Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Single-operator per-oral cholangioscopy for the evaluation and treatment of hepato-biliary-pancreatic disorders

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: What is the clinical and cost effectiveness of single operator per-oral cholangioscopy for diagnostic and therapeutic management of hepato-biliary-pancreatic disorders?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales (HTW) multidisciplinary advisory groups before publication.

2. Health problem

The biliary system forms part of the digestive system and includes the gallbladder, liver and pancreas (NICE 2015a). It aids digestion by releasing bile through the biliary ducts and into the duodenum. However, various disorders can arise and cause narrowing or obstruction of the biliary ducts, including duct stones, benign or malignant tumours, pancreatitis, or primary sclerosing cholangitis.

Access to the biliary system for diagnostic and therapeutic purposes can be challenging. Current standard of care involves endoscopic retrograde cholangio-pancreatography (ERCP) in combination with various tools such as fluoroscopic visualisation, insertion of stents, and stone removal using balloon dilation. However, fluoroscopic visualisation can be limited, and some stones are difficult to remove using current methods due to their size and location.

Approximately 48,000 ERCP procedures are undertaken in the UK each year (NICE 2015a), which would equate to approximately 2,268 procedures in Wales.

3. Health technology

Single operator per-oral cholangioscopy (SOPOC) can be used with ERCP to directly visualise and collect biopsy specimens, in addition to providing therapeutic intervention such as laser-based stone removal. Initial versions of SOPOC used fibreoptic visualisation (SpyGlass Legacy, Boston Scientific), but a more recent iteration uses digital imaging and more advance optics (SpyGlass DS, Boston Scientific). At the time of this report, SpyGlass DS is the only variant of SOPOC

commercially available in the UK[1]. More direct visualisation of the biliary system may give potential for improved diagnostic and therapeutic outcomes for patients.

4. Current guidelines and guidance

Current UK and European guidelines and their relevant recommendations are summarised in Table 1.

In 2015, the National Institute for Health and Care Excellence (NICE) published a Medtech Innovation Briefing for "The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system" (MIB21). MIB21 reported the suggested place in therapy as when standard ERCP is unsuccessful or considered inappropriate (NICE 2015a).

[1] Expert comment, December 2019

Table 1. Current guidelines and guidance

Guidance	Population	Recommendation
European guidelines		
Endoscopic management of common bile duct stones (ESGE 2019)	People with "difficult" biliary stones	• ESGE recommends limited sphincterotomy combined with endoscopic papillary large-balloon dilation as the first-line approach to remove difficult common bile duct stones (Strong recommendation, high quality evidence). • ESGE recommends mechanical lithotripsy for difficult stones when sphincterotomy plus endoscopic papillary large-balloon dilation has failed or is inappropriate (Strong recommendation, moderate quality evidence). • ESGE recommends the use of cholangioscopy-assisted intraluminal lithotripsy (electrohydraulic or laser) as an effective and safe treatment of difficult bile duct stones (Strong recommendation, moderate quality evidence). • ESGE suggests that the type of cholangioscopy and lithotripsy should depend on local availability and experience. (Weak recommendation, low quality evidence).
Endoscopic treatment of chronic pancreatitis (ESGE 2018)	People with pancreatic stones	• ESGE recommends ESWL for the clearance of radiopaque obstructive MPD stones larger than 5mm located in the head/body of the pancreas, and endoscopic retrograde cholangiopancreatography (ERCP) for MPD stones that are radiolucent or smaller than 5mm (Strong recommendation, moderate quality evidence). • ESGE suggests considering pancreatoscopy-guided lithotripsy when ESWL is not available or for stones that were not fragmented after adequately performed ESWL (Weak recommendation, low quality evidence).
Role of endoscopy in primary sclerosing cholangitis (EASL/ESGE 2017)	People with PSC and suspected cholangiocarcinoma	• ESGE/EASL recommend ductal sampling (brush cytology, endobiliary biopsies) as part of the initial investigation for the diagnosis and staging of suspected CCA in patients with PSC (Strong recommendation, high quality evidence). • ESGE/EASL suggest that FISH or equivalent chromosomal assessments are considered in patients with suspected CCA when brush cytology results are equivocal (Weak recommendation, low quality evidence). • ESGE/EASL suggest that additional investigations such as cholangioscopy, endoscopic ultrasound, and probe-based confocal laser endomicroscopy may be useful in selected cases (Weak recommendation, low quality evidence).

Guidance	Population	Recommendation
UK Guidelines		
Pancreatic cancer in adults: diagnosis and management (2018) NICE guideline NG85 (NICE 2018)	People with obstructive jaundice	For people with obstructive jaundice and suspected pancreatic cancer, offer a pancreatic protocol CT scan before draining the bile duct. If the diagnosis is still unclear, offer FDG-PET/CT and/or EUS with EUS-guided tissue sampling. Take a biliary brushing for cytology if: • ERCP is being used to relieve the biliary obstruction and • there is no tissue diagnosis.
	People without jaundice who have pancreatic abnormalities on imaging	Offer a pancreatic protocol CT scan to people with pancreatic abnormalities but no jaundice. If the diagnosis is still unclear, offer FDG-PET/CT and/or EUS with EUS-guided tissue sampling. If cytological or histological samples are needed, offer EUS with EUS-guided tissue sampling.
	People with pancreatic cysts	Offer a pancreatic protocol CT scan or MRI/MRCP to people with pancreatic cysts. If more information is needed after one of these tests, offer the other one. Refer people with any of these high-risk features for resection: • obstructive jaundice with cystic lesions in the head of the pancreas • enhancing solid component in the cyst • a main pancreatic duct that is 10 mm diameter or larger. Offer EUS after CT and MRI/MRCP if more information on the likelihood of malignancy is needed, or if it is not clear whether surgery is needed. Consider fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed. When using fine-needle aspiration, perform CEA assay in addition to cytology if there is sufficient sample.

Guidance	Population	Recommendation
		For people with cysts that are thought to be malignant, follow the recommendations on staging. NICE has published a medtech innovation briefing on the Cellvizio confocal endomicroscopy system for characterising pancreatic cysts.
Suspected cancer: recognition and referral (2015) NICE guideline NG12 (NICE 2015b)	People with pancreatic cancer	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for pancreatic cancer if they are aged 40 and over and have jaundice. Consider an urgent direct access CT scan (to be performed within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following: • diarrhoea • back pain • abdominal pain • nausea • vomiting • constipation • new-onset diabetes.
	People with liver cancer	Consider an urgent direct access ultrasound scan (to be performed within 2 weeks) to assess for liver cancer in people with an upper abdominal mass consistent with an enlarged liver.
Gallstone disease: diagnosis and management (2014) NICE guideline CG188 (NICE 2014)	People with common bile duct stones	Offer bile duct clearance and laparoscopic cholecystectomy to people with symptomatic common bile duct stones or asymptomatic common bile duct stones. Clear the bile duct: • surgically at the time of laparoscopic cholecystectomy or • with endoscopic retrograde cholangiopancreatography (ERCP) before or at the time of laparoscopic cholecystectomy. If the bile duct cannot be cleared with ERCP, use biliary stenting to achieve biliary drainage only as a temporary measure until definitive endoscopic or surgical clearance. Use the lowest-cost option suitable for the clinical situation when choosing between day-case and inpatient procedures for elective ERCP.

Guidance	Population	Recommendation
British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis, (BSG 2019)	People with PSC	We recommend that where cholangiocarcinoma is suspected, contrast-enhanced, cross-sectional imaging remains the initial preferred investigation for diagnosis and staging (strength of recommendation: STRONG; quality of evidence: HIGH). Confirmatory diagnosis relies on histology with the approach to tissue sampling guided by multidisciplinary meeting review. Options include ERCP-guided biliary brush cytology/FISH/ endobiliary biopsy/cholangioscopy/EUS-guided biopsy and/or percutaneous biopsy (strength of recommendation: STRONG; quality of evidence: HIGH).
Updated guideline on the management of common bile duct stones (CBDS), (BSG 2017)	Common bile duct stones	It is recommended that cholangioscopy-guided electrohydraulic lithotripsy or laser lithotripsy be considered when other endoscopic treatment options fail to achieve duct clearance. (Low-quality evidence; strong recommendation)
	Difficult ductal stones	Laparoscopic duct exploration and ERCP (supplemented by endoscopic papillary balloon dilation with prior sphincterotomy, mechanical lithotripsy or cholangioscopy where necessary) are highly successful in removing CBDS. It is recommended that percutaneous radiological stone extraction and open duct exploration should be reserved for the small number of patients in whom these techniques fail or are not possible. (Low-quality evidence; strong recommendation)
CCA: cholangiocarcinoma; CEA: carcinoembryonic antigen; CT: computerised tomography; EASL: European Association for the Study of the Liver; ERCP: endoscopic retrograde cholangio-pancreatography; ESGE: European Society of Gastrointestinal Endoscopy; ESWL: extracorporeal shock wave lithotripsy; EUS: endoscopic ultrasound; FDG-PET: fluorodeoxyglucose-positron emission tomography; FISH: fluorescence in situ hybridisation; MPD: main pancreatic duct; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; PSC: primary sclerosing cholangitis		

5. Evidence search methods

The criteria used to select evidence for this appraisal are outlined in Appendix 1; these were developed following comments from the HTW Assessment Group and UK experts.

Initial exploratory searches identified the following relevant sources of secondary evidence relating to SOPOC:

- a National Institute for Health and Care Excellence (NICE) Medtech innovation briefing (MIB21): SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system
- an ECRI Product Brief: SpyGlass DS Direct Visualization System (Boston Scientific Corp.) for Evaluating and Treating Bile Duct Disorders
- Navaneethan 2015. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review.
- Njei 2016. Systematic review with meta-analysis: endoscopic retrograde cholangiopancreatography-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis.
- Jin 2019. Single-operator peroral cholangioscope in treating difficult biliary stones: A systematic review and meta-analysis.

We used these articles as sources of outcome data and to identify primary studies included within their literature searches. We also performed a systematic literature search on 11 November 2019 and an update search on 12 December 2019 to identify additional literature published after these sources performed their searches. Priority was given to systematic reviews, randomised controlled trials and ongoing studies. Full literature search details are available on request.

Appendix 2 summarises the selection process for articles included in this review.

6. Clinical effectiveness

6.1. Diagnosis of biliary strictures

We identified three systematic reviews that investigated SOPOC. The first review looked at any ERCP-based technologies for the diagnosis of cholangiocarcinoma in people with primary sclerosing cholangitis-induced biliary strictures (Njei et al. 2016); only pooled data for SOPOC alone is reported in this review. Two reviews evaluated SOPOC for diagnosing malignancy in biliary strictures (Badshah et al. 2019, Navaneethan et al. 2015). Navaneethan et al. (2015) included analyses for the following populations:

- biopsies in all biliary strictures.
- biopsies in cholangiocarcinoma, specifically.
- visual findings in biliary strictures.
- biopsies in all biliary strictures, where prior ERCP was negative and/or had failed (Navaneethan et al. 2015).

Study characteristics for the systematic reviews are detailed in Table 2.

We identified a fourth systematic review that evaluated SOPOC as a diagnostic tool (Sun et al. 2015). However, this was excluded as all the studies identified were also included in Navaneethan et al. (2015).

We also identified additional primary studies published after the systematic reviews assessing visualisation and diagnosis of the hepato-biliary-pancreatic system using SOPOC. Characteristics of these studies are listed in Appendix 3.

6.1.1. Diagnosis by biopsy in biliary strictures

All of the identified systematic reviews reported on diagnostic outcomes from SOPOC biopsy (Table 3).

Badshah et al. (2019) included 15 studies that evaluated SOPOC for diagnosis of malignant biliary strictures. For diagnosis via biopsy samples, the pooled sensitivity and specificity of SOPOC was 71.9% (95% confidence interval [CI] 66% to 77%) and 99.1% (95% CI 97% to 99%), respectively.

Navaneethan et al. (2015) identified 10 studies evaluating SOPOC (SpyGlass) visualisation and SpyBite biopsies to diagnose biliary malignancies. Pooled sensitivity and specificity for SOPOC in the diagnosis of malignant biliary strictures was 60.1% (95% CI 54.9% to 65.2%) and 98.0% (95% CI, 96.0% to 99.0%), respectively.

Use of SOPOC in the diagnosis of cholangiocarcinoma specifically was reported in four of the ten studies in Navaneethan et al. (2015), with a sensitivity of 66.2% (95% CI, 59.7%-72.3%) and sensitivity of 97.0% (95% CI, 94.0%-99.0%). Njei et al. (2016) also reported pooled diagnostic accuracy data for various ERCP-based modalities used for the diagnosis of cholangiocarcinoma, but in people with primary sclerosing cholangitis specifically. Sensitivity for SOPOC biopsies in people with primary sclerosing cholangitis (PSC) was 65% (95% CI, 35–87%) and specificity was 97% (95% CI, 87–99%).

We identified four primary studies that were published after the systematic review that reported comparative diagnostic data for SOPOC-guided biopsy (Gerges et al. 2019, Yan&Tejaswi 2019, Lee et al. 2019, Kaura et al. 2019). Of these, only one study was randomised. Outcomes are presented in Table 4.

The randomised controlled trial (n = 57) compared diagnostic accuracy of SOPOC versus transpapillary brushing (Gerges et al. 2019). Diagnosis was reported as either malignant, benign, or still indeterminate. When indeterminate diagnoses were included as part of the false positive or false negative results, sensitivity was 68.2% for SOPOC versus 21.4% for brushing ($p < 0.01$); there was no significant difference in specificity (62.5% versus 84.6%, $p = 0.25$; Table 5). The authors also calculated sensitivity and specificity based on the assumption that all indeterminate diagnoses were benign; this did not alter sensitivity but resulted in 100% specificity for both SOPOC and brushing.

The three non-randomised studies varied in results. Similar to the randomised study, one retrospective case review (n = 22) reported sensitivity of SOPOC versus brushing as 60% and 37.5%, respectively, and specificity of 100% for both approaches. A prospective observational study (n = 59) comparing SOPOC to endoscopic ultrasound-guided fine needle biopsy showed similar sensitivity (92.3% versus 96.0%) and specificity (100% versus 96.3%) between the two modalities. The third, a retrospective cohort study (n = 92), compared various ERCP modalities both alone and in combination (Kaura et al. 2019). SOPOC alone had a sensitivity of 43.3% and specificity of 97.1%, whereas brush cytology alone had sensitivity 44.7% and specificity of 89.4%. Instead, the authors noted that combined SOPOC with brush cytology and FISH had significantly improved specificity compared to brush cytology alone (71.4% versus 44.7%; $p = 0.03$).

Additional non-comparative studies published after the systematic reviews are presented in Appendix 3.

6.1.2. Diagnosis by visualisation

The systematic review by Navaneethan et al. (2015) analysed six studies that reported visual diagnosis of biliary strictures using SOPOC (Table 3). Pooled sensitivity and specificity was 84.5% (95% CI, 79.2%-88.9%) and 82.6% (95% CI, 77.1%-87.3%), respectively.

Two comparative studies published after Navaneethan et al. (2015) included visualisation outcomes for SOPOC and conventional ERCP with brushing. The Gerges et al. (2019) randomised controlled trial reported that visualisation using SOPOC versus brushing had sensitivities of 95.5% versus 66.7% (p = 0.2) and specificities of 66.7% versus 64.3% (p = 0.91). The second study was a non-randomised case review that reported sensitivity of 100% for SOPOC versus 37.5% for brushing; specificity was 100% for both modalities (Yan&Tejaswi 2019).

6.2. Diagnosis by biopsy of biliary strictures following indeterminate or negative conventional ERCP

Four of the ten identified studies in Navaneethan et al. (2015) evaluated diagnosis by biopsy of biliary strictures in cases where ERCP had failed and/or was negative (Table 5). Sensitivity was 74.7% (95% CI, 63.3%-84.0%) and 93.3% (95% CI, 85.1%-97.8%), respectively. One of the studies directly compared SpyBite biopsies with standard brushings and biopsies, which reported a sensitivity of 76.5% compared with brushings (5.8%) and biopsies (29.4%).

In the diagnosis of cholangiocarcinoma (CCA) specifically, SOPOC had a pooled sensitivity and specificity of 67.3% (95% CI, 52.5%-80.1%) and 93.3% (95% CI, 83.1%-98.7%), respectively.

6.3. Treatment of difficult biliary stones

One systematic review was identified that evaluated SOPOC for therapeutic use; specifically, for treating 'difficult' biliary stones where conventional removal methods were either not appropriate or had failed (Jin et al. 2019). Study characteristics are reported in Table 6. Overall, complete stone clearance was reported in 23 studies, with a pooled clearance rate of 94.3% (95% CI 90.2–97.5%).

Three studies in Jin et al. (2019) reported comparative data between SOPOC and an alternative modality; one additional study comparing SOPOC with conventional care was also identified. Study characteristics for these four studies are listed in Table 7. The four studies compared SOPOC to conventional therapy (Buxbaum et al. 2018, Ridtitid et al. 2018), large balloon dilation (Franzini et al. 2018) and extracorporeal shock wave lithotripsy (Aljebreen et al. 2014). Therapeutic outcomes are described in Tables 8 to 10.

6.4. Comparison of SOPOC generations

In most studies, the intervention group included people who had received either SpyGlass Legacy (fibre optic) or SpyGlass DS. Two studies compared both SpyGlass generations for therapeutic use (Appendix 3), and the newer SpyGlass DS has numerically higher rates of therapeutic success (including stone clearance, guidewire insertion, stent removal).

Table 2. Systematic reviews of SOPOC for visualisation or diagnosis of hepato-biliary-pancreatic structures

Study	Study design	Selection criteria	Intervention	Outcomes	Comments on risks of bias/applicability
Badshah et al. (2019)	Systematic review and meta-analysis 15 studies (n = 539)	ERCP studies with cholangioscopy and reported histology. Studies were only included where a 2 x 2 table could be constructed for true negative, true positive, false-negative, and false positive diagnoses.	Index test: SOPOC Reference standard not specified	• Sensitivity and specificity • Positive/negative likelihood ratios • Diagnostic odds ratio	Authors did not report reference standards used for selection or that was used in each study.
Njei et al. (2016)	Systematic review and meta-analysis 21 studies, 4 of which evaluated SOPOC: Tischendorf et al. (2006), Germany, (n = 53) Heif et al. (2013), USA, (n = 15) Kalaitzakis et al. (2014), Sweden and UK, (n = 54) Arnelo et al. (2015), Sweden, (n = 47) Total n = 128 Review period January 1990 to December 2015.	Selection criteria: studies investigating biopsies independently or in combination for the diagnosis of CCA using the following ERCP-based modalities: • Bile duct brushing for cytology • ERCP with brushing for FISH • Probe-based confocal laser endomicroscopy • SOPOC Studies were only included where data to construct 2x2 contingency tables were available. Exclusion criteria: studies that did not evaluate PSC patients with strictures; studies/abstracts with insufficient data; reviews, editorials or correspondence letters that did not report their own data; case reports and studies with <10 patients.	Index test: use of any ERCP-based modality with studies reporting "positive for malignancy" Reference standard: not reported.	• Sensitivity and specificity of all diagnostic modalities • Weighted sensitivity and specificity, positive/negative likelihood ratios • receiver-operator characteristic curve (95% CI)	The review included multiple ERCP-based modalities. Only studies evaluating SOPOC are included in this report. The 4 studies evaluating SOPOC were non-comparative (did not report diagnostic accuracy against standard care) Authors reported use of QUADAS-2 to assess quality and bias. For the SOPOC studies, one had high risk of bias for patient selection (Kalaitzakis 2014). Tischendorf 2006 had high risk of bias for index and reference tests. Authors did not report reference standards used for selection or that was used in each study. For 3 of the 4 SOPOC studies, the reference test was reported as unclear or high risk of bias.

Study	Study design	Selection criteria	Intervention	Outcomes	Comments on risks of bias/applicability
Navaneethan et al. (2015)	Systematic review and meta-analysis Woo et al. (2014), (n = 19) Nishikawa et al. (2013), (n = 33) Draganov et al. (2012), (n = 26) Hartman et al. (2012), (n = 29 [specimens]) Siddiqui et al. (2012), (n = 30) Manta et al. (2013), (n = 52) Kalaitzakis et al. (2012), (n = 74 [procedures]) Ramchandani et al. (2011), (n = 33) Chen et al. (2011), (n = 140) Chen and Pleskow (2007), (n = 20) Total n = 456 Review period January 1980 to October 2014 Sensitivity analyses were performed to	Selection criteria: studies including both cholangioscopy using SpyGlass and SpyBite biopsies in the identification of biliary strictures Exclusion criteria: Studies with sample size <10 Mean age: 62.9 years (SD 16.2 years) Sex: 48.8% male:51.2% female	Index test: SpyGlass with SpyBite biopsy collection Reference standard: not reported.	• Sensitivity and specificity of SpyGlass/SpyBite • Likelihood ratio • Diagnostic odds ratio	Authors reported use of QUADAS-2 to assess quality and bias. The authors noted a lack of comparative data, with only 1 of the studies comparing diagnostic accuracy of SOPOC against other alternatives. Authors did not report the reference standards used for selection / used in each study. They did report low risk of bias for reference standards and its applicability.

Study	Study design	Selection criteria	Intervention	Outcomes	Comments on risks of bias/applicability
	determine undue influence of any particular study.				

CCA: cholangiocarcinoma; ERCP: endoscopic retrograde cholangio-pancreatography; FISH: fluorescence in situ hybridisation; SOPOC: single-operator per-oral cholangioscopy.

Table 3. Diagnostic accuracy of SOPOC for biliary strictures (systematic reviews)

Outcome	Evidence source	Number of studies and patients	Pooled sensitivity	Pooled specificity	Pooled diagnostics odds ratio	Comments
Diagnosis of malignant biliary strictures	Badshah et al. (2019)	15 studies, n = 539	71.9% (95% CI 66% to 77%)	99.1% (95% CI 97% to 99%)	71.6 (95% CI 32.8 to 156.4)	
	Navaneethan et al. (2015), systematic review	10 studies, n = 456	60.1% (95% CI, 54.9%-65.2%)	98.0% (95% CI, 96.0%-99.0%)	66.4 (95% CI, 32.1-137.5)	
Diagnosis of CCA	Navaneethan et al. (2015), systematic review	6 studies, n = 284	66.2% (95% CI, 59.7%-72.3%)	97.0% (95% CI, 94.0%-99.0%)	79.7 (95% CI, 32.7-194.7	
Diagnosis of CCA in PSC	Njei et al. (2016), systematic review	4 studies, n = 128	65% (95% CI, 35-87%)	97% (95% CI, 87-99%)	59 (95% CI, 10-341)	Authors also reported pooled analyses for SOPOC combined with other ERCP-modalities; diagnostic accuracy was lower than SOPOC alone.
Visual findings in biliary strictures	Navaneethan et al. (2015), systematic review	6 studies, n = 274	84.5% (95% CI, 79.2%-88.9%)	82.6% (95% CI, 77.1%-87.3%)	44.3 (95% CI, 15.3-127.9)	Pooled data for proximal and distal strictures could not be calculated due to lack of data.

CCA: cholangiocarcinoma; ERCP: endoscopic retrograde cholangio-pancreatography; PSC: primary sclerosing cholangitis; SOPOC: Single-operator per-oral cholangioscopy

Table 4. Primary studies on SOPOC: visualisation and diagnosis of biliary strictures

Outcome	Evidence source	Number of studies and patients	Sensitivity	Specificity	Diagnostic accuracy	Comments
Diagnosis through biopsy	Gerges et al. (2019), RCT	One study, 57 patients	SOPOC: 68.2% (15/22) TPB: 21.4% (3/14) P <0.01	SOPOC: 62.5% (5/8) TPB: 84.6% (11/13) p = 0.25	SOPOC: 66.7% (20/30) TPB: 51.9% (14/27) P = 0.25	In both arms, diagnosis was reported as malignant, benign or indeterminate. The authors included indeterminate samples in sensitivity/specificity calculations as part of the 'false' populations. Strictures were considered benign at the 6-month final diagnosis if malignancy was not determined.
	Yan&Tejaswi (2019), retrospective case review	One study, 22 patients (13 indeterminate strictures) (9 PSC surveillance)	SOPOC: 60% Cytology brushing: 37.5%	SOPOC: 100% Cytology brushing: 100%		
	Lee et al. (2019), prospective observational study	One study, 59 patients (31 SOPOC, 27 EUS-FNAB)	SOPOC: 92.3 (95% CI 74.9 to 99.1) EUS-FNAB: 96.0 (95% CI 79.7 to 99.9)	SOPOC: 100 (95% CI 47.8 to 100) EUS-FNAB: 96.3 (95% CI 89.2 to 100)	SOPOC: 93.6 (95% CI 84.8 to 100) EUS-FNAB: 96.3 (95% CI 89.2 to 100)	

Outcome	Evidence source	Number of studies and patients	Sensitivity	Specificity	Diagnostic accuracy	Comments
	Kaura et al. (2019), retrospective cohort study	One study, 92 patients	SOPOC (64/92): 43.3% (95% CI 25.5-62.6) Cytology (85/92): 44.7% (95% CI 28.6-61.7) FISH (85/92): 45.9% (95% CI 29.5-63.1) TPB (71/92): 44.1% (95% CI 27.2-62.1) Cytology + FISH (84/92): 56.8% (95% CI 39.5-72.9) Cytology + FISH + SOPOC (58/92): 71.4% (95% CI 51.3-86.8) Cytology + FISH + TPB (64/92): 64.5% (95% CI 45.4-80.8) Cytology + FISH + SOPOC + TPB (49/92): 69.2% (95% CI 48.2-85.7)	SOPOC: 97.1% (95% CI 84.7-99.9) Cytology: 89.4% (95% CI 76.9-96.5) FISH: 95.7% (95% CI 85.5-99.5) TPB: 97.3% (95% CI 85.8-99.9) Cytology + FISH: 89.4% (95% CI 76.9-96.5) Cytology + FISH + SOPOC: 86.7% (95% CI 69.3-96.2) Cytology + FISH + TPB: 84.8% (95% CI 68.1-94.9) Cytology + FISH + SOPOC + TPB: 82.6% (95% CI 61.2-95.0)		
	Gerges et al. (2019) , RCT	One study, 57 patients	SOPOC: 95.5% (21/22) TPB: 66.7% (10/15)	SOPOC: 66.7% (6/9)	SOPOC: 87.1 (27/31) TPB: 65.5 (19/29)	

Outcome	Evidence source	Number of studies and patients	Sensitivity	Specificity	Diagnostic accuracy	Comments
Diagnosis through visualisation			p = 0.2	TPB: 64.3% (9/14) p = 0.91	p = 0.05	
	Yan&Tejaswi (2019), retrospective case review	One study, 22 patients (13 indeterminate strictures) (9 PSC surveillance)	SOPOC: 100% Cytology brushing: 37.5%	SOPOC: 100% Cytology brushing: 100%		Cytology brushing was obtained in 8 out of 10 cases of malignant biliary stricture.
EUS-FNAB: Endoscopic ultrasound-guided fine needle aspiration biopsy ; FISH: fluorescence in situ hybridisation ; SOPOC: single-operator peroral cholangioscopy; TPB: transpapillary biopsy sampling; PSC: primary sclerosing cholangitis; RCT: randomised controlled trial						

Table 5. Diagnostic accuracy of SOPOC for indeterminate biliary strictures (after indeterminate/negative conventional ERCP)

Outcome	Evidence source	Number of studies and patients	Pooled sensitivity	Pooled specificity	Pooled diagnostics odds ratio	Comments
Diagnosis of malignant biliary strictures (following indeterminate ERCP)	Navaneethan et al. (2015), systematic review	4 studies, n = 148	74.7% (95% CI, 63.3%-84.0%)	93.3% (95% CI, 85.1%-97.8%)	46.0 (95% CI, 15.4-138.1)	
Diagnosis of CCA (following indeterminate ERCP)	Navaneethan et al. (2015), systematic review	4 studies, n = 148	67.3% (95% CI, 52.5%-80.1%)	93.3% (95% CI, 83.1%-98.7%)	32.1 (95% CI, 8.3-124.4)	

Table 6. SOPOC for therapeutic use: Systematic review characteristics

Study	Study design	Selection criteria	Intervention	Outcomes	Comments on risks of bias/applicability
Jin 2019	Systematic review and meta-analysis Fishman et al. (2019), n = 128 Maydeo et al. (2011), n = 64 Chen et al. (2011), n = 297 Draganov et al. (2011), n = 75 Kalaitzakis et al. (2012), n = 165 Sepe et al. (2012), n = 13 Alameel et al. (2012), n = 30 Patel et al. (2014), n = 69 Aljebreen et al. (2014), n = 13 Tieu et al. (2015), n = 88 Adler et al. (2015), n = 224 Kurihara (2016), n = 148 Bhandari et al. (2016), n = 34 Navaneethan et al. (2016), n = 105 Buxbaum et al. (2017), n = 42 Wong et al. (2017), n = 17 Laleman et al. (2017), n = 84 Ogura et al. (2017), n = 55 Shah et al. (2017), n = 108 Mizrahi et al. (2017), n = 198 Brewer et al. (2017), n = 407 Turowski et al. (2018), n = 206 Kamiyama et al. (2018), n = 42 Franzini et al. (2018), n = 48 Review period up to April 2018	Selection criteria: studies that used SOPOC for difficult bile duct stone removal with electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL); studies that enrolled more than 10 participants; and full-text articles in English. Exclusion criteria: (duplicate studies (based on the same primary study), in vitro studies, or animal studies; case reports, reviews, abstracts, editorials and letters to editor; and no data on any of the primary or secondary outcomes.	SOPOC with EHL or LL (SpyGlass and SpyGlass DS)	• Complete stone clearance • Single-session stone clearance • Number of sessions required for stone clearance • Adverse events	Authors applied the Newcastle-Ottawa Scale (NOS) for cohort studies to evaluate methodological quality of the included studies. The scale uses a point system with a maximum of nine points to appraise a study in three domains (eight items): selection, comparability, and outcome.

Table 7. Comparative studies of SOPOC for removal of biliary stones: design and characteristics

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Primary studies from Jin et al (2019)					
Buxbaum 2018	Randomised controlled trial Single centre, USA Recruitment period March 2013 to March 2016	Inclusion criteria: • Adult patients with an extrahepatic (common bile or common hepatic) duct stone greater than 1 cm in diameter based on ultrasonography, computed tomography, magnetic resonance imaging, or previous ERCP Exclusion criteria: • history of pancreaticobiliary malignancy or bile duct diversion surgery • age less than 18 years 68% of participants were women Previous ERCP (in past 3 months): 44 patients (74%)	Intervention: cholangioscopy-guided laser lithotripsy, using a single operator disposable cholangioscope with a reusable fibreoptic probe. Conventional therapies, including mechanical lithotripsy and papillary dilation, were also permitted (n = 42). Control: conventional therapy. Techniques used included baskets for mechanical lithotripsy, papillary dilation, and balloon extraction to facilitate stone removal, and in some cases simply balloon or basket (non-lithotripsy) extraction without papillary dilation. (n = 18) For all patients, treatment could be repeated at the discretion of the attending endoscopist, but patients remained in their assigned group. If the procedure was unsuccessful but it was deemed that clearance might be achieved with another attempt using the same endoscopic method, an additional procedure was performed. However, if it was felt that endoscopic clearance was impossible or very unlikely, the patient was referred to surgery.	• Successful endoscopic clearance of bile duct stones (primary outcome) • Procedure time • Fluoroscopy time • Number of procedures • Adverse events	Patients were blinded to assigned treatment. Blinding of clinical staff was not possible, but randomisation was computer generated by an individual not involved in the study and allocation assignments were concealed.

Franzini 2019	Randomised controlled trial Single centre, USA April 2014 to June 2016	Inclusion criteria: • Aged 18 years or older • Presence of difficult biliary stones, defined as multiple (more than 10), size greater than 15mm, presence of disproportion between the stone and distal common bile duct (greater than 2mm) or biliary stricture with a stone upstream Exclusion criteria: • Pregnancy • Previous gastrointestinal surgery or liver transplant • Acute cholangitis 74% of patients were female 81/100 had undergone previous ERCP	All patients underwent ERCP to confirm the presence of a complex biliary stone and conventional techniques were used in an attempt to remove the stone and clear the common bile duct. When these methods failed, patients were randomly assigned to: Intervention: single-operator cholangioscopy (using 1st-generation SpyGlass platform) plus electrohydraulic lithotripsy (= 50) Control: endoscopic papillary large balloon dilation (n = 50) In both groups, in case of failure, either biliary drainage with plastic stents or crossover to the other method was performed immediately. Patients who received a plastic stent were scheduled for crossover in a second attempt.	• Complete stone removal after 2 sessions with different techniques under analysis (primary outcome) • Adverse events • Procedure time • X-ray exposure time	Randomisation was computer-generated. Blinding not reported, but as randomisation was performed mid-procedure (after ERCP and conventional techniques were attempted), it is assumed that patients but not clinical staff were blinded to the intervention assigned. Two patients assigned to the intervention did not receive the allocated treatment due to a different diagnosis: these patients were excluded from the analysis. Twenty five patients crossed over because stone clearance using the assigned procedure failed.

Aljebreen 2014	Retrospective observational study Single centre, Saudi Arabia. Patients in the intervention arm were treated between February 2012 and June 2013. Patients in the control arm were treated between 2000 and January 2012.	Inclusion criteria: All patients who underwent treatment for difficult common bile duct stones. A difficult stone was defined as a stone that could not be removed from the bile duct despite endoscopic sphincterotomy, and using a basket, and/or balloon extractor, and/or mechanical lithotripter and/or after a balloon dilatation of the papilla of Vater. Mean number of ERCP attempts was 2 and 1.6 in the intervention and control arm respectively.	Intervention: single-operator cholangioscopy-guided electrohydraulic lithotripsy (n = 13) Control: extracorporeal shock wave lithotripsy (n = 45)	• Success rate • Number of sessions required • Complications	Data on number of endoscopic sessions required is not clearly reported and has been excluded from our analyses.
Other primary studies					

Ridtitid 2018	Prospective cohort studies, comparing against retrospective data. Single centre, Thailand December 2015 to October 2016	Inclusion criteria: adult patients with common bile duct stones (<15 mm diameter). Exclusion criteria: history of bile duct surgery, bile duct stricture, bile duct tumours, severe comorbid disease For the SOPOC cohort: Mean age 64 years (SD 17 years) 26 males	SOPOC (SpyGlass DS, Boston Scientific) Comparator: conventional ERCP	• Feasibility of SOPOC versus conventional ERCP • Safety • Radiation exposure during treatment	Comparator cohort was identified retrospectively through endoscopy databases, and matched 1:1 with SOPOC patients using propensity score matching analysis. Authors report baseline characteristics between the SOPOC and conventional ERCP cohort to be broadly similar.

Table 8. SOPOC compared to conventional therapy: therapeutic outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Successful stone clearance rate (all patients)	Buxbaum, 2018. Randomised controlled trial	One study, 60 patients	SOPOC: 39/42 (93%); conventional therapy: 12/18 (67%)	Odds ratio 6.50 [1.41, 30.0] (favours SOPOC)	Although differences between groups are statistically significant, small patient numbers and wide confidence intervals indicate considerable uncertainty.
	Rididitid 2018	One study, 100 patients	SOPOC: 45/50 (90%) ERCP: 49/50 (98%) (p = 0.20)		Common bile duct stones
Successful stone clearance rate (patients with previous ERCP)	Buxbaum, 2018. Randomised controlled trial	One study, 44 patients	SOPOC: 28/31 (90%); conventional therapy: 7/13 (54%)	Odds ratio 8.0 [1.59, 40.2] (favours SOPOC)	Although differences between groups are statistically significant, small patient numbers and wide confidence intervals indicate considerable uncertainty.
Mean procedure time (all patients)	Buxbaum, 2018. Randomised controlled trial	One study, 60 patients	SOPOC: 120.7 min; conventional therapy 81.2 min	Mean difference 38.8 min [16.7, 60.8] (favours conventional therapy)	
	Ridtitid 2019	One study, 100 patients	SOPOC: 37 minutes (SD 10 minutes) ERCP: 34 minutes (SD 12 minutes) (p = 0.16; favours neither)		

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Mean procedure time (patients with previous ERCP)	Buxbaum, 2018. Randomised controlled trial	One study, 44 patients	SOPOC: 129.7 min; conventional therapy 98.5 min	Mean difference 31.1 min [3.2, 59.1] (favours conventional therapy)	

Table 9. SOPOC compared to endoscopic papillary large balloon dilation (PLBD): therapeutic outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Successful stone clearance on first procedure	Franzini 2019. Randomised controlled trial	One study, 100 patients	SOPOC: 37/50 (74%); PLBD: 36/50 (72%)	Odd ratio 1.11 [0.46, 2.68] (favour neither intervention]	Study authors excluded two patients and conducted a per-protocol analysis. Intent-to-treat analysis (including all randomised patients) is reported here. Study includes both newly treated patients and those who had previous undergone ERCP (81%).
Mean procedure time (all patients)			SOPOC: 72.3 min; PLBD: 47.1 min	Mean difference 25.2 min [12.5, 22.3] (favours PLBD)	

Table 10. SOPOC compared to extracorporeal shock wave lithotripsy (ESWL): therapeutic outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Relative effect [95% CI] (interpretation)	Comments on reliability
Successful stone clearance	Aljebreen 2014, observational study	One study, 58 patients	SOPOC: 13/13 (100%); ESWL: 30/45 (66.6%)	NR	
Incidence of complications			SOPOC: 1/13 (7.7%%); ESWL: 7/45 (15.5%)	NR	

6.5. Patient management

This review identified four primary studies that reported outcomes relating to patient management. In the first, a single independent reviewer retrospectively reviewed SOPOC procedures (n = 365) performed at a single centre between March 2007 and December 2014 (Reuterwall et al. 2019). The reviewer graded each procedure using a predefined 4-grade scale:

1. No diagnostic or therapeutic value
2. Information gained did not impact clinical decision making and/or patient management
3. Information gained had an impact on clinical decision making and/or patient management
4. Information gained was essential and critical for clinical decision making and/or patient management.

Indications for SOPOC included 'difficult' common bile duct stones or intrahepatic stones (15.9%), indeterminate stricture (non-PSC patients; 32.6%), indeterminate strictures (PSC patients; 22.5%), cystic pancreatic lesions (including intraductal papillary mucinous neoplasm, IPMN; 17.5%), and chronic pancreatitis plus lithotripsy (5.5%). The authors found the SOPOC added significant clinical value (Grade 3 and 4) in 64% of cases (Reuterwall et al. 2019).

Maydeo et al. (2019) reported impact on management for difficult bile duct stones, based on data from a national registry. The authors reported that SOPOC altered patient diagnosis and/or therapy in 91% of patients (143/156). In 83 patients, the need for previously scheduled stone extraction therapy was avoided due to successful stone clearance with SOPOC.

In the third study, Arnelo et al. (2014) reported that SpyGlass for the evaluation of IPMN provided additional diagnostic information in 95% (39/41) of cases, and findings were considered to have affected the clinical decisions made during the multidisciplinary team conferences in 76% of cases. Finally, Prat et al. (2019) evaluated the impact of SOPOC on the management of indeterminate biliary strictures through a prospective multicentre trial. Adequacy between the patient management (as anticipated by the investigators) and the definitive diagnosis was significantly higher after SOPOC versus before SOPOC ($p < 0.0001$), and a change in planned management was seen in 60.7% of cases.

6.6. Ongoing trials

We identified 15 recently completed or ongoing clinical trials on the use of SOPOC, for either diagnostic or therapeutic purposes. These are listed in Table 11.

Table 11. Ongoing primary studies for SOPOC

Title	Setting, Identifier	Target participants	Estimated study completion
Evaluating Suspected Intraductal Papillary Mucinous Neoplasms (IPMN) With SpyGlass Pancreatoscopy	Finland (single centre) NCT03062124	60	December 2019
Evaluation of the Utility of Single-operator Digital Cholangioscopy During Endoscopic Retrograde Cholangiopancreatography in the Diagnosis of Malignant and Benign Biliary Strictures	China (single centre) NCT03307382	40	December 2019

Title	Setting, Identifier	Target participants	Estimated study completion
Italian Registry of ERCP With SpyGlass	Italy (single centre) NCT04009746	150	December 2020
Saline Irrigation Reduces the Residual Bile Duct Stones After ERCP: a Single-arm Prospective Study	China (single centre) NCT03701009	47	January 2020
Assessment of Cholangio-pancreatoscopy for the Diagnosis and the Treatment of Biliary and Pancreatic Diseases Trial " EASYSPY "	France (multi-centre) NCT03190343	67	January 2020
Clinical Feasibility and Efficacy of a New Digital Single-operator Peroral Cholangiopancreatioscopy System: a Multicenter Registry	US (multi-centre) NCT02776709	200	July 2020
Prospective, Multi-center, Randomized Controlled Study Comparing Endoscopic Clearance of Non-Complex Biliary Stones Using Fluoroscopy/Radiation-Free Direct Solitary Cholangioscopy (DSC) to Standard of Care Endoscopic Retrograde Cholangiography (ERC)	US, India, Italy, Japan, Netherlands, Thailand (multi-centre) NCT03421340	250	January 2021
Cholangioscopy in Primary Sclerosing Cholangitis (PSC)	US, Canada, Netherlands, Norway (multi-centre) NCT03766035	105	August 2021
Randomized Controlled Trial of SpyGlass DS Peroral Cholangioscope Guided Laser Lithotripsy or Electrohydraulic Lithotripsy Versus Conventional Basket Mechanical Lithotripsy for Endoscopic Removal of Complicated Bile	China (single centre) NCT03244163	86	December 2021
Primary Peroral Cholangioscopy Versus Endoscopic Retrograde Cholangiopancreatography (With Conventional Sampling - Brushing and Forceps Biopsy- Completed by Fluorescence In Situ Hybridization) in the Diagnosis of Biliary Strictures	Czech Republic (single centre) NCT04010734	66	June 2022
Digital Catheter Based Pancreatoscopy (SpyGlassDS) for the Management of Symptomatic Pancreatic Duct Stones in Selected Patients With Chronic Pancreatitis	Germany (single centre) NCT04131010	43	December 2022

Title	Setting, Identifier	Target participants	Estimated study completion
Per-oral Pancreatoscopy-guided Lithotripsy vs. Extracorporeal Shock Wave Lithotripsy in Chronic Pancreatitis	US (single centre) NCT04115826	150	December 2023
Intra-operative Pancreatoscopy in Patients With Intraductal Papillary Mucinous Neoplasm (IPMN)	US, China, India, Japan, Netherlands, Sweden (multi-centre) NCT03729453	200	July 2026
Extracorporeal Shock Wave Lithotripsy Versus Single Operator Pancreatoscopy and Intraductal Lithotripsy for the Treatment of Pancreatic Duct Stones	US NCT04158297	60	November 2022

7. Safety

Safety data for all studies are reported in Table 12. Overall, the comparative studies showed similar or reduced adverse event rates with SOPOC compared to other modalities. Commonly reported adverse events included cholangitis, pancreatitis and post-sphinctorectomy bleeding.

Table 12. SOPOC: safety outcomes

Evidence source	Number of studies and patients	Absolute effect	Comments on reliability
Comparative safety outcomes			
Gerges et al. (2019)	One study, 60 patients	SOPOC: 6.5 (2/31) TPB: 10.3 (3/29) P = 0.59	
Lee 2019,	One study, 59 patients	SOPOC: 2/37 (6.3%) EUS-FNAB: 1/27 (3.7%)	
Buxbaum, 2018. Randomised controlled trial	One study, 60 patients	SOPOC: 4/42 (9.5%); Conventional therapy: 2/18 (11.1%)	Odds ratio 0.8 [0.1, 5.0] (favours neither treatment)
Kaura 2019	One study, 92 patients	SOPOC alone: 7.8% TPB: 18.3% P = 0.07	Kaura 2019 did not report full safety data for all interventions assessed in the study, particularly for the full population (PSC and non-PSC). Therefore the safety data provided may not accurately represent the cohort.
Franzini 2019. Randomised controlled trial	One study, 100 patients	SOPOC: 2/50 (4%); PLBD: 6/50 (12%)	Odds ratio 0.31 [0.06, 1.59] (favours neither intervention)
Ridtitid 2018	One study, 100 patients	**SOPOC: 5/50 total (10%)** 2/50 (4%) mild pancreatitis 2/50 (4%) post-sphinctorectomy bleeding 1/50 (2%) cholangitis **ERCP: 8/50 (16%) total** 2/50 mild pancreatitis 4/50 (8%) post-sphinctorectomy bleeding 1/50 (2%) duodenal perforation 1/50 (2%) cholangitis	
Aljebreen 2014, observational study	One study, 58 patients	SOPOC: 1/13 (15.5%); ESWL: 7/45 (7.7%)	
Non-comparative safety outcomes			
Yan 2019, retrospective case review	One study, 50 patients	2/50 (4%) cases 1 post-sphinctorectomy bleeding 1 post-procedural cholangitis	

Evidence source	Number of studies and patients	Absolute effect	Comments on reliability
Jang 2019	One study, 105 patients	7/105 (6.7%) 3/105 (2.9%) pancreatitis 3/105 (2.9%) cholangitis 1/105 (1%) bile duct injury	
Urban 2018	One study, 30 patients	2/30 cholangitis	One major and one minor complication of SOPOC occurred. These included two cases of cholangitis. One (3%) female patient with intrahepatic cholangiocarcinoma passed away due to cholangitis despite biliary drainage and antibiotic treatment. The 30-day mortality in the entire group of patients was two (7%). The other patient died due to the cardiovascular comorbidities.
Canena 2019	One study, 17 patients	**6/17 (35.3%) total** 4/17 (23.5%) fever 1/17 (5.9%) mild pancreatitis 1/17 (5.9%) pain	
Bokemeyer 2019	One study, 60 patients	**12/75 (16.0%) total** 8/75 (10.7%) cholangitis 4/75 (5.3%) pancreatitis	
Ang 2019	One study, 28 patients	**7/28 (25%) total** 5/28 (10.6%) cholangitis 1/28 (2.1%) pancreatitis 1/28 (2.1%) sealed perforation after LL	
Sandha 2018	One study, 51 patients	**7/51 (14%) total** 4/51 mild bleeding from EHL 1/51 gastroesophageal junction tear 1/51 cystic duct stump leak 1/51 acute pancreatitis	
Ogawa 2018	One study, 13 patients	**0/13 (0%) total**	
Ogura 2019	One study, 21 patients	1/21 (5.8%) mild pancreatitis	

Evidence source	Number of studies and patients	Absolute effect	Comments on reliability
Arnelo et al. (2014)	One study, 41 patients	**7/41 (17%) pancreatitis**	2 cases of pancreatitis were considered mild and 4 were considered moderate. With the final case, the patient died due to respiratory failure later in the study.
Sejpal et al. (2019)	One study, 93 patients	**3/93 (3.2%) total** 1/93 mild cholangitis 2/93 moderate pancreatitis	
Maydeo et al. (2019)	One study, 156 patients	**3/156 (1.9%)** 1/156 pancreatitis 1/156 perforation due to LL 1/156 cholangitis	
EHL: electrohydraulic lithotripsy; ERCP: endoscopic retrograde cholangiopancreatography; ESWL: extracorporeal shock wave lithotripsy; EUS-FNAB: Endoscopic ultrasound-guided fine needle aspiration biopsy; LL: laser lithotripsy; SOPOC: single operator peroral choliangioscopy; primary sclerosing cholangitis: endoscopic papillary large balloon dilation; PSC: primary sclerosing cholangitis; TPB: transpapillary biopsy sampling			

8. Cost effectiveness

8.1. Health economic evidence review

The titles and abstracts of records identified in the search for this research question were screened and five health economic studies were deemed potentially relevant (Kazumichi et al. 2012, Nam et al. 2013, Sandha et al. 2018, Njei et al. 2017, Deprez et al. 2018). The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, two studies were excluded from the review as they did not contain relevant economic information (Kazumichi et al. 2012, Nam et al. 2013). The remaining three studies were included in the review and are summarised in the tables below (Sandha et al. 2018, Njei et al. 2017, Deprez et al. 2018). All of the studies were only partially applicable to NHS Wales as they considered healthcare systems in other countries.

Njei et al. (2017) described a cost-utility analysis which considered the cost effectiveness of five different strategies for diagnosing cholangiocarcinoma in people with primary sclerosing cholangitis:

1. ERCP with bile duct brushing for cytology
2. ERCP with brushings for cytology and fluorescence in situ hybridisation (FISH)-tristomy
3. ERCP with brushings for cytology and FISH-polysomy
4. ERCP with intraductal biopsy sampling
5. SOPOC with targeted biopsy sampling

The results suggested that, in comparison to ERCP with brushings for cytology and FISH-polysomy, the use of SOPOC was cost-effective with an ICER of $39,277 (£30,077) per QALY below a threshold of $50,000 (£38,143) per QALY. Furthermore, it was reported that SOPOC had a 100% probability of being cost-effective at a threshold of $50,000 (£38,143) per QALY in both deterministic and probabilistic sensitivity analysis. However, several limitations were identified in the analysis. Most notably, the quality of life values used to generate QALYs were not reported and the overall QALY estimates seem low (< 1 QALYs for each strategy over the patient's lifetime). It also appears that uncertainty may not have been fully explored based on the approach adopted in probabilistic sensitivity analysis. It is unclear whether uncertainty was fully explored in deterministic sensitivity analysis as it was not fully described.

Deprez et al. (2018) and Sandha et al. (2018) were not full cost-utility analyses but estimated costs associated with using SOPOC alongside the cost of comparators. Deprez et al. (2018) estimated that the use of SOPOC may lead to cost savings when used therapeutically in people with difficult-to-remove bile duct stones and when used diagnostically in people with indeterminate biliary strictures. However, several limitations were identified in the analysis. Most notably, the cost estimates for the diagnostic component focuses only on true positive and false negative results (i.e. patients with the disease). This will underestimate the overall cost as the costs associated with false positive and true negative results have not been considered. This may also lead to missing some key differences between the diagnostic approaches (if they differ in terms of specificity).

Sandha et al. (2018) estimated the cost of SOPOC in people with difficult-to-remove bile duct stones who had at least one previous ERCP. The results were in agreement with those from Deprez et al. (2018) showing that the use of SOPOC may lead to cost savings in comparison to conventional strategies. However, limitations were also identified with this study. Most notably the upfront capital cost of the SOPOC system was not included in the analysis.

Table 13. Summary of included health economic study: Njei et al. 2017

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Njei et al. 2017 **Country:** United States **Type of economic analysis:** Cost utility analysis **Perspective:** US healthcare perspective **Currency:** US dollars ($) **Price year:** 2015 **Time horizon:** Lifetime **Discounting:** n/a Costs and life years were discounted at 3% per annum **Source of funding:**	**Population** People with primary sclerosing cholangitis-induced biliary strictures **Diagnostic strategies:** 1. ERCP with bile duct brushing for cytology 2. ERCP with brushings for cytology and FISH-tristomy 3. ERCP with brushings for cytology and FISH-polysomy 4. ERCP with intraductal biopsy sampling 5. SOPOC with targeted biopsy sampling **Study design** Decision tree for initial diagnostic process with Markov model to estimate subsequent disease progression.	**Source of baseline and effectiveness data:** Probability estimates for other inputs (including prevalence and survival data) were sourced from previously published data. Diagnostic accuracy data (including sensitivity and specificity) were generated from a systematic review and meta-analysis of published studies. **Source of resource use and cost data:** Cost estimates were sourced from the 2015 Centers for Medicare and Medicaid standardised hospital accounting reports. Since this information gives the amount that hospitals billed rather than the actual cost, the figures were adjusted using a cost-to-charge ratio to remove the difference in mark-up costs. **Source of quality of life data:**	**Costs** 1. ERCP with brushing for cytology $9,309 (£7,101) 2. ERCP with brushings for cytology and FISH-tristomy $45,210 (£34,489) 3. ERCP with brushings for cytology and FISH-polysomy $6,470 (£4,936) 4. ERCP with intraductal biopsy sampling $9,281 (£7,080) 5. SOPOC with targeted biopsy sampling $15,033 (£11,468) **QALYs** 1. ERCP with brushing for cytology 0.83 2. ERCP with brushings for cytology and FISH-tristomy 0.52 3. ERCP with brushings for cytology and FISH-polysomy 0.76 4. ERCP with intraductal biopsy sampling 0.84 5. SOPOC with targeted biopsy sampling	**Applicability** Analysis was deemed to be only partially applicable as it considered the US healthcare perspective which differs substantially from NHS Wales. Furthermore the discount rate applied in the analysis (3%) does not match that applied in UK evaluation (3.5%) **Limitations** Several potentially serious limitations were identified: • Quality of life values applied in the analysis were not reported and the source of the values is not clear. • Overall QALYs estimated for each strategy are very low suggesting extremely high mortality rate. Seems unlikely given prevalence of disease applied in the mode is 20-30%. • One-way sensitivity analysis appears to have

Study details	Study population and design	Data sources	Results	Quality assessment
Lead author received research support for the study from the National Institutes of Health. **Potential conflict of interest:** Authors also disclosed financial relationships relevant to the publication: One author listed as consultant for Boston Scientific and Olympus and another listed as a consultant for Janssen, AbbVie and Takeda.		Utility estimates were sourced from previously published data. However, the utility estimates used in the analysis were not reported and it is unclear how they were derived from the study references provided in the article.	0.97 **ICER (cost per QALY)** ICERs calculated by comparing each strategy against ERCP with brushings for cytology and FISH-polysomy (lowest cost strategy): 1. ERCP with brushing for cytology $39,427 (£30,077) per QALY 2. ERCP with brushings for cytology and FISH-tristomy Dominated (more costly and less effective) 1. ERCP with intraductal biopsy sampling $34,273 (£26,145) per QALY 2. SOPOC with targeted biopsy sampling $39,277 (£29,963) per QALY **Sensitivity analysis** It is reported that one-way sensitivity analysis was conducted and that the results indicated that SOPOC was cost-effective in all analyses (at a threshold of $50,000 (£38,143) per QALY). However, the results of the one-way analysis were not presented and the changes to inputs were not reported.	been conducted but results are not presented and the variations explored in the analysis are not reported • In the probabilistic sensitivity analysis, it was assumed that all variables followed a triangular distribution. This does not match best practice and is unlikely to accurately reflect uncertainty

Study details	Study population and design	Data sources	Results	Quality assessment
			Probabilistic sensitivity analysis showed that SOPOC had a 100% probability of being cost-effective at a threshold of $50,000 (£38,143) per QALY.	

Abbreviations
ERCP: endoscopic retrograde cholangiopancreatography; FISH: fluorescence in situ hybridisation; SOPOC: single operator per-oral cholangioscopy; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

Table 14. Summary of included health economics study: Deprez et al. 2018

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Deprez et al. 2018 **Country:** Belgium **Type of economic analysis:** Budget impact analysis **Perspective:** Belgian hospital perspective **Currency:**	**Population** 1) People with difficult-to-remove bile duct stones 2) People with indeterminate biliary strictures **Study design** Two decision-tree models were developed. One considering treatment options for the management of difficult to-remove bile duct stones and one for the diagnosis of strictures. **Management strategies** In the management model people with difficult stones are initially treated with ERCP and lithotripsy. If	**Source of baseline and effectiveness data:** In the management model, the success rate with intraductal cholangioscopy (87%) was sourced from a review including eight series and the authors own experience. The success rate for ERCP and lithotripsy (62%) was sourced from a study reporting outcomes in 304 patients treated at a hospital in Taiwan between 1996 and 2002. The value appears to be based upon the number of patients	**Total costs** In the management model for population of 62 patients with difficult stones after unsuccessful treatment with first ERCP and lithotripsy: Comparator: • €669,087 (£608,632) for population • €10,792 (£9,817) per patient Intervention: • €596,332 (£542,450) for population of 62 patients	**Applicability** Analysis was deemed to be only partially applicable as it considered the Belgian healthcare perspective rather than the NHS Wales perspective. **Limitations** Several potentially serious limitations were identified: • Generation of device not stated Management model

Study details	Study population and design	Data sources	Results	Quality assessment
Euros (€) **Price year:** 2016 **Time horizon:** 1 year **Discounting:** Not applied given short time horizon. **Source of funding:** Not reported. **Potential conflict of interest:** Lead author has a consultant agreement with Boston Scientific.	this is unsuccessful, then people receive: 1. Intraductal cholangioscopy and holmium laser fibre or electrohydraulic lithotripsy (intervention) 2. a second ERCP and lithotripsy (comparator) In both arms, if the second procedure is unsuccessful, people are assumed to have surgery at a later date. **Diagnostic strategies** In the diagnostic model, people with indeterminate strictures receive: 1. Intraductal cholangioscopy and optically guided biopsy (intervention). 2. ERCP and brushing with biopsy (comparator) Patients with false negative results were assumed to be re-evaluated with a repeat diagnostic procedure (i.e. ERCP + brushing in the comparator arm and intraductal cholangioscopy biopsy in the intervention arm). Those remaining undiagnosed after the repeat procedure were assumed to receive a diagnosis at a later point in time with a more invasive surgical procedure.	whose stone was cleared after two rounds of ERCP and lithotripsy. In the diagnostic model, the sensitivity of intraductal cholangioscopy and optically guided biopsy (86%) was based upon two studies (one single-centre prospective cohort study and one multicentre observational study). The sensitivity for ERCP + brushing procedure (45%) was sourced from a systematic review and meta-analysis that compared the effectiveness of biliary brush cytology with that of intraductal biopsy for the detection of malignant biliary strictures. The specificity of each strategy was not considered in the analysis as it focused only on patients with malignancies (reported to be 73% of those that presented). **Source of resource use and cost data:**	• €9,618 (£8,749) per patient Incremental (Intervention minus comparator): • Saves €72,755 (£66,181) for population • Saves €1,173 (£1,067) per patient In the diagnostic model for population of 49 patients with indeterminate stricture (36 of whom have malignancies): Comparator • €242,316 (£220,421) for population • €6,731 (£6,123) per patient with malignancy Intervention • €229,325 (£208,604) for population • €6,370 (£5,794) per patient with malignancy Incremental (Intervention minus comparator): • Saves €12,990 (£11,816) for population • Saves €361 (£328) per patient	• Unclear whether model accounts for number of procedures needed to clear stones. The study states that the source for the effectiveness of intraductal cholangiography found that 79% of stones were cleared during one procedure • Study notes that the 87% success rate of intraductal cholangioscopy may be an overestimate Diagnostic model • True negatives and false positives were not considered in the analysis. • Repeat tests following a false negative result were assumed to have the same accuracy as in the previous round. • Costs associated with treating malignancy were not considered in the analysis • Study notes that sensitivity for ERCP with brushing may be overstated • No information is given on the time interval between the initial diagnostic procedure and the second. • False negatives after the second round of diagnostic procedures are assumed to

Study details	Study population and design	Data sources	Results	Quality assessment
		Data on unit costs, duration of procedures, length of hospital stay and resource consumption were derived from two Belgian hospitals: Gasthuisberg Leuven and Cliniques Universitaires St.-Luc. The cost of open surgery interventions was estimated using the All Patient Refined-Diagnosis Related Group (APR-DRG) tariffs. The equipment cost for intraductal cholangioscopy was incorporated in the analysis, assuming a 5-year amortization schedule.	**Sensitivity analysis** One-way deterministic sensitivity analysis was performed by changing some model inputs by ± 10%. Parameters varied in sensitivity analysis for the management model were: • percentage of mechanical lithotripsy success • percentage of Intraductal cholangioscopy success • cost of ERCP and lithotripsy • cost of Intraductal cholangioscopy and laser • Intraductal cholangioscopy equipment cost Parameters varied in sensitivity analysis for the diagnostic model were: • total percentage of malignancies • brushing sensitivity • Intraductal cholangioscopy sensitivity • cost of ERCP and brushing • cost of Intraductal cholangioscopy and optically guided biopsy.	receive a diagnosis later in time, involving a more invasive surgical procedure.
Additional notes Management model				

Study details	Study population and design	Data sources	Results	Quality assessment
• Difficult bile duct stones were defined as stones that could not be removed via conventional methods (ERCP with standard extraction balloons, baskets or lithotriptors; large endoscopic papillary balloon dilation) • People in the comparator arm receive a second hospitalisation, whereas those in the intervention arm undergo intraductal cholangioscopy during the same procedure as the first ERCP and lithotripsy. <u>Diagnosis model</u> • Indeterminate biliary strictures defined as strictures that could not be definitively diagnosed with conventional ERCP sampling techniques (brushings, intraductal biopsy). • Assumption that all strictures, even type III and type IV, were studied with ERCP rather than with percutaneous cholangiography.				
Abbreviations ERCP: endoscopic retrograde cholangiopancreatography				

Table 15. Summary of included health economics study: Sandha et al. 2018

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Sandha et al. 2018 **Country:** Canada **Type of economic analysis:** Cost analysis alongside clinical outcomes **Perspective:** Canadian healthcare system	**Population** People with difficult common bile duct stones who had at least one previous ERCP, during which conventional methods to extract the stone were unsuccessful. **Study design** Single centre retrospective study of SOPOC procedures at University of Alberta Hospital **Treatment strategies**	**Source of baseline and effectiveness data:** Retrospective chart review **Source of resource use and cost data:** The cost per case included all ERCPs required to clear the difficult common bile duct stone(s) following the initial failed ERCP. For the cost per person of SOPOC, cost items include SOPOC (legacy or digital), electrohydraulic lithotripsy probe, cost of	**Costs** SOPOC $4,555 (£2,871) ‡$2,647 (£1,668) OCBDE $7,766 (£4,895) LCBDE $6,175 (£3,892) Incremental (SOPOC compared with OCBDE):	**Applicability** Analysis was deemed to be only partially applicable as it considered the Belgian healthcare perspective rather than the NHS Wales perspective. **Limitations** Several potentially serious limitations were identified: • Costs of SOPOC are based on actual costs from cohort, whereas costs of OCBDE and LCBDE are projected

Study details	Study population and design	Data sources	Results	Quality assessment
Currency: Canadian dollars ($) **Price year:** Not reported **Time horizon:** Not reported but appears to cover period relating to procedure and complications. **Discounting:** Not reported. **Source of funding:** Not reported. **Potential conflict of interest:** One of the authors is a consultant and member of the medical advisory board for Boston Scientific.	Intervention: Single-operator per-oral cholangioscopy (SOPOC) Comparator: open common bile duct exploration (OCBDE) Comparator (2): laparoscopic common bile duct exploration (LCBDE)	equipment based on actual resource use, anaesthesia/sedation, staff costs, all adverse events, subsequent surgeries, and hospital stays. Upfront cost of the SOPOC system or surgical instruments not included. Costs of cholecystectomy were not included. For the comparison between the actual cost of SOPOC and projected costs of OBCDE and LCBDE, costs included staff costs, postoperative length of stay. The average length of stay was based on expert opinion from local surgeons and published data from the provincial Alberta Health Services database. Costs were based on the Alberta Health Services reimbursement schedule	€3,211 (£2,024) saved by using SOPOC Incremental (SOPOC compared with LCBDE): €1,620 (£1,021) saved by using SOPOC Costs for treating the most common adverse events were also reported: $4,977 (£3,137) for bile leak $5,216 (£3,288) for an intra-abdominal haemorrhage $3,701 (£2,333) for intra-abdominal abscess.	• Upfront capital cost of the SOPOC system was not included in the analysis • Length of stay used in cost comparison for OCBDE (4 days) and LCBDE (2 days) based on expert opinion. However, study states that published data suggests a length of stay of 12.6 days and 4.2 days respectively. • Total costs for each strategy do not include costs of adverse events • Study states the cost of adverse events but not the rates of these individual adverse events, so costs could not be recalculated for this EAR • In eight patients, an additional 14 ERCPs were performed after SOPOC. Two of these patients had a total of seven ERCPs, but the indication for these subsequent procedures was a CBD stricture rather than the stone. Therefore, the cost of these extra procedures was not factored into the overall cost of SOPOC • In the remaining six patients, seven ERCPs were required to clear the CBD of remnant fragments of stone. The cost associated with these procedures

Study details	Study population and design	Data sources	Results	Quality assessment
				was included in the overall cost of SOPOC.

†Prices converted and inflated using an assumed price year of 2015, which matches the closing date of the data collection period in the study
Additional notes
All patients referred for SOPOC had at least one ERCP, during which conventional methods to extract the stone(s) failed.
People are included in the study if conventional methods of stone extraction have failed. Conventional methods include mechanical basket lithotripsy and dilation-assisted stone extraction
All SOPOC procedures, done as outpatient day procedures, were planned electively and scheduled with general anesthesia (GA). However, if GA was unavailable, endoscopist-administered conscious sedation was performed.
Clinical success was defined as complete clearance of the common bile duct as evidenced by cholangiography done during the index procedure or on any subsequent procedure done to extract any remaining fragments.
People in the study either received SOPOC with the original SpyGlass Legacy single-operator direct visualisation system (n=49) or a newer Digital SpyGlass system (n=9) when this became commercially available

Abbreviations
ERCP: endoscopic retrograde cholangiopancreatography; LCBDE: laparoscopic common bile duct exploration; OCBDE: open common bile duct exploration; SOPOC: single-operator per oral cholangioscopy;

8.2. Exploratory economic analysis for SOPOC in diagnostic setting

An exploratory cost-utility analysis was undertaken to compare SOPOC and conventional therapy when used diagnostically to assess potential malignancy in patients with indeterminate biliary strictures. Two scenarios were considered:

1. SOPOC or standard practice for indeterminate biliary strictures
2. SOPOC or standard practice for indeterminate biliary strictures after inconclusive conventional ERCP

8.2.1. Diagnostic accuracy

Base case estimates of the diagnostic accuracy of SOPOC or standard practice for indeterminate biliary strictures were sourced from Gerges 2019, an RCT comparing SOPOC guided biopsy against ERCP guided brushing for indeterminate biliary strictures.

Gerges 2019 reported sensitivity and specificity values of 21% and 85%, respectively for ERCP guided brushing and 68% and 63%, respectively for SOPOC guided biopsy. However, note that sensitivity and specificity calculations were complicated in Gerges 2019 by the inclusion of an indeterminate outcome in addition to positive and negative. As such, Gerges 2019 additionally reports outcomes for malignant versus non-malignant classification (essentially assuming that indeterminate outcomes would be classified as non-malignant/negative). In this scenario, sensitivity values remain the same but the specificity of each procedure increases to 100%. This latter scenario is used in the base case analysis as it can be more readily linked to patient management.

For the purpose of sensitivity analysis, HTW derived a third scenario using Gerges 2019, in which it was assumed that indeterminate outcomes would be classified as positive. In this scenario, the sensitivity and specificity ERCP guided brushing was estimated to be 57% and 85%, respectively while the sensitivity and specificity of SOPOC was estimated to be 73% and 63%, respectively.

Diagnostic accuracy values for SOPOC for indeterminate biliary strictures after inconclusive conventional ERCP were sourced from the Navaneethan 2015 systematic review. Navaneethan 2015 reported that the sensitivity and specificity of SOPOC following an indeterminate ERCP was 75% and 93%, respectively.

Standard practice for patients with an indeterminate biliary stricture after ERCP is not entirely clear and is likely to be variable. It is possible that a repeat ERCP may be used or that surgery may be undertaken. Diagnostic accuracy data for repeat ERCP and surgery were not available. Therefore it was assumed that the accuracy of ERCP would be equivalent to that of ERCP when used for indeterminate biliary strictures in general (based on Gerges 2019). However, it should be noted that this may overestimate its accuracy in this setting. Surgery was assumed to have 100% sensitivity and specificity.

Table 16 summarises the diagnostic accuracy values applied in the base case analyses. Note that alternative scenarios are explored in sensitivity analysis.

Table 16. Diagnostic values applied in the analyses

Test	Sensitivity	Specificity	Source
Indeterminate biliary strictures			
SOPOC guided biopsy	68%	100%	Gerges 2019
ERCP guided brushing	21%	100%	Gerges 2019

Test	Sensitivity	Specificity	Source
Indeterminate biliary strictures after inconclusive conventional ERCP			
SOPOC guided biopsy	75%	93%	Navaneethan 2015
Repeat ERCP guided brushing	21%	100%	Gerges 2019
Surgery	100%	100%	Assumption

8.2.2. Prevalence of malignancy

The prevalence of malignancy in the two populations considered in the analysis were estimated using prevalence data from studies included in the Navaneethan 2015 systematic review. The prevalence of malignancy in patients with indeterminate biliary strictures was estimated to be 44%. In patients with indeterminate biliary strictures after an ERCP, prevalence was estimated to be 63%.

The reason for the difference observed between prevalence rates in the two populations is not fully known and may be a result of random variability between studies. One possible explanation is that the higher prevalence rate may be a result of the initial ERCP ruling out most patients without disease (because specificity is high) but failing to detect patients with malignancy (because sensitivity is low).

It is also unclear whether these rates would be fully representative of the prevalence rate expected in clinical practice. The impact of using alternative prevalence rates was therefore explored in sensitivity analysis.

8.2.3. Cost data

The cost associated with a diagnostic ERCP with biopsy or cytology was estimated from NHS Reference costs 2017/18. The relevant NHS procedure code was identified as GB10Z, which equates to 'diagnostic ERCP, with biopsy or cytology'. The average cost per procedure in NHS Reference costs 2017/18 was reported to be £1,096.

Costs associated with SOPOC were estimated using the list price reported in Deprez 2018 in conjunction with the relevant procedure cost from NHS Reference costs 2017/18. Deprez 2018 reported that the list price for SOPOC in Belgium was €1,760. This value was converted and inflated to UK 2018 prices, giving an estimate of £1,608. The relevant NHS procedure code was assumed to be the same as that estimated above for a diagnostic ERCP with biopsy (£1,096). Thus total cost for the spyglass procedure was estimated to be £2,704.

The cost of exploration surgery for diagnosis was estimated from NHS Reference costs 2017/18. The relevant procedure codes were estimated to be GA07 and GA06, which equate to intermediate or major hepatobiliary or pancreatic procedures. A weighted average cost across the procedures was calculated using recorded episodes in the NHS Reference costs database. It was estimated that the average cost per procedure was £4,687.

Management costs for patients with malignant disease were also estimated. In order to do this, it was necessary to estimate the proportion of detected malignancies that were likely to be treated surgically. Based on an assumption made by clinical experts in the analysis by Vergel et al. 2006, it was assumed that 10% of patients with malignancy would have resectable disease and receive surgical intervention. Note that the analysis assumes that the proportion of patients with resectable disease would remain the same in patients diagnosed with SOPOC or conventional strategies. It is possible that improvements in diagnostic accuracy may lead to a higher proportion of patients being detected with resectable disease but there is no evidence to support this.

Furthermore, cholangiocarcinoma is often asymptomatic in early stages and so patients present late for diagnosis.

For patients with resectable disease at diagnosis it was estimated that surgery would be undertaken (surgery approach may vary but likely that most would receive hepatectomy). The cost of surgical intervention was estimated from NHS Reference costs 2017/18. The relevant procedure code was identified as GA03, which equates to 'very complex, hepatobiliary or pancreatic procedures'. A weighted average cost across CC scores was calculated using recorded episodes in the NHS Reference costs database and it was estimated that the average cost per procedure was £13,048.

Management costs for malignant disease which is unresectable was estimated assuming that stenting would be performed. The cost of exploration surgery for diagnosis was estimated from NHS Reference costs 2017/18. The relevant procedure code was identified as GB09, which equates to complex therapeutic ERPC. A weighted average cost across CC scores was calculated using recorded episodes in the NHS Reference costs database. It was estimated that the average cost per procedure was £2,894.

Note that chemotherapy costs were not considered in the analysis as it is likely that these costs would not differ between diagnostic strategies.

8.2.4. Effectiveness data

For the purposes of a cost-utility analysis it is necessary to express effectiveness in terms of quality adjusted life years (QALYs). Therefore, a key aspect of the analysis is determining the value of earlier diagnosis of a malignant biliary stricture. It is reasonable to assume that earlier diagnosis could lead to potential improvements in survival and quality of life but quantifying this effect is challenging.

8.2.5. QALY estimation in previous studies

Previous cost-utility analyses evaluating diagnostic approaches for indeterminate biliary strictures (or similar) were reviewed for an approximation of the benefit of earlier diagnosis. A cost-utility analysis by Njei et al. 2017 estimated QALYs for SOPOC and ERCP but did not report how these QALYs were generated or the quality of life values assigned to health states.

A cost-utility analysis by Oliver et al. 2014 reported QALY outcomes for ERCP and EUS in the diagnosis of suspicious biliary strictures. Patients with malignant disease that is detected and subsequently treated (i.e. true positives) were estimated to accrue 2.36 QALYs. This was based upon patients receiving surgical treatment. Patients with malignant disease that is initially undetected (i.e. false negatives) were estimated to accrue 0.68 QALYs. This is based upon survival and quality of life estimates for unresectable disease. It should be noted that this approach effectively makes the assumption that any disease that is initially detected can be treated surgically whereas any disease that is initially undetected cannot because it is too progressed. This is likely to overestimate the benefits of early detection as at least some cases would be unresectable even if diagnosed earlier.

In the Oliver et al study, patients with benign disease that are correctly diagnosed as negative for malignancy (i.e. true negatives) were assumed to accrue 20.64 QALYs (based primarily on actuarial life expectancy). Patients with benign disease that is incorrectly treated (i.e. false positives) were assumed to accrue 15.31 QALYs. This relatively large decrement is based upon worse quality of life and survival associated with 'unnecessary' surgery. It should be noted that this approach makes the assumption that all false positive patients would receive surgery for malignancy and so may overestimate the impact of false positives.

A cost-utility analysis by Vergel et al. 2006 estimated the cost-effectiveness of MR cholangiopancreatography compared to diagnostic ERCP for the investigation of biliary tree obstruction. Quality of life values were applied in the analysis for an untreated extrahepatic malignant stricture (0.37) and for an extrahepatic malignant stricture post intervention (0.61).

A cost-utility analysis of treatments for unresectable cholangiocarcinoma (Suttichaimongkoi et al. 2018) estimated that stenting results in a quality of life gain of 0.20 in comparison to palliative care.

8.2.6. QALY estimation approach in HTW analysis

For the present analysis, the values applied in Oliver et al. 2014 were used as a starting point but were then adjusted to remove the potential for overestimation described above. QALYs for resected malignancy from Oliver 2014 were applied to the 10% of patients assumed to have resectable disease at diagnosis while QALYs for unresected malignancy were applied in the remaining 90%. The benefit of earlier diagnosis in patients with resectable disease was estimated using the quality of values from Vergel et al. 2006 and assuming that patients that are initially false negative are detected six months later. Therefore a quality of life decrement associated with untreated disease was applied for six months (note that the time taken for disease to be detected is adjusted in sensitivity analysis).

The benefit of earlier diagnosis in patients with unresectable disease was estimated using quality of values from a study by Suttichaimongkoi et al. 2018, which estimated that a quality of life gain of 0.20 for stenting in comparison to palliative care. As above, it was assumed that the quality of life decrement would apply for six months.

In patients without malignancy that are untreated, the QALY values from Oliver 2014 for true negatives were applied. In patients without malignancy that are treated (i.e. false positives), the value for false positive patients from Oliver 2014 were applied but only for the 10% of patients that are likely to receive surgical treatment (remaining 90% were assumed to have same quality of life as true negatives).

The QALY values applied in the analysis are summarised in table 17. Note that these are a combination of utility weighting and life expectancy as described above.

Table 17. QALY values applied in the analysis

Diagnostic outcomes	QALYs	Source
True positive	0.85	Oliver 2014 - QALYs for surgically managed malignant disease for 10% and QALYs for unresectable disease for 90%
False negative	0.75	Oliver 2014 - QALYs for surgically managed malignant disease for 10% and QALYs for unresectable disease for 90% Six month QoL decrement for resectable disease of 0.24 from Vergel 2006. Six month QoL decrement for unresectable disease of 0.20 Suttichaimongkoi 2018

Diagnostic outcomes	QALYs	Source
True negative	20.64	Oliver 2014 - QALYs associated with no malignancy
False positive	20.11	Oliver 2014 - QALYs associated with no malignancy, which has incorrectly been treated applied to 10% that receive radical treatment. Remaining 90% assumed to have same QoL as true negatives

8.2.7. Base case results

The analysis was run for a hypothetical cohort of 1000 patients using prevalence rates of 44% and 63% for patients with indeterminate biliary strictures and patients with indeterminate biliary strictures after an ERCP, respectively. The results of the analysis showed that when using SOPOC guided biopsy in the diagnosis of indeterminate biliary strictures, 303 OF 405 malignancies were detected compared to only 95 malignancies detected using ERCP guided brushing. When using SOPOC guided biopsy in the diagnosis of indeterminate biliary strictures after inconclusive conventional ERCP, 470 OF 630 malignancies were detected compared to 135 malignancies detected using repeated ERCP guided brushing and 630 malignancies detected using exploration surgery (as it was assumed to be 100% sensitive).

The base case results of the cost-utility analyses are summarised in table 18.

Table 18. Base case results

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Indeterminate biliary strictures					
ERCP guided brushing	£4,475	-	11.80	-	-
SOPOC guided biopsy	£5,107	£633	11.82	0.02	£29,810
Indeterminate biliary strictures after inconclusive conventional ERCP (assuming repeat ERCP is standard care)					
ERCP guided brushing	£5,877	-	8.13	-	-
SOPOC guided biopsy	£6,009	£133	8.15	0.02	£6,317
Indeterminate biliary strictures after inconclusive conventional ERCP (assuming exploration surgery is standard care)*					
Exploration surgery	£7,149	-	8.18	-	-
SOPOC guided biopsy	£6,009	-£1,140	8.15	-0.03	£38,665

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
*Note that this analysis would also be representative of the clinical scenario where ERCP is inappropriate and cannot be used					

In patients with indeterminate biliary strictures, it can be seen that SOPOC guided biopsy was more costly (£633) and more effective (0.02 QALYs) than ERCP guided brushing with an estimated ICER of £29,810 per QALY. Since the value was above the commonly applied NICE threshold of £20,000 per QALY, SOPOC would not be considered cost-effective in this setting.

In patients with indeterminate strictures after inconclusive conventional ERCP, it can be seen that the results differ greatly depending on what was used as the comparator. In comparison to repeat ERCP guided brushing, SOPOC guided biopsy was found to be more costly (£633) and more effective (0.02 QALYs). The resulting ICER of £6,317 per QALY was less than the NICE threshold of £20,000 per QALY indicating that SOPOC guided biopsy would be cost-effective. In comparison to exploration surgery, SOPOC guided biopsy was found to be less costly (£1,140) and less effective (0.03 QALYs). The resulting ICER of £38,665 per QALY indicates that SOPOC saves £38,665 for each QALY that is lost and as such would be deemed cost-effective using the NICE threshold of £20,000 per QALY.

8.2.8. Sensitivity analysis

A series of deterministic sensitivity analyses were run to explore some key areas of uncertainty in the analysis. The results of the sensitivity analysis are shown in table 19.

It can be seen that the results of the analysis are sensitive to changes in key parameters. Notably the result changes substantially when exploring variations in the prevalence rate or diagnostic accuracy.

Table 19. Sensitivity analysis

Modelled scenario	Indeterminate biliary strictures	Indeterminate biliary strictures after inconclusive conventional ERCP	
	ICER for SOPOC in comparison to ERPC	ICER for SOPOC in comparison to ERCP	ICER for SOPOC in comparison to exploration surgery
Base case	**£29,810**	**£6,317**	**£38,665***
Primary diagnostic values reported from Gerges 2019[1]	Dominated	Dominant	Not varied
Diagnostic values reported from Gerges 2019 assuming indeterminates are classified as positive[2]	Dominated	£17,781	Not varied
Diagnostic accuracy values for SOPOC from Navaneethan et al. 2015[3]	£72,581	Not varied	Not varied

Modelled scenario	Indeterminate biliary strictures	Indeterminate biliary strictures after inconclusive conventional ERCP	
	ICER for SOPOC in comparison to ERPC	ICER for SOPOC in comparison to ERCP	ICER for SOPOC in comparison to exploration surgery
Diagnostic accuracy values from Njei et al. 2017[4]	£152,996	£100,404	£23,897
Prevalence of malignancy = 30%	£66,427	Dominated	£44,112*
Prevalence of malignancy = 40%	£38,331	£2,486,209	£42,578*
Prevalence of malignancy = 50%	£21,474	£52,637	£40,945*
Prevalence of malignancy = 60%	£10,236	£11,699	£39,204*
Spyglass cost = £1,250	£12,949	Dominant	£50,804*
Spyglass cost = £1,000	£1,168	Dominant	£59,286*
Spyglass cost = £750	Dominant	Dominant	£67,768*
Quality of life decrement applied for 1 year	£20,769	£3,695	£31,182*
Quality of life decrement applied over patient's lifetime	£16,983	£2,831	£27,299*

[1]Sensitivity of 21% and specificity of 85% for ERCP guided brushing and sensitivity of 68% and specificity of 63% for SOPOC guided biopsy

[2]Sensitivity of 57% and specificity of 85% for ERCP guided brushing and sensitivity of 73% and specificity of 63% for SOPOC guided biopsy

[3]Sensitivity of 75% and specificity of 93% for SOPOC guided biopsy

[4]Sensitivity of 43% and specificity of 97% for ERCP guided brushing and sensitivity of 60% and specificity of 97% for SOPOC guided biopsy

*Indicates scenarios where SOPOC is cost saving and less effective. In this scenario, values above the NICE threshold of £20,000 per QALY would be considered cost-effective

8.3. De novo economic analysis for SOPOC use in therapeutic setting

A de novo costing analysis was undertaken to compare SOPOC and conventional therapy when used therapeutically for bile duct stones. Two scenarios were considered:

1. SOPOC or conventional therapy as a first line treatment for bile duct stones
2. SOPOC or conventional therapy for bile duct stones after unsuccessful conventional ERCP

8.3.1. Clinical data

Successful stone clearance was used as the key clinical input for the analysis. Estimates of successful stone clearance were sourced from Buxbaum 2018 and Riditittid 2018. Stone clearance rates from Buxbaum 2018 were used in the base case analysis for the analysis of first line treatments for bile duct stones, with values from Riditittid 2018 used in a sensitivity analysis. Stone

clearance rates for patients after unsuccessful conventional ERCP were also sourced from Buxbaum 2018. Table 20 summarises the stone clearance rates applied in the analysis.

Table 20. Stone clearance rates for SOPOC in comparison to conventional therapy when used as first line treatment for bile duct stones

Cost component	SOPOC	Conventional therapy
SOPOC or conventional therapy as a first line treatment for bile duct stones		
Buxbaum 2018 (base case)	93%	67%
Rididitid 2018 (sensitivity analysis)	90%	98%
SOPOC or conventional therapy for bile duct stones after unsuccessful conventional ERCP		
Buxbaum 2018 (base case)	93%	67%

8.3.2. Cost data

The cost associated with a therapeutic ERCP was estimated from NHS Reference costs 2017/18. The relevant NHS procedure codes were identified as GB06, GB05 or GB09, which equate to intermediate, major or complex therapeutic ERCPs. A weighted average cost across the procedures was calculated using recorded episodes in the NHS Reference costs database. It was estimated that the average cost per procedure was £2,028.

Costs associated with SOPOC were estimated using the list price reported in Deprez 2018 in conjunction with the relevant procedure cost from NHS Reference costs 2017/18. Deprez 2018 reported that the list price for SOPOC in Belgium was €1,760. This value was converted and inflated to UK 2018 prices, giving an estimate of £1,608. The relevant NHS procedure code was assumed to be the same as that estimated above for a therapeutic ERCP (£2,028).

Patients without successful stone clearance after the initial therapeutic intervention were assumed to receive further intervention. However, there is some uncertainty around the subsequent intervention that patients would receive. Patients may receive repeat intervention with ERCP or other interventions such as balloon sphincteroplasty and mechanical basket lithotripsy. Open or laparoscopic common bile duct exploration (OCBDE and LCBDE) may also be considered if other interventions have failed.

Given the uncertainties around clinical practice, a range of assumptions around further intervention were explored. It was assumed that patients could receive up to three rounds of interventions before progressing to OCBDE or LCBDE. Note also that the success rates of multiple repeat procedures is not known. It was therefore assumed that the accuracy of all repeat procedures would be equal to the rate reported in Buxbam 2018 for conventional therapy after unsuccessful ERCP for bile duct stones

The cost of OCBDE and LCBDE was estimated from NHS Reference costs 2017/18. The relevant procedure codes for OCBDE and LCBDE were identified as being GA07 and GA06, which equate to intermediate or major hepatobiliary or pancreatic procedures. A weighted average cost across the procedures was calculated using recorded episodes in the NHS Reference costs database. It was estimated that the average cost per procedure was £4,687.

The cost of balloon sphincteroplasty was estimated from NHS Reference costs 2017/18. The relevant procedure code was identified as being the same as that for OCBDE and LCBDE (£4,687). The cost of mechanical basket lithotripsy was estimated from NHS Reference costs 2017/18. The relevant procedure code was identified as being the same as that for a therapeutic ERCP (£2,028).

8.3.3. Results

The results of the costing analysis are presented in Table 21 for a hypothetical cohort of 1,000 patients undergoing SOPOC or conventional therapy as a first line treatment for bile duct stones.

The results in all scenarios show that the initial treatment cost is higher with SOPOC but that this cost increase is partially offset by cost savings accrued through a reduction in subsequent procedures (as a result of the superior stone clearance rate with SOPOC). Overall, it was estimated that the use of SOPOC would cost an additional £380 to £570 per patient when used as first line treatment for bile duct stones.

Table 22 shows the results of the costing analysis for a hypothetical cohort of 1,000 patients undergoing SOPOC or conventional therapy after unsuccessful conventional ERCP for bile duct stones. As above, the results in both scenarios show that the initial treatment cost is higher with SOPOC but that this cost increase offset, at least partially, by cost savings accrued through a reduction in subsequent procedures (as a result of the superior stone clearance rate with SOPOC).

However, it is notable that in the scenario where it is assumed that patients with unsuccessful stone clearance receive surgery, the cost savings accrued through a reduction in subsequent procedures outweighs the higher initial treatment cost resulting in net savings of £102 per patient. In the alternative scenario, where it was assumed that patients may receive two rounds of repeat procedures before progressing to surgery, the use of SOPOC would cost an additional £79 per patient.

Table 21. Cost analysis for SOPOC in comparison to conventional therapy when used as first line treatment for bile duct stones in cohort of 1,000 patients

Cost component	SOPOC	Conventional therapy	Net cost for cohort	Net cost per patient
Assuming three rounds of repeat procedures then surgery	£3,918,500	£3,348,385	£570,115	£570
Assuming two rounds of repeat procedures then surgery	£3,934,862	£3,424,745	£510,118	£510
Assuming surgery after unsuccessful ERCP	£3,970,315	£3,590,191	£380,125	£380

Table 22. Cost analysis for SOPOC in comparison to conventional therapy when used after unsuccessful conventional ERCP for bile duct stones in cohort of 1,000 patients

Cost component	SOPOC	Conventional therapy	Net cost for cohort	Net cost per patient
Assuming two rounds of repeat procedures then surgery	£4,041,090	£3,962,072	£79,018	£79
Assuming surgery after unsuccessful ERCP	£4,089,122	£4,191,150	-£102,028	-£102

8.3.4. Sensitivity scenarios

Alternative assumptions were explored in sensitivity analysis. Table 23 shows the results of the sensitivity analysis for SOPOC or conventional therapy as a first line treatment for bile duct stones, in which stone clearance rates from Rideritid 2018 were applied. The results show that SOPOC was cost increasing in comparison to conventional therapy in all modelled scenarios.

Table 24 shows the results of the sensitivity analysis for SOPOC or conventional therapy after unsuccessful conventional ERCP for bile duct stones. In this scenario, it was assumed that the SOPOC procedure would be performed immediately after the initial failed ERCP procedure, thereby reducing the cost of the SOPOC procedure (as it doesn't require a separate hospitalisation). This approach was used in the analysis by Deprez et al. 2018. The reduction in the upfront cost of the SOPOC procedure results in net cost savings in comparison to conventional therapy.

Table 23. Sensitivity analysis for SOPOC in comparison to conventional therapy when used as first line treatment for bile duct stones in cohort of 1,000 patients

Modelled scenario	SOPOC	Conventional therapy	Net cost
Using stone clearance rates Rideritid 2018			
Assuming three rounds of repeat procedures then surgery	£4,031,702	£2,106,936	£1,924,766
Assuming two rounds of repeat procedures then surgery	£4,054,610	£2,111,518	£1,943,092
Assuming surgery after unsuccessful ERCP	£4,104,243	£2,121,444	£1,982,799

Table 24. Sensitivity analysis for SOPOC in comparison to conventional therapy when used after unsuccessful conventional ERCP for bile duct stones in cohort of 1,000 patients

Modelled scenario	SOPOC	Conventional therapy	Net cost
Assuming SOPOC is performed immediately after failed or ERCP as part of same procedure			
Assuming two rounds of repeat procedures then surgery	£2,013,395	£3,962,072	-£1,948,677
Assuming surgery after unsuccessful ERCP	£2,061,428	£4,191,150	-£2,129,723

9. Organisational issues

SOPOC is not routinely available in Wales and can only be accessed after a successful Independent Patient Funding Request. If SOPOC were to be routinely funded in Wales, clinical expert opinion suggested that SOPOC would be offered in cases where conventional ERCP failed to address the

condition (e.g. diagnosis of strictures or removal of bile duct stones), or in cases where initial pre-ERCP imaging shows conventional ERCP is unlikely to be successful/appropriate[2].

One issue for consideration with the use of SOPOC is the level of experience or training required to perform SOPOC safely and effectively. We identified one study in the clinical literature search that compared visual diagnostic outcomes between novice (<25 prior cholangioscopies), intermediate (25-50 prior cholangioscopies) and expert (>50 cholangioscopies). Overall, sensitivity and specificity increased as experience increased. Novice sensitivity and specificity was 70% and 63.6%, whereas experts had sensitivity and specificity of 96.2% and 95.8%. Expert opinion suggested that either formal and informal exposure, or training, could be provided through established units. Expert comment from the manufacturer noted that they also provide and education programme to support users of SpyGlass DS[2].

Should SOPOC be provided in Wales HTW-sought expert opinion advised that provision should be considered through a limited number of high-volume specialist ERCP centres, with SOPOC performed by a limited number of experts. This would help to increase expertise in a shorter timeframe; however, it was acknowledged that this approach may limit access for some patients[2].

10. Patient issues

No patient issues were identified in the literature.

11. Conclusions

This evidence review identified substantial evidence on the use of SOPOC for the diagnostic and therapeutic use in the hepato-biliary-pancreatic system. Most evidence evaluated SOPOC for malignant diagnosis or stone removal within the bile duct.

For diagnosis via visualisation/biopsy, sensitivity of visualisation was generally higher than with biopsy, with the systematic review from Navaneethan et al. (2015) reporting pooled sensitivity of 84.5% and 60.1%, respectively. The same systematic review reported specificity as 82.6% for visual findings and 98% for biopsy. The systematic review also pooled data from four studies where SOPOC was used following indeterminate or negative conventional ERCP, reporting a sensitivity and specificity of 74.7% and 93.3%, respectively. Comparative data was limited, but three studies showed higher sensitivity for SOPOC versus cytology brushing.

For the removal of difficult bile duct stone using SOPOC, pooled data showed 94.3% stone clearance in 23 studies. Again, comparative data was limited; we identified four studies that were comparative (SOPOC versus another ERCP modality), but the comparator varied among these studies. These studies showed stone clearance was similar or better with SOPOC compared to alternative modalities.

Other studies were identified that evaluated SOPOC for diagnosis or therapeutic use for other purposes, such as biopsy-mapping. However, evidence is these areas was limited. No studies were identified which reported quality-of-life outcomes.

Three partially relevant economic studies were identified. None considered a UK healthcare perspective and so they were all considered to be only partially applicable to the healthcare system in NHS Wales. One of the studies was a cost-utility analysis and results suggested that SOPOC may be cost-effective in comparison to conventional strategies in the diagnosis of malignancy in people with primary sclerosing cholangitis-induced biliary strictures. The other two

[2] Expert comments, December 2019.

studies were cost analyses and the results suggested that the use of SOPOC may lead to cost savings when used therapeutically in people with difficult-to-remove bile duct stones and when used diagnostically in people with indeterminate biliary strictures. However, in addition to applicability concerns, several potentially serious limitations were identified in each of the studies.

The economic analysis conducted by HTW on the use of SOPOC for the diagnosis of indeterminate biliary strictures suggested that SOPOC guided biopsy was more effective and more costly than ERCP guided brushing but was not found to be cost-effective with an ICER above a threshold of £20,000 per QALY. In patients with indeterminate strictures after ERCP, SOPOC guided biopsy was found to be cost-effective in comparison to repeat ERCP guided brushing with an ICER below the threshold of £20,000 per QALY. SOPOC guided biopsy was also found to be cost-effective in this group when compared against exploration surgery (as a result of cost savings). However, it should be noted that this is an exploratory analysis and there is considerable uncertainty around some of the estimations that have been made. Furthermore, sensitivity analysis demonstrates that the results of the analysis were sensitive to changes in some of the key model parameters.

The economic analysis conducted by HTW on the use of SOPOC for the removal of bile duct stones showed that it was likely to lead to increased costs when used as a first line treatment. Conversely, the analysis showed that there was the potential for cost savings when SOPOC was used after unsuccessful conventional ERCP. However, there was uncertainty around results, primarily driven by uncertainty around the treatment approach that may be used after unsuccessful stone clearance.

12. Contributors

This topic was proposed by Andrew Champion, Welsh Health Specialised Services Committee.

The HTW staff and contract researchers involved in writing this report were:

- H Britton – project management
- L Elston – primary researcher and clinical author
- D Jarrom – secondary researcher and editor
- M Prettyjohns – health economist and primary economic author
- J Washington – information scientist, literature searches

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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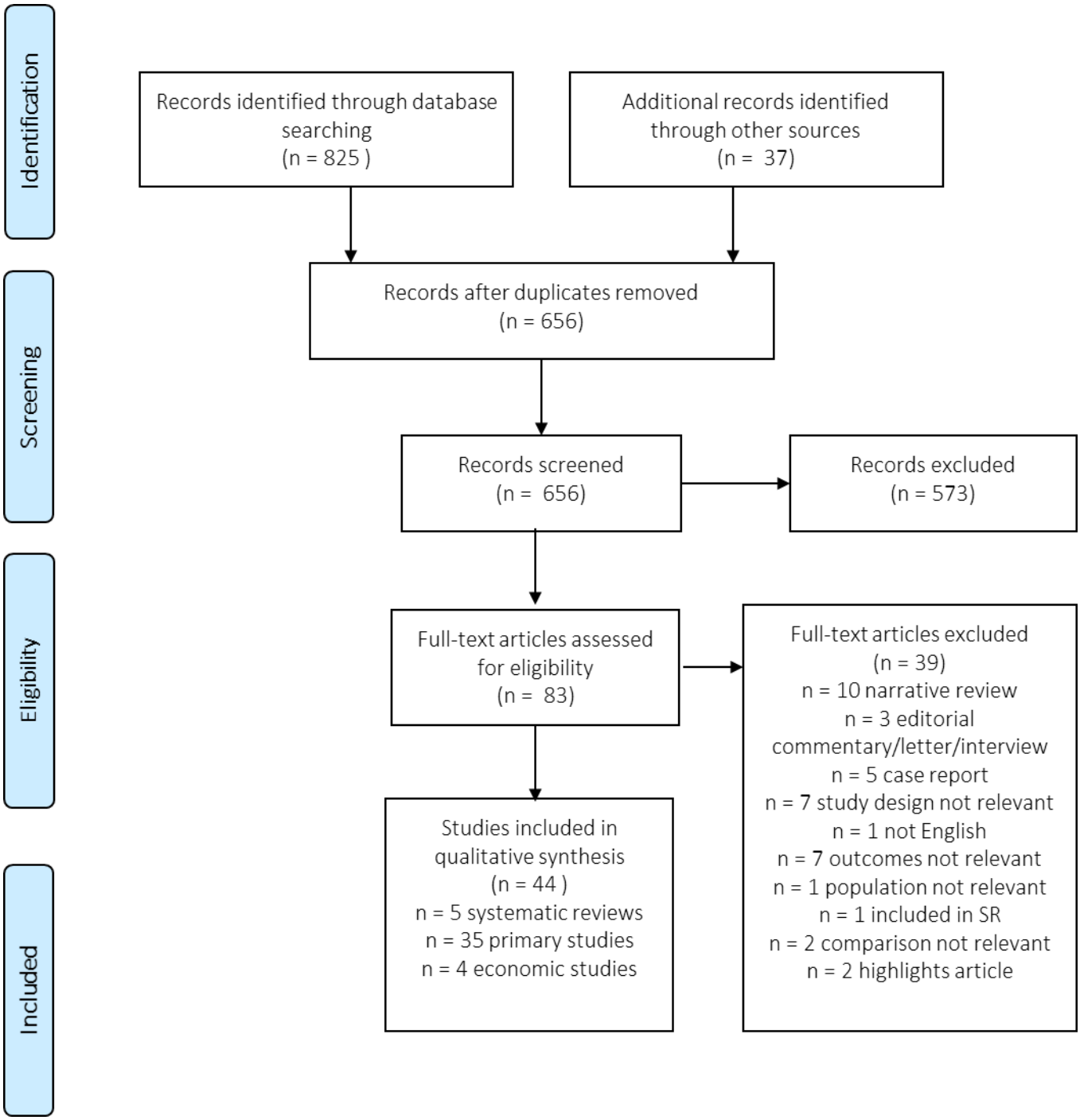
Appendix 1. Criteria used to select evidence

Research Question	What is the clinical and cost effectiveness of single operator per-oral cholangioscopy (SOPOC) for diagnostic and therapeutic management of biliary disorders?

	Inclusion criteria	Exclusion criteria
Population	People with known or suspected hepato-biliary-pancreatic disorders in whom investigation of the hepato-biliary system/pancreas is needed. This includes, but is not limited to: • Investigation and treatment of large stones of the biliary system • Investigation of indeterminate biliary strictures We will search for evidence on the diagnostic or therapeutic use of SOPOC in any indication, however it is likely that therapeutic use will focus on cases of biliary stones. SOPOC is currently used in a 'refractory' population after standard techniques have failed or are inappropriate and other options have been exhausted. We will search for evidence in this 'refractory' population and also for any evidence on use of SpyGlass earlier in the diagnostic or therapeutic pathway.	
Intervention	Single-operator per-oral cholangioscope using the SpyGlass (or SpyGlass DS) direct visualisation system or other proprietary devices, in addition to concurrent endoscopic retrograde cholangio-pancreatography (ERCP)	
Comparison/ Comparators	Standard care, such as, but not limited to: • Standard ERCP • Surgery • Empirical treatment • Nothing (if refractory)	

Outcome measures	Diagnostic accuracy, calculated using an appropriate reference standard such as histopathological assessment of surgical specimens or clinical follow up Procedural success - Visualisation of target lesions - Collection of biopsy specimens - Removal of calculi (stone removal rate) Clinical outcomes - Survival - Quality of life - Symptomatic relief - Adverse events - Change/impact on patient management or clinical decision making	
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised or non-randomised trials. • Non-randomised trials. We will only include evidence for "lower priority" evidence where outcomes are not reported by a "higher priority" source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.	
Search limits	We will only include studies published in English.	

Appendix 2. PRISMA diagram



Appendix 3. Additional study characteristics and outcomes.

Table 1. Studies of SOPOC for diagnostic evaluation and/or therapeutic use: design and characteristics

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
Gerges et al. (2019)	Randomised controlled trial Multicentre (n = 3) Screening and enrolment between May 2017 and December 2018	Inclusion criteria: people 18 years and over with biliary obstructive symptoms and indeterminate biliary stricture suspected to be intrinsic and proximal to the distal common bile duct based on prior MRCP. Exclusion criteria: contraindications to endoscopic intervention, prior ERCP with TPB for assessment of indeterminate biliary stricture, extrabiliary compression identified on prior noninvasive imaging and believed to be the cause of the biliary obstructive symptoms, and age less than 18 years. N = 61 (n = 57 eligible for primary endpoint analysis) Median age 65 years (control) versus 62 years (intervention) 65.5% male (control) versus 54.8% male (intervention)	Study arm: SOPOC (SpyGlass DS, Boston Scientific) and guided biopsy (SpyBite, Boston Scientific). SOPOC impression of malignancy (yes/no/indeterminate) was recorded. Minimum of 3 biopsy specimens were required. Control: ERCP with cholangiography and guided brushing. Cholangiography –based impression of malignancy (yes/no/indeterminate) was recorded. Brushing had a minimum of 9 passes.	• Diagnostic accuracy (at 6 months after the initial procedure). • Correlation between visualisation and biopsy • Technical success of the procedure (ability to collect adequate samples for analysis) • Yield of tissue acquisition • Adverse events (up to 30 days after procedure)	Strictures were considered benign if the malignancy was not confirmed by 6 months after the index procedure. Centre locations were not clearly reported. Patient characteristics were provided for the enrolled population (n = 61), not the primary endpoint population (n = 57)
Sejpal et al. (2019)	Prospective tandem study Multicentre (n = 2), US January 2016 to February 2018	Inclusion criteria: suspected or documented choledocholithiasis and: 1) dilated bile duct ≥12 mm (any portion of duct); and/or 2) the patient underwent mechanical lithotripsy or electrohydraulic lithotripsy for therapy of bile	Intervention: SOPOC (SpyGlass DS, Boston Scientific) If patients met the inclusion criteria, and were negative for residual stones during occlusion angiogram, patients underwent SOPOC to detect residual	• Detection of residual biliary stones.	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
		duct stones. Exclusion criteria: younger than 18 years or who had altered anatomy. Age 65.1 years (SD 1.7 years) 34% male:66% female	stones.		
Yan&Tejaswi (2019)	Retrospective case series Single centre, US Medical records between June 2015 to May 2018	Inclusion criteria: people 18 year and over who were referred for cholangiopancreatoscopy for any indication. N = 50; 21 (42%) bile duct stones 13 (26%) indeterminate biliary strictures 9 (18%) PSC surveillance 7 (14%) miscellaneous 24/50 were women Mean age 61.4 years 42 (84%) had prior ERCP that failed.	Olympus TJF-160F or TJF-180F duodenoscopes (Olympus Medical Systems, Tokyo, Japan) and SpyGlass DS system (Boston Scientific). When necessary, EHL was performed using the Nortech Autolith system (Northgate Technologies Inc., Elgin, IL, USA) (settings: power 80–100%, rate 15 shots/s, 20 shots per foot pedal depression). Following EHL, stone extraction balloons or baskets were utilized for stone debris clearance. For biliary strictures, we obtained SOPOC directed biopsies using the SpyBite Biopsy Forceps.	• Indication referred for SOPOC • Procedural findings and interventions • Procedure success rate • Impact on clinical management	
Lee et al. (2019)	Prospective observational study January 2014 and November 2016	Inclusion criteria: stricture of the extrahepatic bile duct, identified through CT and/or MRI; clinical findings of obstructive jaundice and/or cholangitis; aged 18 years and above; ability to give consent. Exclusion criteria: known bile duct stricture without clinical findings suggestive of malignancy; contraindicated for ERCP; altered GI anatomy or duodenal obstruction; coagulopathy.	Following initial transpapillary forceps biopsy, if the stricture was indeterminate patients were allocated to receive either: • SOPOC (first generation SpyGlass or SpyGlass DS; Boston Scientific) for proximal strictures with distal CBD <10mm in diameter • SOPOC (ultra slim endoscope GIF-XP260NS and GIF-XP290N; Olympus Medical Systems) for proximal strictures >10mm in diameter. • Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB)	• Diagnostic accuracy of SOPOC or EUS-FNAB according to biliary stricture location. • Diagnostic accuracy of initial TPB • Diagnostic accuracy of TPB combined with SOPOC or EUS-FNAB	Centre not reported. SOPOC and EUS-FNAB were deployed for different biliary localities, which may therefore give caution when drawing comparison between the two.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
		N = 181 78/181 female Mean age 73.0 years (IQR 61.5 to 79.0 years)	for distal strictures. Reference standard: final diagnosis was confirmed using one of the following 1) definite result of malignancy in a surgical specimen or biopsy of a metastatic lesion; 2) malignant diagnosis by TPB or EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with malignant disease; and 3) malignancy not found on TPB and EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with benign disease for at least 12 months.		
Jang et al. (2019)	Retrospective observational cohort study. Single centre, US. February 2015 to December 2018	Inclusion criteria: registry patients ≥18 years who received ERCP with SOPOC, for the indication of bile duct stricture. Exclusion criteria: patients with established primary pancreatic, hepaticobiliary malignancy or metastatic cancer with liver involvement (because of the concern for visual interpretation bias); patients without a diagnostic impression, either benign or malignant, in their SOPOC procedure note; patients with established surgical or endoscopic adverse events resulting in bile duct injury; and patients lost to follow-up after the procedure Mean age 62.7 years (SD 14.6	Index test: SpyGlass DS (Boston Scientific) Reference standard: Definitive diagnosis of malignancy through surgical or non-surgical biopsy.	• Diagnostic accuracy of SOPOC (both visualisation and biopsy). • Factors affecting biopsy • Technical success • Procedure-related adverse outcomes	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
		years) 45/105 female			
Dimas et al. (2019)	Retrospective cohort study (using a prospective database) Single Centre, Greece May 2009 to March 2017	Inclusion criteria: adults referred for SOPOC for various indications, including biliary strictures, difficult biliary stones, and migrated or occluded pancreatic or biliary stents. All patients could not be diagnosed or treated by conventional ERCP. Exclusion criteria: Pregnancy, coagulation disorders, ineligibility for ERCP on clinical grounds, and inability to provide informed consent. Mean age 61.4 years (SD 18.1 years) 30/68 female	Fibreoptic SOPOC (SpyGlass, Boston scientific) Digital SOPOC (SpyGlass DS, Boston Scientific) All were performed by experienced endoscopists	• Technical success rate • Diagnostic accuracy • Adverse events	
Ang et al. (2019)	Retrospective Sing centre, Singapore January 2013 to November 2016	Inclusion criteria: all patients who underwent the intervention Exclusion criteria: those who underwent ERCP without the need for SpyGlass examination, and those who were initially scheduled for SpyGlass examination but did not undergo it Mean age 63 years (SD 16 years) 55.3% male	SpyGlass cholangioscopy or pancreatoscopy, using the original system or SpyGlass DS	• Clinical success of interventions • Factors associated with clinical failure • Difference in outcomes between legacy and digital SOPOC	The majority (49/50) procedures were cholangioscopy; only one was pancreatoscopy.
Urban et al. (2018)	Prospective case series Single centre, Czech Republic January 2016 and May 2017	Inclusion criteria: all patients referred for SOPOC for biliary stricture. This included patients with and without tissue sampling attempts at	SpyGlass DS system with SpyBite forceps Reference standard: The final diagnosis was considered benign if no disease progression occurred clinically or at	• Diagnostic accuracy • Treatment following diagnosis	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
		prior ERCP. Exclusion criteria: age <18 y, inability to provide informed consent, clinical or laboratory signs of acute cholangitis, coagulopathy with international normalized ratio >1.5, thrombocytopenia <50 000/mm3 and ongoing antithrombotic treatment Mean age 67.3 years (SD 10.7 years) 63% males	repeated imaging studies during 6-month follow-up. The gold standard for final malignant diagnosis was surgical specimen. In patients not undergoing surgical resection, clinical evaluation methods and repeated imaging studies were used to confirm malignancy during the 6-month follow-up.		
Canena et al. (2019)	Prospective non-comparative study Two centres, Portugal. January 2017 to December 2017	Inclusion criteria: having 1 or more biliary stones that failed treatment by mechanical lithotripsy and/or balloon sphincteroplasty; having impacted stones or stones in difficult locations; having symptomatic chronic calcific pancreatitis with pancreatic stones that were not amenable to being removed by a stone retrieval basket or balloon and/or having obstructing stones (proximal to a stricture) in the pancreatic head or body. Exclusion criteria: Patients with distorted anatomy, malignant strictures, and bleeding diatheses. Median age 72 year (range 42 to 90 years) 6/17 (35%) female	Second generation SpyGlass DS system.	• Clinical success (defined as complete ductal clearance determined by cholangioscopy or pancreatoscopy). • Safety outcomes • Impact of location/number of stones on clinical success • Subgroup comparison of holmium laser technology versus EHL.	
Bokemeyer et al. (2019)	Retrospective non-comparative Two centres, Germany	Inclusion criteria: people with biliary stones that had failed conventional methods.	SOPOC (SpyGlass DS 2.0, Boston scientific)	• Removal rate per procedure • Complete stone removal	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
	August 2015 to July 2018	Median age 66 years (IQR 61 to 75 years). 51.7% female; 48.3% male		• Subgroup comparison of LL and EHL • Adverse events.	
Sanda et al. (2018)	Retrospective non-comparative chart review Single centre, Canada April 2011 to June 2015	Inclusion criteria: difficult common bile duct stones which have failed conventional ERCP Mean age 66 years (range 30 to 88 years) 69% female	SOPOC (SpyGlass Legacy followed by as switch to SpyGlass DS, Boston Scientific)	• Stone clearance	
Ogawa et al. (2018)	Case series Single centre, Japan October 2015 to September 2016	Inclusion criteria: patients diagnosed with extrahepatic cholangiocarcinoma Exclusion criteria: refusal of surgical treatment; definite inoperable factors such as distal metastases and peritoneal dissemination detected by multi-detector row computed tomography (MDCT); tumours that definitely involved both the B4 confluence and the confluence of the right anterior and right posterior segmental ducts on the basis of findings of MDCT, magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography (EUS); and poor general condition (performance status 3 or 4). Mean age 75 years 3/13 females	SpyGlass DS (Boston Scientific)	• Procedural success rate • Diagnostic accuracy of longitudinal tumour extent • Complications/adverse events	Single operator use not clear. Another study at this centre reports mother-baby approach
Kanno et al. (2018)	Retrospective case review Single centre, Japan January 2004 to	Inclusion criteria: patients who underwent surgical resection for extrahepatic bile duct cancer after preoperative	SOPOC (SpyGlass DS, Boston Scientific) Comparator: traditional digital scope, CHF-B260	• Overall preoperative diagnosis • Diagnostic accuracy • Reasons for wrong	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
	September 2015	examinations, including SOPOC, to diagnose the lateral extent of extrahepatic cholangiocarcinoma. Exclusion criteria: those in whom the clinical record on findings of the SOPOC examination could not be obtained or was insufficient for evaluation; those who did not undergo surgical resection after examinations; and those in whom the resected specimen was inappropriate to precisely evaluate the lateral extent.		diagnosis	
Ogura et al. (2019)	Retrospective case series Single centre, Japan October 2016 to August 2017	Inclusion criteria: people with painful CP, with main pancreatic duct stones (> 5 mm) and upstream ductal dilatation Exclusion criteria: patients <20 years old; unable to tolerate ERCP. Median age 55 years (range 17-78 years). 6/21 women	SOPOC (SpyGlass DS, Boston Scientific)	• Stone characteristics • Number of EHL procedures • Complete stone clearance • Adverse events.	
Kaura et al. (2019)	Retrospective cohort study Single centre, US January 2007 to October 2018	Inclusion criteria: consecutive patients who underwent ERCP with SOPOC. Mean age: PSC 61 years (SD 11 years) non-PSC 54 years (SD 14 years) Sex: PSC 61% male Non-PSC 54% male	SpyGlass fibreoptic or spyglass DS digital (Boston Scientific)	• Histopathology and diagnostic yield of SOC guided biopsies and TPB compared to standard ERCP brush cytology. • Adverse events	
Lubb et al. (2015)	Prospective, nested	Inclusion criteria: people who	SpyGlass	• General intra- and post-	SpyGlass version not

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
	case-control cohort study National registry, Sweden January 2007 to December 2012	received ERCP. Age ≥71 years: 25% SpyGlass 48.6% ERCP	Comparator: ERCP	procedural adverse events. • ERCP-associated adverse events	fully defined.
Mizrahi et al. (2018)	Retrospective observational study Single centre, 2009 to 2016	Inclusion criteria: Any patients who underwent ERCP with cholangioscopy. Indications for ERCP-directed cholangioscopy included stone disease in 152/324 (47%), indeterminate stricture in 136/324 (42%) and other indications such as stent migration, pancreatic intraductal papillary mucinous neoplasm, pancreatic stones and strictures in 36/ 324 (11%).	All patients received single-operator cholangioscopy (SOC). Intervention: digital SOC (n = 126) Control: fibreoptic SOC (n = 198)	• Stone clearance • Number of sessions required • Procedure time • Radiation dose • Diagnostic yield • Complications	It is assumed that not all outcomes are relevant to all patients: for example stone clearance is assumed to only be relevant to patients with stone disease; diagnostic yield is assumed to only be relevant to indeterminate strictures. However, this is not clearly reported by the authors; nor is the number of patients for whom outcome data was collected in some cases.
Arnelo et al. (2014)	Prospective cohort study Single centre, Sweden July 2007 to March 2013	Inclusion criteria: Radiological findings suggestive of IPMN Median age 60 years (range 46 to 80 years) 17 female patients: 24 male patients	SOPOC (SpyGlass, Boston Scientific)	• Diagnostic accuracy • Complications	
Maydeo et al. (2019)	Prospective registry Multicentre (n = 17), 10 countries	Inclusion criteria: patients 18 years and over with difficult bile duct stones who underwent SOPOC-guided lithotripsy	SOPOC (SpyGlass DS, Boston Scientific)	• Stone clearance • Impact on patient management • Adverse events	

Study reference	Methods, setting	Participants	Interventions	Outcomes	Comments on risks of bias/applicability
		79.5% had failed stone clearance through previous ERCP 20.5% were referred directly for SOPOC based on assessment. Median age 62 years (range 46 to 76 years) 39.1% male			
MRCP: magnetic resonance cholangiopancreatography; ERCP: endoscopic retrograde cholangiopancreatography; SOPOC: single-operator per-oral cholangioscopy; SD: standard deviation; PSC: primary sclerosing cholangitis; EHL: electrohydraulic lithotripsy; CT: computed tomography; MRI: magnetic resonance imaging; CBD: common bile duct stones; EUS-FNAB: endoscopic ultrasound-guided fine-needle aspiration biopsy; TPB: trans-papillary brushing; GI: gastrointestinal; IQR: interquartile range; LL: laser lithotripsy;					

Table 2. Primary studies on SOPOC: visualisation and diagnosis of indeterminate biliary strictures

Outcome	Evidence source	Number of studies and patients	Sensitivity	Specificity	Diagnostic accuracy	Comments
Diagnosis through biopsy	Jang 2019, retrospective cohort study	One study, 101 patients	69.8 (95% CI 56.5-80.5)	97.9 (95% CI 89.1-99.6)	83.2 (95% CI 74.7-89.2)	
	Dimas 2019	One study, 55 patients			95.0% (19/20)	
	Ang 2019	One study, 11 patients	81.8% (95% CI 48.2%-97.7%)	100.0% (95% CI 15.8%- 100.0%)		
	Urban 2018	One study, 30 patients	92% (95% CI 62-100)	100% (95% CI 78-100)		
Diagnosis through visualisation	Jang 2019, retrospective cohort study	One study, 105 patients	89.1 (95% CI 78.2-94.9)	90 (95% CI 78.6-95.6)	89.5 (95% CI 82.2-94.1)	
	Urban 2018	One study, 30 patients	100% (95% CI 75-100)	76% (95% CI 50-93)		

EUS-FNAB: Endoscopic ultrasound-guided fine needle aspiration biopsy ; FISH: fluorescence in situ hybridisation ; SOPOC: single-operator peroral cholangioscopy; TPB: transpapillary biopsy sampling; PSC: primary sclerosing cholangitis; RCT: randomised controlled trial

Table 3. Non-comparative studies for SOPOC: other outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Comments
Clinical/technical success (all patients)	Yan&Tejaswi (2019), retrospective case review	One study, 50 patients	9/9 (100%) for PSC surveillance 13/13 (100%) for indeterminate strictures	Clinical success was defined as the ability to achieve the therapeutic or diagnostic objective based on the procedure indication. Diagnostic success was achieved through combined SOPOC exam, biopsy and brush cytology
	Lee et al. (2019)	One study, 59 patients	SOPOC: 32/32 (100%)	

			EUS-FNAB: 27/27 (100%)	
	Dimas et al. (2019)	One study 55 patients	SOPOC: 38/55 (69.1%) F-SOPOC: 18/31 (58.1%) D-SOPOC: 20/24 (83.3%) P = 0.07	
	Ogawa et al. (2018)	One study, 13 patients (67 biopsy specimens)	59/67 (88%)	Cholangioscopic-guided mapping biopsy
Diagnostic accuracy (IPMN)	Arnelo et al. (2014)	One study, 41 patients	Sensitivity 84% (16/19) Specificity 75% (9/12)	
Mean procedure time (all patients)	Yan&Tejaswi (2019), retrospective case review	One study, 22 patients (13 indeterminate strictures) (9 PSC surveillance)	74.2 minutes (range 29 to 117 minutes)	Average procedure time for all indications in study was 82 minutes.
	Jang et al. (2019)	One study, 105 patients	53 minutes (SD 20 minutes)	
	Arnelo et al. (2014)	One study, 41 patients	Median 90 minutes (range 40 to 150)	EUS was performed at the same time in 13 (42%) of cases.
PSC: primary sclerosing cholangitis; SOPOC: single-operatory per-oral cholangioscopy; EUS: endoscopic ultrasound; F-SOPOC: fibreoptic SOPOC; D-SOPOC: digital SOPOC; EUS-FNAB: endoscopic ultrasound-guided fine needle aspiration biopsy; IPMN: intraductal papillary mucinous neoplasm.				

Table 4. Non-comparative studies for SOPOC: therapeutic outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect	Comments
Successful stone clearance rate	Jin et al. (2019)	23 studies, 1,205 patients	94.3% (95% CI 90.2 to 97.5)	Publication bias was assessed through funnel plot, Egger's test, and Duval and Tweedie's trim and fill. Funnel showed asymmetry, but Egger's and trim and fill showed no publication bias. Therefore, authors assessed that the potential publication bias had no significant influence on the results.
	Yan&Tejaswi (2019),	One study, 21 patients	19/21 (90.4%)	Biliary stone clearance Complete stone clearance was achieved during the index procedures in 12/21 (57%) cases.

Outcome	Evidence source	Number of studies and patients	Absolute effect	Comments
	retrospective case review			Also 1/2 (50%) for pancreatic duct stones. Method of stone removal varied: 16/21 (76%) was EHL, 4/5 conventional ERCP, 1 due for follow-up ERCP.
	Bokemeyer et al. (2019)	One study, 60 patients	50/75 (66.7%)	Biliary stones.
	Ang et al. (2019)	One study, 28 patients	26/28 (92.9%)	Common bile duct stones
	Canena et al. (2019)	One study, 17 patients	17/17 (100%)	
	Sandha et al. (2018)	One study, 51 patients	47/51 (93%)	Common bile duct stones
	Ogura et al. (2018)	One study, 21 patients	18/21 (85.7%)	Main pancreatic duct stones
	Maydeo et al. (2019)	One study, 156 patients	136/156 (80.1%)	
Successful stone clearance in first session	Ang et al. (2019)	One study, 28 patients	23/28 (82.1%)	
	Canena et al. (2019)	One study, 17 patients	16/17 (94.1%)	
	Yan&Tejaswi (2019),	One study, 21 patients	12/21 (57%)	
	Maydeo et al. (2019)	One study, 156 patients	125/156 (80%, 95% CI 73% to 86%)	
Other technical success	Dimas et al. (2019)	One study, 13 patients	9/13	Technical success was defined as carrying out successful treatment such as guidewire insertion into the area of interest, EHL, or migrated stent removal Most common indication was bile duct stone, but also included others.
Procedure time	Yan&Tejaswi (2019),	One study, 21 patients	Mean 99.5 minutes (range 37 to 234 minutes)	

Outcome	Evidence source	Number of studies and patients	Absolute effect	Comments
	retrospective case review			
	Sandha et al. (2018)	One study, 51 patients	Median 67 minutes (SD 6.5 minutes, 95% CI 61.5 to 73.5)	Calculated based on 56 of 58 procedures – two procedure times were not recorded.
	Canena et al. (2019)	One study, 17 patients	Median 55 minutes (range 30 – 100)	
Detection of residual stones missed by occlusion cholangiogram	Sejpal et al. (2019)	One study, 93 patients	34% detection of residual stones	Following ERCP procedures to remove duct stones, occlusion cholangiogram was performed to identify residual stones. People who were negative through occlusion cholangiogram went on to have SOPOC.
CI: confidence interval; EHL: electrohydraulic lithotripsy; SD: standard deviation; ERCP: endoscopic retrograde cholangiopancreatography; SOPOC: single-operator per-oral cholangioscopy.				

Table 5. Digital SOPOC compared to fibreoptic SOPOC: clinical and safety outcomes

Outcome	Evidence source	Number of studies and patients	Absolute effect
Diagnostic accuracy	Dimas et al. (2019)	One study, 55 patients	D-SOPOC: 100% (9/9) F-SOPOC: 90.9% (10/11) P = 0.99
Successful stone clearance	Mizrahi et al. (2018), retrospective observational study	One study, 94 patients	D-SOPOC: 52/63 (83%); F-SOPOC: 18/32 (58%)
Technical success	Dimas et al. (2019)	One study, 13 patients	D-SOPOC: 4/5 (80%) F-SOPOC: 5/8 (62.5%) P = 0.99
Mean procedure time	Mizrahi et al. (2018), retrospective observational study	One study, 94 patients	D-SOPOC: 49 min (SD 17 min); F-SOPOC: 57 min (SD 21 min) P = 0.032
SOPOC: single-operator per-oral cholangioscopy: D-SOPOC: digital SOPOC; F-SOPOC: fibreoptic SOPOC.			