Intersphincteric injection of silicone biomaterial for severe passive faecal incontinence

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Prema Thavaneswaran and Ms Brita Pekarsky from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). This recommendation was endorsed by the Minister for Health and Ageing on 5 February 2007.

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One of the most common causes of faecal incontinence is anal sphincter dysfunction or defect(s). Intersphincteric injection of silicone biomaterial (ISISB) is indicated for adult patients with severe passive faecal incontinence due to diagnostically confirmed internal anal sphincter (IAS) dysfunction, or single or multiple defects of the IAS, for whom all other conservative therapies have failed.

The aim of this procedure is to improve or restore continence by augmenting the IAS. ISISB is performed as a day case procedure under general or local anaesthesia. An 18 gauge, 2.5 inch needle is typically used to inject the silicone biomaterial within the intersphincteric space at the location of the IAS defect. Injections may be performed under the guidance of endoanal ultrasound or digital palpation.

At present in Australia, the silicone biomaterial is marketed as PTQ™ implants and all of the studies included in this report have used this material.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the 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.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team was engaged to conduct a systematic review of literature on ISISB for severe passive faecal incontinence. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of ISISB for severe passive faecal incontinence

Clinical need

The prevalence of faecal incontinence is difficult to determine, due to the reluctance of patients to report the symptoms of incontinence. In international studies, the prevalence of faecal incontinence in non-institutionalised individuals has been shown to be between 1.4 and 16.9 per cent. Studies in Australia have reported that the prevalence of faecal incontinence in the general population is between 2.3 and 15 per cent.

It is important to note that according to the expert opinion of the advisory panel, only a small number of individuals reporting incontinence suffer from severe passive faecal incontinence due to IAS dysfunction or defect(s). The exact number of these patients is unknown; however, for the purpose of this report we have estimated that it may be in

the order of 300 patients annually. It is unclear whether this figure will represent the first year experience, or indeed the steady state once the initial reservoir of patients waiting for treatment is exhausted.

Safety

Based on the available evidence, it appears that ISISB for the treatment of severe passive faecal incontinence is safe, as complications were not severe and were infrequent. The majority of complications associated with this procedure (pain and infection) occurred due to the incorrect placement of silicone biomaterial into the submucosal, rather than intersphincteric space. This conclusion is however based on a small number of patients and a relatively short follow-up, compromising our ability to detect rare adverse events.

Effectiveness

Limited data from the available studies have demonstrated that ISISB affords a benefit in terms of continence status and quality of life, in patients with severe passive faecal incontinence in the short term. Both of the studies which utilised the disease-specific, faecal incontinence quality of life (FIQL) index demonstrated a consistent, significant improvement in the domains of lifestyle, coping/behaviour and depression/self perception post-procedure. Based on one study, improvements in continence status and quality of life appear to be better in patients injected under the guidance of endoanal ultrasound compared with those injected under the guidance of digital palpation. A recent conference abstract reported a notable deterioration in function at 36 months follow-up, highlighting potential problems with the durability of the procedure. Therefore, whilst ISISB appears to be effective, it is important to recognise that only a small number of patients were analysed and there was limited follow-up of these patients; hence the long-term effectiveness of this procedure is uncertain.

Cost-effectiveness

Due to the lack of comparative data it was not possible to assess the cost-effectiveness of the procedure. We performed a cost analysis which showed that the main driver of the cost of ISISB was overwhelmingly the cost of the injectable silicone biomaterial. On analysis, the total cost per year for ISISB was estimated to be between $3,072,600 and $3,662,655, depending on the success rate of the procedures. The total cost per year for the current treatment pathway was estimated to be $590,055.

Recommendation

Intersphincteric injection of silicone biomaterial for severe passive faecal incontinence appears to be safe.

There is some low level evidence of short-term effectiveness but no evidence of long-term effectiveness.

In view of the lack of acceptable alternative therapies, a limited assessment of the financial impact was carried out. This demonstrated high cost mainly due to the cost of the prosthesis. MSAC does not recommend public funding for this procedure at this time.

The Minister for Health and Ageing endorsed this recommendation on February 5 2007.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of intersphincteric injection of silicone biomaterial (ISISB) for severe passive faecal incontinence. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for ISISB for severe passive faecal incontinence.

Background

Intersphincteric injection of silicone biomaterial for severe passive faecal incontinence

Normal continence results from the interaction of several factors such as mental function, colonic transit, rectal distensibility, stool volume and consistency, anal sphincter function and anorectal reflexes and sensation (Madoff et al 1992). A disruption in one or more of these functions may result in faecal incontinence, defined as 'either the involuntary passage or the inability to control the discharge of faecal matter through the anus' (Rao 2004).

One of the most common causes of faecal incontinence is anal sphincter dysfunction or defect(s) (Cheetham et al 2001). The anal sphincter is comprised of two rings of muscle arranged concentrically around the anal canal, the internal anal sphincter (IAS) and the external anal sphincter (EAS) (Rao 2004). Sphincter function may be disturbed as a result of disease or injury to the IAS, EAS or both, or their nerve supply (Rao 2004).

Some patients with faecal incontinence experience extreme rectal urgency or urge incontinence, which is associated with EAS pathology (Cheetham et al 2001). Other patients are unaware of rectal filling and suffer from passive incontinence, which reflects IAS defect(s) or dysfunction (Rao 2004).

While a detailed clinical assessment can provide important information about the exact nature of the incontinence, anorectal physiological testing and imaging are required in order to precisely define the underlying defect(s) (Cheetham et al 2001). The current application deals with severe passive faecal incontinence due to IAS dysfunction or defect(s). This may be due to a number of factors including degeneration from ageing, anal stretch injuries, prior anorectal surgery, connective tissue disorders and congenital anorectal malformation (Kenefick et al 2002).

The procedure

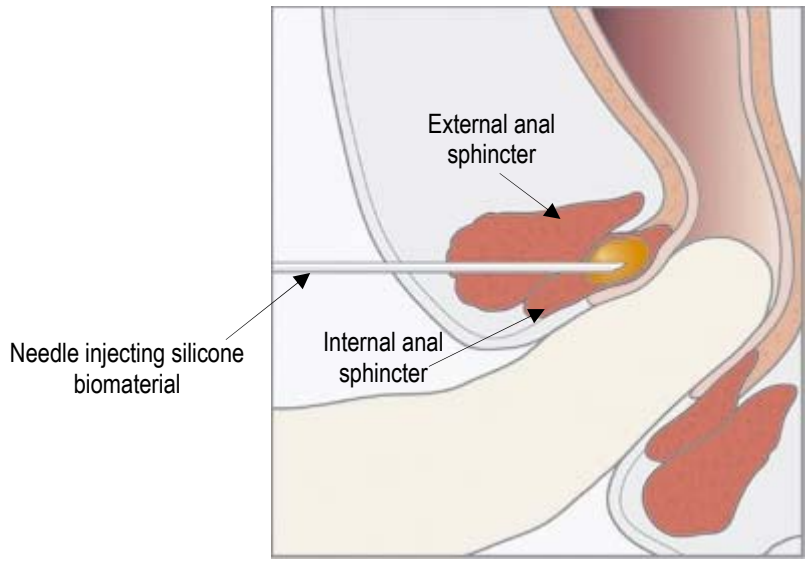
The aim of intersphincteric injection of silicone biomaterial (ISISB) is to improve or restore continence by augmenting the IAS. While the precise mechanism of action is unclear, studies in animals have demonstrated that following the injection the bioexcretable carrier gel polyvinylpyrolidone (PVP) is excreted from the body over a three-day period and is replaced with collagen within six weeks (Beisang et al 1992; Ersek et al 1991). This collagen matrix surrounds the remaining polydimethylsiloxane (PDMS) microspheres, forming a permanent cartilage-like structure which increases the bulk of the IAS.

ISISB is performed as a day case procedure under general or local anaesthesia. An 18 gauge, 2.5 inch needle is typically used to inject the silicone biomaterial within the intersphincteric space at the location of the IAS defect, and injections may be performed under the guidance of endoanal ultrasound or digital palpation (Tjandra et al 2004; Kenefick et al 2002) (Figure 1). If the IAS is weak but intact, a total of four (2.5 ml each) injections are performed respectively in the right anterior, left anterior, right posterior

and left posterior quadrant of the anal canal (Tjandra et al 2004). If there is a localised defect of the IAS, three (2.5 ml each) injections are targeted to the region of the sphincter defect, and a fourth injection into the contralateral site in the anal canal to provide symmetry of the anal canal.

At present in Australia PDMS microspheres are marketed as PTQ™ implants and all of the studies included in this report have used this material.

Figure 1 Intersphincteric injection of silicone biomaterial



Source: DMI Medical

Intended purpose

ISISB is indicated for adult patients with severe passive faecal incontinence due to diagnostically confirmed IAS dysfunction (by anorectal physiological testing, including endoanal ultrasound), or single or multiple defects of the IAS, for whom all other appropriate therapies have failed. Faecal incontinence in these patients may be caused by:

- degeneration from ageing
- anal stretch injuries including obstetric injuries
- prior anorectal surgery, including sphincterotomy or fistulotomy
- rare connective tissue disorders such as progressive systemic sclerosis
- congenital anorectal malformation.

The advisory panel expert opinion believes the following conditions to be contraindications of the procedure (either absolute or relative):

- perianal sepsis
- severe scarring of the perineum
- progressive, degenerative diseases
- immunosuppression
- pregnancy or planning pregnancy
- active Crohn's disease
- active or acute inflammation, infection or malignancy.

Clinical need / burden of disease

The prevalence of faecal incontinence in the general population is commonly underestimated, due to the reluctance of patients to report the symptoms of incontinence. Community-based studies in Australia, New Zealand, the United States, the United Kingdom, Japan, Holland and Germany have employed cross-sectional surveys of randomly selected subjects to determine the prevalence of faecal incontinence in non-institutionalised individuals. These studies have shown prevalence rates of faecal incontinence of between 1.4 and 16.9 per cent (Nelson et al 1995; Roberts et al 1999; Campbell et al 1985; Thomas et al 1984; Drossman et al 1993; Talley et al 1992; Kok et al 1992; Nakanishi et al 1997; Giebel et al 1998). Some of these studies demonstrated a higher prevalence of faecal incontinence in women (Nelson et al 1995; Roberts et al 1999; Campbell et al 1985), while other studies demonstrated a similar or higher prevalence in men (Thomas et al 1984; Drossman et al 1993). Estimates of prevalence were dependent on the definition of faecal incontinence, which varied in each study.

Data from two Australian studies that employed surveys of randomly selected subjects, reported that the prevalence of faecal incontinence in the general population was between 11.2 and 15 per cent (Kalantar et al 2002; Lam et al 1999). The prevalence of faecal incontinence in two other Australian studies which employed either face-to-face (MacLennan et al 2000) or phone (Chiarelli et al 2003) interviews was significantly lower than that reported by Kalantar et al (2002) and Lam et al (1999). MacLennan et al (2000) reported that the prevalence of faecal incontinence in the non-institutionalised population was 2.3 per cent in men and 3.5 per cent in women, while Chiarelli et al (2003) reported that the prevalence of faecal incontinence in women after high-risk delivery was 6.9 per cent.

It is important to note that according to the expert opinion of the advisory panel, only a small number of individuals reporting incontinence suffer from severe passive faecal incontinence due to IAS dysfunction or defect(s). The exact number of these patients is unknown, however for the purpose of this report we have estimated that it may be in the order of 300 patients annually. It is unclear whether this figure will represent the first year

experience, or indeed the steady state once the initial reservoir of patients waiting for treatment is exhausted.

In addition to the significant morbidity it causes in the community, faecal incontinence also places a considerable burden on the health system. In the United States, between $1.5 and $7 billion per year is spent on health care costs associated with treating or managing faecal incontinence among elderly, institutionalised patients (Szurszewski et al 1989), while the average cost per year of treating or managing an outpatient was approximately $17,000 (Mellgan et al 1999). In the United Kingdom, the annual cost of incontinence pads, appliances as well as other prescription items used to treat patients suffering from faecal incontinence in hospitals and nursing care facilities was estimated at £68 million (Sanderson 1991). In addition to the direct health care costs related to faecal incontinence, there are also costs associated with the diminished quality of life and social dysfunction suffered by patients with this disease (Leigh et al 1982), which are more difficult to measure.

Existing procedures

The current clinical decision pathway for the diagnosis and treatment of faecal incontinence is outlined in Figure 2.

Conservative measures including dietary modifications such as altered fibre or caffeine intake, pelvic floor physiotherapy, as well as the use of antidiarrhoeal agents such as loperamide or diphenoxylate/atropine sulphate, may be useful in managing faecal incontinence in some patients; however, many patients do not benefit from these supportive measures (Kenefick et al 2002).

Biofeedback, a behavioural therapy which uses operant conditioning techniques, has been shown to improve both the symptoms of faecal incontinence and objective parameters of anorectal function in up to two thirds of patients with weak anal sphincters and/or impaired rectal sensation (Cheetham et al 2001). Patients with IAS dysfunction, who have failed all of these conservative measures, currently have very few therapeutic options. According to the expert opinion of the advisory panel, the majority of these patients will continue with conservative treatment, while a small percentage will go on to have a stoma, which involves the creation of a colostomy (opening of the large bowel) or ileostomy (opening of the small bowel) on the abdominal wall, to allow the passage and collection of stool in a stoma bag. This procedure is often the last resort in patients suffering from severe passive faecal incontinence, providing a way of managing the condition, rather than restoring continence.

Proposed clinical decision pathway

ISISB is a second- or third-line therapy and should only be used in patients with severe passive faecal incontinence caused by IAS, who have failed all other appropriate conservative management (Figure 3). When IAS dysfunction as a result of degeneration or defect(s) is the underlying problem, ISISB is used as a second-line therapy. While defects of the EAS are amenable to sphincter repair, defect(s) and weakness of the IAS do not usually benefit from surgical repair or tightening. In patients with defects of both the EAS and IAS, ISISB can be used as a third-line therapy to treat weakness in the IAS after surgical repair of the EAS.

Figure 2 Current clinical decision pathway for the diagnosis and treatment of faecal incontinence

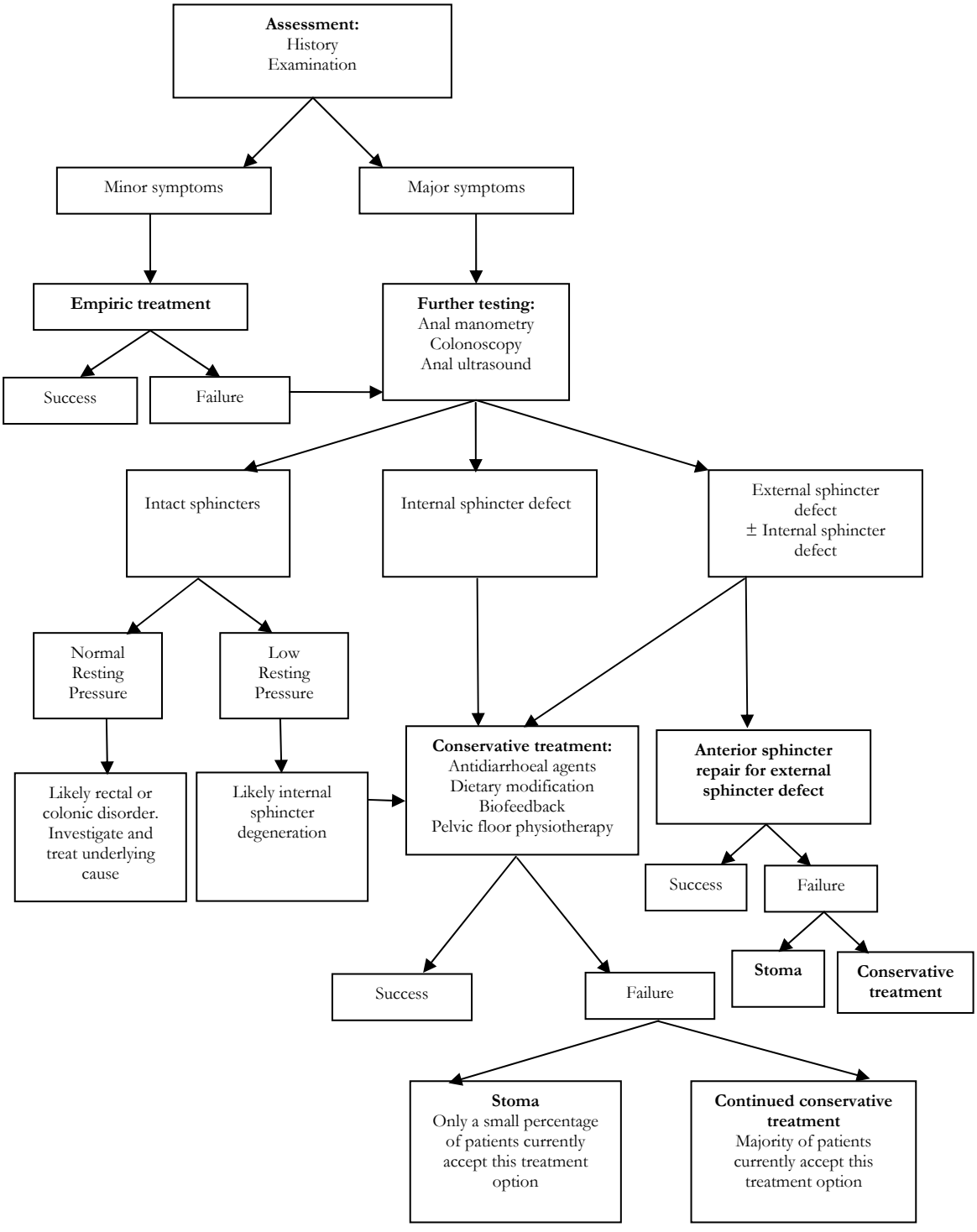
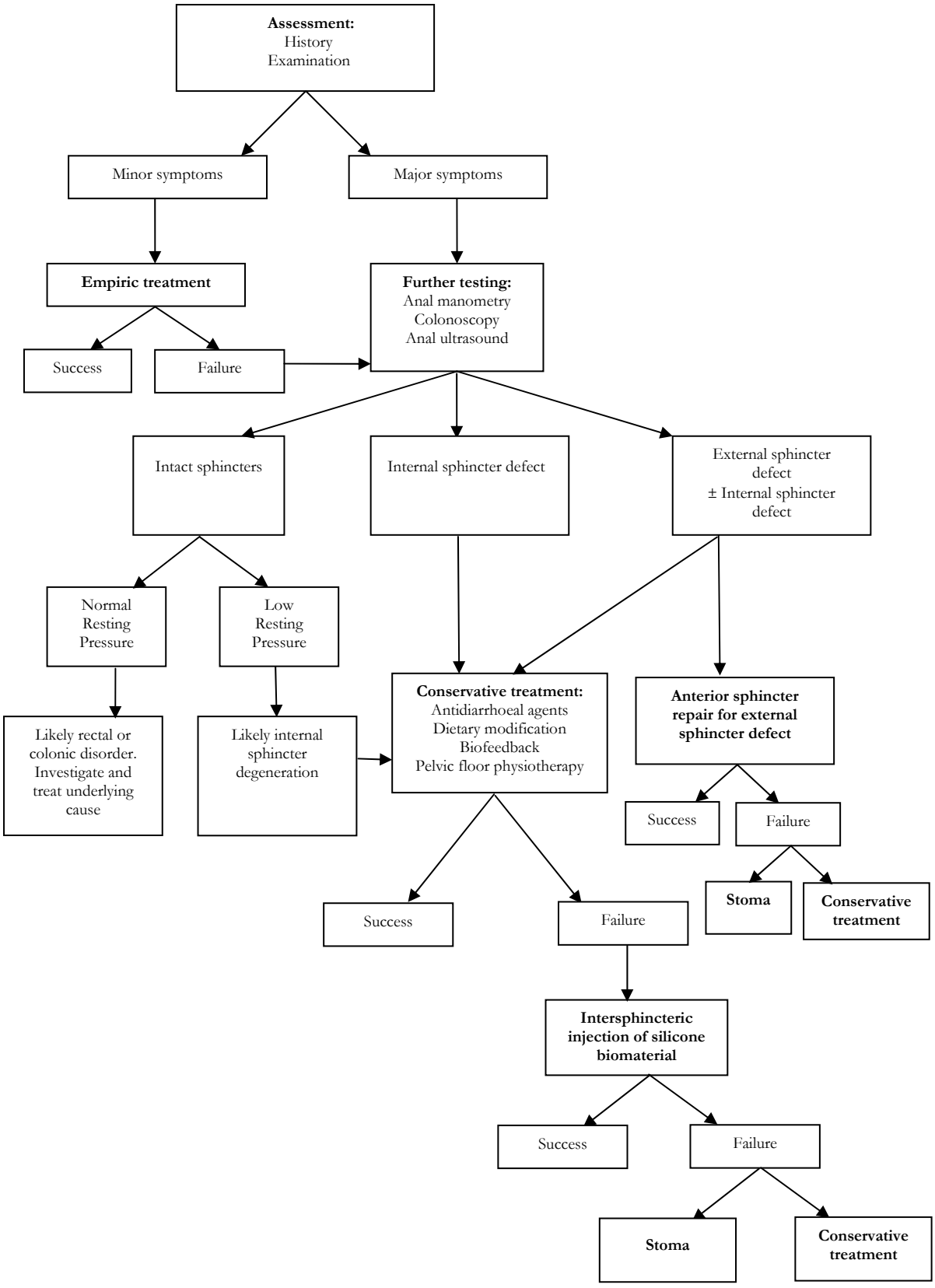


Figure 3 Proposed clinical decision pathway for the diagnosis and treatment of faecal incontinence



Comparator

The appropriate comparators for ISISB for severe passive faecal incontinence are:

- conservative, non-surgical treatments including dietary modification, anti-diarrhoeal agents, pelvic floor physiotherapy and biofeedback.
- stoma formation (colostomy or ileostomy).

Marketing status of the device / technology

In Australia, Bioplastique® implants (including PTQ™) are listed by the Therapeutic Goods Administration (TGA) as 'tissue reconstructive materials' under the Australian Register of Therapeutic Goods (ARTG) number 69960.

Current reimbursement arrangement

There is currently no Medicare Benefit Schedule (MBS) item number for ISISB for the treatment of severe passive faecal incontinence.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies for the period between 1989 and June 2006. Searches were conducted via MEDLINE, EMBASE, Current Contents, PubMed and the Cochrane Library. The York (UK) Centre for Reviews and Dissemination (CRD) databases, Clinicaltrials.gov, National Research Register, relevant online journals and the Internet were also searched. Searches were conducted without language restriction.

The search strategies used were:

MEDLINE, EMBASE and Current Contents

1. (fecal or faecal) and incontinen$
2. anal incontinen$
3. rectal incontinen$
4. bowel incontinen$
5. soiling
6. 1 or 2 or 3 or 4 or 5
7. explode "Prostheses and Implants"/all SUBHEADINGS
8. injectable silicone biomaterial
9. Macroplastique
10. Bioplastique
11. Proctoplastique
12. PTP
13. PTQ
14. perianal inject$
15. (anal or bowel) and sphincter augment$
16. bulking agent$
17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 6 and 17

The Cochrane Library and CRD Databases

(fecal or faecal) and incontinence

As it was anticipated that there would be very little evidence, handsearching of the following online conference proceedings was also undertaken:

- American Society of Colon and Rectal Surgeons Annual Meeting (2003, 2004, 2005, 2006)
- International Continence Society Annual Meeting (2003, 2004, 2005)
- Royal Australasian College of Surgeons Annual Scientific Congress (2003, 2004, 2005, 2006).

Inclusion criteria

Participants

Studies of adult human patients with severe passive faecal incontinence due to IAS dysfunction or defect(s), in whom all other appropriate management has failed to provide adequate continence, were included.

New intervention

Included studies were related to the use of ISISB for the treatment of severe passive faecal incontinence due to IAS dysfunction or defect(s).

Comparative intervention

The main comparators for ISISB were continued conservative treatment and the formation of a stoma (colostomy or ileostomy).

Outcomes

Studies were included if they contained information on at least one of the following outcomes:

- implant migration, erosion or rejection
- fistula formation
- infection
- pain
- leakage
- continence scores
- visual analog quality of life scores
- patient diaries
- SF-12 or SF-36 questionnaire results
- maximum anal resting pressure and maximum squeeze pressure
- pudendal nerve terminal motor latency (PNTML)
- endoanal ultrasound results
- costs and resource use.

Types of studies

Randomised controlled trials (RCTs), other controlled or comparative studies and case series and reports were included. Conference abstracts and manufacturers' information were included if they contained relevant safety and effectiveness data. The English abstracts from foreign language articles were included if they met the study inclusion criteria and contained safety and effectiveness data. In the case of duplicate publications, the latest and most complete study was included.

Economic analysis

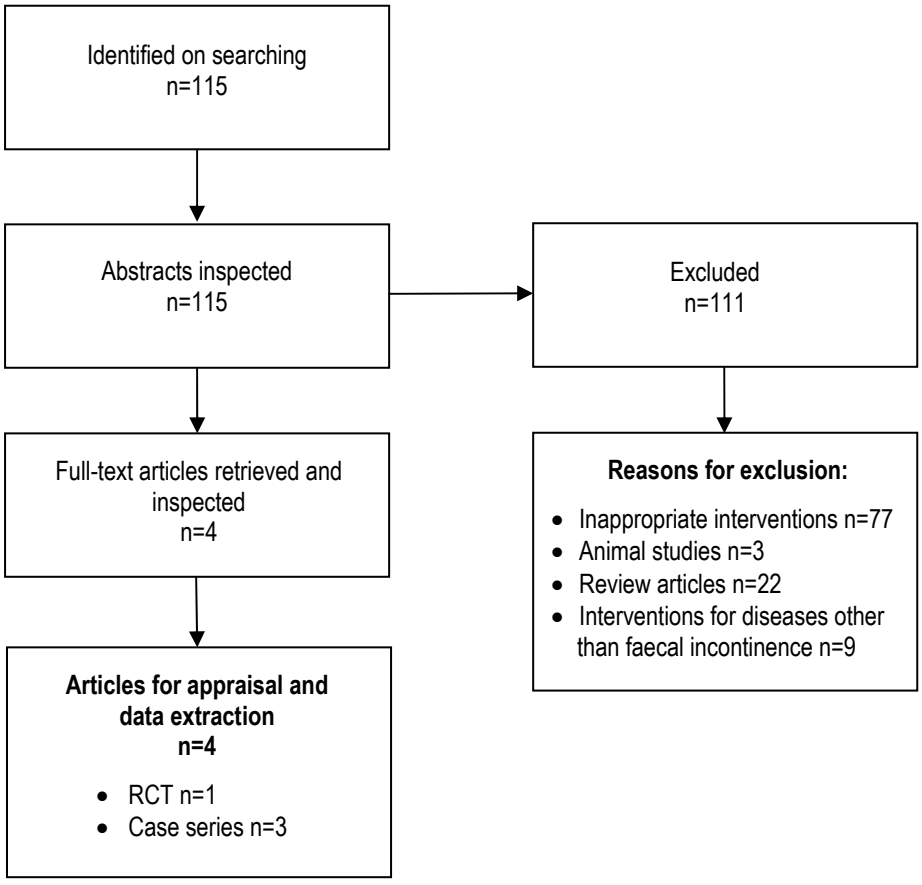
Any studies that reported an evaluation of the costs incurred in using ISISB as a treatment for severe passive faecal incontinence were included. Current costs of the biomaterial and its implementation were also reported. Providing the effectiveness and safety of ISISB could be established, an economic evaluation into the cost and resource utilisation of the treatment was conducted.

Methods of the review

Literature database

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Studies that did not meet the inclusion criteria are listed in Appendix F. The bibliographies of all retrieved publications were handsearched for any relevant references missed in the database search (pearling). The results of this process are shown in Figure 4.

Figure 4 Flowchart for inclusion of studies in the review



Data extraction

Data was extracted by one researcher and checked by a second using standardised data extraction tables developed *a priori*. Data was only reported if stated in the text, tables, graphs or figures of the article, or if it could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated.

Description and methodological quality of included studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 1) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 1 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 2

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 2.

Table 2 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC 1999.

Included studies were critically appraised for study quality according to the guidelines in Chapter 6 of the Cochrane Reviewers' Handbook (Higgins *et al* 2005). Included RCTs were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up and any other aspect of the study design or execution that may have introduced bias. Non-randomised comparative studies were evaluated for the method of patient selection, comparability of the patient groups, completeness of follow-up and any other feature of the study design or execution that may have introduced bias. Case series were examined with respect to the use of consecutive patient selection, losses to follow-up and reporting of outcomes. Two reviewers critically appraised each of the included studies and any differences in interpretation were resolved through discussion. A quality score was not assigned, instead the quality of the included studies was described in a narrative fashion and any important quality issues were highlighted in the discussion of outcomes.

Expert advice

An advisory panel with expertise in colorectal surgery, geriatrics, general practice and stomal therapy/faecal incontinence was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Studies included in the review

Four studies were identified for inclusion in this assessment of the safety and effectiveness of ISISB for the treatment of severe passive faecal incontinence (Table 3). One comparative study (level II evidence) was identified (Tjandra 2004); however, the aim of this study was to evaluate the optimal technique (ultrasound-guided versus palpation) for administration of the silicone biomaterial, and it did not compare the use of ISISB to stoma formation or conservative, non-surgical treatment. Therefore, while this study had a randomised element, we did not consider it to be a true RCT for the purposes of this report and it was designated level IV evidence. The remaining three studies were descriptive case series (level IV evidence) (Chan 2006, Kenefick 2002 and Malouf 2001).

Table 3 Descriptive characteristics of studies included in the review

Study	L of E	Design	Enrolment period	Maximum length of follow-up (months)	Study population		
					n	№. Male (%)	Age (years)
Tjandra 2004[a] AUSTRALIA	IV	case series	NR	12	Guided by ultrasound		Median: 66 Range: 34-89
					42	9 (21.0)	
					Guided by palpation		
					40	9 (23.0)	
Chan 2006[a] AUSTRALIA	IV	case series	2003-2004	20	7	3 (43.0)	Median: 52 Range: 34-67
Kenefick 2002 UK	IV	case series	NR	19	6	4 (67)	Median: 53 Range: 36-65
Malouf 2001 UK	IV	case series	NR	6	10	4 (40.0)	Median: 64 Range: 41-80

NOTE: L of E = level of evidence; a - there may be patient overlap between these two studies; NR = not reported.

Critical appraisal

The descriptive characteristics of the four included studies are listed in Table 3. Two studies were conducted in Australia and two studies were conducted in the UK. The minimum and maximum length of follow-up was six (Malouf 2001) and 20 (Chan 2006) months respectively. The study population varied in size from six (Malouf 2001) to 82 participants (Tjandra 2004). The majority of participants in all but one study (Kenefick 2002) were female. The median age of the participants included in the studies was similar between studies. None of the four studies reported the mean or median duration of faecal incontinence prior to enrolment.

The inclusion and exclusion criteria used to recruit participants in each of the studies are summarised in Table 4. Three studies specified that individuals with passive faecal incontinence for solid or liquid stool were to be included (Tjandra 2004, Kenefick 2002 and Malouf 2001), with two of the studies stating that incontinence had to be severe in nature (Tjandra 2004 and Kenefick 2002) and one study stating that incontinence had to

interfere with daily living (Malouf 2001). Two studies specified that individuals with IAS dysfunction or defect(s) were to be included (Tjandra 2004 and Kenefick 2002). Three studies specified that to be eligible for inclusion, participants had to have failed one or more conservative treatments (Tjandra 2004, Kenefick 2002 and Malouf 2001), while psychological stability and suitability for the procedure were essential criteria for inclusion in two of these studies (Kenefick 2002 and Malouf 2001).

Table 4 Participant selection criteria for studies included in the review

Study	L of E	Design	Inclusion	Exclusion
Tjandra 2004[a] AUSTRALIA	IV	case series	Severe faecal incontinence for solid or liquid stool, caused by IAS dysfunction Low or borderline resting anal canal pressure Either an isolated IAS defect or a circumferentially intact, although often attenuated, IAS Failure of bulking or constipating agents or pelvic floor physiotherapy	Pregnancy Active perianal sepsis Unresected anorectal cancer Immunosuppression
Chan 2006[a] AUSTRALIA	IV	case series	NR	NR
Kenefick 2002 UK	IV	case series	Severe passive faecal incontinence for solid or liquid stool, due to IAS dysfunction IAS muscle degeneration and discrete IAS defects Failure of standard conventional treatment including antidiarrhoeal agents and behavioural therapy (biofeedback) Psychological suitability for enrolment on trial	Perianal sepsis Severe scarring Diabetes Immunosuppression Pregnancy
Malouf 2001 UK	IV	case series	Passive faecal incontinence to solid or liquid stool causing interference with daily living Failure of treatment with antidiarrhoeal agents Psychological stability and suitability for intervention	Perianal sepsis Marked perianal scarring Diabetes Immunosuppression Pregnancy

NOTE: L of E = level of evidence; a - there may be patient overlap between these two studies; NR = not reported.

The validity characteristics of the four included studies are summarised in Table C1, Appendix C. Two of the four studies reported prospective data collection (Tjandra 2004 and Chan 2006) and the remaining two studies did not report study design (Kenefick 2002 and Malouf 2001). None of the included studies reported that participants were consecutively enrolled. Three studies reported explicit inclusion and exclusion criteria (Tjandra 2004, Kenefick 2002 and Malouf 2001), while one study failed to report inclusion or exclusion criteria (Chan 2006). Only one of the four studies reported uniform follow-up of participants (Malouf 2001).

The majority of participants (50% to 100%) included in three of the four studies had faecal incontinence due to prior anorectal surgery (haemorrhoidectomy, sphincterotomy, post-overlap repair), rather than idiopathic IAS degeneration (Chan 2006, Kenefick 2002 and Malouf 2001). Tjandra (2004) did not specify the aetiology of faecal incontinence in all participants, however 33 per cent of participants had prior anorectal surgery (haemorrhoidectomy, sphincterotomy, fistulotomy) and the authors speculated that obstetric injury was also likely to be an important aetiological factor.

Is it safe?

Complications

The case series by Malouf (2001), a pilot study designed to assess the efficacy of single or multiple injections of silicone biomaterial, reported complications in five out of 10 participants. The first six participants in this study were injected using a 1-inch needle, with five participants reporting severe pain or infection/ulceration at the injection site or in the anal canal following the procedure, which required up to 10 weeks of antibiotic therapy to resolve (Malouf 2001). No complications were reported in the four remaining participants who underwent an altered protocol which utilised a 2.5-inch needle (Malouf 2001). Two of the case series reported that all participants tolerated the injection well, and the procedure was safe without any serious complications such as pain, infection, leakage, constipation or erosion of implants (Chan 2006 and Kenefick 2002). It is important to note that these findings were based on a small number of patients and a relatively short follow-up, which may have impaired our ability to detect rare adverse events.

Tjandra (2004) reported that of the 82 participants, six participants noted minor discomfort at anal injection sites that required simple oral analgesia, while 1 participant suffered from persistent anal discomfort for six weeks after the procedure. Further evaluation by endoanal ultrasound and digital rectal examination revealed that the protracted anal pain was most likely due to the silicone biomaterial being injected too superficially, just beneath the anal mucosa. No other complications including allergic reactions, infection, erosion of implants, fistulation or constipation were reported following the procedure.

Is it effective?

Faecal incontinence scores

All four included studies reported the results of incontinence scoring systems used to determine the participants' perception of improvement in their continence status (Table 5). Three studies utilised the Wexner continence score to assess continence status pre- and post-injection (Tjandra 2004, Chan 2006 and Kenefick 2002). The Wexner continence score is based on numerical values assigned to the frequency of occurrence (scored 0-4) in each of several categories including type of incontinence (solid, liquid, gas), pad use and lifestyle alteration. A minimum score of zero indicates perfect continence, and a maximum score of 20 indicates complete incontinence. One study employed a descriptive scale to assess continence status pre- and post-injection, where patients showed either complete (no leakage of solid or liquid stool), marked (minimal leakage of liquid stool and judged by the patient as ≥75 per cent improvement), minor (leakage of liquid stool and judged by the patient as a 20 to 50 per cent improvement) or nil (leakage of liquid and at times solid stool and judged by the patient as <20 per cent) improvement (Malouf 2001).

Tjandra (2004) reported that ISISB significantly improved continence status in both treatment groups, with continued improvements in continence scores observed up to 12 months follow-up in endoanal ultrasound guided participants, and nine months follow-up in palpation guided participants. Significantly more endoanal ultrasound guided participants demonstrated a greater than 50 per cent improvement in Wexner score at three months follow-up, when compared to those who received the injection guided by palpation (data not shown). The improvement in continence scores was similar in both treatment groups regardless of the presence of pudendal neuropathy. A recent conference abstract by Tjandra (2006) reported that following continued improvements in Wexner continence scores at 12 and 24 months post-procedure, a notable deterioration in function was observed at 36 months follow-up (Appendix E).

The case series by Chan (2006) reported a significant improvement in continence status between baseline and three and 12 months follow-up. Similarly, Kenefick (2002) reported a marked improvement in symptoms and participant satisfaction in 5/6 participants who demonstrated a significant improvement in Wexner score between baseline and last follow-up. Malouf (2001) reported that six weeks after the first injection 3/10 participants were asymptomatic, 4/10 demonstrated a marked improvement in their continence status and 3/10 demonstrated no improvement. By six months follow-up; however, the number of participants that reported no relief of their symptoms had increased to 7/10, with 2/10 reporting a sustained marked improvement in continence and 1/10 reporting a sustained minor improvement.

Table 5 Incontinence scores prior to and following ISISB

Study	L of E	Design	Incontinence Tool	Incontinence scores			
				Baseline	Post-injection	n	p-value
Tjandra 2004[a] AUSTRALIA	IV	case series	Wexner continence score	Guided by endoanal ultrasound			
				Median:14.5 Range: 10-20 n=42	Median (range) at: 5 weeks: 10 (3-18) 3 months: 7 (1-12) 6 months: 5 (2-13) 9 months: 4 (2-13) 12 months: 3 (1-12)	 42 38 30 22 10	 <0.001[c] <0.001[c] <0.001[c] <0.001[c] <0.001[c]
				Patients with neuropathy[b]: Mean [SD]: 15.8 [0.66] n=26	 Mean [SD] at: 1 month: 12.3 [0.48] 6 months: 9.6 [0.63]	 26 NR	 NS[cd] NS[cd]
				Patients without neuropathy: Mean [SD]: 13.6 [0.80] n=16	 Mean [SD] at: 1 month: 9.4 [0.71] 6 months: 3.6 [0.65]	 16 NR	 NS[cd] NS[cd]
				Guided by palpation			
				Median:14.5 Range: 11-20 n=40	Median (range) at: 5 weeks: 11 (5-17) 3 months: 9.5 (3-14) 6 months: 8 (2-12) 9 months: 10 (2-13) 12 months: 11 (2-12)	 40 32 21 11 5	 <0.001[c] <0.001[c] <0.001[c] <0.001[c] NS[ce]
				Patients with neuropathy[b]: Mean [SD]: 15.3 [0.56] n=22	 Mean [SD] at: 1 month: 11.5 [0.53] 6 months: 7.3 [0.57]	 22 NR	 NS[cd] NS[cd]
				Patients without neuropathy: Mean [SD]: 14.3 [0.57] n=18	 Mean [SD] at: 1 month: 10.3 [0.54] 6 months: 8.1 [0.75]	 18 NR	 NS[cd] NS[cd]
Chan 2006[a] AUSTRALIA	IV	case series	Wexner continence score	Median: 12 Range: 9-14 n=7	Median (range) at: 3 months: 1 (0-5) 12 months: 2 (1-5)	 7	 <0.02[f]
Kenefick 2002 UK	IV	case series	Wexner continence score	Median: 14 Range: 11-20 n=6	Median (range) at: 18 months: 8 (6-15)	 6	 <0.05[g]
Malouf 2001 UK	IV	case series	NR	NR n=10	6 weeks: complete improvement marked improvement nil improvement 6 months: marked improvement minor improvement nil improvement	 3 4 3 2 1 7	 NR NR NR NR NR NR

NOTE: L of E = level of evidence; Wexner continence score: 0 = perfect continence, 20 = complete incontinence, complete improvement = no leakage of solid or liquid stool, marked improvement = minimal leakage of stool and judged by the patient as ≥75 per cent improvement, minor improvement = leakage of liquid stool and judged by the patient as a 20 to 50 per cent improvement, nil improvement = leakage of liquid and at times solid stool and judged by the patient as <20 per cent improvement; NR = not reported; a - there may be patient overlap between these two studies; b - defined as pudendal nerve terminal motor latency >2.6 ms; c - authors' statistical analysis using a paired t-test; d - no significant difference at p>0.05; e - no significant difference at p>0.01; f - authors' statistical analysis using the Wilcoxon signed-rank test; g - authors' statistical analysis using the Wilcoxon paired samples test.

Quality of life

Three studies reported data on quality of life outcomes using four different quality of life instruments (Tables D1-4, Appendix D). Tjandra (2004) and Chan (2006) utilised both the visual analog scale (VAS) for global quality of life and the faecal incontinence quality of life (FIQL) index. Kenefick (2002) employed the short form-36 (SF-36) questionnaire, while Tjandra (2004) used the short form-12 (SF-12) questionnaire.

The VAS global quality of life scale is a well-validated generic quality of life instrument that is scored from one (very poor) to 10 (very well). Tjandra (2004) reported a significant improvement in global quality of life scores in both treatment groups, with continued improvements observed up to 12 months follow-up in endoanal ultrasound guided participants and nine months follow-up in palpation guided participants. In both treatment groups, the improvement in global quality of life was similar regardless of whether pudendal neuropathy was present. The case series by Chan (2006) reported a significant improvement in VAS global quality of life scores between baseline and three months post-treatment, which continued to the end of assessment at 12 months.

The FIQL index is a validated, disease-specific quality of life instrument. This instrument is a self-administered questionnaire containing 29 items covering four domains: lifestyle, coping/behaviour, depression/self-perception and embarrassment. Each of the 29 items is scored 1-5 and a mean score is obtained within each of the four domains. Tjandra (2004) reported a significant improvement in all four domains of the FIQL index in both treatment groups at a median follow-up of six months, which was independent of the presence of pudendal neuropathy. Chan (2006) reported a significant improvement in lifestyle, coping/behaviour and depression/self-perception 12 months after the procedure; however, no change in the level of embarrassment was observed.

The SF-36 is a validated, generic quality of life instrument. This 36-item questionnaire measures several dimensions of health, including physical and social function. The maximum possible score for each dimension is 100 and the minimum score is zero, with higher scores indicating better health. The case series by Kenefick (2002) reported a significant improvement in SF-36 physical and social function scores at a median follow-up of 18 months.

The SF-12 is an abbreviated version of the SF-36 questionnaire, which produces accurate physical and metal health component summary scores of the SF-36, while placing less of a burden on respondents. In the RCT by Tjandra (2004), the physical and mental health scores of the SF-12 improved significantly in endoanal ultrasound guided participants at a median of six months follow-up; however, no improvement was observed in palpation guided participants. The observed changes in SF-12 physical and mental health scores were independent of the presence of pudendal neuropathy in both treatment groups (data not shown).

Resting and squeeze anal manometry

Anal manometry may be used to assess IAS and EAS function and tone. Resting anal pressure is a measure of IAS function and squeeze anal pressure is thought to reflect EAS function. While individuals with faecal incontinence have been shown to have low resting and squeeze anal sphincter pressures, there is significant overlap between the pressure profiles of normal and incontinent patients.

All four included studies reported data on resting anal pressure pre-and post-injection (Table 6). Tjandra (2004) reported an 89 per cent increase in maximum resting anal pressure three months post-procedure in ultrasound guided participants, while palpation guided participants demonstrated a 42 per cent increase.

The case series by Chan (2006) reported a significant improvement in maximum resting pressures six months post-injection; however, these manometric changes did not correspond to the degree of improvement in incontinence scores. Similarly, Kenefick (2002) reported a significant increase in maximum resting pressures between baseline and last follow-up; however, the case series by Malouf (2001) reported no improvement in maximum resting pressures at either six weeks or six months follow-up.

Table 6 Anal manometry: Maximum resting pressure

Study	L of E	Design	Maximum resting pressure			
			Baseline	Post-injection	n	p-value
Tjandra 2004[a] AUSTRALIA	IV	case series	Guided by ultrasound			
			Mean [SD]: 23 [9.7] mmHg n=42	Mean [SD] at: 6 months: 38 [12.4] mmHg % increase: 89	42	<0.01[b]
			Guided by palpation			
			Mean [SD]: 27 [8.7] mmHg n=40	Mean [SD]: at 6 months: 35 [6.5] mmHg % increase: 42	31	<0.01[b]
Chan 2006[a] AUSTRALIA	IV	case series	Median: 35 mmHg Range: 22-45 n=7	Median (range) at: 6 months: 41 (31-51) mmHg	7	0.016[c]
Kenefick 2002 UK	IV	case series	Median: 46 cm H_2O Range: 20-79 n=6	Median (range) at: 18 months: 75 (57-92) cm H_2O	6	0.03[d]
Malouf 2001 UK	IV	case series	Median: 54 cm H_2O Range: 28-95 n=10	Median (range) at: 6 weeks: 40 (30-86) cm H_2O 6 months: 60 (35-127) cm H_2O	10 10	NS[ef] NS[ef]

NOTE: L of E = level of evidence; normal range of maximum resting pressure in laboratory = 50-70 mmHg; a - there may be patient overlap between these two studies; b - authors' statistical analysis using a Wilcoxon signed-rank test; c - authors' statistical analysis using a Wilcoxon signed-rank test; d - authors' statistical analysis using the Wilcoxon paired samples test; e - authors' statistical analysis using a paired t-test; f - no significant difference at p>0.05.

Squeeze anal pressure values pre-and post-injection were reported in all four included studies, however no significant improvements were observed at follow-up in any of these studies (Table 7).

Table 7 Anal manometry: Maximum squeeze pressure

Study	L of E	Design	Maximum squeeze pressure			
			Baseline	Post-injection	n	p-value
Tjandra 2004[a] AUSTRALIA	IV	case series	Guided by ultrasound			
			Mean [SD]: 106 [22.3] mmHg n=42	Mean [SD] at: 6 months: 116 [21.7] mmHg % increase: 10	42	NS[bc]
			Guided by palpation			
			Mean [SD]: 112 [25.1] mmHg n=40	Mean [SD]: at 6 months: 121 [21.2] mmHg % increase: 10	31	NS[bc]
Chan 2006[a] AUSTRALIA	IV	case series	Median: 126 mmHg Range: 98-163 n=7	Median (range) at: 6 months: 132 (102-156) mmHg	7	NS[de]
Kenefick 2002 UK	IV	case series	Median: 98 cm H_2O Range: 63-268 n=6	Median (range) at: 18 months: 142 (57-300) cm H_2O	6	NS[fg]

NOTE: L of E = level of evidence; normal range of maximum squeeze pressure in laboratory = 100-180 mmHg; a - there may be patient overlap between these two studies; b – authors' statistical analysis using a Wilcoxon signed-rank test; c – no significant difference at p>0.05; d – authors' statistical analysis using the Wilcoxon signed-rank test; e – no significant difference at p>0.05; f – authors' statistical analysis using the Wilcoxon paired samples test; g – no significant difference at p>0.05.

Endoanal ultrasound results

Tjandra (2004) reported that one month after injection, endoanal ultrasound scans revealed no evidence of implant migration in any of the 82 participants, with the silicone biomaterial appearing globular and remaining at the site of injection around the IAS in the middle and upper anal canal.

Endoanal ultrasound scans performed six weeks after the procedure revealed correct placement of the implants in 9/10 participants, while the injected material could still be palpated at the injection sites in 8/10 participants at 6 months follow-up (Malouf 2001). Similarly, Kenefick (2002) reported that in the 5/6 participants who demonstrated a marked improvement in function following the procedure, endoanal ultrasound revealed no local migration of the implants either within or around the IAS.

What are the economic considerations?

As there were no published comparative studies on which to assess the safety and effectiveness of ISISB compared to stoma formation, continued conservative treatment, or any other interventions, it was not possible to assess the cost-effectiveness of the procedure. Furthermore, no studies of the costs or resource use associated with ISISB were identified from the literature searches. The following information only attempts to estimate the pool of patients who may be eligible for ISISB in Australia, and the costs associated in providing this procedure.

Estimation of the potential patient pool for ISISB

Data provided by the applicant (Colorectal Surgical Society of Australia and New Zealand) suggested that in Australia, approximately 300 patients with severe refractory passive faecal incontinence due to IAS dysfunction or defect(s) may be eligible for treatment with ISISB annually (Section 11). Patients that are being considered for ISISB should be assessed clinically as well as by anorectal physiological testing, including endoanal ultrasound. The procedure should be performed by appropriately trained specialists with expertise in the management of faecal incontinence and who have access to specialised anorectal physiology units.

Cost of ISISB

A simple costing is provided below, using information provided by the Applicant, as well as the expert opinion of the advisory panel (Table 8).

Table 8 Cost of ISISB

Health care resource	Cost (A$)	Source of cost
Complete kit of four 2.5 ml syringes of Injectable PTQ™ Implants	9,000	Applicant
Direct Treatment Costs		
Proposed professional fee	300 - 500	Applicant
Cost of endoanal ultrasound to guide injection	50	Applicant
Anaesthetist fee (MBS Item numbers 17603, 23051, 20902)	192	Advisory Panel
Cost of same day surgery facility	600	Advisory Panel
Total	10,242*	

NOTE: *This is calculated at the mid-point of the professional fee range.

Based on these costs, per year the cost of ISISB would be $10,242/patient or $3,072,600 for 300 patients. In addition to these costs would be the cost of treatment failures. This may add anywhere between $0 in the case of a 100 per cent success rate and $590,055 in the case of a 100 per cent failure rate. At present we are unsure where this figure may lie. Therefore the total cost per year of ISISB, including additional costs for treating failures, would be between $3,072,600 and $3,662,655.

Cost of stoma formation

Laparotomy with stoma creation is currently listed on the MBS under item 30375 and the fee for this procedure is $451.10. In the public sector, patients admitted for stoma formation would be assigned to Australian Refined Diagnosis Related Group (AR-DRG) v4.2 G11A. The average total cost of this DRG is $5047 per separation, with an average length of stay of 4.8 days (National Hospital Cost Data Collection Cost Weights for AR-DRG Version 4.2, Round 8, 2003-2004, Australian Institute of Health and Welfare).

Table 9 Cost of stoma

Health care resource	Cost (A$)	Source of cost
Total cost of procedure (including hospital stay)	5047	National Hospital Cost Data Collection – Cost Weights for AR-DRG Version 4.2, Round 8 (2003-2004) (AIHW)
Stoma care products	470 per year	The Continence Aids Assistance Scheme (CAAS) (Department of Health and Ageing)

Based on these costs, the total cost of a stoma per year would be $5517/patient for the first year and $470 for each subsequent year.

Cost of conservative, non-surgical treatment

The expert opinion of the advisory panel suggests that the majority of patients who are eligible for ISISB would, in the absence of this procedure, continue with conservative treatment rather than opt for a stoma. Conservative, non-surgical treatments for faecal incontinence include lifestyle changes such as dietary modifications, combined with health care interventions such as medications to change stool consistency, pelvic floor physiotherapy, biofeedback and 'toileting' strategies. While the impact of lifestyle change on resources may be negligible, the impact of conservative health care interventions for the treatment of faecal incontinence is likely to be considerable; however, could not be quantified from the literature. For the purposes of this evaluation it was assumed that at the very least, continued use of incontinence pants would be required, along with pharmacotherapy with loperamide hydrochloride prescribed for symptom relief (Table 10).

Table 10 Cost of conservative treatment

Health care resource	Cost (A$)	Source of cost
Pharmacotherapy (Loperamide)	419 per year	Allowing for intolerance and patient preference, assumed that 85% of patients are prescribed loperamide hydrochloride, at any average dose of 2 mg x 2 tablets daily (http://www.douglas.com.au/products/otc/pdfs/NEGASTROPI.pdf) Price taken from PBS, April 2006
Incontinence pants	1,361 per year	Unit price from retail pharmacy. An average cost of $2.98 each for Tena pants (a market leader). Frequency of use taken as baseline rate (NICE 2004)
Total per year	1,780	

Based on these costs, the total cost of conservative treatment per year would be $1780/patient.

Cost of treating severe passive faecal incontinence if ISISB is unavailable

The estimated first year costs for the treatment of severe passive faecal incontinence if ISISB is unavailable are provided below (Table 11). These costs are based on the assumption that 95 per cent of people suffering from severe passive faecal incontinence will continue with conservative treatment, while only 5 per cent will opt for a stoma (expert opinion of the advisory panel).

Table 11 First year costs if ISISB is unavailable

	Discounted Cost (A$)		
Year	**Conservative treatment**	**Stoma**	**Total**
1	507,300	82,755	**590,055**

Discussion

Limitations of the evidence

ISISB is a new technology for the treatment of severe passive faecal incontinence due to IAS dysfunction or defect(s). At present the evidence base on this procedure is limited, with no comparative studies identified from the published literature, or from handsearching of recent conference proceedings. Given the small number of patients who suffer from severe passive faecal incontinence, it is unlikely that RCTs in this area will be conducted. The lack of comparative and long-term data made it difficult to draw firm conclusions about the effectiveness of the procedure and consequently it was not possible to determine its cost-effectiveness. In each of the included studies, follow-up was short to medium term (no more than three years) and it was not possible to comment on the long-term durability of the procedure. It is important to note that the bulk of the data in this report is from a single institution and there may be significant patient overlap between studies; however, insufficient detail was provided to determine exactly where this may have occurred.

Safety

Based on the available evidence, it appears that ISISB for the treatment of severe passive faecal incontinence is safe, as complications were not severe and were infrequent. The majority of complications associated with this procedure (pain and infection) occurred due to the incorrect placement of silicone biomaterial into the submucosal, rather than intersphincteric space. This conclusion is however based on a small number of patients and a relatively short follow-up, compromising our ability to detect rare adverse events.

Effectiveness

Limited data from the available studies have demonstrated that ISISB affords a benefit in terms of continence status and quality of life, in patients with severe passive faecal incontinence in the short term. Both of the studies which utilised a disease-specific questionnaire (FIQL index) demonstrated a consistent, significant improvement in the domains of lifestyle, coping/behaviour and depression/self perception post-procedure. Based on one study, improvements in continence status and quality of life appear to be better in patients injected under the guidance of endoanal ultrasound compared with those injected under the guidance of digital palpation. In addition, the post-procedure functional and quality of life outcomes of patients with pudendal neuropathy were not significantly different to those without neuropathy. Three studies demonstrated a significant improvement in maximal resting anal pressure, which may indicate improved IAS function, however the relationship between resting anal pressure and continence status is yet to be established. A recent conference abstract reported a notable deterioration in function at 36 months follow-up, highlighting potential problems with the durability of the procedure. Therefore, whilst ISISB appears to be effective, it is important to recognise that only a small number of patients were analysed and there was limited follow-up of these patients; hence the long term effectiveness of this procedure is uncertain.

Cost-effectiveness

Due to the lack of comparative data it was not possible to assess the cost-effectiveness of the procedure. We performed a cost analysis which showed that the main driver of the cost of ISISB was overwhelmingly the cost of the injectable silicone biomaterial. On analysis, the total cost per year for ISISB was estimated to be between $3,072,600 and $3,662,655, depending on the success rate of the procedure. The total cost per year for conservative treatment was estimated to be $590,055.

Conclusions

ISISB is a minimally invasive intervention for the treatment of severe passive faecal incontinence due to IAS dysfunction or defect(s). The expert opinion of the advisory panel is that all patients being considered for ISISB should undergo anorectal physiological testing, including endoanal ultrasound, in a specialised anorectal physiology unit. This would help ensure that patients receive the appropriate treatment.

Currently the evidence base for this procedure is small, with no comparative studies published to date. ISISB appears to be safe, although there is the potential for a variety of complications including pain, infection and implant migration or leakage, particularly if the injection is placed incorrectly. This procedure has been shown to improve the continence status and quality of life of patients; however, no long-term follow-up data is available and it is not clear how durable the treatment will be.

Due to the lack of comparative studies it was not possible to make any assessment of the relative effectiveness of ISISB compared to stoma formation or continued conservative treatment.

An assessment of the cost-effectiveness of this procedure was not possible. We conducted a cost-analysis and, given the projected numbers, the total cost of ISISB was estimated to be between $3,072,600 and $3,662,655 annually, as opposed to the cost of the current treatment pathway which was $590,055.

Recommendation

Intersphincteric injection of silicone biomaterial for severe passive faecal incontinence appears to be safe.

There is some low level evidence of short-term effectiveness but no evidence of long-term effectiveness.

In view of the lack of acceptable alternative therapies, a limited assessment of the financial impact was carried out. This demonstrated high cost mainly due to the cost of the prosthesis. MSAC does not recommend public funding for this procedure at this time.

The Minister for Health and Ageing endorsed this recommendation on February 5 2007.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Fong	thoracic medicine
Dr David Gillespie	gastroenterology
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Ray Kirk	health research
Associate Professor Frederick Khafagi	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Associate Professor Donald Perry-Keene	endocrinology
Dr Ewa Piejko	general practice

Ms Sheila Rimmer	consumer health issues
Ms Samantha Robertson	Department of Health and Ageing representative
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Dr Mary Turner	Australian Health Ministers' Advisory Council representative
Dr David Wood	orthopaedics

Appendix B Advisory Panel, Project Managers and Evaluators

Advisory panel for MSAC Application 1100

Dr Douglas Travis (Chair) Head of Urology Western Health Melbourne VIC	Member of Medical Services Advisory Committee (MSAC)
Dr Ewa Piejko General Practitioner Melbourne VIC	Member of MSAC
Associate Professor Nicholas Rieger Department of Colorectal Surgery Queen Elizabeth Hospital Adelaide SA	Royal Australasian College of Surgeons nominee
Dr James Keck Director of Anorectal Physiology St Vincent's Hospital Melbourne VIC	Colorectal Surgical Society of Australia and New Zealand nominee
Dr Michael Whishaw Consultant Physician in Geriatric Medicine Royal Melbourne Hospital – Royal Park Campus Melbourne VIC	Co-opted nominee
Ms Sheila Rimmer Consumer Representative Consumers' Health Forum of Australia Sydney NSW	Consumers' Health Forum of Australia nominee

Department of Health and Ageing

Ms Marlene Williamson Senior Project Manager
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Evaluators

Ms Prema Thavaneswaran Research Officer
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)
Adelaide SA

Ms Brita Pekarsky Consultant
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Adelaide SA

Appendix C Validity characteristics of included studies

Table C1 Validity characteristics of studies included in the review

Study	Design	Participants consecutively enrolled	Explicit inclusion/ exclusion criteria	Outcomes assessed in all participants	Uniform follow-up (months)	Indication/disease uniform across participants n/N (%)
Tjandra 2004[a] AUSTRALIA	Prospective	NR	Yes	No	No Median: 6 Range: 1-12	Guided by ultrasound
						Previous sphincter repair 11/42 (26.0) Prior anorectal surgery: Haemorrhoidectomy 9/42 (21.0) Sphincterotomy 3/42 (7.0) Fistulotomy 1/42 (1.0) Prior restorative rectal resection 2/42 (5.0) Internal sphincter: Localised defect 6/42 (14.0) Intact 36/42 (86.0) Pudendal neuropathy[b] 26/42 (62.0)
						Guided by palpation
						Previous sphincter repair 10/40 (25.0) Prior anorectal surgery: Haemorrhoidectomy 10/40 (25.0) Sphincterotomy 3/40 (8.0) Fistulotomy 1/40 (3.0) Prior restorative rectal resection 3/40 (8.0) Internal sphincter: Localised defect 5/40 (13.0) Intact 35/40 (87.0) Pudendal neuropathy[b] 22/40 (55.0)

Table C1 (continued) Validity characteristics of studies included in the review

Study	Design	Participants consecutively enrolled	Explicit inclusion/ exclusion criteria	Outcomes assessed in all participants	Uniform follow-up (months)	Indication/disease uniform across participants n/N (%)
Chan 2006[a] AUSTRALIA	Prospective	NR	No	Yes	No Median: 14 Range: 12-20	Aetiology of faecal incontinence: Conventional haemorrhoidectomy 5/7 (71.0) Stapled haemorrhoidectomy 2/7 (29.0) Internal sphincter defect 7/7 (100.0)
Kenefick 2002 UK	NR	NR	Yes	Yes	No Median: 18 Range: 15-19	Aetiology of faecal incontinence: Post-haemorrhoidectomy 2/6 (33.0) Idiopathic IAS degeneration 2/6 (33.0) Lateral sphincterotomy 2/6 (33.0) Endoanal ultrasound results: Fragmented IAS 2/6 (33.0) Thin atrophic IAS 2/6 (33.0) Discrete IAS 2/6 (33.0)
Malouf 2001 UK	NR	NR	Yes	Yes	Yes Mean: 6	Aetiology of faecal incontinence: Post-haemorrhoidectomy 2/10 (20.0) Idiopathic IAS degeneration 5/10 (50.0) Lateral sphincterotomy 2/10 (20.0) Post-overlap repair 1/10 (10.0) IAS dysfunction 1/10 (10.0) Endoanal ultrasound results: IAS thin but intact 4/10 (40.0) IAS thin and fragmented 1/10 (10.0) IAS defect 4/10 (40.0) Normal IAS 1/10 (10.0)

NOTE: a = there may be patient overlap between these two studies; b = defined as a pudendal nerve terminal motor latency >2.6 ms; NR = not reported; IAS = internal anal sphincter

Appendix D Quality of life outcomes in included studies

Table D1 Quality of life assessed using a visual analog global quality of life scale

Study	L of E	Design	Visual analog global quality of life scores			
			Baseline	Post-injection	n	p-value
Tjandra 2004[a] AUSTRALIA	IV	case series	Guided by ultrasound			
			Median:4 Range: 1-8 n=42	Median (range) at: 5 weeks: 7 (4-9) 3 months: 9 (6-10) 6 months: 9 (6-10) 9 months: 9.5 (8-10) 12 months: 10 (9-10)	 42 38 30 22 10	 <0.001[c] <0.001[c] <0.001[c] <0.001[c] <0.001[c]
			Patients with neuropathy[b]: Mean [SD]: 3.5 [0.34] n=26	 Mean [SD] at: 1 month: 6.0 [0.47] 6 months: 7.4 [0.47]	 26 NR	 NS[cd] NS[cd]
			Patients without neuropathy: Mean [SD]: 4.0 [0.48] n=16	 Mean [SD] at: 1 month: 6.7 [0.45] 6 months: 8.9 [0.51]	 16 NR	 NS[cd] NS[cd]
			Guided by palpation			
			Median:4 Range: 1-7 n=40	Median (range) at: 5 weeks: 8 (1-9) 3 months: 9 (2-10) 6 months: 9 (1-10) 9 months: 8 (2-10) 12 months: 4 (2-10)	 40 32 21 11 5	 <0.001[c] <0.001[c] <0.001[c] <0.001[c] NS[ce]
			Patients with neuropathy[b]: Mean [SD]: 4.2 [0.38] n=22	 Mean [SD] at: 1 month: 7.0 [0.21] 6 months: 8.7 [0.13]	 22 NR	 NS[cd] NS[cd]
			Patients without neuropathy: Mean [SD]: 4.8 [0.34] n=18	 Mean [SD] at: 1 month: 7.6 [0.31] 6 months: 8.6 [0.33]	 18 NR	 NS[cd] NS[cd]
Chan 2006[a] AUSTRALIA	IV	case series	Median: 4 Range: 2-6 n=7	Median (range) at: 3 months: 9 (8-10)	 7	 0.016[f]

NOTE: L of E = level of evidence; visual analog scale = 1-10, 10 being best; NR = not reported; a - there may be patient overlap between these two studies; b - defined as pudendal nerve terminal motor latency >2.6 ms; c - authors' statistical analysis using a paired t-test; d - no significant difference at p>0.05; e - no significant difference at p>0.01; f - authors' statistical analysis using the Wilcoxon signed-rank test.

Table D2 Quality of life assessed using the Faecal Incontinence Quality of Life (FIQL) index

Study	L of E	Design	Faecal Incontinence Quality of Life scores				
			FIQL domain	Baseline	Post-injection	n	p-value
Tjandra 2004[a] AUSTRALIA	IV	case series	Guided by ultrasound				
			Lifestyle	Mean [SD]: 2.9 [0.94] n=42	Mean [SD] at: 5 weeks: 3.3 [0.83] 6 months: 3.7 [0.44]	42 42	<0.001[b] <0.001[b]
			Coping/behavior	Mean [SD]: 2.2 [0.92] n=42	Mean [SD] at: 5 weeks: 2.7 [0.86] 6 months: 3.2 [0.66]	42 42	<0.001[b] <0.001[b]
			Depression/self-perception	Mean [SD]: 3.1 [0.76] n=42	Mean [SD] at: 5 weeks: 3.4 [0.80] 6 months: 3.9 [0.52]	42 42	0.003[b] <0.001[b]
			Embarrassment	Mean [SD]: 2.2 [0.96] n=42	Mean [SD] at: 5 weeks: 2.8 [0.89] 6 months: 3.4 [0.53]	42 42	<0.001[b] <0.001[b]
			Guided by palpation				
			Lifestyle	Mean [SD]: 2.9 [0.88] n=40	Mean [SD] at: 5 weeks: 3.1 [0.86] 6 months: 3.1 [0.83]	40 31	NS[bc] 0.01[b]
			Coping/behavior	Mean [SD]: 2.4 [0.94] n=40	Mean [SD] at: 5 weeks: 2.7 [0.87] 6 months: 2.7 [0.94]	40 31	0.02[b] 0.009[b]
			Depression/self-perception	Mean [SD]: 2.9 [0.79] n=40	Mean [SD] at: 5 weeks: 3.0 [0.77] 6 months: 3.1 [0.82]	40 31	NS[bc] 0.01[b]
			Embarrassment	Mean [SD]: 2.2 [0.88] n=40	Mean [SD] at: 5 weeks: 2.6 [0.90] 6 months: 2.7 [0.91]	40 31	<0.002[b] <0.001[b]
Chan 2006[a] AUSTRALIA	IV	case series	Lifestyle	Mean [SD]: 2.2 [0.78] n=7	Mean [SD] at: 12 months: 3.1 [0.37]	7	0.016[d]
			Coping/behavior	Mean [SD]: 2.2 [0.85] n=7	Mean [SD] at: 12 months: 3.5 [0.53]	7	0.016[d]
			Depression/self-perception	Mean [SD]: 2.4 [0.39] n=7	Mean [SD] at: 12 months: 3.1 [0.40]	7	0.016[d]
			Embarrassment	Mean [SD]: 2.3 [0.70] n=7	Mean [SD] at: 12 months: 3.0 [0.41]	7	NS[de]

NOTE: L of E = level of evidence; FIQL domains: 1-4, 4 being best; a - there may be patient overlap between these two studies; b - authors' statistical analysis using a paired t-test; c - no significant difference at p>0.025; d - authors' statistical analysis using the Wilcoxon signed-rank test; e - no significant difference at p>0.05.

Table D3 Quality of life assessed using the Short Form-36 (SF-36) questionnaire

Study	L of E	Design	SF-36 quality of life scores			
			Baseline	Post-injection	n	p-value
Kenefick 2002 UK	IV	case series	Physical function			
			Median: 26 Range: 5-33 n=6	Median (range) at: 18 months: 79 (25-100)	6	0.02[a]
			Social function			
			Median: 10 Range: 5-37 n=6	Median (range) at: 18 months: 100 (50-100)	6	0.02[a]

NOTE: L of E = level of evidence; SF-36 categories: 1-100, 1 = worst score, 100 = best score; a - authors' statistical analysis using a Wilcoxon paired samples test.

Table D4 Quality of life assessed using the Short Form-12 (SF-12) questionnaire

Study	L of E	Design	SF-12 quality of life scores				
			SF-12 category	Baseline	Post-injection	n	p-value
Tjandra 2004 AUSTRALIA	IV	case series	Guided by ultrasound				
			Physical health	Mean [SD]: 47.1 [1.61] n=42	Mean [SD] at: 5 weeks: 47.8 [10.2] 6 months: 50.6 [8.3]	 42 42	 NS[ab] 0.003
			Mental health	Mean [SD]: 47.5 [1.44] n=42	Mean [SD] at: 5 weeks: 50.1 [9.6] 6 months: 52.3 [7.4]	 42 42	 NS[ab] 0.004[a]
			Guided by palpation				
			Physical health	Mean [SD]: 43.7 [1.62] n=40	Mean [SD] at: 5 weeks: 43.6 [9.9] 6 months: 43.7 [9.9]	 40 31	 NS[ab] NS[ab]
			Mental health	Mean [SD]: 44.3 [1.71] n=40	Mean [SD] at: 5 weeks: 44.6 [10.9] 6 months: 45.2 [9.7]	 40 31	 NS[ab] NS[ab]

NOTE: L of E = level of evidence; SF-12 categories: 1-100, 1 = worst score, 100 = best score; a - authors' statistical analysis using a paired t-test; b - no significant difference at p>0.025.

Appendix E Conference presentations

The descriptive characteristics of abstracts identified from handsearching of conference proceedings are shown in Table E1. There were seven abstracts which reported safety and effectiveness outcomes for ISISB in patients with passive faecal incontinence, and the results from these abstracts generally reflected the findings of the published studies. Much of the data reported in abstracts may also have be reported in full publications, or in more than one abstract; however, insufficient detail was provided to determine exactly where this may have occurred.

Table E1 Descriptive characteristics of abstracts identified from conference proceedings

Study	L of E	Design	Maximum length of follow-up (months)	Study population		
				n	№. Male (%)	Age (years)
Tjandra 2006[a] AUSTRALIA	IV	case series	36	Guided by ultrasound		Median: 51
				114	NR	
				Guided by palpation		
				111	NR	
Tjandra 2005[a] AUSTRALIA	IV	case series	12	Guided by ultrasound		Median: 54
				83	NR	
				Guided by palpation		
				80	NR	
Tjandra 2004[a] AUSTRALIA	IV	case series	15	74[b]	12 (16.0)	Median: 51
Tan 2006[a] AUSTRALIA	IV	case series	12	16	4 (25.0)	NR
Higgs 2005[a] AUSTRALIA	IV	case series	12	36	0 (0.0)	Median: 57
Lindsey 2004 UK	IV	case series	NR	10	NR	NR
Jorge 2004 BRAZIL	IV	case series	6 weeks	12	2 (17.0)	Median: 54

NOTE: L of E = level of evidence; a - there may be patient overlap between these two studies; NR = not reported; b - number of patients in each treatment group (ultrasound versus palpation guided) were not reported separately.

Complications

No procedure-related complications were reported in four conference abstracts (Tjandra 2005, Higgs 2005, Tjandra 2004 and Lindsey 2004). Tjandra (2006) reported that 1/111 of the participants in the palpation guided group developed an intersphincteric abscess which settled with antibiotics, while Jorge (2004) reported that 1/12 participants experienced significant pain during the procedure, which required parenteral analgesia.

Faecal incontinence scores

Wexner continence scores pre- and post-injection were reported in seven conference abstracts (Tjandra 2006, Tan 2006, Tjandra 2005, Higgs 2005, Tjandra 2004, Lindsey 2004 and Jorge 2004), with significant improvements reported in all studies. Significantly more ultrasound guided participants demonstrated a greater than 50 per cent improvement in Wexner continence scores at follow-up, when compared to those who received the injection guided by palpation (Tjandra 2006 and Tjandra 2005). Tan (2006) reported that the improvement in continence status was much greater and more sustained after the initial injection when compared to re-injection six months later. Following continued improvements in Wexner continence scores at 12 and 24 months post-procedure, one abstract reported a notable deterioration in function at 36 months follow-up (Tjandra 2006). Three abstracts reported that the presence of pudendal neuropathy had no effect on functional outcome (Tjandra 2006, Tjandra 2005 and Higgs 2005).

Quality of life

Six conference abstracts reported data on quality of life outcomes using three different quality of life instruments (Tjandra 2006, Tan 2006, Tjandra 2005, Higgs 2005, Tjandra 2004 and Jorge 2004). A significant improvement in all four domains of the FIQL index between baseline and follow-up was reported in five abstracts (Tjandra 2006, Tan 2006, Tjandra 2005, Higgs 2005 and Jorge 2004), while one abstract reported a significant improvement in the domains of lifestyle and embarrassment only (Tjandra 2004). Tan (2006) reported that the improvement in FIQL indices was much greater and more sustained after the initial injection when compared to re-injection six months later.

Three abstracts reported a significant improvement in VAS global quality of life scores post-procedure (Tjandra 2006, Tjandra 2005 and Higgs 2005).

A significant improvement in SF-12 physical and social function scores was reported in two abstracts (Tjandra 2005 and Tjandra 2004) and was greater in ultrasound guided compared to palpation guided participants (Tjandra 2005).

Resting and squeeze anal manometry

Maximum resting anal pressures pre- and post-injection were reported in six conference abstracts (Tjandra 2006, Tjandra 2005, Higgs 2005, Tjandra 2004, Lindsey 2004 and Jorge 2004), with significant improvements between baseline and follow-up observed in five of these studies (Tjandra 2006, Tjandra 2005, Higgs 2005, Tjandra 2004, Lindsey 2004). Three of these abstracts reported that while resting anal pressures were improved in both ultrasound and palpation guided participants, significantly better results were achieved if the injection was performed under the guidance of endoanal ultrasound (Tjandra 2006, Tjandra 2005 and Tjandra 2004).

Maximum squeeze anal pressures were reported in two conference abstracts (Tjandra 2004 and Jorge 2004), with no significant improvements observed in either study.

Endoanal ultrasound results

Two conference abstracts reported the results of endoanal ultrasound scans performed post-injection (Tjandra 2004 and Lindsey 2004), with retention of the silicone biomaterial at the sites of injection demonstrated in both studies at follow-up.

Appendix F Excluded studies and reasons for exclusion

Inappropriate interventions

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Interventions for diseases other than faecal incontinence

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Abbreviations

AHMAC	Australian Health Ministers Advisory Council
AR-DRG	Australian Refined Diagnosis Related Group
ARTG	Australian Register of Therapeutic Goods
EAS	External anal sphincter
FIQL	Faecal Incontinence Quality of Life
IAS	Internal anal sphincter
ISISB	Intersphincteric injection of silicone biomaterial
MBS	Medicare Benefit Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PDMS	Polydimethylsiloxane
PNTML	Pudendal nerve terminal motor latency
PVP	Polyvinylpyrolidone
RCT	Randomised controlled trial
SF-12	Short Form-12
SF-36	Short Form-36
TGA	Therapeutic Goods Administration
VAS	Visual Analog Scale

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