NICE advice

The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system

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Summary

The SpyGlass system is designed for the diagnostic and therapeutic management of biliary system disease. It is intended to be used when standard techniques are unsuccessful or inappropriate. Outcomes from 9 prospective cohort studies have been reported, including procedural success, diagnostic accuracy and inter-observer agreement. The cost of the SpyGlass system is not available.

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Product summary and likely place in therapy	Effectiveness and safety
• The SpyGlass is a visualisation and intervention system that is used for the diagnostic and therapeutic management of indeterminate strictures and large stones of the biliary system when standard endoscopic retrograde cholangiopancreatography (ERCP) is unsuccessful or considered inappropriate. • Unlike standard ERCP, the SpyGlass is a single-operator system designed to visualise and facilitate access to the biliary ducts during both diagnostic and therapeutic procedures. • The SpyGlass system is intended for use in endoscopic units which have both the equipment and expert staff to carry out ERCP. The intended user is a clinician trained in ERCP endoscopy.	• The published evidence summarised in this briefing comes from 9 prospective cohort studies involving a total of 629 people. • Three of the 9 studies (n=297, 75 and 64) investigated the procedural success of cholangioscopy with the SpyGlass to visualise the target lesions, collect adequate biopsy specimens and remove biliary stones. The studies reported overall success rates ranging from 83.3% to 93.3%. • Four studies (n=52, 40, 36 and 11) investigated the diagnostic accuracy of SpyGlass cholangioscopy and SpyBite-targeted biopsies in people with indeterminate biliary strictures. They reported overall accuracy rates of 88.0% to 94.0%. • One study (n=38) investigated the level of inter-observer agreement during cholangioscopy with the SpyGlass. The observers had only slight agreement on their presumed final diagnosis based on SpyGlass visualisation.

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	• The incidence of adverse events in these studies ranged from 4.8% to 13.5%, which is comparable to that of standard ERCP for complex procedures. The adverse events mainly included post-procedure episodes of cholangitis and pancreatitis.
Technical factors • The SpyGlass is a modification of the 'mother-baby' cholangioscopy technique, which involves a 'baby' endoscope with disposable and non-disposable components.	**Cost and resource use** • No publicly-available information exists on the purchase cost of the SpyGlass. • There is very limited published evidence on cost and resource consequences of using the SpyGlass. A conference poster presentation reported the cost per patient to be £1443.

Introduction

The biliary system includes the gallbladder, liver and pancreas, and forms an essential part of the body's digestive system. Its primary function is to aid digestion and elimination of the body's waste through the controlled release of bile into the duodenum. Bile is released through a network of tube-like structures called the biliary ducts.

Various disorders can result in narrowing or obstruction of the biliary ducts. The most common are as follows (Hoad-Robson 2013):

- Bile or pancreatic duct stones: approximately 15% of the adult population are thought to have gallstone disease (for more information, see the NICE guideline on gallstone disease). Benign or malignant tumours: pancreatic cancer has an incidence rate of 139 cases per million population (Cancer Research UK 2014).

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- Pancreatitis (inflammation of the pancreas): incidence of acute pancreatitis in the UK ranges from 150 to 420 cases per million population (Toh et al. 2000).
- Primary sclerosing cholangitis (inflammation of the bile ducts), which has an incidence rate of 30 to 48 cases per million population (Card et al. 2008).

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure used to identify abnormalities in the biliary system. ERCP is done under X-ray guidance using a duodenoscope (an endoscope designed for examination of the duodenum), which is inserted through the mouth of the patient after they have been sedated. Contrast medium (dye that shows up on X-ray) is injected through the endoscope to outline the bile, pancreatic and liver ducts so that they can be examined. ERCP is used both to diagnose the narrowing of the biliary ducts and as a procedure to treat the underlying cause. The latter can involve the insertion of a stent (a small mesh tube) to widen a narrowed duct or fragmentation and removal of stones (lithotripsy).

There are 3 main lithotripsy techniques to break up bile or pancreatic duct stones: mechanical, electrohydraulic and laser. Mechanical lithotripsy is done using a metal-wire basket, used to catch stones. The basket wires are then tightened, which crushes the stones into smaller fragments for removal. In electrohydraulic and laser lithotripsy, a shock wave is delivered directly to the stone (generated by a high voltage spark or a laser beam respectively). The clinician needs to be able to clearly see the biliary ducts when using these lithotripsy techniques in order to avoid damage to the surrounding tissues (Heller 2013).

Approximately 48,000 ERCPs are performed each year in the UK (Green et al. 2007). However, the procedure has limitations, mainly that it cannot provide direct visualisation of the ducts. This is important in cases where the cause of biliary strictures is not known, cases where the distinction between malignant and benign tumours is problematic, and in cases where there are large, difficult to remove stones which may need electrohydraulic or laser lithotripsy.

In cases where direct visualisation of the ducts is necessary, a technique called cholangioscopy is used. To perform standard cholangioscopy, a small-calibre (less than 4.5 mm) endoscope (referred to as the 'baby' endoscope) is inserted through the working channel of a standard ERCP scope (referred to as the 'mother' endoscope) and into the biliary ducts. For a standard 'mother-baby' cholangioscopy such as this, 2 endoscopists are needed: 1 to operate the duodenoscope and the other to operate the cholangioscope. Limitations of the procedure include the fragility of the 'baby' scope, its

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high repair cost, the requirement for 2 endoscopists to be present, and the limited tip deflection which reduces the range of visualisation.

The SpyGlass system is designed to overcome some of the limitations of the 'mother-baby' technique to improve access to the biliary system and reduce the associated costs.

Technology overview

This briefing describes the regulated use of the technology for the indication specified in the setting described and with any other specific equipment referred to. It is the responsibility of health care professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The multiple components of the SpyGlass system (described in the next section) are individually CE marked as Classes 1 to 2b. All components of the SpyGlass system are distributed by Boston Scientific Corporation.

Description

The SpyGlass is a single-operator cholangioscopy system designed to overcome the limitations of the standard 'mother-baby' cholangioscopy procedure. As well as needing only a single operator, the SpyGlass has 4-way tip deflection and a single-use baby endoscope for access and delivery. The system allows users to visually examine the biliary ducts, take biopsy samples and treat large biliary stones by either electrohydraulic or laser lithotripsy. The current system produces fibre-optic images which are generally considered to be inferior to digital images taken with standard video endoscopes (Chen 2007, Alameel et al. 2013, Nguyen et al. 2013).

The system consists of non-disposable and disposable components. The disposable components are listed below:

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- The SpyScope access and delivery catheter (single use), a flexible catheter measuring 3.3 mm in diameter and 2300 mm in length, with single-operator controls. The SpyScope can be inserted through any duodenoscope with a 4.2 mm working channel. It has 3 dedicated ports:
  - 1 for water flushing and aspiration to clear the field of view
  - 1 for the fibre-optic SpyProbe
  - 1 for taking biopsies or applying electrohydraulic lithotripsy fibres (1.2 mm).
- The SpyBite biopsy forceps (single use), allowing biopsy specimens to be taken under direct visualisation.
- The SpyProbe direct visualisation probe (re-useable for up to 20 cases), which is a fibre-optic probe that contains a 6000-pixel image bundle, surrounded by approximately 225 light transmission fibres. There is a lens connected to the image bundle at the distal tip to capture images across a 70-degree field of view. The tip of the probe has 4-way deflection. When loaded into the dedicated optic port, it is designed for complete circumferential visualisation.

The non-disposable components are listed below:

- Light source and cable: the light source uses 300 W Xenon light technology. The light cable is composed of a flexible fibre-optic bundle that transmits the light to the SpyProbe (see below).
- High-resolution LCD monitor (1280 x 1024 pixel) that can attach to a cart.
- Camera system, which includes a camera controller, a camera head, ocular (a mechanical and optical coupler) and video cables for connection to the monitor. The camera uses a sensor that captures light and converts it to digital data which provide 3 types of video outputs (RGB, standard (S)-video or composite). The ocular aids focus and transmission of the image from the SpyProbe.
- Flexible 3-joint arm to hold the camera in place and out of the way.
- Water irrigation pump with footswitch. The irrigation pump and tubing provide water flow to the SpyScope catheter (see below) in order to clear the duct of debris and maintain clear visualisation. The footswitch controls the variable flow rate.

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- The cart, which provides space for the equipment along with 3 storage drawers to fit the system's storage trays.
- Large and small storage trays designed to protect the reusable SpyProbe.
- Power cable pack (5 cables of varying lengths to connect the non-disposable units to the isolation transformer).
- Isolation transformer, to manage all electrical demands of the equipment on the cart.

Optional components which are not part of the system and will need to be purchased separately are as follows:

- Electrohydraulic lithotripsy generator to create oscillating shock waves in short pulses that generate sufficient pressure to fragment the stone.
- Holmium laser.

The reported complications associated with the use of the SpyProbe are inflammation of the biliary system, duct trauma resulting in bleeding or perforation, infection, peritonitis and breakage of the SpyProbe with fragments remaining in the body (Boston Scientific 2007).

Intended use

The SpyGlass system is intended as a first- or second-line alternative to standard ERCP to provide direct visualisation of the biliary system during endoscopic procedures.

Setting and intended user

The SpyGlass system is intended for use in endoscopic units which have both the equipment and expert staff to carry out ERCP. The intended user is a clinician trained in ERCP endoscopy who performs a large number of ERCPs annually. In the UK this will most commonly be a gastroenterologist, an upper gastrointestinal surgeon or an interventional radiologist (Green et al. 2007).

Current NHS options

NICE guidance on gallstone disease states that people with bile duct stones should have ERCP before or at the time of laparoscopic cholecystectomy to remove the stones. If the

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stones cannot be cleared with ERCP, the guideline suggests biliary stenting for temporary biliary drainage until endoscopic or surgical clearance is achieved.

The British Society of Gastroenterology guidelines for the management of difficult to remove stones recommend that endoscopists performing ERCP should be able to supplement standard stone extraction techniques with mechanical lithotripsy when needed (Williams et al. 2008). If mechanical lithotripsy fails, electrohydraulic or laser lithotripsy should be used.

In the case of cholangiocarcinoma, symptoms from biliary obstruction in irresectable disease may be relieved by biliary stent placement. Stent placement resulting in adequate biliary drainage improves survival (Khan et al. 2012).

NICE is aware of other ultra-slim endoscopes that appear to fulfil a similar function to the SpyGlass, a full listing of which is outside the scope of this briefing.

Costs and use of the technology

The manufacturer was unable to provide a purchase price for the SpyGlass system. However, a poster presentation reported an operational cost of £1443 per procedure for the SpyGlass in Japan (Shibata et al. 2012).

A standard ERCP procedure needs to be performed before the SpyGlass can be used. If the NHS reference cost for minor diagnostic ERCP of £794 is added to the estimated cost of the SpyGlass procedure, the average cost per procedure is estimated as £2237. This is more than the weighted average cost (£1768) for all major therapeutic (GB05F-H), intermediate therapeutic (GB06E-H) and minor diagnostic (GB07Z) ERCP procedures (DOH 2013).

No other practical difficulties have been identified in using or adopting the technology. Boston Scientific offers training and ongoing in-case support at no extra cost, as part of the device purchase.

Likely place in therapy

The SpyGlass can be used as a first- or second-line procedure for the diagnostic and therapeutic management of indeterminate strictures and large stones of the biliary system

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when standard ERCP has been unsuccessful or is deemed to be inappropriate. The latter will be at the discretion of the clinician and may occur if MRI or CT findings indicate that ERCP is unlikely to be successful. The SpyGlass requires specialist training and is more expensive than standard ERCP, so it is currently available at only a limited number of centres (NHS Choices 2012b).

Specialist commentator comments

One specialist commentator stated that cholangioscopy with the SpyGlass is a technically demanding procedure which should only be performed by clinicians who carry out a large number of ERCPs annually. Another specialist commentator stated that the basic technical skills needed for both the SpyGlass and ERCP procedures are similar. Two specialist commentators stated that doing 1 or 2 procedures per month using the SpyGlass should be enough to maintain the skills of experienced clinicians who regularly perform ERCPs.

Two specialist commentators stated that ERCP is standard practice in the UK as the first-line procedure for managing biliary strictures and stones. One specialist commentator stated that use of the SpyGlass would vary between a general and a specialist teaching hospital. In specialist units it is more likely that it would be carried out as a first-line procedure because most people are referred from a general hospital after one or more failed attempts with ERCP. Nevertheless, since ERCP is the first step before introducing the cholangioscope, a case could be made that every procedure using the SpyGlass is initially intended as an ERCP session. One specialist commentator also noted that in his experience of working in a specialist unit, patients can be selected to have ERCP with the SpyGlass as a first-line procedure after the clinicians have reviewed their MRI or CT scan findings. One specialist commentator stated that the SpyGlass is currently used in approximately 5% of all the ERCP procedures, but that this is likely to increase to 10% in the next 10 years.

One specialist commentator stated that the SpyGlass has been the most useful development in endoscopic technology for biliary disease in the last 10 years. In their opinion, the SpyGlass offers a relatively cheap and user-friendly alternative to standard 'baby' endoscopes for patients with indeterminate biliary strictures and large stones. Without it, they would have needed repeated ERCPs, CT and MRI scans, biopsies and possibly surgery as a last resort. Without the SpyGlass direct lithotripsy, patients with large stones not managed with mechanical lithotripsy would have to have extracorporeal shock-wave lithotripsy. Success of the latter procedure varies, and patients often need multiple sessions and repeat ERCPs to fully remove the stones. As a result, the number of

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patients having bile duct surgery or complex liver surgery for gallstones might have been larger had the SpyGlass not been used.

One specialist commentator noted that the studies included in this briefing are representative of UK clinical practice. They show that for approximately 80% of patients who needed cholangioscopy with the SpyGlass, there was a significant clinical and cost-saving benefit compared with the alternative options mentioned above.

One specialist commentator noted that the main indications for cholangioscopy with the SpyGlass are for the treatment of difficult intraductal stones and assessment of indeterminate biliary strictures. The same commentator also noted that cholangioscopy will become the standard technique to provide a vehicle for other emerging diagnostic and treatment modalities such as confocal microscopy, other imaging techniques, and laser therapy.

One specialist commentator noted that, although the current version of the SpyGlass is the first single-operator cholangioscopy system, it has significant limitations. Among these are the steep learning curve associated with using the equipment and interpreting images, the fragility of the SpyProbe and the poor image quality delivered by the fibre-optic imaging. Two specialist commentators noted (and the manufacturer confirmed) that a new version of the SpyGlass is being developed which uses a micro videochip, and that this will address the current limitations to the SpyProbe.

Two specialist commentators noted that from their personal experience, cholangioscopy with the SpyGlass is safe. Although the fragility and deterioration of the SpyProbe is a common problem, it has never resulted in patient harm. One specialist commentator stated that from his clinical experience, the SpyProbe only lasts for 10 rather than 20 procedures.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women

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- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No particular equalities issues were raised in the preparation of this briefing.

Evidence review

Clinical and technical evidence

Regulatory bodies

Table 1 lists the summary of adverse events identified from searches of the Medicines and Healthcare Products Regulatory Agency website, or from the US Food and Drug Administration: Manufacturer and User Device Facility Experience (MAUDE) database.

Between 2007 and 2014, 122 events were identified in the MAUDE database. In 63 incidents it was reported that a patient for whom the SpyGlass was used was harmed. However, in many events, a causal relationship between the use of the system and patient harm could not be verified by the information contained in the database. Most were associated with the SpyProbe component, although the manufacturer states that the SpyProbe is reusable (for up to 20 procedures) it is recognised to be extremely fragile. This was identified as the main issue in most of the events. The most recent update to the SpyProbe design was in 2008.

Table 1 Summary of events identified in the MAUDE database for the system

SpyGlass component	Component number	Number of events	Death	Injury	Malfunction
SpyScope access and delivery catheter	M00546230	38	4	23	11
SpyBite biopsy forceps	M00546270	20	0	11	9

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SpyProbe direct visualisation probe	M00546030	58	2	22	34
Irrigation pump	M00546140	4	0	0	4
Total	All components	120	6	56	58

Clinical evidence

Only prospective studies were selected for inclusion in this briefing (see evidence selection), all of which were cohort studies.

Procedural success (diagnostic and therapeutic)

Chen et al. (2011) was the largest (n=297) and only multicentre cohort study to investigate the SpyGlass. The trial was conducted at 10 centres in the USA and 5 in mainland Europe. Procedural success was defined as the ability to see the target lesions, to collect biopsy specimens adequate for histological evaluation, and to see and remove biliary stones. Most patients in the study (86%) had experienced at least one failed attempt at ERCP before enrolment. The overall procedure success rate was 89% (95% confidence interval [CI] 84% to 92%). The incidence of serious procedure-related adverse events was 7.5% for diagnostic and 6.1% for stone treatment procedures (table 2).

The single-centre, USA-based cohort study (n=75) by Draganov et al. (2011) investigated the success of cholangioscopy with the SpyGlass using the same criteria as Chen et al. (2011). Most patients in the study (96%) had experienced at least 1 failed attempt at ERCP before enrolment. The overall procedure success rate was 93.3% and the incidence of procedure-related adverse events was 4.8% (table 3).

The single-centre cohort study (n=64) by Maydeo et al. (2011) evaluated the efficacy and safety of using the SpyGlass for holmium laser lithotripsy of biliary duct stones which were difficult to remove. Biliary stones were characterised as difficult to remove if they were: a) not amenable to treatment by mechanical lithotripsy or balloon sphincteroplasty, b) impacted, c) in the presence of Mirizzi's syndrome, and d) in the presence of lumen-occupying stone casts. Approximately half of the patients in the study (43%) had experienced at least 1 failed intervention with either balloon sphincteroplasty, mechanical lithotripsy or both before enrolment. Lithotripsy guided by the SpyGlass successfully

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cleared the ducts in 83.3% of patients after a single session, whereas 10 patients needs an extra session. The incidence of procedure-related adverse events was 13.5% (consisting of fever, transient abdominal pain and biliary strictures; table 4).

Diagnostic accuracy studies

The single-centre cohort study by Manta et al. (2013) investigated the diagnostic accuracy of endoscopic visualisation with the SpyGlass in distinguishing malignant from benign lesions in 52 people with indeterminate biliary lesions. The targeted biopsy obtained with the SpyBite was used as a reference test. Lesions were defined as malignant, suspicious or benign by 2 experienced endoscopists using predefined published diagnostic criteria. The SpyGlass visual assessment agreed with the histopathologic evaluation of the SpyBite-targeted biopsies in 32 of 42 (76 %) patients. The agreement between the SpyBite-targeted biopsies and histopathological assessment of the surgical specimen was 90%. Overall, by using the SpyGlass system, a definite diagnosis (using clinical or histopathological assessment) was made in 49 (94%) patients. Two adverse events (1 of cholangitis and 1 of pancreatitis) were reported (table 5).

Ramchandani et al. (2011) investigated the diagnostic accuracy of SpyGlass cholangioscopy in distinguishing between malignant and benign lesions in 36 people with indeterminate biliary lesions. The authors investigated agreement between visualisation and targeted biopsies obtained with the SpyGlass system during cholangioscopy. Final diagnosis was based on histopathological assessment of the excised surgical specimen or biopsy, fine-needle aspiration or clinical follow up after 6 months. Lesions were defined as malignant, suspicious or benign by 2 experienced endoscopists using similar criteria to Manta et al (2013). The SpyGlass visual assessment agreed with the histopathologic evaluation of the SpyBite-targeted biopsies in 24 of 27 (88%) patients. Agreement between the SpyBite-targeted biopsies and final diagnosis was 82%. Overall, by using the SpyGlass system, a definite diagnosis was made in 32 (89%) patients. Two adverse events were reported (1 cholangitis and 1 mild pancreatitis; table 6).

Nguyen et al. (2013) evaluated the diagnostic accuracy of ultrasound endoscopy and biopsy guided by the SpyGlass in patients who had indeterminate biliary strictures. The system successfully obtained a biopsy in 18 patients (95%) and provided tissue diagnosis in 16 (88%), with 2 false-negative results from extrinsic pathologies. There was 1 adverse event of severe cholangitis (table 7).

One study by Sethi et al. (2014) investigated the inter-observer agreement during

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cholangioscopy visualisation with the SpyGlass. The authors used anonymised video clips taken during cholangioscopy using the SpyGlass on 38 people. Images were specifically selected that could bias the diagnosis, such as manoeuvres using forceps, or stone fragments. The videos were scored by 7 experienced endoscopists on the presence and severity of 4 features: the presence of a mass inside the duct, stricture, hyperplasia and ulceration (table 8). The observers had only slight agreement on their presumed final diagnosis based on visualisation with the SpyGlass (k=0.18, standard error 0.022).

One single-centre cohort study by Siiki et al. (2014) investigated the clinical feasibility and diagnostic accuracy of cholangioscopy with the SpyGlass in 11 patients with primary sclerosing cholangitis. Direct visualisation of the epithelium at the site of the main stricture as well as taking the SpyGlass-guided biopsies was successful in all cases. Two patients developed moderate pancreatitis. These incidences were reported as adverse events (table 9).

The single-centre cohort study (n=16) by Balderramo et al. (2013) examined the role of cholangioscopy using the SpyGlass in the evaluation of biliary complications after liver transplant. The procedure was successfully completed in 93.8% of patients. The area of the anastomosis or the anastomotic stricture was successfully identified in all patients. One patient developed cholangitis after the procedure (table 10).

Table 2 Summary of the Chen et al. 2011 multicentre cohort study

Study component	Description
Objectives/ hypotheses	To explore the efficacy of cholangioscopy with the SpyGlass.
Study design	Prospective multicentre cohort study.
Setting	10 centres in the United States and 5 centres in Europe. Recruitment period between 2006 and 2009. All patients were evaluated at baseline, 48 to 72 hours and 1 month after the procedure.

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Inclusion/ exclusion criteria	Inclusion criteria: • age 18 years or older and • an indication for ERCP in conjunction with cholangioscopy. Exclusion criteria: • medically unfit to undergo ERCP or other endoscopic procedures.
Primary outcomes	Primary outcome: • procedural success defined as – the ability to visualise target lesions – collect biopsy specimens adequate for histological evaluation – visualise biliary stones and initiate fragmentation and removal. Secondary outcomes: • the impact of using the SpyGlass on managing conditions for which cholangioscopy procedures are indicated • rate of adverse events • the diagnostic sensitivity and specificity of biopsy guided by the SpyGlass.
Statistical methods	A sample size of 300 patients was calculated as sufficient for confirming non-inferiority to a more than 75% procedure success rate. Descriptive statistics consisted of the mean ±SD, median, and IQR. Binary proportions were computed with 95% CIs. Risk factors for adverse events were analysed by logistic regression.

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Participants	n=297, mean age was 62.9 years (SD=16.2), 48.8% were men and 51.2% were women. Of the patients having the study procedure, 64% had it on an outpatient basis. 86% of the patients had undergone ERCP at least once before. The most common pre-existing condition was cholangitis, which was present in 16% of the patients.
Results	The overall procedure success rate was 89% (95% CI 84% to 92%). Adequate tissue for histological examination was obtained from 88% of 140 patients who had a biopsy. The system's overall sensitivity in diagnosing malignancy was 78% for visual impression and 49% for guided biopsy. Sensitivity for intrinsic bile duct malignancies was higher for visual impression and guided biopsy (84% and 66%, respectively). The clinical management of conditions was altered in 64% of patients. The procedure was successful for 92% of the patients with stones and achieved complete stone clearance in 71%. The incidence of serious procedure-related adverse events was 7.5% for diagnostic cholangioscopy and 6.1% for stone treatment.
Conclusions	Evaluation of bile duct disease and biliary stone therapy can be safely performed with a high success rate by using the SpyGlass system.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; IQR, interquartile range.	

Table 3 Summary of the Draganov et al. 2011 single-centre cohort study

Study component	Description
Objectives/ hypotheses	To prospectively evaluate the feasibility, clinical efficacy, and safety of the SpyGlass system.

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Study design	Prospective single-centre cohort study.
Setting	USA centre. Recruitment period between November 2006 and August 2010. Follow up was at the end of the procedure, discharge from the endoscopy unit, and by phone call 24 hours after the procedure.
Inclusion/ exclusion criteria	Inclusion criteria: • all patients referred for ERCP. Exclusion criteria: • age younger than 18 years • pregnancy • inability to provide informed consent.

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Primary outcomes	Primary outcome: • procedure success was defined as — complete stone clearance for patients with stones — advancement of the SpyScope to the desired target, adequate visualisation, and successful application of all necessary diagnostic and therapeutic manoeuvres for patients with non-stone-related lesions. Secondary outcome: • time to set up the equipment • total procedure time • total time to use the SpyGlass • time for the SpyGlass-guided diagnostic or therapeutic manoeuvres • diagnostic findings • adequate sampling • successful therapeutic manoeuvres • rate of adverse events.
Statistical methods	Descriptive statistics consisted of the mean ± SD and frequencies.
Participants	75 patients, median age was 66 years (range, 22–96). 38 were men and 37 women. 70 patients were referred for cholangioscopy and 5 for pancreatoscopy. 26 (35%) of the patients were referred for lithotripsy.

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Results	Procedural success was achieved in 70 of 75 patients (93.3%). Complete stone clearance was achieved in 24 of 26 patients (92.3%). Cholangioscopy for non-stone-related indications was successful in 43 of 44 patients (97.7%). Pancreatoscopy was attempted in 5 patients and was successful in 3 (60%) patients. The mean total procedure time (standard ERCP plus the SpyGlass) was 64.3 minutes, the total time with the SpyGlass was 27.5 minutes, the mean visualisation time with the SpyGlass was 14.2 minutes, the mean sampling time using the SpyBite was 12.1 minutes, the mean treatment time with the SpyGlass was 8.4 minutes, and the mean set-up time was 5 minutes. There were 4 adverse events (4.8%).
Conclusions	ERCP-guided cholangio-pancreatoscopy with the SpyGlass system is technically feasible and can be successfully and safely performed in the majority of patients.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography.	

Table 4 Summary of the Maydeo et al. 2011 single-centre cohort study

Study component	**Description**
Objectives/ hypotheses	To evaluate the efficacy and safety of holmium laser lithotripsy guided by the SpyGlass for difficult biliary and pancreatic duct stones.
Study design	Prospective single-centre cohort study.
Setting	Asian centre. Recruitment period between March 2010 and February 2011.

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Inclusion/ exclusion criteria	Inclusion criteria: • bile duct stones that were not amenable to treatment by mechanical lithotripsy or balloon sphincteroplasty • patients with impacted stones • Mirizzi's syndrome • lumen-occupying stone casts. Exclusion criteria: • patients with stones that were easily managed by standard stone extraction balloon or basket or stones that packed the entire length of the bile duct completely • patients with a predisposition to bleeding • portal hypertension • distorted anatomy • malignant distal biliary strictures.
Primary outcomes	Primary outcome: • the ability to retrieve all biliary or pancreatic stones after laser lithotripsy. Secondary outcome: • procedure duration • rate of adverse events.
Statistical methods	Descriptive statistics consisted of the mean, median and IQR.

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Participants	64 patients, median age was 48 years (range, 24–80). 33 were men and 31 were women. The majority (66%) of the stones were located in the common bile duct. The mean size of the stones was 23.4 mm (range, 15–40).
Results	All 64 patients had successful fragmentation of biliary and pancreatic duct stones with the holmium laser. 50 patients had complete biliary duct clearance after a single session and 10 patients needed an additional session. All pancreatic duct stones were fragmented in a single session. Mean duration of the ERCP session was 45.9 minutes (range 30–90 minutes). Complications were mild and were encountered in 13.5% of the patients; fever (n=3), transient abdominal pain (n=4), and biliary stricture (n=1).
Conclusions	The SpyGlass facilitates trans-papillary access for holmium laser fragmentation of difficult biliary and pancreatic duct stones. The technique is safe and highly effective for single-setting duct clearance. Complications were minimal and transient.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; IQR, interquartile range; ERCP, endoscopic retrograde cholangiopancreatography.	

Table 5 Summary of the Manta et al. 2013 single-centre cohort study

Study component	Description
Objectives/ hypotheses	To prospectively evaluate the SpyGlass system in patients with indeterminate biliary lesions.
Study design	Prospective single-centre cohort study.

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Setting	European centre. Recruitment period between January 2009 and December 2011. Follow up was ≥1 year.
Inclusion/ exclusion criteria	Inclusion criteria: • adults referred for evaluation of indeterminate biliary strictures and filling defects identified at ERCP. Exclusion criteria: • no exclusion criteria provided.
Primary outcomes	Primary outcome: • diagnostic accuracy of the SpyBite-targeted biopsy results in comparison with surgical specimens or clinical follow up. Secondary outcome: • rate of adverse events.
Statistical methods	A sample size of 49 patients was calculated on the assumption that additional diagnostic information of 30% or more could be clinically significant (80% power and a 0.05 significance level). Descriptive statistics consisted of the mean ±SD, range, agreement, sensitivity, specificity, and positive and negative predictive values.
Participants	52 patients, mean age was 51 years (SD=12). 38 were men and 14 were women. The majority (34%) of the patients had cholangiocarcinoma. In 86% of the patients a stent was placed at the time of the procedure.

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Results	Overall, a definite diagnosis was made in 49 (94%) cases. Agreement of the SpyBite biopsy results with surgical specimen diagnosis was found in 38 of 42 (90%) cases. Sensitivity, specificity, and positive and negative predictive values were 88%, 94%, 96%, and 85% respectively. Procedure-related complications consisted of 1 case of mild cholangitis and 1 case of mild pancreatitis.
Conclusions	The SpyGlass system allowed adequate biopsy sampling and definite diagnosis with high accuracy in the majority of patients with indeterminate biliary lesions.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography.	

Table 6 Summary of the Ramchandani et al. 2011 single-centre cohort study

Study component	Description
Objectives/ hypotheses	To assess the accuracy of the SpyGlass system to differentiate malignant from benign disease in patients with indeterminate biliary lesions.
Study design	Prospective, single-centre cohort study.
Setting	Asian centre. Recruitment period between May 2009 and February 2010.

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Inclusion/ exclusion criteria	Inclusion criteria: • older than 18 years of age • had an ERCP for the evaluation of obstructive jaundice • diagnosed as having an indeterminate stricture or filling defect on ERCP. Exclusion criteria: • inability to give informed consent • medically unfit to undergo ERCP.
Primary outcomes	Primary outcome: • diagnostic accuracy. Secondary outcomes: • procedure success • adverse events.
Statistical methods	Descriptive statistics consisted of the mean, standard deviation, and IQR. Sensitivity, specificity, positive and negative predictive values.
Participants	36 patients, mean age was 48.3 years (range 27–68). 22 were men and 14 were women. The majority (50%) of the patients had cholangiocarcinoma.
Results	The overall accuracy of the SpyGlass visual impression for differentiating malignant from benign ductal lesions was 89% (32/36). The accuracy of the SpyBite-guided biopsies for differentiating malignant from benign lesions that were inconclusive on ERCP-guided brushing or biopsy was 82% (27/33) in an ITT analysis. Procedure time, 36±10.5 minutes (range, 20–65). Adverse events reported were 2 patients with cholangitis (5.6%), and 1 patient with mild pancreatitis (2.8%).

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Conclusions	Cholangioscopy with the SpyGlass and biopsies obtained with the SpyBite have a high accuracy with regard to confirming or excluding malignancy in patients with indeterminate biliary lesions.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; IQR, interquartile range; ERCP, endoscopic retrograde cholangiopancreatography.	

Table 7 Summary of the Nguyen et al. 2013 single-centre cohort study

Study component	Description
Objectives/ hypotheses	To evaluate the diagnostic accuracy of EUS and biopsy guided by the SpyGlass in patients who had biliary strictures with negative ductal brushing.
Study design	Prospective, single-centre cohort study.
Setting	Australian centre. Recruitment period between February 2010 to February 2012.
Inclusion/ exclusion criteria	Inclusion criteria: • patients who were referred for cholangioscopy with the SpyGlass to investigate difficult biliary strictures. Exclusion criteria: • no exclusion criteria provided.

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Primary outcomes	Primary outcome: • tissue diagnosis. Secondary outcome: • technical success • adverse events • clinical outcomes.
Statistical methods	Descriptive statistics consisted of the mean and standard error. Fisher's exact test was used for categorical data. Student's unpaired t-test was used for continuous data. The diagnostic yield of a biopsy guided by the SpyGlass was defined as per patient analysis.
Participants	40 patients, mean age was 57.4±2.4 years. 27 were men and 13 were women. The location of biliary stricture was the distal common bile duct in 15 patients, mid common bile duct in 4 patients, proximal/subhilar in 9 patients, and hilar in 12 patients.
Results	Biopsy guided by the SpyGlass was successful in 18 patients (95%) and provided tissue diagnosis in 16 patients (88%), with 2 false-negative results from extrinsic pathologies. Severe cholangitis occurred in one person.
Conclusions	EUS followed by cholangioscopy with SpyGlass provides correct clinical diagnosis in 94% of patients with minimal adverse events.
Abbreviations: EUS, ultrasound endoscopy; CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk.	

Table 8 Summary of the Sethi et al. 2014 single-centre cohort study

Study component	Description

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Objectives/ hypotheses	To assess the inter-observer agreement during cholangioscopy using the SpyGlass cholangioscopy.
Study design	Single-centre cohort study.
Setting	USA centre. Recruitment period between 2008 and 2010.
Inclusion/ exclusion criteria	Inclusion criteria: • videos were included if they contained images that would bias the diagnosis, such as manoeuvres with forceps, or stone fragments. Exclusion criteria: • no exclusion criteria provided.
Primary outcomes	Primary outcome: • inter-observer agreement. Secondary outcome: • diagnostic accuracy.
Statistical methods	The inter-observer agreement was measured using the Fleiss' kappa statistic along with 95% CI. K statistics were interpreted based on the convention by Landis and Koch: poor agreement, ≤0; slight agreement, 0.01–0.20; fair agreement, 0.21–0.40, moderate agreement, 0.41–0.60; substantial agreement, 0.61–0.80; almost perfect agreement: 0.81–1.00.3.
Participants	38 patients, median age 50 years (range, 19–78) with benign (n=34) and malignant (n=4) lesions. 21 were men and 17 were women. The majority (26%) were videos from patients with primary sclerosing cholangitis.

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Results	The overall inter-observer agreement was fair in scoring for the presence of a growth (K=0.28, SE 0.035) and stricture (K=0.32, SE 0.035). Scoring for ulceration was slight to fair (K=0.17, SE 0.035). There was only slight agreement for the presence of hyperplasia (K=0.11, SE 0.035), and presumed final diagnosis based on imaging (K=0.18, SE 0.022).
Conclusions	Inter-observer agreement of SpyGlass cholangioscopy images range from slight to fair.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; IQR, interquartile range; K, kappa;	

Table 9 Summary of the Siiki et al. 2014 single-centre cohort study

Study component	**Description**
Objectives/ hypotheses	To investigate the clinical feasibility and diagnostic accuracy of SpyGlass cholangioscopy in patients with primary sclerosing cholangitis.
Study design	Prospective, single-centre cohort study.
Setting	European centre. Recruitment period between March and August 2012.
Inclusion/ exclusion criteria	Inclusion criteria: • all patients referred for cholangioscopy with the SpyGlass due to progression of PSC. Exclusion criteria: • no exclusion criteria provided.

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Primary outcomes	Primary outcome: • technical success. Secondary outcomes: • frequency of adequate biopsies obtained • rate of adverse events.
Statistical methods	Descriptive statistics consisted of the median, range and frequencies.
Participants	11 patients, median age 45 years (range, 24–66). 6 were men and 5 were women. The median time from the diagnosis of PSC was 8 years (range 1–28 years).
Results	A brush sample or biopsy was successfully obtained in all cases. Samples were adequate for cytological and histological diagnosis in 9 (82%) and 10 patients (91%), respectively. Procedure-related complications consisted of 2 cases of moderate pancreatitis.
Conclusions	SpyGlass is useful for the evaluation of PSC.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; PSC, primary sclerosing cholangitis.	

Table 10 Summary of the Balderramo et al. 2013 single-centre cohort study

Study component	Description
Objectives/ hypotheses	To examine the role of cholangioscopy with the SpyGlass in the evaluation of biliary complications after liver transplantation.
Study design	Single-centre cohort study.

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Setting	European centre. Recruitment period between June and July 2009.
Inclusion/ exclusion criteria	Inclusion criteria: • adult recipients (age >18 years) of deceased donor LT with biliary complications who were referred for ERCP. Exclusion criteria: • a refusal to participate in the study • an inability to provide informed consent • pregnancy • living donor LT • previous Roux-en-Y hepaticojejunostomy • a confirmed malignancy of the biliary tree • advanced liver failure • coagulopathy • hemodynamic instability • sepsis.

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Primary outcomes	Primary outcome: • the feasibility of the procedure in LT recipients with adequate visualisation of anastomotic strictures, biliary anastomoses, and the bile duct mucosa • ability to obtain biopsy samples. Secondary outcomes: • the impact on endoscopic therapy • the incidence of adverse events • the total procedural time • other diagnostic findings.
Statistical methods	Descriptive statistics consisted of the mean ±SD, median and range. Diagnostic accuracy: agreement, sensitivity, specificity, and positive and negative predictive values. Categorical variables were compared with the Chi-square test or Fisher's exact test. Continuous variables were compared with the Student 2-tailed t-test or the Mann-Whitney U test. Associations were specified as odds ratios with confidence intervals established at 95%. A 2-sided probability value <0.05 was considered to be significant.
Participants	16 patients, mean age was 51 years (SD=12). 11 were men and 5 were women. The majority (81%) of the patients had LT due to HCV-related complications.

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Results	The procedure was successfully completed in 15 of the 16 patients (93.8%). The area of the anastomosis or biliary anastomotic stricture was successfully identified in all patients. The total cholangioscopy time was 26.8 6 10.1 minutes. 1 person developed cholangitis after cholangioscopy.
Conclusions	Cholangioscopy with the SpyGlass in LT recipients is feasible and allows adequate visualisation and tissue sampling of anastomotic fistulas and bile ducts.
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography; LT, liver transplant.	

Recent and ongoing studies

Seven ongoing or in-development trials with the SpyGlass were identified in the preparation of this briefing.

- NCT02166099: Choledochoscopy multicentre registry to record information and evaluate the impact of the SpyGlass for choledochoscopy on the management of pancreatico-biliary disorders. This is an ongoing study with estimated completion date in July 2015.
- NCT01414400: a study to investigate the frequency of possible bacterial entry into the bloodstream (bacteremia) and infectious complications associated with the use of the Spyglass during ERCP. The recruitment status of this study is unknown, estimated completion date was in May 2012.
- NCT02057146: Endoscopic evaluation of probe-based confocal laser endomicroscopy in the assessment of suspected premalignant lesions in the biliary duct and in the pancreas. This study is ongoing, the estimated completion date was October 2014.
- NCT01759979: Comparison of laser versus mechanical lithotripsy of bile duct stones. This study is ongoing, the estimated completion date is December 2015.

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- NCT01227382: Diagnostic accuracy of the use of SpyBite forceps when compared to standard biopsy techniques. This study is ongoing, the estimated completion date is September 2016.
- NCT01815619: Comparison of on-site versus off-site pathologic evaluation of cholangioscopy-guided biopsies of the bile duct. This study is ongoing, the estimated completion date is March 2015.
- NCT00861198: Investigation of the clinical utility of cholangioscopy and pancreatoscopy in the diagnosis and management of biliary disorders. This study is ongoing, the estimated completion date is February 2016.

Costs and resource consequences

The UK ERCP Stakeholders Working Party has stated that, based on information from surveys and audits, about 48,000 ERCPs are performed each year in the UK. The group agreed that the likely future incidence of ERCP amounts to 54,000 ERCPs per year across the UK (Green et al. 2007). The SpyGlass system could either be used as a first-line alternative for standard ERCP, or as a secondary modality for diagnosis and therapy in difficult cases. The number of cases where this could be used as a second-line treatment will be much smaller but it is not currently possible to estimate this with available information.

The adoption of the SpyGlass system would not require any change in the way in which current services are organised or delivered. SpyGlass is offered as a day case procedure, as is standard ERCP. The addition of SpyGlass to the care pathway would not increase the patient's hospital stay. No other additional facilities or technologies are needed alongside the technology. Since the intended user is a clinician trained in ERCP endoscopy, there may be a need to provide some training to use the single-use, single-operator controlled system. The manufacturer offers training and ongoing in-case support at no extra cost, as part of the system purchase.

The only published evidence on resource consequences of the SpyGlass system was a 2012 poster presentation that reported a cost of $2048 (£1443 at 2014 prices) for the SpyGlass system, compared with a cost of $1876 (£1322 at 2014 prices) for standard cholangioscopy (Olympus CHF-BP260) in Japan (Shibata et al. 2012). An Australian study compared the use of endoscopic ultrasound and guided biopsy with cholangioscopy with the SpyGlass as a first-line procedure in 40 patients who had biliary strictures (Nguyen et

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al. 2013). The authors reported cost-savings of £77,520 (in 2014 prices) over 2 years with this approach. As endoscopic ultrasound is not considered a first-line procedure in the UK, the relevance of their results for this briefing is unclear.

Strengths and limitations of the evidence

The evidence considered in this briefing ranged from small single-centre to medium size multicentre prospective cohort studies. No randomised controlled trials were identified.

All studies included in this briefing are observational studies without a control group. The observational study design could introduce potential bias and confounders, while the lack of a control group limits the conclusions that can be drawn from these studies. As a result, conclusions cannot be drawn on the potential advantages of using the system for obtaining targeted biopsies in comparison with methods without direct visualisation. Similarly, it remains unclear what proportion of people with stones might benefit from direct visualisation with the system in comparison with non-cholangioscopic approaches.

The observational study design may lead to patient selection bias. In most studies, the patients had already experienced at least 1 failed ERCP before being referred for cholangioscopy with the SpyGlass. For example in Draganov et al. (2011), the mean number of previous ERCP attempts was 3.31. As a result the people included in these studies had pathology that was more advanced or technically difficult to sample or treat. Nevertheless, because the system is intended for use as a secondary modality for diagnosis and therapy in difficult cases, the patient population included is representative of the people considered for the SpyGlass.

Because the indication in most of the studies is to perform cholangioscopy with the SpyGlass after ERCP has failed, it is difficult to design a study that includes a comparable control group: the obvious control is ERCP, which already forms part of the inclusion criteria. Other possible comparators, such as magnetic resonance cholangiopancreatography and endoscopic ultrasound, are not in current NHS use but could be used in future to design controlled studies with the SpyGlass.

Manta et al. (2013) and Chen et al. (2011) had sample size calculations for their primary outcome of procedural success and diagnostic accuracy respectively. However, most studies used a small sample size which reduced their statistical power. This reduces the probability of detecting a difference between groups where a difference exists (type II error), and will also increase the likelihood that a statistically significant finding is

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actually falsely positive (Christley 2010).

The study by Sethi et al. (2014) showed low inter-observer agreement using a set of images selected to represent a diagnostic challenge for the operator. However, their study design was not reflective of everyday clinical practice since most clinicians would not assign a diagnosis based on the cholangioscopy images alone.

The incidence of adverse events in these studies ranged from 4.8% to 13.5%, involving mainly post-procedure episodes of cholangitis and pancreatitis. Follow-up times for the adverse events rates were not clearly defined in all studies.

Lastly, the studies by Chen et al. (2011), Draganov et al. (2011) and Sethi et al. (2014) were funded by the manufacturer and this introduces the potential for bias in the reporting of outcomes.

The SpyGlass system is intended for use in both adults and children, yet very little clinical evidence exists for the safety and efficacy of the system in children. The retrospective case series by Harpavat et al. (2012) is of limited value as it included a small cohort. In 7 of the 11 patients included, the clinical management of the condition was changed because of the use of the SpyGlass cholangioscopy system. The procedure was well tolerated, with 2 cases presenting side effects (1 case of abdominal pain and 1 case of bacteraemia).

Relevance to NICE guidance programmes

The use of SpyGlass is not currently planned into any NICE guidance programme.

The NICE guideline on gallstone disease is relevant to this briefing.

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Search strategy and evidence selection

Search strategy

Embase 1980 to 2014 Week 39, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; searched 1 October 2014

1. Endoscopy, Digestive System/ or cholangioscopy.mp. or Cholangiopancreatography, Endoscopic Retrograde/

2. cholangiopancreatoscopy.mp.

3. cholecystoscopy.mp.

4. ercp.mp.

5. 1 or 2 or 3 or 4

6. single operator.mp.

7. direct visuali?ation.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]

8. 6 or 7

9. 5 and 8

10. spyglass.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]

11. 9 or 10

12. remove duplicates from 11

13. limit 12 to yr="2006 -Current"

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14. limit 13 to english language

15. remove duplicates from 14

The CRD database was searched using the following keywords:

- Any field: spyglass/OR
- Any field: single operator cholangioscopy/OR
- Any field: direct visualisation cholangioscopy

Evidence selection

Clinical evidence

For clinical evidence:

- Total number of publications reviewed: 388
- Total number of publications considered relevant: 42 (74 full publications and 91 abstracts)
- Total number of publications selected for inclusion in this briefing: 8 (8 full publications and 0 abstracts)
- Exclusion criteria: case studies, editorials, letters, reviews, animal studies, and non-English language studies, non prospective studies, ex-vivo studies.

Economic evidence

For economic evidence:

- Total abstracts: 34
- Duplicates: 0
- Abstracts reviewed: 34
- Full papers reviewed: 9

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- Exclusion criteria: case studies, editorials, letters, reviews, animal studies, non-English language studies, not using the SpyGlass
- Studies for review: 1 (poster presentation).

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by KiTEC. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

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