Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1146.3 - Capsule Endoscopy for the Diagnosis of Suspected Small Bowel Crohn's Disease (Resubmission)

Applicant: **Medtronic Australasia Pty Ltd**

Date of MSAC consideration: **MSAC 71st Meeting, 23 November 2017**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The second resubmission from Medtronic Australasia requested new Medicare Benefits Schedule (MBS) listings for capsule endoscopy (CE) for the diagnosis of suspected small bowel Crohn's Disease (SBCD) and assessment of established isolated SBCD.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC did not support public funding of capsule endoscopy for the diagnosis of suspected SBCD due to a high degree of uncertainty regarding the diagnostic accuracy of the capsule endoscopy in this patient population, uncertain clinical utility of the service and highly uncertain cost-effectiveness.

MSAC did not support public funding of capsule endoscopy in the assessment of established isolated SBCD as there was insufficient evidence to support the use of the proposed service in this patient population.

MSAC advised that any resubmission would need to be considered by ESC, however if any re-submission deviates significantly from the PASC-confirmed PICO and has evidence available to support this, consideration by PASC may be warranted.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the population and indication proposed in previous submissions was for diagnosis of Crohn's disease in patients with suspected SBCD. This resubmission also included an additional, separate population and indication - assessment of established isolated SBCD - which was not previously considered as part of MSAC Applications 1146 and 1146.1.

MSAC recalled that the comparator of usual care in MSAC Applications 1146 and 1146.1 was defined as empiric therapy. The current application presents repeat testing (endoscopic

and radiological investigations) until definitive diagnosis as representative of usual care. MSAC noted that defining the comparator is difficult as there is no single test for SBCD that is diagnostic in and of itself. MSAC noted that double-balloon enteroscopy (DBE) could be a potential comparator to capsule endoscopy as it allows direct visualisation and collection of biopsy samples of the whole small bowel segment to confirm diagnosis histologically (although balloon enteroscopy is not currently MBS funded for this indication).

MSAC noted that due to the changes in the population and comparator, the application no longer conforms to the PASC-confirmed PICO. The clinical management algorithm and clinical outcomes assessed as proposed in the resubmission application form for the assessment indication have not been incorporated in the application and healthcare resource consequences do not appear to be included for this new indication.

MSAC noted that the evidence presented for safety was based on eight non-comparative studies of retention rates. MSAC noted that the retention rate applied in the model was low, based on the unpublished, manufacturer-sponsored report (Selby 2008). MSAC noted the studies presented indicated that surgery would be required for approximately 50% of these patients, therefore there are significant safety implications associated with capsule endoscopy. MSAC noted that safety outcomes following capsule endoscopy may be different for the paediatric population, but no safety data has been provided in this population.

MSAC recalled the Committee's outcomes for Application 1146 (July 2011) and 1146.1 (November 2013), noting that in November 2013 for Application 1146.1 the committee had previously accepted that CE appears sufficiently diagnostically accurate. In relation to the newly requested additional patient population with established isolated CD, MSAC noted that no diagnostic accuracy data were provided to support this particular request.

In relation to its previous advice of apparent sufficiency of diagnostic accuracy for the original patient population, MSAC based on its reappraisal of all of the presented evidence, with a particular emphasis on whether any new studies provided greater confidence in drawing this conclusion. MSAC considered that there continued to be a high degree of uncertainty regarding the diagnostic accuracy of capsule endoscopy in patients with suspected but unconfirmed SBCD due to the lack of an adequate reference standard, lack of validated criteria for the diagnosis of SBCD with capsule endoscopy, varying diagnostic criteria across studies and inappropriate statistical methods used in the meta-analysis of the data. All the evidence presented for diagnostic accuracy was based on Level III-2 evidence. The most applicable studies for the proposed population remained Figueiredo P et al (2010), Girelli CM et al (2007), Tukey M et al (2009); this resubmission added Hall B et al (2013) as having similar applicability. All four studies were poorly designed retrospective studies using unvalidated, study specific diagnostic criteria for Crohn's disease. MSAC noted that the prevalence of SBCD in these studies was no greater than approximately 50% regardless of the diagnostic method, which supported the committee's view that empiric treatment may be a valid approach in these patients and reasonable to include in the comparator. MSAC considered that there are sufficient deficiencies for concern around the evidence base for diagnostic accuracy because the limited additional studies available four years later had not provided any greater confidence despite MSAC's previous reservations over the weakness of the earlier evidence. MSAC considered this to be a particular concern because the management of Crohn's disease has changed so the risk/benefit of false test results is not necessarily the same as influenced the previous consideration.

MSAC noted that the only evidence presented for clinical utility was a poor quality retrospective study reporting the change in patient management in patients who were already diagnosed with Crohn's disease (Kalla R et al 2013). There were no studies identified that

compared the health outcomes of symptomatic patients with suspected SBCD, assessed with and without capsule endoscopy.

MSAC considered that there is insufficient evidence to support capsule endoscopy in assessment of patients with established isolated SBCD. MSAC considered that diagnostic accuracy data from studies in patients with suspected SBCD cannot be applied to the population with established isolated SBCD. There were no studies identified that compared the health outcomes of symptomatic patients with established isolated SBCD, assessed with and without capsule endoscopy. MSAC also noted that the applicant had conceded that there was insufficient basis to claim any clinical benefit from this requested use.

MSAC considered that conducting cost-effectiveness analysis with such a limited evidence base for the proposed service was problematic and any ICERs generated would be uncertain on this basis. MSAC noted that in the base case, capsule endoscopy for diagnosis of SBCD was dominant over usual care. However, MSAC considered that this was largely due to the inflated costs of the repeat testing comparator, which was a key driver in the model. The number and type of repeat tests applied in the model were poorly justified and inflated the cost of the comparator. MSAC considered that it was implausible that clinicians would repeat testing each year for five years and that a combination of symptomatic management and consultation would be an option. MSAC noted that if a single cycle of repeat testing is used instead, the ICER increases to approximately $29,600 per QALY.

MSAC considered that the utility values used in the model were inappropriately assigned to the different health states. MSAC noted that all patients in the model with Crohn's disease diagnosed and treated were assumed to experience full remission, which the committee considered to be implausible. A baseline utility for 'mildly active condition' was applied to various other states including: patients with irritable bowel syndrome (IBS) correctly diagnosed and treated, patients incorrectly diagnosed with Crohn's disease or IBS, and indeterminate states for both Crohn's disease and IBS in the comparator. MSAC considered that it was not appropriate to apply the same utility weight to these different health states. MSAC noted that the utilities were not consistent with other relevant studies such as Levesque BG et al (2010).

MSAC noted that capsule retention remains a risk with Crohn's disease even in the presence of radiological investigations that do not show strictures. MSAC noted that in published studies the capsule retention rate ranged from 0 to 15%, and in a recent (2017) meta-analysis published in *Gastrointestinal Endoscopy* the retention rate was 4%. MSAC considered that the costs and disutility for capsule retention should have been included in the base case. Including a 4% risk of retention and a single cycle of repeat testing increases the ICER to $35,600 per QALY. MSAC considered that this would be a more appropriate base case on which to apply sensitivity analyses.

Overall, MSAC considered that the economic model presented is highly uncertain and sensitive to inputs and assumptions. When sensitivity analyses were applied to the re-estimated base case the ICER increased substantially to over $86,600 per QALY and when the utilities reported by Levesque BG et al (2010) are used for the 'IBS indeterminate state' the repeat testing comparator is dominant.

MSAC noted the estimated number of diagnostic capsule endoscopy procedures is relatively low at 755–1,658 patients in year 1 and the cost to MBS for year 1 is estimated at $1.5 million to $3.3 million.

MSAC noted that the current MBS item and fee for capsule endoscopy has been recently reviewed by the Gastroenterology Clinical Committee (GCC) as part of the MBS Review. The GCC were concerned that the utilisation of CE was well above the anticipated use and

could not be accounted for on clinical grounds. The GCC and in turn the MBS Review Taskforce recommended that the item descriptor be amended to better reflect the intended population with those amendments implemented on 1 November 2017. The GCC asked MSAC to review the MBS fee and MSAC recommended a revised fee of $1,229.35 based on: a revised professional component of the fee based on the fee for a one hour service, with no co-claiming of a consultation item allowed; a reduced capsule endoscope consumable cost; and removal of capital costs from the MBS fee.

MSAC considered that overall the evidence presented was insufficient to demonstrate the diagnostic accuracy, clinical utility and health outcomes for capsule endoscopy for diagnosis in symptomatic patients with suspected SBCD or for assessment in patients with established isolated SBCD. MSAC also considered that the base case economic model presented was problematic and highly sensitive to inputs and assumptions. Noting the outcomes of the MBS review of the existing CE items, MSAC was concerned that the anticipated utilisation for suspected SBCD and hence MBS impact was uncertain.

MSAC considered that the assessment indication in people with established isolated SBCD needs quality evidence and a separate model to estimate its costs and clinical benefits.

4. Background

At its July 2011 meeting, MSAC did not support public funding of capsule endoscopy to evaluate suspected small bowel Crohn's disease in patients who have had some previous testing which remains inconclusive (MSAC Application 1146). MSAC concluded that capsule endoscopy had *prima facie* clinical utility, but 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's disease.

At its November 2013 meeting, MSAC did not support public funding of capsule endoscopy for identifying a residual unmet clinical need for a subgroup of patients (5%) with suspected SBCD (MSAC Application 1146.1). MSAC accepted that CE appears safe and sufficiently diagnostically accurate in the investigation of these patients, with an expected improvement in subsequent clinical management, but did not accept the economic evaluation presented a sufficiently robust basis to determine its cost-effectiveness.

Further information is available from the Public Summary Documents for these Applications at http://www.msac.gov.au/

Capsule endoscopy is MBS funded for patients with obscure gastrointestinal bleeding and for patients with Peutz-Jeghers Syndrome.

5. Prerequisites to implementation of any funding advice

There are numerous capsules listed on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

CE is a non-invasive diagnostic test, usually conducted in an outpatient setting, in which the gastrointestinal system is visualised via a camera inside an ingested capsule. The test visualises the gastrointestinal (GI) tract mucosa to diagnose a range of conditions such as obscure gastrointestinal bleeding (OGIB), coeliac disease, small bowel tumours and Peutz-Jeghers syndrome.

This submission proposes the use of CE in two indications:

- Diagnosis of suspected SBCD
- Assessment of established isolated SBCD

CE is positioned after other investigative options, including ileocolonoscopy and cross-sectional imaging (MR enterography or CT enterography or SBFT).

The proposed MBS item descriptors for the two respective indications are summarised in Table 1 and Table 2.

For the first indication, the proposed listing for CE limits its use to patients who have failed to achieve a confirmed positive or negative diagnosis of CD after endoscopy, including colonoscopy with ileoscopy and cross sectional imaging, including SBFT or CTE or MRE. In addition, patients are required to have evidence of underlying inflammation, as indicated by biochemical markers such as erythrocyte sedimentation rate, faecal calprotectin and C-reactive protein.

The second proposed indication of CE is for the evaluation of exacerbation/suspected complications, or assessment of change to therapy in patients with established isolated SBCD. The proposed listing is targeted at patients who have received treatment for SBCD (e.g. pharmacological therapy or surgery) but retain clinical features that remain unexplained by ileocolonoscopy or cross-sectional imaging studies. This could be due to a poor clinical response or suspected small bowel recurrence. Initial diagnosis of SBCD could have been achieved through a range of diagnostic approaches, including CE, ileocolonoscopy or radiologic imaging.

Table 1 Proposed MBS item descriptor for diagnosis of suspected isolated small bowel Crohn's disease

Category 2 – Diagnostic procedures and investigations
CAPSULE ENDOSCOPY to diagnose suspected isolated 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: a) The patient to whom the service is provided : i. is aged 2 years over; and ii. has not been previously diagnosed with Crohn's disease iii. has suspected 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; and 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 c) Prior negative colonoscopy with attempted ileocolonoscopy has been performed on the patient, and has not produced a confirmed positive or negative diagnosis of Crohn's disease; and d) Prior cross sectional diagnostic 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. Cross sectional diagnostic procedures previously used by the patient may include: i. magnetic resonance enterography (MRE), or ii. computed tomography enterography (CTE), or e) small bowel follow through (SBFT) testing, and the service is not associated with balloon enteroscopy This service can only be claimed once per lifetime. **Fee**: $2,039.20 **Benefit**: 75% = $1,529.40 85% = $1,964.70 Conjoint committee 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.

Table 2 Proposed MBS item descriptor for assessment of established isolated small bowel Crohn's disease

Category 2 – Diagnostic procedures and investigations
CAPSULE ENDOSCOPY for the evaluation of exacerbation/suspected complications, or assessment of change to therapy in patients with established isolated 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). The service is available to patients who meet the following additional criteria: a) The patient to whom the service is provided : i. is aged 2 years over; and ii. has been previously diagnosed with Crohn's disease iii. has evidence of underlying inflammation, as indicated by elevated Erythrocyte Sedimentation Rate and/or C-Reactive Protein or other inflammatory markers; and 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 c) The patient has clinical features that remain unexplained by prior ileocolonoscopy and at least one of the following procedures for cross sectional imaging: i. magnetic resonance enterography (MRE), or ii. computed tomography enterography (CTE), or d) small bowel follow through (SBFT) testing, and the service is not associated with balloon enteroscopy This service can only be claimed once in a 12-month period. **Fee**: $2,039.20 **Benefit**: 75% = $1,529.40 85% = $1,964.70 Conjoint committee 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.

7. Summary of Public Consultation Feedback/Consumer Issues

The department received three responses from public consultation which were in support of this application

The feedback indicated that it was thought that this is a complex disease that requires a number of supporting features to make a diagnosis and no single gold standard exists. Crohn's can affect all areas of the GI tract so a rigid algorithm for the diagnosis or ongoing assessment is not practical. It remains the judgement of specialist clinicians to determine the usefulness of various investigations. However the small bowel is not easy to access with conventional endoscopy and mechanisms to do that will be clinically useful as has been the case in small bowel bleeding.

Feedback also suggested that CE would be useful for paediatric patients as diagnosis through this method would give valuable information and would allow for more treatment options, which is important as care and management of children with Crohn's disease is complex and individualised.

The proposed populations and criteria mentioned in the application seem reasonable and would add significantly to the peak body's ability to optimise expensive, but effective treatments for this disease.

8. Proposed intervention's place in clinical management

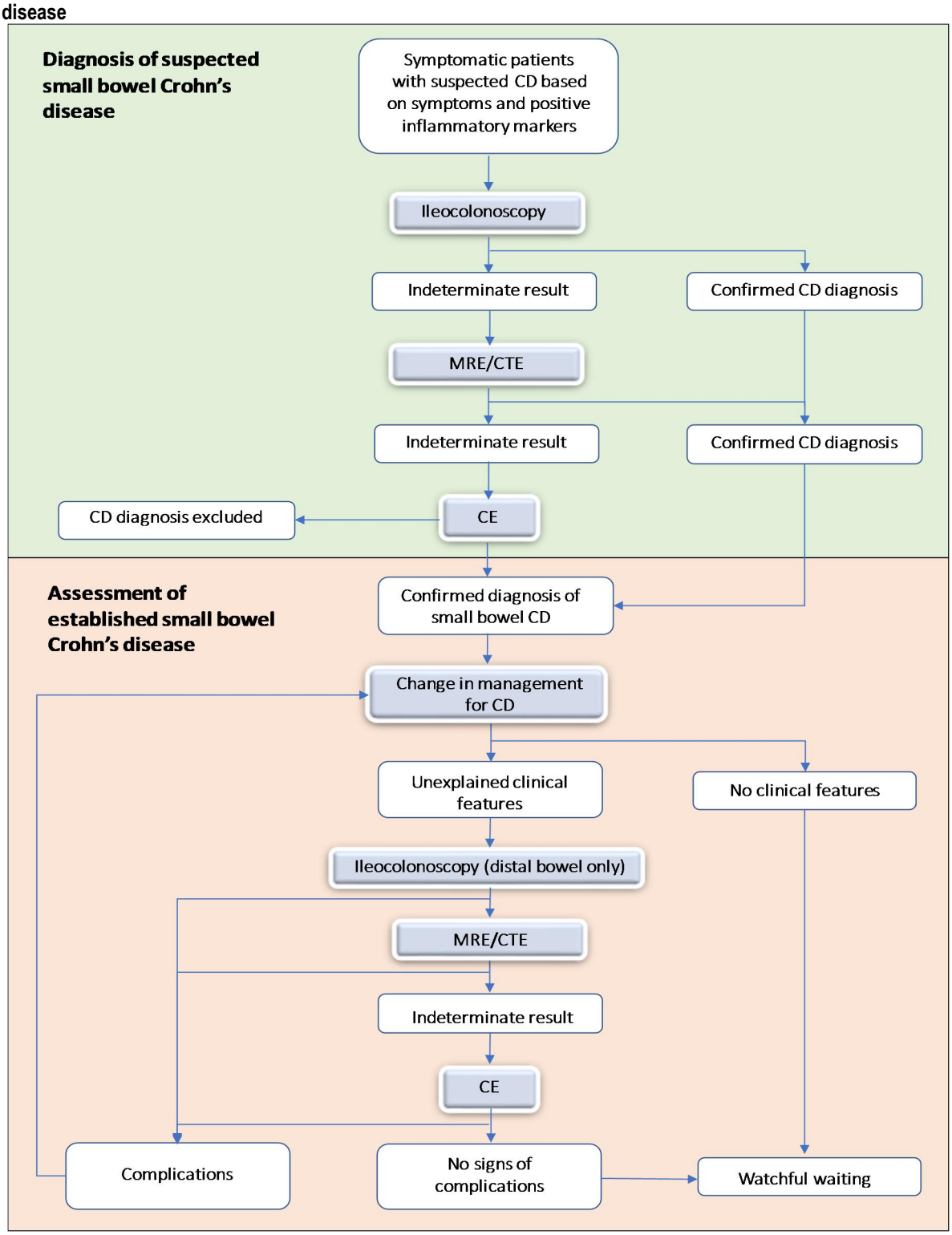
The clinical management algorithm has changed from the previous application (1146.1)

First Indication: It has changed from empiric treatment for undetermined cases to follow-up only without treatment for CD.

Second Indication: The treatment pathway algorithm provided previously did not consider the CE assessment indication.

The revised clinical management algorithm for the use of CE in patients with suspected or known SBCD is presented in Figure 1. Since the population with established isolated SBCD is a subpopulation of the group with suspected SBCD, the clinical management algorithm presented in this submission includes both groups in a single pathway.

Figure 1 Clinical management algorithm for capsule endoscopy in suspected or known small bowel Crohn's disease



Abbreviations: CD, Crohn's disease; CE, capsule endoscopy; CTE, computed tomography enterography; MRE, magnetic resonance enterography

9. Comparator

The main comparator proposed in the resubmission is "usual care" consisting of repeat endoscopic and radiological investigations ("repeat testing") until such time as a patient with suspected SBCD achieve a definitive diagnosis, or until patients with established isolated SBCD are able to have clinical symptoms explained.

The use of repeat radiological imaging in patients with suspected or known CD was confirmed in a recent clinical survey. The results of the survey indicated cycles of investigation (ileocolonoscopy and radiological imaging) are generally continued at yearly intervals until a definitive diagnosis is achieved. As CE allows visualisation of the small bowel mucosa, it allows clinicians to exclude a diagnosis of CD, preventing the need for further, potentially futile, testing. This comparator was also confirmed during feedback received during targeted and public consultation.

In previous applications for CE in the diagnosis of suspected SBCD (Applications 1146 and 1146.1), "empiric therapy" was nominated as the main comparator.

10. Comparative safety

The resubmission provided results of studies providing relevant retention data presented in Table 3. The studies by Figueiredo (2010), Selby (2008) and Valle (2006) are most likely to represent the retention rates that would be seen if capsule endoscopy were reimbursed for the diagnosis of patients with suspected SBCD. In these studies, the capsule retention rates were 5.1% (95% CI: 1.6-12.9%), 0% (0%-3.8%), 0.8% (95% CI: 0-5.0%), and 8.7% (95% CI: 1-28.0%), respectively. The study by Selby (which reported a retention rate of 0.8%) was in an Australian population, and therefore likely to be the most applicable to this resubmission.

Table 3 Adverse events from capsule endoscopy in suspected Crohn's disease

Study	Adverse events		Retention		Surgery following retention		Incomplete CE	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	%	n/N	% (95% CI)
Figueiredo, 2010	0/78	0% (0%-5.6%)	4/78	5.1% (1.6%-12.9%)	2/4	50%	14/78	17.9% (10.9%-28.0%)
Girelli, 2007	0/27	0% (0%-15%)	3/27	11.1% (3.0%-28.9%)	2/3	67%	4/27	14.8% (5.3%-33.1%)
Hall, 2013	0/95	0% (0%-3.8%)	0/95	0%[a] (0%-3.8%)	NR		10/95	10.5% (5.8%-18.3%)
Mitselos, 2016	0/91	0% (0%-4.1%)	0/91	0% (0%-4.1%)	NR		5/91	5.5% (2.3%-12.2%)
Selby, 2008	2/120	1.7% (0%-6.0%)	1/120	0.8% (0%-5.0%)	NR		15/120	12.5% (7.6%-19.7%)
Eliakim, 2004	0/35	0% (0-11.8%)	0/35	0% (0%-11.8%)	N/A		NR	
Ge, 2004	0/20	0% (0%-19.0%)	3/20	15% (4.4%-36.9%)	NR		2/20	10% (1.6%-31.3%)
Valle, 2006	NR		2/23	8.7% (1%-28.0%)	1/2	50%	NR	

Abbreviations: CE, capsule endoscopy; NR not reported
Note: 95% confidence intervals calculated *post hoc* in MS Excel
[a] True SBCE retentions defined as still present in the small bowel 2 weeks after ingestion

The critique noted that CE retention is considered the main adverse event, and rates vary substantially across the included studies (0 to 15%).

Since the adverse event profile of CE has otherwise been comprehensively established in previous assessment reports (MSAC Applications 1146 and 1146.1), the focus of the safety evaluation was an assessment of retention rates.

11. Comparative effectiveness

In this resubmission, the steps involved in the linked evidence approach involve demonstrating that:

(i) CE can accurately diagnose patients with and without CD
(ii) patients who are diagnosed with and without CD after CE experience a change in patient management, and
(iii) these changes lead to improved outcomes.

Accuracy

Table 4 and Table 5 summarise the results of the resubmission's included diagnostic accuracy studies. In the studies where all findings suggestive of Crohn's disease were included in the case definition, the sensitivities were generally within the range of 85-95%, while the specificities reported across the studies were more variable, ranging from 53% (95% CI: 27%-79%) (Solem, 2008) to 100% (95% CI: 72%-100%) (Albert, 2005). The results were pooled to determine the sensitivity and specificity across all studies. The pooled results showed an overall sensitivity of 89% (95% CI: 83%-93%) and specificity of 86% (95% CI: 83%-90%).

The analyses of data in populations that had negative or equivocal results after prior tests are presented in Table 5. More consistent findings were observed in this subgroup, which is considered to have good applicability to the population of relevance to this resubmission, and is the primary source of data in the linked evidence approach. In this analysis, the sensitivity of CE ranged from 85% (95% CI: 55%-98%) in Tukey (2009) to 95% (95% CI: 77%-100%) in Figueiredo (2010). Estimates of specificity ranged from 74% (95% CI: 64%-83%) in Tukey (2009) to 96% (95% CI: 88%-99%) in Hall (2013). The pooled results in the subgroup with negative or equivocal results after prior testing showed an overall sensitivity of 92% (95% CI: 83%-97%) and specificity of 84% (95% CI: 74%-89%).

The negative predictive value (NPV) and positive predictive value (PPV) values in the studies that required negative results on prior testing were also high, with a pooled NPV of 96% and a pooled PPV of 68%.

Table 4 Summary of diagnostic accuracy results: all findings suggestive of CD

Study	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Albert 2005	24	12	0	1	11	92% (64%-100%)	100% (72%-100%)
Casciani 2011	37	11	2	0	24	100% (72%-100%)	92% (75%-99%)
Dubcenco 2005	39	26	0	3	10	90% (73%-98%)	100% (69%-100%)
Figueiredo 2010	72	29	8	2	33	94% (79%-99%)	80% (65%-91%)
Girelli 2007	27	14	2	1	10	93% (68%-100%)	83% (52%-98%)
Jensen 2011	69	16	5	0	48	100% (79%-100%)	91% (79%-97%)
Solem 2008	27	10	7	2	8	83% (52%-98%)	53% (27%-79%)
Tukey 2009	102	11	23	2	66	85% (55%-98%)	74% (64%-83%)
Wiarda 2011	25	4	2	3	16	57% (18%-90%)	89% (65%-99%)
Hall, 2013	95	20	3	2	70	91% (71%-99%)	96% (88%-99%)
Mitselos, 2016	91	7	6	4	74	64% (31%-89%)	93% (84%-97%)
Pooled result	608	160	58	20	370	89% (83%-93%)	86% (83%-90%)

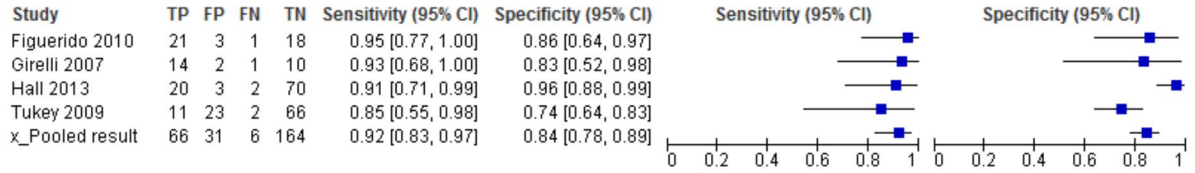
Note: 95% confidence intervals calculated *post hoc* using Review Manager v. 5.2

Table 5 Summary of diagnostic accuracy results: Studies requiring negative or equivocal prior testing

Study	N	TP	FP	FN	TN	Sensitivity	95% CI	Specificity	95% CI
Figueiredo 2010	43	21	3	1	18	95%	77%-100%	86%	64%-97%
Girelli 2007	27	14	2	1	10	93%	68%-100%	83%	52%-98%
Tukey 2009	102	11	23	2	66	85%	55%-98%	74%	64%-83%
Hall 2013	95	20	3	2	70	91%	71%-99%	96%	88%-99%
Pooled	*267*	*66*	*31*	*6*	*164*	*92%*	*83%-97%*	*84%*	*78%-89%*

Note: 95% confidence intervals calculated *post hoc* using Review Manager v. 5.2

Figure 2 Forest plot of diagnostic accuracy results: Studies requiring negative or equivocal prior testing



The critique stated that the reference standard may not adequately discriminate between a true and false diagnosis, and 12 months may not be sufficient time for a definitive diagnosis to occur.

The critique noted that differing diagnostic criteria across the accuracy studies and the lack of an adequate reference standard bring a very high level of uncertainty to the diagnostic performance of CE. This becomes particularly important in the meta-analysis and the economic model. The critique considered that pooling the sensitivity and specificity results of the various diagnostic studies is inappropriate as sensitivity and specificity are dependent variables. A meta-analysis of diagnostic test accuracy has to allow for the trade-off between sensitivity and specificity that occurs between studies that vary in the threshold value used to define test positives and test negatives.

The critique also noted that the main comparator in the application is usual care, consisting of repeat endoscopy and cross-sectional imaging. None of the studies included in this application specifically identify this approach as the main comparator.

Therapeutic efficacy (change in management)
The resubmission identified one study by Kalla et al. (2013) which reported the impact of CE on patient management in patients with suspected and established SBCD. In the subgroup of patients who had suspected SBCD at baseline, 45/265 (17%) had capsule findings suggestive of Crohn's disease. Small bowel CE changed management in 90% (28/31) of patients with an eventual diagnosis of CD.

The critique considered that this study is considered of poor quality and the effect of CE on change in management remains uncertain.

Therapeutic effectiveness (health benefit from change in management)
The resubmission did not identify any prognostic studies reporting health outcomes and costs in treated and untreated patients. The approach used to derive prognostic information for these groups is therefore presented as a translation issue, which identifies utility values in patients with treated and untreated CD and IBS (as a proxy for OBD).

Effectiveness in patients with established isolated SBCD (assessment indication)
The resubmission did not identify any applicable studies reporting the diagnostic performance of CE in patients with established isolated SBCD.

In the subgroup of 50 patients with known SBCD reported by Kalla et al. (2013), management was altered in 73% of patients as a result of active disease on CE of the small bowel (n=24/33). This result generally supports the notion that when CE is used in clinical practice, it produces a change in management for those patients diagnosed with SBCD.

Clinical claim

In patients with suspected SBCD, CE will result in improved quality of life for those patients who receive a confirmed diagnosis of CD, and are able to receive appropriate treatment. Patients in whom CD is excluded will have reduced costs due to a reduction in further investigations, including repeat imaging. In addition, these patients may have improved quality of life through improvements in management when CD is excluded.

In patients with established isolated SBCD, with clinical symptoms that cannot be explained, CE will provide improved quality of life by guiding appropriate patient management. However, it should be noted that the application does not make a clinical claim for this population due to insufficient evidence for a separate linked evidence approach. As such, the use of CE as a repeat test in patients with established isolated SBCD is captured in the economic model as an additional cost item for the CE arm of the economic model developed for the diagnostic indication (with no health gain). This is a conservative approach, biased against CE, because it does not expect that the use of CE in assessing a patient with known SBCD would confer at least some clinical utility in some patients.

12. Economic evaluation

The resubmission provided a modelled cost-effectiveness analysis presented based on a revised model. Table summarises key elements of the presented model.

Table 6 Summary of the economic evaluation – comparison with the June 2013 model

Perspective	June 2013 model	Current model
Comparator	Empiric treatment (i.e., patients treated assuming they have Crohn's disease)	Usual care, consisting of repeat endoscopic and radiological investigations ("futile testing") until such time as a patient with suspected SBCD achieves a definitive diagnosis, or until patients with established isolated CD are able to have clinical symptoms explained. During this time patients receive therapies for symptomatic relief (i.e. not CD treatments).
Type of evaluation	Cost-utility analysis	Cost-utility analysis
Sources of evidence	Diagnostic accuracy of capsule endoscopy: Pooled Tukey 2009, Figueiredo 2010 and Girelli 2007. Utility values based on published evidence. Costing data based on publicly available, Australian sources.	Diagnostic accuracy of capsule endoscopy: Pooled Tukey 2009, Figueiredo 2010, Girelli 2007 and Hall, 2013. Utility values based on published evidence. Costing data based on publicly available, Australian sources.
Time horizon	1 year	5 years
Outcomes	QALYs	QALYs
Methods used to generate results	A decision tree analysis. Health states were defined by the true Crohn's disease status and CE diagnosis (true positive, false negative, true negative or false positive). In the comparator arm,	A Markov decision analysis model with eight health states: • True positive • False negative • Crohn's disease but diagnosis undetermined • True negative

Perspective	June 2013 model	Current model
	patients receive empiric treatment for Crohn's disease.	• False positive • No Crohn's disease (i.e. other bowel disease) but diagnosis undetermined • Post resolution (only applicable to other bowed disease) • Dead In the comparator arm, patients enter the "undetermined" health states depending on their true disease status; they receive usual care and continued monitoring (plus possibility of receiving a confirmed diagnosis).
Discount rate	Not applicable.	5% per annum
Software packages used	TreeAge	TreeAge

The overall costs and outcomes, and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions are presented in Table 7.

Table 7 Incremental cost per QALY calculated by the economic model

Cost/health outcomes	Capsule endoscopy	Usual care	Incremental
Cost	$5,086	$10,489	-$5,403
QALYs	3.1899	3.1638	0.0261
ICER			Dominant

The critique advised that two distinct economic models should be conducted for each CE indication. The model includes two different populations: those with undiagnosed SBCD and those with established SBCD. As previously mentioned, patients included in the second indication are not just a subgroup of the newly-diagnosed population, but a cohort of the prevalent population, i.e. patients who have been living with SBCD. The prevalence estimates would be different for the two populations. These two groups include people with varying severity, history of disease, and management strategies.

The critique was concerned regarding the health states, utilities attributed to them and transitions used in the model. The critique also noted that the economic model does not take into account the CE procedures that are incomplete (10% to 18%, reported in Table 3). Incomplete CE does not result in visualisation of the small bowel and needs to be repeated which should be reflected in the cost input of CE as it may lead to an underestimation of the costs.

Paediatric-onset CD represents a separate subpopulation, usually presenting more severe disease and different course of illness. The critique considered that there is insufficient evidence, and the model does not sufficiently accommodate the differences for paediatric patients in terms of costs and benefits

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of CE for the diagnosis of suspected SBCD and assessment of established isolated SBCD.

The resubmission provided information at Table 8 and Table 9 with the expected cost to the MBS for the diagnostic and assessment indications.

Table 8 Expected total cost of CE to the MBS – diagnostic indication

Variable	Year 1	Year 2	Year 3	Year 4	Year 5
Expected utilisation					
- Based on high yield rate	755	769	783	793	807
- Based on low yield rate	1,685	1,715	1,746	1,769	1,800
Total MBS costs, no copay adjust ($2,039)					
- Based on high yield rate	$1,539,948	$1,568,074	$1,596,201	$1,617,297	$1,645,423
- Based on low yield rate	$3,435,268	$3,498,012	$3,560,757	$3,607,815	$3,670,560
Total MBS costs, at 85% benefit ($1,965)					
- Based on high yield rate	$1,483,687	$1,510,787	$1,537,886	$1,558,210	$1,585,310
- Based on low yield rate	$3,309,764	$3,370,216	$3,430,668	$3,476,008	$3,536,460

Abbreviations: CE, capsule endoscopy

Table 9 Expected total cost of CE to the MBS – assessment indication

Indication	Year 1	Year 2	Year 3	Year 4	Year 5
Assessment procedures	116	233	353	475	598
Total MBS costs, no copay adjust ($2,039)	$235,797	$475,900	$720,311	$967,951	$1,219,898
Total MBS costs, at 85% benefit ($1,965)	$227,182	$458,514	$693,995	$932,588	$1,175,331

The resubmission assumed a high diagnostic yield, the expected cost of diagnostic CE is expected to increase from $1,483,687 per year in the 1st year of MBS listing to $1,585,310 per year in the 5th year of MBS listing (at 85% benefit).

Assuming a low diagnostic yield, the expected cost of diagnostic CE is expected to increase from $3,309,764 per year (1st year of MBS listing) to $3,536,460 per year (5th year of MBS listing) (at 85% benefit).

The presented estimates assume 52.8% of patients diagnosed with SBCD per year would require reassessment due to complications (Gollop et al., 1988). As shown in Table 8, this is equivalent to a cost of $227,182 in Year 1, rising to $1,175,331 in Year 5 (at 85% benefit).

14. Key issues from ESC for MSAC

ESC noted that this is the second resubmission of an application for capsule endoscopy for diagnosis of suspected small bowel Crohn's disease (SBCD). ESC noted that there have been two major changes to the application since the most recent application (1146.1), specifically:

- the comparator of usual care was previously considered to be empiric therapy. The current application presents repeat testing until definitive diagnosis as representative of usual care; and
- a new MBS item is proposed for use of capsule endoscopy to assess patients with established isolated SBCD.

ESC noted that the application was assessed as suitable for an expedited PASC pathway; however the comparator + an additional indication to the clinical management algorithm and the addition of a new population mean that the application no longer matches well to the PASC approved PICO Confirmation. ESC considered that MSAC's previous conclusions regarding the clinical effectiveness in previous submissions cannot necessarily be applied to the current application (1146.3) given the significant changes to the patient population and clinical algorithm.

ESC noted that there is no evidence provided to support the proposed additional MBS item in patients with established isolated SBCD. ESC considered that the diagnostic accuracy data in patients with suspected SBCD is not applicable to this population. ESC noted that this indication needs quality evidence and a separate model for assessment of cost-effectiveness and this population has not been addressed further.

ESC noted that the eligible population is now better defined than in the initial submission with the requirement for evidence of underlying inflammation as indicated by systemic inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and the specification of types of prior imaging. ESC considered that the eligible population could still be more narrowly defined, for example, by specifying thresholds for the systemic inflammation markers. ESC noted the following changes to the proposed item descriptors from the previous application:

- from two occasions in any 12 month period to once per lifetime (or once per 12 months for the assessment indication); and
- removal of the requirement that capsule endoscopy is 'performed within 6 months of the colonoscopy and radiographic imaging'.

ESC noted that the European Society of Gastrointestinal Endoscopy (ESGE) considers ileocolonoscopy and cross-sectional imaging tests are complementary to capsule endoscopy; therefore, clinical follow-up and repeat testing using these techniques may not be the most appropriate comparator. ESC noted that repeat testing is not the intervention that is most likely replaced in practice and that this choice was poorly justified. ESC noted that only six gastroenterologists were surveyed, and 50% of participants, indicated that repeat testing would "sometimes" occur, depending on disease severity and progression. ESC advised that in practice, depending on disease progress and severity, double balloon enteroscopy, empiric treatment, repeat investigations and watchful waiting could all be part of usual care.

ESC noted that capsule endoscopy gives visual images of the mucosa but, as it does not take a biopsy, it is not considered diagnostic because the colon may look inflamed without the presence of SBCD.

ESC noted while two new studies were presented, these were of poor quality and did not provide additional certainty in the linked evidence approach. ESC considered that the evidence base has been researched well and that the exclusion of studies with < 20 patients was appropriate.

ESC noted that there is a high degree of uncertainty regarding the diagnostic accuracy in suspected SBCD due to:

- a lack of validated criteria for diagnosis of Crohn's disease;
- varying diagnostic criteria across studies and the statistical methods used in meta-analysis of these studies; and
- a lack of an adequate reference standard. ESC noted that long term follow-up is problematic as reference standard because the nature of Crohn's disease means that there are periods of activity and remission.

ESC noted that there was only one poor quality study providing evidence for the therapeutic efficacy (change in management or clinical utility) of capsule endoscopy (Kalla R et al 2013). ESC noted that there were no studies identified that compared the health outcomes of symptomatic patients with suspected or established isolated SBCD, assessed with and without capsule endoscopy. Therefore, ESC noted it is uncertain whether changes in management as a result of the proposed service would provide health benefits for patients.

ESC noted that there was one study in paediatric patients; however no safety data is provided in this population and no patients under six years old were included (Casciani E et al 2011). ESC noted that paediatric-onset SBCD may constitute a subpopulation with a different history of disease and different treatment pathways and complications. ESC questioned whether it was appropriate to include patients as young as two years in the item descriptor, given the lack of clinical evidence for safety and efficacy in this population.

ESC noted that the economic modelling presented for the diagnostic indication was poor in terms of the structure and the inputs from the clinical evidence. The base case does not use the most likely and reasonable assumptions and model input values; therefore, the use of one-way sensitivity analysis only is not appropriate. ESC noted that the choice of comparator was a key driver in the model. ESC noted multiple issues with model structure and assumptions that bias the results in favour of the proposed intervention including:

- in the Markov model, eight health states are used in the intervention arm, with more states that can move into the resolved state, compared with two health states in the comparator;
- no possibility of revised diagnosis in the comparator arm;
- the assumption that once SBCD is diagnosed (represented by the true positive state in the model) it will be resolved, which is clinically unrealistic and inappropriate;
- the assumption that all capsule endoscopies will yield diagnostic information noting that in the evidence presented 10% of capsule endoscopies were indeterminate;
- the assumption of repeat testing every year over the time horizon of the model (5 years), despite none of the participating gastroenterologists confirmed that ;
- the assumption of the most expensive mode of repeat testing;
- the exclusion of capsule retention, which should be around 4% based on a 2017 meta-analysis, not 0.8% as used in the sensitivity analysis; and
- the prevalence of 13% true positives is used in the model, based on an outlier study (Tukey M et al 2009). In combination, these assumptions mean that the base case for the diagnostic indication is highly uncertain and favours the proposed intervention.

ESC noted the applicant's pre-ESC response that indicated that a 100% completion rate is assumed because the applicant has agreed to provide a replacement capsule if the procedure proved to be incomplete due to technology.

ESC noted that the recommendations from the Gastroenterology MBS Review indicate that there is higher than predicted usage of the current capsule endoscopy MBS items for different indications that is not explained on clinical grounds. ESC noted that the MBS Review committee has recommended the cost for the existing MBS items for capsule endoscopy be reviewed with revision of the professional component of the fee, setting the capsule endoscope consumable cost at the current market price, and removal of capital costs from the MBS fee.

ESC noted that the application did not address the use of capsule endoscopy in determining the severity of disease for access to biological disease-modifying anti-rheumatic drugs (bDMARDs) on the PBS. ESC noted that this type of use would result in increased use of bDMARDs which is not captured in the model or financial impact estimates.

ESC noted consumer support and support from The Crohn's and Colitis Society Australia for access to the intervention in assisting with early diagnosis, coordination of long term surveillance and monitoring against increased cancer risks and management of medicines for patients.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

ESC Key Issues	ESC Advice	Pre-MSAC Applicant Response
Safety	There was one study in paediatric patients; however, no safety data is provided in this population and no patients under six years old were included (Casciani E et al 2011).	Capsule Endoscopy is TGA-approved for use in adult and paediatric patients over 2 years for visualization and examination of the gastrointestinal tract and is reimbursed via the MBS (Items 11820 & 11823) which is a positive result of submission in February 2013 (Application 1346 & 1119). This submission also supported the safety and utility of CE in children based on a total of 44 publications on 1128 paediatric and adolescent patients, with at least 72 patients between two and nine years old. Paediatric patients with ongoing Crohn's-like symptoms despite repeated imaging and invasive tests pose a significant and specific clinical need which was also supported by the clinician's feedback during public consultation.
Retention Rate	The exclusion of capsule retention, which should be around 4% based on a 2017 meta-analysis, not 0.8% as used in the sensitivity analysis.	Sensitivity analyses included and explored a risk estimate up to 10%, in which CE remained cost-saving while offering health benefits. Moreover, the proposed positioning effectively screens out patients with the potential for interfered capsule passage (e.g., bowel obstructions / strictures), and thus should further reduce the risk from these reported levels.
Diagnostic Accuracy	The diagnostic accuracy data in patients with suspected SBCD is not applicable to the established isolated SBCD population. ESC noted that this indication needs quality evidence and a separate model for assessment of cost-effectiveness and this population has not been addressed further.	Since the newly requested assessment indication represents such a narrowly defined population (patients diagnosed with SBCD using CE, with indeterminate findings after prior cross-sectional imaging), the lack of evidence for diagnostic accuracy is not surprising. The biological rationale for using CE in this group is that patients are already known to have disease that could not be detected using other techniques, due to its location in the isolated small bowel.
Economic Model	The economic modelling presented for the diagnostic indication was poor in terms of the structure and the inputs from the clinical evidence. The base case does not use the most likely and reasonable assumptions and model input values; therefore, the use of one-way sensitivity analysis only is not appropriate. The choice of comparator was a key driver in the model.	A linked evidence approach and, more generally, a modelled evaluation often inevitably have uncertainties. As per the MSAC guidelines, each area of uncertainty was discussed and supported by a pre-modelling study. The model was also acknowledged to have some structural uncertainties given the individualised nature of management pathway for these patients (i.e., uncertain transitions). Comprehensive sensitivity / scenario analyses are hence provided. Base case assumption was acknowledged as an area of uncertainty and hence explored in scenario analyses.
Comparator	ESC noted that the European Society of Gastrointestinal Endoscopy (ESGE) considers ileocolonoscopy and cross-sectional imaging tests are complementary to capsule endoscopy; therefore, clinical follow-up and repeat testing using these techniques may not be the most appropriate comparator.	The main difference between this submission and MSAC Application 1146.1 is that the comparator now consists of repeat imaging rather than empiric therapy. This change was made specifically to address MSAC's concern that patients without a clear diagnosis after endoscopy and radiographic imaging would be unlikely to receive active treatment for CD. The revised comparator selection reflects this concern and was made in consultation with local KOLs and was supported by feedback received during targeted consultation.
Evidence	There was only one poor quality study providing evidence for the therapeutic efficacy (change in management or clinical utility) of capsule endoscopy (Kalla R et al 2013).	MSAC has previously reviewed the evidence base for CE and concluded "CE appears safe and sufficiently diagnostically accurate in the investigation of these patients, with an expected improvement in subsequent clinical management" (PSD, MSAC Application 1146.1). The evidence base also represent the challenge of capturing final outcomes in the diagnostic technologies indicated for this heterogeneous patient group.

The Applicant thanks MSAC and the Department for their evaluation of Application 1146.3. We acknowledge limitations and MSAC's concerns regarding the evidence which reflects the difficulty of developing an evidence base for the proposed patient population to address. Small bowel Crohn's disease is heterogeneous, with a wide spectrum of symptoms, severity, anatomical distribution before and after its diagnosis and response to treatment and its diagnostic pathways are patient specific. This translates to challenges in developing high quality comparative evidence that can capture final clinical and economic outcomes and can only be addressed through linked evidence. A linked evidence approach and a modelled evaluation often inevitably introduces uncertainties which we tried to explore through sensitivity analysis where CE indicated cost saving and cost effectiveness of this technology.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website