
1146.1:

Final Decision
Analytical Protocol
(DAP) to guide the
assessment of
capsule endoscopy
for patients with
suspected small
bowel Crohn's
disease

July 2013

Table of Contents

MSAC and PASC	3
Purpose of this document	3
Issue on which PASC seeks input	3
Purpose of application.....	4
Background	4
Current arrangements for public reimbursement	4
Regulatory status	6
Intervention	7
Description	7
Delivery of the intervention	8
Size of the eligible patient population in Australia	9
Prerequisites	10
Co-administered and associated interventions	10
Listing proposed and options for MSAC consideration	10
Proposed MBS listing	10
Clinical place for proposed intervention	12
Comparator	15
Clinical claim	15
Outcomes and health care resources affected by introduction of proposed intervention	16
Outcomes	16
Health care resources	18
Summary of PICO to be used for assessment of evidence (systematic review)	20
Proposed structure of the decision analytic economic evaluation	21
References	25
Appendix: Applicant’s response to issues in the prior assessment	26
Issues identified in the prior assessment	26
Safety	29

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol (DAP) that will be used to guide the assessment of capsule endoscopy for patients with suspected small bowel Crohn's disease. The draft protocol was prepared by Given Imaging and revised following PASC input. The DAP will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

PASC considered that the service should be performed within 6 months of the prior colonoscopy and radiographic imaging.

Issue on which PASC seeks input

The PASC invites comment on the following matters:

- Is it appropriate to require that capsule endoscopy is performed within six months of the prior radiographic imaging?

Purpose of application

This application requesting MBS listing of capsule endoscopy for patients with suspected small bowel Crohn's disease has been developed by Given Imaging for the Department of Health and Ageing (DoHA). Capsule endoscopy involves using a small pill-shaped camera to examine parts of the small intestine that cannot be seen by other types of endoscopy. By detecting mucosal abnormalities in the small bowel, capsule endoscopy can be used to diagnose patients with small bowel Crohn's disease who are unable to be diagnosed with colonoscopy with ileoscopy and small bowel radiology.

Capsule endoscopy will be used to provide an additional diagnostic modality to those currently available to confirm the diagnosis of Crohn's disease where there is residual diagnostic doubt. MSAC concluded that, in this overall context, a clear clinical need remains for confirmatory diagnosis in a residual small number (estimated at 5%) of patients for whom a clinical suspicion of small bowel Crohn's disease cannot be excluded.

Background

Current arrangements for public reimbursement

Capsule endoscopy is currently listed on the MBS to investigate an episode of obscure gastrointestinal bleeding (OGIB, Item 11820), or to conduct small bowel surveillance of a patient diagnosed with Peutz-Jeghers syndrome (Item 11823). The current MBS item descriptors for these two indications are presented in Table 1 **Error! Reference source not found.** and Table 2.

Table 1 Current MBS item descriptor for Item 11820

Category 2 – Diagnostic procedures and investigations
<p>MBS 11820</p> <p>CAPSULE ENDOSCOPY to investigate an episode of obscure gastrointestinal bleeding, using a capsule endoscopy device approved by the Therapeutic Goods Administration (including administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered), (not being a service associated with double balloon enteroscopy), if:</p> <p>(a) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and</p> <p>(b) the patient to whom the service is provided:</p> <ul style="list-style-type: none"> (i) is aged 10 years or over; and (ii) has recurrent or persistent bleeding; and (iii) is anaemic or has active bleeding; and <p>(c) an upper gastrointestinal endoscopy and a colonoscopy have been performed on the patient and have not identified the cause of the bleeding; and</p> <p>(d) the service is performed within 6 months of the upper gastrointestinal endoscopy and colonoscopy</p> <p>(e) the service is not associated with double balloon enteroscopy</p> <p>(f) the service has not been provided to the same patient:</p> <ul style="list-style-type: none"> (i) more than once in an episode of bleeding, being bleeding occurring within 6 months of the prerequisite upper gastrointestinal endoscopy and colonoscopy (any bleeding after that time is considered to be a new episode); or (ii) on more than 2 occasions in any 12 month period. <p>Fee: \$2,039.20 Benefit: 75% = \$1,529.40 85% = \$1,964.70</p> <p>Capsule endoscopy is primarily used to view the small bowel, which cannot be viewed by upper gastrointestinal endoscopy and colonoscopy.</p> <p>Conjoint committee</p> <p>The Conjoint Committee comprises representatives from the Gastroenterological Society of Australia (GESA), the Royal Australasian College of Physicians (RACP) and the Royal Australasian College of Surgeons (RACS). For the purposes of Item 11820, specialists or consultant physicians performing this procedure must have endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy, and Medicare Australia notified of that recognition.</p>

Table 2: Current MBS item descriptor for Item 11823

Category 2 – Diagnostic procedures and investigations
<p>MBS 11823</p> <p>CAPSULE ENDOSCOPY to conduct small bowel surveillance of a patient diagnosed with Peutz-Jeghers syndrome, using a capsule endoscopy device approved by the Therapeutic Goods Administration. The procedure includes the administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered (not being a service associated with double balloon enteroscopy).</p> <p>Medicare benefits are only payable for this item if:</p> <ol style="list-style-type: none"> 1. the service has been performed by a specialist or consultant physician with endoscopic training that is recognised by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and 2. the patient to whom the service is provided has been conclusively diagnosed with Peutz-Jeghers syndrome (PJS) <p>This item is available once in any two year period.</p> <p>Fee: \$2,039.20 Benefit: 75% = \$1,529.40 85% = \$1,964.70</p> <p>Conjoint committee</p> <p>The Conjoint Committee comprises representatives from the Gastroenterological Society of Australia (GESA), the Royal Australasian College of Physicians (RACP) and the Royal Australasian College of Surgeons (RACS). For the purposes of Item 11823, specialists or consultant physicians performing this procedure must have endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy, and Medicare Australia notified of that recognition.</p>

The utilisation of capsule endoscopy for these indications from 1 June 2003 to 31 July 2012 is presented in Table 3. Capsule endoscopy was first listed for interim funding in 2003 for the treatment of OGIB. The indication was extended to include Peutz-Jeghers syndrome in 2008. Between 1 June 2011 and 31 July 2012, a total of 8,989 services were claimed for both indications.

Table 3 Utilisation of MBS items 11820 and 11823 between 2007 and 2012 (financial year 1 June -31 July)

Item number	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012
11820	134	2,556	3,613	4,957	6,240	7,341	8,165	8,485	8,950
11823	0	0	0	0	0	3	31	27	39
Total	134	2,556	3,613	4,957	6,240	7,344	8,196	8,512	8,989

Source: <https://www.medicareaustralia.gov.au/>

Capsule endoscopy is currently not funded through Medicare for the diagnosis of suspected small bowel Crohn's disease. Patients who wish to use capsule endoscopy to diagnose small bowel Crohn's disease after having failed other diagnostic techniques must pay for the procedure out of their own pockets. In a small number of cases, the procedure may also be paid for by public hospitals.

In the Public Summary Document for the previous application, MSAC noted that a proportion of patients with undiagnosed Crohn's disease may present with OGIB and would currently undergo capsule endoscopy under MBS item 11820 (MSAC 2011, pg. 8).

Regulatory status

PillCam® SB capsules (Given Imaging) have been registered by the TGA since August 2006 (see Table 4). There are no specific conditions on its TGA certification.

Table 4 Registration of PillCam® SB capsule endoscopy with the TGA

ARTG no	Product no	Product description	Device class	Sponsor
130833	215817	Given diagnostic system and PillCam® SB capsule endoscopy (capsule, non-digestible, electronic tracking)	Class IIa	Given Imaging Pty Ltd

Source: TGA (2013)

Other brands of capsule endoscopes that are TGA-listed are:

- MiRo-Cam (Intromedic)
- EndoCapsule (Olympus)
- CapsoVision (CapsoVision Inc.)

The PASC determined that the assessment of capsule endoscopy should include all capsule endoscope devices currently registered by the TGA. The item descriptor for the requested indication should not specify a particular brand of device.

Intervention

Description

Capsule endoscopy is a minimally invasive diagnostic test, conducted in an outpatient setting, in which the gastrointestinal system is visualised via a camera inside an ingested capsule. As the capsule passes through the digestive system, it transmits multiple digital images of the small bowel to sensors on a belt attached to the patient's abdomen. The test visualises the gastrointestinal tract mucosa to diagnose a range of conditions such as OGIB, coeliac disease and small bowel tumours.

The current application requests an extension to the current MBS listing for capsule endoscopy to also include the diagnosis of suspected small bowel Crohn's disease. Crohn's disease is a chronic inflammatory bowel disease that may affect any portion of the gastrointestinal tract but, in cases of small bowel involvement, typically affects the terminal ileum (Yamada et al., 2009). Crohn's disease is believed to be caused by interactions between environmental, immunological and bacterial factors in genetically susceptible individuals. These factors result in a chronic inflammatory disorder, in which the body's immune system attacks the gastrointestinal tract possibly directed at microbial antigens. It primarily causes abdominal pain, diarrhoea, vomiting, or weight loss, but may also cause local complications (e.g., bleeding, obstruction, fistulae) and complications outside the gastrointestinal tract (e.g., skin rashes, arthritis, inflammation of the eye and fatigue).

The primary goal in treating Crohn's disease is to reduce the underlying inflammation, which then relieves symptoms, prevents complications, and corrects nutritional deficiencies. Medications used in reducing inflammation in Crohn's disease include anti-inflammatory drugs, corticosteroids,

immunosuppressants, biologic agents such as TNF-alpha inhibitors, and antibiotics. If drugs are not successful in suppressing inflammation, the alternative is surgery to remove the diseased part of the intestine.

Most patients with isolated small bowel Crohn's disease are diagnosed using colonoscopy with ileoscopy; however diagnosis can be difficult due to the inaccessibility of the small bowel. Capsule endoscopy is able to visualise areas of the small bowel inaccessible to upper and lower endoscopy. Capsule endoscopy will be positioned after small bowel follow through (SBFT) or computed tomography (CT) with or without enterography or magnetic resonance imaging (MRI) with or without enterography. Capsule endoscopy will provide an additional testing modality prior to treatment, based on a suspicion of small bowel Crohn's disease which could not be confirmed through prior testing.

Other techniques used in the diagnosis of Crohn's disease, such as balloon enteroscopy and push enteroscopy, are not widely used and not currently funded by Medicare for the investigation of suspected small bowel Crohn's disease. Therefore, capsule endoscopy should be essentially regarded as a last-line approach to diagnosis, for use in patients who cannot be diagnosed through using other tests. The procedure will be restricted to patients with suspected but unconfirmed small bowel Crohn's disease, as indicated by ongoing symptoms suggestive of Crohn's disease such as abdominal pain, diarrhoea, extraintestinal symptoms or raised inflammatory markers on blood tests.

The PASC determined that patients with known strictures previously identified through small bowel imaging (SBFT, CT or MRI) will not be eligible to undergo capsule endoscopy.

Delivery of the intervention

Capsule endoscopy relies on three pieces of equipment – a video capsule, a data recorder and a workstation. The capsule is disposable and ingestible and contains micro-imaging video technology which includes a battery, camera, transmitter, antenna and light emitting diodes (Sidhu et al., 2008). The data recorder is a system worn at the waist that receives the transmitted images via radiofrequency data transmission. The workstation is a dedicated computer station to which data and images are uploaded for analysis by the clinician.

The procedure may be performed in an outpatient setting. After bowel preparation, where necessary, and fasting for 8 to 12 hours, the patient presents at the specialist's private room (or clinic) to have the data recorder fitted and to swallow the capsule endoscope with a glass of water (Sidhu et al., 2008). Images and data are acquired as the capsule endoscope passes through the digestive system over an 8-hour period. This information is transmitted to the portable recorder attached to a belt worn around the patient's waist. Once the patient swallows the capsule, they can continue with their daily activities. After eight hours, they return to the physician's office with the recorder so the images can be downloaded and reviewed by the physician. The disposable capsule will usually be excreted naturally between 24 and 72 hours after ingestion.

The PASC considered that technical failure rates were likely to be low but that a technical failure would result in a second Medicare claim for a repeat capsule endoscopy procedure. Repeat procedures due to technical failure should be included in the economic evaluation.

If the capsule endoscope is unable to adequately visualise the small bowel for reasons other than technical failure, this would be identified in studies of diagnostic accuracy and will also be accounted for in the economic evaluation. Once a successful reading has been made, it is not expected that capsule endoscopy would be used again in relation to suspected small bowel Crohn's disease. It is proposed that the number of capsule endoscopies allowed for each patient should be limited to a maximum of two per year, to allow for repeat procedures due to technical or other failures.

Patients with Crohn's disease typically have a higher frequency of strictures than other forms of inflammatory bowel disease. The presence of strictures can be identified through prior small bowel imaging with SBFT, CT and/or MRI, which, according to the requested MBS restriction, are prerequisites for access to capsule endoscopy in patients with suspected Crohn's disease. The sensitivity of CT enteroscopy (CTE) and MRI enteroscopy (MRE) in identifying strictures is well-established (Vogel et al., 2007).

Consistent with other MBS listings of capsule endoscopy, it is presumed that capsule endoscopy services will only be reimbursed for public funding when performed by a specialist or consultant physician with endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (and Medicare Australia is notified of that recognition).

Size of the eligible patient population in Australia

So far there is a lack of prevalence data on Crohn's disease in Australia. According to the ABS National Health Survey (NHS) 2004-05, which is based on self-reported data, there were 51,900 people (18,600 males and 33,400 females) with Crohn's disease and ulcerative colitis in Australia in that year. This was equivalent to a prevalence rate of 0.26%. An Access Economics report on the economic costs of Crohn's disease and ulcerative colitis (Access Economics, 2007) combined these data with other sources to estimate that there were 28,000 Australians with Crohn's disease in 2005. As capsule endoscopy will be used in patients with suspected Crohn's disease (i.e. those who have not been diagnosed yet), the prevalence rate is not as important for estimating utilisation as the incidence rate.

Incidence data for Crohn's disease are also scarce; however, one Australian study in the regional Victorian city of Geelong found a crude annual incidence of 17.4 (95% CI =13 to 23) per 100,000 in 2008 (Wilson et al 2010). Using Australian Bureau of Statistics (ABS) population projections, it is expected that the incidence of Crohn's disease in 2013 will be 3,998 patients. Approximately 70% (2,799) of cases will be diagnosed using endoscopy, as there is no small intestine involvement. Because of some of the symptomatic similarities between Crohn's disease and OGIB, a number (approximately 11%) of patients with suspected Crohn's disease will have previously undergone capsule endoscopy using the MBS listing for suspected OGIB. Of those patients who weren't diagnosed through endoscopy (including capsule endoscopy for OGIB), it is estimated that up to 82% could be subsequently diagnosed using CT or CTE (Solem et al., 2008). Once these cases are subtracted from the original incidence of Crohn's disease, there remain approximately 160 unconfirmed true cases of the condition.

Prerequisites

According to the proposed MBS item descriptor, patients eligible to receive capsule endoscopy will have undergone prior endoscopy, including colonoscopy with ileoscopy, and prior radiographic imaging with SBFT, CT/CTE or MRI/MRE.

Capsule endoscopy is already used in Australia, and is currently listed on the MBS to investigate an episode of OGIB (Item 11820), or to conduct small bowel surveillance of a patient diagnosed with Peutz-Jeghers syndrome (Item 11823). If the requested indication is also funded, the technology will continue to be used by the same providers who already have the minimal infrastructure in place.

Co-administered and associated interventions

Capsule endoscopy does not involve or require co-dependent assessment by MSAC or the PBAC. The therapies used by patients diagnosed with Crohn's disease will not change if capsule endoscopy is reimbursed. The clinical claim presented in the current DAP is that by using capsule endoscopy, the proportion of patients who are incorrectly treated (usually with salicylates [e.g., 5-aminosalicylic acid, 5-ASA] or corticosteroids) will decrease.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed MBS item descriptor is presented in Table 5 below.

The PASC determined that the proposed service would be limited to patients aged 2 years and over, consistent with the current TGA listing.

The procedure will be restricted to patients aged 2 years and over with suspected but unconfirmed small bowel Crohn's disease, as indicated by ongoing symptoms suggestive of Crohn's disease such as abdominal pain, diarrhoea, extraintestinal symptoms and raised inflammatory markers on blood tests. Patients who are eligible for capsule endoscopy will have undergone prior endoscopy or radiographic imaging and not have received a confirmed positive or negative diagnosis for Crohn's disease or evidence of strictures.

The PASC considered that patients with suspected strictures on prior imaging would be excluded. Consequently, the PASC determined that the use of a patency capsule was outside the scope of the current DAP.

Radiographic imaging may include magnetic resonance imaging with or without enterography (MRI/MRE), computed tomography with or without enterography (CT/CTE) or SBFT. It should be noted that CT/CTE and SBFT are currently reimbursed through Medicare for the diagnosis of Crohn's disease, while an application to MSAC for the use of MRI/MRE in the same indication is currently being assessed (MSAC Application 1190).

The PASC considered that the service should be performed within 6 months of the prior colonoscopy and radiographic imaging. The PASC also determined that the item descriptor should limit the number of services to 2 in any 12 month period.

The wording around the requirement that capsule endoscopy be administered by a specialist or consultant physician with endoscopic training that is recognised by the Conjoint Committee is adapted from the existing item descriptors for capsule endoscopy in the diagnosis of OGIB and Peutz-Jeghers Syndrome.

Table 5: Proposed MBS item descriptor

Category 2 – Diagnostic procedures and investigations
<p>MBS TBD</p> <p>CAPSULE ENDOSCOPY to diagnose suspected small bowel Crohn's disease, using a capsule endoscopy device approved by the Therapeutic Goods Administration (including administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered), if:</p> <p>(a) the patient to whom the service is provided:</p> <ul style="list-style-type: none"> (i) is aged 2 years or over; and (ii) has not previously been diagnosed with Crohn's disease; and (iii) has suspected small bowel Crohn's disease on the basis of clinical findings and evidence of underlying inflammation, as indicated by elevated Erythrocyte Sedimentation Rate and/or C-Reactive Protein or other inflammatory markers; and <p>(b) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and</p> <p>(c) prior negative endoscopy including colonoscopy with ileoscopy has been performed on the patient, and has not produced a confirmed positive or negative diagnosis of Crohn's disease; and</p> <p>(d) prior radiographic imaging has been performed on the patient, and has not produced a confirmed positive or negative diagnosis of Crohn's disease or evidence of strictures. Radiographic diagnostic procedures previously used by the patient may include:</p> <ul style="list-style-type: none"> (i) computed tomography with or without enterography (CT or CTE), or (ii) small bowel follow through (SBFT) testing; or (iii) magnetic resonance imaging with or without enterography (MRI or MRE); and <p>(e) the service is performed within 6 months of the colonoscopy and radiographic imaging; and</p> <p>(f) the service is not associated with balloon enteroscopy; and</p> <p>(g) the service has not been provided to the same patient on more than 2 occasions in any 12 month period.</p> <p>Fee: \$2,039.20 Benefit: 75% = \$1,529.40 85% = \$1,964.70</p> <p>Conjoint committee</p> <p>The Conjoint Committee comprises representatives from the Gastroenterological Society of Australia (GESA), the Royal Australasian College of Physicians (RACP) and the Royal Australasian College of Surgeons (RACS). For the purposes of Item TBD, specialists or consultant physicians performing this procedure must have endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy, and Medicare Australia notified of that recognition.</p>

Clinical place for proposed intervention

Precise diagnosis is essential for the effective treatment of Crohn's disease; however, achieving a definitive diagnosis can be difficult, partly because of the inaccessibility of the small bowel. Therefore, the diagnostic algorithm for Crohn's disease is based on a composite of endoscopic, radiographic, and pathological findings.

Optimal health outcomes are achieved through accurately identifying positive cases of Crohn's disease, and excluding patients without Crohn's disease as early as possible in the diagnostic pathway. A suspicion of Crohn's disease is usually established on the basis of history, physical examination and the results of blood tests for inflammatory markers, anaemia and infection. Initial assessment usually involves endoscopy, which is reported to be effective in diagnosing approximately 70% of cases (usually those without small intestine involvement). Upper or lower GI endoscopy is used to confirm the diagnosis of Crohn's disease, assess disease location, or obtain tissue for pathological evaluation. Endoscopy can also serve a therapeutic role in the dilation of strictures, particularly those at a surgical anastomosis (Lichtenstien et al., 2009).

If these procedures are unable to achieve a diagnosis, radiologic imaging including MRI, CT or SBFT testing may be used. The effectiveness of these tests is an important determinant of the prevalence of Crohn's disease in patients eligible for investigation with capsule endoscopy. Therefore, the impact of prior testing and applicability of included studies should be considered in an assessment of the safety, effectiveness, cost-effectiveness of capsule endoscopy. A description of each of these radiologic techniques is provided below.

Abdominal CT and CTE

Abdominal CT is a radiological technique used in the diagnosis of small bowel Crohn's disease. This test provides multiplanar images of the lumen, wall and mesentery of the small bowel. These images have a high degree of spatial resolution and are generated via the use of multidetector CT technology following the ingestion of a contrast agent by the patient, either orally (enterography) or via a nasogastric tube (enteroclysis) (Fletcher et al., 2009). In some Australian settings, CTE has superseded barium imaging as the main form of radiological imaging used in the diagnosis of Crohn's disease

Abdomen CT is funded under MBS item 56507 with a fee of \$480.05.

SBFT

SBFT is a radiological technique for imaging the small bowel. Barium is either ingested by the patient or administered via enteroclysis and then x-ray images are taken of the abdomen. In recent years, MR and CT enterography have overtaken SBFT the most commonly used tools for imaging the small bowel in suspected Crohn's disease (Morrison et al., 2009).

SBFT is funded under MBS item 58915 with a fee of \$78.95.

MRI and MRE

MRI is an imaging technique that enables cross-sectional imaging of the small bowel (Yamada 2009). Contrast agents can be administered orally (MRE) or through a nasogastric tube (magnetic resonance

enteroclysis) (Markova et al 2010). Compared with CT, which uses x-ray attenuation, MRI uses multiple tissue parameters to build an image **but, unlike CT and SBFT, does not use ionising radiation.**

MRI is not currently funded through the MBS for small bowel Crohn's disease.

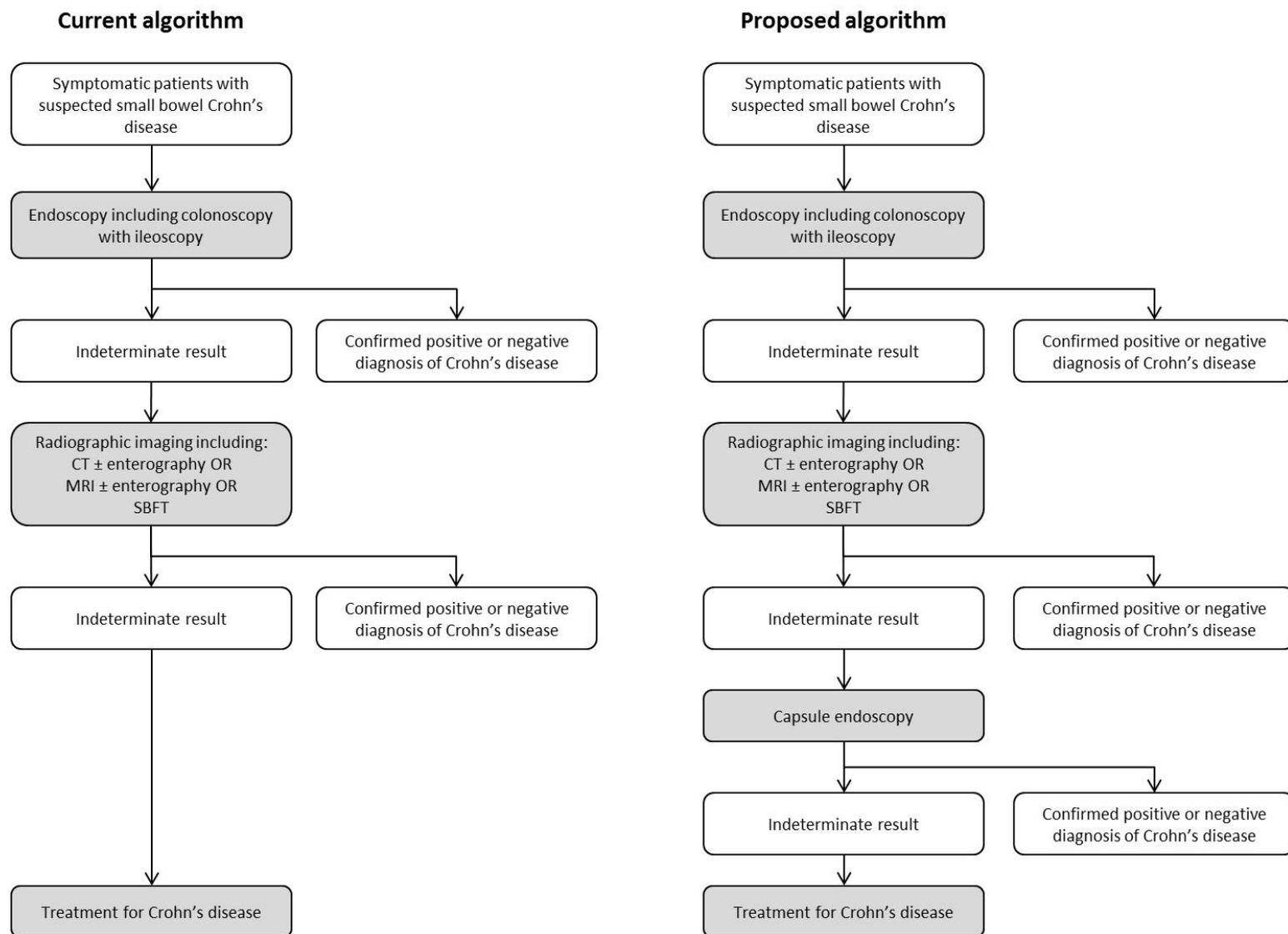
A DAP to guide the assessment of MRI for small bowel Crohn's disease has been prepared (MSAC ID 1190).

The current and proposed diagnostic algorithms for Crohn's disease are presented in Figure 1. Under the current scenario, if a patient still has unconfirmed disease after going through endoscopic and radiographic testing, the only option currently available to patients is presumptive treatment. Note that prior investigations such as colonoscopy, SBFT, CT and MRI are able to make a diagnosis of Crohn's disease in the majority of patients but not in all because of their inability to examine the small bowel mucosa directly. This means that they cannot definitely exclude Crohn's disease if no abnormality is found.

Patients in whom there is a high clinical suspicion of Crohn's disease but who have received inconclusive results from prior endoscopy and radiography are treated under the assumption that they have Crohn's disease, and diagnosis is achieved via response to treatment. In most cases, first-line treatment for small bowel Crohn's disease involves the use of anti-inflammatory agents such as 5-ASA. If patients do not achieve remission with anti-inflammatory drugs, corticosteroids such as oral prednisolone may also relieve symptoms. Maintenance therapy consists of continued use of salicylates or immune-modulators such as azathioprine, 6-mercaptopurine or methotrexate. Patients who fail all of these therapies may be treated with biological agents such as infliximab or adalimumab (Morrison et al., 2009).

Treatment may identify patients with Crohn's disease that are responsive to first-line therapies; however it also carries the risk of unnecessarily exposing non-Crohn's patients to therapies with potentially severe side effects. The benefit associated with treatment is lower in populations with a lower prevalence of Crohn's disease, such as those covered by the current DAP, who have already undergone a range of prior tests.

Figure 1 Current and proposed diagnostic algorithms for patients with suspected small bowel Crohn's disease



Comparator

The PASC noted that capsule endoscopy will not replace treatment. Capsule endoscopy will be used as an additional test prior to treatment. Consequently, the PASC determined that the appropriate comparator for capsule endoscopy is 'no capsule endoscopy'.

Consistent with the current and proposed treatment algorithms presented in Figure 1, the comparator for capsule endoscopy in the diagnosis of suspected Crohn's disease is 'no capsule endoscopy'. The approach to the submission is therefore a cost-effectiveness analysis of capsule endoscopy compared to current clinical practice.

To be eligible for reimbursement, patients with suspected Crohn's disease will have to first undergo endoscopy and at least one form of radiographic imaging, including CT, MRI or SBFT and have no evidence of strictures. In the PSD for the previous MSAC application, MSAC noted the existence of other diagnostic options such as balloon endoscopy (BE) and push endoscopy, but agreed that from a consumer's perspective, capsule endoscopy would be preferable on the grounds of comfort and risk. As BE and push endoscopy are not currently funded for the investigation of Crohn's disease and are not widely used, they are not considered to be appropriate comparators for capsule endoscopy.

Clinical claim

The PASC determined that the main clinical claim in the current DAP is that capsule endoscopy will identify a subgroup of the tested patients for whom a diagnosis of Crohn's disease is excluded. These patients will then avoid inappropriate treatment for Crohn's disease. A key risk associated with this use of capsule endoscopy is that patients may receive a false negative test result and will not receive the required treatment.

While prior tests such as colonoscopy, CT, MRI and SBFT cannot necessarily exclude Crohn's disease, capsule endoscopy can provide definitive diagnoses in patients with and without Crohn's disease (i.e. fewer patients with an uncertain diagnosis). As a result patients without Crohn's disease may be spared the unnecessary harms associated with treatment.

Therefore, the approach taken in the economic evaluation will be a cost-utility analysis, showing that capsule endoscopy is cost-effective compared to no capsule endoscopy in the requested indication. Table 6 shows that cost-utility analysis will be the appropriate form of economic evaluation provided that the assessment can establish the superior effectiveness and superior safety of capsule endoscopy.

Table 6: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	CEA/CUA		CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

The health outcomes upon which the comparative clinical performance of 'capsule endoscopy' testing versus 'no capsule endoscopy' will be measured are based on the impact of testing on treatment decisions and treatment effectiveness. The assessment will present clinical evidence demonstrating that additional health outcomes of capsule endoscopy are generated by additional diagnostic value offered by capsule endoscopy, improving the effectiveness of downstream disease management via improvement in the selection of treatment strategies. That is, in the comparator arm with no capsule endoscopy, all patients presenting with suspected Crohn's disease at baseline would receive treatment for Crohn's disease based on the findings from the previous tests (i.e., CT, MRI, and SBFT). With capsule endoscopy, fewer patients would receive inappropriate treatment for Crohn's disease, thereby improving health outcomes.

The literature review should focus on studies in which the patient population is applicable to the requested listing and consistent with the proposed positioning of capsule endoscopy.

Outcomes

The assessment will present evidence to show that capsule endoscopy leads to improved clinical outcomes in patients with suspected but unconfirmed Crohn's disease, and who could not be diagnosed with prior endoscopy and small bowel imaging, including CT, MRI or SBFT. As noted above, additional health outcomes generated by capsule endoscopy reflect the additional diagnostic value offered by capsule endoscopy, thereby improving the effectiveness of downstream disease management via improvement in the treatment strategy.

The literature review will initially search for direct evidence for the impact of capsule endoscopy on health outcomes; however, based on the results of the previous MSAC Assessment Report for capsule endoscopy in suspected Crohn's disease, it is unlikely that direct evidence will be available. In this case, the assessment may present indirect evidence for the impact of capsule endoscopy on clinical management and patient outcomes i.e. a linked evidence approach. The use of a linked evidence approach is not unusual when looking at the impact of a diagnostic test on clinical outcomes. Studies that might be used in a linked evidence approach include the following:

1. Diagnostic accuracy and diagnostic yield studies of capsule endoscopy in the appropriate population.
2. Studies demonstrating that a capsule endoscopy result leads to a change in patient management.
3. Studies reporting health outcomes and costs in treated/untreated patients with Crohn's disease, a non-Crohn's condition, and patients with an unconfirmed diagnosis.

Where relevant, these studies will provide comparative data with no testing; however, if needed, the search will also include non-comparative studies, or studies including comparisons with other diagnostic modalities.

Specific outcomes that will be searched for in these studies include:

- Diagnostic performance (negative predictive value, positive predictive value, sensitivity, specificity, additional true/false positives, ROC, AUC, Q*, DOR)
- Diagnostic yield
- Impact on patient management
- Patient outcomes (Crohn's disease treatment outcomes, Crohn's disease morbidity, quality of life)
- Safety (retention, adverse events (AEs) associated with capsule endoscopy, treatment-related AEs)

The PASC noted that the risk of capsule retention was low, as patients with small bowel strictures will have been excluded based on prior imaging. If capsule retention occurs, the capsule would be removed surgically or by balloon enteroscopy.

While the literature review will include any studies reporting the aforementioned outcomes, it should be noted that some outcomes may not be identified.

The main clinical claim in the current DAP is that capsule endoscopy will identify a subgroup of the tested patients for whom a diagnosis of Crohn's disease is excluded. These patients will then avoid inappropriate treatment for Crohn's disease. For this claim, the negative predictive value of capsule

endoscopy is the key measure of diagnostic performance, as patients who test negative for Crohn's disease using capsule endoscopy will not receive treatment.

As noted previously, prior investigations such as colonoscopy, SBFT, CT and MRI are able to make a diagnosis of Crohn's disease in the majority of patients but not in all because of their inability to examine the small bowel mucosa directly. This means that they cannot definitely exclude Crohn's disease if no abnormality is found. It is therefore expected that the population eligible for investigation using capsule endoscopy will include a lower prevalence of patients with Crohn's disease than the general population of patients with suspected Crohn's disease. The value of capsule endoscopy will therefore be its ability to exclude the diagnosis in patients without Crohn's disease, and spare them from unnecessary treatment. Therefore, the health outcomes of patients without Crohn's disease are the key outcomes of interest in this assessment.

If the review of clinical evidence demonstrates improved health outcomes as a result of the use of capsule endoscopy, cost-effectiveness and cost-utility analyses would be relevant, and health outcomes would need to be measured as life-years gained and quality-adjusted life-years gained. The relevant patient outcomes are expected to include Crohn's disease progression, treatment selection, morbidity and quality of life.

Health care resources

The use of capsule endoscopy will not alter the treatment of Crohn's disease or any of the diagnostic modalities that precede it in the clinical management pathway. It will, however, alter the proportion and/or timing at which patients receive treatment for Crohn's disease and other conditions. The effect of the introduction of capsule endoscopy on resource use, including hospitalisations and the management of side effects, will also be considered. The proposal therefore includes the costs for the following health care resource items

- Costs for capsule endoscopy
- Costs of retention and other AEs in patients receiving capsule endoscopy
- Costs associated with treatment of patients with suspected Crohn's disease
- Costs associated with the management of Crohn's disease and other bowel diseases
- Costs associated with the management of AEs in patients receiving treatment for Crohn's disease or other bowel diseases

A non-exhaustive list of the resources that would need to be considered in the economic analysis is provided in Table 7. The current MBS item fee for capsule endoscopy (based on MBS item numbers 11820 and 11823) is \$2,039.20. The listed 85% reimbursement fee for capsule endoscopy is \$1964.70. Consequently, the benefit amount and not the full MBS fee will be used in the cost calculations, as using the full fee would double count some of the copayment contribution. According to the 2011 MSAC Assessment report for capsule endoscopy, the average copayment for capsule endoscopy performed in an outpatient setting is \$32.95, which is the average aggregated copayment for MBS items 11820 and 11823 based on their respective number of services.

Table 7 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to deliver capsule endoscopy										
- Capsule endoscopy	Given	Outpatient	100%	1						\$2,039.20
Cost of capsule retention										
- 1936X Prednisolone			The costs of capsule retention will be presented in detail in the re-submission.							
- 30682 Double balloon enteroscopy (DBE)										
- G44C Day hospital facilities (DBE)										
- G05B Surgery (bowel resection)										
Treatment of patients with confirmed diagnosis of Crohn's disease										
- 1936X Prednisolone, 2687K Azathioprine, 9206M Mesalazine			The use of treatments for Crohn's disease will be presented in detail in the re-submission.							
- 13918 Administration cost – IV infusion										
- 110/116 Consultant physician, referred consultation										
- AAC27 Casualty visits										
- G05B Hospitalisation										
- 23 General Practitioner										
- 66512 Blood tests: LFT, U&E, CRP										
Treatment of patients with suspected diagnosis of Crohn's disease										
- 1936X Prednisolone, 2687K Azathioprine, 9206M Mesalazine			The use of treatments for alternative diagnoses will be presented in detail in the re-submission.							
- 13918 Administration cost – IV infusion										
- 110/116 Consultant physician, referred consultation										
- AAC27 Casualty visits										
- G05B Hospitalisation										
- 23 General Practitioner										
- 66512 Blood tests: LFT, U&E, CRP										
- 56507 Abdomen CT										\$480.05
- 58915 Small bowel follow through										\$78.95
Treatment of patients with alternative diagnoses of Crohn's disease										
- 110/116 Consultant physician			The use of resources to manage the side effects of treatment in patients with alternative diagnoses will be presented in detail in the re-submission.							
- AAC27 Casualty visits										
- G05B Hospitalisation										

* Include costs relating to both the standard and extended safety net.

Abbreviations: LFT, liver function test; U&E, urea, electrolytes, creatinine; CRP, C-reactive protein

Summary of PICO to be used for assessment of evidence (systematic review)

The key research question in the re-submission is:

“In symptomatic patients with suspected but unconfirmed Crohn’s disease following colonoscopy and small bowel radiological investigations, what is the value of capsule endoscopy compared with no capsule endoscopy for the diagnosis of suspected small bowel Crohn’s disease?”

The complete details of the research question can be found in the PPICO criteria presented in Table 8.

Consistent with the requested MBS listing, the population of interest is patients with suspected Crohn’s disease. All patients must have attempted diagnosis with prior endoscopy (including colonoscopy with ileoscopy) and small bowel imaging including CT, MRI or SBFT. Under the proposed diagnostic algorithm capsule endoscopy will provide an additional testing modality prior to treatment (see Figure 1).

The PASC agreed that the appropriate reference standard for the clinical response to treatment is 12 months of follow-up.

The literature review presented in the re-submission will be based on the PPICO criteria described in Table 8.

Table 8 Summary of PPICO to define research questions for capsule endoscopy testing

Patients	Prior Tests	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients aged 2 years or over with suspected but unconfirmed small bowel Crohn’s disease on the basis of evidence of underlying inflammation, as indicated by elevated Erythrocyte Sedimentation Rate and/or C-Reactive Protein or other inflammatory markers	Endoscopy including colonoscopy with ileoscopy; AND Radiographic imaging including: i. MRI, or ii. CT, or iii. SBFT	Capsule endoscopy	No capsule endoscopy	<u>Reference Standard</u> Diagnosis at 12 months <u>Diagnostic performance</u> Negative predictive value; Positive predictive value, Sensitivity, Specificity ROC, AUC, Q*, DOR <u>Diagnostic yield</u> <u>Impact on patient management</u> <u>Patient outcomes</u> Crohn’s disease treatment outcomes Crohn’s disease morbidity Quality of life <u>Safety</u> Retention AEs	See Table 7

Proposed structure of the decision analytic economic evaluation

The following section describes a proposed modelling strategy which is subject to change based on the available clinical evidence. However, the fundamental approach would most likely remain unchanged; that is, capsule endoscopy provides additional diagnostic value provides better targeted treatment selection, providing additional health outcomes.

The structure of the economic evaluation will align with the linked evidence approach described earlier. That is, capsule endoscopy affects the proportion of patients who receive a confirmed diagnosis (i.e., diagnostic yield; while some of them may be false diagnoses). Confirmed diagnosis for Crohn's disease or for other conditions informs the downstream treatment strategies and thus affect subsequent health outcomes. Additional diagnostic value offered by capsule endoscopy is expected to improve the effectiveness of downstream disease management via improved treatment selection.

A modelling technique is employed to quantitatively determine the additional health outcomes associated with the use of capsule endoscopy when compared with no capsule endoscopy scenario (i.e., treatment after CT, MRI and/or SBFT). This involves transforming health outcomes (i.e., better targeted treatment selection via improved diagnosis) and their QoL implications to quality-adjusted life years (QALYs).

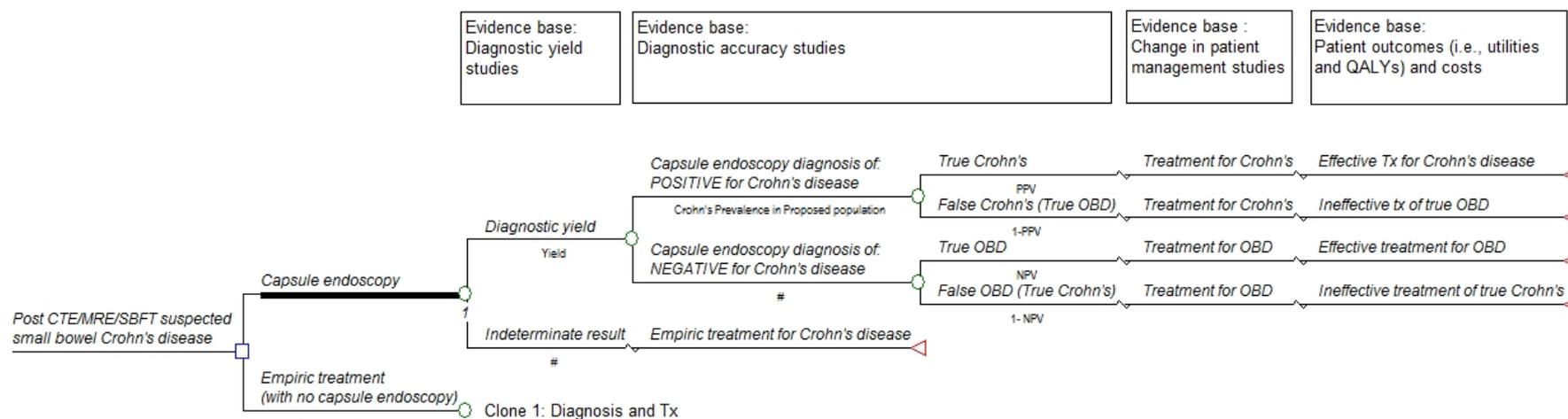
A decision analytic model is employed. It is proposed that health states included in the model are defined by two elements; true disease status (Crohn's disease or other bowel disease) and capsule endoscopy result (confirmed diagnosis of Crohn's disease or other bowel conditions, or indeterminate results).

Figure 2 depicts a proposed model structure as prepared by the applicant and Figure 3 presents an updated and expanded view of the proposed decision tree. In line with the proposed listing, patients enter the model with "suspected Crohn's disease" after having already undergone colonoscopy with ileoscopy and small bowel imaging (including CTE, MRE and/or SBFT). An additional model structure with all the modelling steps fully outlined is presented in

For the 'capsule endoscopy' arm, the hypothetical cohort of patients is distributed into health states depending on their true disease state and their capsule endoscopy results. Patients who receive an indeterminate capsule endoscopy result are assumed to receive treatment for Crohn's disease. For the 'no capsule endoscopy' arm, all patients are assumed to receive treatment for Crohn's disease, while they may or may not in fact have Crohn's disease.

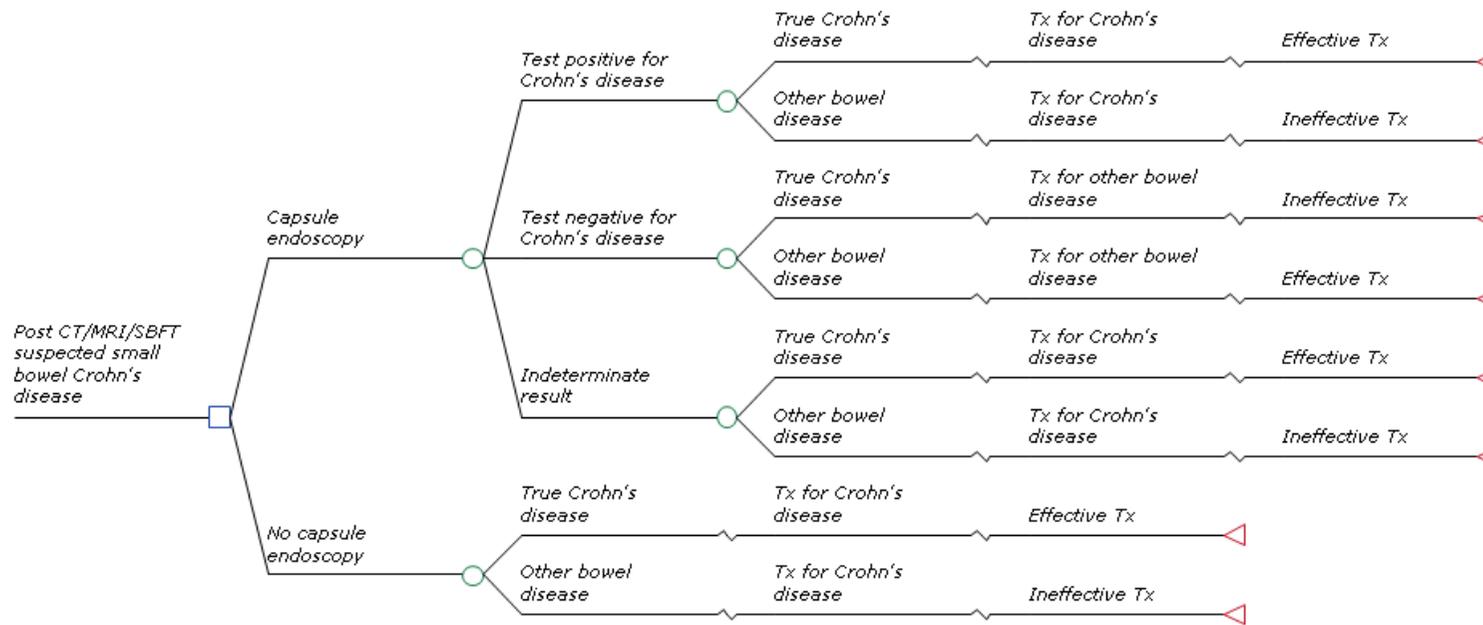
For simplicity, the patient's true disease status is assumed to be either Crohn's disease or other bowel disease. It is envisaged that, as per a similar cost-effectiveness study performed for CTE by Levesque et al (2010), a certain bowel condition such as irritable bowel syndrome will be used as a proxy for the costs and utilities for 'other bowel disease'. It is acknowledged that other conditions can be identified on capsule endoscopy, e.g., malignancy. It is however assumed that the magnitude and nature of healthcare resource use and QoL implications of 'other bowel disease' are adequately captured by those associated with irritable bowel syndrome.

Figure 2 Proposed structure of Markov model for the cost-effectiveness analysis of capsule endoscopy



Abbreviations: CTE, computed tomography enterography; MRE, magnetic resonance enterography; NPV, negative predictive value; OBD, other bowel disease; PPV, positive predictive value; QALY, quality adjusted life year; SBFT; small bowel follow through; Tx, treatment

Figure 3 Expanded structure of a proposed model for the cost-effectiveness analysis of capsule endoscopy versus no capsule endoscopy



Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SBFT; small bowel follow through; Tx, treatment

Cost inputs describing each of the health state would mainly account for the administered treatments. While exact resource items are to be determined, for example, patients treated for Crohn's disease receive a mix of first-line therapies for the condition including 5-aminosalicylates (5-ASAs), corticosteroids, azathioprine and 6-mercaptopurine. In addition, the costs of capsule endoscopy would be added to the capsule endoscopy arm based on the proposed MBS benefit.

The utility values experienced by patients in each health state will be derived from the clinical literature. Incremental QALYs for the capsule endoscopy arm would reflect that the treatment selection would be more targeted, thus producing better effectiveness, when compared with the comparator arm.

It is anticipated that the model includes a time horizon of one year; minimising uncertainty potentially associated with long-term extrapolation. Once patients receive capsule endoscopy, patients remain in their health states for the duration of the model.

Final

References

- Caunedo-Álvarez A., Romero-Vazquez J. and Herrerias-Gutierrez J.M. Patency and agile capsules (2008) *World J Gastroenterol* 14(34):5269-5273.
- Gearry, RB, Ajlouni, Y et al 2007. 5-Aminosalicylic acid (mesalazine) use in Crohn's disease: a survey of the opinions and practice of Australian gastroenterologists, *Inflammatory Bowel Diseases*, 13 (8), 1009-1015.
- Levesque BG, Cipriano LE, Chang SL, Lee KK, Owens DK, Garber AM. Cost effectiveness of alternative imaging strategies for the diagnosis of small-bowel Crohn's disease. *Clin Gastroenterol Hepatol*. 2010 Mar;8(3):261-7
- Li F, Gurudu SR, De PG, Sharma VK, Shiff AD, Heigh RI, Fleischer DE, Post J, Erickson P, Leighton JA. Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. *Gastrointest Endosc* 2008;68:174-180.
- Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009 Feb;104(2):465-83.
- Morrison, G, Headon, B et al 2009. Update in inflammatory bowel disease, *Australian Family Physician*, 38 (12), 956-961.
- Satsangi, J, Silverberg, MS et al 2006. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications, *Gut*, 55 (6), 749-753.
- Sidhu, R, Sanders, DS et al 2008. Guidelines on small bowel enteroscopy and capsule endoscopy in adults, *Gut*, 57 (1), 125-136.
- Solem, CA, Loftus, J et al 2008. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial, *Gastrointestinal Endoscopy*, 68 (2), 255-266.
- Vanfleteren L, van der Schaar P, Goedhard J. Ileus related to wireless capsule retention in suspected Crohn's disease: emergency surgery obviated by early pharmacological treatment. *Endoscopy* 2009;41 Suppl 2:E134-E135.
- Vogel J, Moreira A, Baker M, et al. CT enterography for Crohn's disease: accurate preoperative diagnostic imaging. *Dis Colon Rectum*. 2007;50:1761-1769.
- Yamada, T. 2009. *Textbook of gastroenterology*, 5th edn. Chichester, West Sussex; Hoboken, NJ: Blackwell.

Appendix: Applicant's response to issues in the prior assessment

Issues identified in the prior assessment

An earlier application requesting MBS listing of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease was lodged for consideration by MSAC in February 2010 and was subsequently rejected. At the time, MSAC concluded that the available evidence for the safety, effectiveness and cost-effectiveness of capsule endoscopy under the proposed indication was inconclusive to support the listing; "*there were substantial deficiencies with the evidence base around comparative safety, accuracy and clinical effectiveness data for capsule endoscopy relative to alternative ways of investigating patients with suspected small bowel Crohn disease*" (Public Summary Document, PSD; MSAC 2011, pg13). Nonetheless, MSAC acknowledged a clear clinical need for capsule endoscopy in the requested indication, and recognised that the requested population constitutes a very small subgroup of patients who cannot be diagnosed through other means.

The re-submission will address key issues and data gaps identified in the earlier submission for capsule endoscopy in the diagnosis of small bowel Crohn's disease. Table 9 presents the key issues raised in the previous MSAC submission, as well as the approaches used to address them. In summary, the re-submission will better define the positioning of capsule endoscopy in the diagnosis of small bowel Crohn's disease and present comparative clinical evidence that is relevant to the re-defined positioning (and thus patient population and comparator). Presentation of safety evidence, in particular, the risk of capsule retention, is also expanded. A linked evidence approach (with modelled economic evaluation) will be included to translate the available clinical evidence to final patient outcomes (e.g., life years and/or quality-adjusted life years, QALYs) and allow its relative cost-effectiveness to be adequately assessed by the MSAC.

Table 9: Key issues identified by MSAC in the Public Summary Document for the 2010 submission for capsule endoscopy in the diagnosis of small bowel Crohn's disease

Issue	Proposed changes to the approach of re-submission outlined in this DAP
<p>Clarification of diagnostic algorithm and positioning of capsule endoscopy</p> <p><i>"In the clinical flow chart, capsule endoscopy is a replacement test for repeat radiology (Computed Tomography (CT)/CT enterography (CTE) or magnetic resonance imaging (MRI)/ Magnetic Resonance Enterography (MRE)) and a replacement for treating the patient empirically based on a suspicion of Crohn disease which could not be confirmed (ie incremental to prior testing)."</i></p> <p><i>(Public Summary Document; MSAC 2011, pg 4)</i></p>	<p>It is proposed that capsule endoscopy should be reserved for patients who were not able to achieve a confirmed positive or negative diagnosis for Crohn's disease through prior endoscopy and radiographic imaging. Radiographic imaging may include magnetic resonance enterography (MRE), computed tomography enterography (CTE) or small bowel follow through (SBFT). <u>Therefore, the evidence most relevant to this submission consists of trials of capsule endoscopy versus empirical treatment.</u></p> <p>As acknowledged by MSAC, this represents the patient sub-group that is hardest to diagnose with the current diagnostic technologies (5% of the total patient population with suspected Crohn's disease).</p> <p>This positioning of capsule endoscopy in the diagnosis of small bowel Crohn's disease has received KOL endorsement.</p>
<p>Applicability of clinical data</p> <p><i>"...the assessment indicated that the evidence is not relevant to the proposed population in which it will be used, which is the group of patients who are hardest to diagnose and for which the applicant is indicating capsule endoscopy would assist".</i></p> <p><i>(Public Summary Document; MSAC 2011, pg 8).</i></p>	<p>The evidence most relevant to this submission consists of trials of capsule endoscopy versus empiric treatment. The literature review will search for direct evidence for the impact of capsule endoscopy on health outcomes in the appropriate population (i.e. patients with suspected Crohn's disease who were unable to be diagnosed with CTE, MRE or SBFT).</p>
<p>Comparative diagnostic accuracy</p> <p><i>"...the assessment report provided no basis to conclude that the diagnostic accuracy of capsule endoscopy was superior to the alternative investigations of CT or MRI in any population with suspected Crohn disease."</i></p> <p><i>(Public Summary Document; MSAC 2011, pg 8).</i></p>	<p>The main comparator for capsule endoscopy in the requested indication is empiric treatment. Patients who receive capsule endoscopy will have already undergone small bowel imaging with CTE, MRE or SBFT. Repeat investigations using radiographic imaging do not improve the diagnostic yield.</p>
<p>Linked evidence approach</p> <p><i>"...the assessment did not identify any direct studies comparing the health outcomes of patient populations with suspected small bowel Crohn's disease assessed with and without capsule endoscopy. ESC pointed to the issue that evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes were all achieved using a linked evidence approach" (Public Summary Document; MSAC 2011, pg13).</i></p>	<p>The literature review will search for direct evidence for the impact of capsule endoscopy on health outcomes. In the absence of direct evidence, the re-submission will present indirect evidence indicating the impact of capsule endoscopy on clinical management and patient outcomes. The use of a linked evidence approach is not unusual when looking at the impact of a diagnostic test on clinical outcomes. Studies that might be used in a linked evidence approach include the following:</p> <ul style="list-style-type: none"> - Diagnostic accuracy and diagnostic yield studies of capsule endoscopy in the appropriate population (i.e. patients with suspected Crohn's disease who were unable to be diagnosed with CTE, MRE or SBFT). - Studies reporting the impact of capsule endoscopy on patient management. - Studies reporting health outcomes and costs <p>Ideally, these studies will provide comparative data with empiric treatment;</p>

Issue	Proposed changes to the approach of re-submission outlined in this DAP
	however where necessary the search will also include non-comparative studies, or studies including comparisons with other diagnostic modalities. Decision analytic modeling may be employed in a linked evidence approach by translating the available evidence into final patient outcomes (e.g., life years or/and quality-adjusted life years, QALYs).
<p>Safety of capsule endoscopy</p> <p><i>"MSAC noted ESC advice that the evidence for the safety of the intervention did not address sufficiently the issue of retention of the capsule".</i> <i>(Public Summary Document; MSAC 2011, pg 8).</i></p>	<p>The resubmission will present several reasons for why the risk of capsule retention was overstated in the previous assessment report, including the following:</p> <ul style="list-style-type: none"> - Patients who are eligible for capsule endoscopy will have already undergone CTE or MRE, both of which can be used to identify strictures. - In patients who are suspected of having strictures, Pillcam® SB comes with a dissolvable capsule (Agile™) to test the patency of the gastrointestinal tract before capsule endoscopy. The submission will present clinical evidence to demonstrate the efficacy of the patency capsule in patients with suspected strictures, leading to a reduced risk of harm. - The evidence pertaining to retention identified in the previous MSAC assessment report will be updated and critiqued in the context of the proposed indication - The clinical significance of retention will also be investigated.
<p>Technical failure</p> <p><i>"MSAC noted that capsule endoscopy might fail to provide a diagnostic result for technical reasons which are unique to the technology, such as battery failure before transition through the small bowel, the visual field being obscured due to mucus or intestinal contents, and difficulty in swallowing the 11 mm by 26 mm capsule"</i> <i>(Public Summary Document; MSAC 2011, pg 10).</i></p>	<p>In instances of technical failure, Given Imaging will provide an extra capsule, free of charge under the standard warranty terms. If the Pillcam® SB is unable to adequately visualise the small bowel for other reasons, this would be picked up in studies of diagnostic accuracy and will be accounted for in the economic evaluation.</p>
<p>Justifying cost-effectiveness</p> <p><i>Due to a perceived lack of comparative effectiveness data, the previous MSAC assessment report did not perform a cost-effectiveness analysis. The approach to the economic evaluation was therefore a presentation of the costs and possible consequences of capsule endoscopy and comparators. A healthcare system perspective was used, which included the cost to the government via the MBS and cost to the patient.</i></p>	<p>The submission will present a cost-effectiveness analysis based on a superiority claim (efficacy and/or safety).</p> <p>It is envisaged that a modeled economic evaluation will be presented to translate the diagnostic accuracy/effectiveness data into final patient outcomes (e.g., life years or/and quality-adjusted life years, QALYs). Consistent with the previous MSAC assessment report, a healthcare system perspective will be used, including the cost to the government and cost to the patient.</p>

Abbreviations: CT, computed tomography; CTE, computed tomography enterography; DAP, decision analytic protocol; MBS, Medicare Benefits Schedule; MRI, magnetic resonance imaging; MRE, magnetic resonance enterography; PSD, Public Summary Document

In addition to the issues summarised in , the PSD also highlighted the following points which do not require any additional changes to the approach of the re-submission:

1. MSAC agreed with ESC that the term “small bowel radiology” was ambiguous and implied that CT and/or MRI be included as prerequisite tests rather than alternative tests. MSAC agreed that, if capsule endoscopy were not definitive in its diagnosis of small bowel Crohn disease, patients may still need to be considered for histological examination such as could be obtained with balloon enteroscopy (BE) before being put on long-term drugs which are both toxic and potentially expensive. However, MSAC agreed that, from a consumer’s perspective, capsule endoscopy would be preferable to BE on the grounds of comfort and risk. The clarification that CE is to be used after CTE or MRE removes this issue.
2. MSAC further agreed that the number of patients who would be eligible for the proposed indication for capsule endoscopy would be very small. In most patients with isolated small bowel Crohn’s disease, the disease affects that part of the small bowel which can usually be visualised with terminal ileoscopy at the time of colonoscopy. The re-submission will include updated budget impact calculations.
3. MSAC also agreed that any MBS listing of capsule endoscopy in small bowel Crohn’s disease should not permit monitoring or surveillance of diagnosed patients. The requested item restriction specifically excludes the monitoring or surveillance of diagnosed patients. In fact, MSAC Application 1190 is reviewing the use of MRE for monitoring/surveillance of diagnosed patients.

Safety

The major safety issue raised in the previous assessment report for capsule endoscopy was the possibility of capsule retention. The primary basis for this concern was a single study that reported a capsule retention rate of 15% in patients with suspected Crohn’s disease undergoing capsule endoscopy (Ge et al., 2004). The re-submission will present several reasons for why this risk was overstated in the previous assessment report, including the following:

1. Patients who are eligible for capsule endoscopy will have already undergone CTE or MRE, both of which can be used to identify strictures with a relatively high success rate (Vogel et al., 2007), at no additional cost.
2. In patients who are suspected of having strictures, Pillcam[®] SB comes with a dissolvable capsule (Agile™) to test the patency of the gastrointestinal tract before capsule endoscopy. In an international multi-centre study, 106 patients with known strictures ingested the Agile™ patency capsule. The study found 56% of patients excreted the Agile™ capsule intact and subsequently underwent complete capsule endoscopy. None of these patients subsequently experienced retention after swallowing the Pillcam[®] SB.
3. The evidence pertaining to retention identified in the previous MSAC assessment report will be updated and critiqued in the context of the proposed indication.

4. The clinical significance of retention will also be investigated. For example, most retained capsules are asymptomatic; in one retrospective study of 1000 capsule endoscopies with a 1.4% retention rate, none of the patients had any symptoms of capsule retention (Li et al., 2008). Additionally, in the small number of cases where surgical intervention for capsule recovery is required, they are frequently correctional in nature to address the underlying cause of illness, thereby generating health outcomes in themselves.

Apart from the risk of retention, the previous MSAC Assessment Report for capsule endoscopy concluded the procedure is safe with a low risk of adverse events. Furthermore, capsule endoscopy is associated with no exposure to ionising radiation, like MRI/MRE (which is not currently reimbursed) but unlike SBFT or CT/CTE.

These questions will be addressed and discussed at length in the re-submission.

Final