National Institute for Health and Care Excellence

Additional Submission Information

MT315 Peristeen anal irrigation system

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the original manufacturer submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the manufacturer
b) need to check “real world” assumptions with NICE’s Expert Advisers, or
c) need to ask the manufacturer for additional information or data not included in the original submission

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Summary, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request to Manufacturer or Expert Adviser	Response	Action / Impact / Other comments
Questions to company			
Clinical evidence	Are references in papers to a balloon catheter TAI always referring to Peristeen? Discussion of paper (Chan et al, 2011)	The Peristeen was the first TAI using a balloon catheter, and was the only similar device for several years, but in the last 4 years at least 2 other balloon catheter TAI devices have come onto the market. *Later email:* Deborah Chapman has done some investigating and the Chan paper did indeed use Peristeen.	Chan et al. 2011 included in AR. (Information confirmed by authors)
Clinical evidence	Why was Midrio chosen as the only paediatric paper?	The aim of the guideline would be adult population, as all the economic evidence is for adults. The economic model will be focused on the adult population..	None
Economic evidence	What format will the health economic model be?	In Microsoft Excel	None
Clinical evidence	When would the EAC be able to access the Academic in Confidence paper by Grainger?	Will seek permission from the author and share the paper with EAC/NICE *Later email:* Bruno Gallo Santacruz has also just received confirmation from Paul Skaife that we can share the unpublished Grainger et al manuscript with NICE, and that it's currently under review at the journal Techniques in Coloproctology but we don't have any timelines on that submission as yet. I have attached a copy of the manuscript for your information.	Manuscript included as academic in confidence
Economic evidence	In order to assess the model, the EAC would normally thoroughly review the sources of all the inputs. In this case, although the model has been published, the published paper does not include any details of the audit outcomes. We therefore request that you share the audit data with NICE / Cedar, in the form of anonymised patient level	Jeppe Sorensen from Coloplast should be able to send you the data that they do have and he is happy to follow up this up with a phone call to discuss what further data is available. Coloplast will need to discuss this with Dr Emmanuel to make sure he is happy to share the data and what it would take from him/his team to get the data ready for you. We only have the following data on patient level: • patient diagnosis, • age and gender, • time continuing with Peristeen, • EuroQoL-5D	

	data. This would include as a minimum patient diagnosis, time continuing with Peristeen, occurrence of Sacral Nerve Stimulation / Sacral Anterior / Root Stimulation / Antegrade Continence Enema, Stomas, adverse events, UTI, frequency of FI, hospital admissions, visits to GPs, consultants and dieticians, EuroQoL-5D outcomes and mortality,	We do not have individual patient data on the following: • occurrence of Sacral Nerve Stimulation / Sacral Anterior /Root Stimulation / Antegrade Continence Enema, • Stomas, • adverse events, • UTI, • frequency of FI, • hospital admissions, • visits to GPs, • consultants and dieticians outcomes • mortality *Additional email from Coloplast:* I can confirm that we have some of the below mentioned data on individual patient level and I have just written Anton Emmanuel (lead author of the publication + the one who collected the data) to ask for his permission to share it. I will be in touch as soon as I hear back from him.	
Economic evidence	Summary of telephone discussion on the use of audit data in Peristeen model	Coloplast have a spreadsheet of data at individual patient level that includes information such as diagnosis, age and gender, time using Peristeen, QoL and NBDS score. Coloplast are happy to share this with Cedar / NICE subject to agreement from Anton Emmanuel. This has been requested. Other data used in the model such as occurrence of adverse events, stomas etc was not shared on individual patient level with Coloplast during the model creation. This would have to be obtained directly from Anton Emmanuel. Coloplast will contact Professor Emmanuel to request the information, and this is likely to be followed by discussions directly between Cedar and Anton Emmanuel to determine the availability and format of data that can be shared. Megan Dale (EAC) explained the typical EAC process for critiquing the economic model, where both the model structure and formulae are checked as well as the plausibility of the clinical inputs used. Often these are derived from published papers, where the EAC can consider the appropriateness of the population and intervention as well as any sources of bias in the data. Jeppe Sorensen explained that the data on some long term outcomes such as stoma and SNS came from patients who entered	Added some insight into audit data.

		the service prior to the introduction of Peristeen in 2007. Other outcomes for supportive bowel care such as health care professional contacts, UTI frequency came from the baseline patient completed questionnaires for the 227 patients who are in the audit as starting Peristeen. These are then compared with annual questionnaires in following years, when patients are using Peristeen.	
Economic evidence	Follow up email on request for audit data	I have also reached out to my colleague, who is on leave at the moment, and she brought to my attention that Anton has in fact sent us his data also on resource utilization. However, the data is only available on an aggregate level and not on patient level. I have asked Anton for permission to send this data to you directly and I will do so as soon as I hear from him. I have also asked if I can facilitate contact between you and him for further clarification of the data and I will also get back on this as soon as I hear more.	
Economic evidence	Follow up email on request for audit data	Please find attached a Word-document containing the aggregate data on resource utilization and the Excel-file containing data on age, diagnosis, EQ5D, NBD and time on Peristeen. Also, Anton Emmanuel will be happy to help and answer questions.	Sample of the audit data allowed the EAC to carry out survival analysis, but raised further questions on whole data set.
Economic evidence	As you may be aware, and from the email trail below, we have some queries about the audit data used to inform the economic model. Professor Emmanuel, has kindly answered some questions, however there are still points that could be clarified, possibly by someone with knowledge of how the data is used in the model? It would be helpful to know if there are issues with our understanding of how the data is presented	Following your questions to the CEA we have done a review of the data and model and found a discrepancy between the data in the EQ5D-spreadsheat and the data used for calculating transition probabilities in the model. Earlier today we managed to connect with the project director at ICON responsible for programming the model and he is now looking into the data/model and how we might correct any potential errors in calculation of the transition probabilities. We therefore very much hope to be able to respond to all of your questions tomorrow and will get back as soon as we know more. Meanwhile we have tried to answer some of the questions below: *(see subsequent numbered points)*	
Economic evidence	1. In the transition calculations of the model, there are after 6 years, 177/227 still using Peristeen (78%), 18/227 using SBC, 17/227 3rd line, and 15/227 stoma. The report states	Re. difference between MS-patients in the Passananti-paper (49) vs. Anton's CEA-paper (62) We refer to Anton's previous mail that the data set is continuously updated and believe the difference is caused by the different time points at which Anton and colleagues analysed their data-base.	The EAC do not believe that this completely explains the difference in data.

	that this data was from 2007 onwards and contains 62 patients with MS. In the paper by Passananti, 49 patients with MS were recruited from 2008 onwards, from 2 of the 3 clinics (the third is an orthopaedic clinic). In July 2014 there were 27/49 (55%) patients still using Peristeen.		
Economic evidence	I realise that the data may have been extracted at slightly different points in time, but given the difference in results, it would be helpful to have a little more explanation in how patients were included / excluded etc.. The spreadsheet shared by Coloplast also had different numbers of patients ceasing to use Peristeen, as I interpreted it, as well as other differences.	Re. explanation on how patient were included/excluded in the CEA Below we have pasted in a previous version of figure 1 in the published CEA-paper. The version below was submitted in the first version of the paper, but changed into the published version following comments from the journal reviewers. We hope this gives a clearer overview of the included/excluded patients for both the Peristeen and the SBC-population. Following your questions we are now investigating if the patient counts in the post-TAI arm are correctly modelled/reported. *(Diagram included as Appendix 1)*	This improved the EAC insight into how the audit data was used in the model.
Economic evidence	2. Also in the transition probabilities calculations, for failed SBC there are 20/157 who receive 3rd line, and 33/157 who receive stoma. Could you please clarify where this data is from, and how it fits with the 371 NBD patients who are described in the report as being used to calculate occurrence of stoma in the comparator arm?	Re. background of the transition calculations The logic and data used for the transition calculations is hopefully clear from below figure. The 20/157 who receive 3rd line, and 33/157 who received a stoma are part of the total SBC group of 371 patients seen in the three clinics in the pre-TAI period before introduction of Peristeen in 2007. This group is assumed comparable to the total patient population of 537 patients seen in the three clinics post-TAI out of which 227 patients were found to be eligible to Peristeen-treatment, eg. due to their level of bowel dysfunction. To be able to compare the stoma/3rd line treatment-rates pre/post TAI we used the current proportion of eligible Peristeen users out of the total NBD population post-2007 (227/537=42,3%) to assume a comparable population of 157 potentially eligible Peristeen users (0,423*371) pre-TAI if the treatment had been available.	This improved the EAC insight into how the audit data was used in the model.
Economic evidence	I have a further query about the cost of UTI (responding to initial	Re. the £167.77 input value per UTI-treatment referenced from the Bermingham 2013-paper	Enabled EAC to check reference, but Clark (2016)

	treatment) in the model for Peristeen. I have the Bermingham 2013 paper you have referenced for this input. Can you explain how you came to the £167.77 input value?	This reference is indeed incomplete since the costs/method are taken from Bermingham 2013, but the actual calculation comes from a recent paper by Clark 2016 (supplementary material), which is available here: https://www.nature.com/sc/journal/v54/n1/full/sc2015117a.html	does not give an explanation of how the figure was calculated.
Economic evidence	Would you also be able to advise me on the one-way sensitivity analysis? If I take the model as sent, and run the "Tornado" macro, the values in the OWSA sheet change. I had expected them to stay the same (which is what is presented in the report).	The health economist from ICON is also looking into the OWSA and we will get back tomorrow with more information. *Later email:* Stuart has also looked into the OWSA and it should be working in the attached model.	This model was submitted very close to the AR deadline and the EAC did not have time to verify the functions of the complex macro used.
Economic evidence	Pre-TAI, there was a group of 371 patients, out of which 157 would have been eligible for Peristeen if it were available. It was from this group of 157 patients that the data for 3rd line and stoma in the SBC arm was taken Post –TAI, there was a group of 537 patients, out of which 227 were eligible for Peristeen treatment.	Your understanding below is correct and I hope the patient flows are now more clear	This improved the EAC insight into how the audit data was used in the model.
Economic evidence	Further information submitted on model calculations and an updated model submitted.	Stuart Mealing, the project director from ICON overseeing the model has now reviewed the model and confirmed that the wrong patient counts were somehow used for calculating the transition probabilities (177 responders vs. 150 responders over the 6 year period). This explains the discrepancy you noted between the model and the EQ5D-spreadsheet. The transition probabilities have now been updated in the attached version of the model. Because the patients are distributed differently across the states in the revised model the overall model result also changes from a cost saving of -£21.768 to a cost saving of -£40.440. So the analysis still finds that Peristeen is a cost-saving treatment compared to standard bowel care.	This model is critiqued in the AR. The systematic errors identified by the EAC are still present.
Economic evidence	After checking with NICE on protocol, I wanted to let you know that in the last few days we have identified that the model does not fully cost patients	We have shared your findings with Stuart Mealing from ICON, who fortunately returned very swiftly with below mail and attached revised model. Stuart is also available if you have any additional last-minute questions.	This model was not included in the EAC assessment report, as it was submitted 24 hours prior to the EAC deadline. This

	in the Peristeen arm that return to SBC. If the cost of HCP time and adverse events for these patients is included the cost saving is reduced. This I believe explains the large rise in cost saving in the re-submitted model.	Additional updated model submitted	did not leave sufficient time to analyse the changes
Economic evidence	Request from company	We have received the EAC report via NICE, and would like to request if possible the revised version of the economic model. I know that we had some discussion on this over the last couple of weeks, and as it forms a major part of the response we would very much welcome the opportunity to review the EAC modifications in order that we can respond factually to the report. We do have quite a tight deadline to feedback our response (Wed 21st), so would very much appreciate it if you were able to send over,	Copy of model was shared with company for fact check process
Question to authors of paper, Chan et al. 2011			
Clinical evidence	I have read with interest your 2011 paper in Colorectal Disease: "Rectal irrigation: a useful tool in the armamentarium for functional bowel disorders". Would you please inform me of the specific type/s (make/model) of rectal irrigation system which was used for this study?	We used Peristeen and Qufora Toilet at that time	
Clinical evidence	Could I confirm that the data includes information from patients using both Peristeen and Qufora Toilet?	They all used Peristeen Qufora was not available at this time	Chan et al. (2011) was included in AR
Questions to Expert advisor, and author of published economic model			
Economic evidence	As you are aware, Cedar are acting as the external assessment centre for the NICE MTEP for MT315 Peristeen. I have received a spreadsheet of data from Jeppe Sorensen at Coloplast, taken from an audit that you carried out, and that	Thanks for the email. I will try to answer your questions, point-by-point. (*Responses listed below)*	

	was used in your paper: Emmanuel A, Kumar G, Christensen P, Mealing S, Storling Z. Long-Term Cost-Effectiveness of Transanal Irrigation in Patients with Neurogenic Bowel Dysfunction. PLoS ONE [Electronic Resource] 2016;11(8) Having had a look at the audit data that was shared with us, the published paper and the economic model submitted to NICE, I hope that you may be able to clarify a few points. It may be that I am misreading the spreadsheet, and that some simple explanations will suffice.? *Individual points listed below*		
Economic evidence	1. Are the patients with Multiple Sclerosis also included in the paper by Passananti (Long-term efficacy and safety of transanal irrigation in multiple sclerosis. Neurogastroenterology & Motility 2016 Sep;28(9):1349-55)?	1. Some of the MS patients from the Passananti paper are also included in the PLoS paper.	Confirmation of EAC assumption.
Economic evidence	2. This paper (Passananti, 2016) reports outcomes for consultant visits and hospitalisations etc that are the same as the data shared by Coloplast, however the total number of patients with Multiple Sclerosis is different (49 in Passananti, 55 in the audit data, 62 in Emmanuel, 2016).	2. The numbers of MS patients are as reported in the papers cited - the data set is continuously updated, and at each point that we put together the data for a particular paper we would look at the running totals/averages at the time.	The EAC do not believe that this completely explains the difference in data.
Economic evidence	3. Both the audit data and the patients reported in Emmanuel (2106) are a total of 227 patients, however the diagnoses listed do not	3. As above	The EAC do not believe that this completely explains the difference in data.

	seem to be consistent with each other.		
Economic evidence	4. Am I right that the column with the title “Mo since TAI” is the total months since Peristeen was started, regardless of if it is still being used by that person?	4. Correct	Confirmation of EAC assumption.
Economic evidence	5. Also, where these numbers are underlined, and there is a “y” in subsequent columns, am I correct that these patients no longer use Peristeen?	5. The previous italics were the patients who had stopped - I tried to make it clearer by just underlining those who stopped irrigation. The non-underlined ones are still using the TAI. I have also added in the last columns (yellow) the 1 year data.	Confirmation of EAC assumption.
Economic evidence	6. For these patients, was there a date of cessation recorded, or is it only known that it occurred at some point in the year with “y” recorded?	6. Correct	Confirmation of EAC assumption.
Economic evidence	7. If there is no exact data, could you clarify what assumption you used for calculating survival information. The Kaplan-Meier curve reported in Passananti has a much higher rate of ceasing to use Peristeen, than I arrive at, and it would appear that there are 13 patients with MS who ceased using Peristeen in the audit data, as opposed to 22 patients in the paper by Passananti.	7. We used the mid-point between observations for cessation, or an exact date if there was one available.	EAC used the mid-point between observations. No exact dates were available in audit data seen by EAC.
Economic evidence	I have attached a copy of the spreadsheet that was sent to us by Coloplast. Are you able to share a more complete version, or the most appropriate version so that we can fully understand the economic model that was submitted to NICE (which as	AE: No response received	

	I understand, was the model published in the PLoS paper). To put the request into context, as I have also explained to Jeppe, the process for MTEP is that once NICE receive the economic submission, it is sent to an External Assessment Centre (in this case Cedar), who will look at the structure of the model and the inputs used. Often these inputs will be based on published papers, and we will then assess, for example, the suitability of the patient population, the quality of the paper and possible sources of bias. In this case, we do not have any information on how most of the inputs were derived, which makes it difficult to assess their suitability.		
Questions to expert advisors, 3 responses (1 recieved after assessment report completion), listed for each item with advisor initials.			
Economic evidence	Peristeen System including 2 catheters and 1 water bag: 1 every 6 months	KN: correct - as detailed in their advice	Confirmation of model
		OJ: I think this is a reasonable assumption	
		IB: Very reasonable	
Economic evidence	Peristeen: pack of 15 single use catheters	KN: most patients use catheters once every 2 days; some will use them less frequently and others more so 15 is a reasonable average estimate	Confirmation of model/ EAC opinion
		OJ: This is a highly variable figure between individuals but given that around one half of patient will use the system daily and the other half intermittently, I think this is a reasonable assumption.	
		IB: Very reasonable	
Economic evidence	Initial training: 1 hour consultation, plus 3 x 15 min follow-up phone call	KN: Once again an average estimation	Confirmation of model
		OJ: In our practice, it is a one hour initial consultation and one 15 minute follow-up call. Some require additional support down the years and so I think a total of 2-3 15 minute calls in the aftermath of starting irrigation is a reasonable assumption.	

		IB: Very reasonable	
Economic evidence	Stoma: A weighted average of very complex, complex and major large intestine procedures, from NHS Ref Costs FZ73C to FZ77E. (price quoted is as in model at 2013-14) £7,459.76	KN: No response	None
		OJ: I do not understand what this figure represents. Is this the annual cost of having a stoma?	
		IB: You would know better than me	
Economic evidence	Stoma Equipment: Colostomy bag 2 per day	KN: Depends on the type of stoma bags used. Basically the bag would need to be changed after a stool has evacuated into the bag. If talking about a colostomy not an ileostomy once or twice a day would be average	Confirmation of model
		OJ: This is a reasonable assumption.	
		IB: Very reasonable	
Economic evidence	Stoma Equipment: 1 Belt per month	KN: If required - many / most do not need a belt	Confirmation of model, no changes made.
		OJ: This is a reasonable assumption.	
		IB: Very reasonable	
Economic evidence	Stoma Equipment: Skin barrier per day – 3 applications	KN: No - only when the base plate is used; so for a two piece system where the bag detaches and leaves a base plate - the skin barrier is only required when changing the base plate i.e. every 2 or 3 days. If a one piece system then assuming that the bag is changed 2x a day (see above) then skin barrier would be 2 times a day	Company manual input to model was actually 2 applications/ day. No change made, but variations noted.
		OJ: I think this figure would correlate with the number of bags used per day (i.e. 2 per day). Bags are not generally taken off and then re-applied, so the skin barrier would be used as often as the bag is changed.	
		IB: Very reasonable	
Economic evidence	Stoma Equipment: Adhesive remover per day– 3 applications	KN: same as above	As above
		OJ: Likewise 2 per day, for the reasons outlined for the skin barrier.	
		IB: Very reasonable	
Economic evidence	In your experience, what routine visits to a health care professional would be planned for patients after	KN: If prescribed from a hospital consultant the patient may be offered a further follow up at 6 months with either a nurse or a doctor If managing no further appointments	No changes to model made

	Peristeen was adopted (not including initial training period)? E.g. clinic visits with nurse, consultant appointments etc.	OJ: In my experience, reflecting the Oxford practice, patients are not usually brought back to clinic for a face-to-face meeting with our nurses. The usual circumstances of routine visits are those made with the consultant to see patients not getting alleviation of symptoms with Peristeen. I think around 20% of patients need or get a clinic follow-up with either consultant or nurse for this.	
		IB: Probably 2 x nurse-led visists at 6 month intervals. The seen as required. I would not envisage continued consultant follow up unless required by clinical condition	
Economic evidence	In your experience, what routine visits to a health care professional would be planned for patients using standard bowel care? E.g. clinic visits with nurse, consultant appointments etc.	KN: Depends on whether patient still had symptoms	No changes to model made
		OJ: I think that around 20% of people get follow-up, amongst those using standard care	
		IB: Probably consultant clinic follow up 4 times a year for at least 2 years as unlikely symptoms will improve without additional treatment	
Economic evidence	Where patients have a UTI that doesn't respond to initial treatment and requires hospitalisation, what would be a typical length of stay?	KN: 48 hours if needs to start with iv antibiotics	No changes to model made.
		OJ: Two days.	
		IB: Average 5 days	

Appendix 1 Additional figure contained in email from company.

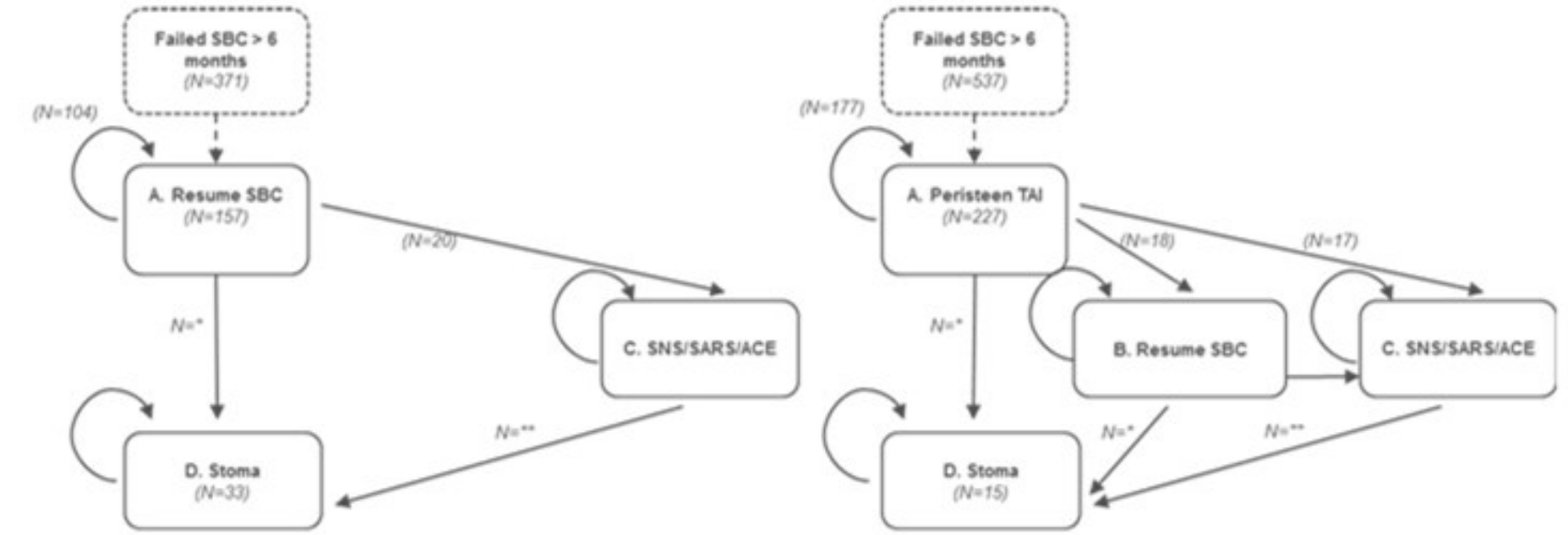

Figure 1. Data and Markov model overview. The boxes represent the health states that a neurogenic patient can transition between after having failed standard bowel care (SBC) before and after 2007.
Figure 1A: Practice pre-TAI. After having failed SBC >6 months, a patient can either a) Resume SBC, c) Progress to SNS/SARS/ACE or d) Progress to stoma (absorbing state).
Figure 1B: Practice post-TAI. After having failed SBC >6 months, a patient can either a) Initiate Peristeen TAI, b) Resume SBC, c) Progress to SNS/SARS/ACE or d) Progress to stoma.
The data used to estimate transition probabilities are reported next to each health state. Pre-TAI data before 2007 was applied to estimate the number of patients receiving stoma prior to having TAI available in the stepped pyramidal treatment approach. The 157 eligible Peristeen users pre-2007 are estimated based on the current proportion of eligible Peristeen users out of the total NBD population post-2007. *The model assumes that patients do not transition directly from SBC/TAI to stoma. **Transition probabilities have been obtained for each 6-month model cycle using GoalSeek in Excel.