External Assessment Centre report

Title: Peristeen anal irrigation system to manage bowel dysfunction

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
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The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
ACE	Antegrade continence enema
ARM	Anorectal malformation
ARS	Anterior Resection Syndrome
ASCRS	American Society of Colon and Rectal Surgeons fecal incontinence score
CBC	Conservative bowel care
CCCSS	Cleveland Clinic constipation scoring system
CCIS	Cleveland Clinic incontinence score
CHQ-pf50	Child health questionnaire parent form
CI	Confidence interval
DH	Department of Health
EAC	External Assessment Centre
EQ5D3L	EuroQoL-5D, Quality of life score with 5 dimensions
FI	Faecal incontinence
FIGS	St Mark's fecal incontinence grading system
FIQOL	Fecal incontinence quality of life (Rockwood et al.,2000)
ICER	Incremental cost effectiveness ratio
IQR	Interquartile range
ITT	Intention to treat
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MS	Multiple sclerosis
MTEP	Medical Technologies Evaluation Programme
NBD	Neurogenic bowel dysfunction
NBDS	Neurogenic bowel dysfunction score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NS	Not statistically significant
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSLAS	Patient symptom linear analogue scale
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SARS	Sacral anterior root stimulator
SBC	Standard bowel care

SD	Standard deviation
SF-36	Short form health survey-36
SNS	Sacral nerve stimulation
TAI	Trans anal irrigation
UTI	Urinary tract infection
VAS	Visual Analogue Scale
vs	Versus
WTP	Willingness to pay

1 Executive Summary

The company submission contained evidence from one RCT, seven observational studies of adult patients and one observational study of children. The EAC included a further four observational studies for adults, and 11 observational studies for children.

The RCT was a reasonable quality study of 87 adult patients with spinal cord injuries. The study reported significant improvements in validated patient reported outcomes for bowel function. Where the observational studies of adults had comparative data (before and after) there was an improvement in in patient reported outcomes for bowel function when using Peristeen. Outcome measures such as incidence of urinary tract infections and faecal incontinence also improved. Outcomes related to general quality of life measures were less widely reported and changes were either not significant, or were significantly improved in only some domains. There were considerable numbers of patients who stopped using Peristeen, particularly in the first few months.

Evidence for the use of Peristeen in children was based entirely on observational studies, with variable quality and less consistent outcome measures. General findings indicated that use of Peristeen resulted in improvements in bowel management.

For both adults and children there were variable numbers of patients who stopped using Peristeen, particularly in the first few months. This was frequently because they disliked using the device, found it painful or ineffective.

The submitted economic model was based on a previously published economic model, and finds that Peristeen is both cost saving and cost effective in the base case and sensitivity analysis. Cost savings arise from reductions in health care staff time, reduced incidence in faecal incontinence, urinary tract infections and hospitalisations. The model relies almost completely on unpublished audit data and does not make reference to the evidence submitted in the clinical submission.

The EAC found serious errors in the submitted model, correction of these reduced the cost saving considerably. The EAC ran additional sensitivity analysis to investigate frequency of use of Peristeen, incidence of faecal incontinence and the cost and incidence of pressure ulcers.

The clinical and economic evidence indicates that some patients find that Peristeen improves their bowel management. It is likely to be very slightly cost saving over a life-time horizon, but there are considerable uncertainties.

2 Background

2.1 Overview and critique of company's description of clinical context

The company presented a thorough description of bowel dysfunction, including the functional forms such as constipation, faecal incontinence and obstructed defecation. It also described neurogenic bowel dysfunction, where nerve innervation to the bowel is damaged, which can be caused by neurological conditions such as spinal cord injury, spina bifida, multiple sclerosis, Parkinson's disease and others associated with impaired or loss of sphincter control and bowel mobility disorders. The background information provided cites NHS Choices and the NICE clinical guideline CG49, Faecal Incontinence in Adults: Management (2007).

The company's submission is partially appropriate and relevant to the decision problem under consideration. The EAC considers the company's decision to exclude most paediatric studies to be inappropriate, as they are included in the scope, and make up over half of the relevant studies found. The EAC has included all relevant paediatric studies.

The device is intended for use by the patient or by a carer. The company's main claimed innovation is that Peristeen has a balloon catheter which holds it in place, allowing it to be used hands-free. This is beneficial for patients with limited hand dexterity. The company claims that unlike other water-based enemas, the Peristeen constant-flow pump is not gravity-based, meaning the user does not need to hang the bag up for the irrigant to flow.

The company present the number of admissions for patients with constipation, and estimate the cost. A weighted mean across all finished episodes for any cause was used which may not reflect the actual costs of admissions for constipation. Not all of these patients would be suitable for Peristeen.

Figures are also presented by the company for the number of patients with faecal incontinence, however not all of these will require, or be suitable for treatment with Peristeen. Passananti et al (2016) found that 22% of patients with MS and bowel dysfunction were suitable for Peristeen, but this may not be generalisable to other patient groups and settings.

The benefits to patients claimed by the company include improvement in the symptoms and frequency of constipation and faecal incontinence, an improvement in quality of life for users and a reduction in urinary tract infections.

Benefits to the healthcare system claimed by the company include reducing the rate of stoma surgery, hospitalisation and urinary tract infections in patients with neurogenic bowel dysfunction.

2.2 Critique of company's definition of the decision problem, Table 1

Decision problem	company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	People with bowel dysfunction in any setting.	Partially	The company has excluded paediatric studies aside from Midrio et al 2016. This is not an appropriate approach, and we have included all paediatric studies that were within the scope.
Intervention	Peristeen anal irrigation system.	Y	
Comparator(s)	Conservative bowel management, which can include: • diet and bowel habit advice • medication (oral drugs, suppositories and enemas) • disposable pads and anal plugs • muscle training/bowel retraining • biofeedback and electrostimulation • digital stimulation and manual evacuation It should be noted that the type of treatment a person receives is highly dependent on their personal preference, ability and the carer support available to them (see also 'Cost analysis' below).	Y	Only one included study was comparative (Christensen et al., 2006), employing conservative bowel management, which was defined as "best supportive bowel care without using irrigation. The Paralyzed Veterans of America clinical practical guidelines for bowel management were recommended". All other included studies are non-comparative.

Outcomes	The outcome measures to consider include: • severity and frequency of incontinence and severity of constipation using appropriate scores (such as Cleveland clinic incontinence and constipation scores [also known as Wexner incontinence and constipation scores], St Mark's faecal incontinence score and neurogenic bowel dysfunction (NBD) score) • quality of life • length and frequency of irrigation • device-related adverse events • frequency of urinary tract infection (UTI) • incidence of stoma surgery and hospitalisations • staff time including primary care and community care visits • individual length of use/user satisfaction	Y	Studies have used a wide variety of outcome scoring measures, with different degrees of validation. The measures used are described in table 5 and Appendix C together with information on their appropriate use. The company have not reported physiological outcomes, and the EAC agree that these are not in the scope, and would be surrogate markers in most cases.
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters,	Y	

	which will include carer costs, patient/carer training costs and costs of treating UTI.		
Subgroups	• neurological bowel dysfunction complications for example Parkinson's disease, stroke, multiple sclerosis, spina bifida and spinal cord injury • bowel dysfunction caused by injury e.g. following childbirth • slow transit constipation (unrelated to childbirth) • obstructed defaecation symptoms • metastatic spinal cord compression • low anterior resection syndrome in people who have had treatment for rectal cancer	Y	All of these indications are covered by the included studies aside from: • bowel dysfunction caused by injury e.g. following childbirth • metastatic spinal cord compression Spina bifida is covered in adult studies with mixed populations, and in paediatric studies.

Special considerations, including issues related to equality

Faecal incontinence and constipation can both be related to disability and can also both be socially stigmatising. The company does not highlight any specific equality-related considerations in their submission. However, the EAC believe that the equality issues in the scope have been addressed in the company's submission.

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The company did not specify if Medline In Process had been searched and it was unclear if all the Cochrane Library databases had been searched. The search strategy used was not comprehensive and as a result, relevant studies may not have been captured. A language limit was applied to the search results. The EAC developed a comprehensive search strategy, incorporating free text terms and subject headings as directed by the MTEP sponsor submission template, which was run across the specified databases as well as some others. The company did not search a wide range of 'grey literature' sources or use supplementary search methods to identify further literature. The company tried to identify unpublished studies but did not search any trials registers. Details of the company's and the EAC searches are described in Appendix A.

3.2 Critique of the company's study selection

The included studies are all relevant to the use of Peristeen in the adult population, and cover a range of conditions for which the device is appropriate. However, the exclusion of all but one paediatric studies is not in accordance with the scope for this assessment. The company included a sole paediatric paper (Midrio et al., 2016) as an "example of best care in the paediatric population", which is not appropriate for an assessment of this type, as it is highly likely to introduce bias into the dataset. The EAC do not agree that all those excluded did not use validated outcome scoring systems. The EAC have included all paediatric studies with relevant outcomes. This gives a more complete compliance with the scope.

3.3 Included and excluded studies

For the adult population, Chan et al. (2011) was not identified in the company search which is relevant to the scope. The device used in the study was not specified. The EAC contacted one of the authors who confirmed that the device was Peristeen. Nafees et al. (2016) is a discrete choice experiment

study that does not directly compare with the other available literature. It is likely to contain high amounts of bias as the patients are a self selecting group of long term Peristeen users. The EAC included this study in the table to provide some useful long term information, but advise that it should be interpreted with caution.

After submission the company clarified that Kim et al (2013) had been identified, but excluded. The company did not identify Whitehouse et al. (2010)

Grainger et al. (2017) was identified by the company as a pre-publication manuscript and is academic in confidence.

For the paediatric population the EAC used broader inclusion criteria, and therefore all those identified as excluded by the company were included by the EAC with the exception of Choi et al. (2015) which used a mix of devices and a locally designed questionnaire, and Marte et al. (2013) which reported surrogate radiological outcomes only. Marzheuser et al. (2016) was not identified by the company.

A summary of papers included by the company and the EAC is presented in tables 2 and 3.

Although the EAC identified additional relevant papers, these do not change the overall direction of the evidence. The RCT is summarised in table 4, all other included studies are summarised in appendix B.

Table 2: Adult studies included by company and EAC

KEY: ✓ included, × explicitly excluded, MS Multiple Sclerosis, SB Spina Bifida, SCI spinal cord injury, NBD neurogenic bowel disfunction, IC idiopathic constipation, ARS anterior resection syndrome, mixed, RCT randomised controlled trial, OBS observational, single arm study DC discrete choice experiment, QUAL qualatitive interviews✓ included, × explicitly excluded

Paper	Country	Study type	popu-lation	n	company	EAC
ADULTS						
Chan 2011	UK	OBS	mixed	91	-	✓
Christensen 2008	Europe incl UK	OBS[#]	SCI	62	✓	✓
Christensen 2006	Europe incl UK	RCT	SCI	87	✓	✓
Del Popolo 2008	Italy	OBS	SCI	36	✓	✓
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	✓	✓
Hamonet-Torny 2013	France	OBS	NBD	16	✓	✓
Kim 2013	S. Korea	OBS	SCI	52	-	✓
Loftus2012	Ireland	OBS	NBD	11	✓	✓
Nafees 2016	UK	DC	mixed	129		✓
Passananti 2016	UK	OBS	MS	49	✓	✓
Preziosi 2012	UK	OBS	MS	30	✓	✓
Rosen 2011	Austria Switzerland	OBS	ARS	14	✓	✓
Whitehouse 2010	UK	OBS	FBD	113	-	✓
CHILDREN						
Alenezi 2014	S.Arabia	OBS	NBD	18	×	✓
Ausili 2010	Italy	OBS	SB	60	×	✓
Choi 2015	S. Korea	OBS	SB	44	×	×
Corbett 2013	UK	OBS	mixed	24	×	✓
Kelly 2016	USA	OBS	NBD	24	×	✓
King 2016	Australia	OBS	SB	20	×	✓
Koppen 2017	Netherlands	OBS	IC	67	×	✓
Lopez Pereira 2010	Spain	OBS	SB	40	×	✓
Marzheuser 2016	Germany	OBS	ARM	40	-	✓
Midrio P. 2016	Italy	OBS	mixed	83	✓	✓
Nasher 2014	UK	OBS	IC	13	×	✓
Pacilli 2013	UK	OBS	mixed	23	×	✓
[#]RCT and OBS paper by Christensen use same patients						

Table 3 Adverse event evidence included by EAC or company

Paper	Country	Study type	popu-lation	n	company	EAC
Adverse events only						
Biering Sorensen 2009	Denmark				✓	✓
Christensen 2009					✓	✓
Christensen 2016					✓	✓
Faaborg 2009					✓	✓
Faaborg 2014					✓	×
Economic						
Christensen 2009					✓	✓
Emmanuel 2016					✓	✓

In the summary of studies, for each of the design, participants and outcomes entries below, the following coding is used:

G	Fully included within the scope
A	Partially included within the scope
R	Not consistent with the scope

As the scope for this topic is very broad, no single paper is likely to fully encompass the scope, however those coded green have participants, and outcomes that are included within the scope.

Table 4. Summary of RCT, additional studies are summarised in Appendix B.						
Included studies	**Design and intervention(s)**	**Participants and setting**	**Outcomes**	**Results**	**Withdrawals**	**EAC Comments**
Christensen (2006)	RCT comparing transanal irrigation using Peristeen with standard bowel care (SBC) for 10 weeks Company funded Intervention G Comparator G	87 randomised (42 Peristeen vs 45 SBC) 62 men, 25 women average age 49.1years. 73 completed 5 European spinal cord injury centres (Sweden, Italy, Germany, UK, Denmark) All patients 18 years or older, at least 3 months after spinal cord injury. G	**Primary outcomes:** CCCS and FIGS **Secondary outcomes:** NBDS, modified ASCRS, numeric box score on: bowel function, influence on daily activities and general satisfaction. Outcomes collected at week 0 and 10, plus weekly telephone interview. G	CCCS, FIGS and NBDS were significantly improved for Peristeen vs SBC. Sub-group analysis found no significant difference for patients who could walk, but significant improvement for those who used wheelchairs or were confined to bed found that these ASCRS scores were significantly improved for Peristeen vs SBC in domains of coping/behaviour but no significant difference for the lifestyle and depression/self-perception domains. The numeric box scores were significantly improved for bowel function, general satisfaction and improvement in quality of life, but not for influence on daily activities.	14 w/d (12 Peristeen, 2 SBC): 73 completed, 5 lost to follow-up	Blinding was not possible. Large number of patients stopped using Peristeen before the end of the study. These were included in ITT analysis using baseline data in place of missing data. Baseline imbalance between groups for number using wheelchair or confined to bed. Sub-group analysis not stated as planned. Study supported by company
CCCS Cleveland Clinic Constipation Score; FIGS St Mark's Faecal Incontinence Grading Score; NBDS Neurogenic Bowel Dysfunction Score						

3.4 Overview of methodologies of all included studies

All but one of the studies included are observational case studies. All of the studies were reported as full papers rather than as abstracts only.

The main outcomes are patient reported outcomes. The nature of the device is that it is used at home by patients, in many cases without any assistance. It is therefore appropriate that the patient reports outcomes that occur at home. Some of these outcomes are objective, such as the incidence of faecal incontinence, some are more subjective, asking how the patient feels about issues. Very few outcomes can be directly measured, and few are recorded at the point they occur, and so will be prone to bias.

No studies are blinded, as this would be impractical for a device of this sort, and since outcomes are largely patient reported, there is no possibility of blinded assessment. While this may be unavoidable, it is likely to introduce bias

Patient reported outcome measures (PROMS)

PROMs are questionnaires for self completion by patients to record their health, symptoms, functioning etc. Generic instruments are used across a variety of patient populations whereas disease or treatment-specific measures are used for a particular population. As part of their development, PROMs are subject to psychometric testing to show whether they are valid, reliable and sensitive to change. Validity is about whether the PROM measures symptoms or other concepts that are relevant to patients. Reliability shows whether the PROM is consistent over time.

PROMs are validated in a specific population. The same PROM may not be valid when used in a different population or setting, for example, if a PROM designed for adults is used for children, the language and context may be inappropriate. Generic PROMs may be insensitive to small changes in the patient's condition which are better measured using a condition-specific PROM, often in combination with the generic PROM.

Locally developed questionnaires which have not been subject to psychometric testing are unlikely to be valid, reliable or sensitive to change.

In addition to papers validating each individual score system, there are also studies comparing several different outcome measures (Hussain 2012)

The most commonly used PROMs in the literature concerning Peristeen in adults are listed in Table 4. A more complete listing including the PROMS used in studies on children is in Appendix C

Table 5 PROMS measures with description and validation information.

CCCS Cleveland Clinic constipation scoring system. Also known as Wexner constipation score.	A scale of constipation severity including impact of symptoms on the patient's life. Scores range from 0 to 30, with higher scores representing more severe symptoms. Widely used, validation compared to physiological measures identified.(Agachan et al.,1996).
CCIS Cleveland Clinic Incontinence Score. Also known as Wexner incontinence score	The CCI Score takes into account the frequency of incontinence and the extent to which it alters a person's life. . Scores range from 0 to 20, with higher scores representing more severe symptoms. Widely used, but no formal validation identified. (Jorge et al., 1993)
FIGS or SMFIGS St Mark's fecal incontinence grading system	A scale of incontinence severity including the impact of symptoms on the patient's life. Scores range from 0-24 with 24 most severe. Widely used and validated for use in adults, specific diagnoses not specified (Vaizey et al., 1999).
NBDS Neurogenic bowel dysfunction score	Ten questions on bowel dysfunction symptoms. Questions do not ask about the impact of symptoms on the patient. Scores range from 0 – 47, with 47 most severe. Widely used, validated for use in patients 15+ years with SCI. (Krogh et al., 2006). It has also been used in other patient groups. Translated into several languages. Available on Coloplast website.
ASCRS American Society of Colon and Rectal Surgeons fecal incontinence score	Symptom related QoL score, with 4 subscales for lifestyle, coping behaviour, depression, embarrassment. Each on a scale of 0-4 with 4 most severe. No information on validation identified.
SF-36 Short Form Health Survey-36	Generic quality of life score. Self administered or by interview. For use in adults 18+ Scores 0-100, with 100 as best health. Very widely used, and validated (McHorney et al,. 1994)
EQ5D3L EuroQoL-5D	Generic quality of life score. With 243 health states descriptive with 5 dimensions, each with 3 levels– mobility, self-care, usual activity, pain/discomfort, anxiety/depression. Scores are used with a validation set for the appropriate country to give a final value of 0-1 with 1 the best possible quality of life. Patient reported outcome, self administered or by interview. For use in ages 12+ Generic across clinical areas, very widely used and validated. (The EuroQol Group 1990)
EQ5D-VAS EuroQoL-5D Visual Anologue Scale	Scores 0-100 where 100 is perfect health. Part of the EQ5D questionnaire.

Adult studies

There was only one randomised controlled trial (Christensen et al., 2006). This study employed supportive bowel care as the comparator, which was defined as “best supportive bowel care without using irrigation”. The study included 87 patients with spinal cord injury and neurogenic bowel dysfunction from 5 European spinal cord injury centres, including the UK. The primary outcomes measures were the CCCS and FIGS questionnaires. Outcomes were collected from patients each week by a researcher who is described as not having participated in patient training, but does not appear to be blinded as to the intervention. Baseline outcome measures and demographics were described for both arms, and it is stated that there was no systematic difference in outcomes between the two groups. There appeared to be a difference in the mobility of participants (wheelchair use = 29/42 intervention; 40/45 control) and this is discussed in reporting the outcomes, and also in the subsequent study (Christensen et al., 2008). Post-hoc sub-group analysis found no significant difference between Peristeen and standard care for patients who could walk, but a significant improvement in the Peristeen group for those who used a wheelchair or were confined to bed.

12 patients in the Peristeen arm and 2 standard care patients withdrew from the study. Patients who stopped using Peristeen or withdrew before the end of the 10 week study were included in intention to treat analysis using a termination form for outcome measures, or baseline data in place of missing values. There was a significant improvement in CCCS, FIGS and NBDS for the Peristeen group compared with standard care. The study is limited by the 10 week follow-up period, so that it does not record longer term outcomes of interest in this assessment. The large number of withdrawals from the study is a weakness, but is consistent with the observational studies where patients withdraw at an early stage if they do not like the device or find it unhelpful. Blinding is not possible, but lack of blinding is a source of potential bias. Strengths of the study include the RCT design, the inclusion of a UK centre and the intention to treat analysis. Sample size calculations were reported, and sufficient sample size reached in the study. The study is described as having been supported by the company.

All the other included studies are observational case series and do not have a comparator. One paper was unpublished, but was being prepared for publication. Nine of these case series are prospective and three are retrospective in design.

Most studies are small, single centre studies. Outcomes are often subjective and may require the patient to recall answers, in some cases up to one year. If patients are expected to report on how they felt in the past, there is a risk of recall bias. PROM tools often specify the recall time period for the questions,

so if these are used retrospectively it may not be valid. The patient populations vary in the observational studies; some are of a single condition such as multiple sclerosis, whereas other studies include patients with a variety of conditions. The observational studies report on inconsistent outcome measures, including some locally devised questionnaires without validation. Some studies conducted follow-up questionnaires by telephone, which may introduce bias, and the telephone interview approach may not be validated for the PROM used.

Studies commonly used sub-groups that appear not to have been pre-specified in the protocol. Several studies grouped results by those who have continued to use Peristeen, compared to those who have ceased or alternatively compare “responders” to “non-responders” (Hammonet-Torny, 2013). This is likely to lead to bias in the results.

Taken overall the evidence appears to show that adult patients who like and continue to use the technology report an improvement in their outcomes. The strength of the evidence is weak, and at risk of bias.

Paediatric studies

The paediatric studies were non-comparative, observational case series. All of the studies were reported as full papers rather than as abstracts only. Six of these observational studies are prospective and five are retrospective in design. One consisted of qualitative interviews with parents and carers.

The outcomes for the studies were of two main types, physiological measurements, and patient reported outcomes. The company have not reported physiological measurements in their submission, and the EAC agree with this approach, given that this would be a surrogate outcome for the effectiveness of the device and these outcomes are not included in the scope. However patient reported outcomes are more difficult to obtain from children, as the PROM tools may not be adapted or validated for children of different ages. For example the NBDS tool is validated for people aged 15 years and over, but in Ausilli et al. (2010) it has been used for a group of patients aged 8-17 years. It is not always clear in the paediatric studies when parents have completed questionnaires and when these have been completed by children. Some studies reported patient and/or parent satisfaction.

The evidence from the paediatric studies is weaker than the evidence for adults. This is partly due to the difficulty in obtaining valid PROM data from children. The patient populations studied include congenital conditions, such as spina bifida, whereas adult patients mainly have acquired conditions. The paediatric studies are small, and they report variable numbers who stop using Peristeen. The great variety of outcomes reported across the studies, together

with the differences in populations and patient ages, makes it difficult to combine the results. Some, but not all outcomes in the studies showed improvements for children using Peristeen. The quality of the evidence is very poor.

3.5 Overview and critique of the company's critical appraisal

The company submitted critical appraisal checklists for all studies that they included, using appropriate forms. The company highlighted the differences in patient populations between the studies, and the use of a variety of validated PROM tools.

The key study (Christensen et al.,2006), is appropriately randomised, but cannot be blinded due to the nature of the device. The company noted that data was gathered from patients who withdrew from the study and the reasons for withdrawal were discussed. In the critical appraisal checklist the company responded 'yes' to the question 'Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?', but the authors of the paper stated that the mobility status of the patients at recruitment was different for the two arms. It is clear that the *outcomes* at baseline for the two groups were similar, but the difference in mobility status could have led to a 'no' response on similarity of *prognostic factors* if mobility status is considered a prognostic factor.

3.6 Results

The results have been grouped by studies that are mainly adult or children, and by the type of outcome. Tables 6 and 7 summarises the main outcome measures used to describe the severity of constipation or incontinence, and quality of life. For adults (table 6) there are standardised patient reported outcome measures that are used in most papers. For paediatric patients (table 7) the reporting uses a wider variety of outcomes and the information that can be reported in a table is limited.

Table 8 shows additional results, including those of key importance for the economic evaluation. This includes the number of people ceasing to use Peristeen during the evaluation period, the number of UTIs, fecal incontinence frequency and adverse events.

The results for the main outcome measures are generalisable in that use of Peristeen is seen to decrease severity of constipation and incontinence according to patient reported measures. Some of these measures also include an element for the impact on patient lives. Outcomes for generic quality of life measures are generally not significantly different before and after Peristeen use.

Table 6 Main outcomes, adult population

Study	n	follow-up	Specific to bowel health / function, high score = worse					General quality of life, high score = better		
			CCCS 0-30	CCIS 0-20	FICS 0-24	NBDS 0-47	ASCRS 0-4, 4 scales	EQ5D 0-1	EQ-VAS 0-100	SF-36
RCT, Peristeen vs CBM										
Christensen 2006	42 vs 45	10 weeks	10.3 vs 13.2 p=0.0016		5 vs 7.3 p=0.015	10.4 vs 13.3 p=0.048	Improved coping and depression NS lifestyle, embarrassment			
Before and after studies										
Chan 2011	91	mean 10.7 months	18.72 to 11.45 p=0.0001	16.2 to 10.8 p=0.005						
Christensen 2008	62	10 weeks	13.4 to 10.2 p<0.0001		8. to 4.5 p<0.0001	15.3 to 10.8 p<0.0001				
Del Popolo 2008	33	3 weeks	non standard questionnaire					non standard questionnaire		
Grainger, pre-publication	[redacted]	[redacted]	[redacted]					[redacted]		
Kim 2013	52	6 months	non standard questionnaire					non standard questionnaire discontinuation rate		
Loftus 2012	11	3-28 months	19.09 to 11.54 p<0.001		12.91 to 5.36 p<0.001	24.55 to 14.18 p<0.005				

Passananti 2016	49	>1 year						All patients: 0.57 to 0.52 Users who stopped: 0.57 to 0.48*	Continued users: 44.5 to 63.4 Users who stopped: 44.5 to 41.9	
Preziosi 2012	30	6 weeks	12 to 8 p=0.001	12 to 4 p<0.001						51.3±7.8 to 50.4±7.8 p=0.051 (NS)
Rosen 2011	14	Median 29 months		17 to 5 p<0.01			Improved for all domains			NS physical, Improvement for mental
Whitehouse 2010	113	mean 42 months							✓ PSLAS	
adopters vs non-adopters										
Hamonet-Torny 2013	16		no baseline data					no baseline data		
* no p values reported, 0.57 (95% CI 0.5,0.65) to 0.52 (95% CI 0.4,0.63) for Peristeen, or 0.48 (95% CI 0.16,0.80) for those who stopped using Peristeen. Using linear regression to control for confounders such as natural disease progression, found no sig difference with Peristeen										

Table 7. Main outcomes, paediatric population

Study	**n**	**Follow-up**	**Specific to bowel health / function, high score = worse**	**General quality of life, high score = better**	**Additional information**
			CCCS 0-30 CCIS 0-20 FICS 0-24 NBDS 0-47 NBDoS 0-41*	**FiQoL SF-36 CHQ-PF50:**	

Alenezi 2014	18	mean 49.6 months			3 withdrew (17%) 15 did not require MACE 44% stop using pads
Ausili 2010	60	3 months	**NBDS:** 17.5 to 8.5 p<0.0001		extraction, suppositories, laxatives all down, all p<0.01 UTI (E.Coli only) 14 to 6 p<0.01 (in 3 month period before and during trial)
Corbett 2013	24	median 1 year		**FiQoL:** 40.5 to 51.5 p<0.0001	5 withdrew (21%) Significant improvement in median: stool frequency/day (3 vs 1), soiling per week (14 vs 1), % of bowel motions in toiled (20 vs 100), time attending to bowel/day (75 vs 35 min), use of pads
Kelly 2016	24	6 months	**NBDoS:** 20.21 to 8.83 p<0.005		only 50% had follow up, but all reported as still using Peristeen at 6 months.
Koppen 2017	67	Median 11 months			18/67 (27%) had stopped using Peristeen Children with occasional FI: 84% prior to Peristeen, 58% after Peristeen
Marzheuser 2016	40	Median 3 years			2 patients discontinued (5%) Peristeen use: 12 patients daily; 25 patients 3 times /week; 1 patient every 5 days. 79% use Peristeen independently
Midrio P. 2016	83	3 months		**SF-36:** sig. Improvement in some areas (more for SCI patients) **CHQ-PF50:** significant improvement in most areas	5 withdrew due to difficulty obtaining the device. No other withdrawals reported. Improvement reported in constipation, FI, symptoms during evacuation, use of laxatives, independence. Results are grouped by anorectal anomaly or spinal cord lesion.
Nasher 2014	13	Mean 21.2 months			3/13 withdrew due to discomfort / did not like procedure (23%) Continence score (unvalidated) improved None required ACE surgery
Pacilli 2013	23	Median 2 years			17% stopped using Peristeen 13% reported discomfort, but still used Peristeen
Pereira 2010	40	Mean 12 months			5 did not complete questionnaire Significant improvement in non validated questionnaire
adopter vs non-adopter					

King 2016	20	Mean 4.1 years	**CCCS:** 13.1 vs 10.8 p=0.24 **FICS:** 14.7 vs 16.7 p=0.27 **NBDS** 11.8 vs 12.5 p=0.58	*NS* *92.9 vs 85.2 p=0.28*	55% stopped using Peristeen pseudocontinence – 8/9 vs 5/11

NBDoS range not reported but calculated by EAC to be 0-41.

Table 8. Additional outcomes relevant to economic model, adult population

Study	**n**	**Study length**		**Discontinued at study end**	**Where reported: FI frequency, UTI, AE, stoma, non SBC interventions, hospitalisations, Peristeen, frequency, independance**
Christensen 2006	42 vs 45	10 weeks		Peristeen: 29% (12/42) SBC: 4% (2/45)	UTI: Peristeen 5.9%, SBC:15.5% p=0.0052 AE: PeristeenI: 4 AE (1 PU predating TAI, 1 bowel distention, 1 repeated explusion of catheter during training (same patient as PU) Hospitalisations: 3 (2 abdominal pain (1 of these discontinued), 1 PU) Peristeen frequency: 6/37 every day, 18/37 every 2 days, 13/37 1-3 times per week
Chan 2011	91	mean 10.7 month	FI	FI: 60% (12/20) discontinued	Incontinence: 7/20 Stoma: 2/20 Non SBC interventions: 3/20 sphincter repair, 2/20 SNS Adverse: 1 patient had constipation and minor rectal bleeding. Discontinued irrigation.
			C	C: 50% (25/50) discontinued	
Christensen 2008	62	10 weeks		27% (17/62). 2 before training, 5 during training, 10 during trial	1 patient withdrew due to adverse events (not stated) 2 due to insufficient effect 1 explulsion of catheter 1 disliked treatment 1 burst balloon Frequency of Peristeen: 20% every day, 48% every second day, 30% 1-3 times per week.
Del Popolo 2008	33	3 weeks		32 completed study	FI Frequency: Before: never/rarely is 20/33, After is 28/33 UTI: 88.9% did not have UTI while using Peristeen 24 patients said they were less dependent on caregivers 2 were more dependent

				6 no variation in dependence Frequency of Peristeen: 5 every day, 18 every second day, 10 patients 1-3 times per week.
Grainger 2017	[redacted]	[redacted]	[redacted]	[redacted]
Hamonet-Torny 2013	16	Mean 2.6 years	4/20 were unable to use. 62.5% (10/16) still using	Peristeen frequency: Mean twice per week Independant use: 37.5% independent Patients that stopped Peristeen: One subocclusive episode that required emergency consultation One had vomiting after use 2 had technical difficulties (takes too long, and one dexterity related)
Kim 2013	52	6 months	40% (21/52) at 1 month, 52% (27/52) at 3 months 65% (34/52) at 6 months	15 (28.8%) had adverse events 6/12 compliant patients and 10/24 non-compliant patients reported adverse effects at 1 month's use of Peristeen. 9 abdominal pain, 3 minor anal bleeding, 1 fatigue, 1 perspiration, 1 general discomfort, 1 perianal discomfort, 1 headache, 1 hot flash.
Loftus2012	11	3-28 months	1/11 wanted not to continue post study	Adverse events: None major during study, I bowel perforation subsequently. Bloating, abdominal pain
Nafees 2016		survey of long term users only	n/a	FI frequency: 75% had some FI. Episodes in the last month: None 33%, 1-2 43%, 3-4 16%, 5-6 5%, most days 3% UTI: 80/129 had UTIs in last 12 months. Mean of 3.1 in last 12 months. Frequency of going to toilet: every 2 days 59%, every day 31%, twice a day 5%, more 5% Independent: 71 independent. 89% of those assisted, were by family or friend.
Passananti 2016	49	>1 year (mean 40 months)	KM plot available. 36.7 % at 6 months, 40.7% at 12 months	UTI: 69 vs 32 in a year hospitalisations: 32 vs 19 in a year. Mean length of stay prior was 4.6 days. 22 had disrupted therapy: 12 (55%) disliked the therapy, 3 (14%) insufficient effect, 2 AEs (1 (4%) anal bleeding, 1 (4.5%) abdominal cramps), 1(4%) burst balloon. Health care resource use: Reduction in GP visits (27% 186 vs 136), specialist (19% from 102 vs), dietician (55% from 32) Independent: 44% decrease in dependency on any carer (family / professional)
Preziosi 2012	30	6 weeks	7/37 discontinued/ lost before 1st follow up.	AE: None 3/16 responders use Peristeen once a week, 13/16 require 2-7 irrigations per week.

			At 6 weeks, 47% 14/30 “non-responders” Not stated if still using.	
Rosen 2011	14	Median 29 months		Reduction of defaecations from 8 (4-12) to 1 (1-2).
Whitehouse 2010	113	Mean 42 months		

3.7 Description of the adverse events

Table 9 Summary of evidence for adverse events

Study	Withdrawals	AEs	Notes
Christensen et al. 2015 (audit)	N/A	49 bowel perforations (across 10 countries audited).	Bowel perforations: 35 were certainly caused by Peristeen, 7 were "probable" and 4 were "possible". This is global audit data, not a typical study.
Christensen et al. 2006	3/4 patients who had AEs	Number of AE = 4/42 (9.5%).	These were all in the Peristeen group.
Biering-Sorensen et al, 2009	N/A	1	Single case study on patient that had a bowel perforation.
Faaborg et al, 2009	86, only 10(12%) of which due to side effects of Peristeen	1 serious AE (rectal perforation requiring emergency surgery).	

Bowel perforation is a potential serious adverse event linked to Peristeen use. It is a rare complication according to the global audit by Christensen et al., (2016). This is based on incidents reported voluntarily to the company and the denominator is based upon sales data. Following device alerts from MHRA the company changed the IFU and the list of contra-indications. The company estimates that these measures have further reduced the risk. Voluntary reporting may underestimate the number of events, but since bowel perforation is a serious adverse event it is reasonable to expect events to be reported. Sales data is a surrogate for the number of procedures undertaken. It potentially overestimates the number of procedures as some stock would be held, and this would underestimate the risk of bowel perforation. Although the absolute figures may be subject to uncertainty, the risk is likely to be extremely low.

Other, less serious adverse events such as abdominal pain, nausea etc. are more common, but individual patients are free to choose whether to continue using Peristeen or to seek an alternative treatment, and it is clear from the evidence that this happens in practice when a proportion of patients try the technology but do not continue to use it long term.

The EAC searched the FDA MAUDE database, and found 62 listings for Peristeen, 31 of which were after 2014. Approximately half the total listings

were for perforations, and 15/31 (48%) for events post 2014. The most common of the remaining events were bleeding and pain.

3.8 Description and critique of evidence synthesis and meta-analysis

The company did not perform a meta-analysis, due to the diverse patient population and outcomes reported in the studies presented. The EAC agrees with this approach.

3.9 Ongoing studies

The company highlighted relevant post-market surveillance data in Christensen et al. (2015), but this audit is primarily concerned with adverse events only. They also present one academic-in-confidence study which has not yet been published, but is in production (Grainger et al.).

The EAC found two additional relevant studies on clinicaltrials.gov. One is a single-armed observation study on Cauda Equina Syndrome patients (NCT01784328) which was completed in July 2016. The other is a randomised crossover study in patients recovering from bowel cancer surgery with Peripheral Nerve Evaluation (PNE) and Peristeen (NCT01313026), which is listed as currently recruiting and due to complete in 2019. The two arms involve both Peristeen and PNE, and differ only in which of the interventions is applied first.

4 Economic evidence

4.1 Published economic evidence

If published studies are NOT to be included, summarise this succinctly and put all details into an appendix.

Critique of the company's search strategy

The company's search strategy was the same as for the clinical evidence and therefore subject to the same limitations. Adding search strings for 'economic' or 'cost effective' did not result in any additional papers.

Critique of the company's study selection

The company included both of the studies identified in their search, which was appropriate.

Included and excluded studies

Two published economic studies are included in the company's review of economic evidence; Christensen et al. (2009) and Emmanuel et al. (2016). In addition the EAC identified two conference abstracts (Emmanuel 2015, 2016), but these were from the same model later published by Emmanuel et al. (2016) and so do not add any new information.

The Christensen et al. (2009) model is from the societal perspective, which does not match the scope. Therefore the EAC excluded this study, although it provides some useful comparison if the societal costs are removed. Although the company included this and provided a quality assessment of the study it did not include the study in its de novo model.

Overview of methodologies of all included economic studies

Christensen et al. (2009) is a cost-effectiveness Markov model based on outcomes of a randomised controlled trial at five spinal centres in Denmark, Germany, Italy, UK and Sweden. The model by Christensen was from a societal perspective with a cycle length of 2 days and a time horizon of 10 weeks. This very short time horizon means that the model focused on differences in UTIs, carer time and products used for bathing and cleaning after leakages. Using a societal perspective it also included patient time spent on bowel management and the resultant lost salary. Long term outcomes and adverse events were not included.

The economic model provided by the company was the same as that described in Emmanuel et al ., (2016), but the company provided more up to date prices for comparison with those used in the model. The Markov model

had a 6 month cycle and a whole life time horizon of 37 years corresponding to the life expectancy of a 30 year old SCI patient. Emmanuel et al. (2016) is a cost-effectiveness model based on audit data from three UK hospitals. The audit database was set up in 2006.

Overview and critique of the company's critical appraisal for each study

The company completed a quality assessment of the economic studies, but critical appraisal is limited.

Does the company's review of economic evidence draw conclusions from the data available?

The company did not draw together the information in the published economic evidence, although the Christensen et al., (2009) results are referred to briefly.

Christensen et al.,(2009) had lower costs associated with Peristeen for carer time for bowel management, frequency of bathing and changing clothes, frequency of UTIs and use of constipation medicine compared to SBC. However the higher cost of providing Peristeen (€12/2 days vs no cost for SBC) meant that the Peristeen was cost incurring until the value of the patient's lost time was included.

Emmanuel et al., (2016), more appropriately, had a long time horizon, with costs included for outcomes such as the requirement for a stoma. It also included adverse events associated with Peristeen, SBC and subsequent management strategies. These longer term outcomes and costs resulted in Peristeen being cost saving.

4.2 Company de novo cost analysis

The company has presented the model from the publication by Emmanuel et al. (2016). Clinical inputs are taken from audit data from three UK hospitals. Although the model is published, very limited information about the audit is included in the published paper. The company has not included data from the published studies that were identified in the clinical evidence section.

The model has a Markov structure, with a variable time horizon representing an average patient lifetime, depending on the patient age selected at entry. Discounting is 3.5% and an NHS and social care perspective are used. Both of these are appropriate.

Patients

The base case is for a male patient, with spinal cord injuries, and 30 years of age. While these inputs are variable, the only resulting change in the model structure or variables is the time horizon used.

Inputs to the model are derived from audit data for a heterogeneous group of patients including those with spinal cord injuries, multiple sclerosis, cauda equina and spina bifida. The model does not include paediatric patients below the age of 17 years, and data on these patients are not included in the model inputs.

Technology

The technology used in the model is Peristeen, in addition to standard bowel care, as required.

Comparator(s)

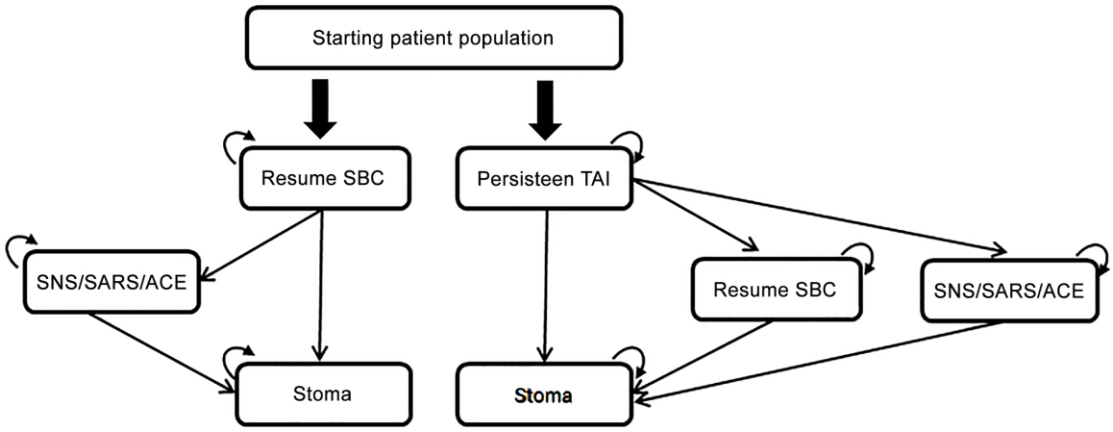
The comparator in the model is standard bowel care.

Model structure

The markov diagram provided by the company is accurate, as shown in figure 1. The submission inaccurately states that patients do not transition directly from SBC or Peristeen to stoma, but instead move to other options first. As the diagram shows, patients are able to move directly to stoma from all states. Once in stoma patients no longer move to any other state.

The submission also states that death was possible from all states, however there is no death state contained in the model. It is assumed that all patients survive until the final time horizon. The time horizon is set by an average life expectancy table for people with spinal cord injuries, according to the age entered by the user. Background mortality rates would normally be included in a model with a life time horizon.

Figure 1, replicating C9.1 from sponsor submission.



Key structural assumptions of the model are:

- All patients enter the model at age 30 and survive for 37 years. There is no death state in the model.
- The probability of ceasing to use Peristeen is assumed to be constant, whereas data from published studies (Passananti et al., 2016) shows a higher probability of reverting to standard bowel care in the first few months of using Peristeen.
- Adverse events are included, but it is assumed that adverse events are reflected as a proportion of the hospitalisations recorded in the audit database and in the number of patients discontinuing Peristeen. Hospital admissions are assumed to be split equally between gastrointestinal infections, pressure ulcers, falls or trauma, abdominal pain and UTI. Bowel perforation is not explicitly included.
- There is a description of patients who are prescribed off-label medications (Lubiprostone and Prucalopride, L/P) however these patients are not included in any of the model calculations.
- The model is stated as being for a patient with SCI, and patients are assumed to be homogeneous, whereas the audit data is actually made up of patients with several different diagnoses, who are likely to have different outcomes.
- The model assumes that variables are constant over time for all patients. Many variables are likely to change with age for all patients, and will also change over time for patients with progressive diseases such as multiple sclerosis.
- Transition probabilities for patients who start using Peristeen, and then revert to SBC are assumed the same as probabilities in the SBC arm.

The submission and the model use the terms 1st line, 2nd line and 3rd line, which can cause some confusion. Table 10 shows the meaning of these terms for each arm. Although the terms imply that most patients will travel through each stage, some patients will pass directly to 3rd line or stoma.

Table 10 Description of states within the model

	Peristeen arm	**SBC arm**
1st line	Peristeen	SBC
2nd line	SBC	not available
3rd line	SNS / SARS / ACE (also referred to as Surgery)	SNS / SARS / ACE (also referred to as Surgery)
stoma	Stoma	Stoma

Summary of the base case

The company's base case is presented in table 11, however the EAC identified serious errors in the model that reduce cost saving considerably.

Table 11 Company's base case results for 30 year time horizon.

	Peristeen	**Standard Bowel Care**	**Cost saving per patient over 37 years**
Device, training and consumables	£55,135#	£29,788	**£25,347**
HCP time	£45,726	£55,590	**-£9,864**
SNS/SARS/ACE costs	£6,924	£6,820	**£104**
Stoma cost	£13,806	£25,917	**-£12,111**
adverse events for Peristeen / SBC	£27,061	£52,084	**-£25,023**
Subsequent adverse events	£299	£521	**-£222**
TOTAL	**£148,951**	**£170,719**	**-£21,768**

#This is the cost of Peristeen plus the cost of SBC for those who returned to this treatment option.

Clinical parameters and variables

Audit data

An audit across three UK hospitals (University College Hospital London, Queen Square and Royal National Orthopaedic Hospital Stanmore) was used for the majority of clinical and resource use parameters (Emmanuel et al., 2016). The audit commenced in 2006, and Peristeen was introduced in these hospitals in 2007.

There is a very limited description of the audit data in the economic paper by Emmanuel et al., (2016), and also a description of a set of patients with multiple sclerosis taken from the same audit (Passananti et al., 2016). The company provided an extract of audit data that was used for quality of life calculations and also gave information on length of use, and if patients had stopped using Peristeen.

The population studied in the audit was 227 patients aged 17 to 70 years with NBD and a variety of neurological diagnoses. At recruitment, patients underwent a structured interview, clinical examination, anorectal physiology study, quality of life assessment and bowel function questionnaire (NBDS). Questionnaires were repeated at each annual follow-up. Resource use data was based on patient recall and validated by comparison to electronic patient records (Passananti et al., 2016). It appears that recruitment has been ongoing for a number of years, with varying lengths of follow up. It is not clear if this has been taken into account in analysing the data.

The comparator (SBC) clinical data was taken from the baseline data for the same patients just prior to commencing treatment with Peristeen, except for the proportion of SBC patients progressing to stoma. The number of SBC patients who have a stoma is taken from retrospective data for 157 patients in the database prior to the introduction of Peristeen. These are patients who did not receive Peristeen, but would have been eligible for Peristeen. Prior to the introduction of Peristeen, patients received standard bowel care.

The EAC do not have sufficient information to fully critique the audit, or its suitability for use in the model. It would seem to be in an appropriate NHS setting, with suitable patient pathways and an appropriate, if heterogenous population. However, there appear to be differences in the data used for 1) the model, 2) Passananti et al., (2016) and 3) an extract provided to the EAC by the company. Some differences may be explained by data having been taken from a live database at different points in time, however this does fully explain all points.

The total number of referrals to the three clinics was 350-390 per year since 2007, but only 227 patients are included as Peristeen users. The other patients were not included in the model, but it is not clear if this is because they were not suitable for Peristeen, or for another reason.

Questionnaires were collected annually, but it is not known at what time point data for resources was taken. Some patients cease using Peristeen, and there is no explanation of how these patients are treated in the data analysis.

Transition rates

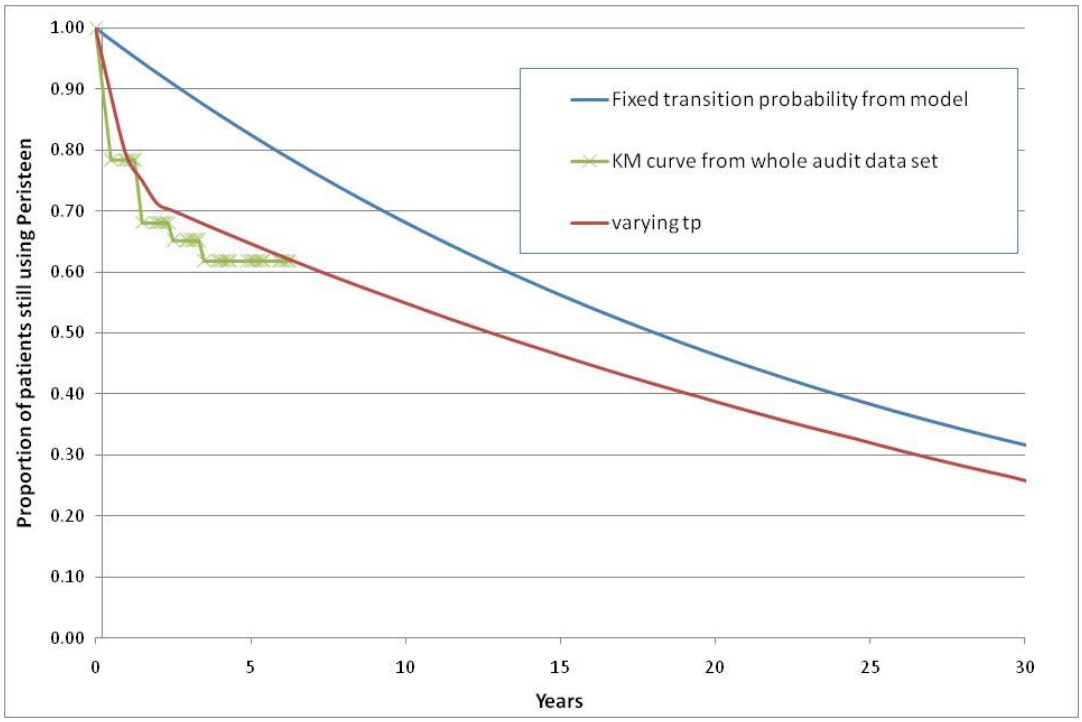
Transition between the states depends on transition probabilities, derived from the audit data, based on the number of observed occurrences at 6 years. The EAC do not have full information on the audit, however it is probable that the patients are not all enrolled at the same point in time, and therefore at a point 6 years after the start of the audit, not all patients will have 6 years' follow up. A survival analysis approach would have been more appropriate. This would capture both the varying length of follow-up and give additional information on the probability of ceasing to use Peristeen over time.

Passananti et al.,(2016) published a Kaplan-Meier curve for patients with multiple sclerosis demonstrating that dropout rates were higher in the first 6 months after starting to use Peristeen. This is in accordance with clinical evidence presented in table 8 previously, and is likely to be dependent on patient preference. The EAC ran survival analysis for the audit data that was supplied to them to give a Kaplan Meier curve. Figure 2 shows the effect of the constant transition probability in the model, compared to the Kaplan Meier curve from audit data, and also compared to three transition probabilities values empirically chosen by the EAC to match the KM curve more closely. With more certainty in the original data, transition probabilities could be calculated more accurately, however the impact of this additional work is likely to be small.

Using a constant transition probability favours Peristeen because more users move to SBC at an early stage in the model and so accumulate these costs for longer with less discounting. It will also increase the number of procedures for SNS/SARS/ACE and stoma. The impact of these changes depends on the magnitude of difference between costs for Peristeen and SBC.

Following enquiries by the EAC concerning calculation of transition probabilities the company submitted an amended model.The impact of the changes is shown in Appendix E, but the EAC did not consider that the changes should be included in the base case.

Figure 2 Proportion of patients still using Peristeen after 30 years



The transition probabilities for movement from Peristeen or SBC to SNS/SARS/ACE and stoma are calculated in the same way, and it is assumed that transitions will be the same for each arm. The EAC did not have audit data available to calculate these values. Transition from SNS/SARS/ACE to stoma was calculated using GoalSeek function in Microsoft Excel, and this was not visible to the EAC.

Tables 12 and 13 show how many patients are in each of the Markov states after 2 years and 30 years for both the base case and the EAC model which includes background mortality and variable transition probabilities for Peristeen.

Table 12 Base case submitted by company, showing the number of patients receiving each treatment after 2 years and 30 years.

	Peristeen arm		**SBC arm**	
	2 years	**30 years**	**2 years**	**30 years**
Peristeen	93%	32%	0%	0%
SBC	3%	10%	90%	20%
SNS / SARS / ACE	3%	20%	4%	16%
stoma	2%	38%	7%	64%
Dead	0%	0%	0%	0%

Table 13. EAC base case showing the number of patients receiving each treatment after 2 years and 30 years, using variable transition probabilities and background mortality.

	Peristeen arm		SBC arm	
	2 years	**30 years**	**2 years**	**30 years**
Peristeen	68.7%	13.4%	0%	0%
SBC	22.4%	3.87%	86.6%	8.7%
SNS / SARS / ACE	2.6%	8.8%	3.53%	7.2%
stoma	2.7%	18.2%	6.34%	28.4%
Dead	3.5%	55.8%	3.6%	55.8%

Faecal Incontinence

The mean incidence of faecal incontinence per week for Peristeen (1.5 per week) and the comparator (3.5 per week) is referenced to Professor Emmanuel. Data was collected as part of the audit, but it is uncertain how this was used in model. Faecal incontinence in the model is used to calculate the number of anal plugs and incontinence pads required for that proportion of patients using them. This is a key driver in the economic model.

Adverse events

There are two categories of adverse event in the model: urinary tract infections (UTI) that respond to treatment; and events that require hospitalisation.

The incidence of UTI not requiring hospitalisation is assumed to be 0.67 events per person per year for Peristeen, and 1.37 for SBC. It appears that this was derived from audit data but as the source (specified as expert opinion) is not made clear in the model, it is difficult to check. Clinical evidence summarised in table 8 supports the association of Peristeen use with a decrease in UTI events. Bermingham et al. (2013) report for SBC, 0.67 events per person per year for non-antibiotic resistant UTI, and 0.8 for UTIs with first line resistance (neither requiring hospitalisation).

The rate of admission to hospital also appears to be from audit data and is 0.28 events per person per year for Peristeen, and 0.63 for SBC. It is assumed that the cause of hospitalisations is equally split between abdominal pain, GI infection, pressure ulcers, falls or trauma and UTI. Pressure ulcers are the event most likely to have an impact on the overall result, as the costs are very high in the model. The proportion of readmissions for pressure ulcers in patients with spinal cord injuries is reported as 3% (Vaidyanathan et al., 1998)) and for “skin problems” as 17% (Savic et al., 2000). Given these

figures an assumption of 20% seems rather high in the model. Additionally both papers report rates of readmission for UTI as just over 40% which is higher than in the model. The discrepancy may be greater than this, since the model assumes pressure ulcers are grade 4, and the reality may be a mix of severity. Both papers are looking at data from nearly 20 years ago, and incidence of pressure ulcers may have changed over time.

Life expectancy

Alternative ages at entry to the model can be selected and this affects the life expectancy which is drawn from a table based on Frankel et al., (1998). This publication is almost 20 years old and so may be inaccurate for the current population. The life expectancy is used to set the time horizon for the model.

A recent publication by Savic et al., (2017) has detailed and more up to date data for the UK based on 70 years' of records, however small changes in life expectancy will not have a large impact on the model outcome.

This publication could also have been used to implement background mortality in the model.

Resource identification, measurement and valuation

Resource identification is a weakness in the submission, due to reliance on unpublished audit data, whereas valuation seems to be more thorough. The NHS reference codes and costs are not from the most recent data set.

Prices were not updated to current values where this data was available. For example, NHS reference costs for 2015-16 are available. In the submission the company lists these for comparison alongside the 2013-14 prices used in the model, rather than altering the model. However cost differences are not large.

The resources, costs and calculations for each model input are described by the EAC in Appendix D. This gives a weekly cost per patient for each item (where appropriate).

Health care staff time for both arms

Health care staff time is included for consultant, dietician and GP visits, and carer time for bowel care. All of these are taken from audit data which is not published and the EAC have no sight of it. The audit data records the number of people who had contact with health care professionals and the number of visits. For carers, the length of daily carer contact is recorded, however the model fails to include it in the calculation.

The audit data for health care staff time is based on an annual patient interview requiring recollection over the previous year. The submitted clinical evidence in table 8 supports some reduction in carer time.

There are issues with how these costs are included into the model. These are discussed in Section 4.5 on EAC changes.

SNS/SARS/ACE costs

For ACE, costs for the procedures are created from NHS reference costs, using a weighted mean over a number of procedures, with an assumption of bi-monthly follow up appointments. The details of these are in Appendix /D.

SARS uses a price that is for the cost of the device only, however changes have little impact on the model.

For SNS there is a procedure cost and an assumption of an additional procedure every 7 years for SNS to replace the battery. The costs are taken from NHS England Clinical Commissioning Policy (2013), but the model did not include follow up appointments which would be annual after the first year. This would have minimal impact on the model result.

Annual costs of SNS/SARS/ACE in the model, after the initial procedure, are lower than costs for either Peristeen or SBC.

Stoma costs

Stoma procedure costs are also calculated from NHS reference costs using weighted means. They are also in line with costs quoted in the NHS England CCP (2013).

Stoma maintenance costs consist of the consumable items required daily, as listed in Appendix D. Clinical advice is that while these are mainly appropriate, there will be some differences depending on the patient and the system used. Impact of changes is not likely to be high.

Annual costs of stoma in the model, after the initial procedure, are lower than costs for either Peristeen or SBC.

UTIs

The model uses a cost of £166.77 per UTI episode, which was originally referenced as from Bermingham et al ., (2013) who quote £49 per symptomatic UTI event. The manufacturer clarified this as being taken from Clark et al (2016). This price is quoted by Clark et al, and referenced as being calculated based on Bermingham et al (2013), with no further information given.

Pressure ulcers

The company identified adverse events as a key driver of the model. The EAC considers in particular the incidence and grade of pressure ulcers and cost of treating them is considerable as these are much more costly to treat than other adverse events. Uncertainty in the proportion of hospital admissions due to pressure ulcers has been discussed in the clinical parameters section. The cost used for pressure ulcers in the model is £24,214 for a grade 4 pressure ulcer, taken from a report by stoma care nurses (SCN High Impact Action Steering Group 2010). This references a report (Touche Ross, 1993) to the Department of Health on the cost of pressure ulcers. This is 24 years old now. An alternative option would be Dealey et al., (2012) with costs of pressure ulcers using bottom-up methodology as below:

grade 1 - £1,214; grade 2 - £5,241; grade 3 - £9,041; grade 4 - £14,108

This is a well researched and widely used paper, although prices are calculated on the assumption that patients are in-patients already and costs are for additional bed-days rather than an admission specifically for pressure ulcer. Both studies consider the general UK population rather than patients with SCI or any other specific diagnosis.

The EAC identified issues with adverse events not being included for SBC patients in the Peristeen arm, these are discussed in EAC model changes.

Technology and comparators' costs

The technology costs for Peristeen and the comparators were taken from the NHS drug tariff for 2015, but this is available with up to date prices for 2017. Although this is unlikely to have a major impact on the results of the model, it would have been better to include current prices

Peristeen consists of a system that is recommended to be replaced after 90 uses (6 months if using on alternate days), and a rectal catheter that is single use only. Users of Peristeen may still require medications such as bulking agents, stimulants, and suppositories. They may also require consumables such as anal plugs and incontinence pads.

Table 14. Annual costs for Peristeen and SBC technologies

	Peristeen annual costs	**SBC annual costs**
System and catheter	£1,712.86#	£0
Training	£217.00 one-off cost	£0

Medication	£315.94	£146.32
anal plug and incontinence pads	£1,875.53	£2,483.57
HCP visits	£807.17	£1,046.12
Carer time	£843.80	£1,673.44
Adverse Events	£2,054.63	£4,598.35
Total:	**£7,609.93 + initial training £217**	**£9,947.80**
#assuming Peristeen used once every two days.		

Frequency of use of Peristeen

The frequency of use of Peristeen is a major driver in the model, and also very variable between patients. More frequent use of the device will require additional packs of catheters and more rapid replacement of the system. The catheter cost has a much larger impact.

The model assumes that patients will use the device every other day. The RCT (Christensen et al., (2006) has the following frequencies 16.2% daily, 48.6% alternate days, 35.1% 1-3 times weekly. This gives a weighted mean of 3.5 times a week (or every other day). Looking at other UK studies that report these values, Passananti et al., (2016) report a weighted mean of 5.1 uses a week for patients with MS, other studies do not report in sufficient detail to allow a mean to be calculated. Values are shown in table 8. It is possible that as well as a natural variation between individuals, there may be a more systematic variation in use for patients with different diagnoses.y model was out of date

SBC medication and products costs

The model includes costs for required medications such as bulking agents, stimulants, and suppositories. The proportion of patients using these is taken from the audit data. This is assumed to be at baseline for the SBC arm and on follow up for Peristeen patients. It is unknown if the dose is also from the audit data, however both doses and costs appear to be appropriate (BNF online). The proportion of patients using these medications is different for SBC or Peristeen patients, however the doses remain the same.

In addition there are costs for anal plugs and incontinence pads. These are calculated as one per day plus one per faecal incontinence (FI) episode for those patients that use them. There is a difference between the proportion of patients using these products in the two arms, and there is also a difference in the incidence of FI assumed for each arm.

Sensitivity analysis

The company submitted sensitivity analysis that was based on ICERs rather than incremental costs. While this may be of interest to the committee, it does not address the key concern of cost saving, and may mask the importance of some variables to the cost impact of the technology.

The one way sensitivity analysis submitted appeared to have been from a base case different to that submitted, and therefore should not be used. Both the one way and probabilistic sensitivity analyses are based on the submitted base case prior to correction of errors that were identified by the EAC and should not be used.

4.3 Interpretation of economic evidence

The company described the strengths of the model as the use of real-life, recent data from three UK clinics, and the use of all relevant NHS costs. While this is potentially a strength, the lack of transparency of the data and how it is used in the model is a major weakness.

The one-way sensitivity analysis is described as cost saving in all eventualities, however the base case submitted has serious errors which means this does not hold true.

The company discuss the impact of frequency of use of Peristeen, which is a compound variable from the time to replace the device and the frequency of use of catheters. Although the company discuss the replacement of the device, it is actually the frequency of use of catheters that is the main driver.

The company describe the current model as having lower numbers of UTIs than in Christensen (2006). This does not appear to be the case in the model submitted, however using the UTI rate from Christensen does not make an appreciable difference to the incremental cost.

4.4 Results of EAC analysis

Due to a number of errors in the submitted model it is not appropriate to summarise the results at this point. The EAC interpretation of the results is presented in section 4.5

4.5 EAC Interpretation of economic evidence

The EAC identified a number of changes that could be made to the model. The first section (items 1-8) were considered as corrections where the model was not doing what the EAC believe was intended.

The majority of these concern how patients that start using Peristeen, but then return to SBC are costed:

In the submitted model these patients had costs included for SBC consumables, but not for health care professional visits, additional carer time or adverse events (items 2,3). These are the changes that had the largest impact.

Although patients returning to SBC had consumables included, it was at the rate calculated for Peristeen. This is inappropriate as these patients are no longer using Peristeen, and will be using the SBC pathway (item 4).

For patients returning to SBC, the incidence of 3rd line treatment or stoma are the same in the model. However in calculating the transition probabilities the incidence is divided by 7 years for SBC and 6 years for Peristeen (item 5).

The model description states that the carer time is included at 19 minutes daily for Peristeen, and 26 minutes daily for SBC. The model as submitted calculated carer costs as 1 hour daily for both arms for the proportion of patients who have paid care. Correcting this increased the cost saving for Peristeen slightly.

Items 1, 7 and 8 do not have any impact on the base case incremental cost.

Table 15. EAC corrections and amendments to submitted model

	Description	**Impact on model**
	EAC corrections to model	
1	Tornado diagram had not been updated with submitted base case.	No impact on base case. Re-run with EAC base case.
2	For patients in the Peristeen arm, who return to SBC: The cost of HCP time for SBC patients is included.	Large decrease in cost saving
3	For patients in the Peristeen arm, who return to SBC: The cost of SBC related adverse events is included.	Large decrease in cost saving
4	For patients in the Peristeen arm, who return to SBC: Costs of consumables used by SBC changed to be the same as in SBC arm.	Decrease in cost saving

5	For patients in the Peristeen arm, who return to SBC: Transition probabilities to surgery or stoma are changed to be the same as in the SBC arm (based on same data).	Decrease in cost saving
6	Carer time calculations for both arms changed to include the minutes spent daily, rather than using an entire hour	Increases cost saving (Peristeen requires less carer time in model)
7	Utility decrements for adverse events multiplied by patients in the relevant state for both arms.	No change to incremental cost. Very slight reduction in incremental utility
8	Adverse event labeling changed to ensure that EAC sensitivity analysis worked correctly.	No change to base case.
Additional EAC work on model		
9	Variable transition probabilities included to model reduction in Peristeen use in first year	Decrease in cost saving
10	Background mortality added (Savic 2017)	Increase in cost saving
11	Cost of pressure ulcer changed to £ £15,134.84(Dealey et al., 2012, £14,108, inflated to 2017).	Decrease in cost saving
12	Cost of UTI changed to £52.57 (Bermingham et al,. 2016 (2012), £49 inflated to 2017).	Decrease in cost saving
13	Pressure ulcer cost and proportion of readmissions investigated in sensitivity analysis	Likely to decrease cost saving.
14	Frequency of Peristeen use investigated in sensitivity analysis	Highly sensitive to this variable.

The second section (items 9-11) were considered as potential improvements in the accuracy of the model.

The transition probabilities have been described fully in section 4.2, Clinical parameters and variables. The submitted evidence in the Section 3 Clinical Evidence suggests that there is a high rate of cessation in the initial months of Peristeen use, as some users find it difficult, painful or ineffective. The EAC used an extract of audit data supplied by the company to estimate variable transition probabilities. This change decreased the cost saving, as more patients switched to SBC in the early months. The impact was not large, due to the previous EAC corrections that had reduced the cost difference between the two treatment strategies.

Background mortality from all states was added as an EAC investigation into the impact. It would typically be included in a model with a long time horizon, however the impact was minimal and in favour of Peristeen. The mortality rates used were for a population with spinal cord injuries. Although the rate would be different for alternative diagnoses, the impact on the model would be small.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The items are grouped together, as the impact value of any one item is dependent on the order in which it is implemented, meaning that a breakdown of changes is potentially confusing and misleading. Each change is to a model in which the previous changes listed have already been made.

Table 16. Impact on incremental cost of additional work by EAC

Model version	Incremental cost (over 37 years
Base Case submitted by company	-£21,768
Changes 1-8: corrections of errors • Patients in Peristeen arm returning to SBC have full costs including appropriate medication, HCP time and adverse events. • Carer time in both arms is corrected • Transition probability for all patients receiving SBC is standardised	-£7,829
Changes 9-10: EAC suggested refinements 9. Reduced number of Peristeen users in first year, using variable transition probability 10. Background mortality added	-£6,976
11. Pressure Ulcer cost changed to £15,134.84	-£3,574
12. UTI cost changed to £52.57	-£3,175
Final EAC base case with all corrections and refinements	**-£3,175**

The impact of Peristeen frequency of use, pressure ulcer frequency and pressure ulcer cost is also important, however due to uncertainties in the correct values, this is investigated in the sensitivity analysis.

The model is cost saving with the base case, although there are both variations in patient groups and uncertainties in data that would lead it to be cost incurring in some situations.

Sensitivity analysis results

The EAC re-ran both sensitivity analysis after all EAC changes (items 1-12), and using incremental cost as an outcome. The tornado diagram in figure 3 and shows that the main driver in the model is the frequency of use of the Peristeen system, with the frequency of faecal incontinence and cost of pressure ulcer treatment as other very important factors. The discount rate also gives high variations, due to the long time horizon, however this is set at a standard rate for all models submitted to NICE.

Figure 3 Tornado diagram of incremental cost, using EAC base case

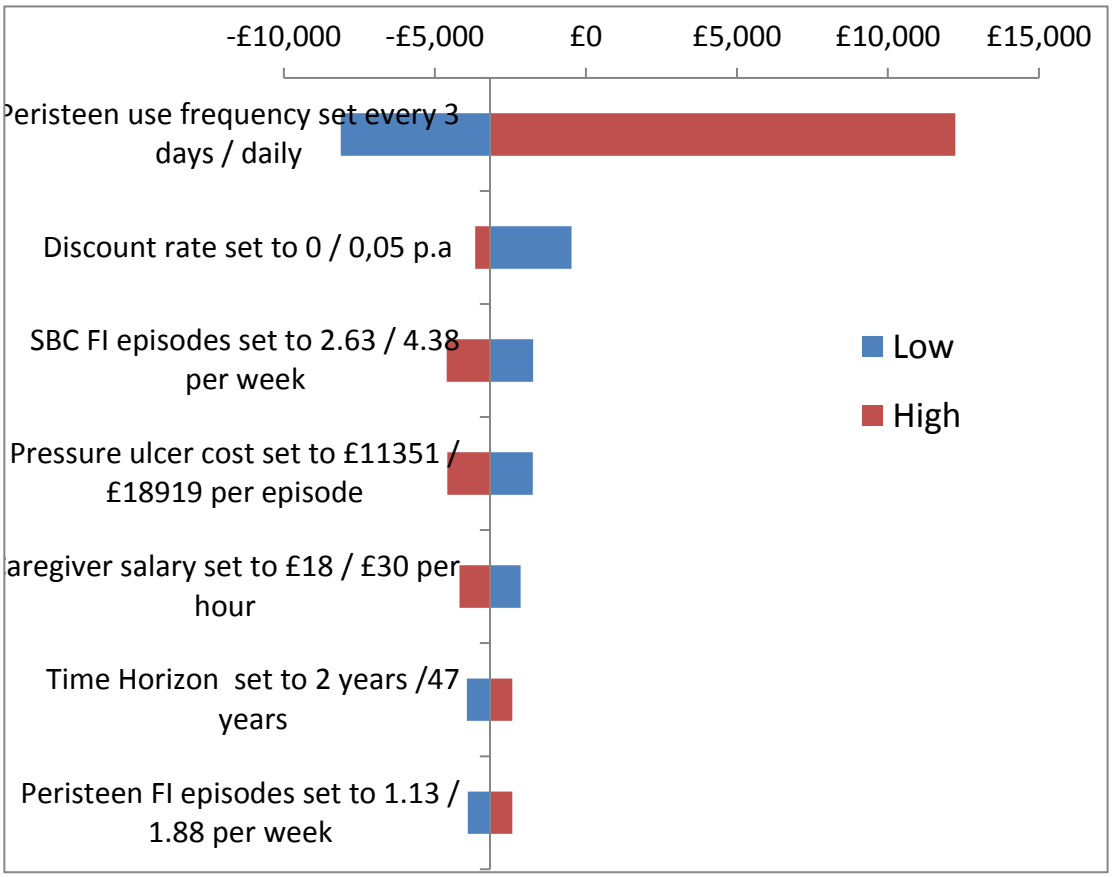


Table 17 Variables with highest impact in one way SA of EAC base case

	High	Incr.Cost (37 years)	Low	Incr.Cost (37 years)
Frequency of Peristeen use	Daily	£12,229	Every 3 days	-£8,115
SBC Faecal incontinence	4.38	-£4,607	2.63	-£1,743
Cost of Pressure Ulcers	£18,919	-£4592	£11,351	-£1757

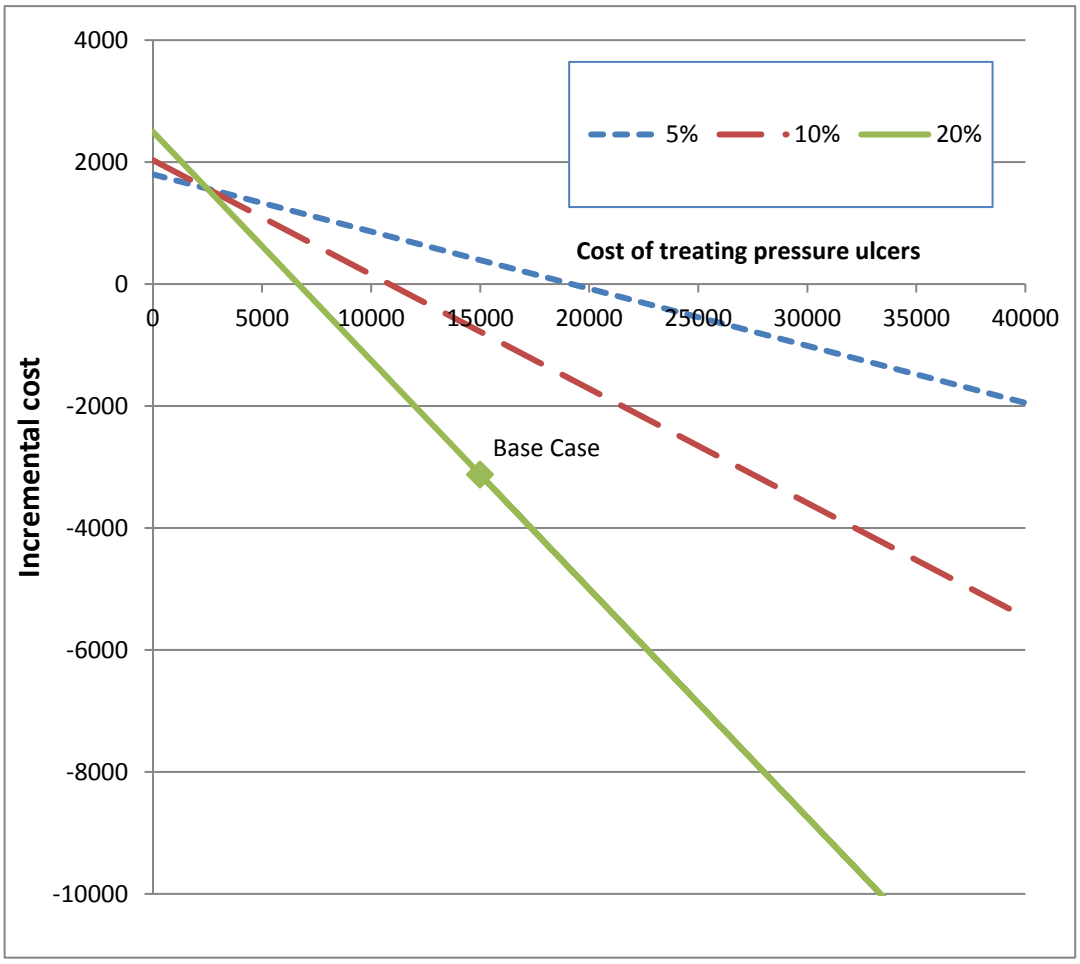
The impact of the time horizon is relatively low because almost all of the costs of the main strategies accumulate on an ongoing basis, rather than being dependant on initial expenditure.

The one-way sensitivity analysis provided by the company focuses mainly on costs of items and does not vary the frequency of their use in the main part. The proportion of re-admissions that are for pressure ulcers is not varied in the analysis.

The EAC has investigated this by plotting incremental cost from a range of potential costs and re-admittance proportions as shown in figure 4. This shows pressure ulcer costs along the x-axis, and plots the incremental cost with a given pressure ulcer costs when the pressure ulcers make up 5, 10 and 15% of re-admissions. As the proportion of pressure ulcers decreases, the model structure means that the proportion of UTIs increases. The point where all three lines meet is where the cost of pressure ulcers is equal to the cost of UTIs, therefore the proportion has no effect. Figure 4 shows that Peristeen would be cost saving at a pressure ulcer cost greater than £5,310 for 20% of readmissions, or £13,790 for 5% of readmissions, assuming Peristeen is used on alternate days and all other variables remain the same.

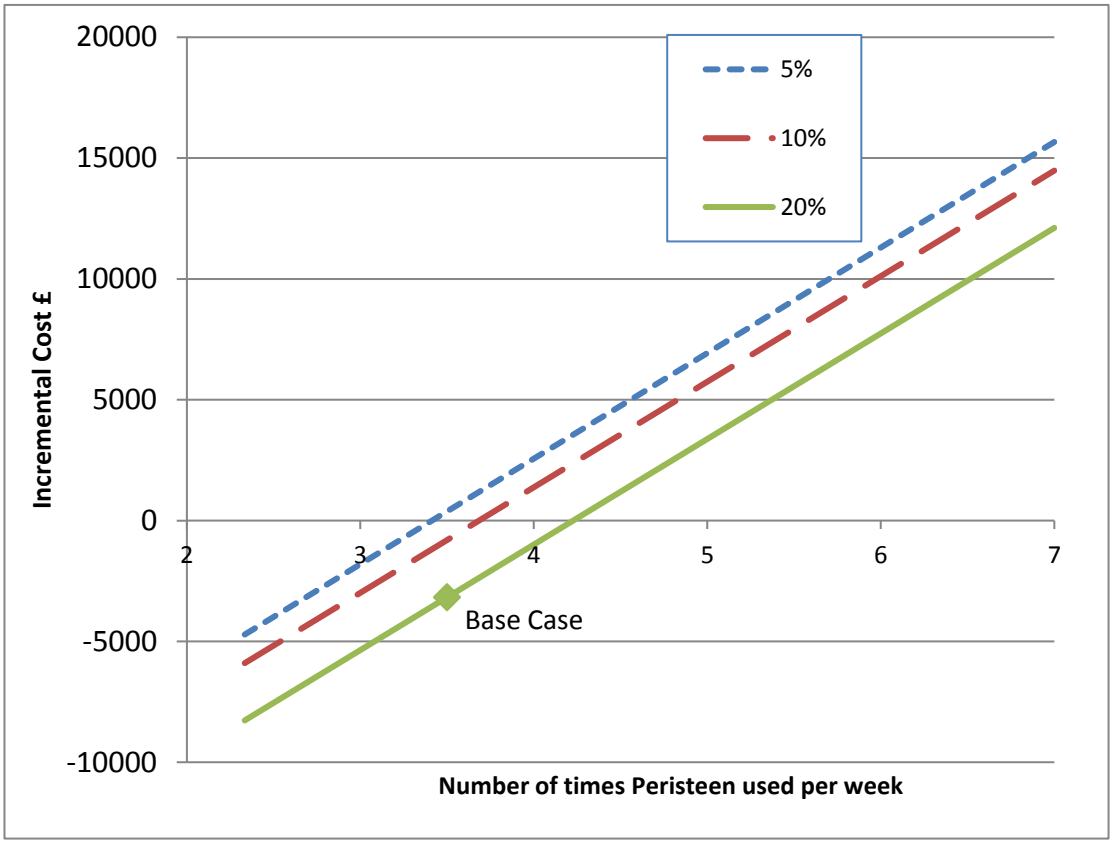
Heterogeneity in the patient population has not been recognised in the model. The population for the audit data consists of patients with a range of neurogenic conditions. It has been observed by Emmanuel et a. (2013) and Christensen et al (2006) that outcomes may differ across patients with different background. It is also likely that other model variables will differ between different patient groups. If sufficient data were available the model would be improved by identifying outcomes and variables appropriate to each of the wide range of patients who use Peristeen.

Figure 4. Incremental cost vs cost of pressure ulcer treatment



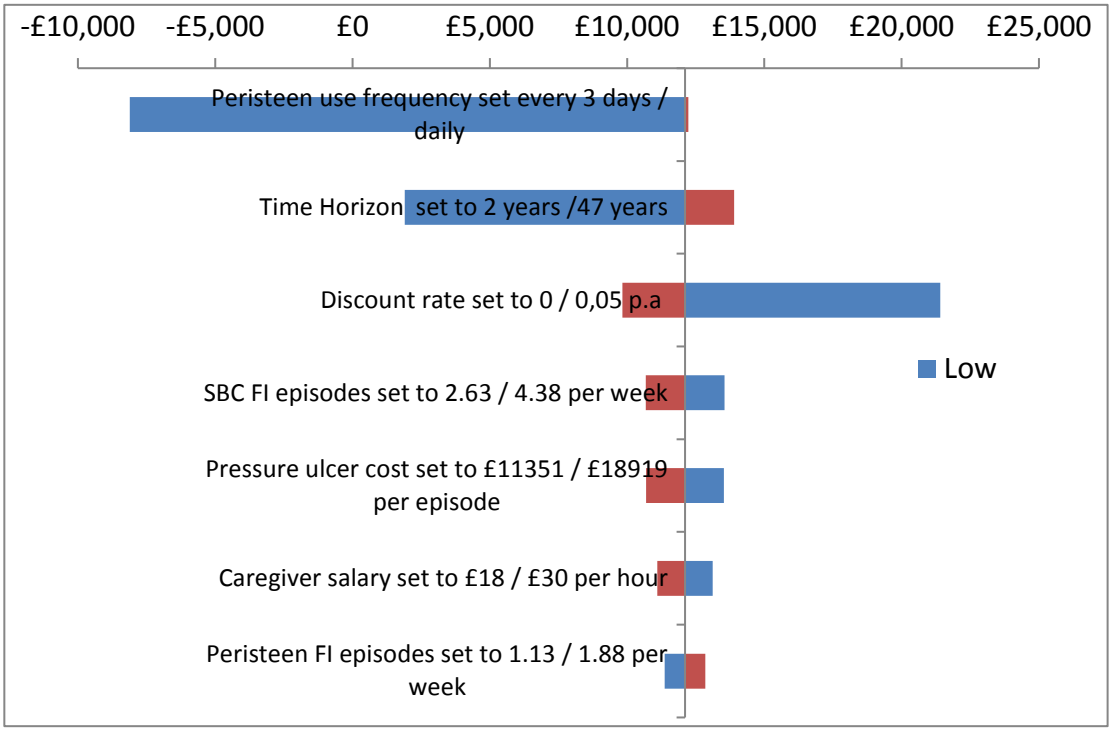
The previous diagram assumes that Peristeen is used on alternate days. Figure 5 varies the frequency of Peristeen along the x-axis, with lines plotted again for the proportion of re-admissions due to pressure ulcers.

Figure 5. Incremental cost vs frequency of Peristeen use, shown for different proportions of hospital admissions for pressure ulcers.



The assumption of frequency of Peristeen use also has implications for how the model responds to sensitivity analysis, as the tornado diagram in figure 6 shows. Here the base case is set to have daily use of Peristeen. The base incremental case is then cost incurring, and due to the difference in costs between the two strategies the time horizon becomes increasingly important.

Figure 6. Tornado diagram using EAC base case adjusted to show daily use of Peristeen.



Probabilistic sensitivity analysis was carried out using the submitted macro on the EAC base case for 10,000 runs. The mean incremental cost due to using Peristeen was -£3,190, with 73.2% being cost saving for Peristeen use.

The PSA in the submitted model did not vary frequency of Peristeen use. The EAC added this as a probabilistic variable using a gamma distribution, and a standard error of 25% of the mean. For the remaining variables the company used a standard error of 10% of the mean, however the EAC felt this did not reflect a realistic variance in frequency of use. After running the modified PSA for 10,000 runs, the mean incremental cost due to using Peristeen was -£3,233, with 69.7% being cost saving for Peristeen use.

Uncertainty relating to transition probabilities is not considered in the PSA, these remain fixed throughout the sensitivity analysis.

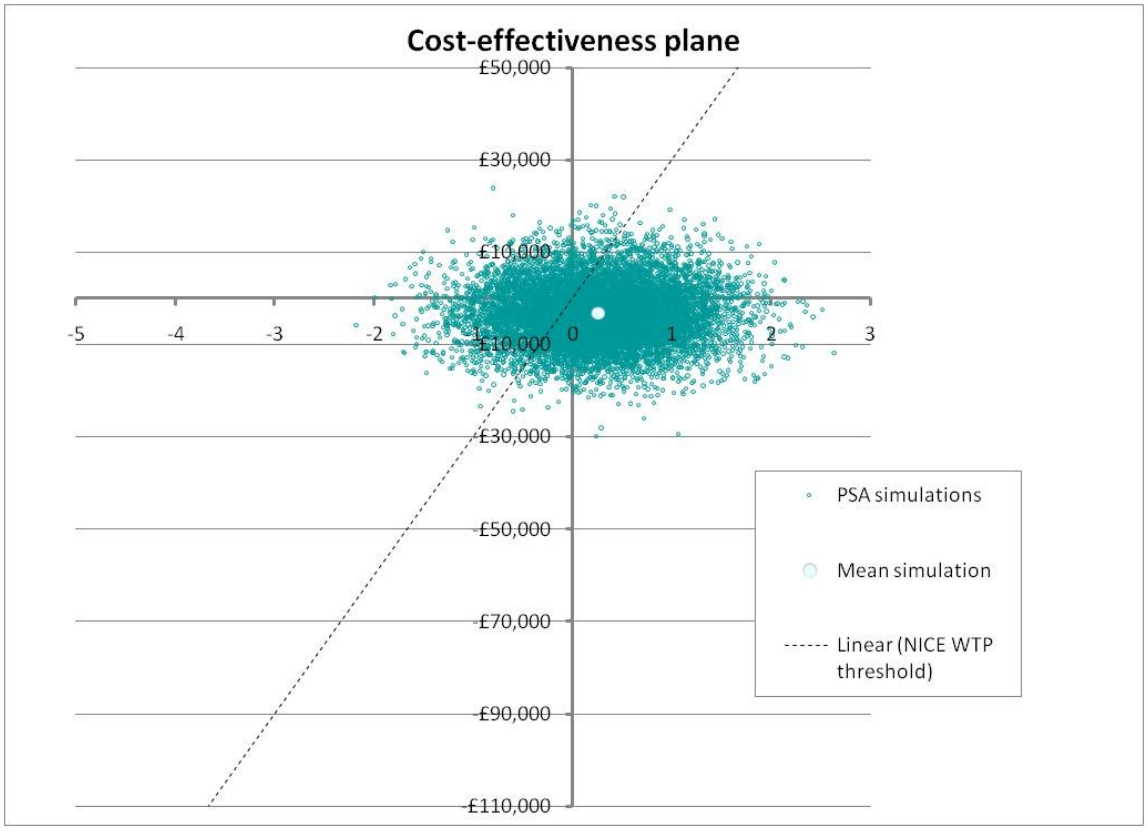
Cost Effectiveness

The submitted model includes cost-effectiveness, using utility values that were collected as part of the clinical audit. The utility data from the audit shows an improvement in quality of life following treatment with Peristeen. The submitted clinical evidence (table 6) for generic quality of life measures does not show an overall improvement. However other outcome measures that are more specific to bowel management do show improvement, and

would be expected to add to the user's quality of life. This is also confirmed by the patient expert testimony.

The PSA, including the EAC modification, was run on the EAC base model for 10,000 runs. This resulted in the intervention being less costly and more effective, and is thus classified as dominant. At a willingness to pay threshold of £30,000 Peristeen would be cost effective in 70.5% of cases.

Figure 7 shows the scatter plot of ICER outcomes that were obtained.



5 Conclusions

5.1 Conclusions on the clinical evidence

The evidence is composed of one RCT and a large number of observational studies mainly of poor quality. The breadth of the scope means that all studies are within the scope.

The company submission contained evidence from one RCT, seven observational studies of adult patients and one observational study of children. The EAC included a further four observational studies for adults, and 11 observational studies for children.

The RCT was a reasonable quality study of 87 adult patients with spinal cord injuries treated in five European centres including the UK. Due to the nature of the device, blinding of patients was not possible, and there was no reporting of data analysis being blinded. In total 14 patients withdrew during the trial, 12 from the intervention arm (using Peristeen), and two from the comparator arm (using conservative bowel management without transanal irrigation). Five further patients were lost to follow up. Data was analysed as intention to treat. The study reported significant improvements in validated patient reported outcomes for bowel function.

The observational studies of adults were mainly before and after treatment comparisons and of variable quality. Eight of the studies included centres from the UK, and a further four from Europe. They included patients with spinal cord injuries, multiple sclerosis, anterior resection syndrome and functional bowel disorder. Where studies were comparative, they all found that Peristeen had some improvement in patient reported outcomes for bowel function. Outcomes related to general quality of life measures were less widely reported and changes were either not significant, or were significantly improved in only some domains. There were considerable numbers of patients who stopped using Peristeen, particularly in the first few months.

Evidence for the use of Peristeen in children was based entirely on observational studies, mainly of poor quality and less consistent outcome measures. The majority (11/12) compared outcomes before and after treatment, three were from the UK and five from Europe. They included patients with spina bifida, anterior resection syndrome, anorectal malformation, hirschsprung's disease, idiopathic constipation and neuropathic bowel dysfunction. General findings indicated that use of Peristeen resulted in improvements in bowel management. There were variable numbers of patients who ceased to use Peristeen.

5.2 Conclusions on the economic evidence

The economic model relies very heavily on unpublished audit data, meaning that the EAC had limited ability to critique or verify it. There remains considerable uncertainty in its findings. The clinical evidence submitted was not used in the economic model, and does not contain information on longer term outcomes such as the need for stomas.

The EAC made corrections and alterations to the economic model which reduced the cost saving due to Peristeen. Following these changes, the EAC completed additional sensitivity analysis.

The cost saving due to use of Peristeen is largely due to reduced time for health care professional visits and carer time; reduced incidence of faecal incontinence requiring the use of incontinence pads; reduced incidence of UTI and fewer hospitalisations.

The model is very sensitive to the frequency of use, pressure ulcer treatment and faecal incontinence, and there is uncertainty about each of these variables. There is limited clinical evidence around the frequency of use, and for an improvement in faecal incontinence. There is no direct clinical evidence linking use of Peristeen to a reduction in pressure ulcers.

Because the difference in costs between Peristeen and SBC are not large, the model is not sensitive to movement of patients between these arms. This would not hold true if the base case changed. The ongoing costs of SARS/SNS/ACE and stoma (after the initial procedure) are lower than annual costs of Peristeen or SBC in the model.

The model does not recognise the heterogeneity in the patient population used to populate the model. The audit data consists of patients with a range of neurogenic conditions, and outcomes may differ between these groups. In addition the model focuses on patients with neurogenic conditions, however there are other groups of patients who use Peristeen. The model results may not be generalisable to these patients.

The EAC corrected model has an incremental cost of -£3,175 when using Peristeen over a 37 year time horizon.

Probabilistic sensitivity analysis with frequency of use included, resulted in 69.7% % of trials being cost saving when using Peristeen.

6 Summary of the combined clinical and economic sections

The evidence indicates that a proportion of patients find that Peristeen is an acceptable treatment that improves their bowel management, while a proportion do not continue with its use either because they have difficulties or pain in use, or because they find it ineffectual. The economic model relies very heavily on unpublished audit data, meaning that there remains considerable uncertainty in its findings. The clinical evidence submitted was not used in the economic model, and does not contain information on longer term outcomes such as the need for stomas.

The EAC made corrections and alterations to the economic model which reduced the cost saving due to Peristeen. The cost saving is largely due to reduced time for health care professional visits and carer time; reduced incidence of faecal incontinence requiring the use of incontinence pads; reduced incidence of UTI and fewer hospitalisations.

The clinical and economic evidence indicates that some patients find that Peristeen improves their bowel management. It is likely to be very slightly cost saving over a life-time horizon, but there are considerable uncertainties in the model.

7 Implications for research

Although the clinical evidence base is not strong, the success of the Peristeen anal irrigation system appears to be strongly determined by personal preference and circumstances. Patients who find it successful will continue to use it, and those who find it ineffectual or painful will stop using it.

The existing RCT is for patients with spinal injuries only and has a short time horizon. This does not capture patients stopping use of Peristeen over time, or the number of patients who go on to require further interventions or stomas.

There is little good quality published evidence on how often Peristeen is used in different groups, considering that frequency of use impacts greatly on the economic case for Peristeen. Similarly there is little published evidence on the impact of Peristeen on susceptibility to UTIs and pressure ulcers across different groups.

Any future studies of Peristeen should carefully record data on the disease process underlying the bowel dysfunction, frequency of use, incidence of faecal incontinence and complications including UTIs and pressure ulcers.

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Appendices

Appendix A Literature search strategy

Company search methodology

Databases searched (accessed via NICE/Open Athens portal):

- EMBASE
- Medline including with full text
- PubMed
- Cochrane database of systematic reviews

Limits: Jan 2002 – March 2017; English language.

The specific search terms used were as follows:
Search Terms 1: Transanal OR retrograde AND irrigation AND bowel
Search Terms 2: Peristeen

The outputs of the 2 searches were then merged to form a single database for review.

Unpublished studies were identified through Coloplast and links with the clinical community.

EAC search methodology

The search strategy below was adapted and run in the databases listed in the table below. The search was designed to identify clinical, economic and adverse event evidence in any language from 2000 to 24 March 2017. The databases searched included ones in which conference abstracts are indexed. Searches were also conducted of: MAUDE and the MHRA to identify notified adverse events; trials registers to identify ongoing and unpublished studies; relevant organisations to identify additional 'grey literature'. Supplemenatry search methods included: reference list checking and citation tracking of studies included by the EAC in the report.

Search strategy

Ovid MEDLINE(R) <1946 to March Week 3 2017>

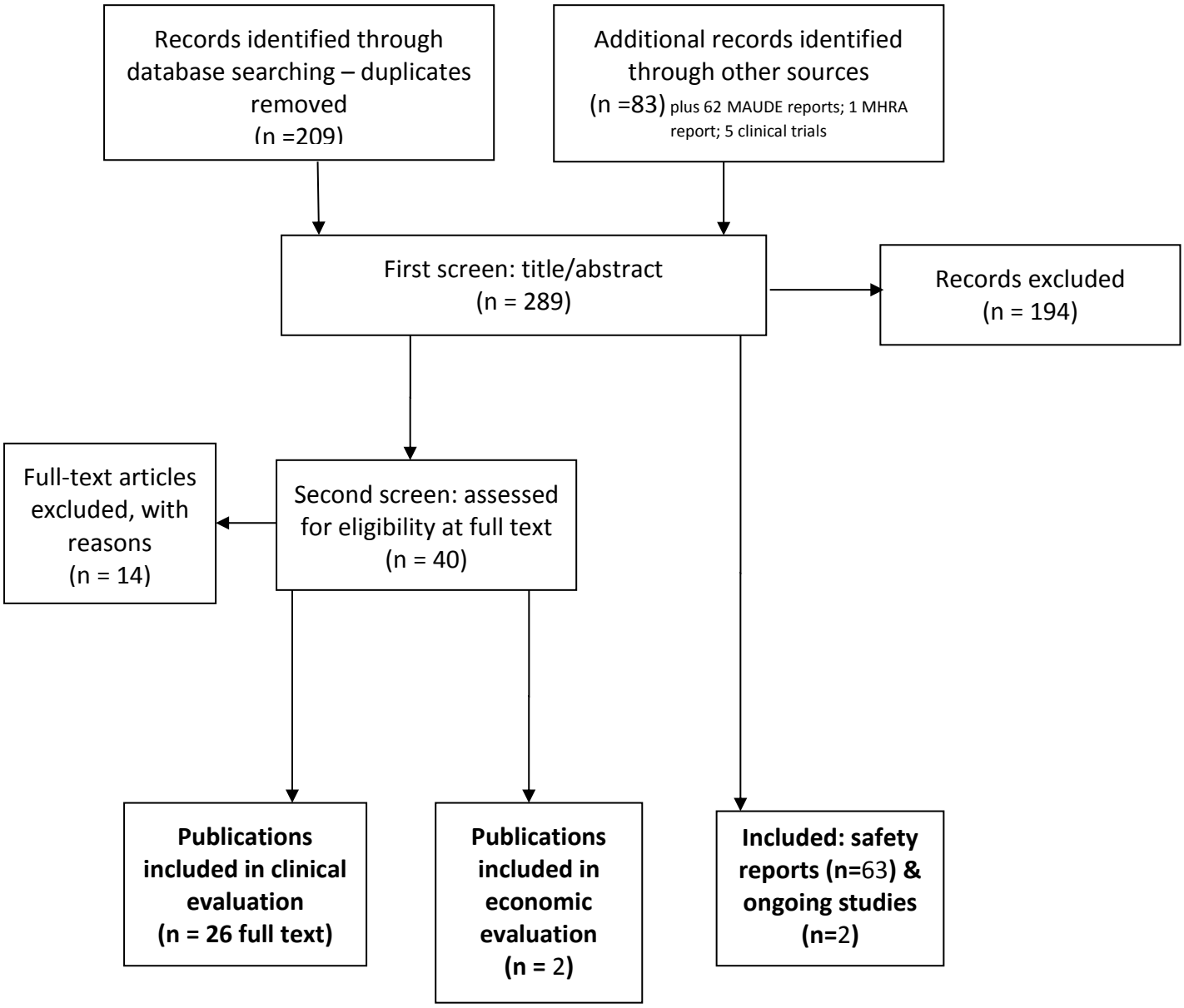
1 transanal irrigation.tw. (42)
2 retrograde continence enema.tw. (0)
3 transanal colonic irrigation.tw. (4)
4 Therapeutic Irrigation/ (16616)
5 peristeen.tw. (15)

6 1 or 2 or 3 or 4 or 5 (16625)
7 Constipation/th [Therapy] (2349)
8 Fecal Incontinence/th [Therapy] (1730)
9 Neurogenic Bowel/th [Therapy] (33)
10 exp Intestinal Diseases/th [Therapy] (45668)
11 (neuro* adj3 bowel adj (dysfunction or disorder*)).tw. (110)
12 7 or 8 or 9 or 10 or 11 (47519)
13 6 and 12 (260)
14 limit 13 to yr="2000 -Current" (134)

Evidence Resource Details

Date	Database Name	Database Host	Total Number of records retrieved
24/03/17	Medline	Ovid	134
24/03/17	Medline In Process	Ovid	8
24/03/17	Embase	Ovid	88
24/03/17	The Cochrane Library CDSR DARE CENTRAL HTA NHS EED	Wiley	12 1 0 11 1 1
24/03/17	Scopus	Elsevier	39
24/03/17	Web of Science	Thomson Reuters	81
24/03/17	EconLit	EBSCO	0
20/03/17	Pubmed	NLM	22
Total number of records from databases after de-duplication =			**209**
27/04/17	MAUDE		62
24/03/17	MHRA		1
24/03/17	Clinical Trials.gov		4
24/03/17	ICTRP		1
Supplementary Searching			
27/04/17	Coloplast website		3 (duplicates of database search)
27/04/17	National Technical Reports Library		1
27/04/17	Bladder & Bowel UK		0
27/04/17	Bowel & Cancer Research		1
08/05/17	Citation tracking of key included papers in Scopus and Web of Science		78

Flow diagram of EACs study selection



Appendix B Included studies for adults and children

For each of the design, participants and outcomes entries below, the following coding is used:

G	Fully included within the scope
A	Partially included within the scope
R	Not consistent with the scope

As the scope for this topic is very broad, no single paper is likely to fully encompass the scope, however those coded green have participants, and outcomes that are included within the scope.

Table B1 Included adult studies

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Chan (2011)	Retrospective case series of Peristeen. 2005-2009 Intervention Comparator	91 patients, with functional bowel disorders. 80 women, 11 men, median age 51 (17-78 years). 60 had constipation, 31 had faecal incontinence.	CCCS, locally set level of <15 as success. CCIS, locally set level of <7 as success	Significant improvement in CCCS Constipation: 83%(50/60) were available for follow-up, with mean use of 10.7 months. 25/50 patients stopped using Peristeen, 18 stated this was due to failure to control symptoms. 10 patients had surgery to control symptoms. Faecal incontinence:65% (20/31) were available for follow-up, with mean use of 11.9 months. 12/20 patients stopped using Peristeen, 7 stated this was due to failure to control symptoms. 2 patients had symptoms resolved, 7 were offered surgery to control symptoms.	21 were lost to follow up. Of those patients followed up, 37 had discontinued use of Peristeen.	Large numbers lost to follow-up, may introduce bias.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Christensen (2006)	RCT comparing transanal irrigation using Peristeen with conservative bowel management (CBM) for 10 weeks Company funded Intervention G Comparator G	87 randomised (42 Peristeen vs 45 CBM) 62 men, 25 women average age 49.1years. 73 completed 5 European spinal cord injury centres (Sweden, Italy, Germany, UK, Denmark) All patients 18 years or older, at least 3 months after spinal cord injury. G	**Primary outcomes:** CCCS and FIGS **Secondary outcomes:** NBDS, modified ASCRS, numeric box score on: bowel function, influence on daily activities and general satisfaction. Outcomes collected at week 0 and 10, plus weekly telephone interview. G	CCCS, FIGS and NBDS were significantly improved for Peristeen vs CBM. Sub-group analysis found no significant difference for patients who could walk, but significant improvement for those who used wheelchairs or were confined to bed found that these ASCRS scores were significantly improved for Peristeen vs SBC in domains of coping/behaviour but no significant difference for the lifestyle and depression/self-perception domains. The numeric box scores were significantly improved for bowel function, general satisfaction and improvement in quality of life, but not for influence on daily activities.	14 w/d (12 Peristeen, 2 SBC): 73 completed, 5 lost to follow-up	FIGS is not validated for spinal cord injury patients. Blinding was not possible. Large number of patients stopped using Peristeen before the end of the study. These were included in ITT analysis using baseline data in place of missing data. Baseline imbalance between groups for number using wheelchair or confined to bed. Sub-group analysis not stated as planned. Study supported by company

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Christensen (2008)	Prospective before and after study of Peristeen with 10 weeks follow-up. 2003-2005. Intervention G Comparator n/a	62 patients with spinal cord injury and neurogenic bowel dysfunction. 45 men and 17 women, mean age 47.5 years, from 5 European centres. 42 patients used Periseteen for 10 weeks as part of Christensen 2006 RCT. 20 additional patients used Peristeen for 10 weeks, after having CBM as the control group in the RCT. G	CCCS, FIGS, NBDS Patients were contacted each week during follow-up to complete a short, structured questionnaire. G	Mean CCCS, FIGS and NBDS improved significantly from baseline to 10 weeks	17 withdrew: 2 withdrew before training, 5 during training, 2 because of insufficient effect, 1 due to expulsion of catheter, 1 disliked treatment, 1 due to burst rectal balloon, 1 because of adverse events, 4 lost to follow-up.	The same patients were also in the Christensen (2006) paper. It is not clear why only 20 patients from the total of 45 in the control group were included. FIGS is not validated for spinal cord injury patients. ITT analysis, 10/17 had assessment at point of withdrawal, 7/17 used baseline data for outcomes. Study results found greater improvement for patients with mobility, contradicting sub-group results for Christensen 2006. Also variability in outcomes between study centres.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Del Popolo (2008)	Prospective multi-centre before and after study of Peristeen. 3 weeks treatment. Data analysis supported by company. Intervention G Comparator n/a	33 patients with spinal cord lesion and severe neurogenic bowel dysfunction (NBD) from 10 centres in Italy. 18 men and 15 women, mean age 31.6 years. The cause of the spinal cord lesions were: trauma 14, spina bifida 12, MS 2, surgery 1, other 3, not recorded 1 G	A newly devised questionnaire in Italian assessing QoL in NBD. Covering urinary function, bowel function, NBD, QoL. A	Significant improvement in: feeling of incomplete evacuation, abdominal pain, leakage of faeces, gas incontinence, time for evacuation, patient opinion of intestingal function, Quality of life score and satisfaction. Following treatment 24 patients considered they were less dependent, 2 were more dependent and 6 reported no change.	1 w/d lost to follow-up.	The questionnaire was not validated. It was designed by experts. There appears to be no patient involvement in the design of the questionnaire. Heterogeneous patient group. Small patient numbers across a large number of centres. Questionnaire not available, possibility of selective reporting of outcomes. Results are not given in detail.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Grainger 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Hamonet -Torny (2013)	Retrospective before and after study of Peristeen G Intervention Comparator n/a	16 patients with NBD from 1 centre in France. 10 women and 6 men, mean age 49 years. Underlying neurological pathology was: spinal cord injury[redacted]), MS (4), cerebral palsy (2), spina bifida (2), cauda equine syndrome (1), stroke (1), multiple system atrophy (1). From 2010. G	CCCS,NBDS, satisfaction with peristeen and training using a score 1-10. All conducted by telephone interview. G	62.5% still using Peristeen after 2.6 years For 10/16 who continued use: No significant difference in laxative consumption after treatment. 77.8% of patients reported technical problems. 85.7% were balloon bursts. Mean patient satisfaction 9.12/10. Mean satisfaction with education 8.66/10. 1 AE, occurrence of rectorragia at beginning of treatment. For patients who stopped using Peristeen:1 subocclusive episode requiring emergency consultation.	6 w/d (4 at 1month, 1 at 3 months, 1 at 23 months, mean 5 months) 2 patients found it too time consuming or difficult to use 1 vomiting after administration 3 stopped because of inefficacy.	The first patients in the centre to use the device. Possible learning curve effect. Small patient group. Main outcomes not compared to baseline data. Outcomes reported only for those who continued with the treatment (10/16). High risk of bias.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Kim (2013)	Prospective observational study of Peristeen G Intervention Comparator n/a	52 patients with NBD secondary to SCI 41 men and 11 women, mean age 44.5 years, from 3 hospitals in South Korea.2010-2012. G	A locally designed questionnaire administered by telephone interview at 1, 3 and 6 months after initiati A of Peristeen.	33/52 reported problems at 1 month. Most common was expulsion of catheter (n=25). adverse effects (n=15), abdominal pain was most common (n=9).	34 withdrew. Use of Peristeen was 31 (59.6%) at 1 month, 25 (48.1%) at 3 months and 18 (34.6%) at 6 months.	Post-hoc comparison of compliant with non-compliant patients introduces bias. Outcomes are not validated. The study was partly supported by Coloplast Korea.
Loftus (2012)	Prospective before and after study of Peristeen with follow-up at varying times between 3 and 28 months. G Intervention Comparator n/a	11 patients with a spinal cord injury (n=9) or spina bifida (n=2) and neurogenic bowel dysfunction from a single centre in Ireland. 4 women and 7 men, mean age 44 years. 2007-2009 G	CCCS, FIGS, NBDS Adverse events. G	Mean CCCS, FIGS and NBDS significantly improved from baseline to follow-up. Significant reductions in bloating ($p<0.05$) and abdominal pain ($p<0.01$) Adverse events included burst balloons (n=NR). 1 patient suffered a clostridium difficile infection. Authors noted that after the study period, one patient had a perforated bowel resulting in sepsis leading to treatment in intensive care and colostomy.	0 w/d	2 (of 11) patients completed the baseline questionnaires retrospectively after treatment had started. Variable follow-up periods. Very small study size.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Nafees (2016)	Prospective discrete choice study for patients from a panel of Peristeen users. Survey completed online. Intervention G Comparator n/a	143 UK participants, 48 with SCI, 69 with MS, 12 with SB, 14 excluded. Mean duration of condition 18.7 years. G	Locally written DCE, plus CCCS and FIGS, EQ5D3L A	98% of patients surveyed currently use Peristeen, with 42% using for 4+ years. There are no comparative results reported. The most important attributes for patients were FI (OR 5.18), risk of UTIs (OR 3.43) and frequency of use (OR 4.69).	14 excluded due to failure on consistency check	Patients chosen from a panel of peristeen users may introduce selective bias. Data only from people who are committed users of device, but does give longer term information SD is large for some outcomes, variability between patients. Data is patient reported, in some cases requiring recall over the last year.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Passanant i (2016)	Prospective case series with a minimum 1 year follow-up. Consecutive recruitment Intervention G Comparator n/a	49 patients with Multiple Sclerosis (MS) were treated with Peristeen, 2008-2013. 37 women (76%),12 men (24%), mean age 51 years, from 2 UK centres. All patients were over 18 years with a confirmed diagnosis of MS and neurogenic bowel disease for at least 6 months. Comparison with data from year prior to introduction of Peristeen. Additional comparisons between patients who continued to use Peristeen and those who stopped. G	Anorectal physiology, EQ5D3L, EQ-VAS, NBDS scores, resource utilisation (patient reported). G	Mean EQ5D utility declined over time for all patients. Patients continuing to use Peristeen showed an increase in EQ-VAS from 44.5 at baseline to 63.4 at latest follow-up. Patients who stopped using Peristeen showed a decline in EQ-VAS from 44.5 to 41.9. Patients who continued with Peristeen improved their NBDS scores, with a shift from more to less severity. Reduction in UTIs per year, number of hospitalisations, need for assistance, and visits to GP, specialist or dietician.	22 w/d from Peristeen treatment. 12 disliked treatment, 3 reported insufficient effect 2 developed adverse events, 1 technical problems (burst balloon, prior to 2011 design change), 2 developed other pathology preventing irrigation, 2 lost to follow up.	Using the patients who discontinued Peristeen as a comparator group introduces selection bias. Potentially those where MS has progressed more are more likely to cease use, and would therefore have lower scores over many areas. Duration of follow-up was variable with a mean of 40 months.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Preziosi (2012)	Prospective before and after study of Peristeen with 6 weeks' follow-up. Intervention G Comparator n/a	30 patients with MS from a single UK centre. G	CCCS and CCIS (described in paper as Wexner Constipation score; Wexner incontinence score); SF-36 Telephone interview at 3 months and 6 months for those still using Peristeen. G	CCCS and CCIS improved significantly baseline to 6 weeks No significant improvement in SF-36.	7 w/d prior to use of Peristeen 4 patients withdrew after the training session, 1 experienced worsening of MS and stopped irrigation, 2 were lost to follow-up. No information on withdrawals after Peristeen was started.	In post-hoc analysis the cohort was split into 16 'responders' (at least 50% improvement in at least one of the Wexner scores) and 14 'non-responders'. 3 month and 6 month follow up only reported for responders. Patients withdrawing before use of Peristeen were excluded from analysis. Patients who ceased use of Peristeen were included as ITT.
Rosen (2011)	Prospective before and after study of Peristeen G Intervention Comparator n/a	14 patients with anterior resection syndrome (ARS) following surgery for rectal cancer from 2 centres, 1 in Austria and 1 in Switzerland. 11 men and 3 women, median age 68 years. Median follow-up 29 months.2006-2009 G	SF-36, ASCRS questionnaire, Cleveland incontinence score (CIS). G	Mean CCIS and ARCS was significantly improved. SF-36 significantly improvement in the mental component. No significant difference for physical component. Significant decrease in mean defaecations during day and night.	[redacted]	SF-36 not reported as overall score. Small number of patients.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Whitehouse 2010	Prospective case series Intervention G Comparator n/a	113 patients with functional bowel disorder (FBD), 96 female, 17 male. Mean age 54.7 years (range 17-83 years. Mean length of follow up 42 months (7-84 months). Single centre in UK. 2001-2 G.	FIGS, patient symptom linear analogue score (PSLAS), history of frequency, success, use of laxatives. Follow up at 6 week, 3 month, 6 month, 12 month, varied according to patient need. G	Significant improvement in PSLAS score for all patients, and sub-groups of patients, grouped by main symptom of FI, Constipation and evacuatory disorder. Other results were not reported.	152 initially identified, but 39 did not receive Peristeen, or were lost to follow up. These were not included.	High risk of bias in results as one of main outcomes not reported. No ITT used, not known which of 39 excluded patients received treatment. Unclear if patients are still using Peristeen, or at what time point results were recorded.

Table B2 Included paediatric studies

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Alenezi (2014)	Prospective case series of Peristeen from 2006-14.	18 children due to undergo reconstructive bladder surgery and the Malone antegrade continence enema (MACE) procedure 11 girls, 7 boys, average age 7.6 years (range 4-15) From a single centre in Saudi Arabia	Successful response to Peristeen defined as complete dryness from stool soiling with minimal or no constipation. Diaper independency, patient and parent satisfaction, weekly frequency of Peristeen use	Mean post-operative follow-up 49.6 months 15 patients (83%) had a successful response, and had bladder surgery without MACE.3 patients(17%) had a poor response. 8 patients (44%) were able to stop using diapers. 1 patient had difficulty retaining the Peristeen system in the rectum during use, 4 patients had mild transient abdominal discomfort.	3 patients did not use Peristeen	Limited baseline data on participants. Limited reporting of results. Small sample
Ausili (2010)	Prospective observational before and after study of Peristeen with 3 months' follow-up	60 children with myelomeningocele 31 boys and 29 girls, mean age 12.5 years (range 8-17) referred to a single centre in Italy.	NBDS, patient satisfaction, time for bowel function, use of oral laxatives, use of manual extraction, frequency of urinary tract infections (UTI), adverse events	Significant improvement in mean NBDS, use of manual extraction, suppositories or enemas and use of oral laxatives, frequency of UTI. No severe AE recorded.	2 w/d (62 started the study).	Short follow up time.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Corbett (20114)	Retrospective case note review of Peristeen from 2006-2013 and quality of life assessment.	24 children with faecal incontinence secondary to myelomeningocele (15), Hirschsprung disease (4) and anorectal anomalies(5). 13 boys and 11 girls, median age at consent 6 years (range 4-16) from 1 UK centre .	Interview with primary carer using FICQOL questionnaire Stool frequency Frequency of incontinence Proportion of motions in toilet Need for pads to control incontinence of stool, impact on child and carer's lives.	Median follow-up was 1 year Significant improvement in median for: quality of life, stool frequency, soiling frequency, proportion of motions in the toilet, time attending to bowel habit. Of those using Peristeen at the end of the study, the number using pads fell (18/19 vs 10/19) Only 3/19 used the device entirely independently.	3 w/d almost immediately, due to burst balloon, abdominal colic or dislike of system. A further 2 patients stopped using the device as its use failed to improve continence.	

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Kelly (2016)	Prospective observational before and after study of Peristeen with 6 months' follow-up	24 patients with NBD secondary to spina bifida, 11 male and 13 female, mean age 10.5 years (range 3 – 21)at a single centre in the USA. 2014-2015.	NBDoS at baseline and 2 weeks, 2 months and 6 months after Peristeen started.	Significant improvement in mean NBDoS at 2 weeks, 2 months and 6 months.	24 (100%) NBoDS scores were recorded for: 24/24 (100%) at 2 weeks, 10/24 (42%) at 2 months 12/24 (50%) at 6 months. All patients reported continuing to use the device at 6 months.	Most common reasons for lack of follow-up were reported as difficulty attending appointments or disconnected phone lines. 16/24 patients were using cone enemas prior to Peristeen. NBDoS validated for paediatric patients Range of scores was calculated by EAC to be 0-41 based on reported questionnaire.
King (2016)	Retrospective case series with questionnaires of Peristeen between January 2006 and July 2013	33 patients with spina bifida in whom Peristeen was tried were identified. 20 families could be contacted and interviewed. Of the 20 children 11 were boys and 9 girls, mean age 14.5 years (SD 5.3). at time of follow up. Patients treated at 2 centres in Australia.	FIQOL,FIGS, CCCS, NBDS	Mean follow-up was 4.1 years (range 1-8 years). No significant difference in FIQOL,FIGS, CCCS, NBDS between those still using Peristeen and those who stopped.	11/20 patients (55%) had stopped using Peristeen	Comparison of those still using Peristeen with those who stopped using it is biased. Large proportion who could not be contacted introduces further bias.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Koppen (2017)	Cross-sectional study between March 2014 and October 2014	67/91 parents of children with intractable functional constipation treated with Peristeen. Mean age of children 11.2 years (4-19yrs)	Use of Peristeen, gastrointestinal symptoms, concomitant medication use, parental satisfaction,	Median duration of use 11 months (1 – 36 months). 22 (33%) children used daily, 15 (22%) used it every other day, 18 (27%) had stopped use. 50% of children used concomitant medication. Prior to treatment 56 (84%) children had occasional episodes of faecal incontinence which had resolved completely in 28 (42%) after treatment, 8 (12%) had < 1 episode/week and 47% ≥1 episode/week. 28 (42%) children experienced pain. 38 (57%) parents reported that rectal irrigation was a feasible treatment. 45 (67%) reported that would continue with Peristeen use.	24/91 (26%) parents did not respond to survey. 18/67 (27%) had stopped using Persisteen	Questionnaire was not validated. Single centre. Differences between users and non-users not investigated.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Marzheuser (2016)	A prospective case series of Peristeen with up to 4 years' follow-up.	40 children with incontinence and faecal soiling secondary to anorectal malformations, mean age 10.95 years at a single centre in Germany. 18 patients as comparative cohort, using other irrigation methods (gravity, electric pump, foley catheter) Median duration 3 years (1-4 yrs)	Soiling, time needed for irrigation, time interval between irrigations	At 12 months, 32 patients (80%) were free from soiling. Significant improvement in median soiling frequency and time for irrigation. The median number of irrigations per week fell (7 vs 3, $p<0.001$). 30/38 were using Peristeen independently(79%). The remainder were all younger than 7 and needed at least some help from carers.	2 patients did not follow the therapeutic regime.	Comparative cohort is out of scope.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Midrio (2015)	A prospective observational before and after study of Peristeen with 3 months' follow-up	83 patients were recruited and 78 completed (41 with anorectal malformations and 37 with spinal cord lesions) aged between 6-17 years from 8 centres in Italy.	Bristol stool score, Local, unvalidated questionnaire for bowel function, Quality of life using SF36 and CHQ-pf50. Adverse events.	Improvements in constipation, incontinence, symptoms during evacuation, daily incontinence to flatus, use of laxatives, evacuation on lavatory and need for carer assistance. Significance was not reported. QoL significant improvements for: Younger patients: most components of CHQ-pf50 For 12-17 yr olds, usingSF36: SCI group: significant improvement for all aspects except bodily pain (9/10). ARM group: only bodily pain, physical component and mental component (3/10) showed significant improvement. Most frequent complications were burst balloon, faecal leakage during irrigation, no useful effect and balloon expulsion.	5 w/d due to difficulty obtaining device through national health system.	SF36 is intended for adults aged 18+ CHQ-pf50 is validated for children >5 years, but should report summary statistics not separate outcomes. Significance not reported for all outcomes.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Nasher, 2014	Retrospective, case series. Mean follow up 21.2 ±0.9 months.	13 patients referred to a single UK centre who would otherwise been offered ACE surgery, 10 treated with Peristeen. 7 boys, 3 girls. 7 with chronic idiopathic constipation (CIC), 2 with Hrischsprung's disease (HD), 1 with anorectal malformation (ARM). Mean age 11.1 ±2.7 years. 2010-2012	Faecal continence scoring system by Rintala 1995,	Mean length of use of Peristeen 12.6 months, mean follow up 21.2 months. Significnant improvement in mean Rintala score. No complications recorded, no patients required ACE procedure.	3/13 were excluded as they found procedure uncomfortable or disliked it.	Continence score reported as validated, but validation method not identified in paper. No rationale for using this scale given. Patients with neuropathic bowel dysfunction excluded.
Pereira 2010	Prospective before and after observational study of Peristeen. Mean follow up 12 months (4-8)	40 children with spina bifida and neuropathic bowel dysfunction enrolled in a single centre in Spain. 35 completed study, of which 18 boys and 17 girls. Mean age 12.5 years (range 6-25). 28 patients had myelomeningolcele.	Locally designed questionnaire	Significant improvements in all aspects of questionnaire – pain, feeling of incomplete evacuation, sweating/headache during defecation, leakage of faeces. These are not comparable to other studies, as non-standard questionnaire.	5 did not complete the questionnaire	Non-validated questionnaire. No information on reason for 5 withdrawals. Time point for questionnaires not stated. Paper describes patients as children, but ages are up to 25 years.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Pacilli, 2014	Retrospective case series of treatments over 5 year period.	23 children treated at a single centre in UK. Median age at start was 7 (2-15) years. Median follow up 2 (0.7-3.4 years). Diagnoses were 11 with spina bifida, 6 with anorectal anomaly, 1 with Hirschsprung's disease, 5 with other complex anomalies. 2007-2012.	General satisfaction, side effects during treatment, use of laxatives.	17% (4/23) stopped using Peristeen due to difficulties and pain on insertion of catheter and expulsion of catheter during irrigation (n=2), persistant soiling (n=2), requirement for more than 2 uses daily (n=1). 13% (3/23) reported mild discomfort and abdominal pain, but remained using Peristeen. No serious adverse events relating to Peristeen were reported.	4 stopped using Peristeen during study period, due to: Difficulty/pain (n=2), Persistant soiling (n=2), Need 2+ uses daily (n=1).	No validated survey used. Very limited reporting of outcome results, and collection methods. Before and after comparisons not reported.

Appendix C Patient reported outcome measures

CCCS Cleveland Clinic constipation scoring system. Also known as Wexner constipation score.	A scale of constipation severity including impact of symptoms on the patient's life. Scores range from 0 to 30, with higher scores representing more severe symptoms. Widely used, validation compared to physiological measures identified.(Agachan et al.,1996).
CCIS Cleveland Clinic Incontinence Score. Also known as Wexner incontinence score	The CCI Score takes into account the frequency of incontinence and the extent to which it alters a person's life. . Scores range from 0 to 20, with higher scores representing more severe symptoms. Widely used, but no formal validation identified. (Jorge et al., 1993)
FIGS or SMFIGS St Mark's fecal incontinence grading system	A scale of incontinence severity including the impact of symptoms on the patient's life. Scores range from 0-24 with 24 most severe. Widely used and validated for use in adults, specific diagnoses not specified (Vaizey et al., 1999).
NBDS Neurogenic bowel dysfunction score	Ten questions on bowel dysfunction symptoms. Questions do not ask about the impact of symptoms on the patient. Scores range from 0 – 47, with 47 most severe. Widely used, validated for use in patients 15+ years with SCI. (Krogh et al., 2006). It has also been used in other patient groups. Translated into several languages. Available on Coloplast website.
ASCRS American Society of Colon and Rectal Surgeons fecal incontinence score	Symptom related QoL score, with 4 subscales for lifestyle, coping behaviour, depression, embarrassment. Each on a scale of 0-4 with 4 most severe. No information on validation identified.
FICQOL Fecal Incontinence/ Constipation Quality of Life	Reports on the impact on quality of life for both children with spina bifida and caregivers. Information on bowel care regimen, functional outcomes, 19 scaled questions on impact of incontinence on child's and carer's lives. Validated for children with spina bifida. (Nanigian et al., 2008)
FIQOL Fecal Incontinence Quality of Life	29 items in 4 QoL scales, including lifestyle, coping/behaviour, depression/self-perception, embarrassment.

	Adults 18+(Rockwood et al., 2000)
Fecal continence score/ Rintala Score	Score to determine the severity of fecal incontinence in children. Scores range from 0-20 with 20 most severe Refered to as validated, but original paper does not appear to contain validation (Rintala et al., 1995). Developed for use in children who had undergone surgical repair for anorectal anomaly.
NBDoS Neurogenic bowel dysfunction score	Score to determine the severity of bowel dysfunction in children, and impact on quality of life. Score range is not explicitly stated. 15 questions, with varying levels of response for each question (0-4). EAC calculated possible range of scores to be 0-41, with 41 as worst health. Validated for children with spina bifida (Kelly, Hannan et al. 2016)
CHQ-pf50 Child Health Questionnaire Parent Form	A generic quality of life score, containing 50 items. Proxy administered (by parent) Paediatric, 5-18 years. Self-administered youth form also available. Score is 0-100, with 100 the best quality of life possible. . Widely used, and validated (Landgraf et al .,1999)
SF-36 Short Form Health Survey-36	Generic quality of life score. Self administered or by interview.For use in adults 18+ Scores 0-100, with 100 as best health. Very widely used, and validated (McHorney et al,. 1994)
EQ5D3L EuroQoL-5D	Generic quality of life score. With 243 health states descriptive with 5 dimensions, each with 3 levels– mobility, self-care, usual activity, pain/discomfort, anxiety/depression. Scores are used with a validation set for the appropriate country to give a final value of 0-1 with 1 the best possible quality of life. Patient reported outcome, self administered or by interview. For use in ages 12+ Generic across clinical areas, very widely used and validated. (The EuroQol Group 1990)
EQ5D-VAS EuroQoL-5D Visual Anologue Scale	Scores 0-100 where 100 is perfect health. Part of the EQ5D questionnaire.

Appendix D Costs and resource use as submitted by the company

Value	unit size	Cost per unit	Resource use	Weekly cost per patient, where applicable	Source
Peristeen					
System	1	£74.78	1 per 6 months	£2.87 Peristeen only	NHS Electronic Drug Tariff, June 2015
Catheters (15 in pack)	1	£130.33	1 per month	£29.96 Peristeen only	NHS Electronic Drug Tariff, June 2015
Initial consultation	1 hour	£142.00	1 at start of Peristeen use	n/a	Consultant visit, PSSRU 2014
Follow-up phone call	1 hour	£100.00	3 x 15 min at start of Peristeen use	n/a	Nurse, day ward, PSSRU 2014
Standard bowel care	**See note below for explanation of frequency calculation**				
Bulking agent: Fybogel sachet (3.5g)	30	£2.29	2.8 sachets per day for those using	£0.88 Peristeen £0.14 SBC	Fybogel 3.5g sachet, BNF 69
Softener: docusate	100	£6.98	430mg per day for those using	£0.71 Peristeen £0.65 SBC	Dioctyl 100mg, BNF 69
Stimulant: bisacodyl	100	£3.43	16mg per day for those using	£0.34 Peristeen £0.45 SBC	Bisacodyl 5mg tablets, BNF 69
Osmotic: Movicol (13.7g sachet – EAC Comment)	50	£11.13	2.9 sachets per day for those using#	£3.01 Peristeen £0.77 SBC	Movicol oral powder, BNF 69
Suppository glycerine	12	£1.94	1.4 every other day for those using#	£0.59 Peristeen £0.49 SBC	Glycerol 4-g mould, BNF 69
Suppository bisacodyl	12	£1.57	1.0 every other day for those using#	£0.02 Peristeen £0.04 SBC	Bisacodyl 10mg suppositories, BNF 69

Enema	1	£0.66	1.2 every other day for those using#	£0.50 Peristeen £0.28 SBC	Norgalax 10-g unit, BNF 69
Anal plug	20	£44.89	1 per day + 1 per episode of faecal incontinence for those using#	£7.65 Peristeen £10.11 SBC	NHS Electronic Drug Tariff, June 2015
Incontinence pad	7	£5.95	1 per day + 1 per episode of faecal incontinence for those using#	£28.30 Peristeen £37.49 SBC	Retail price provided by Coloplast
Off-label					
Lubiprostone	56	£53.48	Not used in model	Not used in model	Amitiza 24ug,BNF 69
Prucalopride	28	£59.52	Not used in model	Not used in model	Resolor 2mg, BNF 69
3rd line treatment	Patients going to 3rd line treatment are given a 33% probability of going to either of the three treatments				
SNS initial procedure	per episode	£9,368.00	Procedure cost	n/a	NICE 2013, inflated
SNS follow up	1 hour	£6,286.00	Follow up, description not given, occurs once in 7 years	£17.40	NICE 2013, inflated
SARS initial procedure	per episode	£7,770.00	Procedure cost	n/a	Dagenais 2013 (10,500 EUR converted to GBP at 1 EUR=0.74 GBP and inflated)
SNS outpatient appointment	1 hour	£118.92	Follow up every two months	£13.67	Colorectal surgery outpatient attendance, NHS reference costs 2013-14
ACE initial procedure	per episode	£3,870.33	Procedure cost	n/a	Major large intestine procedure, NHS reference costs 2013-14

SNS outpatient appointment	1 hour	£118.92	Follow up every two months	£13.67	Colorectal surgery outpatient attendance, NHS reference costs 2013-14
Stoma					
Surgery	1	£7,459.76	Procedure cost	n/a	Very complex, complex and major large intestine procedure, NHS reference costs 2013-14
Colostomy bag	30	£87.00	two per day	£40.60	NHS Electronic Drug Tariff, June 2015
Belt	1	£6.78	one per month	£1.56	NHS Electronic Drug Tariff, June 2015
Skin barrier	30 applications	£22.24	twice per day	£10.38	NHS Electronic Drug Tariff, June 2015
Adhesive remover	30 applications	£14.96	twice per day	£6.98	NHS Electronic Drug Tariff, June 2015
HCP visits					
Consultant	1 hour	£142.00	Peristeen 0.88/year SBC: 1.04/year	Peristeen: £2.40 SBC: £2.84	PSSRU 2014
Dietician	1 hour	£37.00	Peristeen 0.19/year SBC: 0.57/year	Peristeen: £0.14 SBC: £0.40	PSSRU 2014
GP	1 hour	£234.00	Peristeen 2.89/year SBC: 3.75/year	Peristeen: £12.93 SBC: £16.81	PSSRU 2014
Time spent on bowel management					

Caregiver salary	1 hour	£24.00	Peristeen: 19 min/day for 30% SBC: 26 min/day for 44%	Peristeen: £51.07 SBC: £74.01 SHOULD BE: Peristeen: £16.17 SBC: £32.07	PSSRU 2014
AEs					
2nd line					
UTI (responding to initial treatment)	per episode	£167.77	Peristeen: 0.67/year SBC: 1.37/year	Peristeen: £2.17 SBC: £4.41	Bermingham 2013[46]
Overall hospitalisation			Peristeen: 0.28/year SBC: 0.63/year		
Gastrointestinal infection	per episode	£1,998.84	20% of hospitalisations	Peristeen: £2.16 SBC: £4.86	Gastrointestinal infection, NHS reference costs 2013-14
Pressure ulcer management	per episode	£26,188.26	20% of hospitalisations	Peristeen: £28.30 SBC: £63.68	Grade 4 pressure ulcer, SCNs High Impact Action Steering Group 2010, inflated
Falls or other trauma	per episode	£2,326.32	20% of hospitalisations	Peristeen: £2.51 SBC: £5.66	Falls without specific cause, NHS reference costs 2013-14
Abdominal pain	per episode	£1,432.09	20% of hospitalisations	Peristeen: £1.55 SBC: £3.48	Abdominal pain with and without interventions, NHS reference costs 2013-14
UTI	per episode	£2,485.03	20% of hospitalisations	Peristeen: £2.69 SBC: £6.04	Kidney or Urinary Tract Infections, NHS reference costs 2013-14
L/P		£0.00	Not used in model		Assumption

3rd line		£212.34	once per two years	£2.03	NICE 2013, inflated
Stoma					
Peristomal complications	per episode	£34.89	61% of patients, Peristeen 7.3/year SBC: 1/ year	Peristeen £3.13 SBC: 0.42	Meisner 2012[47]
Hernia complications	per episode	£3,355.69	18% of patients, 3/year	£34.71	Hernia procedure, NHS reference costs 2013-14

Appendix E Additional information submitted by the company

Following enquiries by the EAC concerning the audit data and its use in the model, the company provided an extract of the audit data showing quality of life outcomes and length of Peristeen use. Further queries were made by the EAC concerning calculation of transition probabilities, following which the company submitted an amended model based on 150/227 patients stopping Peristeen use over 6 years, rather than 117/227 previously modelled.

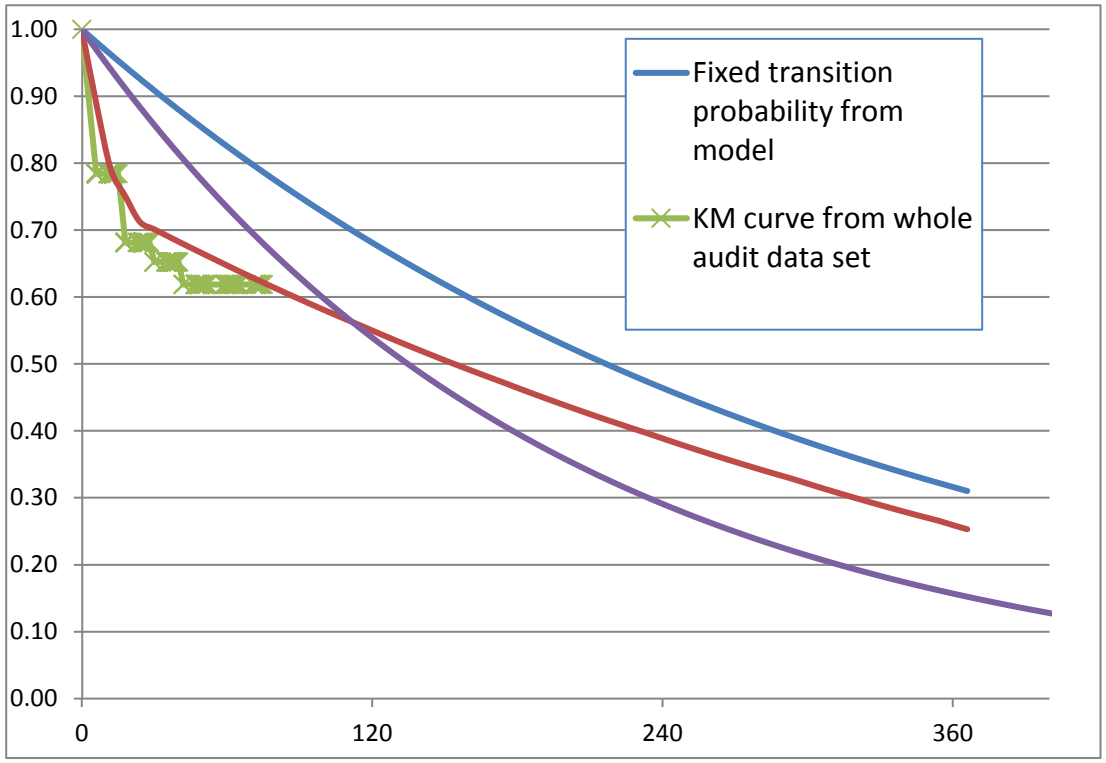
The impact of the altered transition probabilities on the length of Peristeen use that was modelled is shown in figure 8.

The additional model submitted had not been changed to correct the errors identified by the EAC, however when these changes were made (errors 1-8, and cost alterations 11 and 12, in table 15) the result was:

	Peristeen	Standard Bowel Care	Cost saving per patient
TOTAL	**£96,157**	**£99,248**	**-£3,092**

The EAC felt that the variable transition probabilities used in the EAC base case were more appropriate, and no changes were made to the EAC base case or sensitivity analysis.

Figure 8. Effect of different transition probability calculations


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
120
240
360
Fixed transition probability from model
KM curve from whole audit data set

Appendix F Trials identified at Clinicaltrials.gov

ID Number	Status	Title	Condition:	Intervention	Notes
NCT0178432	Completed	Peristeen Bowel Irrigation System in Cauda Equina	Cauda Equina Syndrome	Peristeen Bowel Irrigation System	Single-armed study.
NCT00286520	Completed	Treatment of Faecal Incontinence and Constipation in Patients With Spinal Cord Injury	Constipation, Faecal incontinence, Spinal Cord Injury	Transanal irrigation with Peristeen Anal Irrigation	Included in submission – Christensen 2006
NCT01059370	Completed	Autonomic Dysreflexia in Spinal Cord Injury	Autonomic dysfunction, Spinal cord injury	Bowel emptying	Included in submission – Faarborg 2014
NCT01313026	Recruiting	Treatment of "Low Anterior Resection Syndrome" by Percutaneous Nerve Evaluation and Transanal Irrigation	Rectal Cancer	Intervention: Procedure: Percutaneous nerve evaluation	Randomised crossover trial. Estimated completion date Dec 2019

Appendix G Quality appraisals

Quality appraisal forms are from the following source: Specialist Unit for Review Evidence (SURE)Questions to assist with the critical appraisal of cohort studies[1]

Citation: Chan 2011 *Are there other companion papers from the same study? Don't know*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	**Somewhat.** Not described as a cohort study but as a prospective data collection. Analysis used before-and-after intra-patient comparison. Not clear whether analyses were planned *a priori*.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	**Yes.** P: patients presenting with chronic constipation and/or faecal incontinence (who did not respond to conservative management and in whom surgery was not indicated) E: Instruction in use of rectal irrigation system (may not be Peristeen) C: intra-patient before-after comparison O: CCCS (constipation) & CCIS (incontinence) scores; patient satisfaction; adverse effects
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	**Yes.** Single site, joint functional bowel clinic. Attendance 1/6/05-13/8/09. Outcomes measured after 6 months at OP review. Available for follow-up = 83% constipation group; 65% incontinence group.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	**Can't tell.** Inclusion and exclusion criteria were not specifically defined. May have been bias in patient selection due to subjective inclusion criteria and single consultant/nurse decision-making. Some patients lost to follow-up.
5. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	**Yes.** Baseline table includes age, sex, and predominant symptoms (constipation or

	faecal incontinence). Main analysis was intra-patient comparison so baseline not too important.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	**Exposure:** No record of timing/frequency of (self-administered) treatment. **Outcomes:** CCCS/CCIS are apparently validated measures, but are subjective. But definitions of "success/improvement" relied on arbitrary thresholds.
7. Was bias considered? e.g. recall or selection bias	**Somewhat.** No apparent consideration of selection bias or attrition bias. Acknowledged small numbers when referring to subgroups.
8. Is there a description of how the study size was arrived at?	**No**. All eligible patients presenting to a single clinic over 4 years (n=91). Acknowledged small sample size when referring to subgroups.
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	**Possible error in interpretation**. Authors describe use of non-parametric tests (Wilcoxon's signed ranks), but report mean scores (without SD or confidence intervals).
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	**Some.** • 271 patients reviewed in clinic. • 91 eligible for inclusion (60 constipation; 32 faecal incontinence) • 70 included in follow-up (50; 20) at six months. No details about the 21 patients lost to follow-up. • 37 discontinued treatment (25: 12) – not clear after how long.
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	**No.** • Poor reporting of statistical results (no SD, median/IQR, confidence intervals). • Pre-treatment scores seem to include patients for whom post-treatment scores were unavailable (n=21; 23%). Unlikely to be a fair comparison (patients with poorer outcomes are more likely to have withdrawn).

	• Authors claim that this study demonstrates that rectal irrigation "is effective in managing the symptoms of chronic constipation and faecal incontinence", despite more than half of patients discontinuing treatment due to lack of improvement!
12. Is any sponsorship/conflict of interest reported?	"The authors have no conflicting interests to declare"
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	The only limitation reported by the authors was the small subgroup samples precluding statistical analysis.

Citation: Christensen 2006	
Study Design: RCT	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Patients with spinal cord injury with neurogenic bowel dysfunction Transanal irrigation (Peristeen) Conservative bowel management (best supportive bowel care without irrigation) CCCS & St Mark's fecal incontinence grading system scores (composite primary outcome).
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Yes Yes
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	Computer-generated sequence obtained from opening a sealed numbered envelope.
3. Was allocation to intervention or comparator groups concealed?	Yes
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	"The randomisation sequence could not be previewed".
4. Were participants/investigators blinded to group allocation? If NO,	No. "Due to the nature of the two interventions, any blinding was impossible"

	was assessment of outcomes blinded?	Outcome data was obtained by “an independent observer who had not participated in the training of the subject”; this person did not appear to have been blinded to group allocation.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Can’t tell Not clear whether patients using Peristeen were also provided with other bowel care eg advice regarding diet, fluids and physical activity.
6.	Was ethical approval sought and received? Do the authors report this?	Yes “It was approved by the local research ethics committees”.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Can’t tell No reference to protocol in this manuscript.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Somewhat Baseline outcomes were not statistically dissimilar. Baseline demographics were tabulated without statistical comparisons, but there was an “apparent imbalance” of mobility (wheelchair use = 29/42 intervention; 40/45 control). Authors reported outcomes separately by mobility status, but not in the overall study conclusions. Looks like only those confined to a wheelchair/bed actually benefitted (see table 4).
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Yes Power calculation for primary outcome (combined outcome of constipation + incontinence scores). Needed 80 pts (min 10 per centre). n=87 (ITT); n=81 (PP).
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	 Yes Can’t tell. “Data were analyzed on an intention-to-treat basis” “missing data at termination were substituted with baseline data from the same patient” 10-week follow-up (last 4 weeks included in efficacy analyses; all 10 weeks in safety analyses). Patients “were contacted” each week during follow-up to complete a short, structured questionnaire – not clear how contact was made.

11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Yes ITT analysis. Used last observation carried forward for missing outcome data. In their later publication (Christensen 2008), the authors state that "data from the main study were not corrected for possible confounders" (referring to the finding that immobilised patients showed the greatest improvement in faecal incontinence).
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	St Mark's fecal incontinence scoring system not validated in spinal cord injury patients. Some subjective outcomes used (eg "patients were asked for their level of dependency with actual bowel care"). Device problems (eg burst balloons) were only reported voluntarily in a "space left for comments in the questionnaire" – may be underreported? Some outcomes (frequency of UTI; use of laxatives etc) were only reported in the discussion section, without supporting data.
13. Is any sponsorship/conflict of interest reported?	Study was "Supported by Coloplast A/S" (Peristeen manufacturer). No further declarations were reported.
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Authors refer to potential "information bias", because "many of the patients had struggled with bowel dysfunction for years" and "were offered an opportunity to try transanal irrigation as a novel and attractive solution". In the discussion, the authors note that "the inclusion criteria used selected patients experiencing more severe problems with bowel care. However, many spinal cord-injured patients achieve adequate bowel function with laxatives and digital stimulation alone".

Citation: Christensen 2008 Are there other companion papers from the same study? Yes. Subjects previously participated in the Christensen 2006 RCT	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Not very clear initially, but was able to unpick that this was a intra-patient

	before-after study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	Yes Patients with spinal cord injury and neurogenic bowel dysfunction Transanal irrigation (Peristeen) Intra-patient comparison with conservative bowel management Change in bowel function (CCCS, FIGS & NBD); factors predicting outcome Primary outcome is not specified
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Yes Patients recruited from 5 spinal cord injury centres in 5 European countries (listed in Table 1). 42 patients underwent transanal irrigation for 10 weeks as part of the (previously reported) RCT, with recruitment between Dec 2003 & June 2005. 20 additional patients underwent transanal irrigation for a 10 week extension period, after having received conservative bowel management as participants in the control group in the RCT. Patients “were contacted” each week during follow-up to complete a short, structured questionnaire – not clear how contact was made.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	Yes Patients were originally recruited to the Christensen RCT (note that only patients experiencing severe problems were eligible to participate in the trial). 20 of 62 patients had received best supportive care for 10 weeks under trial conditions prior to initiation of rectal irrigation treatment.
5. Are participant characteristics provided?Consider if: sufficient details; a baseline table is included.	Yes See table 1.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	St Mark’s fecal incontinence scoring system not validated in spinal cord injury patients. Some subjective outcomes used (eg “patients were asked for their level of dependency with actual bowel care”).
7. Was bias considered? e.g. recall or selection bias	May be selection bias. Not clear why only 20 of the 45 patients in the trial control arm were offered transanal irrigation in the extension period.

8. Is there a description of how the study size was arrived at?	No, not for this intra-patient extension. The authors refer to the power calculation from the prior RCT (Christensen 2006) and admit that this "study was not powered to support the multivariate analyses presented in this paper".
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Yes Intra-patient comparison reduces some confounders. Outcomes may be affected by changes in practice over time (though unlikely within a 10 week period). "Data were analysed on an intention-to-treat basis". Used last-observation-carried-forward. It is a limitation that the design did not include a crossover (from intervention to control), which could have improved reliability of the results.
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Yes Details of numbers and reasons for patient withdrawals were provided.
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	There appears to be some contradictory reporting relating to the influence of uncontrolled anal spasms on treatment benefit, however this is not a primary study outcome. Outcomes differed significantly between study centres, suggesting that there were additional confounders which had not been accounted for. The authors do not provide an explanation, except to note that "the lead center, which had the most experience in transanal irrigation, had results in the middle of the range, indicating that the concept of transanal irrigation is transferable to other settings and cultures".
12. Is any sponsorship/conflict of interest reported?	Study was "Supported by Coloplast A/S" (Peristeen manufacturer). No further declarations were reported.
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	This study found that patients who were mobile were more likely to benefit than those who were immobile. This contradicts findings from the main RCT (Christensen 2006). The authors

	attribute this to the fact that “data from the main study were not corrected for possible confounders”.

Citation: Del Popolo 2008 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Multicentre before-and-after study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	P: People with severe neurogenic bowel dysfunctions (NBD) with unsatisfactory bowel management I: Self-administered Transanal irrigation (Peristeen) C: Intra-patient baseline data O: NBD symptoms, QoL. No primary outcome measure specified.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Questionnaire was “hospital administered during initial and control visits” by medical personnel. Not clear how data were collected at follow-up (3 weeks).
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	No specific concerns.
5. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Age/sex reported in main text, other baseline characteristics were reported in table 1.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	The questionnaire was not validated for use in Italian. Many of the outcome measures were subjective.
7. Was bias considered? e.g. recall or selection bias	No
8. Is there a description of how the study size was arrived at?	No (n=36).
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	The McNemar test was used to analyze the ordinal variables and for the before-and-after comparison of dichotomous variables; the Sign test was used for numerical scale variables or value variables (likert scales) and variation for numerical scales (from 0 to 10). Handling of confounders was not addressed, except that “Patients using

	drugs or alternative methods for evacuation discontinued their treatment 7 days before entering the study". Could this have impacted adversely on baseline QoL? This was an intra-patient comparison and therefore some potential confounders would not be relevant.
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	One patient was lost to follow-up (no reason given) and "was accounted for in the analysis using statistical methods" (not specified).
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Numbers of patients giving different responses are presented in tables 3-5; these were reported to be statistically significant (p≤0.001) but without much further detail. Median before/after scores might have been helpful? Some outcomes were reported only as descriptive statistics (eg change in level of dependency).
12. Is any sponsorship/conflict of interest reported?	This research was supported for data analysis by Coloplast Italia.
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	They acknowledge that "only a small number of patients participated in this brief study" and that longer-term follow-up would be of benefit.

Citation: Grainger Pre-publicaton *Are there other companion papers from the same study?*	
	[redacted]
1. Is the study design clearly stated?	[redacted]
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	[redacted]
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	[redacted]

4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	[redacted]
5. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	[redacted]
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	[redacted]
7. Was bias considered? e.g. recall or selection bias	[redacted]
8. Is there a description of how the study size was arrived at?	[redacted]
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	[redacted]
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	[redacted]
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	[redacted]

12. Is any sponsorship/conflict of interest reported?	[redacted]
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	[redacted]

Citation: Hamonet-Torny 2013 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated?	Yes. Retrospective cohort study.
Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	No. "the main objective was to determine the long-term outcome of transanal irrigation with Peristeen and its predictive factors" P: The first patients treated with Peristeen at a single site (for constipation or faecal incontinence) I: Transanal irrigiation using Peristeen (continued use at follow-up, of varying length) C: Patients who had discontinued use of Peristeen at follow-up (varying length) O:Time to discontinuation of Peristeen treatment, reasons for discontinuation, adverse effects, consumption of laxatives, patient satisfaction
Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Location/setting – yes. Treatment was initiated at a single hospital site. Use after discharge differed as some patients were assisted by a nurse and/or family member (at home or in an "institution"), whilst others self-administered treatment. Dates – no: "All patients...since 2010"
Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	No. Simply selected "the first 16 patients treated by Peristeen" [sic] Laxative use was compared for patients who had continued use of Peristeen (n=10), with those who had discontinued use (n=6), for varying lengths of follow-up (overall mean 31 months; SD 18 months; range 7.5-66 months).
Are participant characteristics provided? Consider if: sufficient details; a	Yes. Basic details (age, sex, symptoms, underlying pathology) – see table 1.

baseline table is included.	
Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	No. There was very little control or consistency throughout this study.
Was bias considered? e.g. recall or selection bias	No. Strong likelihood of selection bias.
Is there a description of how the study size was arrived at?	Only that they included “the first patients” who were treated with Peristeen. No sample size calculation, and definitely underpowered.
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	No. Very poor. Only “Quantitative variables were compared using t test of Student and qualitative variables with Fisher test” [sic].
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Some details provided, but the small sample size and variation in lengths of follow-up are important limitations.
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	‘Efficacy’ results (use of laxatives, NBD, CCS) very poorly designed and so would not consider evidence to be robust. May be of use for information about adverse effects.
Is any sponsorship/conflict of interest reported?	“The authors declare that they have no conflicts of interest”.
Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. “Due to the small size of our sample and missing data related to its retrospective nature, our study suffers from a lack of power”.

Citation: Kim 2013 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No

Is the study design clearly stated?	No, described as “a 6-month follow-up study”. Actually a prospective cohort study.
Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	Yes “The aim of this study was to investigate the outcomes of transanal irrigation use by spinal cord injury patients in (South) Korea with the objective of identifying factors significantly related to patient-reported success”.
Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Yes
Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	Yes - no particular concerns. Authors provided statistical information about the differences and similarities between the compliant and non-compliant group.
Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. Demographic (table 1) and baseline data (table 2) were provided for the whole cohort. Demographic and baseline characteristics were compared between compliant and non-compliant groups (table 3).
Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Outcome data was collected by questionnaire. There was no evidence that this was a validated tool.
Was bias considered? e.g. recall or selection bias	Baseline characteristics of compliant and non-compliant patients were compared (presumably to account for any bias). The non-compliant group were those who more often needed assistance.
Is there a description of how the study size was arrived at?	No
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How	Fairly well described. However there was a large number of patients who discontinued treatment, and whose data were not included in the before-after comparison.

loss to follow-up was addressed.	
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Yes – flow diagram with reasons for withdrawals at 1,3, and 6 months.
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Differences between baseline and final measures were only analysed for those patients who continued use of the system for 6 months (18/52, 34%). An ITT analysis is likely to have generated more accurate, and different, results.
Is any sponsorship/conflict of interest reported?	"This study was partly supported by Coloplast Korea".
Finally…Did the authors identify any limitations and, if so, are they captured above?	No.

Citation: Loftus 2012 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated?	"Observational study"
Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	P: Patient with a SCI or spina bifida and NBD who had failed conservative bowel management. I: Transanal irrigation (Peristeen) C: Before-after comparison O: CCCSS, SMFIGS, NBDS
Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Yes. Single site, July 2007-Dec 2009. NB: Two (of 11) patients retrospectively completed their baseline questionnaires as they had already started treatment.
Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed	Lengths of follow-up varied (3-28 months) Intrapatient comparison. All were permitted to use laxatives as

or unexposed.	required, and had access to telephone advice.
Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Basic details. Age, date of onset, and nature of NBD (incomplete/complete SCI & level, or spina bifida) were reported individually for each pt. Also reported total numbers of M/F.
Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Used CCCSS, SMFIGS (not validated for use in these patients), & NBDS. One patient underwent surgery (urostomy) during the study period; Peristeen was stopped temporarily and then restarted (no associated timescales reported).
Was bias considered? e.g. recall or selection bias	Not specifically.
Is there a description of how the study size was arrived at?	No. Small sample (n=11)
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Tests were fairly well described. No reference to missing data or control of confounders. No subgroup analyses reported.
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	More detail about actual lengths of follow-up (distributions) would be useful. We only know that the range was 3-28 months, and that 8 (of 11) patients were followed up between 3-9 months.
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Confidence intervals not reported for the main analyses, but mean, SD and p-values were. It appears that secondary outcomes were only reported where there were significant differences. Some AEs reported. Referred to “burst balloons” but not how many (although gave another reference which may provide more detail about that).

Is any sponsorship/conflict of interest reported?	No, not reported.
Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes – varying lengths of follow-up, and the retrospective completion of baseline data for 2 patients, as mentioned earlier. The authors also suggest that longer-term outcomes would be helpful.

Citation: Nafees 2016 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated?	Discrete choice experiment
Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	P: Patients with NBD (related to SCI, MS or spina bifida) I: Transanal irrigation C: Standard care O: Patient preferences and willingness to pay for identified attributes.
Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	A range of data collection dates would have been helpful but was not reported. Similarly a breakdown of geographical location (within the UK) may have been informative.
Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	"Participants were recruited from a panel that included people who had used Coloplast products at some stage, which could result in possible bias in their experience of Peristeen devices". The study relied upon patients completing a survey online, which required internet access. This was noted by the authors as a possible limitation. "Efforts were made to recruit a representative sample across the UK, including consideration of social stratum".
Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes, demographic (table 2) and clinical (table 3) profiles are provided, as well as details of current care (table 4).

Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	N/A. DCE methods used. EQ-5D-5L, St Mark's FI score and CCCSS were reported in the baseline table (table 2). A consistency check was incorporated into the survey.
Was bias considered? e.g. recall or selection bias	Yes. See no. 4.
Is there a description of how the study size was arrived at?	No. n=129. The authors report "The sample size is relatively limited" and "the sample is too small for reliably exploring differences between the three neurological diseases" (they recommended that the subgroup analyses be treated as exploratory).
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	N/A. DCE methods used. Attributes and levels were combined into choice sets using a published orthogonal array. An orthogonal fractional factorial design was used to identify the minimum specification and the combinations were paired using a fold-over design. Data were analysed using the conditional logit model.
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	N/A. DCE methods used.
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Results are well-described and explained. Odds ratios not reported in the abstract but are fully reported in the full text. Confidence intervals and willingness to pay are fully and clearly reported in the full text.
Is any sponsorship/conflict of interest reported?	Yes. "This study was supported by research funding from Coloplast A/S to ICON plc. However no restrictions were placed on the design of the study, the choice of included data sources, the presentation of results, or the content of the final manuscript". One author had participated in advisory boards for Coloplast and other Peristeen manufacturers. Three

	authors “have conducted this study on behalf of Coloplast”. “The authors report no other conflicts of interest in this work”.
Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes – mostly captured above (sample size, selection bias). The authors also noted that the estimates of “willingness to pay” may have been biased. Their reasoning was that in the UK treatment is usually free at the point of delivery, so “patients do not have experience of making such purchases”.

Citation: Passananti 2016 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated?	Not immediately obvious, but appears to be prospectively collected data used in a before-after study. Also some retrospective cohort aspects.
Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	P: Adults with multiple sclerosis and NBD (which had not responded adequately to lifestyle or optimal laxative therapy). I: Transanal irrigation (Peristeen) C: Before-after intrapatient comparator. Also retrospectively compared those who had discontinued treatment (interrupted therapy, n=22) with those who had not. O: NBDS, EQ-5D (VAS), resource utilisation, predictive factors
Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	Two hospitals in London. July 2008-July 2013. Minimum 1 year follow-up; mean 40 months. Kaplan-Meier plot used to illustrate lengths of follow-up.
Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	Yes. Consecutive recruitment of eligible patients.
Are participant characteristics provided?	Yes. Not tabulated, but narrative description provided for key

Consider if: sufficient details; a baseline table is included.	demographics and baseline measures.
Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Generally, yes. Published protocol available. "All patients were trained to use TAI in a standardized manner by the same clinical nurse specialist". "Adjustments to the regime of irrigation were made by the trainer and patient according to a standardized protocol". The authors indicate that there was an alteration in the balloon and catheter design in 2011. EQ-5D & NBDS both validated tools. Authors note that the generic EQ-5D may not have been sensitive enough for this study.
Was bias considered? e.g. recall or selection bias	"All assessments were collected independent of the trainer to minimize bias". Resource utilization data were based on patient recall, but were validated using electronic patient records.
Is there a description of how the study size was arrived at?	No. n=49. The authors acknowledge that this is a 'modest' sample size. No indication of whether the study had sufficient power.
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Generally yes. Not sure why an unpaired t-test was used, with this being an intrapatient comparison. Perhaps for comparing those who discontinued treatment against those who did not?
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Missing data for anorectal physiology for 1/49 (2%) patients.
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the	Yes.

abstract and the full text.	
Is any sponsorship/conflict of interest reported?	“No funding declared” and “No competing interests declared”.
Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes: No control group ‘Modest’ sample size Absence of stratification for different subtypes of MS (to avoid reducing the power even further).

Citation: Preziosi 2012	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	MS patients with NBD Persisteen Before and after Primary -Wexner Constipation Incontinence scores Secondary – SF-36 health survey
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	N/A
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	N/A
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was	N/A

assessment of outcomes blinded?	
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Good description, no details of other treatments used by patients so assume none
6. Was ethical approval sought and received? Do the authors report this?	Yes
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not reported
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	N/A
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Single centre specialised unit so small sample to recruit from
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Yes, those who discontinued before end of trail were included as 'intention to treat'. 6 month follow-up with interview for those still using Peristeen. No data for those not using.
11. Data analysis Are the statistical methods well described?	No description how ITT data derived.

Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Not a validated score for Wexner Consitipation and Incontinence in MS patients, subjective score SF-36 might not be suitable for MS patients
13. Is any sponsorship/conflict of interest reported?	Funding received from MS Society of Great Britain
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Small sample, no control group

Citation: Rosen 2011	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Patients with low anterior resection syndrome Persisteen Before and after Bowel function & QoL
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	N/A
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	N/A

Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	N/A
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Good description no details if other treatments used as well.
6. Was ethical approval sought and received? Do the authors report this?	Not reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	N/A
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	2 centre study, specialised group so small sample to recruit from(n=14)
10. Were participants properly accounted for? Was follow-up ≥ 80%?	All 14 patients followed-up, all patients followed-up for at least 15 months

Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Adequate
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Subjective measures but unavoidable, QoL questionnaires not validated for this group of patients
13. Is any sponsorship/conflict of interest reported?	Not reported
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Conclusions match Small sample (n=14) but specialised group, subjective measures but unavoidable though not validated for sample

Citation: Whitehouse 2010	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Patients with FBD Persisteen None (before and after) patient symptom linear analogue score (PLAS), faecal incontinence grading system and a review sheet used to collect functional outcomes – not stated if validated
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	N/A
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	N/A
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	

4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	N/A
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Reasonable description but limited details on laxative use or compensatory medicine
6. Was ethical approval sought and received? Do the authors report this?	Not reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not reported
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	N/A
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Reasonable sample size but no power calculation
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Mean length of follow-provided 42 months (7–84) ITT not used, 39/152 were not evaluated (25%)
11. Data analysis Are the statistical methods well	Reasonable

described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Not stated if questionnaire used to evaluate functional outcomes was validated. Conclusions match
13. Is any sponsorship/conflict of interest reported?	Not reported
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Reasonable follow-up ITT not used 25% not evaluated

Studies of children

Citation: Alenezi H et al. 2014 Peristeen anal irrigation Are there other companion papers from the same study? NO	
	Yes/ Can't tell/ No
Is the study design clearly stated? Consider if retrospective or prospective	No – just states prospectively evaluated, no comparison group
Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Yes Population: children with neuropathic bladder & bowel dysfunction Outcomes: response to Peristeen as measured by complete dryness and minimal or constipation, frequency of use, satisfaction, diaper independency
Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Recruitment period: April 2006 to present Follow up 7 – 89months
Are there explicit inclusion/exclusion	Brief – patients intended for

criteria?	reconstructive bladder surgery
Were patients enrolled consecutively?	Not clear
Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Limited detail – age and gender; no table
Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	yes
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	No detail
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Brief details but all patients included
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	Brief details; number and percentage only
Is any sponsorship/conflict of interest reported?	None
Finally…Did the authors identify any limitations and, if so, are they captured above?	Small sample Single centre

Citation: Ausili 2010	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No

Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with myelomeningocele Persisteen No control, Before and after Neurogenic bowel score
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Basic information about intervention, no information regarding if other treatments used
6. Was ethical approval sought and received? Do the authors report this?	Not stated
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants	Not stated

were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample no information on potential number of participants, no sample size calculation
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Data for all participants Follow-up only 3 months
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	reasonable
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Element of subjectivity to answers
13. Is any sponsorship/conflict of interest reported?	Yes - none
14. Finally…consider:	Small sample, lack of control group,

Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	short follow-up

Citation: Corbett P 2014	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with faecal incontinence Peristeen None, before and after Range of functional outcomes
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and	Basic information about intervention, no information regarding if other treatments used

comparison adequate? Was contamination acceptably low?	
6. Was ethical approval sought and received? Do the authors report this?	Yes, reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not stated
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample no information on potential number of participants, no sample size calculation
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Data for all participants
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Basic analysis, Reported as median/range
12. Results Were outcome measures reliable (eg objective or subjective measures)?	Reported as median/range. Consistent reporting

Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	
13. Is any sponsorship/conflict of interest reported?	Yes - none
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Recall bias of questionnaire

Citation: Kelly 2016	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with NGB secondary to spina bifida Persisteen No control Range of functional scores
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	

4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Basic details of intervention, possible compliance issue
6. Was ethical approval sought and received? Do the authors report this?	Not stated
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not stated
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample no information on potential number of participants, no sample size calculation
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Not all patients were available for full follow-up Follow-up for 6 months but only for 10/24
11. Data analysis Are the statistical methods well	reasonable

described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Validated questionnaire used but possible recall bias as subjective. Possible range of scores in questionnaire not stated.
13. Is any sponsorship/conflict of interest reported?	Not reported
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Longer follow-up would be beneficial

Citation: King 2016 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated? Consider if retrospective or prospective	Not clear, but non-comparative prospective follow-up
Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Children with faecal incontinence QoL and functional outcomes
Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes, single centre
Are there explicit inclusion/exclusion criteria?	No, not clear if all potential patients could've been included
Were patients enrolled consecutively?	Not clear
Are participant characteristics provided?	Table provided but displayed as users and non-users

Consider if: sufficient details; a baseline table is included.	
Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Reasonable, validated scores used, but potential for subjective bias
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Reasonable
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Only 20/33 able to be contacted. Good information provided
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	Yes
Is any sponsorship/conflict of interest reported?	None reported
Finally…Did the authors identify any limitations and, if so, are they captured above?	Small sample, possible issue with compliance

Citation: Koppen 2017 *Are there other companion papers from the same study?No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes
3. Are the setting, locations and relevant dates provided?	Yes

Consider: recruitment period; exposure; data collection.	
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Convenience sample from one clinic, specialised group so difficult.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Outcomes self-report but not with validated questionnaire.
7. Is there a description of how the study size was arrived at?	No as convenience sample
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Reasonable
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Only 74% (67/91) responded, no information on those who didn't respond, possible that stopped using Peristeen. 27% (18/67) had stopped using Peristeen.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes
11. Is any sponsorship/conflict of interest reported?	Yes, none
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Children often used other medication but unlikely that this alone accounted for results.

Citation: Lopez Periera 2009	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No

Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with NBD secondary to spina bifida Persitseen No control Bowel function and QoL
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Well described, no details if other methods also used
6. Was ethical approval sought and received? Do the authors report this?	Not reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants	Not reported

were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample (n=35), not clear if all possible participants included
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Follow-up reasonable length (mean 12months)
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Reasonable details
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Reasonable detail and consistent reporting, questionnaire has potential for recall bias
13. Is any sponsorship/conflict of interest reported?	Yes, none
14. Finally…consider:	No other to include

Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	

Citation: Marzheuser 2016		
Study Design: controlled before and after study		
1.	Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
	Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with faecal incontinence secondary to ARM Persisteen Used other irrigation systems Functional outcomes
2.	Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	No
	Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3.	Was allocation to intervention or comparator groups concealed?	No
	Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes
6.	Was ethical approval sought and received? Do the authors report this?	Not stated
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not stated
8.	Were the groups similar at the start of the trial?	I:C – n=2:1; only

Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	compared by ARM
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample (n=40persisteen, 18 control) not clear if all possible patients recruited
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	median follow-up 3 years (1-4)
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	reasonable
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Subjective measures so potential for recall bias
13. Is any sponsorship/conflict of interest reported?	Yes, none
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Yes, small study

Citation: Midrio 2016	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with ARM Persiteen None Bowel function, QoL
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable

Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	
3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Well described, no detail if other methods also used
6. Was ethical approval sought and received? Do the authors report this?	Not reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not reported
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Small sample (n=78), not clear if all potential patients approached, multi-center
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they	3 month follow-up

were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	reasonable
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	No validated Italian questionnaire for bowel function so one was designed
13. Is any sponsorship/conflict of interest reported?	Yes, none
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Lack of validated questionnaire, small sample

Citation: Nasher 2014	
Study Design: uncontrolled before and after	
1. Does the study address a clearly focused question/hypothesis	Yes/Can't tell/No
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Children with faecal incontinence, patients with NBD excluded) Persisteen None (before and after) Bowel function using FC scoring system
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Not applicable
Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	

3. Was allocation to intervention or comparator groups concealed?	Not applicable
Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4. Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Reasonable description, no details if other additional methods used.
6. Was ethical approval sought and received? Do the authors report this?	Not reported
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Not reported
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (eg age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	13 self –selected to enrol in study with 3 excluded, data for 10 patients
10. Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Mean follow-up 21.1 months

11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Adequate
12. Results Were outcome measures reliable (eg objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	Validated scoring system used to assess bowel function and social issues, potential for recall bias but unavoidable.
13. Is any sponsorship/conflict of interest reported?	Yes, none
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Participants self-selected, possible that more motivated and compliant to use Peristeen

Citation: Pacilli 2014 Are there other companion papers from the same study?	
	Yes/ Can't tell/ No
Is the study design clearly stated? Consider if retrospective or prospective	Not clearly stated but identified as retrospective case series
Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Children with faecal incontinence or constipation Satisfaction, presence of side effects
Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes, 2007 – 2012, median follow up 2 years
Are there explicit inclusion/exclusion criteria?	Not stated
Were patients enrolled consecutively?	Retrospective review not clear who selected for Peristeen use

Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	yes
Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Not stated that validated questionnaire used to collect data
Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Only numbers and percentages used
Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	4/23 had stopped using but not clear when stopped using
Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	Lacking detail, 9/23 also using oral laxatives
Is any sponsorship/conflict of interest reported?	Not reported
Finally…Did the authors identify any limitations and, if so, are they captured above?	Small sample