to hospital as an emergency.
- There is no evidence to support the use of hyoscine or proton pump inhibitors in the management of gallbladder symptoms. Antibiotics should be reserved for patients with signs of sepsis.
- There is no evidence of benefit from the use of non-surgical treatments in the definitive management of gallbladder stones (such as gallstone dissolution therapies, ursodeoxycholic acid or extracorporeal lithotripsy).

Appendix 1.3 ASGBI/RCS Triage of biliary patients based on ultrasound scanning and liver function tests[32]

- Biliary colic – short duration of pain, minimal systemic upset, normal liver function tests, no biliary dilatation on ultrasound.
- Acute cholecystitis – pain for over 24 hours, systemic upset (pyrexia, tachycardia), raised white cell count, oedematous thick-walled gallbladder, often with stone stuck in neck on ultrasound (with normal liver function tests unless Mirizzi syndrome).
- Complex biliary disease – variable duration of pain, systemic upset possibly including rigors, pyrexia, deranged liver function tests and dilated biliary tree on ultrasound. High suspicion of gallstones being present in the common bile duct in addition to the gallbladder.
- Gallstone pancreatitis – peri-umbilical pain that radiates to the back of variable duration and intensity, systemic upset, raised amylase or lipase. May have deranged liver function tests and inflammatory markers. USS may reveal a dilated biliary tree. Should have the disease severity stratified on admission and at 24 hours by a validated prognostic scoring system such as Glasgow, APACHE II or CRP.

Appendix 1.4 - A proposed strategy to assign risk of choledocholithiasis in patients with symptomatic cholelithiasis based on clinical predictors, ASGE, 2010[34]

Predictors of choledocholithiasis

Very strong

- Common bile duct stone on trans-abdominal US
- Clinical ascending cholangitis
- Bilirubin > 4 mg/dL

Strong

- Dilated common bile duct on US (>6 mm with gallbladder in situ)
- Bilirubin level 1.8-4 mg/dL

Moderate

- Abnormal liver biochemical test other than bilirubin
- Age older than 55 years
- Clinical gallstone pancreatitis.

Assigning a likelihood of choledocholithiasis based on clinical predictors

- Presence of any very strong predictor: High
- Presence of both strong predictors: High
- No predictors present: Low
- All other patients: Intermediate

Appendix 1.5 - Asymptomatic patients who should be considered for cholecystectomy

World Gastroenterology Association Guidelines[31]

- Patients who are known to have gallstones and may be living in a part of the world that is very remote from medical treatment, should they get a complication.
- Cholecystectomy in asymptomatic patients with gallstones should be considered in individuals living in high risk areas such as Chile and Bolivia in South America.
- Patients with immune suppression e.g. after transplantation. These may have a far higher risk should they develop a complication such as cholangitis. But also cyclosporin A and tacrolimus (FK 506) are prolithogenic because of decreased bile salt export pump function (BSEP).
- Patients with insulin-dependent diabetes do not have a higher prevalence of stones, but when elderly, have a higher risk should they develop inflammatory complications.
- Patients with rapid weight loss, weight cyclers and those with higher risks of complications generally.
- Patients with calcified 'porcelain' gallbladder as these are also at high risk of evolving into cancer.

Duncan and Riall[38]

- Those at increased risk of cancer; patients with a porcelain gallbladder and patients with gallstones >3cm in size.
- Prior to organ transplant, most commonly heart transplant candidates, due to high rates of symptomatic gallstones and operative morbidity and mortality post-transplant.
- Patients with chronic hemolytic syndromes, including sickle cell anaemia, should undergo cholecystectomy for asymptomatic gallstones.
- Cholecystectomy should be considered if gallstones are identified during an abdominal operation for an unrelated reason; however, this depends on the type and reason for the operation being performed, the stability of the patient, and multiple other factors.

Appendix 1.6 – Examples of UK PCT referral thresholds

Yorkshire and Humber Quality Observatory[50]

Elective referral threshold into secondary care:

- Symptomatic gallstones
- Dilated common bile duct on ultrasound
- Asymptomatic gallstones with abnormal liver function test results
- Asymptomatic gall bladder polyp(s) reported on ultrasound
- Symptomatic gall bladder 'sludge' reported on ultrasound.

Surgical threshold for elective cholecystectomy:

- Symptomatic gallstones
- Gall bladder polyps larger than 8mm or growing rapidly
- Common bile duct stones.
- Acute pancreatitis.

Cholecystectomy should be performed laparoscopically in patients with an uncomplicated abdomen and in the absence of contra-indications.

Cholecystectomy should be offered as a day case procedure in the absence of contra-indications.

Routine laparoscopic cholecystectomy does not generally require a consultant outpatient follow up. If the gall bladder is sent for histological examination the results should be reviewed by the requesting consultant and communicated to the GP.

It is expected that a trained laparoscopic surgeon should be able to achieve a minimum laparoscopic cholecystectomy rate of 50% for day case and a minimum 75% rate for day case including a 23-hour stay.

Central and Eastern Cheshire PCT[49]

Surgery for asymptomatic gallstones

- This procedure is considered a Low clinical priority for asymptomatic gallstones.

Asymptomatic gallstones are usually diagnosed incidentally when they are seen on imaging which is done for some unrelated reasons.

Hull Clinical Commissioning Group[51]

NHS Hull CCG will commission elective referral into secondary care for a cholecystectomy assessment in cases where the patient fulfils any of the criteria below:

- Symptomatic gallstones
- A dilated common bile duct on ultrasound
- Asymptomatic gallstones with abnormal liver function test (LFT) results
- Asymptomatic gallbladder polyp(s) reported on ultrasound
- Symptomatic gallbladder 'sludge' reported on ultrasound.

NHS Hull CCG will only commission elective cholecystectomy surgery in cases where the patient fulfils any of the criteria below:

- Symptomatic gallstones
- Gallbladder polyps larger than 8mm or growing rapidly
- Common bile duct stones.
- Acute pancreatitis.

Documentation that the threshold criteria are fulfilled is mandatory and the referral letter or form should, as a minimum, contain:

- a clear indication of the grounds for referral against the threshold criteria;
- any relevant medical history and current medication;
- any known factors affecting the patients fitness for day surgery;
- a recent ultrasound report conducted within 2 months at the point of referral;
- a recent liver function test report conducted within 1 month at point of referral.

Further guidance: Cholecystectomy should be performed laparoscopically in patients with an uncomplicated abdomen and in the absence of contra-indications. (The standard laparoscopic approach uses several small incisions in the abdomen.)

Cholecystectomy should be offered as a day case procedure in the absence of contra-indications. Routine laparoscopic cholecystectomy does not generally require a consultant outpatient follow up. If the gallbladder is sent for histological examination the results should be reviewed by the requesting consultant and communicated to the GP.

Appendix 1.7 Evidence table summarising the data extracted from the cost-effectiveness literature

Study	Intervention	Analysis Details	Clinical and QALY Outcomes	Costs*	Results
Borowski et al. (2010)[46]	LC - elective versus emergency admissions (including management of gallstone disease and its complications).	Country: UK Discount rate: - Perspective: Health care payer Time Horizon: 3 months Model Type: Prospective clinical audit, patient questionnaire (emergencies) (n=114 admitted, 54% emergencies). Cost comparisons used secondary care income (NHS tariff) and estimated cost of hospitalisation, investigations and treatment.	27.4% (17/62) of emergencies presented with gallstone complications. 61% (38/62) had similar symptoms before, 55.3% (21/38) diagnosed in primary care or by another hospital department. 52.4% (11) of these had not been referred for a surgical opinion.	Total cost of cholecystectomy over 3 months = €445,642 equivalent to annual cost = €1.69 million.	Delay in referral of symptomatic patients had substantial cost implications. Earlier referral and avoidance of complications could have saved €21,876 over the 3 months, mainly related to a longer length of stay.
Somasekar et al. (2002)[45]	LC – patient costs when admitted with acute exacerbations of symptoms while waiting for surgery.	Country: UK Discount rate: - Perspective: Health care payer Time Horizon: 1 year Model Type: Retrospective analysis (n=156 patients, n=37) were emergency admittances while on waiting list. Mean duration of 12 months on waiting list).	47 episodes of admissions in total, 32 for biliary colic, 13 for acute cholecystitis, 2 for acute pancreatitis.	Cost per episode of admission €1,631. Total costs of treating the 37 patients €76,654.	Emergency admission with gallstone-related problems common among patients awaiting LC and has significant cost implications. Potential to reduce costs through identification and prioritisation of patients on the waiting list at increased risk of recurrent symptoms and complications.
Lawrentschuk et al. (2003)[44]	Elective LC – impact of surgical waiting times.	Country: Australia Discount rate: - Perspective: Health care payer Time Horizon: 1 Jan 99 - 31 Dec 01 Model Type: Retrospective review (all patients who underwent LC, n=322)	While awaiting surgery, 14% re-presented to ED with biliary symptoms; 6% admitted (21 patients, 28 admissions), of whom 86% were on waiting list for biliary colic symptoms only. Median waiting time for LC was 130 days (1 to 1,481	Total cost-28 admissions €136,525; did not include cost of 13 ERCPs for 11 patients, or cost of attendance at the ED.	Prolonged waiting times for elective LC are associated with morbidity in 14% of patients at the Launceston General Hospital. This, combined with frequent cancellation of elective surgery, may result in

			days) (mean 188 days).		significant costs to health-care sector.
Gutt et al. (2013)[43]	LC - early versus delayed surgery. Patients randomly assigned to receive immediate surgery (ILC) (within 24 hours of admission) or initial antibiotic treatment, followed by delayed LC (DLC) at days 7 to 45.	Country: Germany and Slovenia (35 centres) Discount rate: - Perspective: Health care payer Time Horizon: almost 4 years Model Type: Randomised, prospective, open-label, parallel group trial (n=618, ILC=304, DLC=314). Secondary endpoints included costs. Costs calculated using Germany's DRG classification and cost data from 2010.	Morbidity occurred in 35 ILC patients (12.0%) and 86 DLC patients (33.3%) of the population (P<0.001). Complications significantly less in ILC group.	Costs significantly less in ILC group – €3,071 (95% CI €2,958–€3,183) versus €4,484 (95% CI €4,239–€4,728) for DLC. Cost-effectiveness ratio better for ILC than DLC.	Results show that immediate LC within 24 hours of hospital admission is the therapy of choice and should be implemented as treatment algorithm for this condition. Costs 46% higher in DLC mainly due to longer total hospital stay.
Morris et al. (2014)[47]	Cost-effectiveness of early LC ([a] within 3 days of admission, [b] during same admission but after > 3 days, or [c] electively in subsequent admission) for mild acute gallstone pancreatitis.	Country: UK Discount rate: 3.5% Perspective: Health care payer Time Horizon: 1 year Model Type: Cost-utility analysis – decision tree model. Mean costs calculated in 2011 to 2012 UK pounds sterling and presented in 2011 to 2012 euro using exchange rate of GBP £1 = €1.19 - see Section 2.3 -costs reconverted here.	QALYs were (a) 0·888, (b) 0·888 and (c) 0·884 respectively. Early LC had a 91% probability of being cost-effective at the maximum willingness to pay for a QALY commonly used in the UK.	Costs of (a) were €2,854, (b) €3,679 and (c) €3,896 respectively.	Early LC for patients with mild acute gallstone pancreatitis is cost-effective, but may not be feasible in all settings given resource limitations. After three days, surgery during the same admission conferred little advantage over elective admission at a later date.

Key: C – Cholecystectomy; DLC – delayed laparascopic cholecystectomy; DRG – diagnosis-related group; ILC – immediate laparascopic cholecystectomy; LC– Laparoscopic cholecystectomy; QALY – quality-adjusted life year; UK – United Kingdom.

*Costs reported in each of the studies were inflated to 2013 using the local consumer price index and expressed in Irish Euro using the purchasing power parity exchange rate.

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