NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Consilient Health Ltd

2. **Clarification questions and company responses**
   a. NICE request to the company for clarification on their submission
   b. Company response to NICE's request for clarification

3. **Patient group, professional group and NHS organisation submission** from:
   a. Bladder Health UK

4. **Expert personal perspectives** from:
   a. Jonathan Goddard – clinical expert, nominated by Consilient Health Ltd
   b. Suzanne Biers – clinical expert, nominated by British Association of Urological Surgeons (BAUS)

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)
   a. ERG report updated post FAC
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7. **Technical engagement response from company**
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8. **Technical engagement responses from experts:**
   a. Jonathan Goddard – clinical expert, nominated by Consilient Health Ltd
   b. Suzanne Biers – clinical expert, nominated by British Association of Urological Surgeons

9. **Technical engagement responses from consultees and commentators:**
   a. British Association of Urological Surgeons (BAUS)

10. **Evidence Review Group critique of company response to technical engagement** prepared by School of Health and Related Research (ScHARR)
    a. ERG addendum post technical engagement
    b. ERG second addendum with PAS analyses
    c. ERG addendum correction to Table 1a

11. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Document A

Company evidence submission summary for committee

Consilient Health confirms that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

7th January 2019

File name	Version	Contains confidential information	Date
ID1364_Pentosan polysulfate sodium_Submission Summary_Document A_CIC	**1**	**Yes/no**	**7th January 2019**

ID1364_Pentosan polysulfate sodium_Submission Summary_Document A_v2_CIC	**2**	**Yes/no**	**4th Sept 2019**

Contents

Tables and figures

Submission summary

A.1 Health condition

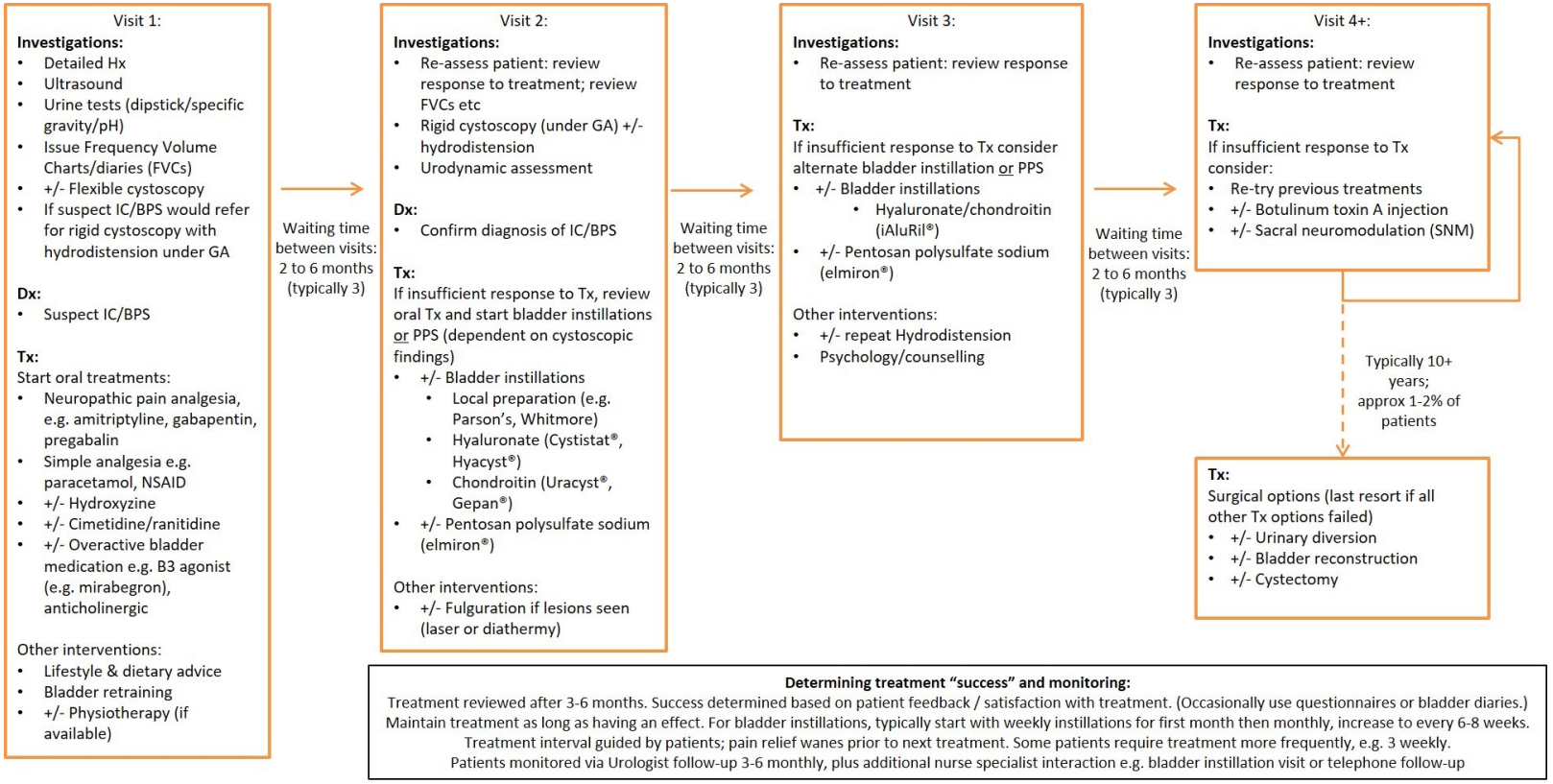
Bladder pain syndrome (BPS) and interstitial cystitis/bladder pain syndrome (IC/BPS) are chronic inflammatory conditions of the bladder wall. They are characterised by pelvic pain or discomfort that occurs during bladder filling, abnormally frequent urination, urgency, and nocturia. Patients may experience periods of exacerbation or remission, and disease severity varies between individuals. In this submission, BPS refers to patients meeting the broader symptomatic criteria of chronic bladder pain, while IC/BPS describes BPS patients who have also been diagnosed with Hunner's lesions (areas of inflammation in the bladder wall) and/or glomerulations (small areas of haemorrhage in the bladder wall). IC/BPS patients comprise the indicated population for pentosan polysulfate sodium (PPS). In the ORPHANET database of rare diseases, IC/BPS has a prevalence of 1–5/10,000 and therefore has designated orphan status (ORPHA:37202).

BPS and IC/BPS have a devastating impact on the quality of life (QoL) of patients. The chronic pain associated with these conditions results in patient suffering and has a major role in poor QoL. Anxiety and depression are highly prevalent among BPS and IC/BPS patients, and some patients report suicidal thoughts because of their symptoms [1,2]. Furthermore, the care pathway for BPS and IC/BPS lacks standardisation and is prolonged, and there is also a lack of effective treatments. Consequently, patients often cycle back through previous failed treatments and this compounds their low QoL (see Appendix M and Appendix N).

A.2 Clinical pathway of care

The clinical care pathway for the use of PPS in patients with IC/BPS (developed at an advisory board with clinical experts) is shown in Figure 1.

Figure 1 Clinical care pathway for use of PPS in IC/BPS (section B.1.3.6, page 27)



A.3 Equality considerations

BPS and IC/BPS affect women more frequently than men, with women nine times more likely to experience the condition [3]. Studies have reported that BPS has a major detrimental effect on women's QoL and ability to participate in the workforce; women with BPS have increased work absences and slower salary increases than women without the condition [4].

A.4 The technology

Table 1 Technology being appraised – B.1.2 (page 14)

UK approved name and brand name	elmiron® (PPS)
Mechanism of action	The hypothetic mechanism of action of PPS includes a local effect in the bladder after systemic administration and excretion into the urine by binding of GAGs to the deficient mucous of the bladder. This binding of GAGs to the bladder mucous reduces bacterial adherence to the inner surface of the bladder and in consequence the incidence of infections is reduced as well. It is hypothesised that the potential barrier function of PPS instead of the damaged urothelial mucus might also play a role in addition to the drug's anti-inflammatory activity.
Marketing authorisation/CE mark status	EMA approval has been received (02/06/2017) and PPS is the only licensed oral medicine for IC/BPS in the UK.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	elmiron®/PPS received marketing authorisation in June 2017. PPS is indicated for the treatment of bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency, and frequency of micturition. Response to treatment with PPS should be reassessed every 6 months. In case no improvement is reached 6 months after treatment initiation, treatment with PPS should be stopped. In responders PPS treatment should be continued chronically as long as the response is maintained.
Method of administration and dosage	In adults, the recommended dose of PPS is 300 mg/day and is administered as 1× 100 mg oral capsule 3× daily.
Additional tests or investigations	Cystoscopy is required to confirm the presence of Hunner's lesions, and cystoscopy with hydrodistension is required to confirm the presence of glomerulations. These investigations are routinely performed as part of the differential diagnosis to exclude other causes in patients with BPS given the similarity in symptoms between BPS and other conditions like urinary tract infection and overactive bladder.
List price and average cost of a course of treatment	£450 per pack of 90 capsules (30 days' supply at licensed dose of 100 mg 3× per day)
Patient access scheme (if applicable)	N/A

Abbreviations: BPS, bladder pain syndrome; EMA, European Medicines Agency; IC/BPS, interstitial cystitis/bladder pain syndrome; GAGs, glycosaminoglycans; N/A, not applicable, PPS, pentosan polysulfate sodium

A.5 Decision problem and NICE reference case

The objective of this appraisal is to determine the clinical and cost-effectiveness of PPS within its marketing authorisation for treating BPS characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition. The submission covers the technology's full marketing authorisation for this indication.

Table 2 Decision problem – B.1.1 (page 11)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with BPS characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition	Adults with BPS characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition	N/A
Intervention	Pentosan polysulfate sodium (elmiron®)	Pentosan polysulfate sodium (elmiron®)	N/A
Comparator(s)	• Bladder instillations (BIs) • For people for whom BIs are inappropriate, cannot be tolerated or are unsuccessful: established clinical management without PPS or BIs (including medicines that do not currently have a marketing authorisation in the UK for this indication)	• Commercially available BIs (sodium hyaluronate [Cystistat®, Hyacyst®], sodium chondroitin sulphate [Uracyst®, Gepan®], sodium hyaluronate/sodium chondroitin sulphate [iAluRil®] • For people for whom BIs are inappropriate, cannot be tolerated or are unsuccessful - no treatment with PPS or BIs (comparison with placebo)	There is no standardised care pathway for BPS patients in the UK and as a result, treatment of BPS is very varied. In clinical practice a wide variety of treatments, including those without marketing authorisation in the UK, could be considered. Please note that there is no established clinical management for patients for whom BIs are inappropriate.
Outcomes	• Bladder pain	• Bladder pain	The key outcomes included in the clinical trials are

	• Urinary urgency • Urinary frequency • Nocturia • Adverse effects of treatment • Health-related quality of life	• Response to treatment (e.g. Global Response Assessment) • Severity of symptoms • Urinary urgency • Urinary frequency • Nocturia • Adverse effects of treatment • Health-related quality of life	assessments of response to treatment and changes in symptom severity as assessed by the patient
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services Perspective. The use of PPS is conditional on the presence of either glomerulations or Hunner's lesions. The economic modelling should include the costs associated with diagnostic testing or Hunner's lesions in people with BPS who would not otherwise have been tested. A sensitivity analysis should be	Sensitivity analyses will be presented using a range of time horizons for the analysis The base case analysis will not include the cost of cystoscopy	There is no standard care pathway for patients with BPS or IC/BPS. This factor, together with the relatively short duration of clinical trials, introduces uncertainty into an economic analysis with a lifetime horizon. Therefore, sensitivity analyses using alternative time horizons are presented Whilst cystoscopy is required to confirm the presence of Hunner's lesions, and cystoscopy with hydrodistension is required to confirm the presence of glomerulations, these investigations are routinely performed on all patients with BPS and not only when they are being considered for treatment with PPS.

	provided without the cost of the diagnostic test.		
Subgroups to be considered	None	None	N/A
Perspective for outcomes	All direct health effects whether for patients or, when relevant, carers	Direct health effects for IC/BPS patients (no relevant carer health effects)	N/A
Perspective for costs	NHS and PSS	NHS (no relevant PSS costs)	N/A
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In the base case, a time horizon of 20 years was chosen, but a lifetime horizon was also presented (54 years)	N/A
Synthesis of evidence on health effects	Based on systematic review	Effectiveness data sourced from systematic review and meta-analysis of available relevant trials	N/A
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Health effects expressed in QALYs and based on EQ-5D-5L preference-based health-related quality of life measure	N/A
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data as reported directly in a survey of BPS patients (section B.3.5.3 of main submission)	N/A
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	EQ-5D-5L responses were valued using the recommended crosswalk to EQ-5D-3L UK value set [5,6]	N/A

Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The evaluation does not include any weighting of QALYs	N/A
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	All costs considered (treatments, healthcare resource use) are based on NHS resources and are valued using relevant unit costs such as the British National Formulary, MIMS or NHS reference costs [7–9]	N/A
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs both discounted at 3.5%	N/A
Abbreviations: BI, bladder instillations; BPS, bladder pain syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; MIMS, Monthly Index of Medical Specialities; N/A, not applicable; NHS, National Health service; PSS, Prescribed Specialised Services; PPS, Pentosan polysulfate sodium; QALY, quality-adjusted life year			

A.6 Clinical effectiveness evidence

Four randomised controlled trials (RCTs) of PPS for the treatment of IC/BPS patients were identified in the systematic literature review [10–13] and a further two RCTs were identified that investigated PPS as a treatment for more broadly defined BPS patient groups [14,15]. All compared PPS with a placebo and trial duration ranged from 3 [11,12] or 4 [13,15] months to 24 weeks [10,14] (

Table 3). In five of the trials a single dose of PPS was assessed in the PPS arm; this was 100 mg administered three times daily with the exception of Holm-Bentzen et al. (1987) in which the dose was 200 mg administered twice daily [15]. In the RCT by Nickel et al. (2015), there were two PPS arms and patients received PPS either once (QD, a third of the normal PPS dose) or three times daily (TID) [14]. The study by Sant et al. (2003) had a randomised 2×2 factorial design, including 4 arms (PPS alone, placebo alone, PPS plus a non-comparator therapy [hydroxyzine], and placebo plus hydroxyzine) [10].

Table 3 Clinical effectiveness evidence

Study title	Sant et al., 2003	Parsons et al., 1993	Mulholland et al., 1990	Parsons and Mulholland, 1987	Nickel et al., 2015	Holm-Bentzen et al., 1987
Study design	Randomised placebo-controlled trial with 2×2 factorial design	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind controlled trial with crossover design	RCT	RCT
Population	Adults (≥18 years) with IC/BPS (Hunner's lesions and glomerulations)	Adults (≥18 years) with IC/BPS (Hunner's lesions and glomerulations)	Adults (≥18 years) with IC/BPS (Hunner's lesions and glomerulations)	Adults (≥18 years) with IC/BPS (Hunner's lesions and glomerulations)	Adults (≥18 years) with BPS	Adults (≥18 years) with BPS
Intervention(s)	PPS	PPS	PPS	PPS	PPS	PPS
Comparator(s)	Placebo Hydroxyzine	Placebo	Placebo	Placebo	Placebo	Placebo
Outcomes specified in the decision problem	GRA ICSI ICPI Wisconsin IC score Urinary frequency	GRA (equivalent measure) Pain and urgency	GRA (equivalent measure) Voided urine volume	Urinary frequency Urgency Nocturia Pain Voided urine volume	GRA ICSI Urinary frequency	N/A
Reference to section in submission	B.2.2 (page 37)	B.2.2 (page 37)	B.2.2 (page 37)	B.2.2 (page 37)	B.2.2 (page 37)	B.2.2 (page 36)
	Abbreviations: GRA, global response assessment; IC/BPS, interstitial cystitis/bladder pain syndrome; ICSI, Interstitial Cystitis Symptom Index; ICPI, Interstitial Cystitis Problem Index; RCT, randomised controlled trial					

A.7 Key results of the clinical effectiveness evidence

Key outcomes of the six trials shown in

Table 3 are listed below. Full details of these and other outcomes are presented in section B.2.6.

A.7.1 *Global Response Assessment (B.2.6.1, page 62)*

- Sant et al. (2003) showed that more patients in the PPS arm had a Global Response Assessment (GRA) score of 6 or 7 compared with the placebo group (34% vs. 18%, p=0.064)
- In the study by Mulholland et al. (1990), 28% patients who received PPS experienced >50% improvement in symptoms compared with 13% in the placebo group (p=0.04) [11]
- In the trial by Parsons et al. (1993) 24 patients (32%) in the PPS group reported ≥50% improvement vs. 12 (16%) in the placebo group (p=0.01) [12]

A.7.2 *O'Leary-Sant Interstitial Cystitis Symptom and Problem Index scores (B.2.6.2, page 65)*

- In the RCT by Sant et al. (2003), the primary analysis showed that PPS generated a decrease of 2.6 points in the mean ICSI score at 24 weeks' follow-up compared with baseline while the placebo only resulted in a decrease of 1.7 points
- The ICPI score decreased by 2.6 points in the PPS group and by 1.9 points in the placebo group
- Nickel et al. (2015) assessed the number of patients who experienced either a >30% decrease or a ≥4 point decrease in the Interstitial Cystitis Symptom Index (ICSI) score from baseline. The TID PPS group had the highest proportion of patients who achieved these outcomes; 42.6% had a ≥30% ICSI score decrease while 49.2% achieved a ≥4 point decrease

A.7.3 *Non-VAS pain outcomes (B.2.6.3, page 66)*

- At 3 months of follow-up in the Parsons et al. (1993) trial, 38% patients in the PPS group reported >50% improvement compared with 18% in the placebo group (p=0.005) using a 5-point pain scale. PPS results in a >1 point decrease in 66% patients receiving PPS compared with 51% in the placebo group (p=0.004)

- Mulholland et al. (1990) used the same 5-point pain scale and found that 27% patients in the PPS group experienced ≥50% improvement compared with 14% in the placebo group (p=0.08)

- In the PPS group of the Parsons and Mulholland (1987) trial, 44% patients reported a ≥50% improvement compared with 15% in the placebo group (p=0.02). The mean percentage improvement was 33.3% in the PPS group and 12.2% in the placebo group (p=0.02)

A.7.4 *Daily urinary frequency (section B.2.6.4, page 68)*

- In the RCT by Parsons and Mulholland (1987), 65% patients receiving PPS reported an improvement in daily urinary frequency compared with 42% who received the placebo at 3 months' follow-up

- In the same study, the mean change in daily frequency among improved patients in the PPS group was -5.4 compared with -1.8 in the placebo group (p>0.05). The mean daily frequency in the PPS group did not change from 18.0 at baseline while in the placebo group it was 19.5 at follow-up vs. 18.8 at baseline (p>0.05).

A.7.5 *Volume/void outcomes (section B.2.6.5, page 69)*

- In the trial by Parsons and Mulholland (1987) [13], the mean volume/void increased from 93.8 mL at baseline to 106.9 mL at the 3-month follow-up in the PPS arm (p=0.06). In the placebo arm, the mean volume/void decreased from 76.7 mL at

baseline to 74.3 mL at follow-up (p=0.3). The difference between the effects of PPS and placebo on the mean volume/void was statistically significant (p=0.009) [13]

- Parsons et al. (1993) [12] found that PPS increased the mean volume/void by 20.4 mL whereas placebo treatment resulted in a decrease of 2.1 mL at 3 months of follow-up (p>0.05). The mean daily voided volume increased by 3 mL in the PPS group while it declined by 42 mL in the placebo group (p>0.05). In the PPS arm, 40% patients achieved ≥20 mL increase in the mean volume/void compared with only 24% in the placebo arm, and this difference was statistically significant (p=0.02).

A.8 Evidence synthesis

A systematic literature review was conducted to identify studies to facilitate an indirect comparison of PPS with other treatments included as comparators in the NICE scope, i.e. commercially available bladder instillations: [see Table 2]. The potential comparators included in the review were defined more broadly than the NICE scope to maximise the possibility of forming a network of trials. Twelve trials met the inclusion criteria. Six trials compared PPS capsules to oral placebo, three Uracyst® to placebo instillation and one each of Uracyst® to dimethyl sulphoxide (DMSO) instillation, iAluRil® to DMSO instillation and Cystistat® to Gepan®. It was therefore not possible to construct a network comparing PPS to all relevant comparators. Only one bladder instillation (BI), Uracyst®, could potentially be compared to PPS indirectly via placebo. However, there was considerable heterogeneity in the trials, which would make a robust indirect comparison of PPS with any comparator challenging (section B.2.9). Notwithstanding these differences, we attempted to compare PPS with a BI (Uracyst®) to meet the requirements of the NICE scope (section B.2.9). The results of the indirect comparison and details of how they have been incorporated into the economic model are described in section B.3.3.1 (Table 40).

A.9 Key clinical issues

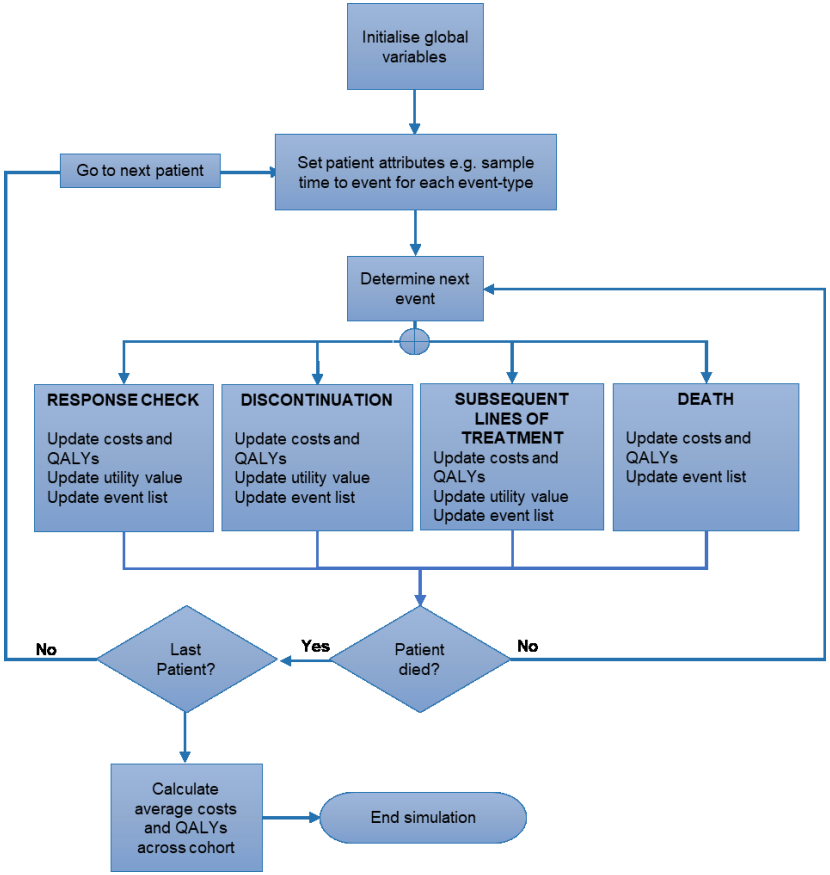
- The placebo effect is particularly apparent in BPS and IC/BPS patients because the requirement to self-report symptoms (e.g. voiding habits) can increase patient awareness of changes before or during treatment. Stress levels may also be reduced by trial participation, clinical contact, and the potential for a solution (for which BPS and IC/BPS patients are often desperate), which could improve symptoms [16]. Despite that large placebo effect in BPS and IC/BPS patients, PPS still showed clinical effectiveness vs. placebo in the reported trials and meta-analysis (section B.2.13)

- There is variation in the timing of the response to PPS between individual patients; some patients experience improvements early in the PPS treatment process while others do not experience a clinical response until after 3–6 months of PPS treatment. Time- and patient-dependent variations can affect mean efficacy and other treatment outcomes because data from patients who do not benefit mask significant improvements in the rest of the population (section B.2.13)

A.10 Overview of the economic analysis

In the absence of published cost-effectiveness analyses of PPS a *de novo* economic model was developed using a discrete event simulation (DES), implemented in Microsoft Excel®.

Figure 2 Discrete event simulation model diagram – B.3.2 (page 96)



A.11 Incorporating clinical evidence into the model

The proportion of patients responding to treatment was informed by meta-analyses of the trials of PPS in IC/BPS [10–13] and sodium chondroitin sulphate (Uracyst®) [17,18] compared to placebo. For patients who initially respond to treatment, time-to-

discontinuation was estimated using data from a study conducted by Hanno and colleagues [19]. A survey of patients with BPS was conducted and a de novo mapping algorithm was developed to derive QoL and cost estimates for incorporation into the economic model. Data on background mortality were taken from Office of National statistics UK population life tables (2014–2016) [20].

A.12 Key model assumptions and inputs

Table 4 Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Clinical effectiveness – section B.3.3.1	Trial data of chondroitin sulphate (Uracyst®) were used to represent the effectiveness of BIs in general.	The two trials of chondroitin sulphate (Uracyst®) represent the only available effectiveness data for BIs which could be used to form an indirect comparison with PPS.
Clinical effectiveness – section B.3.3.1	Patients responding to treatment were assumed to have a lower ICSI score compared to patients not responding to treatment.	The GRA was related to ICSI to infer ICSI values for patients responding/not responding to treatment due to no relevant published data being identified.
Clinical effectiveness – section B.3.3.1	The treatment effect attributed to patients responding to BSC was assumed to be receding 12 months after treatment initiation.	The placebo effect observed in the clinical trial evidence was applied in the model for 12 months as a conservative approach.
Clinical effectiveness – section B.3.3.1	The mean ICSI reduction for PPS (as observed in Sant 2003) was attributed to BIs and BSC	Due to the absence of relevant data for BIs and to avoid alternative assumptions around differential ICSI values for each treatment.
Timing of response assessment – section B.3.2.3	6 months	Most trials assessed treatment response in a period from 3 to 6 months. The PPS SMPC supports that response should be assessed every 6 months.
Health related utilities - section B.3.2.3	Derived from a survey of UK patients with BPS using the EQ-5D and linked to ICSI and ICPI from the trials using a de novo mapping function.	No relevant data for UK population identified in the literature.

Health care costs – section B.3.2.3	Derived from a survey of UK patients with BPS linked to ICSI and ICPI from the trials using a de novo mapping function.	To reflect healthcare resource usage is linked to severity of disease.
Treatment and administration costs – section B.3.2.3	Obtained from national sources (BNF, MIMS, NHS reference costs)	To reflect UK national list prices
Abbreviations: BI, bladder instillations; BSC, best supportive care; GRA, Global response assessment; ICSI, Interstitial Cystitis Symptom Index; PPS, pentosan polysulfate sodium; SMPC, Summary of Product Characteristics		

A.13 Base-case ICER (deterministic)

Table 5 Base-case results (deterministic) – B.3.7 (page 127)

Comparison against BIs and BSC

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Vs. BIs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIs	[redacted]	[redacted]			
Vs. BSC					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Abbreviations: BIs, bladder instillations; BSC, best supportive care ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

A.14 Probabilistic sensitivity analysis

Distributions of parameters varied can be found in section B.3.6.1

Table 6 Base-case results (probabilistic) – B.3.8 (page 128)

Comparison against BIs and BSC

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Vs. BIs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIs	[redacted]	[redacted]			
Vs. BSC					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Abbreviations: BSC, best supportive care; BIs, bladder instillations, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 3 Scatterplot of probabilistic results – B.3.8 (page 129 and page 130)

Comparison against BIs **Comparison against BSC**

A.15 Key sensitivity and scenario analyses

Figure 4 Tornado diagram (vs. BIs – B.3.8 (page 132)

Figure 5 Tornado diagram (vs. BSC – B.3.8 (page 132)

Table 7 Key scenario analyses – vs. BIs

Scenario	PSS costs	PSS QALYs	BI costs	BI QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICPI based utilities and background costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities from literature - (Cervigni 2017)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using least expensive product for BI (subsequent treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% self-administration of BIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate for PPS including 2 wider population clinical trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 Key scenario analyses – vs. BSC

Scenario	PSS costs	PSS QALYs	BSC costs	BSC QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICPI based utilities and background costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities from literature - (Cervigni 2017)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC effect receding at 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC effect not receding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility and background costs given to non-responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate including 2 wider population clinical trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A.16 Innovation

There is a lack of effective and licensed treatments available for BPS and IC/BPS; PPS is an innovative therapeutic intervention, and is the only medicine licensed for IC/BPS in the EU/UK.

PPS is an oral medicine available in a landscape in which the other approved treatments for BPS come in the form of bladder instillations (BIs). BIs are usually administered hospital outpatient setting and are considerably more invasive for patients than an oral medicine. Therefore, in addition to the clinical improvement in symptoms and QoL that can be achieved because of the efficacy of PPS, additional QoL benefits are expected because the mode of administration is less time-consuming and invasive. Furthermore, the proposed mechanism of action of PPS is to protect the bladder from bacterial adherence and consequently reduce inflammation. Although this is also the case for BIs, this proposed mechanism is different to some of the other oral medicines used to treat BPS (e.g. simple analgesia or neuropathic pain analgesia), which are designed to treat the symptoms of the condition rather than the likely cause.

A.17 Budget impact

Please refer to the budget impact analysis submission for a detailed explanation of the approach used for the budget impact model, including assumptions used in calculating the values on healthcare resources and unit costs PPS and current treatment options (commercially available BIs). The submission also refers to the estimated uptake and market share of PPS and BIs. Table 9 shows the estimated net budget impact of PPS over 5 years.

Table 9 Budget impact analysis for PPS (page 15)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population for treatment with PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Population expected to receive PPS (current)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Population expected to receive PPS (revised)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cost of treatment pathway (current)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cost of treatment pathway (revised)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Net budget impact	**£217,346**	**£459,810**	**£727,340**	**£1,019,881**	**£1,337,383**	**£3,761,760**

A.18 Interpretation and conclusions of the evidence

IC/BPS is an extremely distressing condition that has a major detrimental impact on patients' QoL (B.1.3.5 and B.1.3.9). Limited effective treatment options and a lack of standardised care pathway prolong patient suffering. Many existing medicines for IC/BPS are used off-label/unlicensed; PPS is the only available medicine licensed for IC/BPS. Clinical trials have demonstrated the efficacy of PPS in alleviating IC/BPS symptoms and improving QoL. Amongst others benefits of PPS are improved GRA and ICSI scores (B.2.6). PPS is well-tolerated with most adverse events being minor and easily resolvable.

The results of the cost-effectiveness model (B.3.7) demonstrate a notable QALY gain of [redacted] for PPS at an incremental cost of [redacted] when compared with BIs. This resulted in an ICER of [redacted]. The mapping model for utilities had a slightly better fit when ICPI was used compared to ICSI. When using the ICPI models, the ICER decreases to [redacted] compared with BIs.

Bladder instillations represent standard care for BPS; however, there is a very small proportion of patients who are contraindicated or unable to tolerate them and instead receive BSC only. The comparison with BSC gave an ICER of [redacted]; this reflects a high modelled health benefit for people that respond to BSC (placebo response) that would be unlikely to be observed in clinical practice. Unlike the comparison with BIs, the results of the analysis comparing PPS to BSC are sensitive to the choice of outcome measure. When using the ICPI instead of the ICSI to link to costs and utilities, the ICERs decrease [redacted] for this group of patients.

The results show PPS can be considered a cost-effective option for treating adults with IC/BPS when compared with BIs. The ICERs in the comparison with BSC are more uncertain, however the percentage of patients not eligible for BIs is agreed to be low in clinical practice, therefore indicating that PPS can overall be a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question: Please explain why the comparators heparin, lidocaine, sodium bicarbonate or hydrocortisone (which are used as off-label instillations and as subsequent therapies in the UK) are not included in the clinical effectiveness searches outlines in Appendix D.1

[Company: please enter your answer to this question here]

A2. Please provide the search strategies used to identify the non-randomised controlled studies included in Table 27 of the company submission.

[Company: please enter your answer to this question here]

A3. Please explain why a conference abstract limit was applied to the Embase search strategy described on pages 155-156 of Appendix D. Does this limit exclude any unpublished studies?

[Company: please enter your answer to this question here]

A4. Priority question: The proposed treatment pathway in the 'Appendix 2' diagram in Appendix M includes locally prepared bladder instillations (e.g. Parson's, Whitmore). Please clarify why these treatments are not included in the submission.

[Company: please enter your answer to this question here]

A5. The Bade et al. (1997) study mentioned in Appendix D Table 67 is available free to download online and contains outcomes relevant to the scope. Please clarify why this study has been excluded from the literature review.

[Company: please enter your answer to this question here]

A6. Appendix D Table 67 indicates that Gottsch et al. (2011) was excluded because it does not contain the relevant outcomes. However, the study appears to contain outcomes included in the scope. Please clarify why this study has been excluded.

[Company: please enter your answer to this question here]

A7. In Figure 9 of the submission, only 5 of the 6 identified randomised controlled trials in pentosane polysufate sodium are presented for the network link between pentosane polysufate sodium and placebo. Please clarify why one trial has been excluded.

[Company: please enter your answer to this question here]

A8. In Appendix M, the advisory board recommends that the comparability of bladder capacity across trials be assessed. Please summarise the data on bladder capacity across the included trials. If this had been done already, please indicate where this is already summarised in the submission.

[Company: please enter your answer to this question here]

A9. Please explain why the results from Nickel et al. (2015) for the subgroup meeting the National Institute of Diabetes and Digestive and Kidney criteria are not provided in the submission. Please clarify whether this subgroup would match the population indicated for oral pentosane polysufate sodium.

[Company: please enter your answer to this question here]

A9. Please provide the citation(s) for the quality assessment method used in Table 18 of the company submission and Table 68 of Appendix D.

[Company: please enter your answer to this question here]

A10. Page 82 of the company submission reports that 12 trials met the inclusion criteria for the indirect treatment comparison. However, Figure 27 in Appendix D reports that 15 randomised controlled trials met the inclusion criteria. Please clarify why there is a difference in the numbers reported.

[Company: please enter your answer to this question here]

A11. Figure 27 in Appendix D reports that 13 articles relating to 15 randomised controlled trials were considered for the indirect treatment comparison. However, Table 66 in Appendix D presents 13 articles that relate to only 11 randomised controlled trials. Please provide the citations and study details for the other 4 randomised controlled trials considered for the indirect treatment comparison.

[Company: please enter your answer to this question here]

A12. For page 82 of the company submission, please provide in-text citations as indicated in the following paragraph: 'Twelve trials met the inclusion criteria [please insert citations]. Six trials compared PPS capsules to oral placebo [please insert citations], three Uracyst® to placebo instillation [please insert citations] and one each of Uracyst® to DMSO instillation [please insert citation], iAluRil® to DMSO instillation [please insert citation] and Cystistat® to Gepan® [citation please insert citation]'.

[Company: please enter your answer to this question here]

A13. Please clarify whether the Johnson & Johnson (2014) citation included in Table 66 of Appendix D is the study record for the Nickels et al (2015) study (i.e. 2 citations for 1 study)?

[Company: please enter your answer to this question here]

A14. Please clarify whether the Watson Pharmaceuticals (2013) citation included in Table 66 of Appendix D is the study record for the Nickels et al (2012) study (i.e. 2 citations for 1 study)?

[Company: please enter your answer to this question here]

A15. Please clarify why alternative approaches to conducting an indirect comparison between pentosane polysufate sodium and bladder installations (such as that described in 'NICE Decision Support Unit Technical Support Document 18) have not been explored.

[Company: please enter your answer to this question here]

A16. Please specify the 'standard of care' in the 4 placebo controlled studies of pentosane polysufate sodium used in the meta-analyses described on pages 78-81 of the submission.

[Company: please enter your answer to this question here]

A17. Is the effect of treatment with pentosane polysufate sodium identical in each study (assuming an appropriate additive scale)? Could the treatment effect vary between studies?

[Company: please enter your answer to this question here]

A18. In clinical practice, what is the expected response to standard of care (when standard of care corresponds to the placebo used in the trials)?

[Company: please enter your answer to this question here]

A19. Page 77 of the company submission states "There was a high degree of homogeneity in this sensitivity meta-analysis". Please clarify whether this applies to the analysis of the 4 or 6 studies.

[Company: please enter your answer to this question here]

A20. Relating to page 79 of the company submission, please clarify the relevance of the lower bound of the confidence interval (6.3%) being greater than 5%?

[Company: please enter your answer to this question here]

A21. Page 79 of the company submission reports that the meta-analysis by Hwang et al (1997) included 448 patients, whereas Figure 11 reports this number as 454. Please clarify why there is a difference in the numbers reported.

[Company: please enter your answer to this question here]

A22. Table 30 of the submission reports the number of events and number of patients randomised in Nickel et al (2010) as 'NR'. However, these values are reported in Figure 13. Please confirm where these numbers were obtained.

[Company: please enter your answer to this question here]

A23. Please expand on the "assessment of heterogeneity" described on page 85 of the company submission.

[Company: please enter your answer to this question here]

A24. Please provide input data and results of the additional meta-analyses described on page 133 of the company submission, which included the Holm Bentzen (1987) & Nickel (2015) trials.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

B1. The published cost-effectiveness studies section of Appendix G says that no timeframe limit was applied to the search. However, the cost effectiveness evaluations search strategy shows that the date limit 2015-current was applied. Table 69 suggests the eligibility criteria for cost-effectiveness studies is from 1992-present. Please confirm whether a timeframe limit was applied to search.

[Company: please enter your answer to this question here]

B2. Appendix G only contains 1 of the 3 search strategies used to identify cost-effectiveness evaluations and economic models. Please provide strategies for all databases searched.

[Company: please enter your answer to this question here]

B3. Appendices H and I indicate that electronic databases, Medline and Embase were searched to identify studies relating to health-related quality-of-life, cost and healthcare resource use. Please provide the full search strategies for all databases.

[Company: please enter your answer to this question here]

B4. Priority question: Please explain the purpose of each of the subroutines included in the Excel VBA modules. In particular, please clarify why several separate

discrete event simulation models are provided (e.g. DES_IC_BPS(), SA_DES_BI_admin(), SA_DES_BSC_5y(), SA_DES_BSC_6m(), SA_DES_nonresp(), SA_DES_surgery()). These appear to be related to the running of scenario analyses. If so, please clearly indicate the exact subroutines (or sequences of subroutines) which were run for the base-case analysis and each of the scenario analyses presented in the submission. Please provide sufficient detail to allow the ERG to reproduce the analyses.

[Company: please enter your answer to this question here]

B5. Please provide evidence to support the assumption that the change in Interstitial Cystitis Syndrome Index recorded by Sant et al. (2003) is normally distributed within the trial arms.

[Company: please enter your answer to this question here]

B6. Please clarify why the utility values are based on the median Interstitial Cystitis Syndrome Index score in responders and non-responders (as shown in Figure 18) rather than using the mean Interstitial Cystitis Syndrome Index score. If possible, please conduct a sensitivity analysis to demonstrate that the use of the median rather than the mean had not resulted in significant bias.

[Company: please enter your answer to this question here]

B7. Priority question: The method used to estimate mean Interstitial Cystitis Syndrome Index scores for responders and non-responders assumes that responders always have lower Interstitial Cystitis Syndrome Index scores than non-responders. Please clarify whether this is supported by the data from Sant et al. (2003) by providing histograms of the Interstitial Cystitis Syndrome Index scores for patients categorised as responders and non-responders in each arm of the study. Please also provide the mean and standard deviations for Interstitial Cystitis Syndrome Index scores in responders and non-responders for each arm in the study.

[Company: please enter your answer to this question here]

B8. Please clarify why the model applies the Interstitial Cystitis Syndrome Index score for responders and non-responders calculated from the pentosane polysufate sodium arm of Sant et al. (2003) to the bladder instillation arm and the best

supportive care arm of the model (rather than using Interstitial Cystitis Syndrome Index scores specific to these arms).

[Company: please enter your answer to this question here]

B9. Priority question: In the sensitivity analysis, where options for response assessment is set to “OFF” (which sets the named range “selected_response” to 2), the Interstitial Cystitis Syndrome Index post-response assessment for bladder instillations is dependent on the Interstitial Cystitis Syndrome Index reduction for best supportive care (i.e. cell G45 on Sheet “Response & Utility data” is linked to cell G41 and not cell G40). Please explain why this is. If this is an error, please correct and incorporate within a corrected base-case model.

[Company: please enter your answer to this question here]

B10. Priority question: Page 107 of the submission states ‘The first 3 months of the study were assumed to correspond to the response check period’. However, Figure 17 reports the response check period in the company’s economic model to be 6 months. The number of patients at risk at the beginning of the Kaplan-Meier curve (1067 based on the survival analysis presented in the “Cost & Survival data” sheet of the economic model) seems to correspond to the number of patients who remained on treatment for more than 6 months in the Hanno (1997) study. (i.e. 2809 at study start minus 1412 who discontinued by 3 months and 330 who discontinued between 3 and 6 months). Please clarify if the survival analysis presented in Figure 19 excludes patients who discontinued in the first 3 months of Hanno et al. (1997) or excludes those who discontinued in the first 6 months.

[Company: please enter your answer to this question here]

B11. Please clarify why patients in Hanno et al. (1997) stopped treatment (for example, due to lack of response, adverse events, the cost of purchasing study medication, or the requirement to provide follow-up data).

[Company: please enter your answer to this question here]

B12. Priority question: Please provide the data from Hanno et al. (1997) that were used as inputs for the time to discontinuation survival analysis in sufficient detail for

the ERG to validate the reported analyses (i.e. the number at risk, discontinued and censored at each time point).

[Company: please enter your answer to this question here]

B13. Please clarify why only the exponential, Weibull and lognormal time to event distributions were fitted to the data from Hanno et al. (1997) and why alternative parametric survival functions (e.g. generalised gamma, Gompertz and log-logistic) were not fitted. Please provide analyses using these alternative parametric survival functions to demonstrate that the three chosen distributions are preferable.
[Company: please enter your answer to this question here]

B14. Priority question: Page 112 of the submission mentions that reporting guidance was followed but limited details are provided on the utility mapping study. Please provide a full report detailing the utility mapping study, including but not limited to;

a. study recruitment process
b. study questionnaire
c. statistical analysis plan
d. descriptive statistics for the population, including:
    i. the number of data available for each explanatory variable
    ii. means and standard deviations (or other relevant measures of central tendency and distribution) for explanatory variables and other important demographic or clinical variables
    iii. the maximum and minimum values observed for EQ-5D, Interstitial Cystitis Syndrome Index and Interstitial Cystitis Problem Index
e. results of any statistical tests conducted for differences in EQ-5D associated with demographic data, clinical variables or other explanatory variables (for example, results for the difference between bladder pain syndrome and interstitial cystitis/bladder pain syndrome described on page 20 of the submission)
f. results of the correlation analyses described on page 112 of the submission, which were conducted to examine the overlap between the Interstitial Cystitis Syndrome Index and Interstitial Cystitis Problem Index
g. the rationale for the choice of explanatory variables

h. the process used to identify the best fitting model from the set of possible models defined by the set of explanatory variables and the set of possible statistical models available (e.g Ordinary Least Squares, tobit, 2-part, Adjusted Limited Dependent Variable Mixture Model)

i. the variance-covariance matrix for the coefficients of the utility regression (to be incorporated in the probabilistic sensitivity analysis)

When responding to this question, please use the relevant reporting guidance for mapping studies such as the ISPOR best practice guidelines provided by Wailoo et al (Value in Health 2017, 20;18:18-27) or the MAPS statement (reference 82 in the company submission).

[Company: please enter your answer to this question here]

B15. With regards to the regression for mapping from Interstitial Cystitis Problem Index to EQ-5D, please clarify why the covariate for Hunner's lesions / glomerulations was not retained in the mapping model to allow the EQ-5D scores for the population with interstitial cystitis/bladder pain syndrome to be calculated for the economic modelling?

[Company: please enter your answer to this question here]

B16. With regards to the regression for mapping from Interstitial Cystitis Problem Index to EQ-5D, please clarify why previous treatment with bladder instillations was included as a covariate in the mapping algorithm but previous treatment with pentosan polysulfate sodium was not. If the reason was because this information was not gathered in the survey, please clarify why.

[Company: please enter your answer to this question here]

B17. Page 114 of the submission indicates that [redacted]. If this is the case, please clarify why "bladder installations in past 6 months - unsure" appears under the logit part of the model in Table 43. Please also clarify why being unsure of whether you had prior bladder instillations would be a reasonable explanatory variable for utility.

[Company: please enter your answer to this question here]

B18. Priority question: In the utility calculations, the regression coefficient “bladder instillations in past 6 months - yes” appears to be applied to all patients having bladder instillations in the model but not to any patient having pentosan polysulfate sodium or best supportive care. Please clarify whether this is the case. Please also clarify if the regression coefficient is applied in those patients who have stopped bladder instillation treatment after failing to respond and those who have responded at 6 months but then later discontinued. Please explain why prior use of bladder instillations is expected to be predictive of current utility, and indicate whether the face validity of this rationale was discussed with clinicians.

[Company: please enter your answer to this question here]

B19. Priority question: Appendix M states “it was agreed that if patients come off treatment, assuming that they go back to baseline utility is a conservative assumption. As there is likely to be some quality of life decrement as a result of treatment failure and the progressive nature of the condition.” This statement would suggest a utility lower than baseline in non-responders due to treatment failure and disease progression. However, in the model the utility values of non-responders who go on to have no subsequent treatment exceed the values of patients at baseline. Please explain the clinical rationale for this assumption.

[Company: please enter your answer to this question here]

B20. Please clarify whether scenario analyses were conducted to explore whether cost-effectiveness varies with starting age and if so, please provide the results of these analyses.

[Company: please enter your answer to this question here]

B21. Table 57 outlines that “response data (used for mapping)” are based on two individual studies (i.e. Sant et al. (2003) for best supportive care and elmiron and Nickel et al. (2015) for bladder instillations). However, Figures 11 and 12 indicate that the “response data (used for efficacy)” are based on the meta-analyses of GRA using the relative risk scale. Please explain why these data are taken from different sources. In particular, explain why there is a greater response for bladder

installations than pentosan polysulfate sodium in the data used for mapping, when there is a lower response in the data used for efficacy?

[Company: please enter your answer to this question here]

B22. Priority question: Please clarify why the patients who respond to placebo in the best supportive care arm of the economic model are assumed to have their treatment effect recede at 12 months, but all of the responders in the bladder instillations and pentosan polysulfate sodium arms of the model are assumed to have a durable response that persists until they discontinue? If the placebo response observed in the trial is related to patients being recruited during a disease "flare" (which goes on to resolve over the 6 month trial period), or if it is related to a better standard of basic care during the study or more frequent clinical contact, could this also happen in the intervention arms of the trials?

[Company: please enter your answer to this question here]

B23. Priority question: Please provide more details about the resource use survey (described in sections 3.4.3 and 3.5.1 of the submission) used to determine the relationship between Interstitial Cystitis Problem Index and cost / resource use. In particular, the text on page 118 states that both type and number of days were elicited for hospital admissions but only mean frequency appears in Table 49 and therefore no summary data is reported on the length of admission. Please provide a full description of this resource use survey and the analysis of the survey data including:

a. a copy of the questions used to gather resource use data
b. descriptive statistics for responses to each question
c. the rationale for the choice of explanatory variables
d. the method used to determine which resource use items were to be excluded (as described in page 119) because they were accounted for elsewhere in the model (please also clarify if these were excluded from the analysis reported in Table 49, or only from the analysis reported in Table 50)
e. the rationale for choosing a generalised linear model with gamma distribution and results for any alternative models that were considered but discounted.

[Company: please enter your answer to this question here]

B24. Please clarify specifically, whether when filling out the resource use survey described in sections 3.4.3 and 3.5.1, patients were asked to exclude any healthcare usage related to administration /monitoring of bladder instillations / pentosan polysulfate sodium which is already captured elsewhere in the model?

[Company: please enter your answer to this question here]

B25. Please describe how the healthcare resource group codes applied to the categories reported in the resource use survey in Table 49 were selected. Specifically, please clarify:

a. why the outpatient cost given in Table 49 uses the average of all outpatient visits rather than a outpatient cost specific to urology
b. what is meant by “specialist ward” in Table 49 (i.e. admission to urological wards only, or admission to other specialist wards)
c. why specialist ward cost used a weighted average for total healthcare resource group activity across the listed codes instead of a more specific stay type (such as elective inpatient, non-elective or day case)
d. why gynaecology is reported separately from “specialist ward” in Table 49.
e. why the healthcare resource group codes LB15E and LB18Z are considered most relevant for Emergency Department attendances, and what data was used to calculate the “weighted average” of these attendances
f. why the healthcare resource group codes for Emergency Medicine (those starting “VB”) are not used for this category of resource use

[Company: please enter your answer to this question here]

B26. The administration costs for bladder instillations in Table 54 are based on total healthcare resource group activity costs for ‘Introduction of therapeutic substance into the bladder procedure,LB17Z’. Why was a more specific cost for Urology outpatient costs for ‘Introduction of therapeutic substance into the bladder procedure’ not used?

[Company: please enter your answer to this question here]

B27. Page 121 of the submission indicates bladder installations are used “4 weekly”. Why is the cost per instillation multiplied by 12 and not 13 in cell D56 of the model inputs sheet?

[Company: please enter your answer to this question here]

B28. Priority question: The summary of product characteristics for pentosan polysulfate sodium states that “response to treatment with pentosan polysulfate sodium should be reassessed every 6 months”. Please clarify whether the need for clinical monitoring every 6 months would result in additional resource use compared to patients receiving bladder instillations and if so please explain how this is incorporated in the model.

[Company: please enter your answer to this question here]

B29. Priority question: Please clarify whether patients receiving pentosan polysulfate sodium require any regular blood tests (for example, to measure liver function, renal function, platelets, or clotting factors). If so, please clarify the tests required, their frequency, whether they would occur in primary or secondary care and how the costs of these monitoring tests have been incorporated in the economic analysis.

[Company: please enter your answer to this question here]

B30. Please clarify whether the analysis of hospital episode statistics data presented in Appendix O is used as a source of any model inputs or whether it simply provides supporting contextual information to the submission

[Company: please enter your answer to this question here]

B31. Page 108 of the submission states “Mean life expectancy was calculated across all age groups and standard deviations computed for use in the model.” Please clarify why the average mean life expectancy across all age groups is relevant, given knowledge of the age at baseline (and that age is related to life-expectancy).

[Company: please enter your answer to this question here]

B32. Priority question: Please explain why the mean life-expectancy for each starting age is based on the average of male and female life-expectancy and is not

weighted for the distribution of males/females, whereas the standard deviation is weighted by the male/female distribution. If this is an error, please correct and submit a revised base-case model. If doing so, please if possible also update the data to use the latest Office for National Statistics Life Tables released on the 25th of September 2018.

[Company: please enter your answer to this question here]

B33. Priority question: Please clarify why the economic model does not use life-table data to estimate a cumulative probability distribution for time to death and sample empirically from this distribution. Please justify the assumption that time to death is normally distributed around average life-expectancy.

[Company: please enter your answer to this question here]

B34. Please explain the rationale behind the method used to calculate the standard deviation of life-expectancy. In particular, please explain why these are based on the Office for National Statistics data for Lx given that the definition of Lx is "The number of survivors to exact age x of 100,000 live births of the same sex who are assumed to be subject throughout their lives to the mortality rates experienced in the year or years to which the life table relates," and therefore does not relate to the sample size used to estimate mean life-expectancy.

[Company: please enter your answer to this question here]

B35. Please clarify how it was determined that the chosen sample size of 10,000 patients was sufficient to produce consistent results, as stated in Table 38.

[Company: please enter your answer to this question here]

B36. Please clarify how it was determined that 1000 probabilistic sensitivity analysis samples was sufficient to provide stable estimates of incremental costs and incremental QALYs.

[Company: please enter your answer to this question here]

B37. Surgery as part of subsequent treatment is listed in the scenario analysis for pentosan polysulfate sodium vs. best supportive care. However, the results for this scenario are not included in Table 64. Please provide the results for this scenario

analysis within the table.

[Company: please enter your answer to this question here]

B38. Please confirm if the random number stream used to sample from the exponential distribution should also have been applied to the Weibull and lognormal time to event distributions when they are selected as options (i.e. rand(n,2) instead of rnd()). If so, then please correct and submit as part of a revised base-case analysis.

[Company: please enter your answer to this question here]

B39. For Figure 26, please explain why the bars fall solely on the left of the line for the second and third variables from the top.

[Company: please enter your answer to this question here]

B40. Please provide more details of the 3 cost-effectiveness studies that were excluded at the full-text sift.

[Company: please enter your answer to this question here]

B41. The submission suggests that health related quality of life/cost studies were excluded if they did not include any of the listed interventions / comparators. This exclusion criteria would exclude cohort studies examining the relationship between HRQoL/costs and measures of severity. However, Table 72 and Table 76 suggest that Hakimi et al. (2017) was included (despite no relevant intervention / comparator being listed). Please confirm if any studies of health related quality of life/costs in a relevant population were excluded based on the intervention/comparator exclusion criteria. If so, please provide bibliographic details for any studies excluded for this reason.

[Company: please enter your answer to this question here]

B42. Do the costs of bladder instillations used after pentosan polysulfate sodium account for the treatment pathway (which typically has weekly instillations for the first month, then monthly instillations thereafter)? If not, please explain why.

[Company: please enter your answer to this question here]

B43. The weighted average cost of sodium chondroitin sulphate is used for the costs of annual bladder instillation after pentosan polysulfate sodium. However, sodium hyaluronate is considered the first line bladder instillation in the UK and would be offered when patients come off pentosan polysulfate sodium onto bladder instillations. Please clarify why this cost was not used.

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1. Page 43 of the submission states “Concurrent: cimetidine, intravesical heparin, chronic use of acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or sedating histamine-1 receptor antagonists”. Are these permitted or disallowed medications?

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
ID1364_PPS_clarification letter - Company responses_130219_AIC.doc	1	Yes	13th Feb 2019
ID1364 pentosan clarification letter - Company responses_040619_ACIC	2	Yes	4th June 2019
ID1364 pentosan clarification letter - Company responses_040619_ACIC_v3	3	Yes	5th Sept 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question: Please explain why the comparators heparin, lidocaine, sodium bicarbonate or hydrocortisone (which are used as off-label instillations and as subsequent therapies in the UK) are not included in the clinical effectiveness searches outlines in Appendix D.1

Response

We propose to answer Questions A1 and A4 together as we believe that they are closely related.

To answer these questions it is necessary to take into account the development of agents used to treat IC/BPS and appreciate that, historically (and sadly still the case now), there were few approved treatments for this condition.

The bladder instillation dimethyl sulfoxide (DMSO, brand name RIMSO-50) was the first and remains the only FDA-approved bladder instillation specifically for interstitial cystitis; approved in 1978. However, DMSO was never approved for IC/BPS in the UK and because of this and its unpleasant side effect profile is rarely used in the UK. Pentosan polysulfate sodium (elmiron®) was approved by the FDA in 1996 “for the treatment of interstitial cystitis”, but elmiron® only received European marketing

authorisation for IC/BPS in 2017. The commercially available bladder instillations such as Cystistat® (sodium hyaluronate) and Hyacyst® (sodium hyaluronate) were registered as Medical Devices in the UK during the last 10 or so years but these preparations are not FDA approved.

Therefore, over the years, a number of recipes were created for bladder instillations when the current commercially available bladder instillations were not on the market. These locally prepared instillations, also known as 'bladder cocktails', contain various commonly available injectable products (used off-label), which are drawn into a syringe and instilled via a catheter. Typically these will include heparin, a local anaesthetic, an alkalising agent and potentially a corticosteroid and/or an antibiotic. DMSO may also be added to some cocktails, where it is available. The better-known cocktails are named after a physician such as Parsons or Whitmore (as described in question A4). For example, "Whitmore cocktail" (developed by Kristene Whitmore, MD) has bupivacaine, heparin, hydrocortisone, and sodium bicarbonate with or without gentamicin depending on recent UTI history. "Parsons solution" (C. Lowell Parsons, MD) contains heparin, lidocaine and sodium bicarbonate or other buffering agent. Overall, various recipes exist for these cocktails, but they are essentially local and therefore may vary significantly in both composition and dosage regime.

Whilst some UK clinicians may still prepare instillations locally and use such bladder instillations (as per "Appendix 2" in Appendix M), our understanding is that this is not routine and the majority will use one of the commercially available bladder instillations now these are available.

Additionally, most of the ingredients used in these cocktails have other, licensed uses and routes of administration and this would make tracking their use for IC/BPS by any system extremely difficult.

In summary, locally prepared, off-label, bladder cocktails, which can vary by site and include commonly used drugs indicated for other conditions, have not been included in the submission because of the current relatively infrequent use in the UK, the heterogeneity of the mixtures and usage, and the difficulty in sourcing relevant data.

A2. Please provide the search strategies used to identify the non-randomised controlled studies included in Table 27 of the company submission.

Response

To identify all relevant non-randomised studies a literature search using the control terms:

- "cystitis, interstitial" OR ("cystitis" AND "interstitial") OR "interstitial cystitis"

AND

- "pentosan sulfuric polyester" OR ("pentosan" AND "sulfuric" AND "polyester") OR ("pentosan" AND "polysulfate") OR "pentosan polysulfate"

was conducted in DIMDI, MedPilot, and PubMed.

Relevant publications identified after a first review of abstracts were studied in more detail to extract the required information. In addition, relevant references cited in the publications identified as described were hand searched and evaluated."

A3. Please explain why a conference abstract limit was applied to the Embase search strategy described on pages 155-156 of Appendix D. Does this limit exclude any unpublished studies?

Response

Conference abstracts were listed as excluded studies in the final search protocol, so a filter designed to exclude conference abstracts was applied to the Embase search strategy. Had insufficient published studies been identified for the review the search would have been re-run without the conference abstracts filter, but this was not the case. The Cochrane Central Trials Register (CENTRAL), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) were all searched without any limits to identify any unpublished/ in-process trials.

A4. Priority question: The proposed treatment pathway in the 'Appendix 2' diagram in Appendix M includes locally prepared bladder instillations (e.g. Parson's, Whitmore). Please clarify why these treatments are not included in the submission.

Response

Please see our response to A1.

A5. The Bade et al. (1997) study mentioned in Appendix D Table 67 is available free to download online and contains outcomes relevant to the scope. Please clarify why this study has been excluded from the literature review.

Response

The study by Bade et al (1997) compares intravesical PPS compared with placebo bladder instillations. This is not the same as elmiron®, the subject of this appraisal, which is an oral medicine (100 mg PPS as hard capsules).

A6. Appendix D Table 67 indicates that Gottsch et al. (2011) was excluded because it does not contain the relevant outcomes. However, the study appears to contain outcomes included in the scope. Please clarify why this study has been excluded.

Response

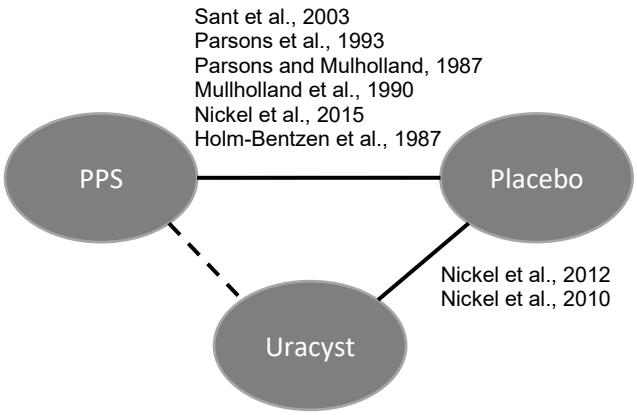
The study by Gottsch et al. was excluded from the review as it did not include any interventions relevant to the appraisal as it compared botulinum toxin to placebo. Following consultation on the draft scope for this appraisal, botulinum toxin was removed from the list of relevant comparators as it is not routinely used in the standard care of patients with IC/BPS and it was agreed that bladder instillations are the relevant comparator for this appraisal. The reason for exclusion in Table 67 should read 'comparator' rather than ‘outcomes’.

A7. In Figure 9 of the submission, only 5 of the 6 identified randomised controlled trials in pentosan polysufate sodium are presented for the network link between pentosan polysufate sodium and placebo. Please clarify why one trial has been excluded.

Response

Thank you for highlighting this. The trial by Mullholland et al 1990 (Mulholland et al., 1990) is missing from the figure as a link between the PPS and placebo comparators. Please note that this trial was included in the analysis. Please see the revised figure below.

Figure 1. Revised figure for possible global response assessment network



A8. In Appendix M, the advisory board recommends that the comparability of bladder capacity across trials be assessed. Please summarise the data on bladder capacity across the included trials. If this had been done already, please indicate where this is already summarised in the submission.

Response

It is important to recognise that there are different ways to measure “bladder capacity” and that it is not possible to compare across these different methodologies. “Anaesthetic bladder capacity” is when bladder capacity is tested by instilling fluid into the bladder when the patient is under anaesthetic (because it is a painful process in BPS patients) to find out the maximum capacity of the bladder; this can be referred to as anatomical bladder capacity.

Bladder capacity can also be assessed based on the volumes voided under normal, everyday conditions. This is referred to as functional bladder capacity and, in healthy adults, ranges from approximately 300 to 400 mL.

The reporting of bladder capacity in the 6 included trials is as follows.

Sant et al. (2003) (Sant et al., 2003): Not reported in the paper.

Parsons et al. (1993) (Parsons et al., 1993): Mean anaesthetic bladder capacity at baseline was 656 cc in the PPS group and 601 cc in the placebo group. No follow-up bladder capacity data were reported.

Mulholland et al. (1990) (Mulholland et al., 1990): Mean anaesthetic bladder capacity at baseline was 569 cc in the PPS group and 585 in the placebo group. No follow-up data on bladder capacity were reported (volume per void outcomes were reported and are in Table 23 of the submission).

Parsons et al. (1987) (Parsons and Mulholland, 1987): This study reported bladder capacity but did not state whether this was functional or anatomical/anaesthetic bladder capacity. There was no change in bladder capacity in the placebo group but the PPS group had an increase in bladder capacity (p=0.6). Average voided volume outcomes are reported in Table 23 of the submission.

Nickel et al. (2015) (Nickel et al., 2015): Not reported in the paper.

Holm-Bentzen et al. (1987) (Holm-Bentzen et al., 1987): Data on maximum bladder capacity under anaesthesia and functional bladder capacity are reported in Figure 5 and Figure 6 of the submission, respectively. Bladder capacity data were reported graphically; maximum bladder capacity under anaesthesia was approximately 250–300 mL at baseline in Protocol A patients and 450–600 mL in Protocol B patients. In patients receiving PPS there was a significant improvement in maximum bladder capacity under anaesthetic ($p<0.05$). The median functional bladder capacity was approximately 125 mL at baseline in Protocol A patients and 175–200 mL in Protocol B patients. There were no significant changes from baseline following either placebo or PPS treatment.

“Bladder capacity” data in the trials are limited and different methodologies for assessing bladder capacity were used. However, where data are available using the same testing procedures, the data do appear comparable particularly with regard to the four core registration trials (Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987). It is worthwhile remembering that the populations from these trials were considered sufficiently similar for the EMA when granting a marketing authorisation for PPS.

A9. Please explain why the results from Nickel et al. (2015) for the subgroup meeting the National Institute of Diabetes and Digestive and Kidney criteria are not provided

in the submission. Please clarify whether this subgroup would match the population indicated for oral pentosane polysulfate sodium.

Response

As noted in Section B.2.4 of the Company Submission, a subgroup analysis of patients meeting NIDDK criteria in the 2015 study by Nickel (Nickel et al., 2015) is presented in the EPAR (Committee for Medicinal Products for Human Use (CHMP), 2016). This subgroup represented 25% of patients included in the study. Whilst this analysis is representative of the IC/BPS population, it was a post hoc analysis that may be subject to bias. Patients were not stratified by NIDDK status in the randomisation of the trial and breaking the randomisation in the analysis is likely to lead to bias in the estimates of relative treatment effect.

A9. Please provide the citation(s) for the quality assessment method used in Table 18 of the company submission and Table 68 of Appendix D.

Response

The citations for the quality assessment methods are as follows: CRD (2009). Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care. J. Higgins (ed.). [Online]. University of York. Available from: https://www.york.ac.uk/inst/crd/index_guidance.htm. (CRD, 2009)

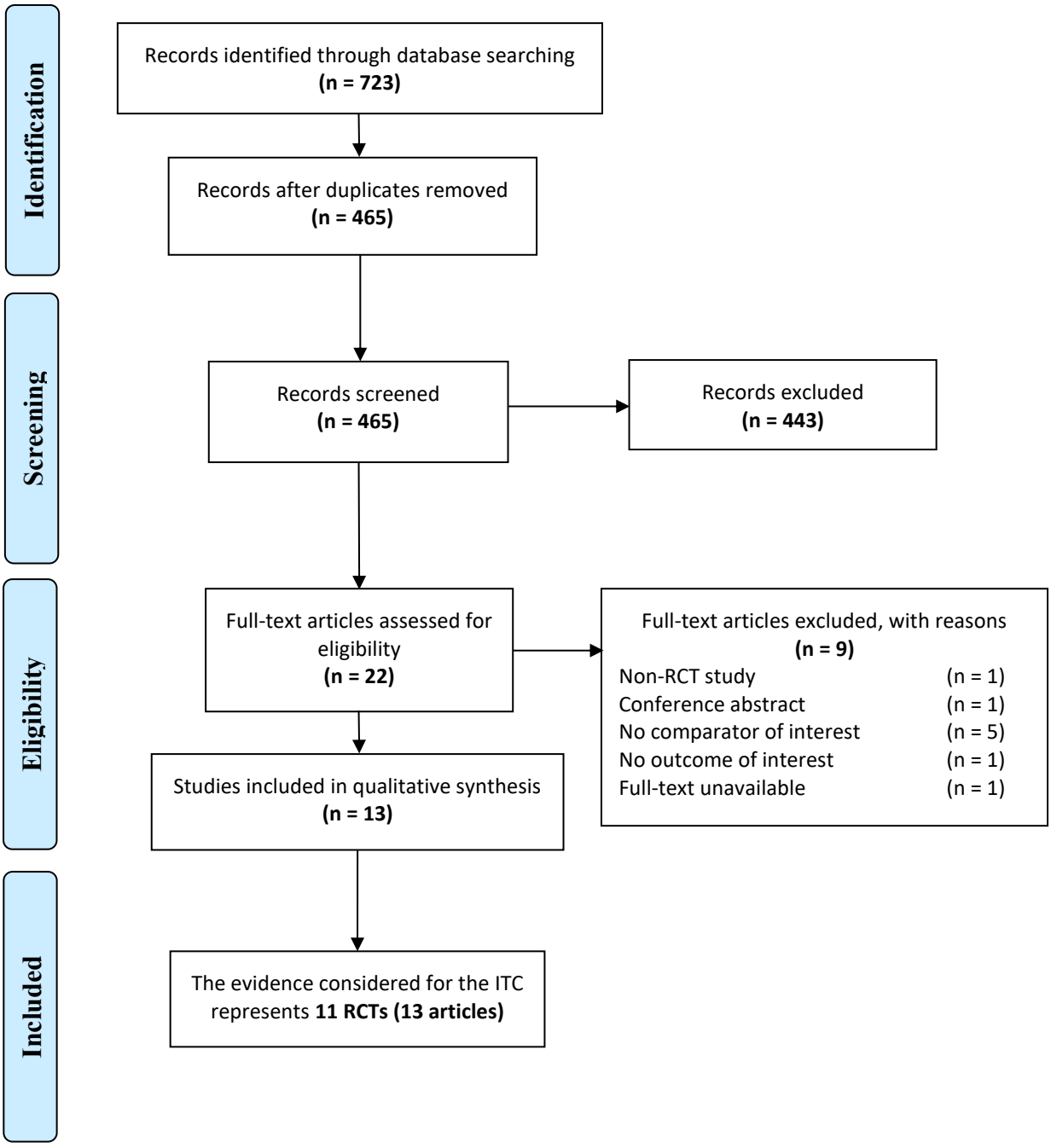
Higgins, J. and Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0. J. Higgins & S. Green (eds.). [Online]. Available from: http://training.cochrane.org/handbook. (Higgins and Green, 2011)

Appendix C in NICE (2012). *The guidelines manual: appendices B-I*. [Online]. Available from: https://www.nice.org.uk/process/pmg6/resources/the-guidelines-manual-pdf-3304416006853. (NICE, 2012)

A10. Page 82 of the company submission reports that 12 trials met the inclusion criteria for the indirect treatment comparison. However, Figure 27 in Appendix D reports that 15 randomised controlled trials met the inclusion criteria. Please clarify why there is a difference in the numbers reported.

Response

Thank you for highlighting this; there is an error in page 82 and Figure 27. The correct number of trials/studies is shown in the amended PRISMA flow (Figure 27) below. (See also response to A12)



A11. Figure 27 in Appendix D reports that 13 articles relating to 15 randomised controlled trials were considered for the indirect treatment comparison. However, Table 66 in Appendix D presents 13 articles that relate to only 11 randomised

controlled trials. Please provide the citations and study details for the other 4 randomised controlled trials considered for the indirect treatment comparison.

Response

Please refer to the revised PRISMA flow in A10.

A12. For page 82 of the company submission, please provide in-text citations as indicated in the following paragraph: 'Twelve trials met the inclusion criteria [please insert citations]. Six trials compared PPS capsules to oral placebo [please insert citations], three Uracyst® to placebo instillation [please insert citations] and one each of Uracyst® to DMSO instillation [please insert citation], iAluRil® to DMSO instillation [please insert citation] and Cystistat® to Gepan® [citation please insert citation]'.

Response

The revised text with added citations is as follows: 'Eleven trials met the inclusion criteria (Nickel et al., 2015; Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Holm-Bentzen et al., 1987; Parsons and Mulholland, 1987; Nickel et al., 2010; Tutolo et al., 2017; Cervigni et al., 2017; Gülpınar et al., 2018; Nickel et al., 2012). Six trials compared PPS capsules to oral placebo (Nickel et al., 2015; Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Holm-Bentzen et al., 1987; Parsons and Mulholland, 1987), two Uracyst® to placebo instillation (Nickel et al., 2010, 2012) and one each of Uracyst® to DMSO instillation (Tutolo et al., 2017), iAluRil® to DMSO instillation (Cervigni et al., 2017) and Cystistat® to Gepan® (Gülpınar et al., 2018)'

A13. Please clarify whether the Johnson & Johnson (2014) citation included in Table 66 of Appendix D is the study record for the Nickels et al (2015) study (i.e. 2 citations for 1 study)?

Response

Johnson & Johnson (2014) is the study record for the Nickel et al. (2015) study.

A14. Please clarify whether the Watson Pharmaceuticals (2013) citation included in Table 66 of Appendix D is the study record for the Nickels et al (2012) study (i.e. 2 citations for 1 study)?

Response

Watson Pharmaceuticals (2013) is the study record for the Nickel et al. (2012) study.

A15. Please clarify why alternative approaches to conducting an indirect comparison between pentosan polysufate sodium and bladder installations (such as that described in 'NICE Decision Support Unit Technical Support Document 18) have not been explored.

Response

NICE Decision Support Unit Technical Support Document 18 provides guidance on methods of indirect comparison where individual patient level data are available from one or more trials. Individual level patient data were not available to Consilient Health for any of the trials and therefore these methods could not be utilised.

A16. Please specify the 'standard of care' in the 4 placebo-controlled studies of pentosan polysufate sodium used in the meta-analyses described on pages 78-81 of the submission.

Response

Information on 'standard of care' is not provided in any of the trials.

A17. Is the effect of treatment with pentosan polysufate sodium identical in each study (assuming an appropriate additive scale)? Could the treatment effect vary between studies?

Response

We do not have adequate evidence to infer the absence of heterogeneity across the considered clinical trials. We have conducted an assessment of heterogeneity as part of our meta-analyses. Please also see response for question A23.

A18. In clinical practice, what is the expected response to standard of care (when standard of care corresponds to the placebo used in the trials)?

Response

We have interpreted this question to ask what response would be expected for patients not receiving PPS or bladder instillations in current practice. The main change in clinical practice since the trials were conducted is that standardised, commercially-available bladder instillations are now routinely used in the treatment of BPS. As noted in our submission, it is difficult to disentangle the effect of placebo in the clinical trials of PPS and BIs. We are unaware of any contemporary data reporting the 'response' to standard of care i.e. initial treatments (e.g. pain management, etc). In our analysis, we have adopted a highly conservative approach of assuming the placebo effect would be observed in clinical practice for a year for patients not receiving PPS or BIs, even though this response is likely to be due to participation in the trials. Please note that this assumption is likely to underestimate the effectiveness of PPS.

A19. Page 77 of the company submission states "There was a high degree of homogeneity in this sensitivity meta-analysis". Please clarify whether this applies to the analysis of the 4 or 6 studies.

Response

The Q-value of 0.470 relates to the analysis of the four trials (Sant et al 2003, Parsons et al 1993, Pasons and Mullholland 1987 and Mullholland et al 1990) and indicates a higher degree of homogeneity compared to the analysis including the additional two trials.

A20. Relating to page 79 of the company submission, please clarify the relevance of the lower bound of the confidence interval (6.3%) being greater than 5%?

Response

Our statement was meant to highlight the additional information of the CI's about the plausibly true effects, that the lower bound of the confidence interval is notably higher than the 0% and represents an improvement that is both statistically significant and clinically meaningful.

A21. Page 79 of the company submission reports that the meta-analysis by Hwang et al (1997) included 448 patients, whereas Figure 11 reports this number as 454. Please clarify why there is a difference in the numbers reported.

Response

Different studies were used for our meta-analysis (Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987) and that by Hwang et al. (Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987; Holm-Bentzen et al., 1987), which explains the discrepancies in patient numbers. The study by Hwang et al does not report meta-analyses for the GRA outcome and is therefore not directly comparable to that reported in Figure 11. The publication by Hwang et al. (1997) (Hwang et al., 1997)reports meta-analyses for 4 outcomes (pain, urgency, frequency and nocturia) and states that this was based on a total of 448 subjects from 4 trials. The number of subjects and trials varied for each of the analyses. The results showed that the overall success rates for PPS were 37% for pain (n=398), 28% for urgency (n=306), 54% for frequency (n=160) and 48% for nocturia (n=106).

A22. Table 30 of the submission reports the number of events and number of patients randomised in Nickel et al (2010) as 'NR'. However, these values are reported in Figure 13. Please confirm where these numbers were obtained.

Response

The numbers reported in Figure 13 of the dossier were obtained from the Nickel et al. (2010) paper (7 GRA responders in the control group and 12 in the chondroitin sulphate group at week 12). These values can be found in Table 2 of the Nickel paper (week 12) (Nickel et al., 2010). The numbers reported in Figure 13 are also shown in Table 30; however, the entries for GRA at follow-up (SD) and GRA response at follow-up (%) are erroneously reversed in Table 30. Please see Table 1 below for a correction.

Table 1. Nickel et al. 2010 – patient responder data

Study	**Nickel et al., 2010** [68]
GRA at follow-up (SD)	NR

GRA response at follow-up (%)	Week 7: 13 (39.4) Week 12: 12 (41.4)	Week 7: 7 (22.6) Week 12: 7 (23.3)

A23. Please expand on the "assessment of heterogeneity" described on page 85 of the company submission.

Response

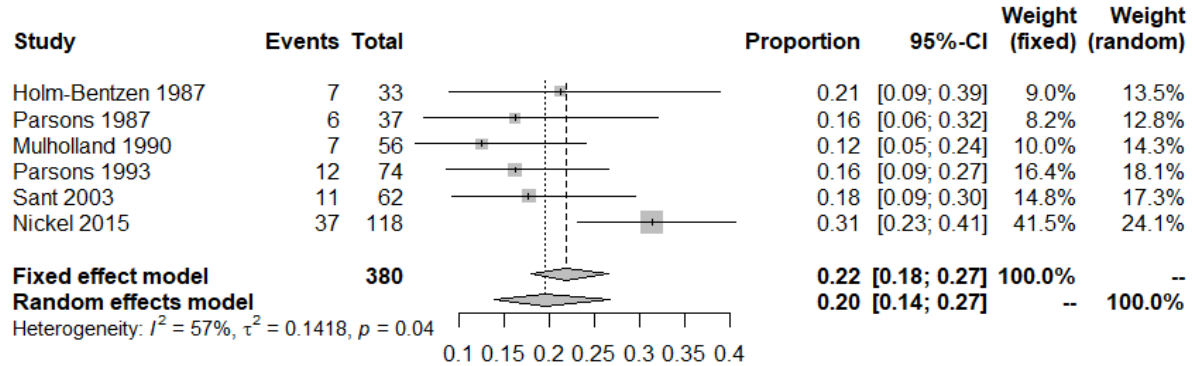
A fixed effect model was chosen if the Q-value was not statistically significant (where a statistically significant result was defined as p<0.1) and the I-squared statistic was ≤ 40%, otherwise a random effects model was selected.

A24. Please provide input data and results of the additional meta-analyses described on page 133 of the company submission, which included the Holm Bentzen (1987) & Nickel (2015) trials.

Response

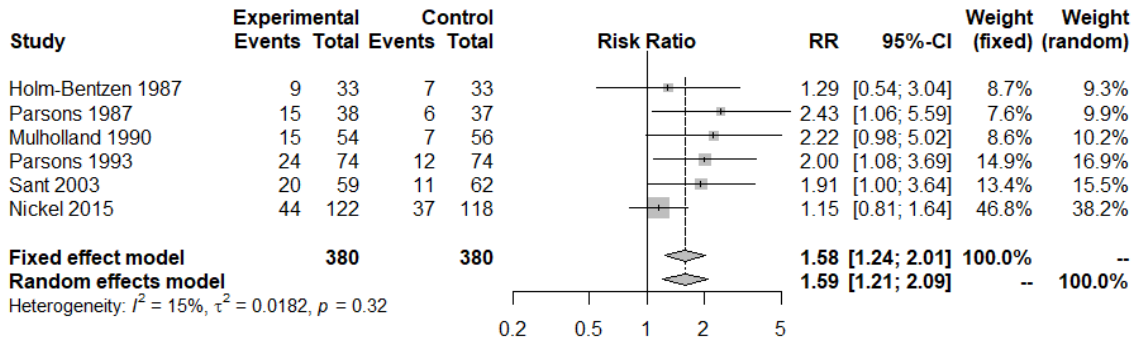
Additional meta-analyses which include the Holm Bentzen (1987) (Holm-Bentzen et al., 1987) & Nickel (2015) (Nickel et al., 2015) trials is provided in the figures below.

Figure 2. Meta-analysis of placebo response rate



Q-statistic: 11.54; Degrees of freedom: 5; P-value: 0.0417

Figure 3. Meta-analysis of PPS RR



Q-statistic: 5.88; Degrees of freedom: 5; P-value: 0.3184

Please note that PPS is still shown to compare favourably to BSC following the addition of the two studies with the broader BPS populations, even though these patients may not fall within the PPS licensed indication.

Section B: Clarification on cost-effectiveness data

B1. The published cost-effectiveness studies section of Appendix G says that no timeframe limit was applied to the search. However, the cost effectiveness evaluations search strategy shows that the date limit 2015-current was applied. Table 69 suggests the eligibility criteria for cost-effectiveness studies is from 1992-present. Please confirm whether a timeframe limit was applied to search.

Response

A timeframe of 1992–present was applied to all economics searches including the cost-effectiveness evaluations searches. As NHS Economic Evaluations Database (NHSEED) coverage is limited to 1995–2014 only it was searched without any date limits. Additional searches were run in Medline and Embase (using the published NHSEED search strategy) to cover the periods 1992–1994 and 2015–present. Full strategies used are listed in a separate document we provide as part of our response to this clarification letter.

B2. Appendix G only contains 1 of the 3 search strategies used to identify cost-effectiveness evaluations and economic models. Please provide strategies for all databases searched.

Response

The search strategies are provided as a separate document.

B3. Appendices H and I indicate that electronic databases, Medline and Embase were searched to identify studies relating to health-related quality-of-life, cost and healthcare resource use. Please provide the full search strategies for all databases.

Response

The search strategies are provided as a separate document.

B4. Priority question: Please explain the purpose of each of the subroutines included in the Excel VBA modules. In particular, please clarify why several separate discrete event simulation models are provided (e.g. DES_IC_BPS(), SA_DES_BI_admin(), SA_DES_BSC_5y(), SA_DES_BSC_6m(), SA_DES_nonresp(), SA_DES_surgery()). These appear to be related to the running of scenario analyses. If so, please clearly indicate the exact subroutines (or sequences of subroutines) which were run for the base-case analysis and each of the scenario analyses presented in the submission. Please provide sufficient detail to allow the ERG to reproduce the analyses.

Response

As noted in your comment, we assigned different VBA modules to run a number of scenario analyses which require more than a change of input. This was done with an aim to keep the code of the core engine (DES_IC_BPS()) as clear as possible. In the "SA" modules we complement the core code with a few lines that enable us to run the scenario analyses in an efficient way. The functionality to access these scenarios is at the lower part of the DSA worksheet (green buttons). The corresponding scenarios to every module are provided in the table below.

Table 2 VBA modules for core engine and scenario analyses

VBA module	Purpose
DES_IC_BPS	Core engine
SA_BI_admin	Scenario analysis - 10% self-administration of BIs (assuming 10% of bladder instillations are self-administered) – implemented as a 10% reduction in administration costs
SA_BSC_5y	Scenario analysis - BSC effect receding at 5 years - assuming the utility and background costs for “responders” will default to the values attributed to non-responders)
SA_BSC_6m	Scenario analysis - BSC effect receding at 6 months - assuming the utility and background costs for “responders” will default to the values attributed to non-responders)

SA_ICPI	Scenario analysis - ICPI based utilities and background costs – exploring the results using a utility mapping algorithm based on ICPI instead of ICSI
SA_nonresp	Scenario analysis - Baseline utility and background costs given to non-responders – assuming non-responders receive no benefit after receiving treatment
SA_surgery	Scenario analysis - Surgery as part of subsequent treatment

B5. Please provide evidence to support the assumption that the change in Interstitial Cystitis Syndrome Index recorded by Sant et al. (2003) is normally distributed within the trial arms.

Response

As highlighted in our submission, Consilient Health does not hold patient level data in order to draw conclusions on how the ICSI data in Sant (2003) (Sant et al., 2003) is distributed. Therefore, the normal distribution was selected due to the absence of data highlighting the use of alternative distribution and due to its ability to represent both negative and non-negative values.

To clarify, the ICSI is an abbreviation of the Interstitial Cystitis Symptom Index. This is one part of the O'Leary Sant measure; the other being the Interstitial Problem Symptom Index (ICPI).

B6. Please clarify why the utility values are based on the median Interstitial Cystitis Syndrome Index score in responders and non-responders (as shown in Figure 18) rather than using the mean Interstitial Cystitis Syndrome Index score. If possible, please conduct a sensitivity analysis to demonstrate that the use of the median rather than the mean had not resulted in significant bias.

Response

The median was simpler to estimate and was considered more intuitive to interpret (Table 3). In theTable 4 below we provide the mean estimates using the formulas for truncated normal distributions and their effect on the model results. Using the median estimates rather than the mean did not result in bias but was found to lead to a more conservative estimation of the ICER.

Table 3. Results using median estimates (base case)

Median ICSI difference for non-responders		-1.11
Median ICSI difference for responders		-5.85
Results (with median estimates)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]

Table 4. Results using mean estimates

Mean ICSI difference for non-responders		-0.72
Mean ICSI difference for responders		-6.27
Results (with mean estimates)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]

B7. Priority question: The method used to estimate mean Interstitial Cystitis Syndrome Index scores for responders and non-responders assumes that responders always have lower Interstitial Cystitis Syndrome Index scores than non-responders. Please clarify whether this is supported by the data from Sant et al. (2003) by providing histograms of the Interstitial Cystitis Syndrome Index scores for patients categorised as responders and non-responders in each arm of the study. Please also provide the mean and standard deviations for Interstitial Cystitis Syndrome Index scores in responders and non-responders for each arm in the study.

Response

As highlighted in our submission, Consilient Health does not hold patient-level data that would enable us to obtain ICSI figures relevant to responders and non-responders. GRA is a symptom-based instrument, therefore by definition, patients that respond to pentosan polysulfate sodium would see a greater improvement in their symptoms compared to non-responders.

B8. Please clarify why the model applies the Interstitial Cystitis Syndrome Index score for responders and non-responders calculated from the pentosan polysulfate sodium arm of Sant et al. (2003) to the bladder instillation arm and the best supportive care arm of the model (rather than using Interstitial Cystitis Syndrome Index scores specific to these arms).

Response

As noted in our submission, the ICSI difference estimated for responders and non-responders based on PPS data was used across all model arms for consistency of modelled benefit for a response. Attributing different benefits to responders of different trial arms would introduce another layer of uncertainty into our analysis.

B9. Priority question: In the sensitivity analysis, where options for response assessment is set to “OFF” (which sets the named range “selected response” to 2), the Interstitial Cystitis Syndrome Index post-response assessment for bladder instillations is dependent on the Interstitial Cystitis Syndrome Index reduction for best supportive care (i.e. cell G45 on Sheet “Response & Utility data” is linked to cell G41 and not cell G40). Please explain why this is. If this is an error, please correct and incorporate within a corrected base-case model.

Response

The selected response switch and the corresponding scenario analysis was only conducted as a model validation exercise. Results from this analysis were not used for either the base case or any of the scenario analyses of the company submission. We have now removed this switch from the model.

B10. Priority question: Page 107 of the submission states ‘The first 3 months of the study were assumed to correspond to the response check period’. However, Figure 17 reports the response check period in the company’s economic model to be 6

months. The number of patients at risk at the beginning of the Kaplan-Meier curve (1067 based on the survival analysis presented in the “Cost & Survival data” sheet of the economic model) seems to correspond to the number of patients who remained on treatment for more than 6 months in the Hanno (1997) study. (i.e. 2809 at study start minus 1412 who discontinued by 3 months and 330 who discontinued between 3 and 6 months). Please clarify if the survival analysis presented in Figure 19 excludes patients who discontinued in the first 3 months of Hanno et al. (1997) or excludes those who discontinued in the first 6 months.

Response

Thank you for your comment. The reference to the "first 3 months of the study" should read "first 6 months of the study". The survival analysis excludes those who discontinued in the first 6 months.

B11. Please clarify why patients in Hanno et al. (1997) stopped treatment (for example, due to lack of response, adverse events, the cost of purchasing study medication, or the requirement to provide follow-up data).

Response

The reasons for discontinuation are summarised in Table II from Hanno et al. (1997) (Hanno, 1997) shown below:

TABLE II. ***Distribution of patient status by length of participation (patients enrolled before 3/1/96)***

Length of Participation (months)	Total Patients (%)	Active Patients	Inactive Patients†	Discontinued Patients	Reason for Discontinuation				
					Adverse Event	Failed to Return	Death	Lack of Efficacy	Other‡
0–3*	1412 (50)	123	50	1239	297	90	2	381	407
3–6	330 (12)	55	9	266	40	15	1	90	102
6–12	353 (13)	83	15	255	30	19	0	99	89
12–18	166 (6)	46	10	110	19	10	1	24	46
18–24	116 (4)	37	3	76	14	4	0	19	33
24–36	149 (5)	63	8	78	14	6	3	16	32
36–48	88 (3)	40	6	42	9	8	0	3	14
48–60	67 (2)	38	3	26	6	2	0	3	13
60+	128 (5)	100	8	20	3	0	0	1	9
Total	2809 (100)	585	112	2112	432	154	7	636	745

* *Most of the patients in this interval did not have any reorders.*
† *Patents lost to follow-up since 8/1/95.*
‡ *Never took study drug, switched to other treatments, transferred physicians, financial, relocated, surgery, unknown, etc.*

B12. Priority question: Please provide the data from Hanno et al. (1997) that were used as inputs for the time to discontinuation survival analysis in sufficient detail for

the ERG to validate the reported analyses (i.e. the number at risk, discontinued and censored at each time point).

Response

The Stata do file we have provided with these response uses the data reported in Table II of Hanno et al. (1997) (Hanno, 1997) to generate a patient level dataset in which individuals discontinue/are censored within the time periods reported in Table II. The resulting dataset is also provided as part of these responses.

B13. Please clarify why only the exponential, Weibull and lognormal time to event distributions were fitted to the data from Hanno et al. (1997) and why alternative parametric survival functions (e.g. generalised gamma, Gompertz and log-logistic) were not fitted. Please provide analyses using these alternative parametric survival functions to demonstrate that the three chosen distributions are preferable.

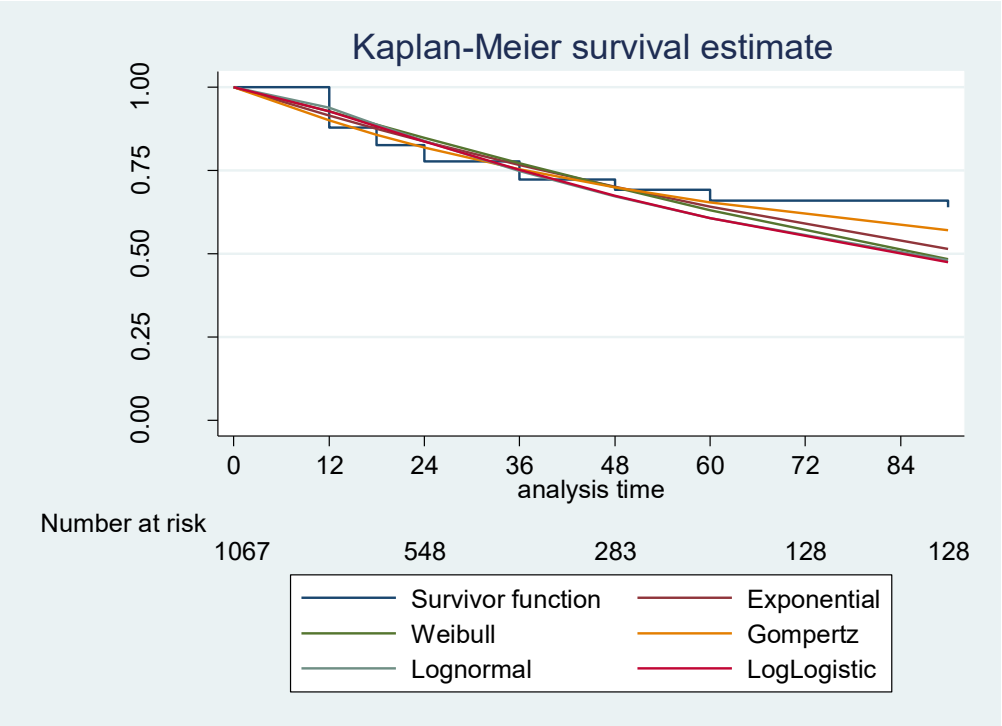
Response

As noted in our submission, we found the exponential, lognormal and Weibull to provide a reasonable range of plausible scenarios. For completeness, we provide the remaining distributions with the relevant summary statistics.

Table 5. Summary statistics - parametric curves for treatment discontinuation

Parametric curve	AIC	BIC	Mean time (years)	Median time (years)	Notes
Exponential	1556.23	1561.20	11.26	7.81	
Weibull	1553.259	1563.205	9.58	7.20	
Gen-Gamma	NA	NA	NA	NA	DNC
Gompertz	1547.576	1557.521	NA	10.88	
Lognormal	1479.714	1489.659	15.70	7.03	
Log-log	1523.13	1533.075	23.75	6.92	
DNC: Did not converge; NA: Not available					

Figure 4. Parametric curves for treatment discontinuation



B14. Priority question: Page 112 of the submission mentions that reporting guidance was followed but limited details are provided on the utility mapping study. Please provide a full report detailing the utility mapping study, including but not limited to;

a. study recruitment process

b. study questionnaire

c. statistical analysis plan

d. descriptive statistics for the population, including:

   i. the number of data available for each explanatory variable

   ii. means and standard deviations (or other relevant measures of central tendency and distribution) for explanatory variables and other important demographic or clinical variables

   iii. the maximum and minimum values observed for EQ-5D, Interstitial Cystitis Syndrome Index and Interstitial Cystitis Problem Index

e. results of any statistical tests conducted for differences in EQ-5D associated with demographic data, clinical variables or other explanatory variables (for example, results for the difference between bladder pain syndrome and interstitial cystitis/bladder pain syndrome described on page 20 of the submission)

f. results of the correlation analyses described on page 112 of the submission, which were conducted to examine the overlap between the Interstitial Cystitis Syndrome Index and Interstitial Cystitis Problem Index

g. the rationale for the choice of explanatory variables

h. the process used to identify the best fitting model from the set of possible models defined by the set of explanatory variables and the set of possible statistical models available (e.g Ordinary Least Squares, tobit, 2-part, Adjusted Limited Dependent Variable Mixture Model)

i. the variance-covariance matrix for the coefficients of the utility regression (to be incorporated in the probabilistic sensitivity analysis)

When responding to this question, please use the relevant reporting guidance for mapping studies such as the ISPOR best practice guidelines provided by Wailoo et al (Value in Health 2017, 20;18:18-27) or the MAPS statement (reference 82 in the company submission).

Response

A detailed technical report has been developed to describe the mapping study and is provided with this response. The MAPS: reporting statement for studies mapping onto preference-based outcome measures guidance was followed (Petrou, Rivero-Arias et al. 2015) The study recruitment process, study questionnaire and descriptive statistics for the population are presented in the report. Statistical analysis plan and study protocol are presented as separate documents.

The variance-covariance matrices for the two-part model are reported below and have been incorporated into the PSA.

Table 6. Variance-covariance matrix – Logit model

ICSI_score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-54 yo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55-64 yo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI unsure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
_cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Variance-covariance matrix – OLS model

ICSI_score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-44 yo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

45-54 yo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55-64 yo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hadBI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI unsure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
_cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B15. With regards to the regression for mapping from Interstitial Cystitis Problem Index to EQ-5D, please clarify why the covariate for Hunner's lesions / glomerulations was not retained in the mapping model to allow the EQ-5D scores for the population with interstitial cystitis/bladder pain syndrome to be calculated for the economic modelling?

Response

Presence of lesions was not retained in the model because it was not statistically significant in the model outputs. The relationship of patient characteristics and clinical characteristics were investigated in subgroup analyses and those considered statistically significant were included in the mapping model (see Table 10 of the mapping summary report). The models including covariates (age and bladder instillation) had better overall performance, based on model fit statistics, the predicted and observed utility and model validation (please see section 4.3 and 4.4 of the mapping summary report for details).

B16. With regards to the regression for mapping from Interstitial Cystitis Problem Index to EQ-5D, please clarify why previous treatment with bladder instillations was included as a covariate in the mapping algorithm but previous treatment with pentosan polysulfate sodium was not. If the reason was because this information was not gathered in the survey, please clarify why.

Response

Recent experience of bladder instillation was included in the mapping algorithm predicting EQ-5D values from the Interstitial Cystitis Problem Index and the mapping algorithm predicting EQ-5D values from the Interstitial Cystitis Symptom Index.

As PPS was previously only available through unlicensed import in the UK, it was anticipated that very few patients would be receiving treatment with PPS in current

clinical practice. Therefore, the survey did not ask a specific question about treatment with PPS. Conversely, bladder instillations are part of standard care of IC/BPS and was therefore included as specific question. However, in addition to the questions about surgical interventions and devices, a free text field was included in the survey, which asked patients to report oral medications that they were currently receiving. Only [redacted] of the [redacted] patients in the survey who stated that they were on any oral medication for their BPS reported treatment with PPS in this time period. With so few patients reporting treatment with PPS it would not have been possible to robustly include a covariate for PPS treatment in the mapping model. Bladder instillations were considered for inclusion in the economic model as they are likely to have an impact on patients' quality of life due to their invasive nature and potential for adverse effects, such as urinary tract infections.

B17. Page 114 of the submission indicates that [redacted]. If this is the case, please clarify why "bladder installations in past 6 months - unsure" appears under the logit part of the model in Table 43. Please also clarify why being unsure of whether you had prior bladder instillations would be a reasonable explanatory variable for utility.

Response

There were [redacted], this resulted in having no regression coefficient in the logit part of the model for patients in this response category.

As noted in response to question B16, recent experience of bladder instillations was considered a potentially important explanatory variable for predicting EQ-5D values. The variable had three response options. In the survey, patients were asked to indicate the number of times they had bladder instillations in the past six months. There were some respondents who did not answer these questions. These non-responders were assigned a separate response category of 'unsure'. Imputing the response as yes or no would have introduced bias. Removing these participants would have reduced the sample size.

B18. Priority question: In the utility calculations, the regression coefficient “bladder instillations in past 6 months - yes” appears to be applied to all patients having bladder instillations in the model but not to any patient having pentosan polysulfate sodium or best supportive care. Please clarify whether this is the case.

Please also clarify if the regression coefficient is applied in those patients who have stopped bladder instillation treatment after failing to respond and those who have responded at 6 months but then later discontinued.

Please explain why prior use of bladder instillations is expected to be predictive of current utility and indicate whether the face validity of this rationale was discussed with clinicians.

Response

The regression coefficient for ‘bladder instillation in the past 6 months’ is applied to all patients currently receiving bladder instillation in the economic model. This is applied to patients in the bladder instillation arm (during treatment) and to patients in the PPS arm during treatment with bladder instillations following discontinuation of PPS.

The regression coefficient for ‘bladder instillation in the past 6 months’ represents current or recent treatment with bladder instillations. It does not represent historic treatment with bladder instillations and is not applied in the model in this way. The decrement in utility is not applied for patients who have ever had a bladder instillation in the model. It is applied to those currently undergoing bladder instillations or who have recently discontinued (within 6 months). Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections (see Appendix M of company submission).

B19. Priority question: Appendix M states “it was agreed that if patients come off treatment, assuming that they go back to baseline utility is a conservative assumption. As there is likely to be some quality of life decrement as a result of

treatment failure and the progressive nature of the condition." This statement would suggest a utility lower than baseline in non-responders due to treatment failure and disease progression. However, in the model the utility values of non-responders who go on to have no subsequent treatment exceed the values of patients at baseline. Please explain the clinical rationale for this assumption.

Response

We acknowledge that the consensus from the advisory board was that patients coming off treatment would carry a lower quality of life than the baseline utility, however we have not been able to identify valid sources to base an assumption around the extent of the utility decrement for this subgroup of patients. In the model base case, we are using utilities generated from the mapping exercise to reduce biases related to combining different utility sources. In a scenario analysis, we have also explored results when attributing the baseline utility to non-responders which decreases the ICER considerably. If a lower than baseline utility value was attributed to non-responders then the ICER would decrease even further. The basecase analysis therefore includes a highly conservative assumption about the utility gain associated with PPS treatment.

B20. Please clarify whether scenario analyses were conducted to explore whether cost-effectiveness varies with starting age and if so, please provide the results of these analyses.

Response

Starting age was not tested as part of the scenario analysis; however, it was tested in the deterministic analysis with lower and upper values of 34 and 57 years, respectively, and was not found to have a notable effect on the results. Starting age is not considered to be a key determinant of cost-effectiveness since the only age-related input in the model is mortality, which is not a main driver of the results.

B21. Table 57 outlines that "response data (used for mapping)" are based on two individual studies (i.e. Sant et al. (2003) for best supportive care and elmiron and Nickel et al. (2015) for bladder instillations). However, Figures 11 and 12 indicate that the "response data (used for efficacy)" are based on the meta-analyses of GRA using the relative risk scale. Please explain why these data are taken from different

sources. In particular, explain why there is a greater response for bladder installations than pentosan polysulfate sodium in the data used for mapping, when there is a lower response in the data used for efficacy?

Response

Response data from Sant et al. (2003) (Sant et al., 2003) were used for the mapping exercise (instead of pooled estimates as conducted in the evidence underpinning effectiveness) in order not to break the internal consistency of the dataset in terms of relationship of ICSI with GRA since that was a crucial element of the mapping exercise. The difference between the two estimates is due to them coming from different sources. Please note that the "Response data (used for mapping)" estimate for bladder instillations is not used in the model (see response to question B8). Please see Table 8 below for a correction.

Table 8. Model inputs – response data

Response data (used for mapping)				
PPS response (also applied to BSC and bladder instillations)	Global	0.34	Not varied	
Response data (used for efficacy)				
BSC response	Global	0.1582	Logit (-1.67,0.18)	
PPS response (RR)	Global	2.09	Lognormal (0.30,0.23)	
Bladder instillation response (RR)	Global	1.39	Lognormal (0.72,0.18)	
Response	Patient-level	Value not predetermined - sampled	Uniform (0,1)	

B22. Priority question: Please clarify why the patients who respond to placebo in the best supportive care arm of the economic model are assumed to have their treatment effect recede at 12 months, but all of the responders in the bladder instillations and pentosan polysulfate sodium arms of the model are assumed to have a durable response that persists until they discontinue? If the placebo response observed in the trial is related to patients being recruited during a disease “flare” (which goes on to resolve over the 6 month trial period), or if it is related to a better

standard of basic care during the study or more frequent clinical contact, could this also happen in the intervention arms of the trials?

Response

The placebo effect is likely caused by participation in the clinical trial and would not be expected to occur in clinical practice or persist beyond the trial. The assumption that the treatment effect recedes in the best supportive care arm was based on clinical opinion from the relevant advisory board (please see appendix M). We have taken a conservative approach, which includes the placebo effect and assumes that this would last for approximately 6 months beyond completion of the trial. This is likely to overestimate the 'response' in the BSC arm. The effectiveness of active treatments is monitored as part of routine patient follow-ups. Furthermore, the addition of a discontinuation element to the model also captures the lack of efficacy of treatments as depicted in Hanno (1997) (Hanno, 1997).

B23. Priority question: Please provide more details about the resource use survey (described in sections 3.4.3 and 3.5.1 of the submission) used to determine the relationship between Interstitial Cystitis Problem Index and cost / resource use. In particular, the text on page 118 states that both type and number of days were elicited for hospital admissions but only mean frequency appears in Table 49 and therefore no summary data is reported on the length of admission. Please provide a full description of this resource use survey and the analysis of the survey data including:

a. a copy of the questions used to gather resource use data
b. descriptive statistics for responses to each question
c. the rationale for the choice of explanatory variables
d. the method used to determine which resource use items were to be excluded (as described in page 119) because they were accounted for elsewhere in the model (please also clarify if these were excluded from the analysis reported in Table 49, or only from the analysis reported in Table 50)
e. the rationale for choosing a generalised linear model with gamma distribution and results for any alternative models that were considered but discounted.

Response

The resource use survey is described within the mapping technical report, including descriptive statistics in the main text and appendix. The regression model using ICSI scores and age is described in section 4.5.2 of the technical report. It describes the selection of covariates, reason for excluding some resource use items and rationale for choosing GLM estimation.

Only contacts with healthcare professionals and hospital admission were included in the regression model. To minimise the potential for double counting, the costs of treatments were not included in the regression model as costs related to treatments and administration were included in the economic model from alternative sources. Whilst we are not able to rule out any double counting associated with administration of treatments, it is anticipated that this would be minimal.

B24. Please clarify specifically, whether when filling out the resource use survey described in sections 3.4.3 and 3.5.1, patients were asked to exclude any healthcare usage related to administration /monitoring of bladder instillations / pentosan polysulfate sodium which is already captured elsewhere in the model?

Response

Patients were not asked to exclude any healthcare usage in the survey, related to administration /monitoring of bladder instillations / pentosan polysulfate sodium. The outcome variable in the cost calculation excluded treatments and procedures. Whilst we are not able to rule out any double counting associated with administration and monitoring of treatments, it is anticipated that this would be minimal.

B25. Please describe how the healthcare resource group codes applied to the categories reported in the resource use survey in Table 49 were selected. Specifically, please clarify:

a. why the outpatient cost given in Table 49 uses the average of all outpatient visits rather than a outpatient cost specific to urology
b. what is meant by “specialist ward” in Table 49 (i.e. admission to urological wards only, or admission to other specialist wards)

c. why specialist ward cost used a weighted average for total healthcare resource group activity across the listed codes instead of a more specific stay type (such as elective inpatient, non-elective or day case)
d. why gynaecology is reported separately from “specialist ward” in Table 49.
e. why the healthcare resource group codes LB15E and LB18Z are considered most relevant for Emergency Department attendances, and what data was used to calculate the “weighted average” of these attendances
f. why the healthcare resource group codes for Emergency Medicine (those starting “VB”) are not used for this category of resource use

Response

Please find our answers below:

a. The outpatient cost applied to the number of outpatient visits uses an average of all outpatient visit unit costs as patients may visit a range of different specialists (e.g. pain management teams, physiotherapy, etc).

b. Specialist ward assumed admission to urology ward since the question asked for hospital admittance due to IC/BPS. The unit cost here was sourced from a weighted average of hospital stay for ureteric or bladder disorder, without interventions, with CC Score 0-1, 2-4 and 5+

c. Information on the specific type of attendance (elective, non-elective or day-case) were not available therefore a weighted average for the unit costs were applied to the data

d. Gynaecology was reported separately because a patient specified 'gynaecology' in the survey when asked to state any 'other' type of ward (than general, ITU and specialist ward for IC/BPS) in the survey.

e & f. HRG codes LB15E and LB18Z were used instead of Emergency Medicine (VB) codes because they were considered more specific to IC/BPS patients than VB codes. Both LB15E and LB18Z are listed within the service description of accident and emergency within the outpatient procedure sheet in NHS referral cost document.

B26. The administration costs for bladder instillations in Table 54 are based on total healthcare resource group activity costs for 'Introduction of therapeutic substance into the bladder procedure,LB17Z'. Why was a more specific cost for Urology outpatient costs for 'Introduction of therapeutic substance into the bladder procedure' not used?

Response

While the majority of the administrations are recognised to be taking place in outpatient settings, a reasonable number of administrations are provided as part of inpatient care or day cases (and not necessarily under urology specialty settings) as also observed in the relevant Hospital Episode Statistics dataset (see Appendix O of the Company Submission). Therefore, the grouped activity unit cost was used as a more accurate estimate.

B27. Page 121 of the submission indicates bladder installations are used "4 weekly". Why is the cost per instillation multiplied by 12 and not 13 in cell D56 of the model inputs sheet?

Response

Thank you for this comment. Cost per bladder instillation is now multiplied by 13 in the revised model submitted with this response. The impact of adding a bladder instillation administration is shown in Table 9.

Table 9. Annual number of bladder instillations used in CE model

Results (12 BI administrations annually)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]
Results (13 BI administrations annually – revised base case)		
	Costs	QALYS

PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]

B28. Priority question: The summary of product characteristics for pentosan polysulfate sodium states that “response to treatment with pentosan polysulfate sodium should be reassessed every 6 months”. Please clarify whether the need for clinical monitoring every 6 months would result in additional resource use compared to patients receiving bladder instillations and if so please explain how this is incorporated in the model.

Response

Response to pentosan polysulfate sodium would be assessed during the standard patient interactions with healthcare professionals; no special tests are required to monitor efficacy or adverse effects (see also B29). These could be assessed easily as part of routine care since patients have to pick up their prescription from specialised or general practice settings. No additional resource use requirements to assess response to pentosan polysulfate sodium were highlighted in the relevant advisory board.

B29. Priority question: Please clarify whether patients receiving pentosan polysulfate sodium require any regular blood tests (for example, to measure liver function, renal function, platelets, or clotting factors). If so, please clarify the tests required, their frequency, whether they would occur in primary or secondary care and how the costs of these monitoring tests have been incorporated in the economic analysis.

Response

No additional blood tests are required for patients receiving PPS, as highlighted by the summary of product characteristics (European Medicines Agency, 2017). Please also refer to the response to question B28.

B30. Please clarify whether the analysis of hospital episode statistics data presented in Appendix O is used as a source of any model inputs or whether it simply provides supporting contextual information to the submission

Response

The analysis of hospital episode statistics presented in Appendix O is only used as contextual information as part of this submission.

B31. Page 108 of the submission states “Mean life expectancy was calculated across all age groups and standard deviations computed for use in the model.” Please clarify why the average mean life expectancy across all age groups is relevant, given knowledge of the age at baseline (and that age is related to life-expectancy).

Response

The reference to the "mean life expectancy was calculated across all age groups..." should read "mean life expectancy was calculated across each year of life".

B32. Priority question: Please explain why the mean life-expectancy for each starting age is based on the average of male and female life-expectancy and is not weighted for the distribution of males/females, whereas the standard deviation is weighted by the male/female distribution. If this is an error, please correct and submit a revised base-case model. If doing so, please if possible also update the data to use the latest Office for National Statistics Life Tables released on the 25th of September 2018.

Response

The mean life-expectancy has now been updated to be estimated as a weighted average of males/females in the revised model submitted together with the company responses. We have also revised the estimation of the weighted average of SDs. Data have been updated using the latest Office for National Statistics Life Tables released on the 25th of September 2018 with no visible impact on the results. These data have been incorporated into the updated economic model included with this response.

B33. Priority question: Please clarify why the economic model does not use life-table data to estimate a cumulative probability distribution for time to death and sample empirically from this distribution. Please justify the assumption that time to death is normally distributed around average life-expectancy.

Response

The simple approach followed was part of the model example in NICE TSD 15 which we used as a guide to develop the present model and was found to provide reasonable estimates. Due to the starting age and the 20-year time horizon used in the model base case, mortality is not considered to be a key driver of the results.

B34. Please explain the rationale behind the method used to calculate the standard deviation of life-expectancy. In particular, please explain why these are based on the Office for National Statistics data for Lx given that the definition of Lx is "The number of survivors to exact age x of 100,000 live births of the same sex who are assumed to be subject throughout their lives to the mortality rates experienced in the year or years to which the life table relates," and therefore does not relate to the sample size used to estimate mean life-expectancy.

Response

The Lx estimate is the hypothetical cohort size at the start of the lifetime calculations and is proportional to the probability of survival. It is used as a scaling factor used in calculating expected lifetime. As such, it would be included in the variance (SD) calculations. We do not consider it the denominator of a mean per se.

B35. Please clarify how it was determined that the chosen sample size of 10,000 patients was sufficient to produce consistent results, as stated in Table 38.

Response

10,000 patients were considered adequate having tested for model convergence observing the individual patient results. Please see the figure below.

Figure 5. Model convergence – Patient level

[redacted]

B36. Please clarify how it was determined that 1000 probabilistic sensitivity analysis samples was sufficient to provide stable estimates of incremental costs and incremental QALYs.

Response

1,000 simulations were considered adequate having tested for model convergence observing the PSA runs. Please see the figure below.

Figure 6. PSA runs

[redacted]

B37. Surgery as part of subsequent treatment is listed in the scenario analysis for pentosan polysulfate sodium vs. best supportive care. However, the results for this scenario are not included in Table 64. Please provide the results for this scenario analysis within the table.

Response

Thank you for your comment. Results for this scenario are provided in the table below.

Table 10 Surgery scenario analysis, vs. best supportive care

Scenario	PPS costs	PPS QALYs	BSC costs	BSC QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery as part of subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B38. Please confirm if the random number stream used to sample from the exponential distribution should also have been applied to the Weibull and lognormal time to event distributions when they are selected as options (i.e. rand(n,2) instead of rnd()). If so, then please correct and submit as part of a revised base-case analysis.

Response

Thank you for your comment. This now has been updated in the revised model.

B39. For Figure 26, please explain why the bars fall solely on the left of the line for the second and third variables from the top.

Response

This indicates that in these two parameters the ICER in either the lower or the upper bound fell below zero. A negative ICER indicates the dominance of a treatment over its comparator.

B40. Please provide more details of the 3 cost-effectiveness studies that were excluded at the full-text sift.

Response

The 3 studies excluded following a full-text screening were: 1. Tung et al. (2017) Characterizing Health Care Utilization, Direct Costs, and Comorbidities Associated with Interstitial Cystitis: A Retrospective Claims Analysis (Tung et al., 2017). 2. Clemens et al. (2008) Costs of interstitial cystitis in a managed care population (Clemens et al., 2008). 3. Wu et al. (2006) Interstitial Cystitis: Cost, treatment and co-morbidities in an employed population (Wu et al., 2006). These studies were excluded because they did not contain cost-effectiveness data.

B41. The submission suggests that health related quality of life/cost studies were excluded if they did not include any of the listed interventions / comparators. This exclusion criteria would exclude cohort studies examining the relationship between HRQoL/costs and measures of severity. However, Table 72 and Table 76 suggest that Hakimi et al. (2017) was included (despite no relevant intervention / comparator being listed). Please confirm if any studies of health-related quality of life/costs in a relevant population were excluded based on the intervention/comparator exclusion criteria. If so, please provide bibliographic details for any studies excluded for this reason.

Response

The review for quality of life/cost studies was limited to the range of interventions described in Appendix D of the company submission. No studies were excluded at full text screen for this reason.

B42. Do the costs of bladder instillations used after pentosan polysulfate sodium account for the treatment pathway (which typically has weekly instillations for the first month, then monthly instillations thereafter)? If not, please explain why.

Response

The annual cost of bladder instillations is considered when these are used as second-line treatments. To simplify the model implementation, the loading dose of bladder instillations is not taken into account in these cases. We expect this simplification to have produced conservative results since more patients in the bladder instillation arm receive subsequent treatments in the model (due to a lower response rate compared to PPS). Also, it would be expected that patients changing their bladder instillation treatment to start with a loading dose (as per manufacturers' instructions), rather than going directly to maintenance dosing at 4 weekly intervals. Again, the assumption taken in the model is a conservative one as it reduces the potential cost of subsequent bladder instillation treatments.

B43. The weighted average cost of sodium chondroitin sulphate is used for the costs of annual bladder instillation after pentosan polysulfate sodium. However, sodium hyaluronate is considered the first line bladder instillation in the UK and would be

offered when patients come off pentosan polysulfate sodium onto bladder instillations. Please clarify why this cost was not used.

Response

The cost of sodium hyaluronate and that of the remaining bladder instillation options are £88.03 and £86.14 respectively. The costs of remaining bladder instillations was used for the second and subsequent lines of bladder instillation treatment. For simplicity this cost was also used for the first-line bladder instillation treatment following discontinuation of PPS. This is a conservative approach as the cost of sodium hyaluronate is higher than that of the remaining bladder instillations. Using the cost of sodium hyaluronate following treatment with PPS would decrease the ICER for PPS.

Section C: Textual clarification and additional points

C1. Page 43 of the submission states “Concurrent: cimetidine, intravesical heparin, chronic use of acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or sedating histamine-1 receptor antagonists”. Are these permitted or disallowed medications?

Response

This refers to disallowed medications in the Sant et al 2003 trial.

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NICE National Institute for Health and Care Excellence

Updated Patient organisation submission

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Bladder Health UK
3. Job title or position	Communication & Media Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Bladder Health UK gives support to people with all forms of chronic bladder illness, together with their families and friends. We are the largest bladder patient support charity in the UK. We are funded by membership subscriptions, donations from our corporate partners and grants from charitable trusts. We have 1,500 members and over 5,000 followers on our Social Media platforms.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient experiences are gathered by the team during our conversations with them on our Advice Line. We also regularly discuss treatment options with our members. The Advice Line is open five days a week between 9.30am and 2.00pm. I am a sufferer myself and an expert patient and familiar with involvement in NICE Guidelines where they relate to bladder illness.
Living with the condition	
6. What is it like to live with the condition? What do carers	The condition – Interstitial Cystitis/ Bladder Pain Syndrome - is not curable, very challenging to manage and extremely painful.

experience when caring for someone with the condition?	The condition is extremely disruptive to normal living. It affects personal relationships, travel, holidays and work life for everyone involved.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The disease is not curable therefore treatments centre around management of symptoms. Not all treatments are available in all areas of the country and as there is no one treatment that suits every patient, sufferers are forced to try various options to find something that will work for them. Some patients find bladder instillations difficult to tolerate due to the pain of catheter insertion or frequent UTI's. These UTI's can linger on for weeks and even months. For patients with IC/BPS the GAG layer of their bladder is badly damaged so when they get a UTI it can be very difficult to eliminate with a simple 3 day course of antibiotics. One of our members, a lady in her 70's, following a bladder instillation contracted a UTI which despite antibiotic treatment culminated in C-difficil and the problem wasn't resolved for over a year. A frightening experience for an elderly lady and one which clearly negatively impacted her quality of life. UTI's for IC/BPS patients can be very difficult to manage. In my case, I got an e-coli infection (not related to bladder instillations) and it took 18 months to get rid of the infection in my bladder and multiple courses of therapy, seriously affecting my quality of life for this time. Whilst not all people with IC?BPS who get a UTI will experience this level of severity of symptoms, these are not isolated cases and it is not unusual for symptoms to last for weeks or even months. We frequently find that patients are unaware of their options for treatment and have to rely on what is available in their region which may not be the most appropriate therapy for them.

8. Is there an unmet need for patients with this condition?	The main difficulty is that treatments are determined by the area in which a patient lives rather than what is actually suitable or available for the individual concerned. We are aware that Elmiron is a suitable and effective means of treatment for a cohort of patients, however it is not always readily available and this forces patients to pay for it privately or use less effective treatments.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Elmiron is particularly suitable for those who find instillation therapy too painful or who find that the introduction of a catheter into the bladder brings with it infection. In addition to the risks of infection associated with bladder instillations, the disruption of attending clinics weekly for 4-6 weeks followed by monthly thereafter can cause serious disruption to patients lives, particularly if they are of working age. This is not a therapy that lasts for a brief period of time but it is one that can continue for many years, provided that a patient continues to receive benefit. Elmiron has the advantage of being a tablet that patients can take wherever they might be. Another problem with bladder instillations is that the manufacturer's recommended maintenance therapy is once a month (after initial start up phase). The NHS would like patients if they can to go to 6 weeks between treatments where possible, and for some patients this can be achieved but for many even 4 weeks is too long to wait for a treatment. Patients can be left in severe pain between treatments.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All sufferers would benefit from being able to try Elmiron and some have already found it very beneficial. • It is particularly useful for those who find instillation of medication directly into the bladder too painful to tolerate. • It is beneficial also for those who suffer with recurrent urinary tract infection alongside the Interstitial Cystitis which can be exacerbated by the introduction of a catheter.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is of equal benefit to men and women who suffer from Interstitial Cystitis.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The main issue for our patient organisation is that Elmiron is only available in a limited number of areas in the country meaning that people have to travel, pay or do without.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Elmiron is already proven treatment option for some sufferers and it should be available as a choice of treatment to all.
- It is particularly useful as an option for those who find instillation therapy too painful for who also suffer from Urinary Tract Infection.
- If Elmiron minimises the impact of this debilitating disease them it should be available to every patient, particularly in view of the fact that treatment options are already so limited.

Thank you for your time.

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Clinical expert statement

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jonathan Charles Goddard**
2. Name of organisation	**University of Leicester Hospitals NHS Trust (Leicester General Hospital)**

3. Job title or position	**Consultant Urological Surgeon**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it **X** I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Pentosan polysulfate sodium is used for the symptomatic relief of pain which is associated with the filling of the bladder in Bladder Pain Syndrome / Interstitial Cystitis (BPS/IC).
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	After starting the medication I review patients after about three months. I would consider any improvement in the distressing symptoms of bladder pain leading to urinary frequency a positive response. In patients who feel the medication is helping, often, due to the necessity of having to take it three times a day, they have inadvertently omitted it or due to the difficultly in getting hold of the medication, they have had a treatment break. In these patients, it is quite common for them to appreciate the benefit, as their symptoms quickly return.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Very much so. BPS/IC is commonly forgotten as a possible diagnosis in patients (usually women) with urinary frequency. It is a difficult condition to diagnose with few treatment options. The patients, who often have been suffering with chronic pain for months or years, commonly have seen multiple doctors before this diagnosis is contemplated. They are frequent attenders and due to the difficulty in diagnosis are often regarded as ‘problem patients’.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Poorly. Outside of super-specialist care the condition often goes unrecognised. Treatment is sporadic, variable and empirical.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Engeler DS, Baranowski AP, Borovicka J, et al. EAU guidelines on chronic pelvic pain. Presented at the EAU Annual Congress London 2017. ISBN 978-90-79754-91-5. EAU Guidelines Office, Arnhem, The Netherlands. https://uroweb.org/guideline/chronic-pelvic- pain. Tirlapur S, Birch J, Carberry C, et al. Greentop guideline no. 70. On behalf of the Royal College of Obstetricians and Gynaecologists. Management of bladder pain syndrome. RCOG/ BSUG Joint Guideline December 2016. Br J Obstet Gynaecol. 2016;124(2):e46-e72. Hanno PM, Burks AB, Clemens JQ, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. American Urological Association. https://www.auanet.org/guidelines/interstitial- cystitis/bladder-pain-syndrome-(2011-amended-2014).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of diagnosis and management is very poorly defined. This is partly due to the difficulty in diagnosis but also due to the difficulty in treatment. There is no accepted stepwise management plan. Patients respond to some treatments but not to others, hence a trial and error approach is often taken. Availability of different treatments in different areas often dictates treatment choice. Having discussed management options with colleagues at British (BAUS) and European (EAU) conferences, it is clear there is a very wide approach to management of this condition.
• What impact would the technology have on the current pathway of care?	It would allow some equality of care across the UK and prevent patients being referred out of area to centres where this medication is used from centres where it is not available. This is an opportunity for NICE to educate and move towards a standard of care for recognition, assessment and management of BPS/IC.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Currently, if patients are correctly diagnosed there is a wide variety of treatments. Some are put on the old 'triple therapy" of Amitriptyline, Cimetizine and Hydroxyzine, some are given intravesical treatments. Pentosan polysulphate is used in many centres by specialists off licence. This would allow it to be used in more areas of the country.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Although BPS/IC is essentially a diagnosis of exclusion, the diagnosis is usually made on a careful history, so it could be started in primary care. However, the exclusion of Hunner's lesions (or other pathology) by cystoscopy is usual and so the patients are often already in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The major input would be education, this condition is often under- or mis-diagnosed.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In those patients in whom it works, it can be life changing.

• Do you expect the technology to increase length of life more than current care?	No.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no standardised diagnostic test for BPS/IC. The Potassium Sensitivity Test is no longer used (rightly). The Local Anaesthetic Challenge Test has been suggested by Curtis Nickel as a guide to indicate the bladder mucosa as the likely site of pelvic pain. However, this has not been tested as a selector for the success of Pentosan Polysulphate. I use it to determine who gets a trial of Pentosan Polysulphate; I would not suggest this has enough evidence beyond my own experience to recommend this.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No. The side effect profile of treatments such as amitriptyline is often more difficult to manage. The tablet has to be take three times a day and coordinated with food and that can be tedious for patients. This will be easier than intravesical therapy. The medication should be discontinued prior to any surgery.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment should be based on a sound history. Treatment should be given for several months and reviewed and stopped if there is no symptomatic improvement. I do not think treatment should be given for Hunner's lesions – these should be treated surgically. I do not think glomerulations should be a basis of giving treatment – these have been shown to be present in normal bladders and are no longer regarded as pathognomonic of BPS/IC.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The condition is under recognised and under treated – I think the ability to use this more freely should improve this.
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I have not seen a significant problem.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Difficult to tell as UK practice is so varied.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Symptom improvement – Validated questionnaires have been used.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s)?	
22. How do data on real-world experience compare with the trial data?	Patients often have multiple pathology (eg. DO and UTIs as well as BPS/IC). Questionnaires are less commonly used. Patients have often been on multiple medications over many years.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Although men account for 10% of patients BPS/IC is often not considered.

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Are cystoscopy and cystoscopy with hydrodistension routinely performed for all patients with suspected bladder pain syndrome?	No. Cystoscopy usually is. Hydrodistension may be carried out.
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • This condition is under recognised. • This condition is poorly managed • The diagnosis is mainly clinical (and one of exclusion) • Hunner's ulcer should be treated surgically • Glomerulations are not diagnostic of this condition	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

About you	
1. Your name	**Suzanne Biers**
2. Name of organisation	**British Association of Urological Surgeons (BAUS)**
3. Job title or position	Urology Consultant Executive committee member of the Female, Neurological and Urodynamic Urology (FNUU) Section of BAUS
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):

5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	x☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Oral pentosan polysulfate sodium (PPS) is a treatment designed to ameliorate the debilitating symptoms of bladder pain syndrome (BPS), and would be considered when other conservative or medical therapies have failed to be of complete benefit (i.e. it is a second-line treatment). It does not reverse or cure the disease process, but its effects may persist after treatment courses have been completed. The preparation being considered in this appraisal is the oral (tablet) form called Elmiron (but BAUS note that it is also available in liquid PPS preparation for direct bladder instillation therapy which can be used as a combination treatment with the oral form to improve the efficacy).

	Of note, BAUS also feel that PPS treatments should be considered/available for recurrent cystitis due to urinary tract infections.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	BPS is a chronic debilitating condition and clinically significant treatment outcomes would be to show improvement of patient symptoms by ≥ 50%. As well as subjective response from the patient, this can be judged using different tools before and after treatment courses, such as visual analogue scales to monitor pain responses, or a validated disease-specific questionnaire such as the O'Leary-Sant or Interstitial Cystitis Symptoms and Problem Indexes. Alternative questionnaires include the pelvic pain and urgency/frequency patient symptoms scale (PUF). Additional resources include an improvement in quality of life, as quantified by patient reported questionnaires (such as the EQ-5D-5L questionnaire).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need. BPS is a chronic condition of unknown aetiology, and patient symptoms are challenging to improve and control; a 'cure' is not available. The wider the armamentarium of treatment options available to urologists and doctors that we have for this condition, the better the ability to treat our patients and improve their quality of life and ability to complete normal activities of daily of life. BAUS notes the variable evidence on oral PPS, and would see this treatment used for patient's symptoms that are resistant to other conservative, medical and even bladder instillation therapies. It is useful to investigate alternative or new medical treatment options that can be used prior to needing to consider invasive and irreversible surgical treatment (such as a laparotomy and ileal conduit formation)
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Treatment of bladder pain syndrome in the UK is based on European Association of Urology (EAU) Guidelines (with input from other national and international guidelines). To date, as oral PPS (Elmiron) has not been licensed in the UK and is expensive to acquire privately, this has not been used commonly in the UK to date. BPS management pathway is followed after full clinical assessment, investigation and after seeking out and treating any reversible underlying conditions. Management is adapted on an individual basis (guided by patient phenotype) and is described as being multi-modal – i.e. patient may need to be on a variety of treatments at the same time. General recognised BPS management pathway (based on AUA guidance): 1. **First-line therapy:** Conservative management: pain education and treatment (pain clinic input), physiotherapy, alteration of diet to avoid pain triggers; acupuncture; psychological support 2. **Second-line therapy:** Oral medication: analgesia, amitripyline, antihistamines, oral PPS (where available) 3. **Second-line therapy:** Intravesical therapies (i.e. Glycosamino glycan/GAG analogues such as hyaluronic acid (HA), chondroitin sulphate (CS), heparin sulphate and dermatan sulphate alone or in combination, also given with alkalinised lignocaine). PPS or other GAG analogues can also be used for instillations in combination with oral PPS to provide a better response where oral PPS effects have been only partially successful (where these treatment are available) 4. **Third-line therapy:** Endoscopic surgery: hydrodistension of the bladder +/- diathermy/resection of Hunner's ulcer if identified 5. **Fourth-line therapy:** Surgical alternatives: botulinum toxin injection of bladder or neuromodulation – not commonly used 6. **Fifth-line therapy:** Immunosuppression medication (cyclosporin) – rarely utilised 7. **Sixth-line therapy:** Open surgery. This option reserved for when no other therapy is of benefit (i.e for refractory BPS), and includes urinary diversion (ileal conduit or neobladder) +/- partial or complete cystectomy (bladder removal) A contemporary review of the BPS guidelines also reports a similar summary of the recommended treatment pathway for BPS [1].

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	EAU guidelines on chronic pain and BPS are used in the UK. Other guidelines that can be accessed and used are the American Urological Association (AUA) guidelines and Greentop guideline No.70 from the Royal College of Obstetricians and Gynaecologists (RCOG) (2017; peer-reviewed by BAUS). Other organisations publishing on BPS include: • International Society of the Study of BPS (ESSIC) • Bladder Pain Syndrome Committee of ICS • Canadian Urological Association (CUA) • International Association of Urogynaecology (IAGU) • International Association for the Study of Pain (IASP) • East Asian guideline • International consultation on Continence (ICI)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In the UK, urologists would tend to follow and offer the first and second-line management pathway treatments (points 1 to 4 above) routinely, however, oral PPS is not currently licensed for use in the UK and is not routinely suggested or offered. Management options (points 5 and 6 above) tend to be used in research rather than clinical practice. Management option 7 (above; open surgery for refractory BPS) is performed for end-stage disease only. Clinical practice is generally uniform, but needs to be adapted on an individual patient basis as some treatments work well for some patients but not for others with the same problem. For example: patients may have received physiotherapy for pelvic floor relaxation and pain killers and also be taking amitripyline, and bladder instillations. When basic treatments have not been completely successful, it is common practice that patients are referred on to specialist centres if some forms of treatment (or specialist expertise) are not available locally, such as intravesical treatments or open surgery.
• What impact would the technology have on the current pathway of care?	Oral PPS would be incorporated into the management pathway at point 2 (oral medication option). BAUS anticipate that oral PPS would be considered as an alternative oral medical therapy if other treatments (amitripyline, nortriptyline, gabapentin, pregabalin or antihistamines alone or in combination) had not been effective. It could be provided on its own, or in combination with another treatment. Evidence suggests that if the patient experiences a partial response to oral PPS (rather than compete response), it is beneficial to add in intravesical bladder instillation of a GAG analogue (such as heparin or PPS). It would also act as an alternative way to provide the patient with GAG analogue therapy, in the group of patient unable to tolerate catheterisation of the urethra for bladder instillations of GAG liquid therapies.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – it would be prescribed as an alternative medical therapy by the urologist (or gynaecologist) in clinic or the GP.
• How does healthcare resource use differ between the technology and current care?	NA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Oral PPS could be used in primary care or secondary care (district general or tertiary referral centres). BAUS suggest that there is careful patient selection in secondary care centres and the prescription can then be continued in primary care if beneficial (i.e. ≥ 50% improvement in symptoms).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional training or facilities would be needed.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It would provide an additional minimally invasive option (i.e. medical option) to help treat this condition. It would add an additional step in the treatment options, before more invasive therapies were considered (i.e. such as catheterisation for bladder instillations or surgery), which would benefit patients if the treatment was effective and avoid the risk of increased side effects which are associated with more invasive treatment options.

• Do you expect the technology to increase length of life more than current care?	No.
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially, if it were effective for patients who had either not responded to other medical therapies, or where they were unable to tolerate other treatment options. BAUS note that success rates are variable in the published literature.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The use of oral PPS would be restricted to patients with bladder pain syndrome (BPS). There is limited evidence that it may be more effective for sub-group of patients with the ulcer form of BPS [8].
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	*'Will the technology be easier or more difficult to use for patients or healthcare professionals than current care?'* No Additional monitoring is not required above and beyond current medical options for BPS.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	BAUS would suggest that oral PPS is trialled after other medical therapies have either been tried and failed, or have only provided partial benefit. This could be trialled instead of intravesical therapy in patients unable to tolerate urethral catheterisation (i.e. bladder instillations require insertion of a temporary catheter in order to instil the treatment which can irritate the urethra and exacerbate symptoms in some patients).
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	If effective, this could mean fewer clinic visits and GP appointments. As Oral PPS (Elmiron) is unlicensed in the UK, it has not been possible to provide accurate cost analysis in the previous NICE evidence summary in 2015 (nice.org.uk/guidance/esuom43), which estimated a mean cost of £4.16 per capsule, or £374.40 for 30 days treatment (100 mg 3 times daily). This was significantly more expensive than the normal treatment standard, amitriptyline which was reported to cost £1.13 to £3.70 for a daily dose of 10mg or 50mg respectively for a 30 day course (drug tariff costs from 2015). In view of this, restricted use of oral PPS for selected cases would be reasonable, as the number of patients with BPS is relatively small and the number eligible for oral PPs would also be small. If further restricted to ulcer BPS disease (as the company suggest), this would only be around 10% of patients with BPS. The supplying company Consilient, suggest 9000 patients would be eligible (but only 100 scripts were written for Elmiron in 2016/17 which reflects its current off-license status). If tolerated and helpful, treatment courses are for a minimal of 6 months. (Please note oral PPS acquisition costs change).
17. Do you consider the technology to be innovative in its	Having an oral GAG analogue treatment is useful for the sub-group of patients with BPS, particularly those with urethral symptoms who are unable to tolerate the placement of a urethral catheter, which is required for instillation of GAG replenishment treatment directly into the bladder.

potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Treatments outcomes for oral PPS in the published literature are variable, and to a degree this reflects the clinical picture, in that patients with BPS need their treatments to be tailored individually as there is generally a variation in response in this group which is unpredictable. However, other than the RCOG, all organisations publishing guidelines on BPS include oral PPS as a treatment option [1]. The evidence has previously been comprehensively documented in the evidence summary published by NICE in April 2015 (nice.org.uk/guidance/esuom43), where outcomes were variable with some evidence supporting a beneficial effect or oral PPS. The EAU give a 'strong' recommendation (based on a grade 1a level of evidence and a grade A strength of evidence) for the use of Elmiron/oral PSS and conclude in their recommendations that it is effective for pain and the related symptoms of BPS [2]. The AUA which is also used as reference for clinical practice in the UK also listed oral PPS as a clinical option, and previously given grade B strength of evidence recommendation [3]. A meta-analysis of four RCTs, published by Hwang P et al. in 1997, compared oral PPS with placebo and found evidence that PPS may, to a certain extent, improve pain, urgency, frequency in BPS; however, positive findings varied across the individual studies as the methods and primary endpoints were inconsistent [4]. Giannantoni A et al. published their systematic review and meta-analysis of RCTs in 2012 and showed that whilst there was some heterogeneity of response from patients again, a positive benefit was demonstrated [5]. Included in this meta-analysis was a paper by Hanno et al. who provided oral PPS 100mg three times per day, and was the study with the longest follow up at 240 weeks available on 128 patients [6]. This identified a 50% positive response rate in pain and urgency as assessed by the VAS scale. In contrast, the most recent double-blind RCT comparing oral PPS with placebo found no statistically significant difference on the Interstitial Cystitis Symptom Index (ICSI) [7], and the RCOG base their recommendation not to offer oral PPS influenced by this publication. Oral PPS appears to more effective if selected for patient with an ulcer form of BPS, and its efficacy is related to duration of treatment rather than dose [8]. In addition, oral PPS may be a more effective treatment if combined with GAG bladder instillations, which is a reasonable treatment regimen, as many patients with this condition require multimodal therapy to control symptoms [9,10].
• Is the technology a 'step-change' in the management of the condition?	Oral PPS is already available and used in the USA and Europe and included in their recommendations [1-3].

• Does the use of the technology address any particular unmet need of the patient population?	It provides an additional treatment option for patients with BPS refractory to other minimally invasive therapies and to those unable to tolerate other treatment or catheterisation of the urethra for bladder instillations.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Reported side effects include: diarrhoea, hair loss, nausea, headache, stomach upset or pain, abdominal pain, dizziness, depressed mood. Oral PPS also has a weak anticoagulant effect. Patients would need to terminate the therapy if they suffered ill effects and attend review with their doctor to consider alternatives.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Symptom improvement (include pain and urinary symptoms improvements) as reported with subjective and objective outcomes.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s)?	Yes. Santos TGD, Miranda IAS, Nygaard CC et al. Systematic Review of Oral Therapy for the Treatment of Symptoms of Bladder Pain Syndrome: The Brazilian Guidelines. Rev Bras Ginecol Obstet. 2018;40(2):96-102. They conclude that PPS should be considered one of the best oral options for BPS. They also reviewed amitripyline, a comparator treatment.

22. How do data on real-world experience compare with the trial data?	Oral PPS is not licensed in the UK for use, but anecdotal reports from patients acquiring this on private prescription are positive in some cases.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Cost may limit the prescription of oral PPS in some locations potentially however, this will be a treatment unlikely to be widely prescribed.
23b. Consider whether these issues are different from issues with current care and why.	No.
Topic-specific questions	
24. Are cystoscopy and cystoscopy with hydrodistension routinely performed for all patients with suspected bladder pain syndrome?	Yes – for diagnostic (and therapeutic) reasons

Key messages
25. In up to 5 bullet points, please summarise the key messages of your statement. • Oral PPS provides an additional treatment options for BPS, however outcomes are variable. • Oral PPS is a useful alternative for patients unable to tolerate the instillation of GAG analogues into the bladder (intravesical therapy) • Patients to receive oral PPS would need to be selected carefully (i.e. tried and failed other treatments, unable to have intravesical instillations) and preferably have evidence of bladder ulcer –type form of BPS. • If the response to oral PPS is partial, there is evidence that the success rate can be improved by additional GAG analogue treatment in the bladder concurrently. • If oral PPS is being considered, it may be advisable to seek a sub-specialist opinion as this is an expensive treatment with variable success.

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Pentosan polysulfate sodium for treating bladder pain syndrome: A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Contributions of authors

Marrissa Martyn-St James and Alison Scope summarised and critiqued the clinical effectiveness data reported within the company's submission. Sarah Davis and Kate Ennis critiqued the health economic analysis submitted by the company. John Stevens critiqued the statistical analyses undertaken by the company. Ruth Wong critiqued the company's search strategy. Ammar Alhasso, Brian Birch, Sudhanshu Chitale, and Henry Lewi, provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AiC	Academic in confidence
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BIs	Bladder instillations
BPS	Bladder pain syndrome
BSC	Best supportive care
CI	Confidence interval
CS	Company submission
DES	Discrete event simulation
DMSO	Dimethyl sulphoxide
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ED	Emergency department
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
EQ-5D-3L	EuroQol 5 Dimensions 3-level version
EQ-5D-5L	EuroQol 5 Dimensions 5-level version
ERG	Evidence Review Group
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GP	General practice
GRA	Global response assessment
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
IC/BPS	Interstitial cystitis/bladder pain syndrome (patients with bladder pain syndrome with Hunner's lesions and/or glomerulations)
ICER	Incremental cost effectiveness ratio
ICPI	Interstitial Cystitis Problem Index
ICSI	Interstitial Cystitis Symptom Index
ITC	Indirect treatment comparison
ITU	Intensive therapy unit
MIMS	Monthly Index of Medical Specialities
mL	Millilitre

mm	Millimetre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
ONS	Office for National Statistics
PSA	Probabilistic sensitivity analysis
PPS	Pentosan polysulfate sodium
PSS	personal and social services
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SLR	Systematic literature review
STA	Single Technology Appraisal
VAS	Visual analogue scale
VBA	Visual Basic for Applications

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS) to be appropriate and relevant to the decision problem set out in the final scope issued by the National Institute for Health and Care Excellence (NICE). The decision problem assesses pentosan polysulfate sodium (PPS) (Elmiron®) for treating interstitial cystitis/bladder pain syndrome (patients with bladder pain syndrome with Hunner's lesions and/or glomerulations) (IC/BPS). In accordance with the NICE scope, the target population in the CS is people with IC/BPS. The comparator in the NICE scope is bladder instillations (BIs). For people in whom this treatment is inappropriate, unsuccessful, or cannot be tolerated, established clinical management without PPS (also referred to as best support care [BSC]) is the comparator. However, the CS only includes clinical effectiveness evidence for bladder instillations containing sodium hyaluronate, sodium chondroitin sulphate, or a combination of both. Clinical advice received by the ERG indicates that there is some variability in the availability of, and ingredients used, in locally prepared instillations across hospitals, but that these instillations could be appropriate and relevant comparators; however, it is unclear how frequently they are used. The company's clarification response stated that locally prepared instillations are not included because of their relatively infrequent use in the UK, the heterogeneity of the different 'cocktails', and the difficulty in sourcing relevant evidence for their use in IC/BPS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The key clinical effectiveness evidence in the CS for PPS in IC/BPS was based primarily on four randomised controlled trials (RCTs). The trial populations in the four RCTs relate to patients who have IC/BPS. All four RCTs compared PPS to placebo (PBO). Two RCTs comparing sodium chondroitin sulphate instillations (Uracyst®) to PBO in BPS were also included which were used to construct an indirect treatment comparison (ITC) based on the Bucher method between PPS and sodium chondroitin sulphate instillations for use in the economic model.

The four RCTs of PPS in IC/BPS were relevant to the decision problem outlined in the final NICE scope.

Two of the RCTs of PPS in IC/BPS reported that the between-group difference in the proportions of patients with a >50% improvement in global response assessment (GRA) at three months was statistically significant in favour of PPS. However, in one RCT the between-group difference in the proportions of patients with a GRA score of six to seven at three months was reported as not statistically significant. As GRA was not assessed in one RCT, the company used non-VAS pain data at three months from the RCT as a proxy for GRA in their meta-analysis for this outcome. The between-group

difference in the proportions of patients with a >50% improvement in non-VAS pain in this RCT was reported as statistically significant. The between-group difference in the proportions of patients with a >50% improvement in non-VAS pain at three months was also reported as statistically significant in one other RCT, but the between-group difference in mean non-VAS pain scores was reported as not statistically significant in two RCTs.

In the company's pairwise meta-analysis of PPS in IC/BPS, the pooled relative risk (RR) for GRA at three months across the four RCTs of PPS in IC/BPS was 2.09 (95% CI: 1.47 to 2.97, fixed effect). These results were used in the economic model. In the company's pairwise meta-analysis of Uracyst® in BPS, the pooled RR for GRA at trial follow-up across the two Uracyst® RCTs was 1.39 (95% CI: 0.88 to 21.7, fixed effect). These results were also used in the economic model. The between-group difference in the proportions of patients with a GRA score of six to seven at the trial follow-up was reported as not statistically significant by both of the Uracyst® RCTs.

In PPS in IC/BPS, the between-group difference in the O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index scores at three months were both reported as not statistically significant by one RCT.

Across the RCTs of PPS in IC/BPS, no statistically significant between-group differences were reported at three months in mean: daily urinary frequency (two RCTs), urinary volume and void outcomes (three RCTs), and nocturia (two RCTs). One RCT did not report whether the between-group difference at three months was significant or not for mean urinary volume and void outcomes, or mean nocturia.

Safety data for PPS were presented from each of the individual RCTs of PPS in IC/BPS, and the company concluded that PPS is well tolerated. Common adverse events in the SmPC are: headache, dizziness, nausea, diarrhoea, dyspepsia, abdominal pain, abdominal enlargement, rectal haemorrhage, peripheral oedema, alopecia, back pain, asthenia, and pelvic pain. However, clinical advice received by the ERG based on named patient use is that AEs are rare with PPS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the searches for clinical effectiveness evidence reported in the CS to be adequate, and believes the included RCTs of PPS to be relevant to the NICE decision problem. The ERG notes that there have been no other published independent studies validating the results of these RCTs since the four pivotal RCTs of PPS in IC/BPS were conducted.

The eligibility criteria applied in the selection of evidence for clinical effectiveness were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope.

However, the company chose to also include RCTs of PPS and comparators that were in the broader BPS population (patients with bladder pain syndrome but without Hunner's lesions and/or glomerulations). Primary endpoints and selected analyses for clinical efficacy were appropriate.

The quality of the included RCTs was assessed using well-established and recognised criteria by NICE. However, the company only quality assessed the RCTs of PPS. Quality assessment of comparator treatment RCTs was not undertaken by the company and was therefore undertaken by the ERG.

The ERG notes limitations in the reporting of outcome data in the PPS RCTs trial reports. Interval estimates (CIs) were not reported and, where between-group differences were reported as not statistically significant, *p*-values were often not reported.

Three of the RCTs of PPS in IC/BPS were considered by the ERG to be of good methodological quality. However, the ERG considers one RCT to be unclear regarding: allocation concealment, details of who was blinded, and the number of patients withdrawing from treatment groups.

The ERG considers that the company's overview of the safety evidence from the RCTs of PPS in IC/BPS reported in the CS and the company's conclusion that PPS is well tolerated to be reasonable.

The ERG has concerns with the two Uracyst® RCTs used for the ITC with PPS. Both of the Uracyst® RCTs were in the broader BPS population (without Hunner's lesions and/or glomerulations), and both compared Uracyst® to a placebo bladder instillation (not a tablet).

The ERG has some concerns with the meta-analyses that were performed by the company and reported in the CS (analysis using risk difference, assessment of heterogeneity, application of a fixed effect model). However, the ERG accepts the company's argument that an unbiased comparison between PPS capsules and all relevant comparators was not possible using a conventional network meta-analysis.

In order to include comparisons of PPS against all comparators listed in the NICE scope, the company provided an ITC between PPS and Uracyst® linked by the placebos. The ERG has some concerns with the method for the ITC (based on the Bucher method) and would prefer a simultaneous comparison between treatments using a Bayesian network meta-analysis as: (i) the Bucher approach allows for separate and unrelated meta-analyses for the effect of PPS versus placebo and the effect of Uracyst® versus placebo whereas a single model incorporates a common random effect; (ii) the posterior distribution for the effect of PPS versus Uracyst® will not follow any standard parametric distribution whereas the Bucher approach involves an assumption of asymptotic normality when making inferences, and; (iii) the relative treatment effects of PPS versus placebo and Uracyst® versus placebo will be

correlated and this will induce correlation between absolute responses to treatment when combined with an external estimate of the baseline response.

1.4 Summary of cost effectiveness submitted evidence by the company

The CS includes a *de novo* economic analysis, which compares PPS to BIs in patients able to receive BIs and PPS to BSC in patients unable to receive BIs. In both cases, the population matches that specified in the marketing authorisation and the NICE scope. The model uses patient-level simulation to estimate expected costs and quality-adjusted life years (QALYs) over a 20-year time-horizon using a discount rate of 3.5% per annum. The company's economic analysis adopts an NHS perspective for costs and benefits are restricted to patients. Benefits to carers and costs falling on personal and social services (PSS) were not considered relevant.

The company submitted a revised model following the clarification request and it is this model that is referred to throughout the report unless otherwise specified. The revisions were mainly corrections of errors in the implementation of the model.

The company's model uses a discrete event simulation (DES) framework, with the main events being a response check at 6 months, a discontinuation event which applies only to responders and death from all-cause mortality. Patients who have responded at 6 months are assumed to remain on their first-line treatment until discontinuation or death. Patients who do not respond are assumed to switch to second-line treatment; this is assumed to be BIs for those patients who are able to receive BIs, and BSC for those unable to receive BIs. Patients having BIs as first-line therapy also have events for each individual BI administration, allowing the frequency of the BIs to vary over time. BIs given as second-line therapy are modelled based on the mean number of administrations per annum without modelling each administration as a separate event.

The key model inputs are the response rates for each first-line treatment option, costs and utilities for responders and non-responders and time to treatment discontinuation for first-line treatment. The response rates were based on the company's systematic review and meta-analyses. The comparison between PPS and BIs was based on a simple unadjusted indirect comparison using the Bucher method. The costs and utilities for responders and non-responders are estimated based on the expected Interstitial Cystitis Symptom Index (ICSI) scores for responders and non-responders, estimated using data from the PPS arm of one RCT. The relationship between ICSI score and costs and utilities has been estimated from regressions fitted to data from a patient survey. Utilities were estimated by mapping from the EQ-5D-5L responses obtained in the patient survey to the EQ-5D-3L UK valuation set. Disease costs were estimated by combining resource use data obtained in the patient survey with NHS reference costs. In the regression applied in the model, disease costs are dependent only on age and ICSI score, but utilities

are also dependent on whether patients have received BIs in the past 6 months. Time to treatment discontinuation for PPS has been estimated from a published observational study with long-term discontinuation rates extrapolated based on a parametric survival analysis. The time to treatment discontinuation for BIs has been assumed to be equivalent to that for PPS. Life expectancy in the model was based on general population mortality rates for all treatment options with none of the treatments having any impact on mortality. In addition to disease-related costs that depend on the expected ICSI score, treatment-related costs include acquisition costs for PPS and BIs and administration costs for BIs. Costs and health impacts related to AEs were not included in the model.

In the population able to receive BIs, the company's revised deterministic model estimated that PPS would generate 0.25 additional QALYS in comparison to BIs, at an additional cost of [redacted]; giving an ICER of [redacted] per QALY gained. The base-case probabilistic ICER for PPS versus BIs was [redacted] per QALY gained with a 0.54 probability of PPS being cost-effective compared to BI at a willingness-to-pay threshold of £20,000 and a 0.61 probability of PPS being cost-effective compared to BI at a willingness-to-pay threshold of £30,000.

In the population unable to receive BIs, the company's revised deterministic model estimates that PPS generates 0.32 additional QALYS in comparison to BSC, at an additional cost of [redacted]; giving an ICER of [redacted] per QALY gained. The company's base-case probabilistic ICER for PPS versus BSC was [redacted] per QALY gained, with a 0.15 probability of being cost-effectiveness at the £20,000 willingness to pay threshold and a 0.33 probability of being cost-effective at the £30,000 willingness to pay threshold.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The company's model is generally in line with the NICE reference case, with the main significant deviations being: 1) that the comparison between PPS and BIs is based on a simple unadjusted indirect comparison using the Bucher method; and 2) that the estimates of clinical effectiveness for BIs versus placebo were taken from the broader population with BPS rather than the population with IC/BPS that matches the licensed indication for PPS. In addition, the ERG believes that a lifetime horizon would have been preferable to the company's 20-year time horizon.

The key areas of concern identified by the ERG were:

- The application of a utility decrement for patients receiving BIs estimated from the patient survey which the ERG did not consider robust given that the handling of missing data on BI usage had not been adequately explored in the analysis of the survey data.
- Uncertainty surrounding the likely rate of response in patients receiving BSC in clinical practice which affects the absolute difference in response attributable to PPS in the model.

- Inconsistent assumptions around the durability of response in those receiving BSC and those receiving either PPS or BIs.
- The assumption that 4-weekly administration of BIs (i.e. 13 per annum) continues indefinitely when the ERG believes that the frequency of administration is likely to fall over time as the spacing between doses is increased to the longest interval that patients can tolerate.
- Underestimation of discontinuation rates from Hanno *et al.* (1997) which affects the lifetime treatment costs, particularly for the comparison of PPS versus BSC.
- The assumption that patients who do not respond to BSC have some long-term persistent utility gain and cost savings relative to baseline.
- The assumption that the long-term cumulative rate of response to second-line BIs is equivalent to the short-term response to first-line BIs.
- Low rates of self-administration for BIs which may overestimate costs relative to established clinical practice in some parts of the NHS.
- The simplistic approach to estimating expected ICSI scores for responders and non-responders.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG considers the data on clinical effectiveness in the CS to be reasonably well-reported and that three of the four pivotal RCTs of PPS in IC/BPS are of reasonably good quality. However, there are aspects of uncertainty surrounding one RCT of PPS in IC/BPS.

The safety profile submitted by the company is based on the adverse events reported in the four RCTs of PPS in IC/BPS. Common adverse events (AEs) listed in the SmPC are: headache, dizziness, nausea, diarrhoea, dyspepsia, abdominal pain, abdominal enlargement, rectal haemorrhage, peripheral oedema, alopecia, back pain, asthenia, and pelvic pain. However, clinical advice based on named patient use received by the ERG is that AEs with PPS are uncommon.

The company provides a valid argument that an unbiased comparison between PPS capsules and all relevant comparators was not possible using a conventional network meta-analysis. Nevertheless, as required for the economic evaluation, the company provided an unadjusted ITC between PPS and Uracyst® linked by the placebos. In the absence of any direct measure of health-related quality of life from the RCTs, the company has conducted a patient survey to estimate utility values derived from the EQ-5D that comply with the NICE reference case.

1.6.2 Weaknesses and areas of uncertainty

The four pivotal RCTs of PPS in IC/BPS were conducted between 1987 and 2003, and there is commonality across trial investigators. The FDA queried the independence of investigators across two

of the RCTs, along with the possibility of a treatment-by-investigator effect for one of seven study centres in one RCT. To date, there has been no further, independent, published study validating the results of the four RCTs of PPS in IC/BPS.

The ERG has concerns with the pairwise meta-analyses that were performed by the company and reported in the CS (analysis using risk difference, assessment of heterogeneity, application of a fixed effect model). There are also concerns with the method for the ITC (based on the Bucher method) and the ERG would prefer a simultaneous comparison between treatments using a Bayesian network meta-analysis.

The likely rate of response in patients receiving BSC without either PPS or BIs in clinical practice is uncertain and the estimates of cost-effectiveness are very sensitive to this rate. It is unclear what costs and utilities values should be assumed in the model for patients who respond to BSC. The relationship between prior use of BIs and utility is not considered to be robust given that the handling of missing data on BI usage had not been adequately explored in the analysis of the survey data. The CS does not contain any data describing the frequency of BIs in clinical practice and whether this decreases over time, or any data on the rate of self-administration with BIs. Several strong assumptions have had to be made in the company's model to deal with a lack of data on: (a) long term discontinuation rates for BIs; (b) the relative effectiveness of BIs and PPS; (c) the effectiveness of BIs in the population with IC/BPS; (d) the long-term response rate for patients cycling through multiple BIs after failing to respond to a first-line BI treatment, and (e) the relationship between ICSI scores and response to treatment.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook seven sets of exploratory analysis by implementing changes to the company's revised model. The ERG's preferred base-case incorporates all of these seven model amendments:

1. Use of all discontinuations reported by Hanno *et al.* (1997) for the time to treatment discontinuation survival analysis.
2. Switch to 6-weekly dosing for first-line BIs after the first year of treatment and 6-weekly for all second-line BIs (affects PPS vs BI only).
3. Use of regression for utility based on ICSI scores which excludes term for prior usage of BI.
4. Use of a lifetime horizon.
5. Return to baseline utilities for non-responders when BSC is second-line option (affects PPS versus BSC scenario only).
6. Remove assumption that response stops at 12 month for responders to BSC (PPS versus BSC scenario only as already implemented in PPS versus BI base-case).
7. Use of log-normal distribution to model the time to treatment discontinuation

The exploratory analysis demonstrated that the ICER for PPS vs BIs was most sensitive to changes in the frequency of BIs instillations (ICER increased to [redacted] per QALY gained) and the use of the utility regression that excludes the coefficient for recent BI usage (ICER increased to [redacted] per QALY gained). The ICER for the ERG's preferred base-case was [redacted] per QALY gained.

The exploratory analysis demonstrated that the ICER for PPS vs BSC was most sensitive to the removal of the assumption that the BSC response recedes at 12 months (ICER increased to [redacted] per QALY gained) and changes to the data on time to treatment discontinuation (ICER increased to [redacted] per QALY gained when the exponential distribution was used and [redacted] per QALY gained when the log-normal distribution was used). The ICER reduced significantly to [redacted] per QALY gained when assuming that non-responders on BSC return to base-line values for utility and costs. Overall, the ICER for the ERG's preferred base-case was [redacted] per QALY gained.

The ERG also conducted further sensitivity analyses around their preferred base-case to explore the impact of several data inputs and assumptions that remain uncertain. This produced ICERs ranging from [redacted] [redacted] per QALY gained for PPS vs BIs and ICERs ranging from [redacted] [redacted] per QALY gained for PPS vs BSC. The ICERs were particularly sensitive to uncertainty regarding the proportion of patients who would be expected to respond to BSC and uncertainty regarding the likely rate of self-administration of BIs in clinical practice.

2 BACKGROUND

This report provides a review of the evidence submitted by Consilient Health in support of pentosan polysulfate sodium (PPS) (Elmiron®) for treating interstitial cystitis/bladder pain syndrome (IC/BPS). It considers both the original company submission[1] (CS) received on 9th January 2019 and a subsequent response to clarification questions supplied by Consilient Health on 13th February 2019.[1]

2.1 Critique of company's description of underlying health problem

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission[1] (CS) to be appropriate, mostly up-to-date and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope.[2] The ERG provides a brief summary of the underlying health problem in this section.

Clinical features and nomenclature

The European Association of Urology 2018 guidelines on chronic pelvic pain describes bladder pain syndrome (BPS) as a chronic bladder condition characterised by persistent or recurrent pain, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency.[3] Other terms that have been used, but that are no longer recommended by the European Association of Urology include: interstitial cystitis (IC), painful bladder syndrome (PBS), and PBS/IC or BPS/IC.[3] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria for the diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) includes a diagnosis of IC based on glomerulations (haemorrhages in the bladder wall) or Hunner's lesions (distinctive inflammatory lesions that rupture the bladder lining) on cystoscopic examination.[4] The CS[1] uses the term BPS to describe patients meeting the broader symptomatic criteria of chronic bladder pain,[5] and IC/BPS to describe those with symptoms of BPS who also have glomerulations and/or Hunner's lesions and who comprise the indicated population for PPS.

Aetiology

The aetiologies of both BPS and IC/BPS are unknown, although several theories have postulated, including that of a deficient glycosaminoglycan (GAG) layer in the bladder.[6]

Prevalence

In the UK, BPS may affect approximately 400,000 people, 90% of whom are women.[7] and is more common in women than men. Up to 50% of patients with symptoms of BPS will have spontaneous resolution in time.[8] In Europe, estimates of the prevalence of BPS associated with inflammation in the bladder (for example, characterised by Hunner's lesions or glomerulations) range from 0.3 to 10.2 per 10,000 patients.[9-11]

Diagnosis

Clinical diagnosis of BPS is often made once specific causes such as infection and malignancy have been ruled out.[12, 13] Diagnosis is made using symptoms, examination, urine analysis and urine culture (to rule out a urinary tract infection), cystoscopy with or without hydrodistension (to rule out bladder cancer, vesical stones, urethral diverticula and intravesical foreign bodies), and biopsy (to exclude other pathologies).[8]

2.2 Critique of company's overview of current service provision

The ERG considers the company's overview of current service provision to be reasonable, in that the company acknowledges that there is currently no NICE guidance on the management of BPS or IC/BPS. The company presents a proposed patient/treatment pathway for IC/BPS. The ERG provides a brief summary of this in this section.

Proposed patient/treatment pathway

For people with IC/BPS, an advisory board to the company concluded that PPS or bladder instillations are second-line treatments after standard management (e.g. analgesics, hydroxyzine, lifestyle/dietary advice, bladder retraining).[1] An advisory board to the company proposed both a patient and a treatment pathway. The proposed patient pathway by reproduced from the CS,[1] is presented in Figure 1. The proposed treatment pathway reproduced from the CS,[1] is presented in Figure 2.

The company's advisory board also concluded that bladder instillations include commercially available instillations, such as sodium hyaluronate (Cystistat® , Hyacyst®) and sodium chondroitin sulphate (Uracyst® , Gepan®), or locally prepared instillations using ingredients (off-label) such as heparin, lignocaine, sodium bicarbonate or hydrocortisone (CS, page 23). However, whilst the proposed treatment pathway presented in the CS included locally prepared instillations, evidence for these was not included in the CS.

During the clarification process, the ERG asked the company why these treatments were not included in the CS. In response, the company stated that these locally prepared instillations, also known as 'bladder cocktails', can vary by site and include commonly used drugs indicated for other conditions. Further, that these have not been included in the company's submission because of their relatively infrequent use in the UK, the heterogeneity of the different cocktails, and the difficulty in sourcing relevant evidence of their use in IC/BPS.[1]

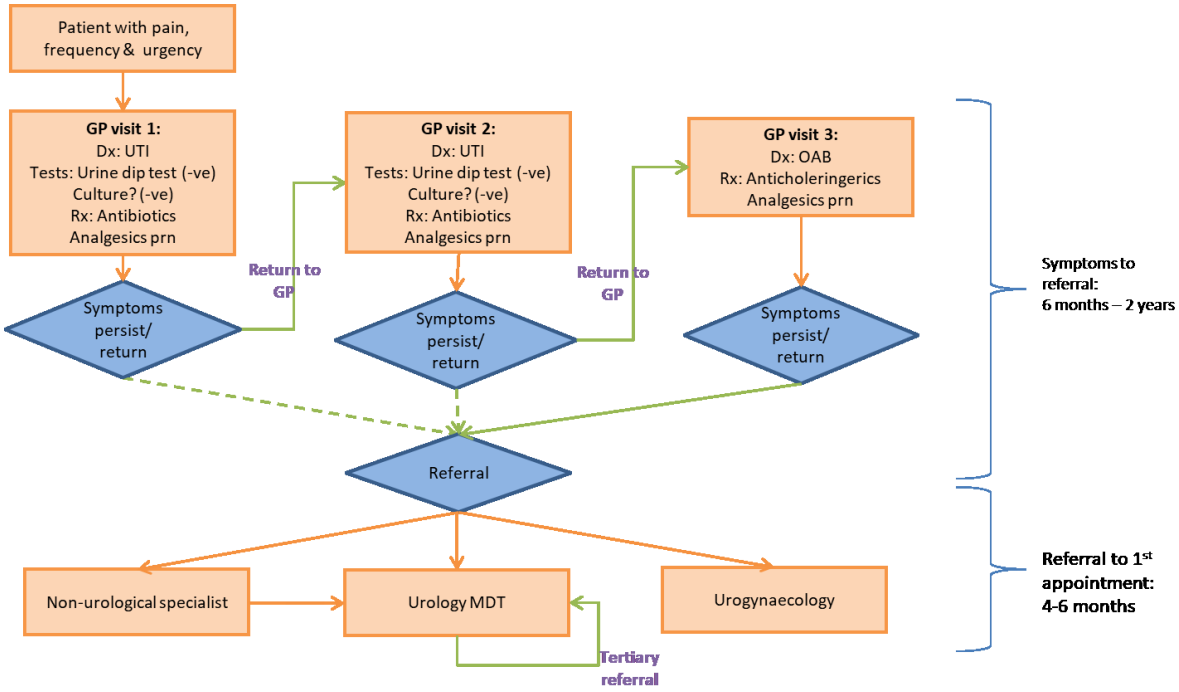
The advisory board to the company also concluded that sodium hyaluronate/sodium chondroitin sulphate (iAluRil®) is often not used until later in the pathway as a third-line treatment if other

instillations are unsuccessful (CS, page 23). The company's advisory board also noted that prior to the UK launch of licensed Elmiron® (PPS) in September 2018, oral PPS was only available as an unlicensed special import (CS, page 24). The advisory board to the company concluded that surgery including urinary diversion, bladder reconstruction (i.e., augmentation), and cystectomy, is considered as a last resort (CS, page 24) and that the proportion of IC/BPS patients receiving surgery is low (2%) (CS,[1] Figure 2).

Clinical advice received by the ERG on the proposed patient/treatment pathway varied. Some clinical experts expressed a wish to use PPS before BIs as it is less invasive, whilst others felt that it would be used after failure of BIs. Clinical advice received by the ERG on the experience of using PPS and its availability off-label varied. There was no consensus on the use of locally prepared bladder instillations containing heparin, lignocaine, sodium bicarbonate or hydrocortisone; or the use of botulinum toxin A in treating IC/BPS. However, there was consensus that the proportion of IC/BPS patients receiving surgery in the UK is very low (2% to 5%).

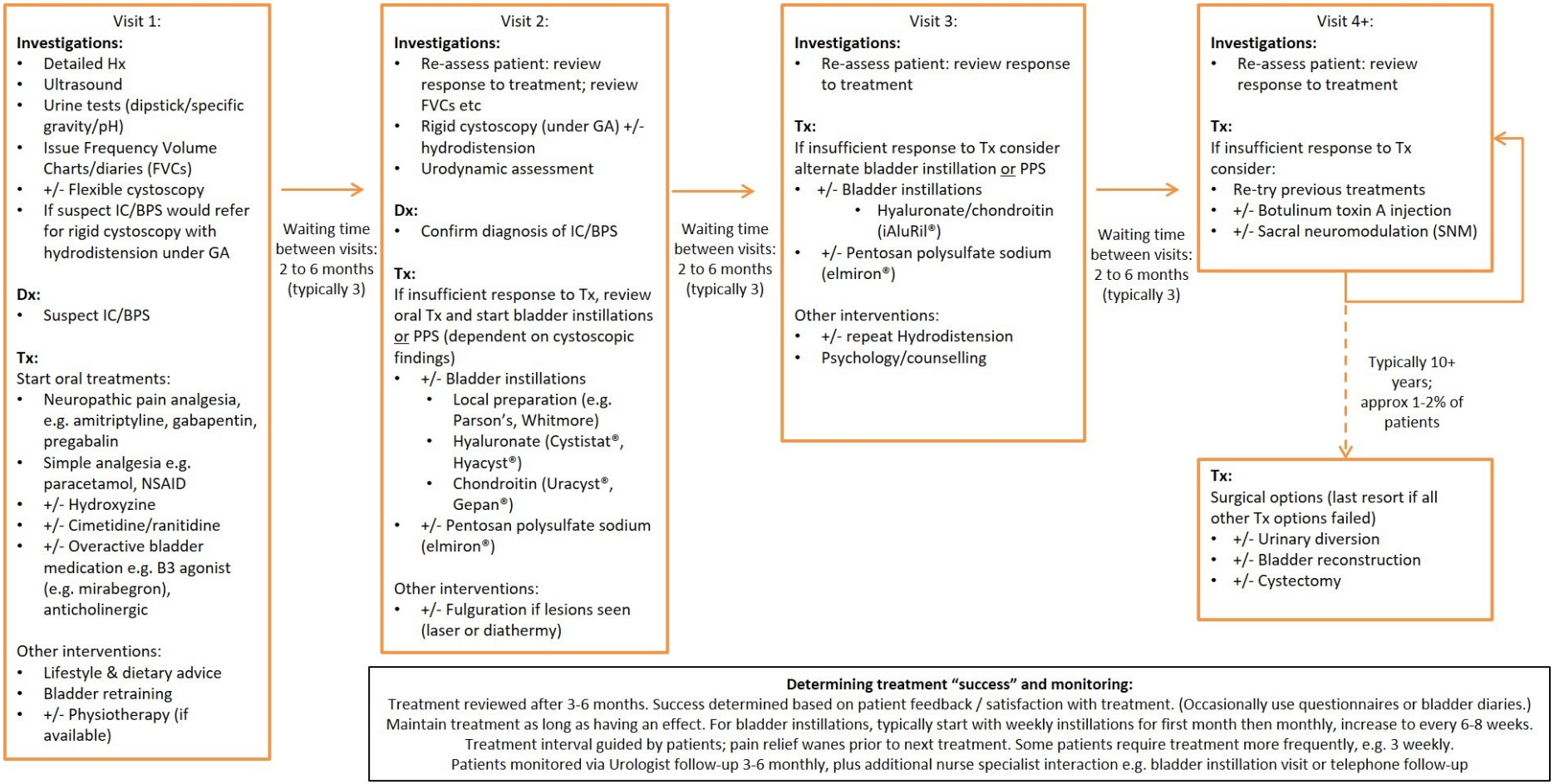
The advisory board to the company suggested that the number of BPS patients for whom BIs are contraindicated or who refuse bladder instillations is <5%.[1] The ERG's clinical advisors believe this to be reasonable.

Figure 2 of the CS (Figure 2) states that bladder instillations typically start weekly for the first month, then monthly, then decrease in frequency to every six to eight weeks. Clinical advice received by the ERG on the proposed frequency of instillations varied, but was generally consistent with weekly instillations for the first four to six weeks, prior to lengthening the treatment interval.



Reproduced from the CS page 25.[1]

Figure 1: Patient pathway for IC/BPS proposed by the advisory board to the company presented in the CS (Figure 1)



Reproduced from the CS page 26.[1]

Figure 2: Treatment pathway for IC/BPS proposed by the advisory board to the company presented in the CS (Figure 2)

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

Pentosan polysulfate sodium (PPS) (Elmiron® , Consilient Health) has a marketing authorisation in the Europe for treating IC/BPS. The target population in the company's decision problem matches the population described in the final NICE scope which is 'adults with bladder pain syndrome characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition',[2] which is narrower than the marketing authorisation.

The key clinical evidence submitted by the company is derived from four randomised controlled trials (RCTs) of PPS in IC/BPS.[14-17] These RCTs all recruited patients with glomerulations and/or Hunner's lesions and were undertaken in the United States. Clinical advice received by the ERG suggested that the populations in these RCTs are generally comparable to the UK IC/BPS population. The company also included two additional RCTs of PPS in the broader BPS population that did not include a cystoscopic evaluation for glomerulations or Hunner's lesions at baseline.[18, 19] These two RCTs did not contribute to the pairwise meta-analysis of global response used in the company's base-case economic model, but did contribute to other meta-analyses in the clinical section of the CS. In addition, the impact on the cost-effectiveness estimates of including them in the meta-analysis used to estimate the rate of response for PPS in the company's model was examined in a scenario analysis. These two RCTs are not considered further in this section of the ERG report, but are summarised briefly in Section 4.2.5.

3.2 Intervention

The intervention evaluated in the CS is Elmiron® (pentosan polysulfate sodium, PPS), a semi-synthetic heparin-like substance that resembles glycosaminoglycans (GAGs). Although its exact mechanism of action is unclear, PPS is hypothesised to bind to the damaged GAG layer in the bladder, which protects the bladder by reducing the adherence of bacteria to the mucosal lining, in turn reducing inflammation. In addition to its anti-inflammatory activity, PPS may also have a barrier function instead of the damaged urothelial mucus.[1] The intervention matches that in the NICE scope.[2]

PPS received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 23rd March 2017 for the treatment of IC/BPS, and received EMA marketing authorisation June 2017.[8]

The Summary of Product Characteristics (SmPC)[8] reports that PPS is contraindicated in patients who actively bleed (excluding menstruation).[8]

The SmPC recommends that patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding should be evaluated for haemorrhagic events, and patients who have a history of heparin or PPS induced thrombocytopenia should be carefully monitored.[8] The ERG's clinical advisors agreed with this.

Common adverse events (AEs) listed in the SmPC are: headache, dizziness, nausea, diarrhoea, dyspepsia, abdominal pain, abdominal enlargement, rectal haemorrhage, peripheral oedema, alopecia, back pain, asthenia, and pelvic pain.[8] Clinical advice received by the ERG from experience of using PPS on a named patient basis is that AEs are rare.

PPS is administered orally three times per day. The list price for PPS is £450.00 per pack (90 x 100 mg capsules). The cost-effectiveness results presented by the company are based on the list price.

3.3 Comparators

Two comparators are listed in the final NICE scope: (i) bladder instillations, and (ii) for people for whom bladder instillations are inappropriate, cannot be tolerated or are unsuccessful: established clinical management without PPS or bladder instillations (including medicines that do not currently have a marketing authorisation in the UK for this indication).[2]

Whilst the CS reports that bladder instillations include commercially available instillations, such as sodium hyaluronate (Cystistat® , Hyacyst®) and sodium chondroitin sulphate (Uracyst® , Gepan®), or locally prepared instillations using ingredients (off-label) such as heparin, lignocaine, sodium bicarbonate or hydrocortisone, only evidence relating to sodium hyaluronate, sodium chondroitin sulphate or a combination of the two (iAluRil®) was searched for.[1] Clinical advice received by the ERG on the use of off-label instillations in IC/BPS varied. There was no consensus regarding the use of locally prepared instillations using ingredients (off-label) such as heparin, lignocaine, sodium bicarbonate or hydrocortisone. The ERG sought clarification (question A4) with the company regarding these treatments not being including in the CS. The company's clarification response stated these locally prepared instillations, also known as 'bladder cocktails', can vary by site and include commonly used drugs indicated for other conditions. Further, that these have not been included in the company's submission because of their relatively infrequent use in the UK, the heterogeneity of the different cocktails, and the difficulty in sourcing relevant evidence for their use in IC/BPS.[1]

Two RCTs in sodium chondroitin sulphate (Uracyst®) in patients with BPS[20, 21] were included in the ITC presented in the CS.[1]

3.4 Outcomes

The outcomes in the decision problem in the CS are:

- bladder pain, response to treatment (e.g., Global Response Assessment [GRA], a standardised outcome in IC/BPS),
- severity of symptoms,
- urinary urgency,
- urinary frequency,
- nocturia,
- adverse effects of treatment, and
- health-related quality (HRQoL) of life.[1]

These outcomes match those in the NICE scope.[2]

Across the four included RCTs of PPS in IC/BPS,[14-17] the CS[1] presents outcome data on: GRA; the Interstitial Cystitis Symptom Index (ICSI);[22] Interstitial Cystitis Problem Index (ICPI), non-VAS pain outcomes (not defined in the CS), urinary frequency, void/volume outcomes, nocturia, and adverse events.

Additional outcomes of maximum bladder capacity, cystoscopic outcomes, cystometric outcomes, and mast cell count are also reported for one RCT in the broader BPS population.[18] The CS notes that the advisory board recommended that the comparability of bladder capacity at baseline across trials be assessed. However, this was not included in the CS. The company's clarification response included baseline bladder capacity reported across the included RCTs.[1]

The CS states that the measures of GRA from the four RCTs of PPS in IC/BPS[14-17] are equivalent.[1] Clinical advice received by the ERG was generally in agreement with this. Clinical advice received by the ERG also indicated the possibility of a 20% to 40% response to BSC in clinical practice for this outcome in clinical practice.

3.5 Other relevant factors

Equity

The CS reports that the evaluation does not include weighting of quality-adjusted life years (QALYs) (CS,[1] Table 39).

Adherence

Adherence to treatment is not measured in the CS.[1] The CS describes the hypothesised mechanism of action for PPS in binding to the GAG layer of the bladder, thus reducing adherence of bacteria and reducing inflammation (CS, page 14). The ERG's clinical advisors suggest that PPS may take up to three months to be effective. The clinical advisors stated that IC/BPS patients are advised to continue with other current treatment which will continue to have some therapeutic effect after starting PPS and that IC/PPS patients tend to stay on a treatment that is working and that stopping treatment may result in an IC/BPS symptoms flare.

Ongoing studies

The company searched appropriate sources to identify ongoing studies; the CS states that no ongoing studies of PPS in IC/BPS were identified (CS, Section B.2.11).[1]

Patient Access Scheme

The CS reports that a Patient Access Scheme for PPS is not applicable (CS, Table 2).[1]

4 CLINICAL EFFECTIVENESS

This section presents a review of the clinical evidence reported in the CS[1] for pentosan polysulfate sodium (PPS) for treating interstitial cystitis/bladder pain syndrome (patients with bladder pain syndrome with Hunner's lesions and/or glomerulations) (IC/BPS). The RCTs are presented in evidence tables in the CS and in this ERG report in reverse chronological order (most recent first).

4.1 Critique of the methods of review(s)

The clinical evidence provided in the CS comprises a systematic review of RCTs of PPS for both IC/BPS (four RCTs[14-17]) and BPS (two RCTs, [18, 19] summarised in Section 4.2.5), a pairwise meta-analysis of four RCTs of PPS in IC/BPS[14-17], a pairwise meta-analysis of two RCTs in sodium chondroitin sulphate instillations (Uracyst®) in BPS,[20, 21] and an ITC of PPS in IC/BPS compared to Uracyst® in BPS. Safety evidence provided in the CS comprises a narrative synthesis of four RCTs of PPS in IC/BPS [14-17] and two RCTs of Uracyst® in BPS.[20, 21]

4.1.1 Searches

The company performed a systematic literature review (SLR) to identify all clinical and safety studies of pentosan polysulfate sodium and its comparators for the treatment of patients with or without cystitis or bladder pain.

For the original searches, several electronic bibliographic databases were searched in June 2018 including MEDLINE [via Ovid], MEDLINE Epub Ahead of Print, in Process [via Ovid], Embase [via Ovid], Cochrane Database of Systematic Reviews [via Wiley], Cochrane Central Register of Controlled Trials and the Health Technology Assessment database [via Wiley], Database of Abstracts of Reviews of Effects [via Wiley] and the Health Technology Assessment Database [via Wiley]. The company did not search conference proceedings websites or databases (clarification question A3) for unpublished studies. However, the company searched two key clinical trials registers (clinicaltrials.gov, WHO International Clinical Trials Registry Platform).

In Appendix D (RCTs and non-RCTs), the company only reported the full literature search strategies for identifying RCTs. The company's response to clarification question A3 stated that the comparators heparin, lignocaine, sodium bicarbonate and hydrocortisone were excluded from the clinical effectiveness search because of infrequent use in the UK, the heterogeneity of the mixtures and usage and the difficulty in sourcing relevant data

In response to clarification question A2, the company provided search strategies for the clinical effectiveness evidence search for non-randomised studies (reported in Table 27 of the CS). It is unclear

why the company only searched one electronic database (PubMed via NIH) and two other web sources DIMDI and MedPilot rather than Embase and Cochrane Library. The company performed a high precision search of interstitial cystitis combined with pentosan sulphuric polyester in PubMed but did not report on the strategy for searching DIMDI and MedPilot. The ERG was unable to assess the adequacy of the non-RCT searches. For the reasons described above, the ERG was also unable to assess the adequacy of the searches for Medline and Cochrane Library.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the systematic review are reported in the CS[1] are in accordance with the NICE scope,[2] with the exception of locally prepared instillations using ingredients (off-label) such as heparin, lignocaine, sodium bicarbonate or hydrocortisone. The ERG sought clarification from the company regarding the exclusion of these treatments from the CS.

A copy of the inclusion and exclusion criteria, reproduced from the CS[1] are presented in Table 1.

Table 1: Inclusion and exclusion criteria in systematic review search strategy (reproduced from Table 65 of the CS)

Characteristics	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years) with interstitial cystitis/bladder pain syndrome (IC/BPS) or BPS	Paediatric patients (<18 years)
Interventions	Elmiron® (pentosan polysulfate sodium/sodium pentosan polysulfate)	NA
Comparators	• Cystistat® (sodium hyaluronate/hyaluronic acid 0.08%) • Hyacyst® (sodium hyaluronate/hyaluronic acid 0.08% or 0.24%) • Gepan® (sodium chondroitin sulphate 0.2%) • Uracyst® (sodium chondroitin sulphate 2%) • iAlurRl® (hyaluronic acid/sodium hyaluronate 1.6% and sodium chondroitin sulphate 2%) • Placebo	Studies not comparing the intervention with a comparator or studies not comparing two comparators
Outcomes	• Cystometric first sensation and bladder capacity • Cystoscopic appearance • Maximal bladder capacity (hydrodistension) • Mast cell count • Voided urine volume • Urinary frequency • Global Response Assessment (GRA) • Pain Visual Analogue Scale (VAS) • O'Leary-Sant (OLS) Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) • Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) • Patient-reported improvement and pain scales	Outcome not listed in the inclusion criteria
Study type	Randomised controlled trials (RCTs)	• Reviews/systematic reviews/pooled trial analyses • Studies indexed as case reports, case series, editorials and letters • Conference abstracts • Non-human studies

Appendix D of the CS[1] reports that the citation sifting stage and study selection at the full-text stage were undertaken by two reviewers, which is considered best practice in systematic reviewing. However, it is not clear if, at both of these stages of the study selection process, the reviewers worked collaboratively or independently (the latter reflects best practice). It is also not clear in the CS (CS, Appendix D)[1] what proportion of citations at the sifting stage were double-checked (i.e., by both reviewers).

4.1.3 Critique of data extraction

Details regarding the company's data extraction methods (number of reviewers involved, items extracted, or a copy of a data extraction sheet) are not reported in the CS.[1]

Data extracted from the four included PPS in IC/BPS RCTs[14-17] are reported in Sections 4.1.4 to 4.2 and data extracted from the two Uracyst® in BPS RCTs[20, 21] reported in the CS[1] are reported below in Section 4.3. All data were checked against the published trial reports[14-17, 20, 21] by the ERG. Although the CS reports that two reviewers were involved in the study selection process, it is unclear how many were involved in the data extraction process and the ERG identified several data extraction errors. However, these errors did not impact on the analyses undertaken by the company.

4.1.4 Quality assessment

Quality assessment of the four RCTs of PPS in IC/BPS[14-17] is presented in Section B.2.5 and Appendix D of the CS.[1] The CS does not report where the quality assessment items were taken from, only that these were 'NICE criteria'. The ERG sought clarification with the company regarding this issue. The company's clarification response[1] stated that the items assessed were taken from the NICE Guidelines Manual.[23] These are appropriate criteria for assessing the methodological quality/risk of bias in RCTs.

It is considered good systematic review practice for two reviewers either to independently perform quality assessment or to check assessed items, but this was not reported in the CS. The ERG checked the company's quality assessment against the publications of the RCTs relevant to the decision problem.

Table 11 presents the company's quality assessment of the four RCTs of PPS in IC/BPS RCTs14-17 (Section 4.2.4 of this report).

4.1.5 Evidence synthesis

The company presented a narrative synthesis of the evidence for PPS in IC/BPS and sodium chondroitin sulphate instillations (Uracyst®) in BPS. The ERG considers the narrative synthesis approach undertaken by the company to be acceptable. In addition, the company provided the following justification for not undertaking a network meta-analysis (CS, page 82): "*Twelve trials met the inclusion*

criteria. Six trials compared PPS capsules to oral placebo, three Uracyst® to placebo instillation and one each of Uracyst® to DMSO instillation, iAluRil® to DMSO instillation and Cystistat® to Gepan® . It was therefore not possible to construct a network comparing PPS to all relevant comparators. Only one bladder instillation, Uracyst®, could potentially be compared to PPS indirectly via placebo. However, there was considerable heterogeneity in the trials, which would make a robust ITC of PPS with any comparator challenging."

The company undertook a pairwise meta-analysis of RCTs of PPS compared to placebo in IC/BPS, a pairwise meta-analysis of Uracyst® compared to placebo in BPS, and an ITC of PPS in IC/BPS compared to Uracyst® in BPS. Further details of the PPS trials can be found in Section 4.2, further details of the Uracyst® trials can be found in Section 4.3, and further details of the ITC can be found in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included trials of PPS in IC/BPS

The company identified four RCTs of PPS which were considered relevant to the decision problem (Sant *et al.*, 2003;[17] Parsons *et al.*, 1993;[15] Mulholland *et al.*, 1990;[14] Parsons and Mulholland, 1987[16]). All four trials included a comparison for PPS 100 mg three times per day to placebo. Sant *et al.*, (2003)[17] also evaluated hydroxyzine 50 mg administered orally once daily and hydroxyzine plus PPS (four treatment groups) in a factorial design. Placebo was three times per day.

In the RCT reported by Parsons and Mulholland (1987),[16] one study centre compared PPS 100 mg three times per day to PBO, and one study centre compared PPS 200 mg twice per day to PBO (two study centres). However, results for this trial are presented as both PPS groups combined compared to both PBO groups combined. The CS[1] (page 38) reports that 200 mg twice per day is comparable to the approved dose (300 mg per day). The EMA (EPAR, page 58) reports that across the pivotal studies, few patients received a dose of PPS 200 mg twice per day. However, the associated patient numbers are not presented.[8]

Eligibility criteria

All four RCTs recruited patients age ≥18 years old. With reference to the decision problem criteria in the NICE scope for IC/BPS patients with Hunner's lesions and/or glomerulations: in Sant *et al.* (2003)[17], IC/BPS was confirmed by cystoscopy and hydrodistention, following NIDDK[4] and Digestive and Kidney Diseases criteria;[24] in Mulholland *et al.* (1990)[14], patients had to have cystoscopic examination under anaesthesia showing petechial haemorrhages or ulcers; and in Parsons and Mulholland (1987)[16], patients also had to have cystoscopic examination showing ulcer or petechial haemorrhage. In Parsons

et al. (1993),[15] patients were recruited based on bladder capacity, number of voids per day, voided volume, and nocturia. Patients lacking one or two of these criteria had to also have pain and/or moderate urgency, negative urinary cytology studies and cultures, and cystoscopic findings of petechial haemorrhages and blood in the fluid return after bladder distension.

Eligibility criteria the four PPS in IC/BPS RCTs included in the CS are presented in Table 2.

Table 2: Patient eligibility criteria for the pentosan polysulfate sodium RCTs relevant to the decision problem (adapted from Tables 10 to 13 of the CS)

Trial	Inclusion criteria	Exclusion criteria
Sant *et al.*, 2003[17]	Patients ≥18 years old with a diagnosis of IC/BPS, confirmed by cystoscopy and hydrodistention, following National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases criteria. Patients had moderate symptoms of urinary frequency (≥11 time/day) and pain/discomfort (≥4 on a 0–9 Likert scale) for >24 weeks prior to trial entry.	Patients with history of: cyclophosphamide, pelvic radiation, augmentation cystoplasty, cystectomy, or cystolysis, neurectomy, implanted peripheral nerve stimulator, prostate surgery or treatment (men only). In prior 24 weeks: intravesical bacillus Calmette-Guerin, cystocele, rectocele, urinary incontinence surgery, transvaginal surgery, hysterectomy, prolapse, vaginal delivery, or caesarean section (women only) Prior 6–12 weeks: urethral dilatation, cystometrogram, urodynamics, cystoscopy/hydrodistention, bladder biopsy, prostate biopsy (men only), any intravesical treatment other than BCG Prior 4 weeks: initiation of any new medications for IC, washout for oral PPS and hydroxyzine Any history of bladder calculus, tuberculous cystitis, neurological disease or diabetic cystopathy, malignant bladder tumours, urethral cancer Last 3 years: uterine, cervical or vaginal cancer (women only) Last 6–12 weeks: bacterial urinary tract infection; active genital herpes, gross haematuria Concurrent: active urethral calculus, ureteral calculus, symptomatic urethral diverticulum, documented chronic bacterial prostatitis (men only), active vaginitis, pregnant, breast-feeding (women only) Concurrent: urinary void with a maximum volume >350 cc; residual urine volume ≥150 cc by ultrasound or catheter (men only), liver function test >1.5× upper limit of normal, abnormal blood coagulation tests
Parsons *et al.*, 1993[15]	Patients ≥18 years old with 8 or more voids per day; average voided volume of 50–200 cc; anaesthetic bladder capacity of 350–1,000 cc; and nocturia (at least 1 or 2 episodes) OR any patients lacking 1 or 2 of these criteria if they had pain and/or moderate urgency, negative urinary cytology studies and cultures, and cystoscopic findings of petechial haemorrhages and blood in the fluid return after bladder distension	Patients <18 years old or who were unavailable for the duration of the trial or unable to follow instructions; pregnant or lactating women; premenopausal women not practicing an effective means of birth control. Patients with evidence of active bleeding peptic ulcer disease or bleeding diathesis; signs of recurrent bacteriuria or obvious neurological impairment. Patients who had: received previous treatment with known bladder irritants; a history of pelvic irradiation, bladder carcinoma, urinary tuberculosis or schistosomiasis; a known allergy to PPS

Trial	Inclusion criteria	Exclusion criteria
Mulholland *et al.*, 1990[14]	Patients with urgency expressed as moderate on a 5-point analogue scale (not reported in the trial report if it is a visual analogue scale or not); frequency of at least 10 voids/day; nocturia of at least 2 voids/night; pain as recorded on a 5-point analogue scale; continuous duration of symptoms of at least 1 year; failed previous conventional therapy e.g., chlorpactin, hydrodilatation, DMSO; average voided volume of 200 ml or less measured over a 3-day period; negative urine culture and cytology; cystoscopic examination under anaesthesia showing petechial haemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 800 ml or less	Patients aged <18 years; lack of availability for the duration of the trial or inability to follow instructions; pregnancy; premenopausal and not practicing effective means of birth control; lactating mothers; evidence of active bleeding peptic ulcer disease; bleeding diathesis; known allergy to PPS; treatment with PPS within six weeks of trial; signs of: recurrent bacteriuria, obvious neurologic impairment, history of pelvic irradiation, previous treatment with known bladder irritants, bladder carcinoma, urinary tuberculosis, shistosomiasis
Parsons and Mulholland, 1987[16]	Patients aged >18 years old with ≥1 year of symptoms (urgency, frequency, nocturia and/or pain), negative urine cultures, cystoscopic examination showing ulcer or petechial haemorrhage (after bladder distension), biopsy-proved inflammation, and negative cytology studies.	Not reported

Trial characteristics

Details of trial location treatments and numbers randomised, prohibited concomitant medications and other outcomes reported by the four PPS in IC/BPS RCTs included in the CS are presented in Table 3.

All four RCTs of PPS in IC/BPS were multicentre trials conducted in the USA.[14-17] The number of centres ranged from two[16] to seven.[15, 17] Numbers randomised to PBO and PPS 100 mg were 31 and 29 respectively in Sant *et al.* (2003),[17] 74 and 74 respectively in Parsons *et al.* (1993),[15] and 56 and 54 respectively in Mulholland *et al.* (1990).[14] Parsons and Mulholland (1987)[16] did not report numbers randomised by group, but that 75 patients were randomised across two centres to PBO, PPS 100 mg, or PPS 200 mg.

In Sant *et al.* (2003),[17] prohibited medication included: cimetidine, intravesical heparin, chronic use of acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or sedating histamine-1 receptor antagonists. Prohibited medications were similar in Parsons *et al.* (1993)[15] and Mulholland *et al.*, 1990.[14] The RCT by Parsons and Mulholland, 1987[16] did not report on permitted or prohibited medication.

Global response assessment (GRA) varied across the four RCTs of PPS in IC/BPS.[14-17] In Sant *et al.* (2003),[17] responders were those who six or seven (moderately or markedly improved) on a seven-point scale (markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved and markedly improved). In Parsons *et al.* (1993),[15] responders were those with >50% overall improvement in symptoms (improvement rated as: slight, 25%; moderate, 50%; great, 75%; symptoms gone, 100%). In Mulholland *et al.* (1990),[14] a >50% overall improvement in symptoms on a six-point scale ranging from worse to excellent was considered by the company as comparable to GRA for the purpose of analysis. In Parsons and Mulholland (1987),[16] symptoms of urgency, frequency, nocturia and pain were graded as 0%, 25%, 50%, 75%, or 100% improvement. The company considered >50% pain improvement comparable to GRA for the purpose of analysis. The ERG's clinical advisors did not all agree that the measures of GRA were comparable across the RCTs.

One RCT reported that outcome follow-up was at 24 weeks,[17] and two reported that outcome follow-up was at three months.[14, 15] In the RCT by Parsons and Mulholland (1987),[16] if the patient failed to respond to therapy at three months (PPS or PBO), patients were switched to the alternative treatment (from PPS to PBO, or from PBO to PPS). The CS[1] reports data at three months, prior to the switch.

Table 3: Trial locations, treatments and numbers randomised, concomitant medication, and outcomes for the pentosan polysulfate sodium RCTs relevant to the decision problem (adapted from Tables 10 to 13 of the CS)

Trial Location	Treatments, numbers randomised and follow-up	Permitted and prohibited concomitant medication	Primary outcomes	Other outcomes used in the economic model/specified in the scope
Sant *et al.*, 2003[17] **USA (7 centres)**	PBO, 31 PPS 100 mg, 29 Both TID	Prohibited: cimetidine, intravesical heparin, chronic use of acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or sedating histamine-1 receptor antagonists	*Global Response Assessment:* - n (%) moderately/markedly improved (score of 6 or 7) (24 weeks)	*Pain and urgency (scope only):* - mean change in non-VAS pain score (time point: 24 weeks) - mean change in urgency score (time point: 24 weeks) *O'Leary-Sant/ICSI and ICPI scores (model and scope):* - mean ICSI change (time point: 24 weeks) - mean ICPI change (time point: 24 weeks) *Urinary frequency (scope only):* - - mean daily frequency change (time point: 24 weeks)
Parsons *et al.*, 1993[15] **USA (7 centres)**	PBO, 74 PPS 100 mg, 74 Both TID	Prohibited: anticoagulant therapy; chronic use of narcotics; artificial sweeteners; PPS within 4 weeks of the trial	*Global Response Assessment:* - n patients reporting >50% overall improvement in symptoms (time point: 3 months)	*Voided urine volume (scope only):* - mean volume/void change (cc) (time point: 3 months) - % patients with increase of >20 cc in volume/void (time point: 3 months) - mean total daily volume change (cc) (time point: 3 months) *Pain and urgency (scope only):* - patient-reported degree of pain and urgency on a scale of 0 to 5, in which 0 is none, 1 is mild, 3 is moderate, and 5 is severe (time point: 3 months)

Trial Location	Treatments, numbers randomised and follow-up	Permitted and prohibited concomitant medication	Primary outcomes	Other outcomes used in the economic model/specified in the scope
				Investigator evaluation of overall improvement (scope only): - - overall changes in condition were evaluated as worse, no change, fair (25%), good (50%), very good (75%), and excellent (100%) (time point: 3 months)
Mulholland *et al.*, 1990[14] **USA (5 centres)**	PBO, 56 PPS 100 mg, 54 Both TID	Prohibited: anticoagulant therapy; chronic use of narcotics; use of artificial sweeteners; treatment within PPS within 6 weeks of the trial	*6-point patient-reported improvement (considered comparable to GRA for the purpose of analysis):* - n patients reporting >50% overall improvement in symptoms (time point: 3 months)	*6-point investigator-evaluated improvement (scope only):* - % >50% improved (time point: 3 months) *Patient-reported pain improvement (scope only):* - % >50% improved (time point: 3 months) - % reporting decrease of >1 point (time point: 3 months) - mean reduction in pain score (time point: 3 months) *Voided urine volume (scope only):* - Mean volume/void change (cc) (time point: 3 months) - % patients with increase of >20 cc in volume/void (time point: 3 months) - Mean total daily volume change (cc) (time point: 3 months)
Parsons and Mulholland, 1987[16] **USA (2 centres)**	Total PBO, PPS 100 mg TID, and PPS 200 mg BID; 75	NR	*Global Response Assessment:* - Patient-reported pain improvement (time point: 3 months [before crossover]) (considered comparable to GRA for the purpose of analysis) *Urinary frequency:*	*Voided urine volume (scope only):* - mean volume/void (mL) (time point: 3 months [before crossover])

Trial Location	Treatments, numbers randomised and follow-up	Permitted and prohibited concomitant medication	Primary outcomes	Other outcomes used in the economic model/specified in the scope
	For 3 months initially then, if PBO or PPS failure, cross-over to PBO or PPS for a further 3 months		- n (%) any improvement (time point: 3 months [before crossover]) - mean daily change (improved patients only) (time point: 3 months [before crossover]) - mean daily frequency (time point: 3 months [before crossover]) *Urinary urgency:* - n (%) any improvement (time point: 3 months [before crossover]) - mean % improvement (time point: 3 months [before crossover]) *Nocturia:* - mean improvement (time point: 3 months [before crossover])	

BID, twice per day; GRA, global response assessment; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; NR, not reported; PBO, placebo; PPS, pentosan polysulfate sodium; TID, three times per day

Sample size and power calculation

The CS[1] (Table 17) reports on sample size and power calculations. In the Sant *et al.* (2003) RCT,[17] "*the projected sample size of 136 participants planned to be recruited during 10 months was selected to detect a difference in response rates of 30% and 65% (80% power at a 2-sided significance level of 5%)*". One hundred twenty-one (121) participants were randomised to four treatment groups. No sample sizes were defined prospectively for the trials by Parsons *et al.* (1993);[15] Mulholland *et al.* (1990);[14] or Parsons and Mulholland (1987);[16]. The European Medicines Agency (EMA) consider this is a weakness of the literature-based application in the European public assessment report (EPAR).[8]

Baseline characteristics of trial participants

Details of participant baseline characteristics in the four PPS in IC/BPS RCTs included in the CS are presented in Table 4.

The proportion of patients who were female across treatment groups was >89% in all four RCTs.[14-17] Where age was reported, patients were in the fifth decade of life.[14, 15, 17]

The RCTs by Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990)[14] reported Hunner's ulcers in ≤8% of patients. However, Parsons and Mulholland (1987) reported that across PBO, PPS 100 mg, and PPS 200 mg treatment groups, 28% had Hunner's ulcers. Sant *et al.* (2003)[17] did not report on Hunner's ulcers. Petechial haemorrhage was not reported by Sant *et al.* (2003)[17] or Parsons and Mulholland (1987). Across the RCTs, Parsons *et al.* (1993)[15] and Parsons and Mulholland (1987),[16] the proportions of patients with petechial haemorrhage varied depending on numbers with haemorrhages, but with between 40% and 50% of patents having a moderate number (not defined) of petechial haemorrhage in both of these RCTs.

The ERG's clinical advisors believed that the populations in these RCTs were generally comparable to the UK IC/BPS population.

Baseline pain and urinary details were only reported by Sant *et al.* (2003),[17] and baseline bladder capacity was only reported by Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990).[14]

Table 4: Baseline characteristics of participants in the pentosan polysulfate sodium RCTs relevant to the decision problem (adapted from Table 16 of the CS and the trial reports)

Trial Location	n/N (%) female	Mean (SD) age years	N/n (%) with ulcers/haemorrhage	Other characteristics
Sant *et al.*, 2003[17]	PBO, 28/31 (90%) PPS, 26/29 (90%)	PBO, 41.6 (15.5) PPS, 48.7 (15.1)	NR	*Prior symptoms for ≥ 52 weeks, n (%):* PBO, 28 (90%); PPS, 28 (96%) *Pain score (0 to 9), mean (SD):* PBO, 6.0 (1.3); PPS, 6.3 (1.4) *Urinary score (0 to 9), mean (SD)* PBO, 6.5 (1.5); PPS, 6.9 (1.2) *24-hour frequency score (0 to 9), mean (SD):* PBO, 18.9 (10.3); PPS, 18.3 (6.8) *ICSI, mean (SD):* PBO, 14.6 (3.3); PPS, 14.3 (3.3) *ICPI, mean (SD):* PBO, 12.8 (2.4); PPS, 12.8 (2.7) *Wisconsin IC score (0 to 42), mean (SD):* PBO, 32.9 (6.7); PPS, 30.4 (6.8)
Parsons *et al.*, 1993[15]	PBO, 74/74 (100%) PPS, 66/74 (93%)	PBO, 45.5 (NR) PPS, 42.7 (NR)	Hunner's ulcer: PBO, NR (4%) PPS, NR (4%) Petechial haemorrhage: PBO, NR (none, 1%; few, 8%; moderate, 43%; many, 47%) PPS, NR (none, 1%; few, 9%; moderate, 41%; many, 49%)	*Other abnormalities:* PBO, 8%; PPS, 11% *Bladder capacity under anaesthesia, mean (cc):* PBO, 601; PPS, 656
Mulholland *et al.*, 1990[14]	PBO, 45/56 (87%) PPS, 49/54 (91%)	PBO, 45.3 (NR) PPS, 43.3 (NR)	Hunner's ulcer: PBO, NR (4%) PPS, NR (8%) Petechial haemorrhage: PBO, NR (few, 27%; moderate, 48%; many, 25%) PPS, NR (few, 26%; moderate, 46%; many, 28%)	*Disease duration mean years:* PBO, 5.6; PBO, 7.4 *Other abnormalities:* PBO, 11%; PPS, 4% *Bladder capacity under anaesthesia, mean (cc):* PBO, 585; PPS, 569 *Patients with severe disease:* PBO, 59%; PPS, 59%

Trial Location	n/N (%) female	Mean (SD) age years	N/n (%) with ulcers/haemorrhage	Other characteristics
Parsons and Mulholland, 1987[16]	Overall (PBO, PPS 100 mg & 200mg), 68/75 (90%)	NR	Ulcers: Overall, 28% Haemorrhage: NR	NR

NR, not reported; PBO, placebo; PPS, pentosan polysulfate sodium

Participants completing / included in analysis in PPS RCTs

In the RCT by Sant *et al.* (2003),[17] an intention-to-treat analysis for the primary endpoint of GRA was used, where all participants who did not complete the 24-week follow-up assessment were classified as non-responders. In the RCT by Parsons *et al.* (1993),[15] 148 participants were randomised and the proportion of participants with the primary endpoint for 50% overall improvement is expressed as a proportion of the number randomised per group (n=74). However, nine participants per group were reported as not completing the study.

In the RCT by Mulholland *et al.* (1990),[14] whilst 110 participants were randomised, it is unclear from the trial report how many patients contributed data to each of the analyses as only the proportion (%) of participants (not n/N) with overall improvement at three months and other outcomes are reported. Three participants treated with PPS and nine treated with PBO failed to complete the study. However, the CS[1] reports that the primary efficacy analysis was as intention-to-treat (all participants randomised) (CS, Figure 31).

In the RCT by Parsons and Mulholland (1987),[16] 62 of the 75 participants randomised were reported to have completed the study, which included two study phases - before and after treatment switching (from PPS to PBO, or from PBO to PPS at three months). The CS[1] reports data at three months, prior to the switch. The CS[1] reports that the primary efficacy analysis was based on completers (n=62) (CS, Figure 33). However, the numbers in the trial report prior to switching (Tables 1 and 5 of the trial report) are discrepant with this. The ERG also notes that participant numbers after switching (Table 2 of the trial report) are greater than the number randomised, implying that double-counting of patients might have occurred in the analyses following cross-over.

Trial authorship

The ERG notes that there is some author commonality across all four RCTs of PPS in IC/BPS. The author Parsons is cited as a trial author on three of the trial reports,[14-16] the author Mulholland is cited as an author on two trial reports,[14, 16] and the author Sant is cited as an author on three trial reports.[14, 15, 17] All four RCTs were undertaken in the USA and published between 1987 and 2003. The ERG notes there have been no other published independent studies validating the results of these RCTs.

The Food and Drug Administration (FDA)[25] statistical and medical reviews note that, as part of the 1994 non-approval issues, that the RCTs by Mulholland *et al.* (1990),[14] and Parsons *et al.* (1993)[15] were not considered to be independent because the majority of the efficacy database for each of these studies was generated by the same three site investigators. One of the Medical Officers for the FDA observed that three investigators (Hanno, Parsons, and Sant) participated in both of the RCTs by Mulholland *et al.* (1990),[14] and Parsons *et al.* (1993),[15] and that these three investigators were accountable for 75%

(82 of 110) patients in Mulholland *et al.* (1990),[14] and 57% (95 of 148) patients in Parsons *et al.* (1993).[15] As such, that these RCTs could not be considered as independent trials.[25]

The FDA also notes that the RCT by Parsons *et al.* (1993),[15] may have included a positive "treatment-by-investigator effect" for one of the seven included study sites. When data from the site were excluded from the analysis, a trend in favour of PPS remained, but was no longer statistically significant.[25] The FDA notes regarding the site investigator that the sponsor submission states that (page 258): "*Dr Parsons had a prior arrangement with [FDA redacted] to receive a royalty on the sales of Elmiron"* (FDA page 258).[25]

4.2.2 Efficacy results for trials of PPS in IC/BPS

Global response assessment

Details of the three RCTs of PPS in IC/BPS that reported GRA as an outcome[14, 15, 17] are presented in Table 5. In the RCT by Sant *et al.* (2003),[17] which used a factorial design, a greater proportion of patients receiving PPS (PPS and PPS plus hydroxyzine groups combined) had a GRA score of six or seven compared to PBO (PPS and hydroxyzine placebo groups combined) at 24 weeks, but the between-group difference in proportions was not statistically significant (PBO 18% vs. PPS 34%, p=0.064, CI not reported).

The trials by Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990)[14] both reported the proportions of patients with a >50% improvement in GRA as both patient-reported and investigator-reported outcomes. The between-group difference in patient-reported GRA at three months was statistically significant in favour of PPS in both the Parsons *et al.* (1993) trial (5-point scale, PBO 16% vs PPS 32%, p=0.01, CI not reported)[15] and the Mulholland *et al.* (1990) trial (6-point scale, PBO 13% vs PPS 28%, p=0.04, CI not reported).[14] The between-group difference investigator-reported GRA at three months was also statistically significant in favour of PPS in both the Parsons *et al.* (1993) trial (5-point scale, PBO 15% vs PPS 36%, p=0.002, CI not reported)[15] and the Mulholland *et al.* (1990) trial (6-point scale, PBO 11% vs PPS 26%, p=0.03, CI not reported).[14]

The CS[1] reports that the GRA assessment methods in Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990)[14] were considered by the company to be equivalent to GRA scored as six or seven on a seven-point scale, as this was considered equivalent by the EMA[26] (CS, page 62).

The ERG notes that the Sant *et al.* (2003) trial[17] was a feasibility study that reported that a prospective Phase 3 study was not warranted. The authors report that the reason for this was partly because the investigators concluded that PPS did not improve the GRA sufficiently to initiate a larger clinical trial in spite of the authors stating that a minimal important clinical difference had not been determined by

the trial, and not giving consideration to the range of plausible treatment effects that would be suggested by confidence intervals (no CIs were reported).[17] In addition, the CS reports a "further analysis" of GRA that suggested that the effect of PPS was statistically significant (p=0.039) (CS, Section B.2.8.1),[1] whereas Sant *et al.* (2003)[17] reported the p-value as 0.064 (CI not reported). The difference between these two p-values seems to be because Sant *et al.* (2003)[17] accounted for clinical centre clustering using a Mantel-Haenzsel test, whereas the CS ignored clustering and used a Z-test. Furthermore, the distinction is important when considering the meta-analysis using the evidence from Sant *et al.* (2003)[17] because the company's approach effectively underestimates the standard error of the sample estimate of treatment effect.

Table 5: Details of global response assessment in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Table 19)

Trial	**Sant *et al.*, 2003[17]**	**Parsons *et al.*, 1993[15]**	**Mulholland *et al.*, 1990[14]**
GRA assessment method	Score of 6-7 on 7-point scale	>50% overall improvement in symptoms on a 5-point scale	>50% overall improvement in symptoms on a 6-point scale
Follow-up time point	24 weeks	3 months	3 months
N (%) score of 6 or 7	PBO, 11/62 (18) PPS 20/59 (34)	NR	NR
P value (between groups)	0.064	NA	NA
N (%) ≥50% improved (patient-reported)	NR	PBO, 12/74 (16) PPS, 24/74 (32)	PBO, NR (13) PPS, NR (28)
P value (between groups)	NA	0.01	0.04
N (%) ≥50% improved (investigator-reported)	NR	PBO, NR (15) PPS, NR (36)	PBO, NR (11) PPS, NR (26)
P value (between groups)	NA	0.002	0.03
NA, not applicable; NR, not reported; PBO, placebo; PPS, pentosan polysulfate sodium			

Pain data from Parsons and Mulholland 1987 used as a proxy for GRA in the CS analyses

For outcome data, please see the next section on non-VAS pain outcomes in this ERG report.

Although the pain data presented in the CS for Parsons and Mulholland (1987)[16] at three months concur with the trial report[16] (PBO, 3/20 (15%); PPS, 12/27 (44%); CS Table 21), these data do not concur with the data for this RCT presented in the GRA forest plot in Figure 11 of the CS (PBO, 6/37; PPS, 15/38).[1] However, the data in the CS Figure 11 for Parsons and Mulholland (1987)[16] do concur with those presented by the EMA in the EPAR (EPAR, Table 30).[8] The EPAR states (EPAR, page 91): "*Although no global response assessment was conducted in the study reported by Parsons and Mulholland, 1987, the data imputation used for the meta-analysis conducted by the applicant is deemed sufficiently comparable."* However, details of this data imputation are not reported in the EPAR.[8]

Details of non-VAS pain outcomes for all four RCTs of PPS in IC/BPS[14-17] are presented in Table 6 of this ERG report.

Non-VAS pain outcomes

All four RCTs of PPS in IC/BPS reported on non-VAS pain,[14-17] assessment of this outcome varied. Details of the assessment methods and results are presented in Table 6. Sant *et al.* (2003)[17] used a patient-reported 0–9 Likert scale (lower is better, participant inclusion criterion score of ≥4), Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990)[14] both assessed pain on a 0–5 scale (0 = no pain, 5 = severe pain). The RCT by Parsons and Mulholland (1987)[16] assessed patient-graded improvements of 0%, 25%, 50%, 75%, or 100%.

Between-group differences in change-from-baseline were reported by Sant *et al.* (2003)[17] at 24 weeks and Mulholland *et al.* (1990)[14] at three months. Both reported a reduction in change-from-baseline in both PPS and PBO. Sant *et al.* (2003)[17] reported PPS -0.8 vs. PBO -1.0 and Mulholland *et al.* (1990)[14] reported PPS -0.05 vs. PBO -0.02 (incorrectly reported in the CS as PPS 0.05 vs. PBO 0.02). In both trials, the between-group difference was not statistically significant (*p*-values or CIs not reported).

Parsons *et al.* (1993),[15] Mulholland *et al.* (1990)[14] and Parsons and Mulholland (1987),[16] all reported on the proportion of participants with a >50% pain improvement at three months. Respective values were: PPS 18% vs. PBO 38% (p=0.005), PPS 27% vs, PBO 14% (p=0.08), and PPS 44% vs. PBO 15% (p=0.02, CI not reported).

Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990),[14] also reported on the proportion of participants with a decrease of >1 point at three months. Respective values were: PPS 66% vs. PBO 51% (p=0.04 in trial report, CI not reported;[15] incorrectly reported in CS as p=0.004), and PPS 46% vs. PBO 29% (p=0.07, CI not reported).

Parsons and Mulholland (1987),[16] also reported on the mean percentage improvement at three months: PPS 33.3 (SD 35) vs. PBO 12.2 (SD 14.3) (p=0.02, CI not reported).

Table 6: Details of non-VAS pain outcomes in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Table 21)

Trial	Sant *et al.*, 2003[17]	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
Follow-up time point	24 weeks	3 months	3 months	3 months
Pain measurement scale	PR: 0–9 scale	PR: 0–5 scale	PR: 0–5 scale	PR: 0%, 25%, 50%, 75% or 100% improvement
Mean (SD) score (baseline)	PBO, 6.0 (1.3) PPS, 6.3 (1.4)	NR	NR	NR
Mean (SD) score (follow-up)	NR	NR	NR	NR
Mean (SD) change from baseline	PBO, -1.0 (1.8) PPS, -0.8 (1.8)	NR	PBO, -0.02 (NR) PPS, -0.05 (NR)	NR
P value (change from baseline)	NR	NA	PBO, NS/NR PPS, 0.05	NA
P value (between groups)	NS	NA	NS	NA
N (%) >50% improved	NR	PBO, NR (18%) PPS, NR (38%)	PBO, NR (14%) PPS, NR (27%)	PBO, 3/20 (15%) PPS, 12/27 (44%)
P value (between groups)	NA	0.005	0.08	0.02
N (%) decrease of >1 point	NR	PBO, NR (51%) PPS, NR (66%)	PBO, NR (29%) PPS, NR (46%)	NR
P value (between groups)	NA	0.04	0.07	NA
Mean (SD) % improvement	NR	NR	NR	PBO, 12.2 (14.3) PPS, 33.3 (35)
P value (between groups)	NA	NA	NA	0.02

NA, not applicable; NR, not reported; NS, not significant; PBO, placebo; PPS, pentosan polysulfate sodium; PR, patient-reported; SD, standard deviation

O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index scores

The RCT by Sant *et al.* (2003),[17] was the only RCT of PPS in IC/BPS in the CS to report on Interstitial Cystitis Symptom Index and Problem Index scores (ICSI and ICPI).[22] In Sant *et al.* (2003),[17] which used a factorial design, there was no statistically significant between-group difference in change over time in either ICSI or ICPI (*p*-values or CIs, not reported). Details of these outcomes are presented in Table 7.

Table 7: Details of O'Leary-Sant Interstitial Cystitis Symptom and Problems for Sant *et al.* (2003) (adapted from the CS Table 19)

Trial	**Sant *et al.*, 2003[17]**
Follow-up time point	24 weeks
Mean (SD) ICSI score (baseline)	PBO, 14.6 + 3.3 PPS 14.3 + 3.3
Mean (SD) ICSI score change from baseline	PBO, -1.7 (3.5) PPS -2.6 (3.4)
P value (between groups)	NS
Mean (SD) ICPI score (baseline)	PBO, 12.8 + 2.4 PPS 12.8 + 2.7
Mean (SD) ICPI score change from baseline	PBO, -1.9 (2.8) PPS -2.6 (3.5)
P value (between groups)	NS
NS, not significant; PBO, placebo; PPS, pentosan polysulfate sodium; SD, standard deviation	

Daily urinary frequency

Two RCTs of PPS in IC/BPS, assessed daily urinary frequency.[16, 17] Details of the assessment methods and results are presented in Table 8.

At 24 weeks, Sant *et al.* (2003)[17] that there was no statistically significant between-group difference in change-from-baseline in mean daily frequency (PBO, -0.5 (SD 5.3) vs. PPS, -0.2 (SD 5.0); *p*-value or CI, not reported).

In the RCT by Parsons and Mulholland (1987),[16] at three months there were no statistically significant between-group differences evident in the proportion of participants with any improvement at follow-up (PBO, 10/24 (42%) vs. PPS, 20/31 (65%); p=0.06, CI not reported), or mean change from baseline in frequency (PBO, -1.8 vs. PPS, -5.4; p=0.06; SDs or CIs, NR).

Table 8: Details of daily urinary frequency outcomes in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Table 22)

Trial	Sant *et al.*, 2003[17]	Parsons and Mulholland, 1987[16]
Follow-up time point	24 weeks	3 months
Mean (SD) daily frequency (baseline)	PBO, 18.9 (10.3) PPS, 18.3 (6.8)	PBO, 18.8 (NR)* PPS, 18.0 (NR)
Mean (SD) daily frequency (follow-up)	NR	PBO, 19.5 (NR) PPS, 18.0 (NR)
Mean (SD) daily frequency (change from baseline)	PBO, -0.5 (5.3) PPS, -0.2 (5.0)	NR NR
P value (between groups)	NS	*P*=0.06
N (%) any improvement (follow-up)	NR	PBO, 10/24 (42%) PPS, 20/31 (65%)
P value (between groups)	NA	*p*=0.06
Mean change (improved patients, change from baseline)	NR	PBO, -1.8 PPS, -5.4
P value (between groups)	NA	*p*=0.06

NA, not applicable; NR, not reported; NS, not significant; PBO, placebo; PPS, pentosan polysulfate sodium; SD, standard deviation
* Incorrect in CS, PBO reported as 18.0 in the CS

Volume/void outcomes

Three of the RCTs of PPS in IC/BPS, assessed volume/void outcomes.[14-16] Details of the assessment methods and results are presented in Table 9.

In the RCTs by Parsons *et al.* (1993)[15] and Mulholland *et al.* (1987),[16] at three months there were no statistically significant between-group difference evident in the mean void volume (mL) at follow-up (PBO, -2.1 vs. PPS, 20.4; *p*-value NR; SDs or CIs, NR and PBO, 7.6 vs. PPS, 9.8; *p*-value NR; SDs or CIs, NR; respectively).

In the RCT by Parsons and Mulholland (1987),[16] at three months the respective values were PBO, 74.3 vs. PPS, 106.9 (SDs or CIs, NR). Table 23 of the CS[1] reports that the between-group difference was statistically significant at *p*=0.009. However, this *p*-value is for the PPS group only after treatment switching (Table 3 of the trial report,[16] values PBO 84.6 (SD 53), *p*=0.05 vs. PPS 102.5 (SD 57), *p*=0.009). A *p*-value or CI for the between-group difference prior to switching, at three months, is not reported in the trial report (Table 5 of the trial report[16]).

Table 9: Details of daily void/volume outcomes in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Table 23)

Trial	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
Follow-up time point	3 months	3 months	3 months
Mean volume/void, mL (baseline)	NR	NR	PBO, 76.7 PPS, 93.8
Mean volume/void, mL (follow-up)	NR	NR	PBO, 74.3 PPS, 106.9
Mean volume/void, mL (change from baseline)	PBO, -2.1 PPS, 20.4	PBO, 7.6 PPS, 9.8	NR
P value (change from baseline)	NR	NR	PBO, 0.6 PPS, 0.06
P value (between groups)	NS	NS	NR
Mean total daily voided volume, mL (change from baseline)	PBO, -42 PPS, 3	PBO, -20 PPS, 60	NR
P value (between groups)	NS	NS	NA
% patients with >20 mL increase (follow-up)	PBO, 25% PPS, 40%	PBO, 20% PPS, 30%	NR
P value (between groups)	0.02	NS	NA

mL, millilitre; NA, not applicable; NR, not reported; PBO, placebo; PPS, pentosan polysulfate sodium
* Incorrect in CS, PBO reported as 0.3 in the CS

Nocturia

In Table 24 of the CS, the company reports that in the RCT by Parsons and Mulholland (1987)[16] at three months the mean improvement in nocturia was PBO -0.09 (SD 0.8) vs. PPS -2.1 (SD 2.2), p=0.05 (CI not reported). This is the only RCT in IC/BPS for which the company report nocturia data in the CS.[1] However, the trial reports by Mulholland *et al.* (1990)[14] and Parsons *et al.* (1993),[15] both report on this outcome.

Mulholland et al (1990)[14] reported that at three months there was no statistically significant between-group difference in change in nocturia PBO -0.5 vs. PPS -0.8, p-value or CI, NR). Parsons *et al.* (1993)[15] also reported that at three months, there was no statistically significant between group difference in nocturia (no data reported). In Parsons *et al.* (1993),[15] increase in nocturia was recorded as an adverse event. The numbers (%) of patients experiencing this AE were PBO 0 (0%) vs. PPS 1 (1.4%) (p-value or CI, NR). This AE for Parsons *et al.* (1993)[15] is not presented in the Section B.2.10. of the CS on AEs, Table 32,[1] as there was not >1 patient in either treatment group with this AE.

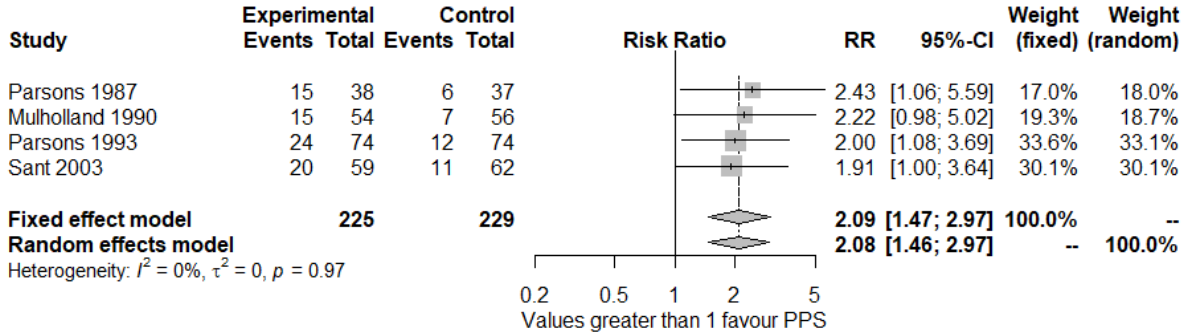
Other outcomes

No other clinical effectiveness outcomes for RCTs of PPS in IC/BPS were reported in the CS.[1]

Pairwise meta-analysis of effectiveness

The company presented a pairwise meta-analyses of GRA across the four RTCs of PPS in IC/BPS[14-17] (CS, figure 11). The forest plot for this analysis is presented in Figure 3 below. The fixed effect RR of 2.09 (95%CI: 1.47 to 2.97) was applied by the company in the economic model.

The pooled estimate was used by the company to compare to the pooled GRA estimate from the pairwise meta-analyses across the two Uracyst® RCTs[20, 21] based on the Bucher method. Further details of this are presented in Section 4.4 of this ERG report.



Reproduced from the CS page 84.[1]

Figure 3: Meta-analysis of Global Response Assessment in RCTs of PPS in IC/BPS (risk ratio) (CS, figure 11)

4.2.3 Safety results for trials of PPS in IC/BPS

Details of the summaries of adverse events presented in the CS for the four RCTs of PPS in IC/BPS[14-17] are presented in Table 10.

Sant *et al.* (2003),[17] which used a factorial design study, reported that there was no statistically significant difference in the overall adverse event rates between treatment arms (*p*-values or CIs, not reported). Parsons *et al.* (1993)[15] reported that there were no "*clinically significant differences between the treatment groups for any of the laboratory data, and there were no patients with laboratory findings critically outside the normal range for any of the parameters*" (*p*-values or CIs, not reported). Mulholland *et al.* (1990)[14] reported that the observed reactions were "*not different from those that might be observed in any random population over a three month period and were not serious*". Parsons and Mulholland (1987),[16] reported that among the 62 patients who completed the study, only a single side effect (skin rash) was noted in one participant. However, it was not reported which treatment group this was in, or whether this was before or after treatment switching at three months.

The CS[1] summarises that across the RCTs of PPS in IC/BPS, PPS is well tolerated. The ERG notes that AEs in Sant *et al.* (2003),[17] were recorded according to a grading system for 0 (none) to 3 (severe), and that >50% patients receiving PPS or PBO had moderate (grade 2) AEs. However, the trial report summarises that (page 812): "*The majority of [AEs] were minor, and not specifically related to PPS or hydroxyzine. The primary areas were constitutional symptoms (fatigue and drowsiness), gastrointestinal disturbances, and pain (abdominal/pelvic and other locations). There was no statistically significant difference in the overall adverse event rates between treatment arms*".[17]

Common adverse events (AEs) listed in the SmPC are: headache, dizziness, nausea, diarrhoea, dyspepsia, abdominal pain, abdominal enlargement, rectal haemorrhage, peripheral oedema, alopecia, back pain, asthenia, and pelvic pain.[8] Clinical advice received by the ERG from experience of using PPS on a named patient basis is that AEs are rare.

With respect to mortality, the EPAR for PPS reports that (EPAR, page 99): '*7 deaths were reported in a long-term, open-label study (Hanno et al. 1997),[27] considered as not related to study medication. 3 deaths were reported in the study published by Jepsen et al. (1998),[28] considered as not related to study medication.*'[8]

Table 10: Details of adverse events in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Tables 31 to 34)

Sant *et al.*, 2003[17]		
Adverse event severity	**PPS (n=59), n (%)**	**Placebo (n=62), n (%)**
Grade 0 (none)	9 (15)	11 (18)
Grade 1 (mild)	8 (14)	7 (11)
Grade 2 (moderate)	30 (51)	34 (55)
Grade 3 (severe)	12 (20)	10 (16)
Parsons *et al.*, 1993[15] Adverse events occurring in more than one patient		
Adverse event	**PPS (n=74), n (%)**	**Placebo (n=74), n (%)**
Nausea	1 (1.4)	3 (4.1)
Diarrhoea	2 (2.7)	2 (2.7)
Vomiting	0	2 (2.7)
Sensation of euphoria	1 (1.4)	1 (1.4)
Watery eyes	1 (1.4)	1 (1.4)
Total reactions	12	19
Total patients (%)	7 (9)	10 (14)
Mulholland *et al.*, 1990[14]		
Adverse event	**PPS (n=54), n (%)**	**Placebo (n=56), n (%)**
Headache	1 (1.9)	2 (3.6)
Nausea	1 (1.9)	0
Indigestion	1 (1.9)	0
Increased perspiration	1 (1.9)	0
Severe mood swings	1 (1.9)	0
Suicidal ideation	1 (1/9)	0
Diarrhoea	0	2 (3.6)
Explosive diarrhoea	0	1 (1.8)
Severe joint pain	0	1 (1.8)
Skin rash (arms)	0	1 (1.8)
Itching	0	1 (1.8)
Total reactions	6	8
Total patients (%)	3 (6)	7 (13)
Parsons and Mulholland, 1987[16] after cross-over		
Adverse event	**PPS and PBO (n=62), n (%)**	
Skin rash	1 (16) unclear if PPS or PBO, or if before or after cross-over	

4.2.4 Quality assessment results for trials of PPS in IC/BPS

Table 11 presents the company's quality assessment of the four RCTs of PPS in IC/BPS.14-17

Details of the generation of the randomisation sequence, concealment of allocation, blinding, and imbalances in drop-outs were not reported in one of the published RCT reports (Parsons and Mulholland, 1987[16]) but were provided following communication with the trial author in Appendix Q of the CS.[1]

The ERG considers the company's quality assessment to be broadly accurate for three of the RCTs of PPS in IC/BPS.[14-16] However, the ERG considers some of the company's quality assessment judgements for the Sant *et al.* (2003) RCT[17] to be discrepant compared with the published report.[17]

Unlike the other three RCTs that report that the randomisation sequence was computer generated, Sant *et al.* (2003)[17] only report that a block randomisation by clinical site was performed, without details of the sequence randomisation generation method.

With respect to allocation concealment and blinding of participants and personnel, whilst the other three RCTs report that these aspects of trial design were undertaken, there is no record of allocation concealment being undertaken in the Sant *et al.* (2003) trial report and, although the Sant *et al.* (2003) trial is described as 'double-masked', unlike the other three RCTs, specific details of who was blinded is not reported.[17]

With respect to attrition bias, unlike the other three RCTs that report the number of drop-outs for PPS and placebo, Sant *et al.* (2003),[17] which used a factorial design resulting in four treatment groups, only reported the total number of drop-outs overall (20.6% across the four treatment groups – PPS, PBO, hydroxyzine, and PPS plus hydroxyzine). As such, it is unclear what attrition occurred in each of the treatment groups. Given the methodological quality issues in the Sant *et al.* (2003) RCT,[17] the ERG considers that the results from this trial should be interpreted with caution.

Table 11: Quality assessment of the pentosan polysulfate sodium RCTs relevant to the decision problem (adapted from Table 68 of the CS)

NICE criteria[23]	Sant *et al.*, 2003[17]	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes (CS) Block randomised, so probably (ERG)	Yes Computer (ERG)	Yes Computer (ERG)	Yes Computer (ERG)
There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes (CS) Not reported (ERG)	Yes	Yes	Yes
The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	Yes	Yes	Yes
Based on your answers to the above, in your opinion was selection bias present?	No (CS) Unclear (ERG)	No	No	No
Likely direction of effect	NA	NA	NA	NA

NICE criteria[23]	Sant *et al.*, 2003[17]	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
The comparison groups received the same care apart from the intervention(s) studied	Yes	Yes	Yes	Yes
Participants receiving care were kept 'blind' to treatment allocation	Yes	Yes	Yes	Yes
Individuals administering care were kept 'blind' to treatment allocation	Yes	Yes	Unclear	Yes
Based on your answers to the above, in your opinion was performance bias present?	No	No	No	No
Likely direction of effect	NA	NA	NA	NA
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Yes	Yes	Yes
a. How many participants did not complete treatment in each group?	25 patients total (CS) Across PPS, hydroxyzine, PPS+ hydroxyzine, and PBO groups (ERG)	PPS: 9 Placebo: 9	PPS: 3 Placebo: 9	13 patients total
b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	Yes	No: more patients in placebo group did not complete the trial	No: more patients in placebo group did not complete the trial
For how many participants in each group were no outcome data available?	Unclear	PPS: 6 Placebo: 4	Unclear	13 patients total
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	Yes	More dropouts in placebo group	More dropouts in placebo group

NICE criteria[23]	Sant *et al.*, 2003[17]	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
Based on your answers to the above, in your opinion was attrition bias present?	No	No	Unclear	No
Likely direction of effect	NA	NA	Unclear	NA
The study had an appropriate length of follow-up	Yes	Yes	Yes	Yes
The study used a precise definition of outcome	Yes	Yes	Yes	Yes
A valid and reliable method was used to determine the outcome	Yes	Yes	Yes	Yes
Investigators were kept 'blind' to participants' exposure to the intervention	Yes	Yes	Yes	Yes
Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	Yes	Yes	Yes
Based on your answers to the above, in your opinion was detection bias present?	No	No	No	No
Likely direction of effect	NA	NA	NA	NA

4.2.5 Summary of trials of PPS in the broader BPS population

The RCT by Holm-Bentzen *et al.* (1987)[18] was conducted in the UK and Denmark, whilst the RCT by Nickel *et al.* (2015)[19] was conducted in the USA and Canada.

Holm-Bentzen *et al.* (1987)[18] evaluated PPS 100 mg three times per day compared to PBO, whilst Nickel *et al.* (2015)[19] evaluated PPS 100 mg once per day or three times per day compared to PBO (three treatment groups).

The characteristics of the patients enrolled in both RCTs were broader than those indicated for PPS because the presence of Hunner's lesions and/or glomerulations were not part of the inclusion criteria.

In the RCT by Holm-Bentzen *et al.* (1987),[18] at four months there were no statistically significant between-group differences in symptoms, urodynamic parameters, cystoscopic appearance or mast cell counts (*p*-values or CIs, not reported). In the RCT by Nickel *et al.*, (2015),[19] at 24 weeks there was no statistically significant between-group difference in response defined as ≥30% reduction from the baseline in ICSI total score (*p*-values or CIs, not reported).

In summary, these two RCTs did not demonstrate evidence of a treatment effect of PPS in the broader BPS population.

In addition to the overall analysis, Nickel *et al.* (2015)[19] also reported a *post hoc* analysis of the primary end point in a subgroup of 94 participants who had objective findings of IC on cystoscopy meeting NIDDK criteria, done 30 days or more before enrolment or during the study. In this subgroup, the responder rate was greater with PBO than PPS (16/32, 50% vs. 10/29, 34.5%). These results were not presented in the CS.[1] In response to a request for clarification from the ERG, the company stated that the participants in Nickel *et al.* (2015)[19] were not stratified by NIDDK status at the randomisation of the trial, and breaking the randomisation in the *post hoc* analysis is likely to lead to bias in the estimates of relative treatment effect.[1]

The EMA also notes the limitations to both RCTs including patients in the broader BPS population.[8] The EMA also notes severe limitations of the Nickel *et al.*, (2015) study[19] (EPAR, page 93): "*patients with milder disease entering during a symptom flare, regression to the mean, introduction (inadvertent or not) of conservative therapy, which accentuated the benefits of placebo, and failure of clinical sites to keep patients in the trial are acknowledged by the CHMP. In addition, the results of Holm-Bentzen study are difficult to interpret as the GRA was not used as primary endpoint.*"

4.2.6 Included observational study on the increase in response rate over time

The CS[1] includes a section regarding the timing of response with PPS in IC/BPS, stating that "*Although some patients may experience improvements early in the PPS treatment process, others may not experience a clinical response until they have received 3–6 months of continuous PPS therapy*" (CS, page 81). In the CS, the company report on an increase in response rate over time reported in the single-arm study by Hanno (1997)[27] (Figure 4 below).

The ERG notes that of the 2809 participants recruited to the study by Hanno (1997),[27] 46% withdrew in the first three months and at 36 months there were only 149 (5%) participants left in the study. Therefore, the ERG considers that the results from this study should be interpreted with caution. In addition, the ERG considers the information difficult to interpret without a control group with which to estimate relative treatment effects.

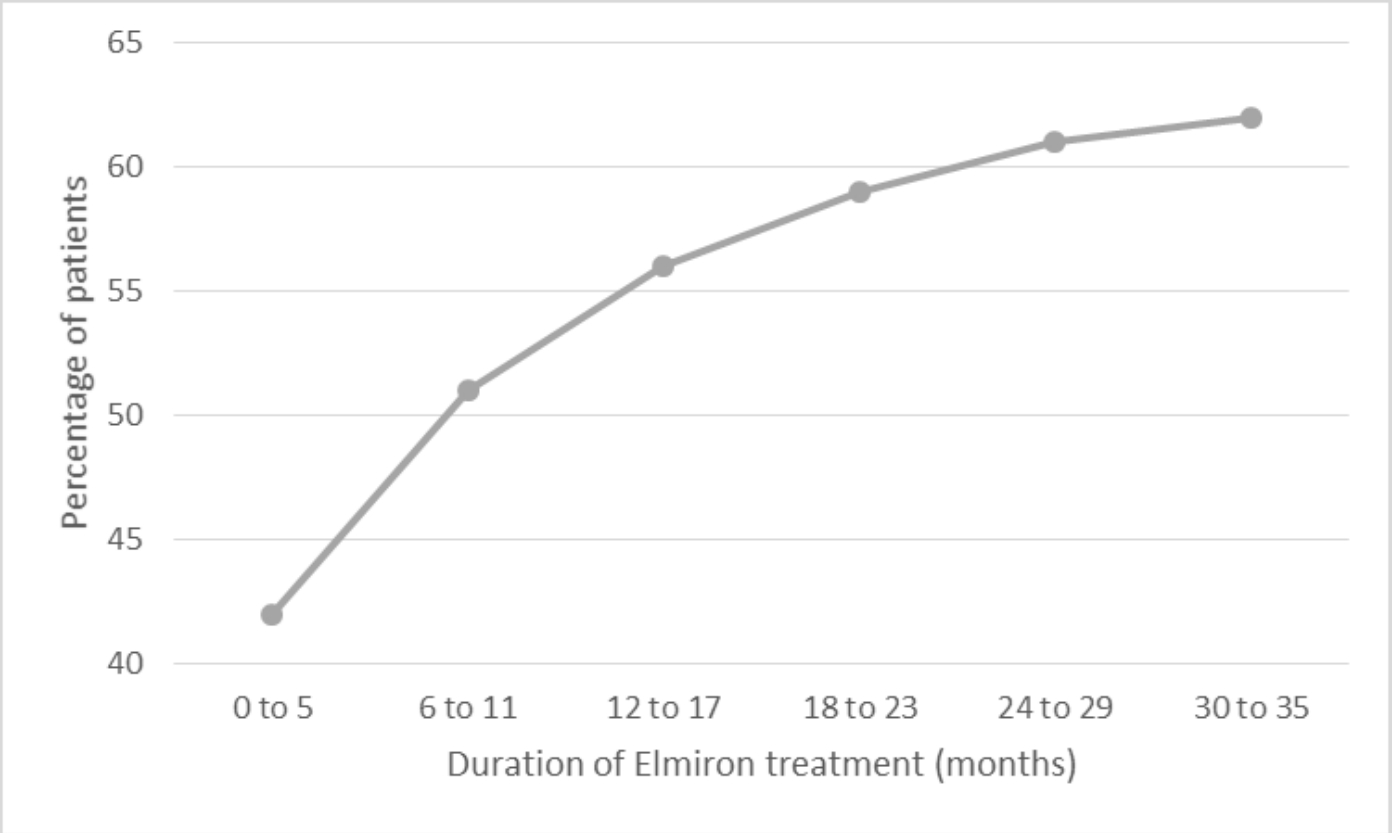


Figure 4: Percentage of patients with moderate or better improvement in patient global evaluation scale (reproduced from CS, figure 8, adapted by the company from Hanno 1997)

4.3 Critique of trials identified and included in the indirect treatment comparison

Details of the identification and methodology of the Uracyst® studies proposed to be included in an ITC analysis are described below. Details of the four PPS RCTs in IC/BPS, also included in the ITC are described in Section 4.2.

4.3.1 Search Strategy

The CS[1] (page 80) states that a systematic literature review (SLR) was conducted to identify studies to facilitate an ITC of PPS compared to other treatments included as comparators in the NICE scope.[2] Although not specifically stated in Section B.2.9 of the CS[1] (page 80), it appears that the trials proposed to be included in the ITC were identified from the SLR methods described in Section 4.1.

4.3.2 Study selection criteria

The CS states that the potential comparators in the review were defined more broadly than the NICE scope[2] to maximise the possibility of forming a network of trials. Although, Section B.2.9 of the CS[1] does not state explicitly whether the inclusion criteria for the ITC were the same as those for the clinical

effectiveness review (CS, section B.2.1), it is stated that the inclusion criteria for the ITC were the same in Appendix D.1 of the CS.[1] The ERG does not consider that any eligible trials have been missed.

4.3.3 Studies identified

The CS[1] (page 81) states that twelve trials met the inclusion criteria for the ITC. Of these, six trials compared PPS to placebo, and three trials compared Uracyst® to placebo instillation. The remaining three trials were excluded from the ITC as they did not include relevant comparators in order to construct a network. References to the excluded RCTs are not provided in this section; however, with reference to Table 66 in Appendix D of the CS[1] (page 163), it appears that the three studies identified as excluded are Tutolo *et al.*, (2017)[29]; Cervigni *et al.*, (2017)[30]; Gulpinar *et al.*, (2018).[31] The reasons for exclusion are presented in Table 12. The ERG considers the reasons for exclusion of these trials to be appropriate.

Table 12: List of studies excluded from the proposed ITC

Trial ID	Reason for exclusion
Tutolo *et al.*, (2017)[29]	Uracyst® compared to DMSO instillation
Cervigni *et al.*, (2017)[30]	iALuRil compared to DMSO instillation
Gulpinar *et al.*, (2018)[31]	Cystistat compared to Gepan

The PRISMA flow diagram reported in Appendix D of the CS[1] (page 162) shows that 15 RCTs (13 articles) were considered for inclusion in an ITC; this does not align with the information is reported on page 82 of the CS ("*Twelve trials met the inclusion criteria*"). In response to a request for clarification from the ERG, the company confirmed that this was an error and that 11 trials with 13 related citations had been considered for the ITC.

The CS presents proposed networks in Figures 9 and 10 on page 82 of the CS[1]. These figures list seven RCTs eligible for inclusion. These are five RCTs comparing PPS with placebo (Sant *et al.*, 2003;[17] Parsons *et al.*, 1993 ;[15] Parsons and Mulholland, 1987 ;[16] Nickel *et al.*, 2015 ;[19] and Holm-Bentsen *et al.*, 1987[18]), and two RCTs comparing Uracyst® with placebo (Nickel *et al.*, 2012[21] and Nickel *et al.*, 2010[20]). However, neither of these analyses were performed by the company due to considerable heterogeneity across the trials. For this reason, the company present only a meta-analyses of the data from the two Uracyst® trials versus placebo and compare this to the meta-analysis of data from the PPS versus placebo trials using the Bucher method.

Data from the PPS versus placebo trials have been critiqued in Section 4.1. In this section, we present a critique of the two Uracyst® versus placebo trials (Nickel *et al.*, 2012[21] and Nickel *et al.*, 2010[20]). These trials were selected for inclusion in order to compare PPS and Uracyst® in IC/BPS patients.

4.3.4 Quality assessment of studies included in the ITCs

It is unclear if the company performed quality assessment for Nickel *et al.* (2010)[20] and Nickel *et al.* (2012),[21] as neither the methods nor results of quality assessment were reported in the CS.[1] It is considered good systematic review practice for two reviewers either to independently perform quality assessment or to check assessed items; neither the quality assessment nor the checking was reported to have been done independently in the CS.[1] The ERG has completed the quality assessment for these two studies using the same criteria applied by the company for the main trials of interest which, although not referenced, is described as 'NICE criteria'. The ERG sought clarification with the company regarding this issue. The company's clarification response[1] stated that the items assessed were taken from the NICE Guidelines Manual.[23] These are appropriate criteria for assessing the methodological quality/risk of bias in RCTs.

As the CS does not present a quality assessment for Nickel *et al.* (2010)[20] and Nickel *et al.* (2012),[21] this was undertaken by the ERG using the quality assessment method applied by the company to the four RCTs of PPS in IC/BPS,[14-17] and is presented in Table 13 below.

Table 13: **Quality assessment of the trials used in the ITC**

NICE criteria	Nickel *et al.*, 2010[20]	Nickel *et al.*, 2012[21]
An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Unclear - a predetermined randomization schedule	Yes - randomization schedule generated using a permuted block by a randomization statistician
There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Unclear - this information is not provided.	Unclear - The women were randomized in a blinded fashion to the study treatment arms in a 1:1 ratio.
The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	yes
Based on your answers to the above, in your opinion was selection bias present?	Unclear	Unclear
Likely direction of effect	Unclear	Unclear
The comparison groups received the same care apart from the intervention(s) studied	Yes	yes
Participants receiving care were kept 'blind' to treatment allocation	Yes	Yes
Individuals administering care were kept 'blind' to treatment allocation	Unclear - documentation of blinding does not specify, investigators, clinicians and participants	Unclear - documentation of blinding does not specify, investigators, clinicians and participants
Based on your answers to the above, in your opinion was performance bias present?	Unclear	Unclear
Likely direction of effect	Unclear	Unclear

NICE criteria	Nickel *et al.*, 2010[20]	Nickel *et al.*, 2012[21]
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Yes
a. How many participants did not complete treatment in each group?	3 control, 4 intervention	9 control, 8 intervention
b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	Yes
For how many participants in each group were no outcome data available?	1	0
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	Yes
Based on your answers to the above, in your opinion was attrition bias present?	No	No
Likely direction of effect	Unclear	Unclear
The study had an appropriate length of follow-up	Yes	Yes
The study used a precise definition of outcome	Yes	Yes
A valid and reliable method was used to determine the outcome	Yes	Yes
Investigators were kept 'blind' to participants' exposure to the intervention	Unclear	Unclear

NICE criteria	Nickel *et al.*, 2010[20]	Nickel *et al.*, 2012[21]
Investigators were kept 'blind' to other important confounding and prognostic factors	Unclear	Unclear
Based on your answers to the above, in your opinion was detection bias present?	Unclear	Unclear
Likely direction of effect	Unclear	Unclear

Details of the generation of random sequence was not reported by Nickel *et al.* (2010)[20], but in Nickel *et al.* (2012)[21] it was reported that the randomisation schedule was generated using a permuted block. In Nickel *et al.* (2010)[20] it was not clearly stated that concealment of allocation had taken place, although in Nickel *et al.* (2012)[21] it was stated that the women were randomised in a blinded fashion, implying that concealment of allocation had taken place. Although both studies were described as double-blind, and methods for blinding regarding active or vehicle controlled instillation was described in Nickel *et al.* (2010),[20] neither clearly outlined which study personnel were blinded to the study arms. With respect to attrition bias, the number of drop-outs in each arm are provided, and appear balanced in both studies. On the basis of the quality assessment, the ERG concludes that these trials were of moderate to low quality.

4.3.5 Critique of studies included

4.3.5.1 Study designs

Both trials report that they were multicentre, double-blind, and randomised. Both trials appear to have been conducted in Canada, and the number of centres was reported as 12 in Nickel *et al.* (2010)[20], but was not reported in Nickel *et al.* (2012)[21]. Nickel *et al.* (2010)[20] is described as an inactive vehicle-controlled study, parallel group pilot evaluation, whilst Nickel *et al.* (2012)[21] is described as an inactive control trial, parallel group evaluation. Detail regarding when the trials were initiated and completed are not available in the CS or the trial papers. The studies were conducted relatively recently and broadly represent best practice in the UK.

4.3.5.2 Population characteristics

Eligibility criteria of the included studies were not outlined in the CS. Nickel *et al.* (2010)[20] specified that patients had to be 18 years old or over, but this was not specified in Nickel *et al.* (2012).[21] There did not appear to be an age cut off for either trial. Nickel *et al.* (2012)[21] only included women, whereas Nickel *et al.* (2010)[20] included both men and women, although only one male was randomised into the

study and was part of the control group. Both trials were described as being in the IC/PBS population; however, the diagnostic criteria did not include the presence of ulcers or petechial haemorrhage on cystoscopy (see Table 14). The CS[1] (Table 30) defined the populations in both trials as BPS.

Table 14: **Diagnostic eligibility criteria for the included studies derived from study reports**

Nickel *et al.* (2010)[20]	**Nickel *et al.* (2012)[21]**
Clinical diagnosis of IC/PBS The diagnosis of IC/PBS was consistent with current clinical definitions, including the diagnostic criteria described in the IC Data Base Study,[12] as well as the most recent definition of IC/PBS described at the NIH Urologic Chronic Pelvic Pain consensus (Baltimore, December 2007). IC/PBS was diagnosed on the basis of pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as urgency or frequency.	Diagnosed or re-diagnosed with IC/BPS within the previous 2 years; had a subject-reported average urinary frequency of 8 times/24 hours during the screening period, as captured by a 3-day diary; had a pain/pressure/discomfort score of 40-80 mm on a pain visual analogue scale (VAS).

Baseline characteristics appeared to be broadly comparable across the trial arms in both trials. Details of the ethnicity of the patients were not reported in the CS or in the trial report for Nickel *et al.* (2010)[20], whilst the ethnicity of the patients was reported in Nickel *et al.* (2012)[21] and was comparable across trial arms, and appeared to be broadly generalisable to the UK population.

The eligibility criteria detailed in the trial papers included a diagnosis of IC/BPS, but do not report that Hunner's lesions and/or glomerulations are part of the diagnosis. However, patients in these trials are defined in the CS [1] as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations. Therefore, it is not clear that the patients in either trial met the criteria for this NICE scope (see Table 14). The ERG also notes that neither the CS[1] or the individual trial papers report numbers of patients overall or in each arm with either Hunner's lesions or glomerulations. (see Section 4.2.1 for further discussion).

4.3.5.3 Intervention characteristics

The intervention characteristics for the RCTs are listed in Table 15. The intervention appears to be consistent with the NICE scope[2] in terms of dosing and administration, and is broadly comparable with UK practice.

Table 15: Characteristics and results of Uracyst® trials (adapted from CS, Table 30 p.85-86)

Study	**Nickel *et al.* (2010) [20]**		**Nickel *et al.* (2012) [21]**	
Study type	Prospective, randomised, double-blind, inactive vehicle-controlled study		Multicentre, double-blind, inactive control trial	
Population	Adult patients with BPS		Women with BPS	
Intervention	2% sodium chondroitin sulphate (Uracyst®)	Intravesical vehicle control	2% sodium chondroitin sulphate (Uracyst®)	Inactive control instillation
Sample size	33	32	50	48
Mean follow-up time	6 weeks (12 week study with 6 weeks of treatment and 6 weeks of follow-up)		11 weeks	

Abbreviations: GRA, global response assessment; ICPI, interstitial cystitis problem index; ICSI, interstitial cystitis symptom index; NR, not reported; SD, standard deviation.

4.3.5.4 Outcome assessment

The CS reports some outcome data for the trials (see Table 16). These are consistent with those outlined in the NICE scope.[2] The CS does not report information about the methods for assessing outcomes in the trials. In Nickel *et al.* (2010),[20] patients underwent a six week treatment period, followed by a 6 week follow up period. The primary outcome was the number of patients in each group who moderately or markedly improved on the Global Response Assessment (GRA) scale. Outcomes were reported at weeks 7 and 12, with 7-week outcomes as the primary measure. Secondary efficacy endpoints were the O'Leary-Sant interstitial cystitis Symptom Index/Problem Index (ICSI/ICPI), the Female Sexual Function Index (FSFI), the Short Form 12 quality of life Questionnaire (SF-12), daily urinary frequency, the Likert pain scale, and safety outcomes. In Nickel *et al.* (2012)[21] there was a 7 week treatment period, followed by a 4 week follow up period, with primary and secondary endpoints assessed at week 11. The primary outcome was GRA; the secondary outcomes were the ICPI, average daily urinary frequency, average urine volume per void, average daily urgency episodes and pain VAS score.

Although the timing of the primary outcome differed in the trials, comparable data for end of follow up was available from the trial reports, and these data were used in the meta-analyses. Only data on the primary outcome, GRA, and secondary outcomes ICSI and ICPI were reported and meta-analysed in the CS. The definitions of the outcomes and follow up time appear comparable across the trials, although details of the outcome assessor are not available in the trials. None of the findings were statistically significant (for p-values see Table 16, CIs not reported).

An inconsistency between the data reported in the CS and those reported in the original trial reports was noted by the ERG. The mean (SD) ICSI at baseline for Nickel *et al.* (2010)[20] for the intervention group was reported as 12.4 (3.26) in the CS; however, these data were reported as 13.8 (3.55) in the trial paper.

Table 16: Results of Uracyst® trials (adapted from CS, Table 30 p.85-86)

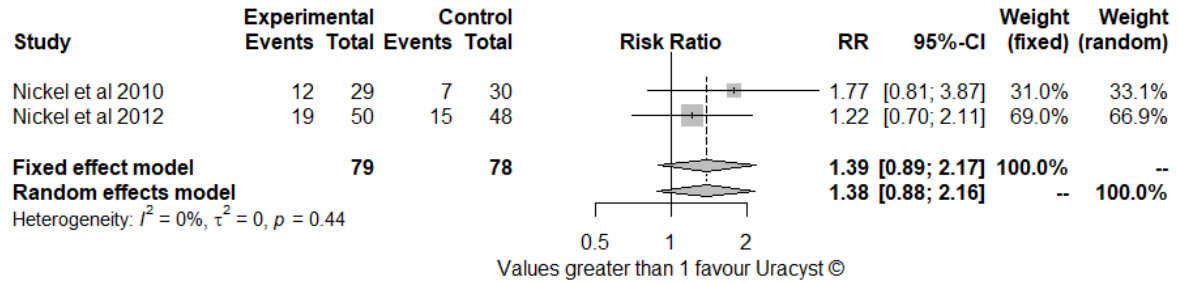
Study	Nickel *et al.* (2010) [20]		Nickel *et al.* (2012) [21]	
GRA at follow-up (SD)	Week 7: 13 (39.4) Week 12: 12 (41.4)	Week 7: 7 (22.6) Week 12: 7 (23.3)	NR	
GRA response at follow-up (%)	NR		Yes: 19 (38.0) No: 31 (62.0)	Yes: 15 (31.3) No: 33 (68.8)
P value (between groups)	Week 7: 0.1470 Week 12: 0.1381		0.4828	
Mean ICSI at baseline (SD)	12.4 (3.26)	14.7 (3.02)	12.9 (3.40)	12.8 (3.46)
Mean ICSI change from baseline (SD)	Week 7: -2.8 (3.68) Week 12: -2.7 (4.07)	Week 7: -2.8 (2.39) Week 12: -3.2 (3.5)	NR	
Mean ICSI at follow-up (SD)	NR		9.7 (4.99)	9.7 (4.92)
P value (between groups)	Week 7: 0.8458 Week 12: 0.7069		0.9536	
Mean ICPI at baseline (SD)	12.4 (3.26)	12.9 (2.28)	12.4 (2.69)	11.7 (3.00)
Mean ICPI change from baseline (SD)	Week 7: -2.9 (3.26) Week 12:-3.0 (3.75)	Week 7: -3.1 (3.23) Week 12: -2.9 (3.63)	NR	
Mean ICPI at follow-up (SD)	NR		7.9 (4.59)	8.3 (4.51)
P value (between groups)	Week 7: 0.7668 Week 12: 0.8771		0.4656	

Abbreviations: GRA, global response assessment; ICPI, interstitial cystitis problem index; ICSI, interstitial cystitis symptom index; NR, not reported; SD, standard deviation.

Pairwise meta-analysis of effectiveness

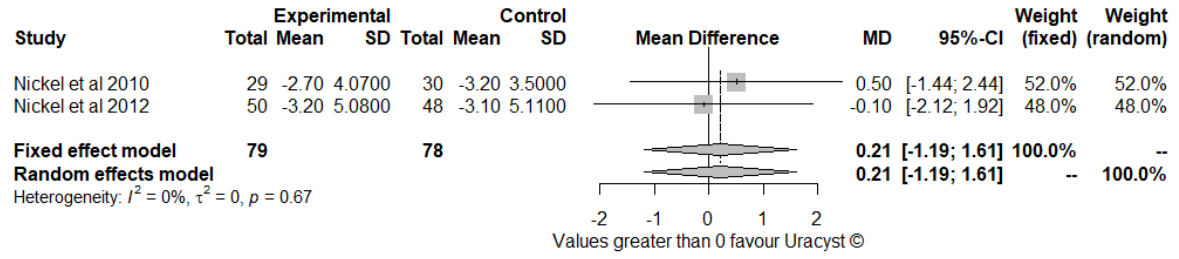
The company presented pairwise meta-analyses across the two Uracyst® RCTs[20, 21] for GRA, ICSI and ICPI (CS, figures 13 to 15). The forest plots for these analyses are presented in Figure 5, Figure 6 and Figure 7 below. For GRA, the fixed effect RR of 1.39 (95%CI: 0.88 to 21.7) was applied by the company in the economic model.

The pooled estimate was used to compare to the pooled GRA estimate from the pairwise meta-analyses across four RTCs of PPS in IC/BPS[14-17] based on the Bucher method. Further details of this are presented in Section 4.4 of this ERG report.



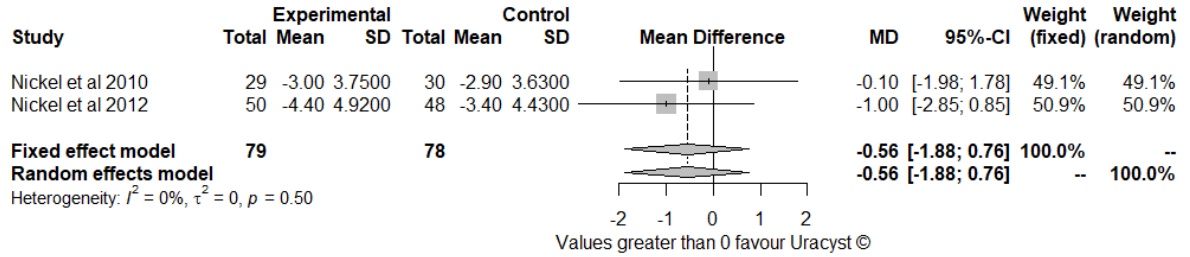
Reproduced from the CS page 86.1

Figure 5: Meta-analysis of Global Response Assessment in RCTs of Uracyst® in /BPS (risk ratio) (CS, figure 13)



Reproduced from the CS page 87.[1]

Figure 6: Meta-analysis of for mean change in Interstitial Cystitis Symptom Index in RCTs of Uracyst® in /BPS (risk ratio) (CS, figure 14)



Reproduced from the CS page 87.[1]

Figure 7: Meta-analysis of for mean change in Interstitial Cystitis Problem Index in RCTs of Uracyst® in /BPS (risk ratio) (CS, figure 15)

Adverse events

Adverse events for the Uracyst® trials were not reported in the CS. Nickel *et al.* (2010)[20] reported that 76.9% of the patients in the study reported at least 1 adverse event (AE) , 87.5% (28/32) of the control group reported 86 AEs compared with 66.7% (22/33) of the treatment group reported 67 AEs. Most AEs were reported as being mild in severity (56 and 45 for control and treatment groups respectively). There were 25 and 17 moderate AEs reported for the control and treatment groups, respectively, whereas 10 severe AEs were reported overall (5 in each group). Only nine intervention-related AEs were reported in three patients of the control group, compared with two intervention-related AEs in one patient in the treatment group. Intervention-related AEs were considered mild in the treatment group and mostly mild or moderate in the control group.

Nickel *et al.* (2012)[21] reported that 70.4% of the patients in the study experienced one or more AE (57.1% reported as mild intensity). However, the investigators reported that there was no "difference" was reported between the control group (71.4%) and the treatment group (69.4%). Only 7.6% of the AEs were intervention-related (10.3% in the control group and 5.2% in the treatment group). Four unrelated but serious, AEs occurred in 3 patients (suicide ideation and angina in 2 patients in the control group; and rectal bleeding and chronic colitis in 1 patient in the active treatment group). One patient in the active treatment group discontinued because of an unrelated AE. *P*-values or CIs were not reported.

4.4 Critique of the pairwise meta-analyses and indirect treatment comparison

Results of the pairwise meta-analyses undertaken by the company are presented in Sections 4.2.2 and 4.3.3 of this ERG report.

The ERG has some concerns with the company's meta-analyses (CS, Section B.2.8.1).[1] The aim of the meta-analysis was to determine the efficacy of PPS for the treatment of IC/BPS in comparison with placebo. In general, the aim of a meta-analysis is to generate an estimate of the treatment effect on an

additive scale that can be transported and used to estimate absolute risk in a target population. In addition, an objective in this submission is to generate a (posterior) distribution for the treatment effect and an estimate of the baseline effect that can be used together to represent uncertainty about absolute responses to treatment in the economic model:

- Table 28 of the CS[1] presents a meta-analysis of four studies on the risk difference scale for GRA. While a meta-analysis of risk difference may be appropriate when the baseline event rates are similar among the studies, treatment effects are more likely to be additive on a relative scale such as the log-odds ratio or log-relative risk.
- The company concluded that "There was a high degree of homogeneity in this sensitivity meta-analysis …" based on Cochran's Q value. The ERG has concern with the use of Cochran's Q value to assess and conclude homogeneity of relative treatment effects across studies,[32] and has a preference for estimating the between-study standard deviation and its uncertainty. In addition, it is unclear to the ERG why the company refers to this meta-analysis as a sensitivity analysis.
- The company's misinterpretation of Cochran's Q value is repeated when they include two additional studies with a broader BPS population[18, 19] that the ERG recognises do not satisfy the inclusion/exclusion criteria for the assessment. The company claims that "there is no indication of heterogeneity" rather than the more appropriate interpretation that there is insufficient evidence to reject the null hypothesis that there is homogeneity of treatment effects. Furthermore, and somewhat contradictory, the company goes on to state that the results were heterogeneous.
- It is not clear whether the meta-analysis presented in Table 29 of the CS[1] is based on a fixed or random effects model, and the predictive distribution of an effect is not provided. The use of a fixed effect meta-analysis is appropriate if interest is in a conditional inference of whether treatment had an effect in the available studies or if all of the factors that could affect the effect size on an appropriate additive scale are the same in all study populations. When there is reason to believe that the effect size may not be identical in the available or any future studies that might be conducted then a random effects meta-analysis should be performed; the choice between a fixed effect and random effects model should not be based on a test of heterogeneity of treatment effects.
- The company has used standard frequentist methods assuming asymptotic normality which may not be optimal given the samples sizes used and the number of observed events in the available studies. An exact analysis of the data using a Binomial likelihood and generation of the (posterior) distribution for the treatment effect could have been done using Bayesian methods.
- It is unclear what the relevance is of the lower limit of the 95% confidence interval for the pooled estimate of the absolute difference in GRA response being less than 5%. The lower limit of the

95% confidence interval suggests that it is unlikely that treatment effects smaller than 6.4% (not 6.3% as stated in the CS) are consistent with the data. The ERG notes that this does not mean that the 95% confidence interval contains clinically meaningful values which would require specification of and comparison with a minimum clinically important effect size.

Section B.2.8.2 of the CS[1] describes a meta-analysis conducted by Hwang *et al.* (1997).[33] The CS erroneously states that the meta-analysis included Sant *et al.* (2003),[17] which is impossible given that Sant *et al.* (2003)[17] was published after Hwang *et al.* (1997).[33] The CS[1] reports arm-based pooled estimates of response rates which is generally not recommended and implied wrongly that Hwang *et al.* (1997)[33] used these to make inferences about treatment effects.

The CS[1] discusses the impact on outcomes as a consequence of patients being enrolled in a clinical trial. The ERG considers the placebo effect to be irrelevant in the context of estimating a relative treatment effect that is transportable assuming that the relative treatment effect is estimated on an appropriate additive scale. On the basis that the relative treatment effect is estimated on an appropriate additive scale then it is necessary only to specify the absolute effect on the same scale for the control treatment when used in clinical practice in the target population in order to generate absolute effects.

The company presents data from Hanno (1997),[4] describing the percentage of patients with moderate or better improvement in patient global evaluation scale following treatment with PPS at six-monthly intervals over three years. The ERG considers the information difficult to interpret without a control group with which to estimate relative treatment effects.

Overall, the ERG accepts the company's argument that an unbiased comparison between PPS capsules and all relevant comparators was not possible using a conventional network meta-analysis because the studies of Uracyst® included patients in the wider BPS population, the placebo in the Uracyst® studies was a placebo instillation whereas the comparator in the PPS trials was a placebo capsule, and the timing of assessments differed between studies.

Nevertheless, in order to satisfy the NICE scope, the company provided an ITC between PPS and Uracyst® linked by the placebos using the Bucher method.[34] The ERG has a preference for performing a simultaneous comparison between treatments using a Bayesian network meta-analysis for the following primary reasons: (1) the Bucher approach allows for separate and unrelated meta-analyses for the effect of PPS versus placebo and the effect of Uracyst® versus placebo whereas a single model incorporates a common random effect, (2) the posterior distribution for the effect of PPS versus Uracyst® will not follow any standard parametric distribution whereas the Bucher approach involves an assumption of asymptotic normality when making inferences, and (3) the relative treatment effects

of PPS versus placebo and Uracyst® versus placebo will be correlated and this will induce correlation between absolute responses to treatment when combined with an external estimate of the baseline response. In addition, in the absence of evidence that there is no heterogeneity of treatment effects between studies, the ERG has a preference for a random effects model allowing for uncertainty in the estimate of the between-study standard deviation and estimation of the predictive distribution of treatment effect which is straightforward and exact using a Bayesian approach.

The company summarised the GRA data on the relative risk scale to characterise uncertainty about relative treatment effects for use in the economic model. The ERG notes that treatment effects should be estimated on an additive scale and that if treatment effects are additive on one scale such as the absolute scale as presented in Tables 28 and 29 of the CS then they cannot be additive on another scale as presented in Figure 11 of the CS. Estimation of the treatment effect may be appropriate on the risk difference scale if the GRA response rate is assumed to be zero in clinical practice or if the baseline event rates are similar among the studies being analysed; otherwise, the ERG has a preference for analysing the data on the logit scale.

The CS presents results from fixed effect and random effects models in order to estimate the relative effects of PPS versus placebo and of Uracyst® versus placebo using a frequentist approach. A frequentist approach assumes that the variance of the pooled estimate is known and ignores uncertainty in both the within-study estimate of variance and the between-study estimate of variance. Accurate inferences require reasonably large studies with which to estimate the within-study variance precisely and a reasonably large number of studies (i.e., at least five) with which to estimate the between-study variance. Consequently, the ERG suggests that there is insufficient information with which to assess heterogeneity as claimed by the company and that the results of the random effects models presented in Figures 11-15 of the CS should be treated with caution. Nevertheless, the ERG has a preference for random effects models except when making conditional inferences or when it is known that studies are estimating the same underlying treatment effect. This could be done using a Bayesian approach incorporating external information about the between-study standard deviation.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was required to be undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The ERG considers that the company's search strategy is sufficiently comprehensive to retrieve important citations relating to clinical effectiveness and safety of pentosan polysulfate (PPS) for treating Interstitial cystitis/bladder pain syndrome (patients with bladder pain syndrome with Hunner's lesions and/or glomerulations) (IC/BPS).

The four RCTs of PPS in IC/BPS were relevant to the decision problem outlined in the final NICE scope. Three of the RCTs of PPS in IC/BPS (Parsons *et al.*, 1993, Mulholland *et al.*, 1990 and Parsons and Mulholland, 1987) were considered by the ERG to be of good methodological quality. However, the ERG considered one RCT (Sant *et al.*, 2003) to be unclear regarding: allocation concealment, details of who was blinded, and numbers of patients withdrawing from treatment groups. As such, that the results from this trial should be interpreted with caution.

The ERG notes potential issues surrounding study power and sample size as three of the RCTs of PPS in IC/BPS did not prospectively define the sample size (Parsons *et al.*, 1993; Mulholland *et al.*, 1990; Parsons and Mulholland, 1987), and the one RCT which reported a power calculation failed to recruit the target number of patients (Sant *et al.*, 2003).

The ERG also notes limitations in the reporting of outcome data in the PPS RCTs trial reports. Interval estimates (CIs) were not reported and, where between-group differences were reported as not statistically significant, *p*-values were often not reported.

All four RCTs of PPS in IC/BPS were multicentre trials conducted in the USA and published between 1987 and 2003. The ERG notes that there is some author commonality across all four RCTs of PPS in IC/BPS and that subsequently, there has not been any further published study undertaken by an independent study group which has attempted to validate the results of the four RCTs of PPS in IC/BPS.

The between-group difference in the proportions of patients with a patient-reported >50% improvement in global response assessment (GRA) at three months was reported as being statistically significant in favour of PPS by two RCTs (Parsons et al, 1993, PBO 16% vs PPS 32%, p=0.01; and Mulholland *et al.*, 1990, PBO 13% vs PPS 28%, p=0.04; CIs not reported), but the between-group difference in the proportions of patients with a GRA score of six to seven at three months was reported as not statistically significant by one RCT (Sant *et al.*, 2003, PBO 18% vs. PPS 34%, p=0.064). As GRA was not assessed in one RCT (Parsons and Mulholland, 1987), the proportions of patients with a >50% improvement in non-VAS pain was used as a proxy for GRA in the analysis undertaken by the company. The between-group difference in non-VAS pain reported by Parsons and Mulholland (1987) was statistically significant (PPS 44% vs. PBO 15%, p=0.02; CI not reported).

The between-group difference in in the proportions of patients with a >50% improvement in non-VAS pain at three months was reported as being statistically significant in one other RCT (Parsons *et al.*, 1993; p=0.005). However, the between-group the between-group difference in mean non-VAS pain

scores were reported as not being statistically significant at three months for two other RCTs (Sant *et al*., 2003; Mulholland *et al.*, 1990; *p*-values or CIs, not reported).

The between-group difference in the O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index mean scores at three months were reported as being not statistically significant in one RCT (Sant *et al.*, 2003, *p*-values not reported). There were no statistically significant between-group differences in mean daily urinary frequency at three months reported by two RCTs (Sant *et al.*, 2003, *p*-value not reported; Parsons and Mulholland, 1987, $p=0.06$). There were no statistically significant between-group differences in mean urinary volume and void outcomes at three months reported by two RCTs (Parsons *et al.*, 1993; Mulholland *et al.*, 1990; *p*-values not reported), and one RCT did not report whether the between-group difference was significant or not, or a *p*-value for the between-group difference (Parsons and Mulholland, 1987). There were no statistically significant between-group differences in mean nocturia at three months reported by two RCTs (Mulholland *et al.*, 1990, *p*-value not reported; Parsons *et al.*, 1993, no data reported), and one RCT did not report whether the between-group difference was significant or not, or a *p*-value or CI, for the between-group difference (Parsons and Mulholland, 1987).

Safety data for PPS were presented in the CS from each of the individual RCTs of PPS in IC/BPS, and the company concluded that PPS is well tolerated. Common adverse events in the SmPC are: headache, dizziness, nausea, diarrhoea, dyspepsia, abdominal pain, abdominal enlargement, rectal haemorrhage, peripheral oedema, alopecia, back pain, asthenia, and pelvic pain. However, clinical advice received by the ERG based on named patient use is that AEs are rare with PPS.

The ERG has some concerns with the pairwise meta-analyses that were performed by the company and reported in the CS (the choice of scale for the analysis, the use of hypothesis testing to assess heterogeneity, and the use of a fixed effect model in the absence of evidence that there is not between study heterogeneity). The ERG accepts the arguments suggested by the company for not performing an NMA. Nevertheless, an ITC between PPS and Uracyst® was required and the company did this using the Bucher method, with the placebos as the reference treatment. While neither an NMA nor the Bucher approach are ideal in this case, the ERG does not believe that the Bucher approach mitigates all of the concerns associated with performing an NMA, including: not using a single model to incorporate random effects; making the assumption of asymptotic normality when making inferences and characterising uncertainty about the relative treatment effect used in the economic model.

5 COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

This section presents a review of the cost-effectiveness evidence reported in the CS[1] for pentosan polysulfate sodium (PPS) for treating IC/BPS (defined as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations).

5.1.1 Objective of cost effectiveness review

The company undertook a systematic literature review in order to identify cost-effectiveness evidence for IC/BPS and BPS treatments.

Two searches were performed to identify economic evaluations of IC/BPS and BPS. The following databases were searched for economic evaluations in June 2018: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], Embase [via Wiley], NHS EED [via Wiley]. The company carried out supplementary searches within health technology appraisals via the NICE website.

In the company's clarification response (question B1), the company reported that publication date limits were not applied to the economic and cost-effectiveness evaluations searches. The NHS EED database coverage is limited to 1995-2014 whereas limits of 1992-1994 and 2015-present were applied in the MEDLINE and Embase search. The reasons and implications of not including all years in MEDLINE and Embase were not given. The ERG is unable to confirm if any key economic evaluations have been missed as a result applying these limits.

The company performed two searches to identify health-related quality-of-life studies for IC/BPS and BPS. Details of these searches were provided in response to a request for clarification from the ERG (question B3).[35] The following three sources were searched in June 2018: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid] and Embase [via Ovid]. The company cross-checked lists of included articles with records from the electronic searches. The ERG considers that the searches are sufficiently comprehensive to retrieve all the eligible studies.

The company performed two searches to identify cost and resource use evidence for IC/BPS and BPS. Details of these searches were provided in response to a request for clarification from the ERG (question B3).[35] The following two sources were searched in June 2018: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid] and Embase [via Ovid The company cross-checked lists of included articles with records from the electronic searches. The ERG identified one study that should have been included.[36] The ERG cross-checked the study against the MEDLINE and Embase search results and confirmed that the record would have been missed by the company's searches.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria for the cost-effectiveness review was included in Appendix G (Table 69) of the CS[1]. The ERG believes that the company's criteria were acceptable in order to identify relevant studies of cost-effectiveness in the population of interest. The ERG believes that the exclusion criteria used for cost and healthcare resource use studies could have excluded potential studies that could provide data for model inputs for costs and resource use. The ERG believes that the exclusion criteria (no intervention/comparator) used for HRQoL studies could have excluded potential studies reporting baseline quality of life data in the population defined in the NICE scope.

5.1.3 Findings of the cost effectiveness review

Four studies were identified for full text screening with only one study identified and included within the cost-effectiveness review. This study, conducted by Cervigni (2017)[30],was a within trial economic evaluation of iAluRil® vs. DMSO and provided baseline EQ-5D values for patients with IC/BPS which were based on Italian population values. Three studies were excluded at the full text stage as they were not economic analyses. The details of these three excluded studies were provided by the company during the clarification process (question B41). No studies assessing the cost-effectiveness of PPS for the treatment of IC/BPS were identified. Additional searches undertaken to identify cost and healthcare resource use studies identified two studies for data extraction, one of which was the aforementioned Cervigni 2017[30]. The ERG notes that the CS[1] and the clarification responses[1] state that the three studies excluded from the main cost-effectiveness review were excluded as they only contained costs and healthcare resource use data. The ERG is unsure why these studies were therefore not identified and included in the additional costs and healthcare resource use reviews. In addition, an ad hoc search conducted by the ERG identified a costing study related to treatment costs of IC/BPS in Austria[36] which meets the company's inclusion criteria for cost and healthcare resource use studies, yet was not included. The ERG is unsure why a study with no intervention /comparator[37] was included in the HRQoL studies when the exclusion criteria states that these studies would be excluded.

5.1.4 Conclusions of the cost effectiveness review

The ERG is satisfied that the identified published cost-effectiveness study[3] is not appropriate to address the decision problem in the NICE scope,[2] and therefore that the development of a de novo model is appropriate. However, the ERG has some concerns about the date limits applied to the company's economic searches and is unable to confirm if any key economic evaluations have been missed as a result of applying these limits. In addition, the ERG has some concerns with the quality of the searches undertaken for additional studies of cost and healthcare resource use data and HRQoL studies.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Please note that the company submitted a revised model following the clarification request and it is this model that is referred to throughout the report unless otherwise specified. The revisions made in this model were mainly corrections of errors in the implementation of the model and did not concern the model structure, assumptions or data sources, with the exception of the life-table data being updated to the most recent dataset available.

5.2.1 NICE reference case checklist

Table 17: Compliance with the NICE reference case[38]

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The population modelled is adults with BPS characterised by either glomerulations or Hunner's lesions, which is consistent with the NICE scope and the licensed indication for PPS. The evidence on the effectiveness of PPS compared to BSC is taken from trials in the relevant population.[14-17] However, the evidence on the effectiveness of BI compared to placebo, comes from the broader population of patients with BPS which is not restricted to those with either glomerulations or Hunner's lesions. The model evaluates the cost-effectiveness of PPS separately in the subgroup able to receive BIs and the subgroup who are contraindicated or unable to tolerate BIs as both the comparators and subsequent treatments differ in these populations. The scope explicitly states that the economic modelling should include the costs associated with diagnostic testing for glomerulations or Hunner's lesions in people with bladder pain syndrome who would not otherwise have been tested. The model does not incorporate any costs for diagnostic testing. However, the ERG is satisfied that this is reasonable based on the advice provided by their clinical

		experts which stated that the relevant test would be carried out as part of the standard diagnostic pathway, whether or not PPS was being considered as a treatment option.
Comparator(s)	As listed in the scope developed by NICE	• BIs in the population able to receive BIs • BSC in the population unable to receive BIs These are consistent with the scope
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model estimates direct health effects for patients but not carers which is considered by the ERG to be reasonable in this case. In estimating the QALYs, the model does not capture AEs of either PPS or BIs; however, this is not considered to have significantly biased the assessment of cost-effectiveness
Perspective on costs	NHS and PSS	The model includes only NHS costs as the CS[1] states that PSS costs are not relevant. This is considered to be a reasonable deviation from the reference case in this case.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The submitted model provides a cost-utility analysis with outcomes presented as the incremental cost per QALY gained for two comparisons; • PPS versus BIs in the population able to receive BIs • PPS versus BSC in the population unable to receive BIs The ERG considers this approach to be reasonable given that BIs are the current standard of care and BSC would only be given to those patients who are unable to receive BIs.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The base-case analysis uses a 20-year time-horizon; sensitivity analyses are provided using a lifetime horizon. The ERG considers the lifetime horizon more appropriate for the reference case analysis given that the survival function used to extrapolate time to discontinuation predicts that 18% of patients remain on treatment at 20 years.

Synthesis of evidence on health effects	Based on systematic review	The estimates of treatment effect for PPS versus BSC are based on a systematic review and meta-analysis of RCTs. The estimate of treatment effect for BIs versus BSC are based on a systematic review and meta-analysis of RCTs for commercial BIs. Evidence was only identified for one form of BIs. The model assumes that all BIs are equally efficacious. A simple indirect comparison, using the Bucher method[34], has been used to compare PPS to BSC rather than a network meta-analysis.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects are expressed in QALYs with utility values based on the EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L responses were measured in a patient survey along with a measure of disease severity (ICSI).[39] Utility scores for the model were estimated by mapping from ICSI scores to EQ-5D.[39] The measure of efficacy in the model is the response rate. The expected ICSI scores for responders and non-responders were estimated from a single trial arm (PPS arm of Sant 2003[17]) and were applied universally to all patients in the model according to their response to treatment.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The EQ-5D-5L responses from the survey[39] were cross-walked to the UK EQ-5D-3L valuation set using the mapping function developed by van Hout.[40] This is consistent with the approach recommended for reference case analyses according to NICE's current position statement on this topic.[41]
Equity considerations	An additional QALY has the same weight regardless of the other	No weighting of QALYs has been applied. This is consistent with the NICE reference case.

	characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS[1] states that resource use has been costed using standard prices relevant to the NHS such as NHS reference costs and list prices. The price of PPS was sourced from the manufacturer. The price of one of the BIs was also sourced from the manufacturer, but all other drug prices were based on public list prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	In line with the NICE reference case, costs and health effects are discounted at a rate of 3.5% per annum.

5.2.2 Model structure

The company's model is a discrete event simulation (DES) which estimates the mean costs and QALYs for a cohort of patients by simulating outcomes for 10,000 individuals with identical characteristics at baseline. The model simulates the clinical events occurring over the time horizon for each individual and uses these to predict lifetime costs and QALYs for each individual. Even though patients have identical characteristics at baseline, their path through the model is allowed to vary stochastically (i.e. according to chance) by sampling the time that the various possible events will occur for each individual from time-to-event distributions. The costs and QALYs expected for an average patient are estimated by taking the average across the simulated cohort of individuals. This provides a stable estimate of the expected costs and QALYs if outcomes for a sufficient number of individuals are sampled. The outcomes are simulated for the whole cohort for each treatment option (i.e. once for PPS, BI, and BSC) and then the average outcomes for each treatment option are compared to provide estimates of the incremental costs and QALYs between alternative treatment options.

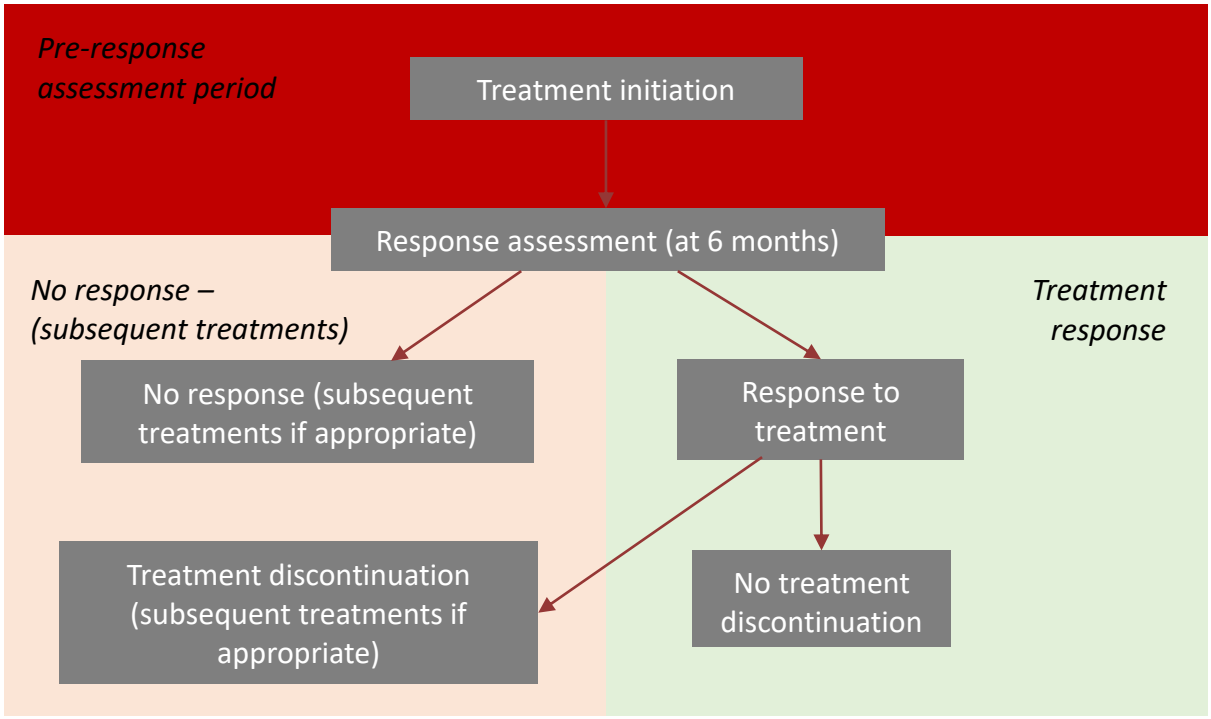


Figure 8: DES – patient flow (copied from Figure 17 of the CS)

In the company's model (summarised in Figure 8), patients are initiated on first-line therapy (i.e. the chosen treatment option) and then all patients are subject to a response check at 6 months. Non-responders are assumed to switch to second-line therapy (including subsequent treatments if appropriate) at this point. Responders remain on their first-line therapy until they discontinue, at which point they switch to second-line therapy. Patients are at risk of dying from all-cause mortality at any point during the model and survival is assumed not to vary by treatment. When BIs are given as the first-line treatment, the model estimates treatment costs and QALYs accrued during BIs by modelling each treatment administration as a separate model event. This allows the frequency of BIs to vary over time. When BIs are given as second-line treatments, the separate treatment administrations are not modelled explicitly and instead annualised costs and QALYs are calculated based on the duration of second-line treatment and the mean number of BI administrations per annum. Therefore, the main events modelled are:

- Response check at 6 months
- Administration of BI (when BI is used as first-line treatment only)
- Treatment discontinuation (in responders only)
- Death from all-cause mortality
- End model due to reaching time horizon (20 years) before death.

The company's model captures the benefit of treatments for IC/BPS through their impact on response rates as patients who respond and stay on treatment are assumed to have higher utility values and lower disease management costs.

The ERG does not understand why the company did not build a state transition model. With the exception of the administration of BIs, the costs and QALYs are determined mainly by the time spent on first and second-line treatment. Therefore, a simple Markov model could have been constructed with health states for:

- Patient on treatment before the re-response check
- Non-responders who have switched to second-line treatment
- Responders remaining on first-line treatment
- Responders who have discontinued and moved to second-line treatment
- Death.

Although the frequency of BIs varies in the first 6 months of the model, it is constant thereafter. Therefore, the varying cost of BIs could have be incorporated simply by having a 6-month cycle length and a different cost in the first cycle. The company claims that the DES structure allows ICSI to be incorporated as a continuous variable. However, ICSI is not implemented in the DES as a continuous variable. Instead average costs and utilities are estimated for responders and non-responders based on their estimated median ICSI scores. This would therefore allow costs and utilities to be easily attributed to the health states listed above. The ERG considers that a state-transition approach would have been more parsimonious but that this does not mean that the DES approach is incorrect.

5.2.3 Population

The modelled population is adults with bladder pain syndrome characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition. The ERG considers the overall population to be consistent with the NICE scope[2] and the licensed indication for PPS.[8]

However, the ERG notes that based on the company's presentation of the clinical pathway in Figure 2 of the CS, patients would not receive a cystoscopy and a confirmed diagnosis of IC/BPS until after they had failed to respond to first-line oral therapies including analgesics, antihistamines and other non-pharmaceutical interventions including as dietary and lifestyle advice. Therefore, the population modelled is assumed to be those who did not respond to these initial interventions and the cost-effectiveness results should not be extrapolated to patients earlier in the clinical pathway.

The CS[1] presents cost-effectiveness analyses for two distinct subpopulations;

- Patients able to receive BIs
- Patients for whom BIs are contraindicated or who are unable to tolerate BIs.

The ERG considers it reasonable for the company to present separate estimates of cost-effectiveness for these two subpopulations, as patients unable to receive BIs have different first and subsequent treatment options available.

The ERG is satisfied that it is not necessary for the company to present an analysis of PPS versus BSC in the population able to receive BIs, as offering BIs was considered by the ERG's clinical experts to be established practice in the NHS for this population.

The CS[1] states that all patients are assumed in the model to have a starting age of 45.57 years based on the characteristics of patients in the RCT reported by Sant *et al.* (2003).[17] The company states that 89% of the modelled population are female, but in practice, the sex of the patients is not varied within the cohort, and instead the all-cause mortality rate is calculated as a weighted average of males and females using the proportion who were female (89%) in the Sant *et al.* (2003) RCT.[17] The ERG's clinical experts confirmed that the majority of patients they see with IC/BPS are female and the populations in the included RCTs including Sant (2003) were generally comparable to the UK IC/BPS population. The ERG notes that the error introduced from not modelling males and females separately is likely to be small given that they are assumed to differ only in their life-expectancy and the model is limited to a 20-year time-horizon.

5.2.4 Interventions and comparators

The treatment pathways modelled are summarised in Table 18. In the population able to receive BIs, patients who do not respond to the first-line treatment, or who respond initially but later discontinue, are offered BIs as second-line treatment. It is assumed that these patients cycle through the various commercial BI preparations indefinitely until death or the time horizon (20 years) is reached. It is assumed in the model that sodium hyaluronate is used as the first-line BI. Although the ERG heard from clinical experts that there was no standard order of sequence for trying BIs, the similarity in price of the various commercially available BIs meant that the ERG was not concerned that this assumption had significantly biased the estimates of cost-effectiveness.

Table 18: Modelled treatment pathways

Population	First-line treatment	Second-line treatment given after non-response or discontinuation of first-line treatment
Patients able to receive BIs	PPS given orally as three 100mg doses per day	BIs given every 4 weeks using either sodium chondroitin (2%, Uracyst®; 0.2%, Gepan®) or a combination of sodium hyaluronate and sodium chondroitin (iAluRil®).
	BIs with sodium hyaluronate (Hyacyst®, Cystistat®) given weekly for 4 weeks, then every 4 weeks	BIs given every 4 weeks using either sodium chondroitin (2%, Uracyst®; 0.2%, Gepan®) or a combination of sodium hyaluronate and sodium chondroitin (iAluRil®).
Patients unable to receive BIs	PPS given orally as three 100mg doses per day	BSC
	BSC	BSC

The ERG notes that some clinicians have access to locally prepared BIs which may be lower cost than the commercially prepared BIs. However, these were noted to vary from hospital to hospital and therefore cannot be considered to be part of established practice in the NHS in England. Given that there are licensed commercial bladder instillations available, which the ERG's clinical experts accepted were part of the standard care in the NHS in England, the ERG considered it reasonable to exclude the locally prepared BIs from the economic modelling.

Patients unable to receive BIs who have BSC as their first-line treatment are assumed to continue with BSC regardless of whether they respond as no alternative treatments are available in patients unable to receive BIs.

5.2.5 Perspective, time horizon and discounting

The model takes an NHS perspective. The CS states that PSS costs are not relevant to the decision problem. [1] This was considered reasonable by the ERG.

The base-case analysis uses a time-horizon of 20-years, but also presents a scenario analysis using a lifetime horizon. The ERG considers the use of a lifetime horizon more appropriate for the reference case analysis given that the survival function used to extrapolate time to discontinuation predicts that 18% of patients remain on treatment at 20 years. Therefore, under the company's assumption, the

decision to offer PPS will potentially incur costs that fall outside of their preferred 20-year time horizon, which is inconsistent with the NICE reference case. [38]

The model applies discount rates of 3.5% to both costs and QALYs and is therefore consistent with the NICE reference case.[38]

5.2.6 Sources and assumptions used to inform the model

The key sources used to inform the model are summarised in Table 19. These data sources are discussed in more detail in sections 5.2.7 to 5.2.10.

Table 19*:* Summary of data sources used to inform the company's base-case analyses

Parameter group	**Source**
Patient characteristics (age, gender)	Based on characteristics of trial participants in Sant *et al.* (2003)[17]
Mortality - general population	Derived from interim life tables for England (2015-2017)[42]
BSC response rate	Company's meta-analysis of four RCTs of PPS versus placebo in patients with IC/BPS[14-17].
PPS response rate	RR from company's meta-analysis of four RCTs of PPS versus placebo multiplied by BSC response rate[14-17]
BI response rate	RR from company's meta-analysis of two RCTs in patients with BPS multiplied by BSC response rate[20, 21]
TTD – PPS	Exponential model fitted to observed time to discontinuation data for PPS patients reported in Hanno *et al*.(1997)[27]
TTD – BI	TTD data for PPS used for time to discontinuation of BIs
ICSI scores for responders and non-responders	Mean ICSI scores for responders and non-responders were estimated based on ICSI scores in the PPS arm of RCT by Sant *et al* (2003)[17]
HRQoL	EQ-5D-5L and disease severity measure (ICSI) data collected from a survey conducted by the company of 252 BPS patients [39]. EQ-5D-5L responses valued using crosswalk to EQ-5D-3L UK value set [40]. Utility scores estimated by mapping from ICSI score to EQ-5D [39]. Mapping regression also contained terms for age and recent

Parameter group	Source
	use of BIs with the coefficient for recent use of BIs applied to those receiving BIs in the model.
Disease-related resource use	Company's survey of 252 BPS patients [39]
Disease-related costs	Resource use data from the patient survey[39] were combined with unit costs from the NHS Reference Costs (2017/18)[43] and PSSRU (2017)[44] to estimate disease-related costs as a function of ICSI scores.
PPS drug acquisition costs	Provided by the company
BI drug acquisition costs	Monthly Index of Medical Specialties (MIMS) 2018, NHS Electronic Drug Tariff [45], Company provided Uracyst® cost from manufacturer
Drug administration costs	NHS Reference costs (2017/2018) [43]

The key structural assumptions within the model are as follows:

- The mean placebo response rate from the RCTs of PPS is assumed to apply to patients having BSC
- The effectiveness of first-line BIs with sodium hyaluronate is assumed to be the same as the effectiveness of sodium chondroitin sulphate
- The cumulative rate of response across all subsequent lines of BIs is assumed to be the same as the effectiveness of sodium chondroitin sulphate
- Those responding to either PPS or BI at 6 months are assumed to continue to respond until treatment discontinuation
- Those responding to BSC at 6 months are assumed to continue to responder for 12 months
- Non-responders who have BSC as their second-line treatment are assumed to maintain any changes in utility that occurred during the first 6 months for the rest of the model horizon
- Patients who respond to treatment are assumed to have lower ICSI scores than non-responders and the change in ICSI scores is assumed to be normally distributed.
- The change in ICSI scores for responders and non-responders is the same for all treatments
- Time to treatment discontinuation for BIs is assumed to be the same as for PPS.

These assumptions are discussed in more detail in sections 5.2.7 to 5.2.10.

5.2.7 Treatment effectiveness – response rate

For the comparisons of both PPS versus placebo and BI versus placebo, the trial outcome of GRA has been used to determine whether the patient has received an adequate response to treatment.

The treatment effectiveness of PPS versus BSC is based on a meta-analysis of the four key trials which were conducted in patients with IC/BPS[14-17] (i.e. those with BPS and evidence of either Hunner's lesions or glomerulations). The forest plot for this meta-analysis is provided in Figure 11 of the CS[1] and the fixed effects RR of 2.09 (CI 1.47-2.97) has been applied in the model.

The treatment effectiveness of BI compared with BSC is based on a meta-analysis of two studies[20, 21] in patients with BPS (i.e. no requirement to have evidence of either Hunner's lesions or glomerulations). The forest plot is provided in Figure 13 of the CS[1] and the fixed effects RR of 1.39 (CI 0.89-2.17) has been applied in the model.

An estimate of the GRA baseline response is required in order to generate an estimate of the absolute GRA response rates for each treatment for inclusion in the economic model. The response rate for BSC in the economic model has been estimated by meta-analysing the response rates in the placebo arms of the 4 RCTs which compared PPS to placebo in the IC/BPS population[14-17] (16%, 95%CI 0.12-0.21, see Figure 12 of the CS).

The ERG notes that the estimates of relative treatment effect for response to treatment for PPS versus BI, that inform the estimate of incremental cost-effectiveness for PPS versus BI, are dependent on the company's simple unadjusted indirect comparison between PPS and BI. In practice, this means that the rate of response in the PPS group is equal to the rate of response for BSC (16%) multiplied by the RR for PPS vs placebo from the meta-analysis (2.09) to give a response rate for PPS of 33%. Similarly, the response rate in the BI group is the response rate for BSC multiplied by the RR for BI vs placebo (1.39) to give a response rate for BI of 22%. Therefore, the effective RR in the model for PPS versus BI based on the indirect comparison is 1.50 (=2.09/1.39). A critique of the company's systematic review and meta-analysis, which inform these estimates of relative treatment effect, including the ERG's concerns regarding the indirect comparison, is provided in Section 4.

The ERG has a concern with the relevance of the estimate of GRA baseline response (16%) given that the company has stated that the RCTs of PPS and chondroitin sulphate reported high response rates in their placebo arms (see page 104 of the CS). The estimate of the GRA response rate expected in an untreated population in clinical practice can come from sources other than clinical trials, for example, registries and expert opinion. Clinical advisors to the ERG suggested that 20-30% of patients with IC/BPS (especially those with milder symptoms) would be expected to report an improvement in

clinical practice in the absence of treatment with either bladder instillations or oral PPS. On the other hand, the CS states that the high placebo response rates observed in the clinical trials, estimated by the company to be 16% (CS, Figure 12), are unlikely to be observed in clinical practice.[1] As part of the clarification process, the ERG asked the company to state the expected GRA response for patients receiving standard of care in clinical practice (see clarification question A18). The company replied:

> *"The main change in clinical practice since the trials were conducted is that standardised, commercially-available bladder instillations are now routinely used in the treatment of BPS. As noted in our submission, it is difficult to disentangle the effect of placebo in the clinical trials of PPS and BIs. We are unaware of any contemporary data reporting the 'response' to standard of care i.e. initial treatments (e.g. pain management, etc). In our analysis, we have adopted a highly conservative approach of assuming the placebo effect would be observed in clinical practice for a year for patients not receiving PPS or BIs, even though this response is likely to be due to participation in the trials. Please note that this assumption is likely to underestimate the effectiveness of PPS,"* (clarification response, question A18).[1]

The ERG notes that assuming a GRA response rate for BSC that is similar to the placebo response in the clinical trials (that is believed to be higher than expected for an untreated population as a consequence of participating in a clinical trial) is likely to benefit the company rather than being conservative. This is because the absolute effect of PPS is estimated by applying a relative risk and the absolute difference becomes greater with increasing baseline response. The exact impact on the ICER will depend on whether incremental costs and QALYs vary at the same rate when the baseline risk is varied. The ERG considers that the true response rate for patients receiving BSC in clinical practice is uncertain. The ERG therefore conducted exploratory analyses to examine the impact on the ICER of raising and lowering the response rate in the BSC arm of the model (see Section 5.3).

In addition to the ERG's concerns regarding the lack of an appropriate estimate of response rate for patients receiving BSC, the ERG also notes that the company makes different assumptions in the model about the durability of the response achieved for patients in different arms of the model. The company argues that the response rates observed in the placebo arms of the RCTs would be unlikely to be observed in patients receiving BSC in clinical practice because they are "*likely to be a result of participating in the clinical trial*." To account for this in the model, the company limited the benefits for responders in the BSC arm to the first 12 months of the model. In contrast, the responses achieved in patients receiving PPS or BIs as first-line treatment are assumed to persist until treatment is discontinued.

The ERG considered that it was inconsistent to assume that all of the responses observed in the PPS and BI arms of the RCTs were durable, in that they would persist until treatment ceased, but all of the responses observed in the placebo arms of the RCTs were not durable and would cease at 12 months.

If the response rate observed in the placebo arms of the RCTs was related to the experience of being enrolled in a clinical trial, then it may also apply to a proportion of the patients who responded in trial arms receiving either PPS or BI. If the response rate in the placebo arm is related to the fact that patients may enrol in the trial when experiencing a flare-up in their symptoms, which resolves naturally over the course of the trial (i.e. regression to the mean), then again, it does not seem reasonable to assume that this response is time limited in patients receiving BSC, but continues indefinitely in those receiving PPS or BI. RCTs are designed to provide an unbiased estimate of the relative treatment effect. It is this relative treatment effect that should inform the differences in outcomes between treatments within the economic model. However, the company's assumption that benefits are limited to 12 months in patients responding to BSC introduces a difference in the model that is separate from the relative treatment effect measured in the trial. The ERG does not consider that this is reasonable given that the company has provided no evidence to demonstrate that the durability of response differs in patients receiving BSC compared to those receiving either PPS or BI.

5.2.8 Treatment effectiveness – extrapolation

In the PPS and BI arms of the model, patients who have responded after 6 months of treatment are assumed to continue receiving the full treatment effect until they discontinue. The time-to-discontinuation survival function is based on data from Hanno *et al.* (1997)[27] which has a maximum follow-up of 10 years. An exponential survival function is then used to extrapolate discontinuation rates over the remainder of the model. The median time to discontinuation in the company's model, based on their preferred parametric survival function, is 7 years with 18% of patients estimated to still be on treatment after 20 years. The effectiveness of PPS and BIs has therefore been extrapolated for some patients for up to 20 years in the company's base-case analysis. This is in contrast to the RCTs having a maximum of 6-month follow-up for assessment of response based on GRA. The ERG is concerned that there is a lack of data on the long-term efficacy of PPS despite the drug having being available in Canada, Australia and the US for over 20 years. Whilst some data on efficacy up to 36 months are provided in the CS, these are from an observational study which is poorly reported and as such are difficult to interpret. (see Section 4.2.6)

In addition, the data on discontinuation are based on a study in patients treated with PPS, but the same survival function for time to discontinuation is also applied in the model to patients receiving BIs as first-line treatment. No evidence is provided to support the assumption that rates of discontinuation would be the same for BIs and PPS. Given that these treatments vary substantially in their mode of

administration, it is possible that the rate of discontinuation may differ substantially. For example, given the invasive nature of BIs, it is possible that patients may stop and restart treatment according to the severity of their symptoms, resulting in fewer BIs per annum than predicted by the model. One of the ERG's clinical experts also stated that they considered it unlikely that 18% of patients would still be taking BIs at 20 years given that BIs are an invasive treatment. Therefore, the ERG considered that the discontinuation rates for BIs lacked face validity.

Patients starting second-line treatment with BIs are assumed to continue on second-line BIs for the rest of the model horizon. Therefore, the effectiveness of BIs compared with BSC in second-line patients has been extrapolated for up to 20 years in the base-case analysis. Patients are assumed to cycle through the various BIs available until they achieve a response. The response, or lack of response, to each subsequent BI is not modelled explicitly. Instead, the costs and utilities in patients having BIs as second-line treatment are based on the mean response rate to BIs when used as first-line treatments. No evidence is provided to support the assumption that the cumulative response rate achieved over numerous lines of subsequent BIs will be the same as the response achieved during first-line BI treatment. It is also unclear whether patients are likely to cycle through second-line BI treatments indefinitely (including treatments that they have previously failed on, as claimed on page 34 of the CS), or whether some would transition to BSC over time. This is important given that the costs and utilities applied to those on BSC differ to those remaining on second-line BIs. However, it is difficult for the ERG to estimate the size and direction of any potential bias, given that response to second-line BIs and discontinuation from second-line BIs is not explicitly captured in the company's model structure.

5.2.9 Health-related quality of life

The model estimates ICSI scores for responders and non-responders using data from the PPS arm of the RCT by Sant *et al.* (2003[17]). Data from a patient survey of 252 BPS patients were used to map from ICSI scores to utilities as measured by the EQ-5D.[39] The EQ-5D-5L responses from the patient survey were mapped to EQ-5D-3L responses using the algorithm reported by van Hout *et al.*[40] and the UK valuation set for EQ-5D-3L were applied. A mapping regression was then fitted to estimate EQ-5D-3L utilities as a function of ICSI, age and a term that captured prior use of BIs (see Table 43 of the CS). The different ICSI scores predicted for non-responders and responders from the PPS arm of the RCT by Sant *et al.* is therefore used to determine the utility gains associated with a response to treatment in the model. The regression coefficient for the term "received a bladder instillation in the previous 6 months" was applied to all patients having BIs in the model. This included those having first-line BIs before the response check, those responding to first-line BIs and those having BIs as a second-line treatment after either first-line PPS or first-line BIs.

The utility scores applied in the model are summarised in Figure 9 according to whether patients respond or do not respond to first-line treatment and according to whether they discontinue following response (see Table 48 of the CS[1] for the numerical values). We have illustrated the scenarios in Figure 9 assuming that patients who discontinue do so at exactly 7 years as this is the median time of treatment discontinuation; however, in the model patients can discontinue at any time from 6 months to 20 years according to the survival function for time to discontinuation.

Figure 9:

It can be seen from Figure 9 (panels A and B) that patients who respond to PPS or BIs are assumed to continue to benefit from improved HRQoL until they discontinue treatment, but may continue to benefit for the full model horizon if their time to discontinuation is sampled to be greater than 20 years; this occurs in 18% of responders. In contrast, patients who respond on BSC, are assumed to have a HRQoL benefit that lasts only from the response check at 6 months to 1 year after the start of the model (NB: alternative scenarios are provided in the CS[1] where the treatment effect stops immediately after the 6-month response check or at 5 years).

It can also be seen from Figure 9, that in the scenario where patients cannot have BIs (panels C and D), patients who do not respond to either PPS or BSC experience some HRQoL improvement due to an assumed improvement in ICSI scores in non-responders compared with baseline. The ERG notes that the utility score of non-responders having BSC in this scenario ([redacted]), is [redacted] than the average utility score achieved by patients having BIs as second-line treatment ([redacted]) even though 22% of these patients respond to second-line BIs. This inconsistency is being driven by the utility decrement associated with receiving BIs which results from the regression coefficient for having "received a bladder instillation in the previous 6 months". The ERG notes that only 53% of the undiscounted QALY gain for PPS versus BIs is accrued in patients who responded on PPS but would not have responded on BIs. The remainder is due to differences in QALYs that result from time spent on first-line BIs due to the application of the regression coefficient for having "received a bladder instillation in the previous 6 months".

The ERG does not understand the clinical rationale for there being a utility decrement associated with having previously received BIs. In response to a request for clarification, the company stated *"Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections*".[1] However, the ERG is concerned that the difference in utility detected in the patient survey[39] may reflect differences in patient characteristics in the survey population between those who have recently used BIs and those who have not recently used BIs. In this case it would not be appropriate to apply it only to those having BIs in the model as it is related to the population and not the current treatment. Furthermore, although the survey did ask about oral medications, the number reporting use of oral PPS was considered by the company to be insufficient to robustly include a covariate for PPS treatment in the mapping model.[39] Therefore, it is not possible to know if there is a similar decrement associated with taking PPS that could not be detected in the survey.

[redacted]

[redacted] The ERG decided to use the regression including age and ICSI score but not BI usage in their base-case analysis as the ERG was not satisfied that [redacted]

The EQ-5D values for responders and non-responders are based on estimates of median ICSI scores for responders and non-responders. These have been calculated by assuming that ICSI scores in the PPS arm of the RCT by Sant *et al.* (2013)[17] are normally distributed and that all patient who respond have ICSI scores that are lower (i.e. better) than all patients who do not respond (see Figure 18 of the CS). The ERG notes that the company were unable to provide any data to support these because they do not hold any relevant patient-level trial data (see company response to clarification question B5).[1] Based on these assumptions, the ICSI score for the median responder and the median non-responder was calculated from the normal distribution of the ICSI scores.

The ERG has concern with the assumptions made when relating GRA response to ICSI. The company has effectively assumed a step function such that all patients who have a change from baseline to Week 24 of greater than (approximately) -4.1 in ICSI are considered as non-responders and all patients who have a change from baseline to Week 24 of less than (approximately) -4.1 in ICSI are considered as responders and that this applies irrespective of treatment (CS, pages 104-105). The ERG suggests that it is unlikely that such a dichotomy according to baseline ICSI will be true or that there will be no treatment effect. In addition, the ERG has additional concerns with the analysis as implemented by the company:

- The company assumes that the underlying model for the ICSI data is a normal distribution without providing any justification for this.

- The assumptions regarding the 33.9% (20/55) GRA response rate, and the sample mean and standard deviation for the change from baseline to week 24 ICSI from Sant *et al.*, 2003[17] ignore uncertainty in their estimates.
- The absolute central estimates of ICSI response for non-responders and responders were estimated by adding the median estimates (-1.11 for non-responders and -5.85 for responders) to a baseline response. The ERG suggests that means would be more appropriate than medians, which it estimates to be -6.33 and -0.76 approximately for responders and non-responders, respectively. The ERG notes that when the company did this it had a minimal impact on the ICER (see response to clarification question B6),[1] although this scenario analysis did not address the ERG's concern that all responders are assumed to have higher ICSI scores than all non-responders.

The same ISCI scores were assumed to apply to responders in the BI and BSC arms of the model. This was done to ensure that the benefits received by responders compared to non-responders were consistent across the model. The ERG considers that whilst this is a pragmatic approach which simplifies the model inputs, it is implausible to assume that all responders have the same degree of response. Given that the company states in its rationale for using a DES structure, "*As well as considering response, the DES allowed the incorporation of evidence on likely magnitude of response based on a continuous scale"*, it seems fairly crude to then reduce the model to one based on a binary response / no response outcome, with identical benefits assumed for all responders.

The ERG noted that utility values in non-responders were generally [redacted] than the utility values pre-response assessment which were based on baseline ICSI scores. It may be reasonable that there is some [redacted] in ICSI scores in those patients who do not have a sufficient reduction in symptoms to be classed as a responder, and therefore there is a predicted [redacted] in utility for non-responders at 6 months. However, the utility values for non-responders after 6 months of treatment are being applied in the model to patients who discontinue treatment after being classed as non-responders. Therefore, it would seem reasonable that [redacted] and it would be more appropriate to assume that non-responders return to their baseline utility value unless they switch onto another active treatment.

The ERG noted that the pre-response assessment utility value based on baseline ICSI scores is being applied as a constant value during the first 6 months. This may be considered conservative if there is some symptomatic benefit from the day treatment is started. However, the ERG's clinical experts advised that the treatment effect is known to build slowly over time for both PPS and BIs, and therefore

the company's assumption that utility values for responders are not updated until 6 months is reasonable.

Finally, the ERG notes that the utility values in the model are not adjusted for age-related utility decrements. The ERG notes that the highest utility value applied in the model [redacted]. However, the ERG considers that it would have been preferable to either have capped the utility values at the values for age-matched general population norms in the company's lifetime horizon or to have estimated a proportional utility decrement relative to general population norms which could then be applied to age-related general population norms in the model. Furthermore, the application of constant utilities across time appears to contradict the evidence from general population studies that utilities generally decline with age. The ERG accepts that it is technically more difficult to apply age-related utility decrements within a DES model than within a state transition model, because utility values can only be updated at the point that events occur in a DES rather than every cycle in a state transition model. However, the ERG notes that age-adjustment of utilities can be achieved using either dummy events which update the utility values at regular intervals (say every 5 years), or by assuming a linear change in utilities between the previous and the current event and using this assumption to estimate the average utility in the period since the last event.

5.2.10 Resources and costs

The costs included in the model are summarised in Table 20 and the costs over time for patients having different model trajectories are plotted in Figure 10. It should be noted that the graphs in Figure 10 illustrate the equivalent costs per annum (i.e. the actual costs accrued in the first 6 months are doubled to see their size relative to costs accrued per annum in later periods) and the example for a patient who discontinues assumes that they do so at exactly 7 years whereas patients can discontinue anytime from 6 months to 20 years and the exact time varies from patient to patient.

Table 20: Summary of costs applied in the company's model

Description of cost	Annual costs*	Source
Disease-related costs for pre-response assessment (PPS/BIs/BSC)	[redacted]	Regression for costs as a function of ICSI based on resource use reported in patient survey[39] combined with NHS reference costs[45]
Disease-related costs in responders (PPS/ BI / BSC)	[redacted]	
Disease-related costs in non-responders who have switched to second-line BIs (a proportion of whom are assumed to respond to second-line BIs).	[redacted]	
Disease-related costs in patients on BSC after non-response to either PPS or BSC	[redacted]	
PPS drug treatments (pre-response and responders up to discontinuation)	[redacted]	Company[1]
BI as first-line treatment pre-response assessment - 9 administrations in 6 months with acquisition cost of £88.03 for BI cost of £183.37 for administration	[redacted]	MIMS[47] for list prices of medical devices and NHS reference costs[45] for administration
BI as first-line treatment in responders - 13 administrations in a year with acquisition cost of £88.03 for BI cost of £183.37 for administration	£3,535	
Drug costs for BIs as first-line p.a. 13 administrations** in a year with acquisition cost of £86.14 for BI cost of £183.37 for administration	£3,510**	

* except first-line BI pre-response check which is given as per 6 months

** updated by company in revised model post clarification process

Figure 10:

The three main types of resource use incorporated in the model are: (i) acquisition costs for PPS and BIs; (ii) administration costs for BIs, and (iii) disease-related costs. The latter is assumed to be related to disease severity as measured by the patient's ICSI scores. Data from the patient survey were used to estimate the relationship between costs in the previous 6 months and ICSI scores.[39] This relationship was used to estimate annual costs for responders and non-responders using the ICSI scores previously calculated for estimating utility based on ICSI. Again, as when calculating utilities, age was also included in the regression for costs, but the costs were calculated based on patient age at the start of the model and were not updated as patients aged in the model. The main difference between the approach used for utility and that used for resource use was that no explanatory term related to previous BI use was included in the regression linking ICSI scores to health care costs.

It should also be noted that the company attempted to remove any double counting of costs directly related to interventions. However, in the survey, patients were asked separately about hospital visits and treatments received without any information being gathered on whether the resource use was related to treatments received.[39] Therefore, it is possible that treatment-related resource use has not been adequately excluded as intended. This may mean that disease-related costs are over-estimated in the model.

In calculating the overall cost in the previous 6 months from the survey results, the company applied HRG costs to the resource use data.[39, 45] In several cases, it was unclear how the various HRG costs were selected and why other values were not applied. For example, the HRG cost applied for hospital admissions is the weighted mean across elective, non-elective and day-case admissions for that HRG code. In their response to clarification question B25, the company stated that, [redacted] The data collected [redacted] do not appear to have been used to inform the average HRG cost for hospital admission.

The ERG asked their clinical experts whether patients with poorer disease control, and therefore higher ICSI scores would be likely to incur greater resource use and whether the types of resource use reported in the patient survey (Table 49 of the CS)[1] were typical based on their experience. The ERG's clinical experts agreed that patients with poor symptom control may be more likely to access NHS services, but these were likely to be outpatient services rather than inpatient admissions or emergency department (ED) attendances. One clinician noted that the incidence of GP appointments may increase if the patient

does not have easy access to outpatient services. The ERG noted that whilst [redacted] of the costs in Table 49 of the CS[1] were related to outpatient visits, the proportion relating [redacted] respectively. The ERG was not convinced that these costs were necessarily related to IC/BPS. In particular, the inclusions of costs [redacted]. The ERG was concerned that no attempt had been made to estimate the costs in patients with IC/BPS relative to matched controls without IC/BPS. The ERG's concern is that the disease-related costs have been overestimated as not all of the resource use reported in the survey is attributable to IC/BPS.

A comparison of the HRG costs applied by the company (in Table 49 of the CS) and those preferred by the ERG is provided in Appendix 1. The ERG's concern here is that disease-related costs may have been overestimated in the model, but based on the comparison presented in Appendix 1 any overestimation is likely to be small at around 6% of the total cost estimated by the company.

None of the individual HRG costs are applied directly in the model. Instead the model inputs are based on the outputs of the regression, with the regression coefficient for ICSI score being key in determining the difference in costs between treatment arms. The ERG was not able to revise the HRG costs and update the regression analysis to re-estimate the regression coefficient for ICSI score without access to the full patient survey data. Therefore, it was not possible for the ERG to quantify the extent of any bias introduced from the choice of HRG costs. Instead the ERG explored whether the relationship between ICSI scores and resource use was an important determinant of cost-effectiveness by removing the dependence of resource use on ICSI scores in a scenario analysis (see exploratory analysis 3 in section 5.3).

The drug costs for PPS were provided by the company. The acquisition cost for BIs was based on the mean cost for two preparations of sodium hyaluronate, weighted using their market share. Prices for bladder instillations were generally taken from MIMS,[47] but these were cross-checked by the ERG with the NHS Electronic Drug Tariff (Feb 2019). The exception was Uracyst where the CS[1] stated that the price was sourced from the manufacturer and consequently this price could not be verified by the ERG.

No costs associated with monitoring or administration were applied to patients receiving PPS. The ERG's clinical experts generally agreed that patients on oral PPS would not require more intensive monitoring than patients not having oral PPS, as patients with IC/BPS would generally be seen every 3 to 6 months in clinic irrespective of whether they were on oral PPS treatment.

The cost for administration of a BI was based on the HRG for "Introduction of a therapeutic substance into the bladder". The company applied the mean cost across all types of care, rather than applying the specific cost for day case or outpatient procedures. The clinical advisors to the ERG stated that BIs are

commonly given as outpatient procedures, although one also stated that they were sometimes done as day-case procedures. The costs for the relevant HRG code are £151 for outpatient and £223 for day-case procedures, with a weighted mean of £185, which is close to the cost applied in the company's model. However, given that the majority of the clinical experts reporting BIs being administered as outpatient procedures, the ERG conducted a sensitivity analysis applying this cost (see ERG sensitivity analysis 4 in section 5.3).

In their base-case analysis, the company assumed that no patient would self-administer their BIs, although a self-administration rate of 10% was explored in a scenario analysis. The ERG asked their clinical experts what their experience was regarding patients self-administering BIs. There appeared to be significant variation in usual practice, with two clinical experts suggesting it was not routine practice for patients to self-administer and two reporting that a high proportion (64% and 80%) are able to self-administer once they have been trained to do so. The ERG therefore conducted a scenario analysis exploring the impact of high rates of self-administration of BIs on the cost-effectiveness of PPS relative to BI (see ERG sensitivity analysis 5 in section 5.3).

The company assumed that first-line BIs would be given every week for 4 weeks followed by every 4 weeks thereafter. They also conducted a sensitivity analysis exploring the impact of assuming administration every 6 weeks after the first month. The ERG asked their clinical experts what the frequency of BIs was in routine clinical practice. There did not seem to be a consistent protocol for the frequency of BI administration, although all of the clinical experts agreed that the frequency of administrations would be weekly initially and would then reduce. Some stated that the interval between instillations would be dependent on the maximum interval the patient could tolerate and in some patients the interval could be as long as 2-3 months depending on response. It was also noted by several clinical experts that patients may discontinue once their symptoms are under control and then they may return several years later after experiencing a flare-up of symptoms. Overall, the ERG considered that treatment frequency for BIs was likely to be higher than 6-weekly in the first year of treatment, but the average frequency was likely to be lower than 4-weekly in the long-term. The ERG decided to implement 6-weekly administrations of BIs from 1 years onwards for first-line BIs and for all patients receiving second-line BIs in their base-case scenario (see ERG exploratory analysis 2 in section 5.3).

Although the NICE scope for this STA explicitly states that the economic modelling should include the costs associated with diagnostic testing for glomerulations or Hunner's lesions in people with bladder pain syndrome who would not otherwise have been tested, the company's model does not incorporate any costs for cystoscopy because the CS argues that cystoscopy is carried out in all patients as part of the standard diagnostic pathway.[1] The ERG is satisfied that this is reasonable based on the advice provided by their clinical experts who stated that IC/BPS is generally a 'diagnosis by exclusion', and

cystoscopy is routinely used to exclude other conditions with similar symptoms before the diagnosis of IC/BPS is made.

The ERG notes that no adverse events are included in the economic model although it is stated in several places in the CS that BIs are associated with UTIs (see pages 34-36 of the CS). The ERG asked their clinical experts whether UTIs were likely to significantly impact either costs or HRQoL and were reassured that UTIs associated with BIs were usually easily avoided or easily treated if they occurred. The ERG considered that the omission of AEs from the model was unlikely to have significantly biased the estimates of cost-effectiveness.

5.2.10 Time to treatment discontinuation

The ERG noted that in the model, some patients are still on first-line treatment at 20 years and patients are able to stay on second-line treatment indefinitely. The ERG asked their clinical experts about the likely rate of treatment discontinuation from treatment. In general, there was agreement that some patients would come off treatment after a period of successful response but others would need long-term treatment for IC/BPS. One clinical expert stated that patients generally do not stay on treatment for 10-15 years. One clinical expert noted that it would be unlikely for 18% of patients to remain on the same treatment for 20 years, as predicted by the company's base-case model. Based on these responses, the ERG is concerned that the model may overestimate lifetime treatment costs for patients.

The ERG reviewed the study by Hanno *et al.*(1997)[27] that was used by the company to determine time to treatment discontinuation for both PPS and first-line BIs. Patients in this open-label "physician's usage" study had to provide data and receive medical assessments every 3 months. They also had to pay for the medication themselves. Although Hanno *et al.* (1997) state that the minimum duration of treatment was 3 months and the maximum was 35 months, this appears to relate only to patients included in the efficacy assessment.[27] Data on treatment discontinuation in Table II of Hanno *et al*, appear to be provided for all subjects with follow-up from 0 to 60+ months, with the study described as having run from 1986 to 1996. [27]

In response to a request for clarification, the company provided additional information on the dataset extracted from Table II of Hanno *et al.*(1997)[27] and used in the company's survival analysis (see company response to clarification questions B10 to B12).[1] The number of patients known to have discontinued in the company's dataset matched the sum total of those reporting their reason for discontinuation as being "adverse event" or "lack of efficacy" (column E of Table 21). This was less than the total number known to have discontinued (column D of Table 21).

The ERG did not agree with the company's interpretation of the data presented by Hanno *et al.* (1997)[27] The ERG considers that it would have been more reasonable to include all patients known to have discontinued (column D of Table 21) when estimating the survival function for time to discontinuation. Furthermore, the ERG noted that the totals given for all reasons in Table II of Hanno *et al.*, including the "other" category, did not add up to the total number of discontinuations, suggesting that data on the reasons for discontinuation were incomplete. The ERG therefore did not believe that it was reasonable to allocate some patients recorded as having discontinued to be censored based on their reason for discontinuation. In addition, the company assumed a discontinuation time of 90 months for those reported to have follow-up of 60+ months. The ERG preferred to assume that these patients were censored at 60 months as their exact time of discontinuation is not known.

The company's analysis excluded patients who discontinued in the first 6 months of treatment as they intended to estimate time to discontinuation from the response check at 6 months. The ERG was satisfied that it was reasonable to exclude these patients as the time to treatment discontinuation survival function is applied only from 6 months in the model (these patients have been excluded from Table 21 accordingly). However, the ERG noted that the dataset used in the company's survival analysis used time reported from starting treatment rather than time from completing 6 months of treatment.

The study separates those patients who have not formally discontinued into active and inactive patients, with inactive patients being those that did not have any shipments of the drug in the last year of the study. The company's analysis assumes that both active and inactive patients are censored at the end of their study participation. This seems somewhat inaccurate as inactive patients have discontinued in the sense that they have stopped receiving shipment of the drug. However, due to the poor reporting in Hanno *et al.*(1997)[27] it is difficult to determine how to categorise inactive patients in the survival analysis. The ERG therefore believes that the discontinuation data from Hanno *et al.* (1997)[27] should be interpreted with caution.

The ERG generated an alternative survival data set from the data presented by Hanno *et al.*,[27] with the following changes: time measured from 6 months; all patients recorded as discontinuers included as "failures" in the survival analysis (column D of Table 21) and all other patients categorised as being censored at their longest follow-up (column A minus column D of Table 21), including those whose discontinued after 60 months (column A of the last row of Table 21). Although the ERG prefers this interpretation of the data from Hanno *et al.*(1997) [27] the study is reported poorly and the correct interpretation is unclear.

Table 21: Summary of discontinuation data from Hanno *et al. (1997)*[27] restricted to those with at least months of study participation

Length of participation in months*	Total patients	Active	Inactive	All discontinued	Discontinued due to adverse event or lack of efficacy	Other reason for discontinuation**
Column indicator	A	B	C	D	E	F
6-12	353	83	15	255	129	108
12-18	166	46	10	110	43	57
24-36	116	37	3	76	33	37
36-48	149	63	8	78	30	41
48-60	88	40	6	42	12	22
60+	67	38	3	26	9	15

* interpreted by the ERG to mean maximum follow-up for that individual (ERG has excluded the data from Hanno *et al.*(1997)[27] for patients who participated for less than 6 months)

** the ERG has combined those reporting death, failed to return or "other" as their reason for discontinuation in column F

Table 22 shows the regression parameters for the company's survival analysis with the corresponding Kaplan-Meier data and fitted survival functions shown in Figure 11. The ERG re-analysed the data using their preferred dataset using STATA(version 15.0)[48] using the STATA function 'stset, dist()' for commonly used probability distributions (see Appendix 4 for details). The regression coefficients for the ERG's survival analysis are provided in Table 23 and Figure 12 shows the Kaplan-Meier data and fitted survival functions. The scale parameter for the exponential distribution (the company's preferred distribution) was 0.0074 when using the company's dataset (Table 22) and 0.0229 when using the ERG's preferred dataset (Table 23). Therefore, the rate of discontinuation was approximately 3 times higher when using the ERG's preferred dataset and the company's preferred model. The ERG explored the impact on the ICER of this higher discontinuation rate (see ERG's exploratory analyses section 5.3).

Table 22: Regression parameters for company's survival analysis of time to discontinuation data

Survival function	Scale	Shape	AIC	BIC	Mean time (months)	Median time (months)
Exponential	0.0074	NA	1556.23	1561.20	135.14	93.67
Weibull	0.0047	/ln_p= 0.1132	1553.26	1563.21	114.95	86.37
Gompertz	0.0093	/gamma= -0.0095957	1547.58	1557.52	NE	130.57
Loglogistic	4.4193	/lngamma= -.2789774	1523.13	1533.08	285.05	83.04
Lognormal	4.4347	/ln_sig= 0.2376	1479.71	1489.66	188.44	84.32

NA, not applicable; NE, not estimable

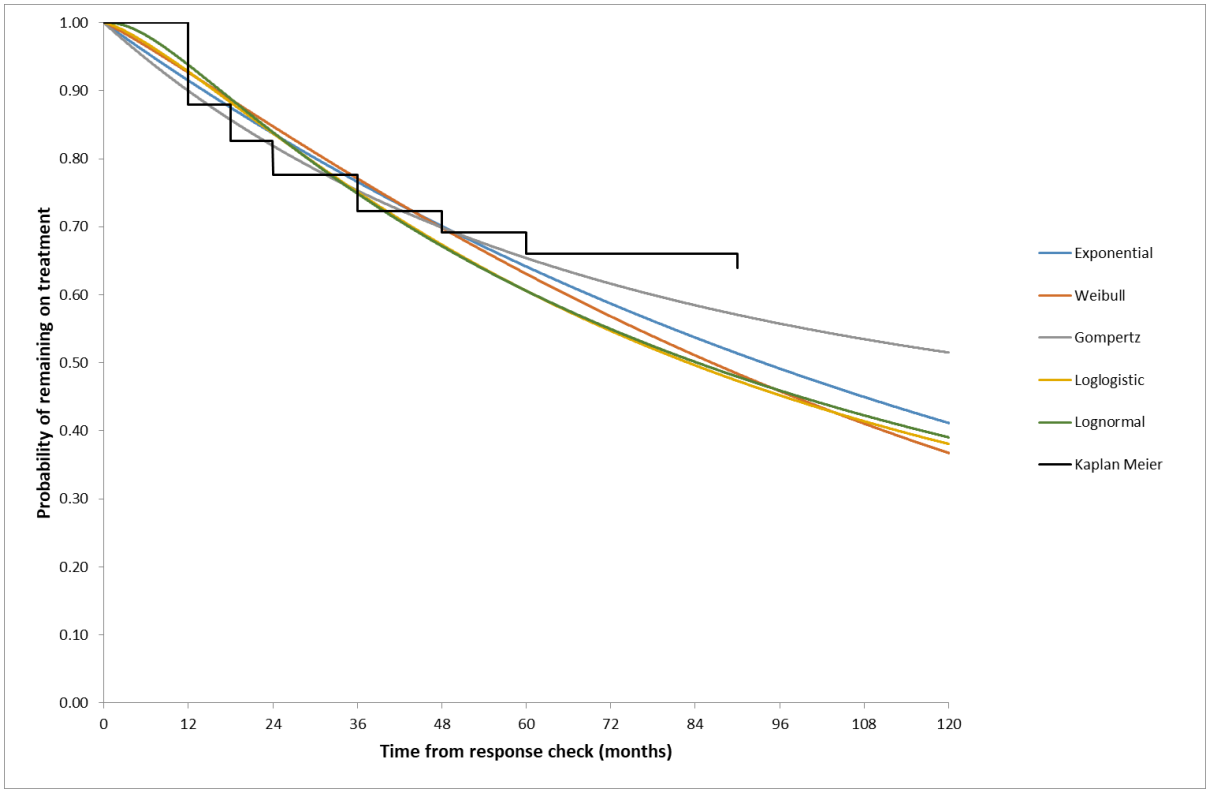


Figure 11: Company's time to treatment discontinuation parametric functions and Kaplan-Meier, reproduced by the ERG

Table 23: Regression parameters for ERG's survival analysis for time to discontinuation

Survival function	Scale	Shape	AIC	BIC	Mean time (months)	Median time (months)
Exponential	0.022874	NA	2659.28	2664.25	43.72	30.30
Weibull	0.021829	ln_p= 0.01329	2661.12	2671.07	43.32	30.34
Gompertz	0.02966	/gamma = -0.0143	2634.45	2644.39	NE	28.44
Loglogistic	3.273407	/ln_gam = -0.29674	2578.45	2588.39	85.38	26.40
Lognormal	3.302363	/ln_sig = 0.18185	2521.39	2531.34	55.80	27.18

NA, not applicable; NE, not estimable

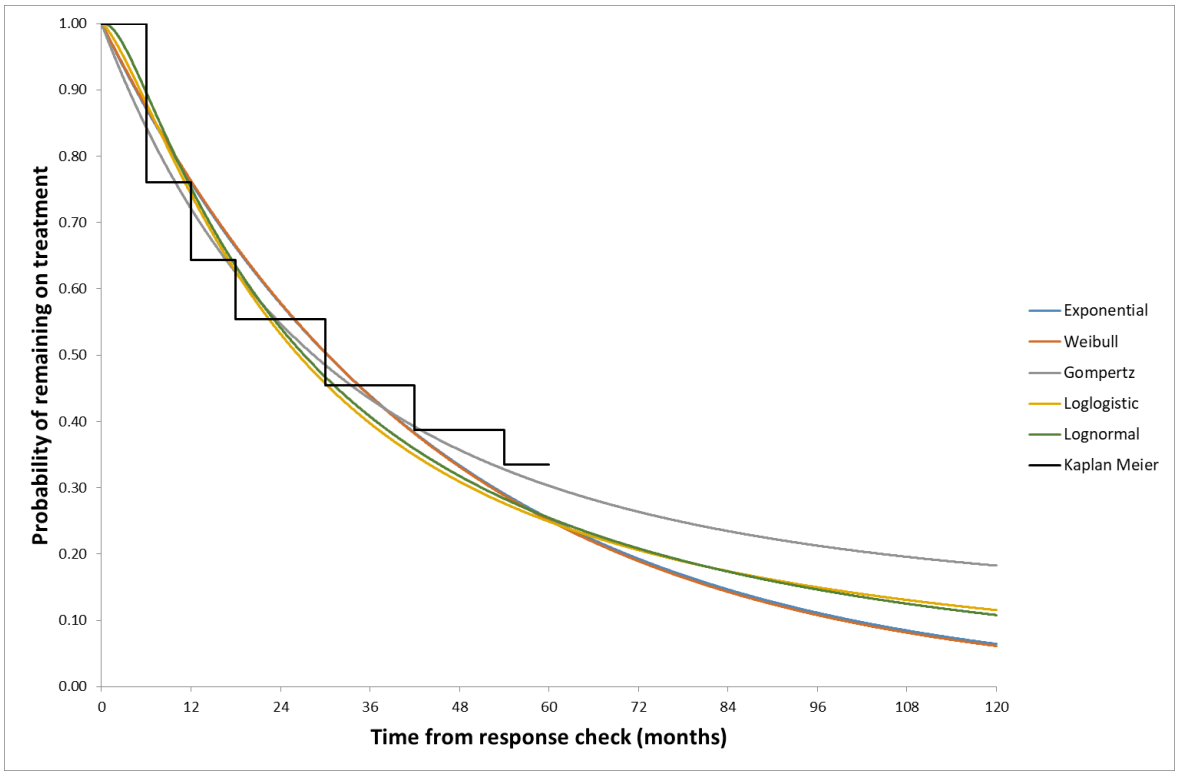


Figure 12: Time to treatment discontinuation parametric functions based on the ERG's preferred interpretation of the data from Hanno *et al.* (1997)[27]

The company's base-case uses the exponential survival function for the time to discontinuation (Figure 11). The ERG notes that the log normal distribution has lower AIC and BIC values in both the ERG's (see Table 23) and the company's analysis (see response to clarification question B13 and Table 22).[1] The log normal distribution predicts a longer mean time on treatment and a shorter median time on treatment than the exponential distribution, reflecting higher discontinuation rates initially which reduce over time. The ERG believed this better reflected the view of the clinical experts: that discontinuation rates would be high initially as some patients achieved resolution of their symptoms and came off treatment, but that discontinuation rates would fall over time, with a subset of patients staying on treatment long-term. The ERG explored the impact on the ICER of using the log normal distribution for time to treatment discontinuation in their exploratory analyses (see Section 5.3).

5.2.11 Mortality

No survival benefit is assumed in the model and mortality risks are constant between arms. The company calculates a normally distributed life expectancy from the data provided in the ONS life-tables.[42] The ERG were not satisfied with their explanation regarding how the SD for this distribution was calculated from the data provided in the ONS life-tables despite the company providing further details in response to a request for clarification (see responses to clarification questions B32, B33 and B34).[1]

The ERG was not satisfied with the company's assumption that life expectancy at a given age would be normally distributed. The company argued in their response to the clarification request that their rationale for using a normal distribution for life-expectancy was based on the example model provided with the NICE DSU's Technical Support Document on patient-level simulation (TSD15).[1, 49] Whilst such an assumption is used in the simple example model provided with TSD15, it is not recommended as the best method for sampling life expectancy from life tables within TSD15.[49] The ERG's preferred method is to use the OLS life tables data to generate an empirical distribution for life expectancy dependent on the starting age. However, because survival in the model is assumed to be identical for patients receiving PPS, BI and BSC, the ERG did expect any significant bias to have been introduced by the company's approach to modelling survival.

5.2.12 Company's approach to sensitivity analysis

The CS provides deterministic sensitivity analyses in the form of tornado diagrams, which examine the impact of raising and lowering individual parameters, and scenario analyses, which explore alternative data sources and model assumptions. The CS also provided a probabilistic sensitivity analysis (PSA) using the original model submitted by the company but results from the PSA were not provided for the revised model provided following the clarification request.

The ERG notes that the parameter ranges used to generate the tornado diagram were arbitrarily set at either ±10% or ±25% of the base-case value for all parameters except the discount rates (varied from 1% to 6%) and the time to discontinuation hazard (varied from 0.0065529 to 0.0083562). The ERG also notes that the original company model did not incorporate the parameter uncertainty associated with the regression used to predict utilities within their PSA. This was included in the revised model submitted following the clarification request (see response to clarification question B14)[1] but the method used to sample the regression coefficients using the variance-covariance matrix was not one familiar to the ERG. The ERG's preferred method for sampling regression coefficients, which are usually correlated, would be to assume that they follow a multivariate normal distribution which can be sampled using excel functions provided by the Centre for Bayesian Statistics in Health Economics (CHEBS).[50] The ERG compared the sampled utility values generated by the company's method with those generated using the CHEBs functions (for a fixed ICSI score). These are shown in Figure 13, where it can be seen that the distribution of utility values is much narrower when using the company's method. The ERG therefore concluded that uncertainty in the utility parameters is likely to have been underestimated in the company's PSA.

The ERG notes that in addition, several parameters have not been varied probabilistically within the PSA. These include the parameters for the survival functions used to estimate time to treatment discontinuation, the proportion of responders used to estimate median ICSI scores in responders and non-responders and the regression coefficients for the relationship between ICIS scores and resource use. The exclusion of these parameters from the PSA will also tend to underestimate the parameter uncertainty in the company's PSA.

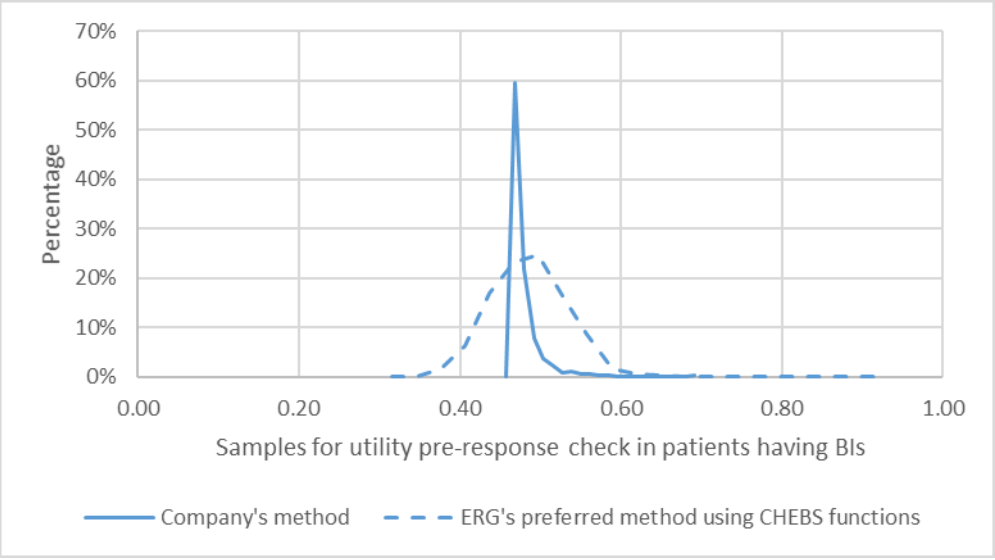


Figure 13: Comparison of utility values sampled as PSA inputs using the company method and the ERG's preferred method

The CS presents a scenario analysis in which a small percentage (2%) of those receiving BIs as subsequent treatment for a prolonged period go on to have a bladder procedure. This was implemented in the model by applying a fixed cost in the 10th year that patients receive second-line BIs. The cost of surgery was based on the weighted average of costs across eight different HRG codes. The scenario analysis did not adjust treatment-related or disease-related costs incurred following surgery but instead continued to apply the costs for BIs as second-line treatment until death or the model time horizon was reached. The scenario analysis also did not adjust QALYs to account for the impact of surgery on health outcomes.

The ERG considered that this scenario analysis lacked clinical face validity because it did not capture the impact of surgery on future utilities or costs and instead focused only on the one-off cost of the surgical procedure. However, it is unclear whether the ICER would increase or decrease if these factors were properly considered. Furthermore, the ERG did not understand why surgery was not an option for patients who have an inadequate response to BSC but who are unable to receive BIs. This would potentially bias the estimates of cost-effectiveness in favour of BSC under the company's current assumptions regarding surgery. However, the extent of any bias is likely to be small given that the company assumed that only 2% would go on to have surgical management. As the ERG's clinical advisors agreed that the frequency of surgical management for IC/BPS was low in current practice, the ERG did not conduct any exploratory analyses to explore the issues related to the modelling of surgical intervention in the scenario analysis as it was anticipated that the impact of any changes on the ICER would be small.

5.2.12 Cost effectiveness results

This section summarises the cost-effectiveness results presented in the CS. Following the clarification process, the company submitted a revised base case after rectifying a number of minor errors highlighted by the ERG. This section reports the updated base case results provided by the company.

Company's base-case analysis 1 (PPS versus bladder instillations)

Table 24 presents the estimates of cost-effectiveness generated using the company's revised model for the comparison of PPS versus bladder instillations. Compared to treatment with BIs, the probabilistic version of the model estimated that PPS would generate [redacted] additional QALYs at an additional cost of [redacted]; corresponding ICER of [redacted] per QALY gained. The deterministic model estimated a slightly lower ICER of [redacted] per QALY gained.

Table 24: Company's revised base-case results for PPS versus bladder instillations

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Probabilistic model					
[redacted] PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model					
[redacted] PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's base-case analysis 2 (PPS versus BSC):

For those patients who are not eligible for bladder instillations, due to them being inappropriate, poorly tolerated or unsuccessful, PPS is compared against best supportive care. Table 25 presents the base-case cost-effectiveness estimates of PPS versus BSC generated from the company's revised model. The probabilistic model estimates that PPS generates [redacted] additional QALYS in comparison to BSC, at an additional cost of [redacted]. This results in a much higher ICER than the PPS versus BI scenario of [redacted] per QALY gained. The deterministic version of the model estimated a slightly higher ICER of [redacted]

Table 25: Company's revised base-case results for PPS versus BSC

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Probabilistic model					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.13 Sensitivity analyses

The ERG notes that the following factors were significant drivers of cost-effectiveness based on the CS:

- Utilities in responders and non-responders

- Durability of response in responders to BSC (i.e. the time at which the treatment response recedes)
- Frequency of BI administration in the long-term
- Administration costs for BIs
- Inclusion of studies in broader BPS when estimating treatment effectiveness of PSS vs placebo
- Utilities and costs determined by ICPI instead of ICSI (particularly in PPS vs BSC)
- Application of baseline utilities and costs in non-responders
- Rates of self-administration of BIs
- Choice of time to treatment discontinuation curve (particularly in PPS vs BSC).

The company provided results of the deterministic and probabilistic sensitivity analysis within the original CS. However, updated versions of these were not provided following the company's update of their base-case model submitted with their response to the clarification letter. The PSA and DSA results presented in this section were generated by the ERG using the company's revised model.

Company's probabilistic sensitivity analysis (base-case analysis 1)

Figure 14 and Figure 15 show the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) for PPS versus bladder instillations. The probability that PPS produces more net benefit than BIs at willingness to pay thresholds of £20,000 and £30,000 per QALY gained is 0.54 and 0.61, respectively. Although the ERG notes that these estimates should be interpreted with caution given their concern that the parameter uncertainty has underestimated in the PSA (see Section 5.2.12).

Figure 14:

Figure 15:

Company's deterministic sensitivity analysis (base-case analysis 1)

The company presented the results of the DSA in the form of a tornado diagram, which was reproduced by the ERG using the company's revised model (Figure 16). Based on varying the parameters chosen in this analysis, the ICER is estimated to range from per QALY gained. The largest influences on the ICER were the utility of responders to both PPS and BI and administration costs of bladder instillations, both of which had a corresponding ICER above per QALY gained.

Figure 16:

Company's scenario analysis (base-case analysis 1)

The company conducted a number of scenario analyses in the original CS, which the ERG have updated using the revised model provided following the clarification process (see Table 26). The results of the scenario analyses suggest that the ICER is most sensitive to changes in parameters affecting the overall costs of bladder instillations, such as, the frequency of bladder administrations (post initial first month treatment) and bladder instillations being self-administered by the patient (implemented in the model through a reduction in the administration cost of bladder instillations). The ICER was also sensitive to using meta-analysed response rates for PPS that include two wider population trials; however, the populations included in these trials were outside of the NICE scope.

Table 26: Company scenario analysis for PPS versus bladder instillations, reproduced by the ERG using the company's revised model

Scenario	PPS costs	PPS QALYs	BI costs	BI QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case			**£71,641**	**7.771**			
ICPI based utilities and background costs			£70,754	8.106			

Utilities from literature - (Cervigni 2017)[30]	[redacted]	[redacted]	£71,641	5.358	[redacted]	[redacted]	[redacted]
Lifetime horizon	[redacted]	[redacted]	£105,935	11.383	[redacted]	[redacted]	[redacted]
Discounting 1.5%	[redacted]	[redacted]	£85,542	9.292	[redacted]	[redacted]	[redacted]
Using least expensive product for BI (subsequent treatment)	[redacted]	[redacted]	£68,737	7.771	[redacted]	[redacted]	[redacted]
10% self-administration of BIs	[redacted]	[redacted]	£68,136	7.771	[redacted]	[redacted]	[redacted]
3-month response check	[redacted]	[redacted]	£71,588	7.788	[redacted]	[redacted]	[redacted]
Time horizon - 5 years	[redacted]	[redacted]	£22,812	2.474	[redacted]	[redacted]	[redacted]
Time horizon - 10 years	[redacted]	[redacted]	£41,698	4.565	[redacted]	[redacted]	[redacted]
Time horizon - 15 years	[redacted]	[redacted]	£57,882	6.310	[redacted]	[redacted]	[redacted]
Surgery as part of subsequent treatment	[redacted]	[redacted]	£71,675	7.771	[redacted]	[redacted]	[redacted]
Response rate for PPS including 2 wider population clinical trials	[redacted]	[redacted]	£70,929	7.896	[redacted]	[redacted]	[redacted]
Frequency BI administrations (post 1st month) set to 6 weeks (base-case is 4 weeks)	[redacted]	[redacted]	£69,149	7.771	[redacted]	[redacted]	[redacted]
Weibull distribution for time-to-discontinuation data	[redacted]	[redacted]	£71,838	7.761	[redacted]	[redacted]	[redacted]
Log-normal distribution for time-to discontinuation data	[redacted]	[redacted]	£71,504	7.768	[redacted]	[redacted]	[redacted]

Company's probabilistic sensitivity analysis (base-case analysis 2)

The company's revised model suggests that the probabilistic ICER for PPS versus BSC is [redacted] per QALY gained; this is lower than the company's deterministic ICER [redacted] per QALY gained). Figure 17 shows the cost-effectiveness plane for PPS versus BSC, with the corresponding CEAC shown Figure 18. These show that for those patients unable to receive bladder instillations, the probability that PPS produces more net benefit than BSC at willingness to pay thresholds of £20,000 and £30,000 is 0.15 and 0.33, respectively. Although the ERG notes that these estimates should be interpreted with caution given their concern that the parameter uncertainty has underestimated in the PSA (see Section 5.2.12).

Figure 17: [redacted]

Figure 18: [redacted]

Company's deterministic sensitivity analysis (base-case analysis 2)

The company's revised model DSA (Figure 19) found that the ICER was strongly impacted by changes in the utility of non-responders for both PPS and BSC with both higher and lower values, lowering the ICER significantly. However, changes in the utility of responders to PPS to the lower value used in the DSA resulted in much higher ICER [redacted]).

Figure 19: [redacted]

Company's scenario analysis (base-case analysis 2)

Table 27 shows the results of the scenario analysis for PPS versus BSC, reproduced by the ERG using the company's revised model. The results of the scenario analyses suggest that the ICER is particularly sensitive to changes in the duration of the receding effect for the placebo response of BSC (ICER ranging from [redacted] per QALY gained). Utilities used in the model also had a large impact on the ICER, with utilities based on Cervigni 2017[30] largely reducing the ICER to [redacted] per QALY whilst basing utilities and background costs on ICPI scores as opposed to ICSI reduced the ICER to [redacted] per QALY gained.

Table 27: Company scenario analysis for PPS versus BSC, reproduced by the ERG using the company's revised model

Scenario	PPS costs	PPS QALYs	BSC costs	BSC QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	£23,448	8.017	[redacted]	[redacted]	[redacted]
ICPI based utilities and background costs	[redacted]	[redacted]	£23,017	8.030	[redacted]	[redacted]	[redacted]
Utilities from literature - (Cervigni 2017)[30]	[redacted]	[redacted]	£23,448	3.647	[redacted]	[redacted]	[redacted]
Lifetime horizon	[redacted]	[redacted]	£34,487	11.802	[redacted]	[redacted]	[redacted]
Discounting 1.5%	[redacted]	[redacted]	£28,039	9.592	[redacted]	[redacted]	[redacted]
BSC effect receding at 6 months	[redacted]	[redacted]	£23,501	8.007	[redacted]	[redacted]	[redacted]
BSC effect receding at 5 years	[redacted]	[redacted]	£23,055	8.097	[redacted]	[redacted]	[redacted]
BSC effect not receding	[redacted]	[redacted]	£22,344	8.167	[redacted]	[redacted]	[redacted]
Baseline utility and background costs given to non-responders	[redacted]	[redacted]	£26,368	7.595	[redacted]	[redacted]	[redacted]
3-month response assessment	[redacted]	[redacted]	£23,395	8.025	[redacted]	[redacted]	[redacted]
Time horizon - 5 years	[redacted]	[redacted]	£7,484	2.544	[redacted]	[redacted]	[redacted]
Time horizon - 10 years	[redacted]	[redacted]	£13,742	4.690	[redacted]	[redacted]	[redacted]
Time horizon - 15 years	[redacted]	[redacted]	£19,012	6.496	[redacted]	[redacted]	[redacted]
Response rate including 2 wider population clinical trials	[redacted]	[redacted]	£23,436	8.020	[redacted]	[redacted]	[redacted]
Weibull distribution for time-to-discontinuation data	[redacted]	[redacted]	£23,448	8.017	[redacted]	[redacted]	[redacted]
Log-normal distribution for time-to discontinuation data	[redacted]	[redacted]	£23,448	8.017	[redacted]	[redacted]	[redacted]
Surgery – same as base-case as not affected							

5.2.14 Model validation and face validity check

The ERG validated the implementation of the sampling of time to discontinuation by plotting the cumulative survival functions from the samples generated by the VBA code. In doing so, it was identified that the survival function for the Weibull distribution was not correctly implemented in the company's original base-case. This was due to an incorrect translation between two different parameterisations of the Weibull survival function. However, the company corrected this in their model submitted with their response to the clarification request,[1] and so this error does not affect the results presented in Sections 5.2.12 and 5.2.13.

The ERG validated the VBA code by stepping through the code for patients with different trajectories (i.e. responders and non-responders in each arm), by using the locals window to observe the changes to the costs and QALYs at each event and by checking lifetime costs and QALYs for selected individual patients using the patient-level model output data. In doing so, it was identified that the time to response check was being converted from months to years for all instances where it was being used in the VBA except when calculating the "other costs" accrued between the time of the response check and the time of discontinuation. This resulted in some cases in the cost per annum being multiplied by a negative period of time. The company corrected this for the VBA code used to run the base-case analysis in their model submitted with their response to the clarification request,[1] and so this error does not affect the results presented in Sections 5.2.12 and 5.2.13. However, the correction was not carried through to the separate VBA subroutines used to run the scenario analysis and therefore these were corrected by the ERG (see Appendix 2 for details of the correction).

The ERG checked the patient-level results against the expected values for individual patients with various trajectories based on the ERG's understanding of the CS.[1] The ERG was satisfied that the model was behaving in the expected manner at the individual level.

The ERG rebuilt the model as a state-transitions model to determine whether this was feasible without altering the conceptual model and to provide an external validation of the company's DES approach. The ERG was satisfied that the ICERs were sufficiently close to exclude there being a significant unidentified error in the DES or a significant error in the ERG's understanding of the conceptual model. The ERG notes that it was possible to rebuild the model as a simple state-transition model without the need to include any non-Markovian fixes or time-dependent transition probabilities when using the exponential time to treatment discontinuation curve. However, implementation of alternative parametric forms with time varying risks of discontinuation, such as the log normal, would have required the use of time-dependent transition probabilities. The ERG considers that a state-transition approach would have been more parsimonious but that this does not mean that the DES approach is incorrect.

The DES model did not allow for the reporting of costs and QALYs according to the individual's trajectory through the model, which would be analogous to the costs and QALYs accrued in various health states for a state transition model. To address this, the ERG identified the proportion of the QALY gain associated with additional patients who respond in PPS vs BSC by examining patient-level QALY gains. It found that only 53% of the QALY gains for PPS versus BI and 53% of the QALY gains for PPS versus BSC were accrued due to the higher rate of response achieved by PPS. In the comparison against BI, the remainder of the QALY gains were associated with the utility decrement for "previous BI usage" from the regression analysis of the patient survey data.[1] In the comparison against BSC, the remainder of the QALY gains were related to the assumption that responders to BSC benefit for a maximum of 12 months whereas responders to PPS benefit until they discontinue.

To check the internal validity of the model, the ERG calculated the proportion of responders from the patient-level results and noted that the average rate of responders was 33.8%, 22.8% and 16.5% based on the first 10,000 patients sampled whereas the input values for these parameters were 33.1%, 22.0% and 15.8% respectively. The ERG suspected that this slightly discrepancy was due to the stochastic nature of the model whereby stable outputs are only achieved if sufficient patients have been simulated. The ERG conducted a large run of 100,000 patients and found that the ICERs based on the first 10,000 patients was within £500 per QALY of the ICER based on the larger run of 100,000 patients. The ERG was therefore satisfied that the results provided by the model, which were based on 10,000 patients, were sufficiently accurate for decision making.

The ERG noticed that there were a number of minor discrepancies between the values provided in the CS[1] and those included in the model (e.g. ICSI scores in Table 41, mean and standard deviation for time to death in Table 57), but the correct values had been included in the model. The ERG also noticed a minor discrepancy between the source study and the values used in the CS[1] for the mean starting age based on the data from Sant *et al.* 2003,[17] but the difference was too small to make any difference to the model (45.57 years vs 45.41 years with the life-expectancy data being based on patients aged 45 years).

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG's exploratory analysis- methods

Following concerns highlighted in Section 5.2, the ERG undertook seven sets of exploratory analyses by implementing changes to the company's revised model. Two of these changes were not applicable to the comparison of PPS against BIs because they related to the modelling of BSC and one of these changes was not applicable to the comparison of PPS against BSC because it related to the modelling of BI. Combining all of the changes applicable to each comparison forms the ERGs preferred base-case for that comparison. The seven changes are discussed in turn below.

Exploratory analysis 1: Use of all discontinuations from Hanno et al (1997)[27] *for survival analysis of time to treatment discontinuation*

As noted in Section 5.2.10, the ERG had concerns with how the time to discontinuation data provided by Hanno *et al.*[27] had been interpreted by the company when estimating the cumulative probability of remaining on treatment. The ERG therefore conducted a scenario analysis which incorporates their preferred interpretation of the data which include: using all patients know to have discontinued from the Hanno *et al.* (1997) study;[27] censor patients at 60 months for those reported to have follow up for 60+ months and time measured from 6 months. In exploratory analysis 1, the ERG used the company's preferred parametric function which was the exponential. The ERG's preferred parametric function is considered in exploratory analysis 7.

Exploratory analysis 2: Switch to 6-weekly dosing for first-line BIs after first year of treatment and 6-weekly for all 2nd line BIs

The ERG believes that long-term dosing of BIs is likely to be overestimated in the company's model and that dosing with BIs will decrease in the long-term (Section 5.2.9). The ERG therefore implemented a switch to 6-weekly dosing from year 1 for first-line BI treatment and 6-weekly BI treatments for all those receiving BI as subsequent treatment.

Exploratory analysis 3: Use regression for utility based on ICSI scores which excludes term for prior usage of BI

As noted in Section 5.2.9, the ERG believes that applying a utility decrement to patients who responded to having current/recent treatment with bladder instillation is inappropriate, as the differences detected through the survey may reflect differences in patient characteristics as opposed to differences associated directly with treatment with bladder instillations. In additional, it was unclear if there is any decrement associated with PPS treatment and the ERG was not satisfied with how missing data for recent treatment with bladder instillations in the survey had been handled. Therefore, the ERG applied the company's alternative regression which included coefficients for age and ICSI, but no coefficient for bladder instillations (model identified as "Twopm 1" in Table 86 of the CS).

Exploratory analysis 4: Use of a lifetime horizon

As the survival function predicts that some patients will remain on treatment at the end of the 20-year time horizon, the ERG used a lifetime horizon to ensure all costs and benefits associated with treatment are captured within the model.

Exploratory analysis 5: Return to baseline utilities and costs for non-responders when BSC is second-line option (PPS versus BSC scenario only)

The ERG does not believe that it is clinically valid to assume that patients not responding to BSC or PPS would benefit from an improvement in ICSI scores, and an associated improvement in both cost and utilities, for the remainder of their lifetime. Therefore, the ERG instead assumed that patients return to baseline utility and cost levels following no response to BSC.

Exploratory analysis 6: Switch off receding baseline response for BSC (PPS versus BSC scenario only as already implemented in PPS versus BI base-case)

As noted in Section 5.2.7, the ERG believe it is inconsistent to assume that the placebo response for BSC would cease at 12 months yet responses for BI and PPS remain durable for the remainder of treatment. The ERG believed a more consistent approach would be to apply the same durability of response for all arms and therefore removed the receding baseline response for BSC.

Exploratory analysis 7: Use of log-normal function to model time to discontinuation

Based on the results of statistical fit (AIC and BIC), time to treatment discontinuation was modelled using a log-normal survival function for the dataset based on the ERG's preferred interpretation of the time to discontinuation data presented by Hanno *et al.*[27] (see exploratory analysis 1).

5.3.2 Results of ERG's exploratory analysis

All of the results presented below have been generated using mean parameter inputs (i.e. using the 'deterministic' rather than the PSA version of the model).

ERG's preferred analysis 1 (PPS versus bladder instillations)

Results for PPS versus BIs are presented in Table 28 as individual changes to the company's revised model, with all changes (1 to 7) then combined to give the ERGs preferred base-case.

Table 28: Results of ERG's preferred analysis for PPS versus BI

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base-case (revised base-case model, deterministic)					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 1: Use of all discontinuation data for survival analysis inputs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 2: Switch to 6 weekly dosing for first line BIs after first year of treatment and 6 weekly for all 2nd line BIs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 3: Utility regression used excludes 'had BI' coefficient					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 4: Lifetime horizon					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 5: Return to baseline utilities and costs for non-responders when BSC is second line option (*Not applicable)*					
ERG exploratory analysis 6: Switch off receding baseline response for BSC (*Not applicable)*					
ERG exploratory analysis 7: Log-normal distribution for time to discontinuation					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (including all ERG individual amendments 1-7)					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The updates made to the time to discontinuation data (log-normal distribution and ERG preferred survival analysis inputs) do not have a large impact on the ICER, but both result in a more favourable ICER relative to the company's revised base-case. The application of a lifetime horizon resulted in a slight increase in the ICER; however, the largest increases resulted from individual changes to bladder instillation dosing (exploratory analysis 2, ICER [redacted] per QALY gained) and the application of the utility regression excluding bladder instillation use (exploratory analysis 3, ICER [redacted] per QALY gained). The ERG's preferred base-case, which combines all individual changes (exploratory analyses 1-7), resulted in an ICER of [redacted] per QALY gained; this is significantly higher than the company's revised base-case of [redacted] per QALY gained.

ERG's preferred analysis 2 (PPS versus BSC)

Results for the ERG's exploratory analysis for PPS versus BSC are shown in Table 29, presented as individual changes to the company's revised model, with all changes then combined to give the ERGs preferred base-case.

Table 29: Results of ERG's preferred analysis for PPS versus BSC

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base-case (revised base-case model, deterministic)					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 1: Use of all discontinuation data for survival analysis inputs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 2: Switch to 6 weekly dosing for first line BIs after first year of treatment and 6 weekly for all 2nd line BIs (*not applicable)*					
ERG exploratory analysis 3: Utility regression used excludes 'had BI' coefficient					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 4: Lifetime horizon					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 5: Non-responders receiving BSC return to baseline utility and cost values					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 6: Receding effect of placebo response switched off					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG exploratory analysis 7: Log-normal distribution for time to discontinuation					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base-case (including all ERG individual amendments 1-7)					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The use of the ERG's preferred survival analysis inputs increased the ICER from a base-case of [redacted] per QALY gained. This was a much greater impact than observed in the PPS vs BI comparison because in this scenario only the PPS arm is altered by the time to discontinuation data. When using the ERG's preferred interpretation of the data from Hanno *et al.*,[27] the switch from the exponential to the log-normal parametric function had a small impact and decreased the ICER slightly relative to the company's preferred choice of the exponential function (scenario 7 compared to scenario 1). Non-responders returning to baseline utility values (exploratory analysis 5) resulted in a decrease in the ICER to [redacted] per QALY gained. The assumption regarding the receding effect of the placebo response for BSC was shown to be the key driver of the ICER (exploratory analysis 6). The ERG's preferred

base-case combining all scenarios (1-7) results in a substantially higher ICER of [redacted] per QALY gained compared to the company's revised base-case analysis.

5.3.3 Additional sensitivity analysis undertaken using the ERG's preferred base-case model

Additional sensitivity analyses were also undertaken using the ERG's preferred base-case model in order to explore different assumptions made within the model:

- All costs based on baseline ISCI scores removing the relationship between response to treatment and costs
- Explore different baseline response rates through changes to response rate of BSC based on upper and lower confidence intervals reported in the literature.
- Urology outpatient cost used for administration of bladder instillations (PPS versus BI only)
- 80% of patients self-administer bladder instillations (PPS versus BI only)

Again, all of the results presented below have been generated using mean parameter inputs (i.e. using the 'deterministic' rather than the PSA version of the model).

Additional sensitivity analysis results: PPS versus BI

Table 30: Additional sensitivity analysis undertaken using ERG preferred base-case model for PPS versus BI

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred base-case					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 1: All costs based on baseline ISCI scores removing the relationship between response to treatment and costs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 2: Response rate of BSC set to 5% (equal to lower confidence interval from Mulholland *et al.* 1990)[14]					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 3: Response rate of BSC set to 32% (equal to upper confidence interval from Parsons *et al.* 1987)[16]					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 4: Urology outpatient cost used for administration of bladder instillations					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 5: 80% rate of self-administration of bladder instillations					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30 presents the results for the ERG's additional sensitivity analysis conducted using the ERG's preferred base-case model. Removing the assumption regarding a relationship between patients' response to treatment and healthcare costs (sensitivity analysis 1) leads to a small increase in the ICER, as the resulting increase in costs for PPS is slightly larger than that in BIs.

The ERG explored its concerns with the reliability of the data used for the response rate of BSC, as previously mention in Section 5.2.6, through conducting sensitivity analyses on the percentage of BSC responders used in the model (sensitivity analysis 2 and 3). Upper and lower extremes were used based on the highest and lowest confidence intervals reported in the literature used to form the meta-analysis. The ICER was very sensitive to changes in the response rate of BSC, but the direction of change is somewhat counterintuitive. It can be seen that the lower response rate results in a smaller QALY gain, as the difference in the absolute number of responders between PPS and BIs decreases. However, the ICER reduces because the incremental costs decrease more than the incremental QALYs giving an ICER of [redacted] per QALY gained. This is because patients on PPS have a reduction in costs when they fail to respond, but patients on BSC have a slight increase in costs when they fail to respond (see Figure 2). The opposite is true in sensitivity analysis 3, with the increase in response rate for BSC resulting in a larger QALY gain but a higher ICER of [redacted] per QALY gained. Table 30 also shows that the ICER was also sensitive to changes in administration of bladder instillations (sensitivity analyses 4 and 5). Using a urology specific outpatient cost (£151) for administration of bladder instillations increased the ICER to [redacted] per QALY gained, compared to [redacted] per QALY gained when the company's cost of £183 was used. Given that the ERG's clinical experts reported varying experiences regarding the proportion of patients who self-catheterise for BIs, ranging from none to 80%, the ERG explored a scenario in which a high proportion of patients self-administer BIs, resulting in a large increase in the ICER.

Additional sensitivity analysis results: PPS versus BSC

Table 31: Additional sensitivity analysis undertaken using ERG preferred base-case model for PPS versus BSC

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred base-case					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 1: All costs based on baseline ISCI scores removing the relationship between response to treatment and costs					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 2: Response rate of BSC set to 5% (equal to lower confidence interval from Mulholland *et al.* 1990)[14]					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis 3: Response rate of BSC set to 32% (equal to upper confidence interval from Parsons *et al.* 1987)[16]					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 31 reports the results of additional sensitivity analyses for PPS versus BSC using the ERG's preferred base-case analysis. As in the PPS versus BI analysis, the ICER was somewhat sensitive to changes in the assumptions on the relationship between treatment response and healthcare costs, resulting in a marginally higher ICER. Implementing changes to the response rate of BSC again had a large impact on the ICER, with a lower response rate of 5% resulting in a higher ICER of [redacted] per QALY gained and a higher response rate of 32% for BSC resulting in a lower ICER of [redacted] per QALY gained. The ERG notes that the impact on the ICER for PPS versus BSC is in opposite direction to that observed in the PPS versus BI scenario. This is because in the comparison of PPS versus BSC, the lower response rate results in a larger proportionate reduction in incremental QALYs than incremental costs.

5.4 Conclusions of the cost effectiveness section

The ERG was satisfied that the only cost-effectiveness paper identified in the company's review of published cost-effectiveness analyses was not sufficiently applicable to the decision problem specified in the scope and therefore a *de novo* analysis was necessary. The ERG had some concerns regarding whether the company's review of studies reporting costs, resource use and HRQoL data had been adequate.

The ERG considered that the company's *de novo* analysis was relevant to decision problem specified in the final NICE scope for this appraisal in terms of the population considered and the interventions and comparators considered.

The ERG was broadly satisfied with the structure of the company's economic model, although it considered that the use of a DES structure was unnecessary in this case and a more parsimonious model could have been constructed using a state transition modelling approach.

The ERG identified several important uncertainties in the model inputs which have the potential to have a large impact on the ICER. The key areas of concern identified by the ERG were:

- The application of a utility decrement for patients receiving BIs, estimated from the patient survey, which the ERG did not consider was robust given that the handling of missing data on BI usage had not been adequately explored in the analysis of the survey data.
- Uncertainty surrounding the likely rate of response in patients receiving BSC in clinical practice which affects the absolute difference in response attributable to PPS in the model
- Inconsistent assumptions around the durability of response in those receiving BSC and those receiving either PPS or BIs
- The assumption that 4 weekly administrations of BIs continues indefinitely when the ERG believes that the frequency of administration is likely to fall over time
- The underestimation of treatment discontinuation rates which affects the lifetime treatment costs, particularly for PPS versus BSC
- The assumption that patients who do not respond to BSC have some long-term persistent utility gain relative to baseline
- Low rates of self-administration for BIs which may overestimate costs relative to established clinical practice in some parts of the NHS

The impact on the ICER of these concerns was demonstrated in the ERG's exploratory analysis which produced an ERG preferred ICER of [redacted] per QALY for PPS vs BSC and [redacted] per QALY for PPS vs BI. However, there were some data inputs and assumptions that remain uncertain and which the ERG explored in further sensitivity analyses. These were found to have the potential to increase the ICER to [redacted] for PPS versus BI and up to [redacted] for PPS versus BSC.

The ERG also had additional concerns regarding the robustness of the data used to inform the model which were related to:

- the use of an unadjusted indirect comparison between PPS and BI to determine relative response rate

- the use of data from the broader population with BPS rather than the population with IC/BPS to estimate the efficacy of BI versus placebo
- The assumption that the long-term cumulative rate of response to second-line BIs is equivalent to the short-term response to first-line BIs
- the assumption of equal discontinuation rates for PPS and BI
- the method used to estimate ICSI scores for responders and non-responders
- the choice of HRG costs applied in the patient survey and the robustness of the relationship between ICSI score and disease-related costs
- the under estimation of parameter uncertainty within the PSA

6 END OF LIFE

The end of life criteria are not considered relevant in this appraisal as the company has not made a case that they should be considered and the ERG is not aware of any evidence that IC/BPS has any impact on life expectancy.

7 OVERALL CONCLUSIONS

The company's systematic review of clinical effectiveness suggests PPS to be significantly better than placebo for treating IC/BPS on improvement global response assessment in some RCTs but not others. Similar results in favour of PPS were also evident for non-VAS pain.

The company's systematic review of clinical effectiveness also indicated there to be no statistically significant between-group differences in: mean O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index scores (*p*-values or CI, not reported), mean daily urinary frequency (*p*-value not reported and $p=0.06$, CIs not reported), mean urinary volume and void outcomes (*p*-values or CIs, not reported), or mean nocturia (*p*-values or CIs, not reported), reported by the RCTs of PPS compared to placebo for treating IC/BPS.

The ERG's critique of the clinical effectiveness evidence identified that study quality in one of the four included RCTs of PPS for IC/BPS was unclear regarding: allocation concealment, details of who was blind, and numbers of patients withdrawing from treatment groups. As such, the ERG considers that the results from this RCT should be interpreted with caution.

The ERG notes that there is some author commonality across all four RCTs of PPS for IC/BPS and that no further published studies, undertaken by an independent study group, have attempted to validate the results of the four RCTs of PPS for IC/BPS.

The ERG also notes limitations in the reporting of outcome data in the PPS RCT trial reports (no interval estimates and *p*-values for non-significance often not reported).

The company's pairwise meta-analysis across RCTs suggests PPS to be significantly better than placebo for treating IC/BPS on improvement in global response assessment (RR, 2.09; 95%CI, 1.47 to 2.97; fixed effect).

The ERG has some concerns with the pairwise meta-analyses that were performed by the company (choice of scale for the analysis, the use of hypothesis testing to assess heterogeneity, and the use of a fixed effect model in the absence of evidence that there is not between study heterogeneity). The company also undertook an indirect comparison between PPS and Uracyst using the Bucher method with the placebos as the reference treatment. This gave an effective RR for PPS versus BI of 1.50. The ERG accepts the arguments suggested by the company for not performing an NMA. However, the ERG does not believe that the Bucher approach mitigates all of the concerns associated with performing an NMA, including: not using a single model to incorporate random effects; making the assumption of

asymptotic normality when making inferences and characterising uncertainty about the relative treatment effect used in the economic model.

An NMA or ITC of AEs was not undertaken by the company. Instead, a summary of AEs reported in the four RCTs of PPS for IC/BPS were presented. The ERG notes that >50% of patients in both PPS and PBO treatment groups were reported as experiencing moderate AEs in one RCT. However, the ERG accepts the company's conclusion that PPS is well tolerated, given that clinical advice received by the ERG is that AEs with PPS are rare.

The ERG considered the company's economic model to be consistent with the decision problem specified in the NICE scope[2]. The company's model is generally in line with the NICE reference case,[38] although the ERG had some concerns regarding the efficacy data used to inform the model. These included the use of data from trials in the broader BPS population to estimate the efficacy of BIs versus placebo and the methods used for the ITC.

The ERG considered that the structure of the company's model was appropriate. However, the ERG had concerns regarding some of the data inputs and assumptions used in the model. Several areas of uncertainty were identified which have the potential to have a significant impact on the ICER. These included: the likely response rate for BSC in clinical practice; the durability of response in those who have responded to BSC at 6 months; the expected ICSI scores for responders and non-responders and in particular the expected ICSI scores in patients who do not respond to BSC; the rate of persistence with treatment in the long-term for both PPS and BIs; the frequency of treatment with BIs in the long-term; the setting for administering BIs (outpatient versus day-case versus self-administered at home) and whether there is a utility decrement associated with treatment with BIs.

Based on the ERG's exploratory analyses which examined many of these factors, the ERG considers that the ICERs are likely to be much higher than presented in the company's base-case analysis and that there remains substantial uncertainty around the cost-effectiveness of PPS for treating IC/BPS.

7.1 Implications for research

The ERG believes that a three arm open-label study comparing PPS, BIs and placebo would provide valuable additional evidence. This would address the fact that no prospective Phase 3 study of PPS was conducted following the RCT by Sant *et al.* It would also address the lack of any direct evidence comparing PPS to BIs which are the current standard of care for IC/BPS. Any such trial should aim to collect evidence on the patient's global response to treatment (GRA) and the impact of treatment on HRQoL using both generic and disease specific instruments.

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9 APPENDICES

Appendix 1: Unit costs and resource use for disease-related costs

	CS[1] unit cost	Reference in CS	Exact codes that were used	ERG preferred unit cost	Reference	Resource use	Average costs using ERG preferred costs	CS average costs
Community healthcare								
GP visit	£37.00	PSSRU (2017)[44]				[redacted]	[redacted]	[redacted]
Nurse visit	£10.50	PSSRU (2017)[44]	Uncertain of how per visit cost obtained- PSSRU 2017 reports cost per hour £36			[redacted]	[redacted]	[redacted]
Outpatients								
Outpatient visits	£125.00	NHS Reference Costs (2017/18)[43] Average of total outpatient attendances		£110.00	Outpatient visits to urology- service code 101 NHS Reference Costs (2017/18)[43]	[redacted]	[redacted]	[redacted]
Hospital admissions								

ITU LOS	£1,466.60	NHS Reference Costs (2017/18)[43] XC01Z Non-specific, General Adult Critical Care Patients Predominate. Unit cost is a weighted average of adult critical care, with 0-6+ organs supported.	NHS Reference Costs (2017/18)[43] XC01Z-XC07Z	£1,287.24	NHS Reference Costs (2017/18)[43] XC05Z- XC07Z Non-specific, General Adult Critical Care Patients Predominate. Unit cost is a weighted average of adult critical care, with **0-2 organs supported**.	[redacted]	[redacted]	[redacted]
General ward LOS	£327.00	NHS Reference Costs (2017/18)[43] Index- regular day or night admissions				[redacted]	[redacted]	[redacted]
Specialist ward LOS	£957.08	NHS Reference Costs (2017/18)[43] LB19E, LB19F & LB19G	Total HRGS- total LB19E, LB19F & LB19G			[redacted]	[redacted]	[redacted]

		Ureteric or Bladder Disorders, without Interventions						
Day case	£742.00	NHS Reference Costs (2017/18)[43] Index- (DC) day case	HRG of all types of day cases	£309.00	Day case- LB15E- Minor Bladder Procedures, 19 years and over NHS Reference Costs (2017/18)[43]	[redacted]	[redacted]	[redacted]
Gynaecology	£921.00	NHS Reference Costs (2017/18)[43] LB15E Service description: Gynaecology Currency description: Minor Bladder Procedures, 19 years and over	Elective inpatient			[redacted]	[redacted]	[redacted]
Accident and emergency								

Emergency	£244.93	NHS Reference Costs (2017/18)[43] LB15e, LB18Z Weighted average of all A&E visits directly linked to the bladder	Outpatient procedures- Accident and Emergency- LB15E and LB18Z weighted average			[redacted]	[redacted]	[redacted]
Ambulance	£252.00	NHS Reference Costs (2017/18)[43] ASS02 Currency description: See and Treat and Convey				[redacted]	[redacted]	[redacted]
Total							[redacted]	[redacted]
Difference							[redacted]	

Appendix 2: Corrections of unequivocal errors which were necessary to generate results for the scenario analyses for the company's revised base-case

The ERG identified an error in the company's original model which the company corrected in the VBA code (subroutine "DES_IC_BPS") used to run the base-case analysis in the company's revised model, submitted as part of the clarification responses[1] and received by the ERG on 13th February 2019. However, equivalent corrections were not carried through to the VBA code used to run their scenario analyses. The following corrections were necessary in order for the ERG to generate the scenario analyses provided in Table 26 and Table 27.

Correction 1: The ERG implemented the following change to correct the use of time to discontinuation without adjusting from months to years in the subroutines "SA_BI_admin", "SA_BSC_5y" ,"SA_BSC_6m", "SA_nonresp" and "SA_surery".

Original code;

```
CostsAccrued = CostsAccrued + (OtherCosts_resp * (T2TD - Range("time_response_check")))
DCostsAccrued = DCostsAccrued + (OtherCosts_resp * (Exp(T2TD * (0 - DRCosti)) - Exp(Range("time_response_check") * (0 - DRCosti))) / (0 - DRCosti))"
```

Corrected code;

```
CostsAccrued = CostsAccrued + (OtherCosts_resp * (T2TD - Range("time_response_check") / 12))
DCostsAccrued = DCostsAccrued + (OtherCosts_resp * (Exp(T2TD * (0 - DRCosti)) - Exp((Range("time_response_check") / 12) * (0 - DRCosti))) / (0 - DRCosti))
```

Correction 2: Typo in VBA code for running surgery scenario analysis where "Rsnd" was used instead of "Rand" in subroutine "SA_DES_surgery()"

Original code;

```
T2TD = Range("time_response_check") / 12 + (Exp(Constant_logn + Application.WorksheetFunction.Norm_S_Inv(Rsnd(n, 2)) * Shape_logn)) / 12
```

Corrected code;

```
T2TD = Range("time_response_check") / 12 + (Exp(Constant_logn + Application.WorksheetFunction.Norm_S_Inv(Rand(n, 2)) * Shape_logn)) / 12
```

Appendix 3: Technical appendix detailing methods for implementing ERG's exploratory analyses and additional sensitivity analyses

This appendix details the changes made by the ERG to implement exploratory analysis to create the ERG's preferred base case. All additional sensitivity analyses were conducted with all changes to exploratory analyses 1-7 implemented. All ERG model amendments were made to the company's revised model, submitted as part of the clarification responses[1] and received by the ERG on 13th February 2019.

Exploratory analysis 1: Use of ERG preferred survival analysis

A new worksheet has been added to the ERG revised model which contains STATA outputs using the ERGs preferred survival analysis data. In order to reproduce the STATA outputs copy columns A-C in worksheet "ERG survival curve" into a new STATA data editor. Run the STATA do file attached in appendix 4

Model parameters from the STATA output were pasted into cells 'K5:M13' in new worksheet "ERG survival curve".

Cells 'K5:M14' in new worksheet "ERG survival curve", were copy and pasted into worksheet "Model inputs", cells 'H119:J128'.

In worksheet "Model inputs", the following changes were made:

Set cell 'F120' equal to cell 'J120'. Named cell "Constant_exp_ERG".

Set cell 'F125' equal to cell 'J121'. Named cell "Constant_wei_ERG"

Set cell 'F126' equal to "=EXP(J122)". Named cell "Shape_wei_ERG"

Set cell 'F131' equal to cell 'J127'. Named cell "Constant_logn_ERG"

Set cell 'F132' equal to "=EXP(J128)". Named cell "Shape_logn_ERG"

In VBA module "DES", a new variable was defined to switch to ERG preferred inputs for time to discontinuation using the following code:

"*Dim T2TD_ERG_flag As Integer*"

"*T2TD_ERG_flag = Range("T2TD_ERG_flag").Value*"

Added "*If T2TD_ERG_flag = 0 Then*" before the following VBA code:

```
Constant_exp = Range("Constant_exp")
 Constant_wei = Range("Constant_wei")
 Shape_wei = Range("Shape_wei")
 Constant_logn = Range("Constant_logn")
 Shape_logn = Range("Shape_logn")
```

Added the following code immediately after the above code:

ElseIf T2TD_ERG_flag = 1 Then
Constant_exp = Range("Constant_exp_ERG")
Constant_wei = Range("Constant_wei_ERG")
Shape_wei = Range("Shape_wei_ERG")
Constant_logn = Range("Constant_logn_ERG")
Shape_logn = Range("Shape_logn_ERG")
Else
MsgBox "survival parameters not selected"
End If

These amendments can be implemented by entering a value of "1" into worksheet "ERG options" cell B14 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2 prior to running the model.

Exploratory analysis 2: Switch to 6-weekly dosing for first line BIs after first year of treatment and 6-weekly for all 2nd line BIs

In VBA module "DES", a new variable was defined used to switch on increased spacing of bladder instillation doses post year 1 using the following code:
"*Dim Dosing_flag As Integer*"
Dosing_flag = Range("dose_spacing_flag").Value

In 'Case 4: Next event is drug administration' section of DES module, under:

'If DrugAdministrationCount < 4 Then
T2DrugAdministration = T2DrugAdministration + (1 / 52)'

The following new code was added to allow for increased dosing after 1 year:

"ElseIf DrugAdministrationCount >= 15 And Dosing_flag = 1 Then T2DrugAdministration = T2DrugAdministration + (6 / 52)"

The value in worksheet "Model inputs", cell D56, the formula has been revised to the following to allow for 6 weekly dosing for all second line BI treatments:
"=IF(dose_spacing_flag=0,(D46+D51)*13,(D46+D51)*(52/6))"

These amendments can be implemented by entering a value of "1" into worksheet "ERG options" cell B15 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2 prior to running the model.

Exploratory analysis 3: Use regression for utility based on ICSI scores which excludes term for prior usage of BI

Data from the regression analysis excluding recent/current usage of bladder instillations has been copied from the company's additional document 'ID1364_PPS_utilities_generation_report_AIC', provided during clarification process,[1] into worksheet 'Response & Utility data' in cells E61:F95
Within the worksheet 'Response & Utility data', the following cells were amended:

- The formula in cell H50 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G50+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G50+$F$66))))"

- The formula in cell H51 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G51+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G51+$F$66))))"

- The formula in cell H52 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G52+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G52+$F$66))))"

- The formula in cell H53 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G53+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G53+$F$66))))"

- The formula in cell H54 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G54+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G54+$F$66))))"

- The formula in cell H55 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G55+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G55+$F$66))))"

- The formula in cell H56 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G56+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G56+$F$66))))"

- The formula in cell H57 was amended to "=IF('ERG options'!$B$16=0,1/(1+EXP(-1*($C$78+$C$62*G57+$C$68))),1/(1+EXP(-1*($F$75+$F$62*G57+$F$66))))"

- The formula in cell I50 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G50+$C$87,$F$94+$F$78*G50+$F$83)"

- The formula in cell I51 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G51+$C$87+$C$93,$F$94+$F$78*G51+$F$83)"

- The formula in cell I52 was amended to "IF('ERG options'!$B$16=0,$C$97+$C$81*G52+$C$87,$F$94+$F$78*G52+$F$83)"

- The formula in cell I53 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G53+$C$87,$F$94+$F$78*G53+$F$83)"

- The formula in cell I54 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G54+$C$87+$C$93,$F$94+$F$78*G54+$F$83)"

- The formula in cell I55 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G55+$C$87+$C$93,$F$94+$F$78*G55+$F$83)"

- The formula in cell I56 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G56+$C$87,$F$94+$F$78*G56+$F$83)"

- The formula in cell I57 was amended to "=IF('ERG options'!$B$16=0,$C$97+$C$81*G57+$C$87,$F$94+$F$78*G57+$F$83)"

These amendments can be implemented by entering a value of "1" into worksheet "ERG options" cell B16 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2

Exploratory analysis 4: Use of a lifetime horizon

Value in worksheet "Model inputs", cell D13 was replaced with "*=IF('ERG options'!B17=0,20,100)*"
This amendment can be implemented by entering a value of "1" into worksheet "ERG options" cell B17 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2 prior to running the model.

Exploratory analysis 5: Return to baseline utilities and costs for non-responders when BSC is second line option (PPS versus BSC scenario only)

- In VBA module "DES", a new variable was defined to switch on the option for patients receiving BSC to return to baseline costs and utilities, by adding the following code:

"*Dim return2baseline_flag As Integer*"
"return2baseline_flag = Range("return2baseline").Value
If return2baseline_flag = 1 Then Sheet5.Range("Selected_2nd") = 2"

- To set costs to return baseline values for non-responder, the below code:

"bladcost_annual = Choose(Range("Selected_2nd"), Range("blad_cost_annual") + Range("blad_cost_2nd"), Range("bsc_cost_nonresp_no2nd"))"

Is replaced with the following:

"Dim temp As Double
If return2baseline_flag = 0 Then
temp = Range("bsc_cost_nonresp_no2nd")
Else
temp = Range("bsc_cost_pre")
End If
bladcost_annual = Choose(Range("Selected_2nd"), Range("blad_cost_annual") + Range("blad_cost_2nd"), temp)"

- To set utilities to baseline values for non-responders, the following code under 'If i=1 Then':
  "Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), Range("elmiron_utility_nonresp_no2nd"))"

  Is replaced with the following:
  " *If return2baseline_flag = 0 Then*
  temp = Range("elmiron_utility_nonresp_no2nd")
  Else
  temp = Range("elmiron_utility_pre")
  End If
  Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), temp)"

- To set utilities to baseline values for non-responders, the following code under 'If i=2 Then':
  "Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), Range("bsc_utility_nonresp_no2nd"))"

  Is replaced with the following:
  "*If return2baseline_flag = 0 Then*
  temp = Range("bsc_utility_nonresp_no2nd")
  Else
  temp = Range("bsc_utility_pre")
  End If
  Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), temp)"

- To set utilities to baseline values for non-responders, the following code under 'If i=3 Then': "Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), Range("blad_utility_nonresp"))"

  Is replaced with the following:
  "*If return2baseline_flag = 0 Then*
  temp = Range("blad_utility_nonresp")
  Else
  temp = Range("blad_utility_pre")
  End If
  Utility_nonresp = Choose(Range("Selected_2nd"), Range("blad_utility_2nd"), temp)"

These amendments can be implemented by entering a value of "1" into worksheet "ERG options" cell B18 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2

Exploratory analysis 6: Switch off receding baseline response for BSC (PPS versus BSC scenario only as already implemented in PPS versus BI base case)
Set 'Placebo effect receding' switch on worksheet 'Model inputs' to "NO".

Exploratory analysis 7: Use of log-normal function to model time to discontinuation
Apply all changes from ERG exploratory analysis 1.
Set drop down selection on worksheet 'Model inputs', cell C110 to "Lognormal"

Additional sensitivity analysis 1: All costs based on baseline ISCI scores removing the relationship between response to treatment and costs
Within worksheet "Cost & Survival data", the following cells were amended:

- The formula in Cell D38 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!D36,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D39 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!G44,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D40 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!H44,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D42 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!G45,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D43 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!H45,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D45 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!G46,'Response & Utility data'!D36)+$C$54)"

- The formula in Cell D45 was amended to "=EXP($C$58+$C$50*IF('ERG options'!B26=0,'Response & Utility data'!H46,'Response & Utility data'!D36)+$C$54)"

These amendments can be implemented by entering a value of "1" into worksheet "ERG options" cell B26 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2

Additional sensitivity analysis 2: Explore different baseline response rates through changes to response rate of BSC based on upper and lower confidence intervals reported in the literature.
A value of 5% was added to worksheet "Response & Utility data", cell K27.
A value of 32% was added to worksheet "Response & Utility data", cell L27.

Formula in worksheet "Response & Utility data", cell J24, was replaced with the following formula:
"=IF('ERG options'!B27=0,G27,IF('ERG options'!B27=-1,'Response & Utility data'!K27,'Response & Utility data'!L27))"

These amendments can be implemented by entering a value of "-1" for lower response rate of 5% or a value of "1" for upper response rate of 32% into worksheet "ERG options" cell B27 and selecting 'Click to apply default values to model' in worksheet "Control", cell C2.

Additional sensitivity analysis 4 & 5: Urology outpatient cost used for administration of BIs & 80% self-administer BIs (PPS versus BI only)
A value of £151.05 was added to worksheet "Cost & Survival data", cell C16.

Value in worksheet "Control", cell C15, was replaced with the following formula:
*"=IF((AND('ERG options'!B25=0,'ERG options'!B28=0)),'Cost & Survival data'!C15,(IF('ERG options'!B25=1,'Cost & Survival data'!C16,('Cost & Survival data'!C15-('Cost & Survival data'!C15*0.8)))))*"

Amendments to sensitivity analysis 4 can be implemented by entering a value of "1" into worksheet "ERG options" cell B28.

Amendments to sensitivity analysis 5 can be implemented by entering a value of "1" into worksheet "ERG options" cell B29.

Appendix 4: STATA code used to run ERG's survival analysis of time to treatment discontinuation

```
stset time,failure(failure) id(id)

streg, dist(exponential)
estat ic
predict mean_time_ex, mean time
predict median_time_ex, time

streg, dist(weibull)
estat ic
predict mean_time_we, mean time
predict median_time_we, time

streg, dist(lognormal)
estat ic
predict mean_time_ln, mean time
predict median_time_ln, time

streg, dist(gompertz)
estat ic
predict median_time_gpz, time

streg, dist(loglogistic)
estat ic
predict mean_time_lgl, mean time
predict median_time_lgl, time

sts graph,xlabel(0(6)60) risktable
```

Pentosan polysulfate sodium for treating bladder pain syndrome: A Single Technology Appraisal

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3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

Pentosan polysulfate sodium (PPS) (Elmiron® , Consilient Health) has a marketing authorisation in the Europe for treating IC/BPS. The target population in the company's decision problem matches the population described in the final NICE scope which is 'adults with bladder pain syndrome characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition',[2] which is in line with the marketing authorisation.

The key clinical evidence submitted by the company is derived from four randomised controlled trials (RCTs) of PPS in IC/BPS.[14-17] These RCTs all recruited patients with glomerulations and/or Hunner's lesions and were undertaken in the United States. Clinical advice received by the ERG suggested that the populations in these RCTs are generally comparable to the UK IC/BPS population. The company also included two additional RCTs of PPS in the broader BPS population that did not include a cystoscopic evaluation for glomerulations or Hunner's lesions at baseline.[18, 19] These two RCTs did not contribute to the pairwise meta-analysis of global response used in the company's base-case economic model, but did contribute to other meta-analyses in the clinical section of the CS. In addition, the impact on the cost-effectiveness estimates of including them in the meta-analysis used to estimate the rate of response for PPS in the company's model was examined in a scenario analysis. These two RCTs are not considered further in this section of the ERG report, but are summarised briefly in Section **Error! Reference source not found.**.

3.2 Intervention

The intervention evaluated in the CS is Elmiron® (pentosan polysulfate sodium, PPS), a semi-synthetic heparin-like substance that resembles glycosaminoglycans (GAGs). Although its exact mechanism of action is unclear, PPS is hypothesised to bind to the damaged GAG layer in the bladder, which protects the bladder by reducing the adherence of bacteria to the mucosal lining, in turn reducing inflammation. In addition to its anti-inflammatory activity, PPS may also have a barrier function instead of the damaged urothelial mucus.[1] The intervention matches that in the NICE scope.[2]

PPS received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 23rd March 2017 for the treatment of IC/BPS, and received EMA marketing authorisation June 2017.[8]

The Summary of Product Characteristics (SmPC)[8] reports that PPS is contraindicated in patients who actively bleed (excluding menstruation).[8]

Table 1: Baseline characteristics of participants in the pentosan polysulfate sodium RCTs relevant to the decision problem (adapted from Table 16 of the CS and the trial reports)

Trial Location	n/N (%) female	Mean (SD) age years	N/n (%) with ulcers/haemorrhage	Other characteristics
Sant *et al.*, 2003[17]	PBO, 28/31 (90%) PPS, 26/29 (90%)	PBO, 41.6 (15.5) PPS, 48.7 (15.1)	NR	*Prior symptoms for ≥ 52 weeks, n (%):* PBO, 29 (94%); PPS, 28 (96%) *Pain score (0 to 9), mean (SD):* PBO, 6.0 (1.3); PPS, 6.3 (1.4) *Urinary score (0 to 9), mean (SD)* PBO, 6.5 (1.5); PPS, 6.9 (1.2) *24-hour frequency score (0 to 9), mean (SD):* PBO, 18.9 (10.3); PPS, 18.3 (6.8) *ICSI, mean (SD):* PBO, 14.6 (3.3); PPS, 14.3 (3.3) *ICPI, mean (SD):* PBO, 12.8 (2.4); PPS, 12.8 (2.7) *Wisconsin IC score (0 to 42), mean (SD):* PBO, 32.9 (6.7); PPS, 30.4 (6.8)
Parsons *et al.*, 1993[15]	PBO, 74/74 (100%) PPS, 66/74 (93%)	PBO, 45.5 (NR) PPS, 42.7 (NR)	Hunner's ulcer: PBO, NR (4%) PPS, NR (4%) Petechial haemorrhage: PBO, NR (none, 1%; few, 8%; moderate, 43%; many, 47%) PPS, NR (none, 1%; few, 9%; moderate, 41%; many, 49%)	*Other abnormalities:* PBO, 8%; PPS, 11% *Bladder capacity under anaesthesia, mean (cc):* PBO, 601; PPS, 656
Mulholland *et al.*, 1990[14]	PBO, 45/56 (87%) PPS, 49/54 (91%)	PBO, 45.3 (NR) PPS, 43.3 (NR)	Hunner's ulcer: PBO, NR (4%) PPS, NR (8%) Petechial haemorrhage: PBO, NR (few, 27%; moderate, 48%; many, 25%) PPS, NR (few, 26%; moderate, 46%; many, 28%)	*Disease duration mean years:* PBO, 5.8; PBO, 7.4 *Other abnormalities:* PBO, 11%; PPS, 4% *Bladder capacity under anaesthesia, mean (cc):* PBO, 585; PPS, 569 *Patients with severe disease:* PBO, 59%; PPS, 59%

Details of non-VAS pain outcomes for all four RCTs of PPS in IC/BPS[14-17] are presented in **Error! Reference source not found.**
of this ERG report.

Non-VAS pain outcomes

All four RCTs of PPS in IC/BPS reported on non-VAS pain,[14-17] assessment of this outcome varied. Details of the assessment methods and results are presented in **Error! Reference source not found.**. Sant *et al.* (2003)[17] used a patient-reported 0–9 Likert scale (lower is better, participant inclusion criterion score of ≥4), Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990)[14] both assessed pain on a 0–5 scale (0 = no pain, 5 = severe pain). The RCT by Parsons and Mulholland (1987)[16] assessed patient-graded improvements of 0%, 25%, 50%, 75%, or 100%.

Between-group differences in change-from-baseline were reported by Sant *et al.* (2003)[17] at 24 weeks and Mulholland *et al.* (1990)[14] at three months. Both reported a reduction in change-from-baseline in both PPS and PBO. Sant *et al.* (2003)[17] reported PPS -0.8 vs. PBO -1.0 and Mulholland *et al.* (1990)[14] reported PPS -0.05 vs. PBO -0.02 (incorrectly reported in the CS as PPS 0.05 vs. PBO 0.02). In both trials, the between-group difference was not statistically significant (*p*-values or CIs not reported).

Parsons *et al.* (1993),[15] Mulholland *et al.* (1990)[14] and Parsons and Mulholland (1987),[16] all reported on the proportion of participants with a >50% pain improvement at three months. Respective values were: PPS 38% vs. PBO 18% (p=0.005), PPS 27% vs, PBO 14% (p=0.08), and PPS 44% vs. PBO 15% (p=0.02, CI not reported).

Parsons *et al.* (1993)[15] and Mulholland *et al.* (1990),[14] also reported on the proportion of participants with a decrease of >1 point at three months. Respective values were: PPS 66% vs. PBO 51% (p=0.04 in trial report, CI not reported;[15] incorrectly reported in CS as p=0.004), and PPS 46% vs. PBO 29% (p=0.07, CI not reported).

Parsons and Mulholland (1987),[16] also reported on the mean percentage improvement at three months: PPS 33.3 (SD 35) vs. PBO 12.2 (SD 14.3) (p=0.02, CI not reported).

Table 2: Details of daily void/volume outcomes in the pentosan polysulfate sodium RCTs in IC/BPS (adapted from the CS Table 23)

Trial	Parsons *et al.*, 1993[15]	Mulholland *et al.*, 1990[14]	Parsons and Mulholland, 1987[16]
Follow-up time point	3 months	3 months	3 months
Mean volume/void, mL (baseline)	NR	NR	PBO, 76.7 PPS, 93.8
Mean volume/void, mL (follow-up)	NR	NR	PBO, 74.3 PPS, 106.9
Mean volume/void, mL (change from baseline)	PBO, -2.1 PPS, 20.4	PBO, 7.6 PPS, 9.8	NR
P value (change from baseline)	NR	NR	PBO, 0.6 PPS, 0.06
P value (between groups)	NS	NS	NR
Mean total daily voided volume, mL (change from baseline)	PBO, -42 PPS, 3	PBO, -20 PPS, 60	NR
P value (between groups)	NS	NS	NA
% patients with >20 mL increase (follow-up)	PBO, 25% PPS, 40%	PBO, 20% PPS, 30%	NR
P value (between groups)	0.02	NS	NA

mL, millilitre; NA, not applicable; NR, not reported; PBO, placebo; PPS, pentosan polysulfate sodium
* Incorrect in CS, PBO reported as 0.3 in the CS

Nocturia

In Table 24 of the CS, the company reports that in the RCT by Parsons and Mulholland (1987)[16] at three months the mean improvement in nocturia was PBO -0.9 (SD 0.8) vs. PPS -2.1 (SD 2.2), p=0.05 (CI not reported). This is the only RCT in IC/BPS for which the company report nocturia data in the CS.[1] However, the trial reports by Mulholland *et al.* (1990)[14] and Parsons *et al.* (1993),[15] both report on this outcome.

Mulholland et al (1990)[14] reported that at three months there was no statistically significant between-group difference in change in nocturia PBO -0.5 vs. PPS -0.8, p-value or CI, NR). Parsons *et al.* (1993)[15] also reported that at three months, there was no statistically significant between group difference in nocturia (no data reported). In Parsons *et al.* (1993),[15] increase in nocturia was recorded as an adverse event. The numbers (%) of patients experiencing this AE were PBO 0 (0%) vs. PPS 1 (1.4%) (p-value or CI, NR). This AE for Parsons *et al.* (1993)[15] is not presented in the Section B.2.10. of the CS on AEs, Table 32,[1] as there was not >1 patient in either treatment group with this AE.

Other outcomes

No other clinical effectiveness outcomes for RCTs of PPS in IC/BPS were reported in the CS.[1]

study and was part of the control group. Both trials were described as being in the IC/PBS population; however, the diagnostic criteria did not include the presence of ulcers or petechial haemorrhage on cystoscopy (see Table 3). The CS[1] (Table 30) defined the populations in both trials as BPS.

Table 3: **Diagnostic eligibility criteria for the included studies derived from study reports**

Nickel *et al.* (2010)[20]	**Nickel *et al.* (2012)[21]**
Clinical diagnosis of IC/PBS The diagnosis of IC/PBS was consistent with current clinical definitions, including the diagnostic criteria described in the IC Data Base Study,[12] as well as the most recent definition of IC/PBS described at the NIH Urologic Chronic Pelvic Pain consensus (Baltimore, December 2007). IC/PBS was diagnosed on the basis of pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as urgency or frequency.	Diagnosed or re-diagnosed with IC/BPS within the previous 2 years; had a subject-reported average urinary frequency of 8 times/24 hours during the screening period, as captured by a 3-day diary; had a pain/pressure/discomfort score of 40-80 mm on a pain visual analogue scale (VAS).

Baseline characteristics appeared to be broadly comparable across the trial arms in both trials. Details of the ethnicity of the patients were not reported in the CS or in the trial report for Nickel *et al.* (2010)[20], whilst the ethnicity of the patients was reported in Nickel *et al.* (2012)[21] and was comparable across trial arms, and appeared to be broadly generalisable to the UK population.

The eligibility criteria detailed in the trial papers included a diagnosis of IC/BPS, but do not report that Hunner's lesions and/or glomerulations are part of the diagnosis. Therefore, it is not clear that the patients in either trial met the criteria for this NICE scope (see Table 3). The ERG also notes that neither the CS[1] or the individual trial papers report numbers of patients overall or in each arm with either Hunner's lesions or glomerulations. (see Section 4.2.1 for further discussion).

additive scale that can be transported and used to estimate absolute risk in a target population. In addition, an objective in this submission is to generate a (posterior) distribution for the treatment effect and an estimate of the baseline effect that can be used together to represent uncertainty about absolute responses to treatment in the economic model:

- Table 28 of the CS[1] presents a meta-analysis of four studies on the risk difference scale for GRA. While a meta-analysis of risk difference may be appropriate when the baseline event rates are similar among the studies, treatment effects are more likely to be additive on a relative scale such as the log-odds ratio or log-relative risk.
- The company concluded that "There was a high degree of homogeneity in this sensitivity meta-analysis …" based on Cochran's Q value. The ERG has concern with the use of Cochran's Q value to assess and conclude homogeneity of relative treatment effects across studies,[32] and has a preference for estimating the between-study standard deviation and its uncertainty. In addition, it is unclear to the ERG why the company refers to this meta-analysis as a sensitivity analysis.
- The company's misinterpretation of Cochran's Q value is repeated when they include two additional studies with a broader BPS population[18, 19] that the ERG recognises do not satisfy the inclusion/exclusion criteria for the assessment. The company claims that "there is no indication of heterogeneity" rather than the more appropriate interpretation that there is insufficient evidence to reject the null hypothesis that there is homogeneity of treatment effects. Furthermore, and somewhat contradictory, the company goes on to state that the results were heterogeneous.
- It is not clear whether the meta-analysis presented in Table 29 of the CS[1] is based on a fixed or random effects model, and the predictive distribution of an effect is not provided. The use of a fixed effect meta-analysis is appropriate if interest is in a conditional inference of whether treatment had an effect in the available studies or if all of the factors that could affect the effect size on an appropriate additive scale are the same in all study populations. When there is reason to believe that the effect size may not be identical in the available or any future studies that might be conducted then a random effects meta-analysis should be performed; the choice between a fixed effect and random effects model should not be based on a test of heterogeneity of treatment effects.
- The company has used standard frequentist methods assuming asymptotic normality which may not be optimal given the samples sizes used and the number of observed events in the available studies. An exact analysis of the data using a Binomial likelihood and generation of the (posterior) distribution for the treatment effect could have been done using Bayesian methods.
- It is unclear what the relevance is of the lower limit of the 95% confidence interval for the pooled estimate of the absolute difference in GRA response being less than 5%. The lower limit of the

5. COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

This section presents a review of the cost-effectiveness evidence reported in the CS[1] for pentosan polysulfate sodium (PPS) for treating IC/BPS (defined as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations).

5.1.1 Objective of cost effectiveness review

The company undertook a systematic literature review in order to identify cost-effectiveness evidence for IC/BPS and BPS treatments.

Five searches were performed to identify economic evaluations of IC/BPS or BPS. These consisted of three searches for cost-effectiveness evaluations and two searches for economic models. The following databases were searched for economic evaluations in June 2018: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], Embase [via Wiley], NHS EED [via Wiley]. The company carried out supplementary searches within health technology appraisals via the NICE website.

In the company's clarification response (question B1), the company reported that publication date limits were not applied to the economic and cost-effectiveness evaluations searches. The NHS EED database coverage is limited to 1995-2014 whereas limits of 1992-1994 and 2015-present were applied in the MEDLINE and Embase search. The reason given for limiting the MEDLINE and Embase searches was to cover the periods not already covered by NHS EED. The ERG notes that it is usual practice in reviews of economic evaluations to search multiple databases and then to exclude duplicates, rather than to assume that a single database has captured all relevant economic evaluations in the period it covers. The ERG is unable to confirm if any key economic evaluations have been missed as a result of the company limiting their searches of EMBASE and MEDLINE to the time period not covered by NHS EED.

The company performed two searches to identify health-related quality-of-life studies for IC/BPS and BPS. Details of these searches were provided in response to a request for clarification from the ERG (question B3).[35] The following three sources were searched in June 2018: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid] and Embase [via Ovid]. The company cross-checked lists of included articles with records from the electronic searches. The ERG considers that the searches are sufficiently comprehensive to retrieve all the eligible studies.

5.1.4 Conclusions of the cost effectiveness review

The ERG is satisfied that the identified published cost-effectiveness study[30] is not appropriate to address the decision problem in the NICE scope,[2] and therefore that the development of a de novo model is appropriate. However, the ERG has some concerns with the company limiting their searches of EMBASE and MEDLINE for cost-effectiveness evaluations to the time period not covered by NHSEED and is unable to confirm if any key economic evaluations have been missed as a result of this. In addition, the ERG has some concerns with the quality of the searches undertaken for additional studies of cost and healthcare resource use data and the exclusion criteria applied to the HRQoL studies.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Please note that the company submitted a revised model following the clarification request and it is this model that is referred to throughout the report unless otherwise specified. The revisions made in this model were mainly corrections of errors in the implementation of the model and did not concern the model structure, assumptions or data sources, with the exception of the life-table data being updated to the most recent dataset available.

5.2.1 NICE reference case checklist

Table 4: Compliance with the NICE reference case[38]

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The population modelled is adults with BPS characterised by either glomerulations or Hunner's lesions, which is consistent with the NICE scope and the licensed indication for PPS. The evidence on the effectiveness of PPS compared to BSC is taken from trials in the relevant population.[14-17] However, the evidence on the effectiveness of BI compared to placebo, comes from the broader population of patients with BPS which is not restricted to those with either glomerulations or Hunner's lesions. The model evaluates the cost-effectiveness of PPS separately in the subgroup able to receive BIs and the subgroup who are contraindicated or unable to tolerate BIs

The ERG does not understand why the company did not build a state transition model. With the exception of the administration of BIs, the costs and QALYs are determined mainly by the time spent on first and second-line treatment. Therefore, a simple Markov model could have been constructed with health states for:

- Patient on treatment before the re-response check
- Non-responders who have switched to second-line treatment
- Responders remaining on first-line treatment
- Responders who have discontinued and moved to second-line treatment
- Death.

Although the frequency of BIs varies in the first 6 months of the model, it is constant thereafter. Therefore, the varying cost of BIs could have be incorporated simply by having a 6-month cycle length and a different cost in the first cycle. The company claims that the DES structure allows ICSI to be incorporated as a continuous variable. However, ICSI is not implemented in the DES as a continuous variable. Instead average costs and utilities are estimated for responders and non-responders based on their estimated median ICSI scores. This would therefore allow costs and utilities to be easily attributed to the health states listed above. The ERG considers that a state-transition approach would have been more parsimonious but that this does not mean that the DES approach is incorrect.

5.2.3 Population

The modelled population is adults with bladder pain syndrome characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition. The ERG considers the overall population to be consistent with the NICE scope[2] and the licensed indication for PPS.[8]

However, the ERG notes that based on the company's presentation of the clinical pathway in **Error! Reference source not found.** of the CS, patients would not receive bladder instillations until after they had failed to respond to first-line oral therapies including analgesics, antihistamines and other non-pharmaceutical interventions including as dietary and lifestyle advice. Therefore, the population modelled is assumed to be those who did not respond to these initial interventions and the cost-effectiveness results should not be extrapolated to patients earlier in the clinical pathway.

The CS[1] presents cost-effectiveness analyses for two distinct subpopulations;

- Patients able to receive BIs
- Patients for whom BIs are contraindicated or who are unable to tolerate BIs.

The ERG considered that it was inconsistent to assume that all of the responses observed in the PPS and BI arms of the RCTs were durable, in that they would persist until treatment ceased, but all of the responses observed in the placebo arms of the RCTs were not durable and would cease at 12 months.

If the response rate observed in the placebo arms of the RCTs was related to the experience of being enrolled in a clinical trial, then it may also apply to a proportion of the patients who responded in trial arms receiving either PPS or BI. If the response rate in the placebo arm is related to the fact that patients may enrol in the trial when experiencing a flare-up in their symptoms, which resolves naturally over the course of the trial (i.e. regression to the mean), then again, it does not seem reasonable to assume that this response is time limited in patients receiving BSC, but continues indefinitely in those receiving PPS or BI. RCTs are designed to provide an unbiased estimate of the relative treatment effect. It is this relative treatment effect that should inform the differences in outcomes between treatments within the economic model. However, the company's assumption that benefits are limited to 12 months in patients responding to BSC introduces a difference in the model that is separate from the relative treatment effect measured in the trial. The ERG does not consider that this is reasonable given that the only evidence provided by the company to demonstrate that the durability of response differs in patients receiving BSC compared to those receiving either PPS or BI is a consensus statement from clinical experts (Appendix M of the CS).

Treatment effectiveness – extrapolation

In the PPS and BI arms of the model, patients who have responded after 6 months of treatment are assumed to continue receiving the full treatment effect until they discontinue. The time-to-discontinuation survival function is based on data from Hanno *et al.* (1997)[27] which has a maximum follow-up of 10 years. An exponential survival function is then used to extrapolate discontinuation rates over the remainder of the model. The median time to discontinuation in the company's model, based on their preferred parametric survival function, is 7 years with 18% of patients estimated to still be on treatment after 20 years. The effectiveness of PPS and BIs has therefore been extrapolated for some patients for up to 20 years in the company's base-case analysis. This is in contrast to the RCTs having a maximum of 6-month follow-up for assessment of response based on GRA. The ERG is concerned that there is a lack of data on the long-term efficacy of PPS despite the drug having being available in Canada, Australia and the US for over 20 years. Whilst some data on efficacy up to 36 months are provided in the CS, these are from an observational study which is poorly reported and as such are difficult to interpret. (see Section **Error! Reference source not found.**)

In addition, the data on discontinuation are based on a study in patients treated with PPS, but the same survival function for time to discontinuation is also applied in the model to patients receiving BIs as first-line treatment. No evidence is provided to support the assumption that rates of discontinuation

It can be seen from **Error! Reference source not found.** (panels A and B) that patients who respond to PPS or BIs are assumed to continue to benefit from improved HRQoL until they discontinue treatment, but may continue to benefit for the full model horizon if their time to discontinuation is sampled to be greater than 20 years; this occurs in 18% of responders. In contrast, patients who respond on BSC, are assumed to have a HRQoL benefit that lasts only from the response check at 6 months to 1 year after the start of the model (NB: alternative scenarios are provided in the CS[1] where the treatment effect stops immediately after the 6-month response check or at 5 years).

It can also be seen from **Error! Reference source not found.**, that in the scenario where patients cannot have BIs (panels C and D), patients who do not respond to either PPS or BSC experience some HRQoL improvement due to an assumed improvement in ICSI scores in non-responders compared with baseline. The ERG notes that the utility score of non-responders having BSC in this scenario ([redacted]), is [redacted] than the average utility score achieved by patients having BIs as second-line treatment [redacted]) even though 22% of these patients respond to second-line BIs. This inconsistency is being driven by the utility decrement associated with receiving BIs which results from the regression coefficient for having "received a bladder instillation in the previous 6 months". The ERG notes that only 53% of the undiscounted QALY gain for PPS versus BIs is accrued in patients who responded on PPS but would not have responded on BIs. The remainder is due to differences in QALYs that result from time spent on first-line BIs due to the application of the regression coefficient for having "received a bladder instillation in the previous 6 months".

The ERG does not understand the clinical rationale for there being a utility decrement associated with having received BIs in the previous 6 months. In response to a request for clarification, the company stated *"Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections*".[1] However, the ERG is concerned that the difference in utility detected in the patient survey[39] may reflect differences in patient characteristics in the survey population between those who have recently used BIs and those who have not recently used BIs. In this case it would not be appropriate to apply it only to those having BIs in the model as it is related to the population and not the current treatment. Furthermore, although the survey did ask about oral medications, the number reporting use of oral PPS was considered by the company to be insufficient to robustly include a covariate for PPS treatment in the mapping model.[39] Therefore, it is not possible to know if there is a similar decrement associated with taking PPS that could not be detected in the survey.

[redacted] The ERG decided to use the regression including age and ICSI score but not BI usage in their base-case analysis as the ERG was not satisfied that [redacted].

The EQ-5D values for responders and non-responders are based on estimates of median ICSI scores for responders and non-responders. These have been calculated by assuming that ICSI scores in the PPS arm of the RCT by Sant *et al.* (2003)[17] are normally distributed and that all patients who respond have ICSI scores that are lower (i.e. better) than all patients who do not respond (see Figure 18 of the CS). The ERG notes that the company were unable to provide any data to support these because they do not hold any relevant patient-level trial data (see company response to clarification question B5).[1] Based on these assumptions, the ICSI score for the median responder and the median non-responder was calculated from the normal distribution of the ICSI scores.

The ERG has concern with the assumptions made when relating GRA response to ICSI. The company has effectively assumed a step function such that all patients who have a change from baseline to Week 24 of greater than (approximately) -4.1 in ICSI are considered as non-responders and all patients who have a change from baseline to Week 24 of less than (approximately) -4.1 in ICSI are considered as responders and that this applies irrespective of treatment (CS, pages 104-105). The ERG suggests that it is unlikely that such a dichotomy according to baseline ICSI will be true or that there will be no

The three main types of resource use incorporated in the model are: (i) acquisition costs for PPS and BIs; (ii) administration costs for BIs, and (iii) disease-related costs. The latter is assumed to be related to disease severity as measured by the patient's ICSI scores. Data from the patient survey were used to estimate the relationship between costs in the previous 6 months and ICSI scores.[39] This relationship was used to estimate annual costs for responders and non-responders using the ICSI scores previously calculated for estimating utility based on ICSI. Again, as when calculating utilities, age was also included in the regression for costs, but the costs were calculated based on patient age at the start of the model and were not updated as patients aged in the model. The main difference between the approach used for utility and that used for resource use was that no explanatory term related to BI usage in the previous 6 months was included in the regression linking ICSI scores to health care costs.

It should also be noted that the company attempted to remove any double counting of costs directly related to interventions. However, in the survey, patients were asked separately about hospital visits and treatments received without any information being gathered on whether the resource use was related to treatments received.[39] Therefore, it is possible that treatment-related resource use has not been adequately excluded as intended. This may mean that disease-related costs are over-estimated in the model.

In calculating the overall cost in the previous 6 months from the survey results, the company applied HRG costs to the resource use data.[39, 45] In several cases, it was unclear how the various HRG costs were selected and why other values were not applied. For example, the HRG cost applied for hospital admissions is the weighted mean across elective, non-elective and day-case admissions for that HRG code. In their response to clarification question B25, the company stated that, [redacted] The data collected [redacted] do not appear to have been used to inform the average HRG cost for hospital admission.

The ERG asked their clinical experts whether patients with poorer disease control, and therefore higher ICSI scores would be likely to incur greater resource use and whether the types of resource use reported in the patient survey (Table 49 of the CS)[1] were typical based on their experience. The ERG's clinical experts agreed that patients with poor symptom control may be more likely to access NHS services, but these were likely to be outpatient services rather than inpatient admissions or emergency department ED) attendances. One clinician noted that the incidence of GP appointments may increase if the patient

The DES model did not allow for the reporting of costs and QALYs according to the individual's trajectory through the model, which would be analogous to the costs and QALYs accrued in various health states for a state transition model. To address this, the ERG identified the proportion of the QALY gain associated with additional patients who respond in PPS vs BSC by examining patient-level QALY gains. It found that only 53% of the QALY gains for PPS versus BI and 53% of the QALY gains for PPS versus BSC were accrued due to the higher rate of response achieved by PPS. In the comparison against BI, the remainder of the QALY gains were associated with the utility decrement for "BI usage in the previous 6 months" from the regression analysis of the patient survey data.[1] In the comparison against BSC, the remainder of the QALY gains were related to the assumption that responders to BSC benefit for a maximum of 12 months whereas responders to PPS benefit until they discontinue.

To check the internal validity of the model, the ERG calculated the proportion of responders from the patient-level results and noted that the average rate of responders was 33.8%, 22.8% and 16.5% based on the first 10,000 patients sampled whereas the input values for these parameters were 33.1%, 22.0% and 15.8% respectively. The ERG suspected that this slightly discrepancy was due to the stochastic nature of the model whereby stable outputs are only achieved if sufficient patients have been simulated. The ERG conducted a large run of 100,000 patients and found that the ICERs based on the first 10,000 patients was within £500 per QALY of the ICER based on the larger run of 100,000 patients. The ERG was therefore satisfied that the results provided by the model, which were based on 10,000 patients, were sufficiently accurate for decision making.

The ERG noticed that there were a number of minor discrepancies between the values provided in the CS[1] and those included in the model (e.g. ICSI scores in Table 41, mean and standard deviation for time to death in Table 57), but the correct values had been included in the model. The ERG also noticed a minor discrepancy between the source study and the values used in the CS[1] for the mean starting age based on the data from Sant *et al.* 2003,[17] but the difference was too small to make any difference to the model (45.57 years vs 45.41 years with the life-expectancy data being based on patients aged 45 years).

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG's exploratory analysis- methods

Following concerns highlighted in Section 5.2, the ERG undertook seven sets of exploratory analyses by implementing changes to the company's revised model. Two of these changes were not applicable to the comparison of PPS against BIs because they related to the modelling of BSC and one of these changes was not applicable to the comparison of PPS against BSC because it related to the modelling

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BIs)

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (includes median response rates from company's NMA)	**Addresses issues 2 and 4 plus new evidence on issue 1**	[redacted]	
1. Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	[redacted]	[redacted]
2. 6-weekly administration for second line BIs and first line BIs after first year	Issue 7	[redacted]	[redacted]
3. Combined changes 1 and 2 (remove BI usage covariate + 6-weekly BIs)	Issue 7 and 5	[redacted]	[redacted]
4. **ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)**	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	[redacted]	[redacted]

† this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs

Table 1b: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BSC)

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (includes median response rates from company's NMA)	**Addresses issues 2 and 4 plus new evidence on issue 1**	[redacted]	
5. Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	[redacted]	
6. 6-weekly administration for second line BIs and first line BIs after first year	Issue 7	[redacted]	
7. **ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)**	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	[redacted]	[redacted]

† this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs

Table 2: Detailed results for company updated base-case (PPS vs BSC)

BASE-CASE	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICER per QALY
Best supportive care	[redacted]	[redacted]	-	-	-
elmiron®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Q1: Would you be able to send me the % of patients on treatment predicted by the ERG and company models at 5, 10, 20 and 30 years for PPS and for bladder instillations? If this is something that could easily be accessed in the model, could you send instructions on how to do this?

R1: *The actual duration of time on treatment isn't something that the model outputs. It outputs the time to discontinuation samples, but only in those patients who actually discontinue making it necessary to impute the time on treatment in those who die before discontinuing or who reach the end of the time horizon before either dying or discontinuing. I have done this and have provided graphs of the proportion remaining on treatment over time for both the company basecase and the ERG preferred basecase scenario (see figures 1 and 2). I have also tabulated the proportions at the requested time points in Table 1. Please note that the numbers on treatment fall to zero in the company basecase because of the 20 year time horizon they have applied. The initial fall at 6 months is due to non-responders coming off treatment and PPS and BI have been plotted separately as they have a different response rate.*

However, I'm not sure if this is what you were requesting or whether you simply wanted the proportion of responders predicted to remain on treatment at the various time points which is equivalent to extracting data points from Figure 11 and Figure 12 of the ERG report. So I have also tabulated this data for you in Table 2. Please note; 1) that the figures in Table 2 assume that patients do not stop treatment due to dying from all-cause mortality; 2) the figures in Table 2 are the same for both PPS and BIs as they assumed equivalent time to treatment discontinuation and 3) that survival curves give time to discontinuation from the 6 month response check but I've assumed that you were asking about total time in the model so I have extracted survival at 4.5 years instead of 5 years etc

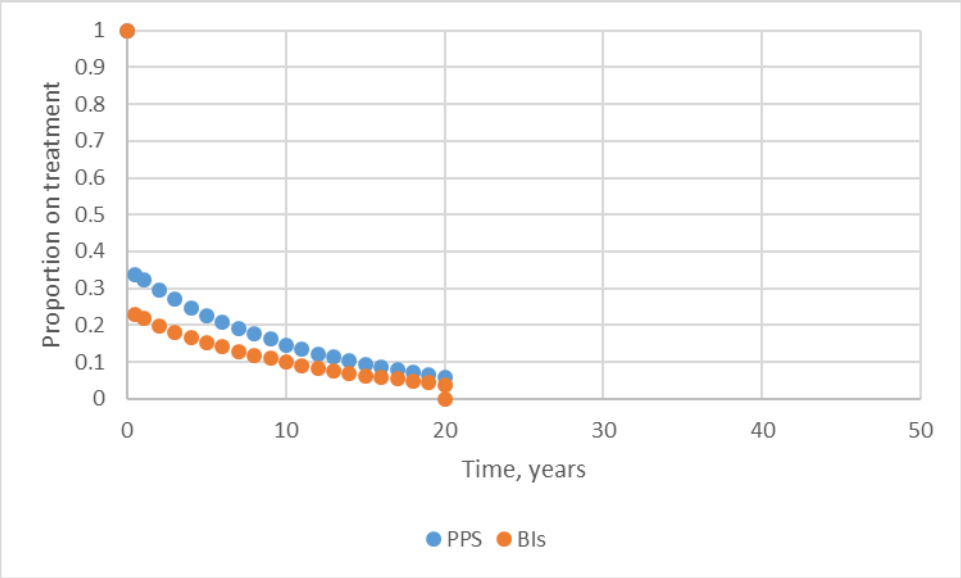

Figure 1: Proportion of initial cohort remaining on first-line treatment in the company basecase

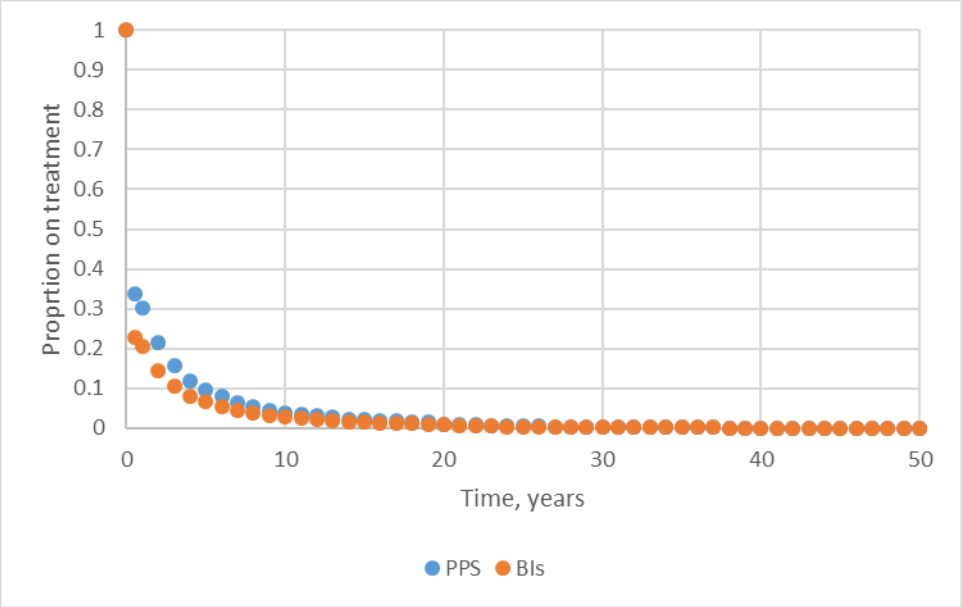

Figure 2: Proportion of initial cohort remaining on first-line treatment in the ERG preferred basecase

Table 1: Proportion of initial cohort remaining on treatment

	Company basecase (exponential)		ERG preferred (log normal with revised data from Hanno 1997)	
Time (years) from start of treatment	PPS	BI	PPS	BI
0.5	34%	23%	34%	23%
5	22%	15%	9%	7%
10	15%	10%	4%	3%
20	6%	4%	1%	1%
30	NA	NA	0.2%	0.1%

NA, not applicable as company basecase applies a 20 year horizon

Table 2: Proportion of responders remaining on treatment when assuming zero mortality (same for BI and PPS as equivalent time to discontinuation data applied)

Time (years) from response check	Time (years) from start of treatment	Company basecase (exponential)	ERG preferred (log normal with revised data from Hanno 1997)
0	0.5	100%	100%
4.5	5	67%	28%
9.5	10	43%	12%
19.5	20	18%	4%
29.5	30	7%	2%

Q2: To aid engagement, could you give me the value of the utility score decrement associated with previous bladder instillations that the company's model assumes?

R2: The regression coefficient for previous BI usage is [redacted]. The exact size of the utility difference between the utility estimates for BI and PPS patients with equivalent ICSI scores is slightly different across the health states because of the two part model, but it is [redacted] to the nearest 2 d.p. when using the ICSI scores for responders, non-responders and patients pre-response check.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 22 March 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.1, page 22 "The target population in the company's decision problem matches the population described in the final NICE scope which is 'adults with bladder pain syndrome characterised by either glomerulations or Hunner's	"…which is the same as the marketing authorisation."	This is an incorrect statement. The elmiron EPAR states: "elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of	The ERG has replaced the final line with 'which is in line with the marketing authorisation.'

lesions with moderate to severe pain, urgency, and frequency of micturition', which is narrower than the marketing authorisation."		micturition."	

Issue 2 Searches

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.1.1 Page 73 *"Two searches were performed to identify economic evaluations of IC/BPS and BPS"*	Amend to *"Three searches were performed to identify economic evaluations of IC/BPS or BPS"*	Current text is incorrect.	The two searches referred to are the separate search strategies used to identify cost-effectiveness evaluations and economic models. To clearly state this, the text has been replaced in the erratum with "*Five searches were performed to identify economic evaluations of IC/BPS or BPS. These consisted of three searches for cost-effectiveness evaluations and two searches for economic models"*

Issue 3 Searches

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.1.1 Page 73 *"In the company's clarification response (question B1), the company reported that publication date limits were not applied to the*	Removal of paragraph quoted.	We have previously clarified that we did not limit the searches for economic evaluations by date. The scope of the review was 1992-current. NHSEED coverage is	The ERG has deleted the sentence "*The reasons and implications of not including all years in MEDLINE and Embase were not given"* and

economic and cost-effectiveness evaluations searches. The NHS EED database coverage is limited to 1995-2014 whereas limits of 1992-1994 and 2015-present were applied in the MEDLINE and Embase search. The reasons and implications of not including all years in MEDLINE and Embase were not given. The ERG is unable to confirm if any key economic evaluations have been missed as a result applying these limits."		limited to 1995-2014 only, so we ran additional searches of Medline and Embase (using the published NHSEED search strategies) to ensure that the periods 1992-1994 and 2015- current were also searched. Therefore, the total date-range covered by the searches was 1992 to current. Including all years in the additional Medline and Embase searches was unnecessary as both databases have already been searched from 1995 to 2014 using the NHSEED search strategies in order to populate the NHSEED database. Final sentence re missed evaluations is factually correct but the inference that date-limits applied mean we might have missed evaluations is incorrect. Details of this were provided in our clarification letter.	have replaced it with, "The reason given for limiting the MEDLINE and Embase searches was to cover the periods not already covered by NHS EED." We have also added the following comment on this rationale. "The ERG notes it is usual practice in reviews of economic evaluations to search multiple databases and then to exclude duplicates, rather than to assume that a single database has captured all relevant economic evaluations in the period it covers" The final sentence has been amended to say, "*The ERG is unable to confirm if any key economic evaluations have been missed as a result of company limiting their searches of EMBASE and MEDLINE to the time period not covered by NHS EED"*

Issue 4 Searches

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.1.4 Page 73 Conclusions of the cost-effectiveness review	Amend to *"However, the ERG has some concerns with the quality of the searches undertaken for additional studies of cost and*	See Issue 2 above for reasons ERG concern that date limits applied to the economic searches might mean	In line with the ERGs response to Issue 3, the first sentence has been amended to say "*However, the ERG has some*

"However, the ERG has some concerns about the date limits applied to the company's economic searches and is unable to confirm if any key economic evaluations have been missed as a result of applying these limits. In addition, the ERG has some concerns with the quality of the searches undertaken for additional studies of cost and healthcare resource use data and HRQoL studies."	*healthcare resource use data."*	key economic evaluations were missed is incorrect. No concerns with the searches for HRQoL studies are mentioned in the ERG report. The only comment on the HRQoL searches was *"The ERG considers that the searches are sufficiently comprehensive to retrieve all the eligible studies"* (Section 5.1.4 Page 73*)*.	*concerns with the company limiting their searches of EMBASE and MEDLINE for cost-effectiveness evaluations to the time period not covered by NHSEED and is unable to confirm if any key economic evaluations have been missed as a result of this "* The concerns with the searches undertaken for HRQoL data refer to the ERGs concerns with the exclusion criteria applied to the searches, as mentioned in section 5.1.2. To explicitly state this, the final sentence has been amended to say "*In addition, the ERG has some concerns with the quality of the searches undertaken for additional studies of cost and healthcare resource use data and the exclusion criteria applied to the HRQoL studies."*

Issue 5 Cost data

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.2.10, page 97 "In calculating the overall cost in	Revision of paragraph quoted	The example provided by the ERG to demonstrate use of unclear HRG	The ERG report was factually accurate given the information

the previous 6 months from the survey results, the company applied HRG costs to the resource use data. In several cases, it was unclear how the various HRG costs were selected and why other values were not applied. For example, the HRG cost applied for hospital admissions is the weighted mean across elective, non-elective and day-case admissions for that HRG code. In their response to clarification question B25, the company stated that, "information on the specific type of attendance (elective, non-elective or day-case) were not available". This contradicts both Table 1 of the study report which includes number of elective or emergency admissions as a resource use item and the copy of the survey itself which was provided by the company. However, no data appear to be reported on this item in the study report. The data collected on whether the admissions were elective or non-elective do not appear to have been used to inform the average HRG cost for hospital admission."		costs is not correct. The ERG rightly noted that specific type of attendance (elective or non-elective) data were collected. However, hospital stay was measured using the total number of nights in the past six months in the general ward, specialised ward, ITU and/or others. The two questions used two different units of measurement and the information on elective and non-elective admissions could not be applied. For instance, a person who reported 10 days in general ward could have had that over two admissions, one on elective and the other as emergency. Hence a weighted mean across all admissions was used as HRG code (section B.3.5.1, page 118 of company submission).	available to the ERG at the time the report was written. The ERG would argue that the information on the proportion of admissions that are elective or non-elective should have been included in the study report as these data were collected. The reason why these data were not used to obtain a weighted mean of elective and non-elective inpatient stays could have been provided at the clarification stage in response to question B25c which asked "why specialist ward cost used a weighted average for total healthcare resource group activity across the listed codes instead of a more specific stay type (such as elective inpatient, non-elective or day case)" Instead the company stated in response to question B25c that "information on the specific type of attendance (elective, non-elective or day-case) were not available". If the company had wished to provide a more detailed explanation as to why the available data could not be used to calculate a weighted average then this could have been provided in response to

			clarification question B25.

Issue 6 Utility data

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report states that the analysis to develop the mapping algorithm should have imputed a value of zero for the missing data regarding bladder instillations.	We suggest that this is deleted.	[redacted] Therefore, it was not possible to make this assumption. Mapping is described in section B.3.4.3 (page 109) of the CS.	The ERG argue that the alternative assumptions regarding the possible explanations for this missing data have not been adequately explored and therefore it is better to use the regression without this variable.

Issue 7 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	
Table 4, page 39 For Sant et al. (2003) in 'Other characteristics" column: *Prior symptoms for ≥ 52 weeks, n (%):* PBO, 28 (90%); PPS, 28 (96%)	*Prior symptoms for ≥ 52 weeks, n (%):* PBO, **29 (94%);** PPS, 28 (96%)	Current text is incorrect	We have replaced with 'PBO, 29 (94%)'

Issue 8 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	
Table 4, page 39 For Mulholland et al. (1990) in 'Other characteristics' column: *Disease duration mean years:* PBO, 5.6; PBO, 7.4	Disease duration mean years: PBO, **5.8**; PBO, 7.4	Current text is incorrect	We have replaced with 'PBO,5.8'

Issue 9 Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.2.2, page 44: "Parsons et al. (1993), Mulholland et al. (1990) and Parsons and Mulholland (1987), all reported on the proportion of participants with a >50% pain improvement at three months. Respective values were: PPS 18% vs. PBO 38% (p=0.005), PPS 27% vs, PBO 14% (p=0.08), and PPS 44% vs. PBO 15% (p=0.02, CI not reported)."	"Parsons et al. (1993), Mulholland et al. (1990) and Parsons and Mulholland (1987), all reported on the proportion of participants with a >50% pain improvement at three months. Respective values were: PPS **38%** vs. PBO **18%** (p=0.005), PPS 27% vs, PBO 14% (p=0.08), and PPS 44% vs. PBO 15% (p=0.02, CI not reported)."	Current text is incorrect	We have replaced with 'Respective values were: PPS 38% vs. PBO 18%'

Issue 10 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.2.2, page 48: "In Table 24 of the CS, the company reports that in the RCT by Parsons and Mulholland (1987)16 at three months the mean improvement in nocturia was PBO -0.09 (SD 0.8) vs. PPS -2.1 (SD 2.2), p=0.05 (CI not reported)."	"In Table 24 of the CS, the company reports that in the RCT by Parsons and Mulholland (1987) at three months the mean improvement in nocturia was PBO **-0.9** (SD 0.8) vs. PPS -2.1 (SD 2.2), p=0.05 (CI not reported)."	Current text is incorrect	We have amended to 'improvement in nocturia was PBO -0.9'

Issue 11 Meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.4, page 68 "In addition, it is unclear to the ERG why the company refers to this meta-analysis as a sensitivity analysis."	Removal of sentence quoted	As part of the meta-analysis different scenarios investigating the effects of the inclusion and exclusion of RCTs were conducted/calculated to verify the sensitivity/consistency of results (section B.2.8.1, page 77 of the CS).	Section B.2.8.1 presents the results of two meta-analyses: 1) "An analysis of GRA was conducted in the 4 studies that reported a homogeneous patient population (patients who met the NIDDK criteria for IC/BPS and the European Society for the Study of Interstitial Cystitis (ESSIC) categories 2X or 3C" as in "The SPC [which] focuses on four trials in patients with IC/BPS (i.e. patients with Hunner's lesions and/or glomerulations)", and 2) "An

			additional analysis that includes the two studies with a broader BPS population is also presented". The first meta-analysis is the primary analysis, whilst the second meta-analysis is a sensitivity analysis. No change.

Issue 12 Clinical pathway

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.2.3, page 80 "However, the ERG notes that based on the company's presentation of the clinical pathway in Figure 2 of the CS, patients would not receive a cystoscopy and a confirmed diagnosis of IC/BPS until after they had failed to respond to first-line oral therapies including analgesics, antihistamines and other non-pharmaceutical interventions including as dietary and lifestyle advice. Therefore, the population modelled is assumed to be those who did not respond to these initial interventions and the cost-effectiveness results should	Removal / revision of the paragraph quoted	The paragraph quoted is inaccurate. Patients undergoing cystoscopy and confirmation of a diagnosis of IC/BPS is not dependent on their failure to respond to first-line treatments initiated at visit 1. Key investigations, including rigid cystoscopy +/- hydrodistension, that are needed to confirm the suspected diagnosis of BPS or IC/BPS typically need to be carried out at a follow-up visit. However, because there is often a long time between visits 1 and 2 (and the patient is, by definition, in pain) first line treatments will be started based on symptoms at Visit 1. These will be reviewed at visit 2 and a decision	We misunderstood Figure 2 of the CS. The text has been amended to reflect the fact that diagnosis may happen after initiation of first line therapy without the need for failure on first line therapy. However, we still believe that the relevant population is those who have failed the first line therapies described as being initiated in visit 1 as Figure 2 of the CS clearly states that bladder instillations would only be started on visit 2 if patients had failed to response to the treatments already initiated at

not be extrapolated to patients earlier in the clinical pathway."		on subsequent treatment(s) made in light of response to these treatments as well as the ultimate confirmed diagnosis. This information is provided in the Advisory Board (Appendix M of CS).	visit 1. The text now says "However, the ERG notes that based on the company's presentation of the clinical pathway in Figure 2 of the CS, patients would not receive bladder instillations a cystoscopy and a confirmed diagnosis of IC/BPS until after they had failed to respond to first-line oral therapies including analgesics, antihistamines and other non-pharmaceutical interventions including as dietary and lifestyle advice. Therefore, the population modelled is assumed to be those who did not respond to these initial interventions and the cost-effectiveness results should not be extrapolated to patients earlier in the clinical pathway."

Issue 13 Quality of Sant trial

Description of problem	Description of proposed amendment	Justification for amendment	
Section 1.6.1, page 14 "However, there are aspects of uncertainty surrounding one RCT of PPS in IC/BPS." And	Amend to note that the study was double-blind.	The trial by Sant et al. (2003) is described in the paper as double-masked; further we think it should be recognised that in their review of the study, the EMA concluded that this study was double-blinded (page	The ERG report was factually accurate given the information available from the Sant et al. (2003) trial report which did not report how the random sequence was generated or

Section 4.2.4, page 51 “With respect to allocation concealment and blinding of participants and personnel, whilst the other three RCTs report that these aspects of trial design were undertaken, there is no record of allocation concealment being undertaken in the Sant et al. (2003) trial report and, although the Sant et al. (2003) trial is described as ‘double-masked’, unlike the other three RCTs, specific details of who was blinded is not reported.”		43 of the elmiron® EPAR).	how allocation was undertaken. Blinding/masking is not part of this process. In the other PPS trials allocation was undertaken either using a code established and maintained by a separate centre, or by the pharmacy. The term double blind/masked is not adequate to indicate exactly who was blind – patients, care givers, investigators, outcome assessors, etc.

Issue 14 Screening process

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.1.2, page 29 "However, it is not clear if, at both of these stages of the study selection process, the reviewers worked collaboratively or independently (the latter reflects best practice). It is also not clear in the CS (CS, Appendix D) what proportion of citations at the sifting stage were double-checked (i.e., by both reviewers)."	"Abstract/title and full text screening were performed by two reviewers who worked independently."	The two reviewers worked independently throughout the screening process.	The ERG report was factually accurate given the company submission does not state that the study selection process was undertaken independently by two reviewers

Issue 15 Indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	
Page 62 "The eligibility criteria detailed in the trial papers included a diagnosis of IC/BPS, but do not report that Hunner's lesions and/or glomerulations are part of the diagnosis. However, patients in these trials are defined in the CS as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations."	Delete sentence "However, patients in these trials are defined in the CS as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations."	These (the 2 Uracyst® trials) were defined as having a BPS population in the CS. See page 82 "Differences in trial populations – most of the PPS trials comprised patients in the population of interest (i.e. IC/BPS), whereas the trials of Uracyst® included patients from the wider BPS population. This is also shown in Table 30 (Characteristics of Uracyst® studies) of the CS, which is replicated in Table 15 of the ERG report.	The ERG has deleted 'However, patients in these trials are defined in the CS as patients with bladder pain syndrome with Hunner's lesions and/or glomerulations.'

Issue 16 Durability of placebo response

Description of problem	Description of proposed amendment	Justification for amendment	
Page 87: The ERG states that "… the company has provided no evidence to demonstrate that the durability of response differs in patients receiving BSC compared to those receiving either PPS or BI."	This should be amended to refer to the evidence provided.	The statement is incorrect. Evidence was provided to NICE to support the assertion that the response observed for patients receiving placebo in the clinical trials would not endure beyond the trial period. This is provided in Appendix M of the CS. This clearly states that consensus was reached with 9 clinical experts that "Whilst active comparator response maintained over time, the placebo response recedes."	The ERG has amended this statement to "The ERG does not consider that this is reasonable given that the only evidence provided by the company has provided no evidence to demonstrate that the durability of response differs in patients receiving BSC compared to those receiving either PPS or BI is a consensus statement from clinical experts (Appendix M of the CS)."

Issue 17 Impact of bladder instillations on quality of life

Description of problem	Description of proposed amendment	Justification for amendment	
Page 91: The ERG report states that "The ERG does not understand the clinical rationale for there being a utility decrement associated with having previously received BIs" The ERG report states that "The ERG asked their clinical experts	All references to the utility decrement for current or recent experience of bladder instillations should be referred to as [having] "received a bladder instillation in the previous 6 months" Suggest deleting statement or amending to include the evidence from the consensus of the clinical experts at the Advisory Board (provided	The text currently implies that the utility decrement is applied if a patient has ever received a bladder instillation, whereas the survey specifically asked about recent experience. As previously stated in our submission and response to clarification, bladder instillations can have a substantial impact on patients' quality of life. This was	The ERG has amended the text on page 91 to say ""The ERG does not understand the clinical rationale for there being a utility decrement associated with having received BIs in the previous 6 months" An additional change has also been made on page 92 to

whether UTIs were likely to significantly impact either costs or HRQoL and were reassured that UTIs associated with BIs were usually easily avoided or easily treated if they occurred."	in Appendix M of the CS).	agreed at the advisory board involving 9 clinical experts in the treatment of BPS. For balance, we consider that this should also be reflected in the ERG report.	change "previous BI usage" to "usage of BIs in the previous 6 months" on 2 occasions. A similar change has also been made on page 97 and 119. The ERG report already states the company's position that bladder instillations are invasive and uncomfortable on page 91 of the ERG report where the involvement of clinical experts in informing this position is made clear.

Issue 18 Frequency of bladder instillations

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG assumes that bladder instillations are administered 6-weekly after one year.	This should be amended to 4-weekly.	The interval between instillations is variable and individualised to patients' need i.e. consideration of how quickly pain returns after an instillation and before the next instillation is administered. Whilst clinicians may aim for longer intervals e.g. 6–8 weeks, some patients require more frequent instillations e.g. 3-weekly.	This is not a factual inaccuracy. The ERG made an alternative assumption to the company's preferred assumption on the frequency of bladder instillations in the long-term based on their discussions with clinical experts.

		Therefore, the advisory board consensus (Appendix M of the CS) was to use weekly and then 4-weekly instillations in the model. This is also in accordance with the manufacturers' instructions which stipulate monthly administration in their product instructions.	

Issue 19 Indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	
Page 56, section 4.3.1 "Although not specifically stated in Section B.2.9 of the CS (page 80), it appears that the trials proposed to be included in the ITC were identified from the SLR methods described in Section 4.1 ."	"The trials proposed to be included in the ITC were identified from the SLR methods described in section 4.1."	The SLR methods were used to identify the trials for the ITC.	The ERG report was factually accurate given the information available in B.2.9 of the company submission does not specifically state that this was the same SLR

Issue 20 Inclusion of studies with broader BPS population

Description of problem	Description of proposed amendment	Justification for amendment	
Page 68, section 4.4 "The company's misinterpretation of Cochran's Q value is repeated when they include two additional studies with a broader BPS population (18, 19) that the ERG recognises do not satisfy the inclusion/exclusion criteria for the assessment..."	Revision of the paragraph quoted.	The 2 additional studies that considered a broader population were included as a sensitivity analysis and reported in the notion of using all available evidence.	The original wording in the ERG report acknowledged that the second meta-analysis included two trial that did not satisfy the inclusion criteria but did not specifically state that this was a sensitivity analysis Additional text has been added to clarify that the second meta-analysis was done as a sensitivity analysis. Text changed to: "The company's misinterpretation of Cochran's

			Q value is repeated when they include two additional studies with a broader BPS population (18, 19) that the ERG recognises do not satisfy the inclusion/exclusion criteria for the assessment but was performed as a sensitivity analysis."

Issue 21 Including deaths in time to discontinuation analysis

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.2.10 The ERG revised the time to discontinuation analysis by adding more reasons for discontinuation other than the lack of efficacy or adverse events. The additional discontinuation categories are: a) Failed to return (n=154) b) Death (n=7) c) Other (Never took study drug, switched to other treatments, transferred physicians, financial, relocated, surgery, unknown, etc.) (n=745) d) A remainder (n=138) who are included in the total figure who discontinued but are not listed under any of the above categories Although arguments can be given for excluding/including certain categories, we feel that including deaths as a reason for discontinuation results in	We suggest excluding deaths as a reason for discontinuation in the analysis used as an input in the ERG model base case.	Including deaths twice in the economic model introduces bias in the analysis. Excluding deaths from the time to discontinuation estimation is not expected to have a significant impact on the results.	We have reconsidered this and we agree that patients who died should be treated as censored as death and treatment discontinuation are competing events within the DES model structure. However, we agree with the company that excluding deaths from the time to discontinuation estimation is not expected to have a significant impact on the results. The ERG estimates that the impact on the ICER is

double counting deaths as an event in the cost-effectiveness model.			likely to be less than 0.5% and therefore we have not updated all of the results to correct for this error.

Issue 22 BSC response rate - Impact on ICER

Description of problem	Description of proposed amendment	Justification for amendment	
Section 7 The likely response rate for BSC in clinical practice is mentioned in the conclusion as a factor with potentially significant impact on the ICER.	We suggest removing the statement that BSC response rate is a factor with a significant impact on the ICER.	In the most relevant comparison (against bladder instillations) even in the extreme scenario of doubling the BSC response rate, the ICER increases by 15% (in the company submitted base case).	Changing the response rate from 5% to 32% had a very large impact on the ICER in the ERG's exploratory analyses (see Tables 30 and 31). Therefore it appropriate for us to report this a key area of uncertainty in section 7.

Issue 23 Amendment in discontinuation rate affecting the results of the comparison with Bladder instillations

Description of problem	Description of proposed amendment	Justification for amendment	
Section 1.5 "Underestimation of discontinuation rates from Hanno et al. (1997) which affects the lifetime treatment costs, particularly for the comparison of PPS versus BSC."	"Underestimation of discontinuation rates from Hanno et al. (1997) which affects the results in the comparison of PPS versus BSC."	Alternative assumptions on including/excluding reasons for discontinuation do not have any notable effect on the comparison versus bladder instillations.	Whilst we accept that the impact on the ICER for the comparison of PPS vs BBI is minimal, it would be inaccurate to say that this has no impact which is why we have phrased the statement to say that this is a key area of concern "particularly for the comparison of PPS versus BSC".

Issue 24 Statement around the durability of response in BSC, BI and PPS

Description of problem	Description of proposed amendment	Justification for amendment	
Section 1.5 "Inconsistent assumptions around the durability of response in those receiving BSC and those receiving either PPS or BIs."	Revision of the sentence quoted	The statement is incorrect. Evidence was provided to NICE to support the assertion that the response observed for patients receiving placebo in the clinical trials would not endure beyond the trial period. This is provided in Appendix M of the CS. This clearly states that consensus was reached with 9 clinical experts that "Whilst active comparator response maintained over time, the placebo response recedes."	This is not a factual inaccuracy. The company's model does make inconsistent assumptions around the durability of response in those receiving BSC and those receiving either PPS or BIs.

Issue 25 Use of 20-year time horizon

Description of problem	Description of proposed amendment	Justification for amendment	
Section 1.5 – pg 13 "In addition, the ERG believes that a lifetime horizon would have been preferable to the company's 20-year time horizon."	Revision of the sentence quoted	The 20-year time horizon captures the great majority of the cost and health effects in the modelled treatments. Using a lifetime horizon in the base case does not have a notable effect in the cost-effectiveness results.	This is not a factual inaccuracy.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 17 May 2019 at 5pm**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	**Michael Ho**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Consilient Health**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Indirect treatment comparison	
Mindful that there are challenges with all approaches for comparing pentosan polysulfate sodium with bladder instillations, which is the best indirect treatment comparison to use in this appraisal (an indirect treatment comparison using a Bayesian network meta-analysis or the Bucher method)?	The original company submission has used the Bucher method recognising there was considerable heterogeneity in the trials to allow for a robust indirect comparison. As highlighted by the ERG, neither the Bucher method nor a Bayesian network meta-analysis (NMA) are ideal for comparing PPS and bladder instillation due to challenges with both approaches. The ERG expressed a preference for a Bayesian NMA because: • The Bucher method maintains treatment effect estimates from the separate underlying meta-analyses, whereas a Bayesian NMA incorporates all the data into estimating a common random treatment effect (which the ERG considers to be preferable) • As implemented, the Bucher method assumes that the sample estimate of the effect of PPS compared to Uracyst follows an approximately normal distribution; the ERG considers that this assumption may not hold. To respond to the ERG's request, the company conducted a Bayesian NMA using the same clinical data considered in the original submission (section B.2.8). As noted in our original submission, we are using the placebo arm of the relevant clinical trials to source the treatment effectiveness of BSC since we are unaware of any contemporary data reporting the 'response' to standard of care i.e. initial treatments (e.g. pain management, etc). Both a fixed effect and random effects model were run in line with NICE guidelines, both of which generated results similar to the pairwise meta-analyses (Bucher approach). Due to the between-study standard deviation (sd) being non-stationary in the random effects model which used a uniform vague prior for the sd, the model was re-parameterised to sample from the between-study

precision (1/sd^2) instead of the sd as we think the uniform priors trialled for the sd were causing extreme values in the chains. The distribution we used to model precision is a vague Gamma prior in line with NICE guidelines and taken from the NICE DSU TSD 2. All analyses were conducted on the logit scale, relative risk estimates were obtained by back-transforming resulting parameter estimates to the probability scale.

The random-effects model using the re-parameterisation gave a lower DIC and total residual deviance than the previous parameterisation, and closer treatment estimates to the fixed effect model. Separate documents which include the WinBUGS code and the detailed results are also submitted as part of this response.

Table 1: Results of the network meta-analysis – treatment response rates

Random effects model			
Treatment effect	Lower 95% CL	Median	Upper 95% CL
Placebo	0.1462	0.1887	0.2369
PPS	0.2887	0.3843	0.4881
Uracyst	0.1608	0.2804	0.4414
DIC = 66.506 Total residual deviance = 9.311			
Fixed effects model			
Treatment effect	Lower 95% CL	Median	Upper 95% CL
Placebo	0.1473	0.1896	0.2377
PPS	0.3044	0.3843	0.4691
Uracyst	0.1728	0.2793	0.4181
DIC = 66.561 Total residual deviance = 8.94			

Both fixed effect and random effect models had similar DIC and total residual deviance and therefore no model dominated with regards to model fit. The differences between models are very minor however the random effects model was deemed more appropriate as the base case in order to model the between-study heterogeneity and account for the clinical, patient and trial differences between studies.

The outputs of the random effects model were used as inputs for the cost-effectiveness model. To obtain the relevant cost-effectiveness results, the Excel model was updated to reflect the discussions held at the NICE technical engagement tele-conference (10/05/19). The following amendments were applied and now formulate the updated company basecase:

- Time horizon is lifetime (Issue 2)
- The effectiveness of BSC is not receding through the time horizon (Issue 3)
- The ERG treatment discontinuation is now adopted (Issue 4)
- A revised mapping algorithm including alternative approach for handling missing data is now applied (Issue 5)
- The HRQoL for non-responders who move onto best supportive care returns to baseline after the 6-month response check (Issue 6)

Using the treatment response rate outputs for each comparator from the random effects model as inputs for the cost-effectiveness model increased the ICER reported in the updated company base-case (using the Bucher method) by [redacted]. This is due to the Bayesian NMA generating treatment response rates comparable to those generated by the Bucher comparison approach.

Table 2: Cost-effectiveness results

Results vs BI – original company base-case (Bucher method)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]
Results vs BI – updated company base-case (Bucher method)		
	Costs	QALYS
PPS	[redacted]	[redacted]

	Bladder instillations [redacted] [redacted] ICER [redacted] Results vs BI (Bayesian NMA – random effects model) - using updated company basecase Costs / QALYS PPS [redacted] [redacted] Bladder instillations [redacted] [redacted] ICER [redacted] See Appendices B-F.
Issue 2: Time horizon in economic model	
Are there any costs or consequences associated with PPS that would fall outside of a 20-year time horizon?	As outlined by the ERG's exploratory analysis, when imputing the time on treatment in those who die before discontinuing treatment or who reach the end of the time horizon before either dying or discontinuing, the percentage of patients on PPS and BI treatment is at 6% and 4% respectively. Using a lifetime horizon in the updated company base case does not have a notable effect in the cost-effectiveness results. In the company revised base case, the ICER in the comparison versus

	BIs increases by [redacted] per additional QALY gained when switching from a 20-year time horizon to a lifetime horizon. The original company basecase analysis used a 20-year time horizon since it believes it captures the great majority of cost and health effects. To align with the ERG's preference, the revised company base-case now includes a lifetime horizon. *(The model accounts for any differences in all-cause mortality between males and females reflected in the overall life expectancy.)*
Issue 3: Modelled response rate	
Based on a meta-analysis, the company assume 16% of patients would respond to best supportive care with no intervention. Is this assumption reasonable?	The meta-analysis was based on 4 published trials in the licensed population. There was a high level of consistency demonstrated across all four studies regarding the observed response to best supportive care (BSC). No other published evidence exists to our knowledge; consequently, we sought to validate the meta-analysis result by asking UK clinical experts what they saw in day-to-day practice. Answers were received from 10 clinical experts and their responses are tabulated in the attached Appendix G. Whilst there was variation in their responses to the question regarding the proportion of patients who, if managed with BSC alone would have symptom resolution, it is clear that between 0 and 30 % would receive some symptom resolution and up to 50% might have some level of symptom improvement. The meta-analysis finding of 16% responding to BSC would appear to be broadly in line with the experience of UK clinicians. All the clinical experts agreed that the symptom improvement/resolution would be short-lived. This view is reiterated by Suzanne Biers in her correspondence with the Committee (11 May 2019). Patients receiving symptom resolution or symptom relief are unlikely to receive either bladder instillations or PPS until such time as their symptoms deteriorate or return.

The company assume that any response in patients receiving best supportive care would not last more than 12 months. Is this assumption appropriate?	Input from 10 UK clinical experts on the durability of response to best supportive care (BSC) was received (see Appendix G). The overall consensus was that in those patients that did respond, symptoms would return and that relapse would occur in about 6 months, though responses did vary from <3 months to 1 year. Based on these responses, it is therefore quite conservative to assume a response would last as long as 12 months. This is consistent with the comments received by Suzanne Biers in her correspondence with the Committee (11 May 2019). It is important to note that for the purposes of the appraisal and economic model (and as seen in clinical practice) it was assumed that all patients will, either leading up to or for a period following diagnosis, be managed with BSC. The point at which patients with be considered for either bladder instillations or PPS is when BSC is no longer sufficient to manage all the patients symptoms. Our appraisal submission and economic model for the comparison of bladder instillations v PPS starts at this point. The comparison of PPS versus BSC in our economic model only applies to patients for whom bladder instillations are not an option for treatment, e.g. due to a history of UTI's or known allergies. This is only a small minority of <5% (based on expert opinion, see Appendix P of original submission). These patients are already being sub-optimally managed with BSC alone hence the decision to add something else into their treatment regimen. To therefore expect to see long-lasting improvements in their symptoms when they are continuing on a therapy that is already not working is unrealistic. Whilst we believe that the assumptions made in the original model are valid and conservative, we have incorporated the ERG's recommendations into our basecase.
Issue 4: Time to treatment discontinuation	
Should the survival analysis account for all known discontinuations?	The ERG revised the time to discontinuation analysis by including more reasons for discontinuation other than the lack of efficacy or adverse events.

	The additional discontinuation categories are: a) Failed to return (n=154) b) Death (n=7) c) Other (Never took study drug, switched to other treatments, transferred physicians, financial, relocated, surgery, unknown, etc.) (n=745) d) A remainder (n=138) who are included in the total figure who discontinued but are not listed under any of the above categories As already highlighted to the ERG, including deaths as a reason for discontinuation results in double counting deaths as an event in the cost-effectiveness model. Although we accept that this is not expected to have a significant impact on the results. Regarding items c) and d), depict a mixture of patients who were lost to follow up and those who switched treatments. The exact reasons for discontinuation are unclear. It is possible that those who 'transferred physicians' or who 'relocated' would have continued treatment in alternative locations/clinical practices. Given the way the data are reported it is not possible to separate these groups out from the other patients. The updated company basecase now considers the ERG treatment discontinuation approach although we consider it to be overly conservative.
The company's model predicts that the proportion of patients remaining on PPS at 5, 10 and 20 years would be 22%, 15% and 6%, and the ERG's model predicts these proportions to be 9%, 4% and 1% (see Table A). Which set of predictions is most reasonable?	Please see response above.
The company's model predicts that the proportion of patients remaining on BIs at 5, 10 and 20 years would be 15%, 10% and 4%, and the ERG's model predicts these proportions to be 7%, 3% and 2% (see Table A). Which set of predictions is most reasonable?	Please see response above.

Issue 5: Utilities associated with the use of bladder instillations	
The company assume a utility decrement (a reduction in quality of life) of around [redacted] associated with the use of BIs. Is this assumption appropriate?	Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects (as also portrayed in the patient cases studies we submitted in the original company submission, Appendix N). Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections (UTIs). This is summarised in Appendix M of the original company submission and also mentioned by the clinical expert participating in this appraisal process. Suzanne Biers (as per comments in the original Technical Engagement Papers): "…It would provide an additional minimally invasive option (i.e. medical option) to help treat this condition. It would add an additional step in the treatment options, before more invasive therapies were considered (i.e. such as catheterization for bladder instillations or surgery), which would benefit patients if the treatment was effective and avoid the risk of increased side effects which are associated with more invasive treatment options." "…(i.e. bladder instillations require insertion of a temporary catheter in order to instil the treatment which can irritate the urethra and exacerbate symptoms in some patients)." In relation to urinary infections, these are known to be associated to bladder instillations (alongside bladder pain) (BAUS 2017). A systematic review of the impact of UTIs on health-related quality of life conducted as part of the NICE clinical guideline (CG139 and Bermingham 2012) on healthcare associated infections found that individuals with UTIs had significantly lower quality of life (QoL) compared to individuals without UTIs. The systematic review reported results for 6 studies which used a variety of quality of life instruments (SF36 mapped to EQ-5D SF-6D, SF12 mapped to EQ-5D, HUI2 and QWB). The utility difference for UTI vs no UTI groups varied, however on average it was found to be approximately 0.10. Considering that UTI is one of the most common side-effects for bladder instillations and not the only side-effect associated to their

invasive nature, we consider the decrement of 0.06 reflective of this fact and appropriate for use in the cost-effectiveness model.

Table 3: Utilities associated with urinary tract infections

Study	Instrument	No UTI	UTI	Difference
Ellis and Verma 2000	EQ-5D (mapped from SF-36)	0.922	0.724	0.20
Abrahamian 2011	EQ-5D (mapped from SF-36)	0.584	0.565	0.02
Ernst 2005	QWB (using VAS)	0.82	0.68	0.14
Maxwell 2009	HUI2	0.49	0.4	0.09
Vogel 2002	EQ-5D (mapped from SF-12)	0.831	0.738	0.09
Haran 2005	SF-6D	0.68	0.58	0.10
Haran 2005	SF-6D	0.7	0.6	0.10

We note the ERG's concerns regarding the handling of missing data for the variable 'BI use in the previous 6 months' in the analysis. We have explored two alternative approaches. One approach suggested by the ERG was to impute a value of zero for the missing data regarding bladder instillation use. Our analysis found that this would not be appropriate since respondents who did not complete the question regarding frequency of bladder instillations were different from those who reported receiving no bladder instillations within the preceding 6 months as reported in the fact check to the ERG. Specifically, [redacted]. In an alternative analysis, respondents with missing data for this question were excluded. The results of the mapping function including missing data as 'missing' (i.e. dropped from analysis) are shown in Table 4. The impact of this on the results is to reduce the ICERs.

Table 4 Mapping coefficients using ICSI score, age and bladder instillation

EQ-5D	Coefficient (SE)
Logit	
ICSI score	[redacted]
	[redacted]
18 to 34 years	[redacted]
35 to 44 years	[redacted]
45 to 54 years	[redacted]
	[redacted]
55 to 65 years	[redacted]
	[redacted]
65 years or older	[redacted]

Bladder instillation no	[redacted]	
Bladder instillation yes	[redacted]	
Constant	[redacted]	
	[redacted]	
OLS		
ICSI score	[redacted]	
	[redacted]	
18 to 34 years	[redacted]	
35 to 44 years	[redacted]	
	[redacted]	
45 to 54 years	[redacted]	

	[redacted]	
55 to 65 years	[redacted]	
	[redacted]	
65 years or older	[redacted]	
	[redacted]	
Bladder instillation no	[redacted]	
Bladder instillation yes	[redacted]	
	[redacted]	
Constant	[redacted]	
	[redacted]	
Log likelihood	[redacted]	[redacted]
Pseudo R square	[redacted]	

AIC	[redacted]	[redacted]
BIC	[redacted]	[redacted]
RMSE		[redacted]

Table 5: Mean EQ-5D values for each health state

	Basecase	Excluding missing data
elmiron pre-response assessment	[redacted]	[redacted]
elmiron non-responders	[redacted]	[redacted]
elmiron responders	[redacted]	[redacted]
Bladder instillations pre-response	[redacted]	[redacted]
Bladder instillations non-responders	[redacted]	[redacted]
Bladder instillations responders	[redacted]	[redacted]
BSC pre-response assessment	[redacted]	[redacted]
BSC non-responders	[redacted]	[redacted]
BSC responders	[redacted]	[redacted]

The resulting ICER for this scenario is summarised in the table below.

Table 6: Updated cost-effectiveness results using revised mapping algorithm

Results vs BIs (including missing data)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]
Results vs BIs (excluding missing data)		
	Costs	QALYS
PPS	[redacted]	[redacted]
Bladder instillations	[redacted]	[redacted]
ICER		[redacted]

Whilst it is not possible to conclude a cause/effect relationship between bladder installations and quality of life from this cross-sectional survey, it does provide evidence of an association. In the absence of other data, this survey represents the best available evidence of the quality of life of patients with BPS. The quality of life data have been collected and analysed using methods recognised by NICE: data have been collected directly from patients experiencing the condition using NICE's preferred outcome measure (EQ-5D). The analysis accounts for disease severity

<table>
<tr><td></td><td>and age of the patient within the model. Further exploration of potential confounding variables have been considered and ruled out, and are reported below.

The inclusion of a utility decrement is consistent with feedback from the clinical experts that BIs have a negative impact on the quality of life of patients. Furthermore, the utility decrement is broadly consistent with evidence on the impact of UTIs on health-related utility. It is noted from the patient case studies (see original submission Appendix N) that the UTIs experienced by patients with IC/BPS may have a significantly greater impact on their lives than a UTI in the general population.

The mapping analysis is robust to alternative approaches for handling missing data and therefore it is part of the updated company basecase.</td></tr>
<tr><td>Could ‘usage of BIs in the previous 6 months’ reflect any other markers that may have not been explicitly modelled (such as time since diagnosis, or disease severity)?</td><td>Disease severity is already accounted for in the analysis through the ICSI and ICPI measures. The negative impact of recent bladder instillation is in addition to the adjustment for disease severity.

We have investigated whether usage of BIs in the previous 6 months could reflect time since diagnosis as suggested and conclude that this is not the case.

Time since diagnosis was recorded as part of the survey. The analysis reported below demonstrates that there is no statistically significant relationship between time since diagnosis and the probability of undergoing a BI in the preceding 6 months (logistic regression model, ‘bladder instillation in the previous 6 months’ as the dependant variable).

Table 7: Relationship between bladder instillation and time since diagnosis
<table>
<tr><td>Variable</td><td>Coef.</td><td>Std. Err.</td><td>z</td><td>P>z</td><td>[95% Conf.</td><td>Interval]</td></tr>
<tr><td>Years since diagnosis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Constant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

Issue 6: Utilities associated with response	
Is it reasonable to assume that health related quality of life for non-responders who move onto best supportive care will return to baseline after the 6-month response check?	We accept ERG's/NICE's comments.
Issue 7: Modelled costs and resource use	
In clinical practice, what is the frequency of BI administrations?	Regarding the frequency of bladder instillations, the manufacturers' recommendations for administration of the bladder instillations is typically weekly for 4 weeks then increased to once every 4 weeks. This was also discussed at an advisory board, run by Consilient Health in September 2018 with 9 urology/urogynaecology consultants or specialist nurses. The ad board agreed that treatment should be tailored to the individual patient's needs, and frequency of bladder instillations was typically guided by when the patient experienced a return of painful symptoms. This leads to a degree of variability in the dosing frequency of bladder instillations in clinical practice; while some patients are able to tolerate a longer interval than 4 weeks, but some patients unfortunately require even more frequent instillations. Therefore, on balance, the advisory board consensus statement on the dosing regime for bladder instillation use was weekly for 4 weeks then once every 4 weeks thereafter, consistent with the manufacturers' recommendations. Bladder instillation are indicated for, and used in, multiple conditions (such as recurrent bacterial cystitis, radiotherapy-induced cystitis and BPS) and, while not typically specified in the manufacturers' information, those which are used for transient conditions may be limited to a 6 month course. The Consilient Health advisory board recognised that IC/BPS is a long-term, chronic condition requiring long-term treatment. We believe that the 6 month course mentioned by Suzanne Biers in her response (11 May 2019) may relate to BIs being used in all conditions, or be related to local protocols linked to cost control. We have sought further input from UK experts: see Appendix G. Considering the feedback from these 10 respondents again shows there is a degree of variability in clinical practice and while

	intervals of longer than 4 weeks are used in some patients, there is a not insignificant minority (10-30%) that require more frequent instillations. It is worth considering the patient experience when using bladder instillations. We understand that the effect of a bladder instillation wanes over time following the dose and, increasingly, the pain returns before they get their next dose. Therefore, extending the interval between instillations is not without adverse consequences for patients and their quality of life. It should also be noted that in the model, we have taken the conservative assumption that when a patient changes bladder instillation that they immediately go onto a maintenance dosing regime of once every 4 weeks, as opposed to restarting with initiation dosing i.e. weekly for 4 weeks as the patient had previously failed on their current bladder instillation and was therefore in pain. Overall, there is variability in clinical practice with regard to frequency of bladder instillations, with some patients requiring instillations more often than 4 weekly and some less often. Therefore, we propose to stay with the manufacturers' recommendations of weekly instillations for 4 weeks then once every 4 weeks thereafter as our model basecase.
In clinical practice, what proportion of patients would be admitted through inpatient services for IC/BPS?	We agree that the majority of resources used by patients suffering with IC/BPS would be incurred in an outpatient setting. However, considering the procedures and side effects that may be required by IC/BPS patients, it is not unreasonable to expect that there will be some proportion resources used in an inpatient setting that are directly attributable to their condition. For example, patients undergoing rigid cystoscopy require general anaesthesia, which carries the risk of complications and may require patients to stay overnight. Catheterisation of IC/BPS patients, either for examination/diagnostic purposes, can result in infections, which, if severe or undertreated could lead to hospitalisation for IV antibiotics. This is reflected in the comments by Suzanne Biers (11 May 2019) that events requiring inpatient care are uncommon but can occur. An analysis of HES data (as supplied with the original submission Appendix O) indicates that whilst the majority of patients with IC/BPS are managed on an out-patient basis, a small

	percentage of patients will require an inpatient stay either for the management of a UTI, delivery of a bladder instillation or cystoscopy with hydrodistension (delivered under general anaesthesia). A copy of the full analysis of HES has been supplied as Appendix H to this response.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient Access Scheme submission template

January 2019

1 Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) the transition arrangements as set out in paragraph 3.28 states that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the VPAS (2019), any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow NICE to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies

This document is the Patient Access Scheme submission template for technology appraisals. If companies want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal April 2018. The 'User guide for company evidence submission template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

3.2 Please outline the rationale for developing the Patient Access Scheme.

A confidential Simple Discount scheme to reduce the effect price to the NHS to improve the cost effectiveness of the medicine

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

A confidential Simple Discount scheme of [redacted] is proposed reducing the list price from £450.00 (per pack of 90 capsules) to [redacted].

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

As per the NICE submission, the PAS covers the technology's full marketing authorisation for this indication.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain

criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme will apply to all patients; it is not dependent on any certain criteria.

Note: to maintain the confidentiality of the Simple Discount supply will be via NHS Hospitals (or contracted-out dispensing of NHS outpatient prescriptions by non-NHS organisations). Due to practical issues with implementing a confidential PAS price in primary care, the discount cannot be offered to community pharmacies. However, this is a rare, specialist diagnosed condition so patients can be managed via secondary care.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100%

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The Simple Discount will be applied to the original invoice to the purchasing organisation.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The Simple Discount will be applied to the original invoice to the purchasing organisation. No additional information is required to be collected by the NHS.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

N/A. The Simple Discount will be applied to the original invoice to the purchasing organisation.

3.10 Please provide details of the duration of the scheme.

In accordance with the PASLU Patient Access Scheme proposal template (Simple Discount scheme), the simple discount scheme will be in place from the date of guidance publication and until NICE next reviews the guidance on the product and a final decision has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The scheme applies to the full population defined in the marketing authorisation and is the same as presented in the submission.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

The cost-effectiveness results presented below are based on the economic model previously submitted with the amendments outlined in the response to the Technical Engagement document. No amendments in addition to the PAS have been made.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the appraisal committee considered most plausible.

The PAS has been incorporated into the model as a simple [redacted] price reduction to the list price.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

The clinical effectiveness data used in the economic model is the same as that reported in the submission document. The analysis was based on a indirect comparison of PPS with bladder instillations using data on Global Response Assessment from 4 trials of PPS compared to placebo and 2 trials of Uracyst compared to placebo:

- Mulholland, S.G., Sant, G.R., Hanno, P., Staskin, D.R. and Parsons, L. (1990). Pentosan polysulfate sodium for therapyof interstitial cystitis. *Urology*. [Online]. 35 (6). p.pp. 552–558

- Parsons, C.L., Benson, G., Childs, S.J., Hanno, P., Sant, G.R. and Webster, G. (1993). A Quantitatively Controlled Method to Study Prospectively Interstitial Cystitis and Demonstrate the Efficacy of Pentosanpolysulfate. *The Journal of Urology*. [Online]. 150 (3). p.pp. 845–848

- Sant, G.R., Propert, K.J., Hanno, P.M., Burks, D., Culkin, D., Diokno, A.C., et al. (2003). A Pilot Clinical Trial of Oral Pentosan Polysulfate And Oral Hydroxyzine in Patients With Interstitial Cystitis. *The Journal of Urology*. [Online]. 170 (3). p.pp. 810–815.

- Parsons, C.L. and Mulholland, S.G. (1987). Successful Therapy of Interstitial Cystitis with Pentosanpolysulfate. *The Journal of Urology*. [Online]. 138 (3). p.pp. 513–516

- Nickel, J.C., Egerdie, R.B., Steinhoff, G., Palmer, B. and Hanno, P. (2010). A Multicenter, Randomized, Double-blind, Parallel Group Pilot Evaluation of the Efficacy and Safety of Intravesical Sodium Chondroitin Sulfate Versus Vehicle Control in Patients With Interstitial Cystitis/Painful Bladder Syndrome. *Urology*. [Online]. 76 (4). p.pp. 804–809.

- Nickel, J.C., Hanno, P., Kumar, K. and Thomas, H. (2012). Second Multicenter, Randomized, Double-blind, Parallel-group Evaluation of Effectiveness and Safety of Intravesical Sodium Chondroitin Sulfate Compared With Inactive Vehicle Control in Subjects With Interstitial Cystitis/Bladder Pain Syndrome. *Urology*. [Online]. 79 (6). p.pp. 1220–1225.

The indirect comparison of PPS versus Uracyst® was conducted in the economic model using the Bucher method by comparing meta-analysed data from the two Uracyst® trials to the meta-analysis of data from the PPS trials. Treatment response for the two treatments was obtained by applying the relevant risk ratios to the placebo response rate observed in the 4 PPS trials (Table 1). More details can be found on section 6 - Response to treatment.

Table 1 Modelled treatment response

Treatment	**Response % (CI)**	**Source**
BSC (placebo)	0.158 (0.116, 0.212)	Parsons (1987), Mulholland (1990), Parsons (1993), Sant (2003)
Treatment	**Relative risk (CI)**	**Source**
PPS	2.09 (1.47, 2.97)	Parsons (1987), Mulholland (1990), Parsons (1993), Sant (2003)
Bladder instillations	1.39 (0.89, 2.17)	Nickel (2010), Nickel (2012)
Treatment	**Response %**	
PPS	0.331	Product of applying the relevant risk ratios on the placebo response rate
Bladder instillations	0.220	

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 3.5 of the 'User guide for company evidence submission template'**Error! Hyperlink reference not valid.**.

The scheme is offered as a simple price discount and has no additional costs associated with its implementation.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

The scheme is offered as a simple price discount and has no additional treatment-related costs associated with its implementation.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

The economic model does not output broken down figures for treatment costs and other costs.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 2. Comparison versus bladder instillations

BASE-CASE	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICER per QALY
Bladder Instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PAS discount	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICER per QALY
Bladder Instillations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. Comparison versus BSC

BASE-CASE	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICER per QALY
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PAS discount	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICER per QALY
Best supportive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

care					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1. DSA - Comparison versus bladder instillations

[redacted]

Figure 2. DSA - Comparison versus best supportive care

[redacted]

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 3. Scatter plot - Comparison versus bladder instillations

Figure 4. CEAC - Comparison versus bladder instillations

Figure 5. Scatter plot - Comparison versus best supportive care

Figure 6. CEAC - Comparison versus best supportive care

4.11 Please present scenario analysis results as described for the main company submission of evidence for the technology appraisal.

Table 4. Comparison versus bladder instillations

Scenario	PPS costs	PPS QALYs	BI costs	BI QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using the Bayesian NMA meta-analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICPI based utilities and background costs (including BI missing data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities from literature - (Cervigni 2017)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using least expensive product for BI (subsequent treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% self-administration of BIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-month response check	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon - 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery as part of subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate for PPS including 2 wider population clinical trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frequency BI administrations (post 1st month) set to 6 weeks (base-case is 4 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. Comparison versus best supportive care

Scenario	PPS costs	PPS QALYs	BSC costs	BSC QALYs	Incremental Cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using the Bayesian NMA meta-analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICPI based utilities and background costs (excluding BI missing data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities from literature - (Cervigni 2017)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC effect sustained and receding at 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC effect sustained and receding at 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-month response assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery as part of subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon – 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate including 2 wider population clinical trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the appraisal committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is

shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the appraisal committee considered to be most plausible.

Table 6. Results showing the impact of Patient Access Scheme on ICERs

	ICER for intervention versus:			
	Bladder instillations		**Best supportive care**	
	Without PAS	**With PAS**	**Without PAS**	**With PAS**
Basecase analysis	[redacted]	[redacted]	[redacted]	[redacted]

PAS: Patient Access Scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection

- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A

5.4 Please specify the period between the time points when the additional evidence will be considered.

N/A

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

N/A

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

N/A

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

N/A

Correspondence with clinical expert

Jonathan Goddard (Consultant urological surgeon) – TC 12/04/2019

Quality of clinical evidence for pentosan polysulfate sodium (PPS)

Questions to expert	• Is the available evidence for pentosan polysulfate sodium (PPS) generalisable to UK clinical practice?
Summary of clinical expert input	• There is not much evidence available, and unlikely to be anything newer than the trials identified before the meeting. • The evidence supporting the appraisal focuses on the population with glomerulations or Hunner's lesions • Diagnostic tests aren't perfect in this disease area • Glomerulations can occur in a normal bladder, and I would not typically use these to diagnose interstitial cystitis/bladder pain syndrome however, I am aware that EAU & AUA guidelines do include these in their diagnostic pathway. Also these were used as inclusion in the original trials. • Hunner's lesions are associated with interstitial cystitis/bladder pain syndrome • Hunner's lesions would typically be managed with surgery rather than with PPS or instillations (although PPS or instillations are ~~is~~ sometimes given to people with Hunner's lesions) • Wouldn't deny treatment with PPS for patient with Hunner's lesions, but wouldn't actively to choose it as a primary treatment • Perhaps would consider in patients with Hunner's lesions if they were unfit for surgery, but this is likely to be rare or if surgery did not work • It would be unusual for me to use PPS or instillations as a primary treatment in the indicated population; PPS works, but in a different population (i.e. not patients with Hunner's lesions)

Clinical population

Questions to expert	• Would people with bladder pain syndrome be expected to have the same response to therapy (with bladder instillations or PPS) as people with interstitial cystitis/bladder pain syndrome with glomerulations or Hunner's lesions?
Summary of clinical expert input	• People with Hunner's lesions are likely to be treated surgically and so are ~~not~~ less likely to have bladder instillations or PPS so it is difficult to answer that. • If people with Hunner's lesions were to be given bladder instillations or PPS, expected response would be different to people with general bladder pain syndrome •

Treatment of condition in clinical population

Questions to expert	• Would Hunner's lesions ever be treated with laser surgery? Would this be used at the same point in the pathway as PPS? • Would intravesical DMSO ever be used in this population? • For people without Hunner's lesions, would you consider pelvic floor exercises to be included in best supportive care?
Summary of clinical expert input	• Laser surgery, resection and other forms of intravesical management are all likely to be used to treat Hunner's Lesions • In people with Hunner's lesions, laser surgery (or any cautery) is likely to give better response than PPS • However, results with surgery may be short-lived; after this might use a bladder instillation or PPS but less likely to be successful • DMSO was previously used but hasn't been used routinely for the last 10 years • This is because DMSO is expensive and difficult for the pharmacy to mix (it also has some unpleasant side effects)

Modelled response rate

Questions to expert	• In clinical practice, what level of response would you expect to see in people receiving best supportive care? • Would this response be likely to last longer than 12 months?
Summary of clinical expert input	• Best supportive care involves regular contact with a nurse; being supported and listened to improves reported response • People may report positive response because they want to continue with current approach of managing condition (e.g. bladder instillations, support from nurse, amitriptyline) – attitude of 'better this than nothing' • I've been thinking about this since our conversation – would you include Amitriptyline as 'best supportive care'? – I would class that as 'palliative' • I'm not sure I made this clear before – Non-specific treatments such as amitriptyline, cimetidine or hydralazine (which I think you are including in best supportive care) are not used by me as initial treatments. I used these if I do not think the diagnosis id BPS/IC or if bladder specific treatments (PPS or instillations) have not worked – ie. Palliative care. I hope that's clearer.

Time to treatment discontinuation

Questions to expert	• In clinical practice, what proportion of patients would remain on pentosan polysulfate sodium at 5, 10, 20 and 30 years? • In clinical practice, what proportion of patients would remain on bladder instillations at 5, 10, 20 and 30 years?

Summary of clinical expert input	• Most patients in whom the treatment works want to stay on treatment indefinitely • Expect to see the same response to bladder instillations and PPS, but different patient groups – Instillations used in PPS failures in my practice. • People would continue treatment with either for as long as they have a response, so would expect discontinuation proportions to be similar in PPS and bladder instillation arms • I note some centres have specified a 6 month course of instillations only. I wonder if there is some confusion between the use of bladder instillations for recurrent UTIs (rUTIs) – the licence suggests 6 months and a 6 month follow up review for this indication, however, for BPS/IC my understanding is the treatment is reviewed after the initial course (in my case 4 instillations) and if helpful, continued monthly. Obviously, if on review the efficacy wains it is stopped.

Utilities (quality of life)

Questions to expert	• Is it reasonable to assume a worse quality of life associated with previous use of bladder instillations (regardless of response to treatment)? • Is it reasonable to assume that quality of life of non-responders return to baseline after the first 6 months of treatment? • Is a response check at 6 months reflective of clinical practice? • Is it appropriate to assess response based on a split in ICSI change from baseline of 4.1 points?
Summary of clinical expert input	• Can see the argument because bladder instillations are more invasive than PPS • However, this is likely to be minimal compared to the effect that disease control has on health-related quality of life ie patients will tolerate any inconvenience if symptoms improve • PPS is also very inconvenient to administer because patients must take it 3 times a day and co-ordinate this with meal times • Some patients can be taught to self-administer bladder instillations at home • PPS may be more convenient to take than bladder instillations but impact on relative health-related quality of life is likely to be small. However, I give PPS before instillations as instillations takes up more Daycase and nursing time. I appreciate some specialist give the patient the option

	to choose pill or instillation, I accept that by giving PPS first I may reduce patient choice for cost saving (Daycase resource) – I may be wrong. • Stopping treatment leads to any gains from treatment going away and symptoms returning • In clinical practice, response check is typically at 3 months rather than 6 months • PPS and bladder instillations are likely to work or not work; unlikely that there will be any improvement to be maintained in non-responders

Modelled cost and resource use

Questions to expert	• In clinical practice, what is the frequency of bladder instillation administrations? • In clinical practice, what proportion of patients would be admitted through inpatient services for the treatment of interstitial cystitis/bladder pain syndrome?
Summary of clinical expert input	• Bladder instillations would be administered weekly for the first month and then monthly after this see note above – this is different to our rUTIs regime • It is realistic to assume some inpatient resource use (but not lots); inpatient services would usually be accessed before treatment • Expect to see lots of outpatient resource use • Bladder instillations involve lots of hospital resource use for nurses and staff scheduling appointments/handling telephone calls • Finally I think it is important to note that the overall numbers of patients treated is relatively small. I have been the major referral point for Leicestershire for over 10 years (population just over 1 million + some out of area referrals) and I have seen less than 200 patients with suspected BPS/IC. I probably have about 20 patients only on repeat PPS prescriptions and probably about the same number or a little less on instillations.

Appendix 1

Questions and accompanying text for clinical experts [ID1364]

Quality of clinical evidence for pentosan polysulfate sodium (PPS)

The marketing authorisation for pentosan polysulfate sodium (PPS) is based on 4 randomised controlled trials published in the USA comparing PPS with placebo in people with interstitial cystitis/bladder pain syndrome who have Hunner's lesions and/or glomerulations (IC/BPS) (Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987). The European Public Assessment Report highlights that prospective sample sizes were not calculated for 3 of the trials, and that the target sample size for the Sant et al. (2003) was not met.

- Is the available evidence for pentosan polysulfate sodium generalisable to UK clinical practice?

Clinical population

The evidence supporting the marketing authorisation for PPS is in trial populations with interstitial cystitis/bladder pain syndrome who have Hunner's lesions and/or glomerulations (IC/BPS). The company submitted evidence from two trial of Uracyst compared to placebo to provide information about bladder instillations, but these were in the broader bladder pain syndrome (BPS) population, with no requirement to have Hunner's lesions and/or glomerulations.

- Would people with BPS be expected to have the same response to therapy (with bladder instillations or PPS) as people with IC/BPS?

Treatment of condition in clinical practice

Comparators in the NICE scope are bladder instillations in people for whom they are suitable, or established clinical management without bladder instillations. The company have provided evidence from trials in Uracyst to represent bladder instillations and the placebo arm of trials to represent best supportive care.

- Would Hunner's lesions ever be treated with laser surgery? Would this be used at the same point in the pathway as PPS?
- Would intravesical DMSO ever be used in this population?
- For people without Hunner's lesions, would you consider pelvic floor exercises to be included in best supportive care?

Modelled response rate

The company consider the response rate in the placebo arms of the trials to be high (with an estimated 16% of patients on placebo reporting a response). Because of this, in its economic model the company cap the duration of any response in the placebo arm to 12 months. The ERG considers that the placebo response rates may be explained by regression to the mean, where the variability of the condition over time means there is a natural improvement of symptoms after a 'flare-up' which is unrelated to any intervention. Any regression to the mean present in the placebo arms of the clinical trials would also be present in the PPS and Uracyst arms of the trials, and so should not be adjusted for. Removing the 12 month cap has a big effect on the ICER.

- In clinical practice, what level of response would you expect to see in people receiving best supportive care?
- Would this response be likely to last longer than 12 months?

Time to treatment discontinuation

The ERG estimates the following proportions of patients remaining on treatment over time based on the company and ERG's preferred models:

	Company base-case		ERG preferred	
Time (years) from start of treatment	**Pentosan polysulfate sodium**	**Bladder instillations**	**Pentosan polysulfate sodium**	**Bladder instillations**
0.5	34%	23%	34%	23%
5	9%	15%	9%	7%
10	4%	10%	4%	3%
20	6%	4%	1%	2%
30	NA[1]		0.2%	0.1%

- In clinical practice, what proportion of patients would remain on pentosan polysulfate sodium at 5, 10, 20 and 30 years?
- In clinical practice, what proportion of patients would remain on bladder instillations at 5, 10, 20 and 30 years?

Utilities (quality of life)

The company's analysis assumed that people who had received a bladder instillation in the past 6 months would have worse quality of life that those who hadn't. This led to some non-responders who were on best supportive care having a better quality of life than patients who responded to second-line bladder instillations, which the ERG considered to be unrealistic.

- Is it reasonable to assume a worse quality of life associated with previous use of bladder instillations (regardless of response to treatment)?

The company also assumed that any [redacted] in quality of life made before the 6-month response check by people classed as non-responders who move onto best supportive care would be maintained after stopping treatment with pentosan polysulfate sodium. However, the ERG preferred to assume that quality of life of non-responders would return to baseline after the 6-month response check.

- Is it reasonable to assume that quality of life of non-responders return to baseline after the first 6 months of treatment?

Modelled cost and resource use

The company modelled [redacted]. The ERG considers that these admissions may not necessarily be related to bladder pain syndrome and is concerned that disease-related costs may have been overestimated in the model.

The company modelled weekly administrations of first-line bladder instillations for the first 4 weeks, and 4-weekly administrations after this point (also applied to all second-line bladder instillations). as administered weekly for the first 4 weeks, and every 4 weeks thereafter. Based on clinical expert advice, the ERG preferred to model 6-weekly administrations of BIs after the first year of first-line instillations, and for all second-line BIs.

- In clinical practice, what is the frequency of bladder instillation administrations?
- In clinical practice, what proportion of patients would be admitted through inpatient services for the treatment of interstitial cystitis/bladder pain syndrome?

Correspondence with clinical expert

Suzanne Biers (Clinical expert from British Association of Urological Surgeons) – Email 11/05/19

Quality of clinical evidence for pentosan polysulfate sodium (PPS)

Questions to expert	• Is the available evidence for pentosan polysulfate sodium (PPS) generalisable to UK clinical practice?
Summary of clinical expert input	• US and UK populations of bladder pain syndrome patients will have similar features and similar management pathways (i.e. similar presentations, assessments and treatment regimens, as we tend to follow the American Association of Urology (AUA) guidelines on the management of bladder pain syndrome.

Clinical population

Questions to expert	• Would people with bladder pain syndrome be expected to have the same response to therapy (with bladder instillations or PPS) as people with interstitial cystitis/bladder pain syndrome with glomerulations or Hunner's lesions?
Summary of clinical expert input	• The terminology used here is confusing. Bladder pain syndrome patients can have a normal looking bladder, or glomerulations or Hunners ulcers (+/- glomerulations). These appearances change the classification of the disease, but not strictly speaking the patient treatment options. • In essence, you are comparing patients with bladder pain syndrome and ulcer disease versus bladder pain syndrome without ulcer disease - these are slightly different disease processes, and there is some difference in response to management between these two groups described in the literature, however, the AUA management guideline pathways do not distinguish between the two when suggesting treatments on the whole.

Treatment of condition in clinical population

Questions to expert	• Would Hunner's lesions ever be treated with laser surgery? Would this be used at the same point in the pathway as PPS? • Would intravesical DMSO ever be used in this population? • For people without Hunner's lesions, would you consider pelvic floor exercises to be included in best supportive care?
Summary of clinical expert input	• YES. Alternative equivalent surgical options that are used are fulguration (or diathermy with roller ball) or resection. • The American Association of Urology (AUA) guidelines place surgery after trial of oral/tablet medications (i.e. this would be after PPS), but in clinical practice, we commonly arrange cystoscopy as part of patient investigation prior to medications, in which case, I would treat a Hunner's ulcer at that investigative stage (i.e. prior to medication trial/PPS). • No - in the UK DMSO is not licensed for use. • No - specifically for bladder pain syndrome, pelvic floor exercises are not indicated for patient with or without Hunner ulcer disease types. Pelvic floor relaxation therapy would be considered for patient with a phenotpye (or set of symptoms) indicating pain or problems in relaxing the pelvic floor.

Modelled response rate

Questions to expert	• In clinical practice, what level of response would you expect to see in people receiving best supportive care? • Would this response be likely to last longer than 12 months?
Summary of clinical expert input	• Typically in large placebo controlled drug trials (in general/not specific to this condition or treatment) placebo is around 35%. In clinical practice, with bladder pain syndrome, I suspect that placebo response is lower, so 16% may not be unreasonable. • In general, my understanding is that placebo response is relatively short-lived, so I would anticipate that placebo would last for less than 12 months.

Time to treatment discontinuation

Questions to expert	• In clinical practice, what proportion of patients would remain on pentosan polysulfate sodium at 5, 10, 20 and 30 years? • In clinical practice, what proportion of patients would remain on bladder instillations at 5, 10, 20 and 30 years?
Summary of clinical expert input	• I anticipate that the number of patients on PPS at 5,10,20 and 30 years is somewhere between the two figures provided. • Regarding bladder instillations: • On the whole, bladder instillations (Gylcoasaminoglycan analogs) are provided as an induction and maintenance regimen for a defined period of time, and then stopped. For example, one treatment regimen would be to provide bladder instillations once per week for 6 weeks and if clinically effective, to then continue with maintenance therapy once per month for 6 months, with the aim of completing the course and then stopping. Bladder instillation therapy is different to tablet medication (PPS) as it is not anticipated to be continuous over 5, 10 or 20 years. Once a treatment is completed, we would aim for benefit for months or years (therefore repeat instillations continuously are not required). There is small sub-group of patients whose symptoms can only be controlled by continuing on bladder instillations, and in clinical practice, we still try to slowly increase the interval between instillations with the aim of ultimately stopping. In my practice, around 5-10% of patients with bladder pain syndrome require prolonged treatment with bladder instillations beyond the desired maintenance treatment (these may be provided 4 times per year for example for an additional 1-2 years). Other patients may return for a repeat bladder instillation treatment regimen when their symptoms return after cessation of several years, as they have found it helpful previously. This group would undertake further induction and maintenance therapy and then stop again. • In summary, it is difficult to use this model to compare the proportion of patients staying on bladder instillations versus those continuing on PPS, however, due to the nature of the treatment dosing and regimen, but it would be reasonable to assume that fewer patients would continue on bladder instillations than with medication (PPS) due to the above reasons.

Utilities (quality of life)

Questions to expert	• Is it reasonable to assume a worse quality of life associated with previous use of bladder instillations (regardless of response to treatment)? • Is it reasonable to assume that quality of life of non-responders return to baseline after the first 6 months of treatment? • Is a response check at 6 months reflective of clinical practice? • Is it appropriate to assess response based on a split in ICSI change from baseline of 4.1 points?
Summary of clinical expert input	• Some patients with bladder pain syndrome have an adverse reaction to the procedure – rarely due to the glycosaminoglycan analog liquid drug that is instilled into the bladder, but more often a sub-set of patients cannot tolerate the in-and-out catheter insertions needed for the instillations, which can be associated with urethral or bladder pain or urinary tract infection. These would reasons to stop the instillations, so quality of life should only temporarily be affected secondary to bladder instillations specifically. It would be uncommon for bladder instillations to cause a permanent effect on quality of life. • However, in general, bladder instillations are recommended as a 'second line therapy'. In clinic practice they are utilised after conservative and medical management with tablet medications has been tried and failed, or has only been partially effective and another treatment modality is required in order to sufficiently control symptoms. In this respect, they may represent patients with a slightly worse disease severity (i.e. as compared to patient's whose symptoms are controlled with tablet medication alone). • I would think so *(that quality of life of non-responders return to baseline after the first 6 months of treatment).* • We tend to review patients after 3 months after starting a new treatment or changing a therapy, but a 6 months review is also reasonable. • Seems reasonable I think *(that it is appropriate to assess response based on a split in ICSI change from baseline of 4.1 points)*

Modelled cost and resource use

Questions to expert	• In clinical practice, what is the frequency of bladder instillation administrations? • In clinical practice, what proportion of patients would be admitted through inpatient services for the treatment of interstitial cystitis/bladder pain syndrome?
Summary of clinical expert input	• See response above for frequency of bladder instillation administrations. • This figure is minimal in my practice. This is a chronic condition which we encounter most commonly in the elective outpatient setting. Patients may access inpatient services if they have experienced a complication after an investigation (i.e. infection or pain after cystoscopy or urodynamics), but this is uncommon.

Appendix 1

Questions and accompanying text for clinical experts [ID1364]

Quality of clinical evidence for pentosan polysulfate sodium (PPS)

The marketing authorisation for pentosan polysulfate sodium (PPS) is based on 4 randomised controlled trials published in the USA comparing PPS with placebo in people with interstitial cystitis/bladder pain syndrome who have Hunner's lesions and/or glomerulations (IC/BPS) (Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987). The European Public Assessment Report highlights that prospective sample sizes were not calculated for 3 of the trials, and that the target sample size for the Sant et al. (2003) was not met.

- Is the available evidence for pentosan polysulfate sodium generalisable to UK clinical practice?

Clinical population

The evidence supporting the marketing authorisation for PPS is in trial populations with interstitial cystitis/bladder pain syndrome who have Hunner's lesions and/or glomerulations (IC/BPS). The company submitted evidence from two trial of Uracyst compared to placebo to provide information about bladder instillations, but these were in the broader bladder pain syndrome (BPS) population, with no requirement to have Hunner's lesions and/or glomerulations.

- Would people with BPS be expected to have the same response to therapy (with bladder instillations or PPS) as people with IC/BPS?

Treatment of condition in clinical practice

Comparators in the NICE scope are bladder instillations in people for whom they are suitable, or established clinical management without bladder instillations. The company have provided evidence from trials in Uracyst to represent bladder instillations and the placebo arm of trials to represent best supportive care.

- Would Hunner's lesions ever be treated with laser surgery? Would this be used at the same point in the pathway as PPS?
- Would intravesical DMSO ever be used in this population?
- For people without Hunner's lesions, would you consider pelvic floor exercises to be included in best supportive care?

Modelled response rate

The company consider the response rate in the placebo arms of the trials to be high (with an estimated 16% of patients on placebo reporting a response). Because of this, in its economic model the company cap the duration of any response in the placebo arm to 12 months. The ERG considers that the placebo response rates may be explained by regression to the mean, where the variability of the condition over time means there is a natural improvement of symptoms after a 'flare-up' which is unrelated to any intervention. Any regression to the mean present in the placebo arms of the clinical trials would also be present in the PPS and Uracyst arms of the trials, and so should not be adjusted for. Removing the 12 month cap has a big effect on the ICER.

- In clinical practice, what level of response would you expect to see in people receiving best supportive care?
- Would this response be likely to last longer than 12 months?

Time to treatment discontinuation

The ERG estimates the following proportions of patients remaining on treatment over time based on the company and ERG's preferred models:

	Company base-case		ERG preferred	
Time (years) from start of treatment	**Pentosan polysulfate sodium**	**Bladder instillations**	**Pentosan polysulfate sodium**	**Bladder instillations**
0.5	34%	23%	34%	23%
5	9%	15%	9%	7%
10	4%	10%	4%	3%
20	6%	4%	1%	2%
30	NA[1]		0.2%	0.1%

- In clinical practice, what proportion of patients would remain on pentosan polysulfate sodium at 5, 10, 20 and 30 years?
- In clinical practice, what proportion of patients would remain on bladder instillations at 5, 10, 20 and 30 years?

Utilities (quality of life)

The company's analysis assumed that people who had received a bladder instillation in the past 6 months would have worse quality of life that those who hadn't. This led to some non-responders who were on best supportive care having a better quality of life than patients who responded to second-line bladder instillations, which the ERG considered to be unrealistic.

- Is it reasonable to assume a worse quality of life associated with previous use of bladder instillations (regardless of response to treatment)?

The company also assumed that any [redacted] in quality of life made before the 6-month response check by people classed as non-responders who move onto best supportive care would be maintained after stopping treatment with pentosan polysulfate sodium. However, the ERG preferred to assume that quality of life of non-responders would return to baseline after the 6-month response check.

- Is it reasonable to assume that quality of life of non-responders return to baseline after the first 6 months of treatment?

Modelled cost and resource use

The company modelled [redacted]. The ERG considers that these admissions may not necessarily be related to bladder pain syndrome and is concerned that disease-related costs may have been overestimated in the model.

The company modelled weekly administrations of first-line bladder instillations for the first 4 weeks, and 4-weekly administrations after this point (also applied to all second-line bladder instillations). as administered weekly for the first 4 weeks, and every 4 weeks thereafter. Based on clinical expert advice, the ERG preferred to model 6-weekly administrations of BIs after the first year of first-line instillations, and for all second-line BIs.

- In clinical practice, what is the frequency of bladder instillation administrations?
- In clinical practice, what proportion of patients would be admitted through inpatient services for the treatment of interstitial cystitis/bladder pain syndrome?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 17 May 2019 at 5pm**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**British Association of Urological Surgeons Representative** [redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Association of Urological Surgeons (BAUS)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

Questions for engagement

Issue 1: Indirect treatment comparison	
Mindful that there are challenges with all approaches for comparing pentosan polysulfate sodium with bladder instillations, which is the best indirect treatment comparison to use in this appraisal (an indirect treatment comparison using a Bayesian network meta-analysis or the Bucher method)?	From the supporting information provided, I feel that the view of the technical team preliminary scientific judgement and rationale suggesting using the Bayesian network meta-analysis method, is reasonable.
Issue 2: Time horizon in economic model	
Are there any costs or consequences associated with PPS that would fall outside of a 20-year time horizon?	From the supporting information and estimated figures provided, I would suggest that the view of the technical team preliminary scientific judgement and rationale on this point 'that a lifetime horizon is appropriate for the economic model' appears reasonable.
Issue 3: Modelled response rate	
Based on a meta-analysis, the company assume 16% of patients would respond to best supportive care with no intervention. Is this assumption reasonable?	Placebo effects are variable. Larger placebo-controlled drug trials have shown an average placebo effect of 35%. Therefore, 16% seems a little low (would be in the lower range of expected), however, as this data is based on meta-analysis, an assumption of 16% response to best supportive care with no intervention would appear reasonable.
The company assume that any response in patients receiving best supportive care would not last more than 12 months. Is this assumption appropriate?	Placebo affects are usually shorter-lived, therefore from a clinical perspective it would be reasonable to assume the effects would not last beyond 12 months. I do note that this differs from the conclusion of the team and previous statements: 'the ERG assumes that BSC response rates

	do not recede over time' and the view of the technical team preliminary scientific judgement and rationale is that 'it is acceptable to assume that BSC response rates (based on the placebo response rate from the meta-analysis) do not recede over time'.
Issue 4: Time to treatment discontinuation	
Should the survival analysis account for all known discontinuations?T	The statement from the technical team that 'survival datatset (which includes all known discontinuations from the study and censors at the last recorded follow-up) is less subject to bias and so is preferable' seems reasonable.
The company's model predicts that the proportion of patients remaining on PPS at 5, 10 and 20 years would be 22%, 15% and 6%, and the ERG's model predicts these proportions to be 9%, 4% and 1% (see Table A). Which set of predictions is most reasonable?	I suspect the clinical picture is between these two sets of ranges. Either is reasonable, although with the side effects noted to be associated with drug, potentially the ERG's model may reflect a slightly more accurate picture.
The company's model predicts that the proportion of patients remaining on BIs at 5, 10 and 20 years would be 15%, 10% and 4%, and the ERG's model predicts these proportions to be 7%, 3% and 2% (see Table A). Which set of predictions is most reasonable?	On the whole, bladder instillations (Gylcoasaminoglycan analogs) are provided as an induction and maintenance regimen for defined period of time, and then stopped. For example, one treatment regimen would be to provide bladder instillations once per week for 6 weeks and if clinically effective, to then continue with maintenance therapy once per month for 6 months, with the aim of completing the course and then stopping. Bladder instillation therapy is different to tablet medication (PPS) as it is not anticipated to be continuous over 5, 10 or 20 years. Once a treatment is completed, we would aim for benefit for months or years (therefore repeat instillations continuously are not required). There is small sub-group of patients whose symptoms can only be controlled by continuing on bladder instillations, and in clinical practice, we still try to slowly

	increase the interval between instillations with the aim of ultimately stopping. In my practice, around 5-10% of patients with bladder pain syndrome require prolonged treatment with bladder instillations beyond the desired maintenance treatment (these may be provided 4 times per year for example for an additional 1-2 years). Other patients may return for a repeat bladder instillation treatment regimen when their symptoms return after cessation of several years, as they have found it helpful previously. This group would undertake further induction and maintenance therapy and then stop again. In summary, it is difficult to use this model to compare the proportion of patients staying on bladder instillations versus those continuing on PPS, however, due to the nature of the treatment dosing and regimen, but it would be reasonable to assume that fewer patients would continue on bladder instillations than with medication (PPS) due to the above reasons.
Issue 5: Utilities associated with the use of bladder instillations	
The company assume a utility decrement (a reduction in quality of life) of around [redacted] associated with the use of BIs. Is this assumption appropriate?	Some patients with bladder pain syndrome have an adverse reaction to the procedure – rarely due to the glycosaminoglycan analog liquid that is instilled into the bladder, but more often a sub-set of patients cannot tolerate the in-and-out catheter insertions needed for the instillations, which can be associated with urethral or bladder pain or urinary tract infection. These would reasons to stop the instillations, so quality of life should only temporarily be affected secondary to bladder instillations specifically. It would be uncommon for bladder instillations to cause a permanent effect on quality of life.

Could 'usage of BIs in the previous 6 months' reflect any other markers that may have not been explicitly modelled (such as time since diagnosis, or disease severity)?	Generally, bladder instillations are recommended as a 'second line therapy'. In clinic practice they are utilised after conservative and medical management with tablet medications has been tried and failed, or has only been partially effective and another treatment modality is required in order to sufficiently control symptoms. In this respect, they may represent patients with a slightly worse disease severity (i.e. as compared to patient's whose symptoms are controlled with tablet medication alone).
Issue 6: Utilities associated with response	
Is it reasonable to assume that health related quality of life for non-responders who move onto best supportive care will return to baseline after the 6-month response check?	Yes – this seems reasonable.
Issue 7: Modelled costs and resource use	
In clinical practice, what is the frequency of BI administrations?	In clinical practice, I would estimate that at least 50% of patients with a diagnosis of bladder pain syndrome may progress to bladder instillations. Treatment is individualised according to the patient phenotype and most bothersome symptoms components, and it is common for patients to be on table medications at the same time a bladder instillations. There is no consensus guideline or gold-standard for the regimen used for bladder instillations, so practice is guided by clinical trial results. Typical regimens for the administration of bladder instillations are as follows: • Induction treatments once per week for 4-6 weeks (regimen varies with product used)

	• If benefit or improvement over 50% to progress to maintenance therapy which is one instillation monthly for 4-6 months then review (and most patients would then stop treatment).
In clinical practice, what proportion of patients would be admitted through inpatient services for IC/BPS?	This figure is minimal in my practice. This is a chronic condition which we encounter most commonly in the elective outpatient setting. Patients may access inpatient services if they have experienced a complication after an investigation (i.e. infection or pain after cystoscopy or urodynamics), but this is uncommon.

Clinical expert comment:

Please note, although information has been provided to support the ability of the clinical expert to assess these technical engagement response points, these questions (1-4) are outside the normal area of clinical expertise, and are completed to the best of my ability within these limitations. I would suggest they would be better discussed in a NICE forum with the appropriate sub-specialists in statistics and data analysis available for additional expert support at the group meeting on 20th June 2019.

Pentosan polysulfate sodium for treating bladder pain syndrome: A Single Technology Appraisal: addendum prepared after technical engagement

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None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

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Contributions of authors

Sarah Davis and Kate Ennis critiqued the additional health economic analysis submitted by the company. John Stevens critiqued the additional statistical analyses undertaken by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AIC	Akaike Information Criterion
BI	Bladder instillation
BIC	Bayesian Information Criterion
BPS	Bladder pain syndrome
BSC	Best supportive care
CI	Confidence interval
CrI	Credible interval
CS	Company Submission
DIC	Deviance information criteria
DSU	Decision support unit
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
GRA	Global response assessment
HES	Hospital episode statistics
HUI-2	Health-utilities index -2
ICER	Incremental Cost Effectiveness Ratio
ICPI	Interstitial Cystitis Problem Index
ICSI	Interstitial Cystitis Symptom Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PPS	Pentosan polysulfate sodium
PSA	Probabilistic sensitivity analysis
QALY	Quality-Adjusted Life Year
QWB	Quality of Well Being
RCT	Randomised Controlled Trial
SCI	Spinal cord injury
SF-6D	Short form 6 dimensions
SF-12	Short form 12 items
STA	Single Technology Appraisal
TSD	Technical support document
UTI	Urinary tract infection
VAS	Visual analogue scale

1 INTRODUCTION

This addendum to the Evidence Review Group (ERG) report provides the ERG critique of additional evidence provided by Consilient Health in their Technical Engagement Response Form, during the technical engagement for the appraisal of pentosan polysulfate sodium (PPS) for the treatment of bladder pain syndrome (BPS). The draft Technical Report, which was shared with stakeholders during technical engagement, outlined seven key issues for consideration and provides the technical team's preliminary scientific judgement on each issue.

In summary, the technical team considered the following:

- For both base-case analyses:
  - An indirect treatment comparison using a Bayesian network meta-analysis is preferable to the Bucher method (Issue 1).
  - A lifetime horizon in the economic model is appropriate (Issue 2).
  - It is preferable to use the ERG's time-to-discontinuation datatset (but with deaths excluded from being 'failures' in the analysis) and a log-normal extrapolation (Issue 4).
  - It is preferable not to include 'previous use of bladder instillations in the past 6 months' as a covariate in the utilities regression (Issue 5).
- For the analysis of pentosan polysulfate sodium compared to BSC:
  - It is not appropriate to assume that utilities and costs of non-responders who move onto BSC are maintained after the initial 6-month response check (Issue 6).
  - Length of any response in the BSC arm should not be limited to 12 months (Issue 3).
- For the analysis of pentosan polysulfate sodium compared to bladder instillations:
  - It is preferable to model 6-weekly administration of second line bladder instillations and first line bladder instillations after the first year (Issue 7).

The company's response to the draft Technical Report indicated that they accepted the technical team's preliminary judgement on Issue 6, so this issue is not discussed in this addendum. In response to issue 2, the company reiterated their preference for the 20-year time-horizon but incorporated the life-time horizon in their updated base-case. This issue is therefore not discussed further in this addendum. The company's responses to the remaining five issues are discussed in turn in sections 2.1 to 2.5.

The company also provided an appendix providing clarification on the role of surgery in the population likely to receive PPS capsules and an appendix describing the potential for ocular adverse events while receiving PPS capsules. Neither of these appendices is critiqued here as due to the limited time available, the ERG has chosen to focus on the seven key issues identified in the technical report.

2 Description and critique of additional evidence

2.1 Indirect treatment comparison (Issue 1)

In the ERG report, the ERG accepted the company's argument that an unbiased comparison between PPS capsules and all relevant comparators was not possible using a conventional network meta-analysis.[1] The main reasons for this were that the populations defined by the PPS capsules and Uracyst® (bladder instillation [BI]) studies were different, as were the placebo treatments; the PPS capsule studies recruited the more relevant IC/BPS population while the Uracyst® studies recruited a broader population with BPS. A formal indirect comparison between PPS capsules and Uracyst® would involve methods such as a population-adjusted indirect comparison. Nevertheless, in order to satisfy the NICE scope, the company provided an indirect comparison between PPS capsules and Uracyst® using the Bucher method linked by the placebo treatments in the PPS capsules and Uracyst® studies. Although the ERG stated that it had a preference for performing a simultaneous comparison between treatments using a Bayesian network meta-analysis rather than the Bucher method, this was not intended to contradict the ERG's assertion that there are problems associated with using both the Bucher method and a conventional network meta-analysis to make an indirect comparison between PPS capsules and Uracyst® in this submission. While the use of a conventional network meta-analysis deals with limitations associated with the Bucher method, neither method deals with the fact that the populations and placebo treatments in the PPS capsules and Uracyst® studies are not the same.

The ERG is unclear what the company meant when it wrote in the Technical Engagement Response Form that the between-study standard deviation is non-stationary in the random effects model.[2] The ERG assumes that the company had problems when implementing a random effects model using a vague prior distribution for the between-study standard deviation. Vague, so-called non-informative, prior distributions for variance parameters are not non-informative when there is limited sample data (i.e. studies) with which to estimate a variance parameter. If the prior distribution for the between-study standard deviation does not represent reasonable prior beliefs then, with limited studies, there will be limited Bayesian updating and the posterior distribution for the between-study standard deviation will not represent reasonable posterior beliefs.[3] Furthermore, the ERG believes that the company has misinterpreted the discussion on the use of a gamma prior distribution for the between-study standard deviation as described in NICE DSU TSD 2.[4] In particular, a prior distribution for precision, with between-study standard deviation, τ, such that $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$ "puts more weight on values of τ near zero" without any justification. When there are limited studies and it is believed that a posterior distribution using a vague prior distribution is implausible then it is necessary to use external information to specify the prior distribution for the between-study standard deviation either through

elicitation of experts' beliefs, using the predictive distribution for the between-study standard deviation in a new study or a justified ad hoc approach.[5]

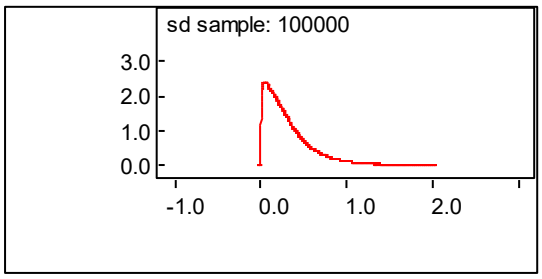
The ERG does not believe that using the deviance information criteria (DIC) is appropriate to compare the results of fixed effect and random effects meta-analyses because the DIC cannot quantify the plausibility of the prior distribution for the between-study standard deviation. The ERG considers a random effects model to be most appropriate on the basis that heterogeneity is expected between studies using different protocols.

The ERG re-ran the company's treatment effects model using the following prior distributions:

- Baseline log odds: $N(0, 1000)$
- Log odds ratios for PPS capsules and Uracyst® versus placebo: $N(0, 1000)$
- Between-study standard deviation: $U(0, 2)$
-

The ERG experienced no difficulty with implementing this model. The analysis was performed using a burn-in of 100,000 iterations of the Markov chain, and estimating parameters based on 100,000 of the Markov chain, thinning the chain by retaining every 10th sample. There was updating of the prior distribution for the between-study standard deviation (Figure 1). Thus, in the absence of any external information regarding the true value of the between-study standard deviation, the ERG prefers its analysis using the prior distributions described above.

Figure 1: Treatment effects model -posterior distribution for the between-study standard deviation



The between-study standard deviation in the treatment effects model was estimated as 0.24 (95% CrI: 0.01, 1.19).

In the presence of unexplained heterogeneity, the random effects mean does not represent the treatment effect in any particular population and it is better to use the predictive distribution for the effect of treatment in a new study (Table 1), which incorporates greater uncertainty, rather than the mean of the

random effects distribution as used by the company. It is not possible to compare the ERG results with the company results because the company did not report their estimates of odds ratios in their Technical Engagement Response Form.

The company used a technically incorrect and unnecessary approach to characterising uncertainty about the absolute responses to treatment as required in the cost-effectiveness analysis.[4] The company used a logit link function to estimate log odds (odds) ratios for the effects of PPS capsules and Uracyst® relative to placebo and combined these with an estimate of the placebo response on the logit scale based on an average of the placebo arms in the four PPS capsule studies and two Uracyst® studies within the same analysis. See Section 2.2. (Issue 3) for a discussion on why the company's approach to generating the absolute response to placebo is technically incorrect. (The company also computed, but did not make use of, the relative risks of PPS capsules and Uracyst® relative to placebo by dividing the absolute responses to PPS capsules and Uracyst® by the absolute response to placebo. If the company had an interest in estimating relative risks then it should have used a log link function rather than a logit link function, although the ERG notes that estimating relative risks using Markov chain Monte Carlo simulation tends to be computationally problematic.)

Table 1: ERG Random Effects Network Meta-Analysis

	Median (95% CrI)
Odds ratio versus Placebo	
PPS capsules	2.69 (1.44, 5.19)
Uracyst®	1.67 (0.69, 4.32)
Predictive odds ratio versus Placebo	
PPS capsules	2.69 (0.90, 8.44)
Uracyst®	1.67 (0.48, 6.31)

For completeness, Table 2 presents a comparison of the company's revised estimates of absolute response as presented in the Technical Engagement Response Form and the ERG's estimates. Two sets of estimates are presented based on the ERG's analysis: estimates of the placebo absolute response based on 100,000 iterations of the Markov chain of the baseline model; estimates of the absolute response to each treatment based on a subset of 10,000 iterations of the Markov chains of separate baseline and treatment effect models as used in the economic model. The subset of iterations of the Markov chain gives comparable results to the results based on 100,000 iterations with a prediction interval that is narrower by only 0.005 i.e. 0.5%. The company's revised point estimates are consistently higher than the ERG's point estimates, as are the differences in point estimates when comparing PPS capsule studies and Uracyst® with placebo, and the ERG's uncertainty about parameters is greater than the company's uncertainty about parameters. The ERG notes that the company's revised base case cost-

effectiveness analysis used a higher estimate of the placebo response rate (i.e. 18.9%) than that used in the original submission and justified in its response to Issue 3 (i.e. 16%).

The company has used a technically incorrect approach to characterising uncertainty about the absolute responses to each treatment: 1) absolute and relative treatment effects should be estimates in separate models, 2) posterior distributions of parameters from a Bayesian network meta-analysis will not follow any standard parametric distribution and any assumed distribution for parameters will be an approximation, 3) parameters in a Bayesian analysis will be correlated because they are estimated at each iteration of the Markov chain by sampling from their conditional distributions given current values of all other parameters, 4) estimates of the absolute response to treatment will be correlated because they each include estimates of the response to placebo. Nevertheless, the company has taken the means and standard deviations of the marginal posterior distributions of response to each treatment on the logit scale from their single baseline and treatment effects model and has assumed that these arise from independent normal distributions within the economic model. A correct approach would involve separate baseline and treatment effects models, would sample values from their respective posterior distributions at each iteration of the Markov chain and would save them in a look-up table such as Excel. The sampled values from the baseline and relative treatment effects models would then be combined at each iteration of the Markov chain to give absolute estimates of the response to each treatment and read in to the economic model, thereby preserving the true underlying joint distribution and correlation between parameters.

Table 2: Comparison of the company's revised and ERG's estimates of absolute response rates (GRA)

	Company's Revised Estimates[a]	**ERGs Estimates Predictive Intervals**	
		Baseline Model[b]	**Combining Separate Baseline and Treatment Effects Models**[c]
	Median (95% CrI)	**Median (95% CrI)**	**Median (95% CrI)**
Placebo	0.189 (0.146, 0.237)	0.155 (0.051, 0.370	0.154 (0.054, 0.368)
PPS	0.384 (0.289, 0.488)		0.328 (0.086, 0.722)
BIs	0.280 (0.161, 0.441)		0.237 (0.053, 0.652)

BI, bladder instillations; CrI, credible interval; GRA, global response assessment; PPS, pentosan polysulfate sodium
a, adapted from Table 1 of the company's response to the technical engagement
b, based on 100,000 iterations of the Markov chain;
c, based on 10,000 iterations of the Markov chain as used in the ERGs economic model

The ERG notes that the company's revised base-case cost-effectiveness analysis presented in Table 2 of the Technical Engagement Response Form uses a response rate for BSC of 18.9% based on data from the placebo arms of the PPS capsules and Uracyst® studies, which the ERG considers to be inappropriate (Issue 3). In particular, it is plausible that the response rate may be different in the broader BPS population than in the specific population with IC/BPS because the BPS population may contain a subset of patients with less severe disease and with a disease type more responsive to treatment. Therefore, although the ERG has a preference for using an external estimate of response rate to BSC, the ERG believes that the estimate of the response rate to BSC used in the cost-effectiveness analysis should be based only on the data from the placebo arms of the PPS capsule studies. This is discussed further in section 2.2 (Issue 3).

2.2 Modelled response rate (Issue 3)

The ERG considers it a limitation that the company is unable to quantify the absolute response to BSC in clinical practice using evidence other than from the available clinical trials. An estimate of the absolute response to BSC in clinical practice is required in order to estimate the absolute responses to treatment with PPS capsules and Uracyst®. NICE DSU TSD 5[4] states that, "Investigators should take care to justify their choice of data sources to inform the baseline, which could include a subset of the trials identified in the systematic review of relative effect data, cohort studies, patient registers, expert opinion, or combinations of these." While estimates of relative treatment effect from a randomised controlled trial are generally transportable across patient populations, it is not necessarily true that the baseline response in the target population is comparable to a simple summary of the baseline response in the available clinical trials. Indeed, in the company submission it was argued that there was a placebo effect, which the ERG interpreted to mean that the responses in the placebo arms of clinical trials were higher than would be expected in clinical practice. Nevertheless, the company used these to estimate the absolute response to BSC in clinical practice.

In the original submission, the company used data from the placebo arms of the PPS capsule studies, whereas in the updated analysis the company included the placebo arms of the Uracyst® studies. The patient populations and placebo treatments in the Uracyst® studies were different to those in the PPS capsule studies, and the placebo responses in the Uracyst® studies were higher than the placebo responses in the PPS capsule studies. Furthermore, the company estimated the response to BSC within the same analysis as the treatment effects model and estimated it as the average of the available studies, "an approach which is not recommended under any circumstances".[4] The ERG prefers to run separate baseline and treatment effects models to ensure that the information in the baseline model does not affect the relative treatment effects model. In addition, when using data from RCTs, the ERG prefers to

generate the baseline response as the predictive distribution of the baseline response in a new study using a random effects model.

The ERG analysed the data from the placebo arms of the PPS capsules studies using a random effects model with the following prior distributions:

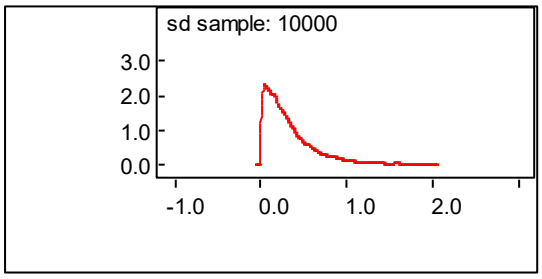
- Baseline log odds: $N(0, 1000)$
- Between-study standard deviation: $U(0, 2)$

In the absence of any external information regarding the true value of the between-study standard deviation, the ERG prefers its analysis using the prior distributions described above.

The between-study standard deviation in the baseline response model was estimated as 0.24 (95% CrI: 0.01, 1.36) (Figure 2).

The ERG's estimate of the baseline response based on the predictive distribution for the response in a new study was estimated as 15.5% (95% CrI: 5.1%, 37.0%) (Table 3). This compares to the company's estimate of the baseline response of 16% (95% CI: 12%, 21%) in the original submission and its estimate of 18.9% (95% CrI: 14.6%, 23.7%) as reported by the company in Table 1 of the Technical Engagement Response Form.

Figure 2: Baseline response model -posterior distribution for the between-study standard deviation



The company has provided a summary of advice received from 10 clinical experts regarding the modelled response rate and the likelihood of response persisting beyond 12 months in patients who initially respond to BSC. The company reported that whilst there was variation in the clinical expert's responses, the proportion of patients having symptom resolution to BSC was likely to be between 0 to 30%, with the proportion of patients having some level of improvement could be as high as 50%. The company claims that the range of values provided by the clinical experts is consistent with the proportion of patients responding to treatment with placebo as estimated in their original meta-analysis

of the four RCTs comparing PPS capsules to placebo in IC/BPS (16%). The ERG acknowledges the attempt by the company to validate the response to BSC used in clinical practice. However, in the experience of the ERG, asking questions about population values of interest in this way is unlikely to generate meaningful quantities, and does not capture uncertainty regarding experts' beliefs. Furthermore, the question did not ask about the response to BSC at a time-point consistent with the duration of the clinical trials, which is important given that the treatment effect is estimated within clinical trials of specific duration. Nevertheless, the range of values provided by the clinical experts does seem broadly consistent with the ERG's predictive distribution (shown in Table 3).

Table 3: ERG Random Effects Baseline Response Model

	Median (95% CrI
Random effects mean	15.5% (8.8%, 24.7%)
Predictive distribution	15.5% (5.1%, 37.0%)

The company's Technical Engagement Response Form also provides their response to the question *"The company assume that any response in patients receiving best supportive care would not last more than 12 months. Is this assumption appropriate?"*. In their response, the company describes a survey of 10 clinical experts (Appendix G of the company's Technical Engagement Response Form). The company states that the clinical experts surveyed by the company were supportive of the company's assumption that patients who respond to BSC are likely to have a response that does not persists beyond 12 months. The company's conclusion is that their original assumption was valid and conservative but they have incorporated the ERG's preferred assumption in their revised base-case.

The ERG notes that the company has not provided any long-term studies demonstrating that the response in patients randomised to having BSC does not persist past 12 months, whilst the response in patients randomised to PPS capsules is sustained until treatment is discontinued.

2.3 Time to treatment discontinuation (Issue 4)

The company reiterated their position, previously outlined in the factual accuracy check (FAC), that patients who died during the 'physician usage' study reported by Hanno et al. (1997)[6] should be not be considered to have discontinued treatment but accepts that this is unlikely to have significantly biased the cost-effectiveness estimates. The company asserts that some of the remaining patients who are described by Hanno et al. (1997)[6] as having discontinued treatment for reasons other than having experienced an adverse event or lack of efficacy, such as those who have transferred physicians' or 'relocated', may have in fact continued treatment elsewhere. However, the company accepts that it is difficult to separate these groups from other patients who would be considered to have discontinued

treatment. The company has therefore incorporated the ERG's revised time to treatment discontinuation analysis in their revised base-case.

The ERGs preferred approach remains that presented in the ERG report but with the exclusion of those who died during follow-up. The ERG updated their survival analysis to treat those who died as censored at the time of death. The updated regression parameters are presented in Table 4 and the survival functions are provided in Figure 3. It can be seen that the lognormal distribution has the lowest AIC and BIC values and that the survival functions are very similar to those used in the ERG's previous base-case (see Figure 12 of the ERG report). The proportion of patients remaining on PPS at 10 years (9.5 years after the response check) based on the lognormal distribution is 12%, which is the same as in the ERG's original analysis (see Table 2 of the ERG's response to questions from the NICE team).

Although the ERG prefers their interpretation of the data from Hanno et al. (1997), the ERG acknowledges that the study is reported poorly and the correct interpretation of the data is unclear.

Table 4: Regression parameters for ERG's survival analysis for time to discontinuation when treating those who died as censored at the time of death

Survival function	Parameters	AIC	BIC	Mean time (months)	Median time (months)
Exponential	Rate = 0.0227184	2654.41	2659.38	44.02	30.51
Weibull	Shape = 0.0219137 Log scale = 0.0102594	2656.31	2666.26	43.70	30.53
Gompertz	Shape = 0.0296015 Scale = -0.01459	2628.72	2638.67	NE	28.65
Loglogistic	Shape = 3.280549 Log scale = -0.29186	2574.40	2584.35	87.38	26.59
Lognormal	Location = 3.309338	2517.20	2527.15	56.56	27.37

	Log scale = 0.186486				

NA, not applicable; NE, not estimable

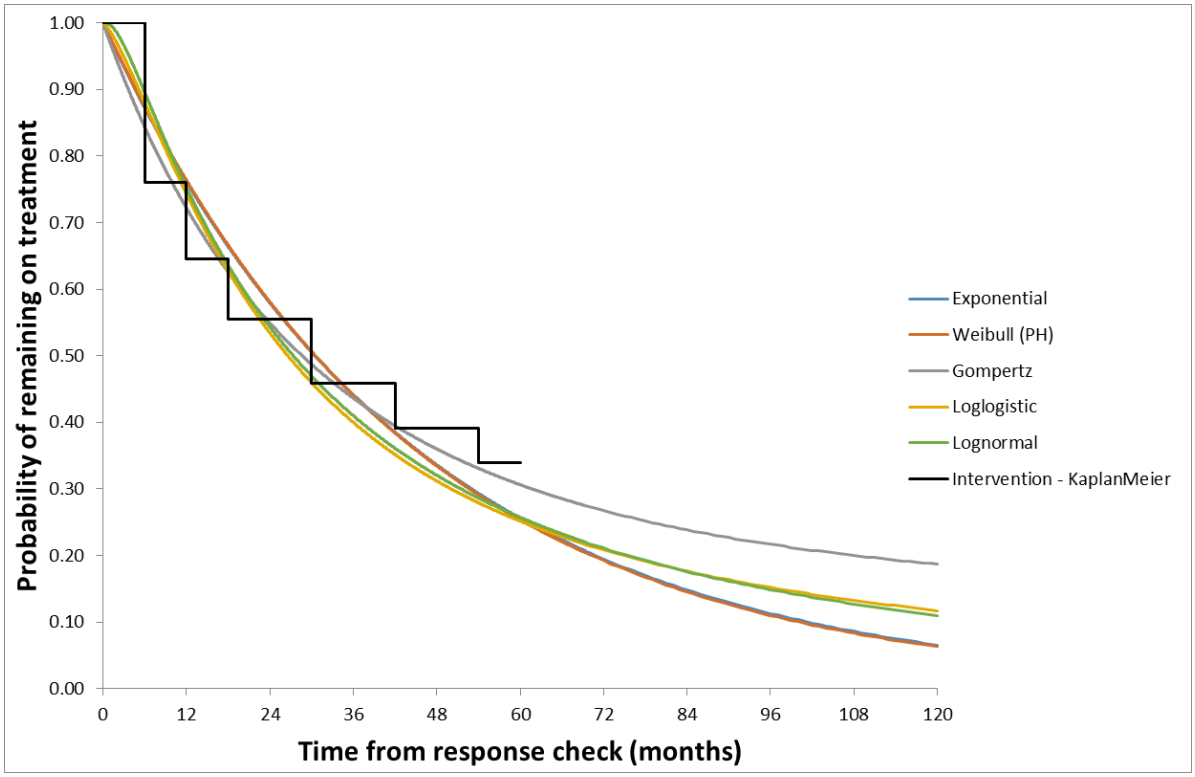


Figure 3: Time to treatment discontinuation based on the ERG's preferred interpretation of the data from Hanno *et al.* (1997) when treating deaths as censoring events

2.4 Utilities associated with the use of bladder instillations (Issue 5)

The company has provided a table of utility values associated with urinary tract infections (Table 3 of the company's Technical Engagement Response Form) sourced from a systematic review by Bermingham et al. (2012). The utility values presented by the company range from 0.02 to 0.20. The company states that, "the utility difference for UTI vs no UTI groups varied, however on average it was found to be approximately 0.10". The company then compares this utility decrement for UTI to the utility decrement from their utility regression, which provides a decrement of [redacted] for patients having BIs in the previous 6 months compared to patients who reported not having any BIs in the previous 6 months. The company states, *"considering that UTI is one of the most common side-effects for bladder instillations and not the only side-effect associated to their invasive nature, we consider the decrement of* [redacted] *reflective of this fact and appropriate for use in the cost-effectiveness model."*

The ERG does not accept that it is reasonable to compare these two disutility estimates because one relates to the utility decrement for UTI compared to no UTI, whereas the other relates to the decrement for patients having BIs versus those not having BIs. The decrement associated with having had BIs in

the previous 6 months is applied continuously to all patients having BIs in the model. Therefore, it would only be reasonable to compare these two utility decrements if all patients having BIs experienced UTIs and the UTI symptoms were ongoing from one BI administration to the next. The ERG would consider it reasonable to apply a utility decrement for UTIs in the model if it were applied only to the proportion of patients having UTIs under each treatment option, and only for a period of time that reflects the duration of symptoms experienced when a UTI occurs. To do this, the model would need to explicitly capture the rate of UTIs for patients receiving PPS, BIs and BSC, but the company's model does not explicitly capture the incidence of UTIs.

The company submission provides the incidence of UTIs reported in Nickle (2015) which was an RCT of PPS versus placebo, conducted in the broader population with BPS. Table 35 of the CS reports the incidence of UTIs as 6.6% for PPS (licensed dose) and 3.4% for placebo. The ERG checked the other studies of PPS versus placebo included in the CS and found that none of the other 5 RCTs of PPS versus placebo reported the incidence of UTIs as an adverse event (Mullhollad 1990, Parsons and Mullholland 1987, Parsons 1993, Sant 2003, Holm-Bentzen 1987). Of the two trials of Uracyst® (BI) versus placebo that were included in the company's indirect treatment comparison (Nickle 2010, Nickle 2012), only one specifically reported the incidence of UTIs as an adverse event. In Nickle et al. (2010), mild UTI symptoms were reported in 3.0% of patients having Uracyst® (BI) and 3.1% of patients having placebo.

The ERG's clinical advisers reported that the risk of UTIs following BIs remains low at around 1-5% and that they are easily treated with antibiotics. The company also sought advice on the incidence of UTIs in their original Advisory Board meeting. In the summary of that meeting (Appendix M of the CS), it is stated that "they also agreed that BI patients may experience negative QoL impacts due to UTIs. It was thought that these patients have a risk of symptomatic UTI of between approx. 10-20%." Therefore, the ERG considers that the low rate of UTIs reported in the single RCT of BIs versus placebo are in line with clinical advice provided to both the ERG and the company.

The company's analysis of HES data found that 3.0% of patients having BIs (16/530) had UTIs whereas 0.6% of patients not having BIs (5/898) had UTIs (Table 82 in Appendix O of the CS). The ERG notes that these estimates are based on observational data and not on a randomised comparison and therefore there may be confounding if other variables that predict the likelihood of experiencing UTIs are not similar across these two groups. As the company does not present any information regarding the characteristics of patients in each group, it is not possible to assess whether the groups are similar. Also, the ERG was unable to understand, in the limited time they had to critique the additional evidence, how the data from the HES analysis reported in Appendix O of the original company submission correlated

with the spreadsheet detailing the HES analysis, which was provided during the technical engagement (Appendix H of the company's response to technical engagement). For example, the number of patients having BIs in the spreadsheet was given as [redacted] with confirmed IC/BPS), whereas the number of patients having BIs in Appendix O is given as [redacted]). Therefore, the ERG would require further explanation regarding the differences between these two datasets before accepting the figures from the HES analysis.

The ERG considers that none of the sources of evidence described above provides robust evidence for an increased risk of UTIs in those patients having BIs compared to those treated with either BSC or PPS. In addition, the incidence of UTI reported in all of the sources is generally low and is not consistent with an assumption that all patients having BIs experience UTIs. Therefore, the ERG does not consider that it is reasonable to expect the utility decrement attributable to UTIs to be comparable to the utility decrement experienced during treatment with BIs.

The ERG also notes that the company provided limited details on the utility studies included in the review by Bermingham et al. (2012),[7] making it difficult to judge the relevance of these estimates to UTIs experienced in patients having BIs. The ERG has provided further details on these studies in Table 5. The ERG notes that several of the studies are in patients with significant comorbidities that may affect their health state valuation, such as older adults living in care homes, and individuals with spinal cord injury (Maxwell et al., 2009;[8] Vogel et al., 2002;[9] Haran et al., 2005[10]). Only three of the estimates used the EQ-5D (Ellis and Verma, 2000;[11] Abrahamina et al., 2011;[12] Vogel et al., 2002[9]), which is NICE's preferred instrument for valuing health states. The ERG considered that the most relevant estimate was that provided by Ellis and Verma because the EQ-5D was administered at the time of the UTI in a population recruited from both primary and secondary care and this was compared to age matched healthy controls. However, the ERG also notes that the control population was described as "healthy undergraduate" women and therefore the difference observed between patients with and without UTI may be confounded by lower levels of comorbidities in the 'healthy' control population. Also, the short time-frame (1 day after UTI symptoms began) may fail to capture any improvement in symptoms with treatment over time. The study by [redacted] reported that Quality of Well Being (QWB) Scores improved over the first 5 days in patients receiving effective treatment, suggesting that any decrement is short-lived.

Overall, the ERG considers that any utility decrement attributable to UTI symptoms associated with BIs is likely to apply to a minority of patients and to be time-limited. Therefore, symptoms related to

UTIs are unlikely to account for the utility decrement of [redacted] associated with having had a BI in the previous 6 months which is applied in the model.

The ERG reiterates that it has concerns regarding the handling of missing data for the variable 'BI use in the previous 6 months' in the analysis. Treating missing data as a third category (i.e. Yes, No, Unsure) creates a regression model that is difficult to interpret and with coefficients for other variables in the model that are adjusted in an unpredictable way. The ERG suggested that it would be reasonable to assume that patients who did not report whether or not that had BI use in the previous 6 months were likely to not have had BI use in the previous 6 months. However, the company suggested that *"this would not be appropriate since respondents who did not complete the question regarding frequency of bladder instillations were different from those who reported receiving no bladder instillations within the preceding 6 months as reported in the fact check to the ERG"* on the basis that there were [redacted].[2] Thus, the company is asserting that the missing data relating to BI use in the previous 6 months is non-ignorable missing data (i.e. is not missing at random).

According to Ibrahim et al., (2012),[14] when there are missing covariates in a regression analysis and no missing responses then analyses either assuming missing at random or missing not at random are superior to a complete case analysis in terms of bias and efficiency of the parameter estimates. Also, when there are both missing responses and covariates in a dataset then an analysis either assuming missing at random or no missing at random is superior to a complete case analysis in terms of bias and efficiency provided that the sampling model and the missing data mechanism are assumed to be correct or approximately correct.

In the company's Technical Engagement Response Form, The company provided a revised regression analysis based on a compete case dataset in which patients with missing data on BI use within the previous 6 months are excluded. Given the potential impact on bias and efficiency, the ERG does not believe that the company's revised regression is preferred. The ERG also believes that the company's revised regression still fails to adequately account for missing data. The ERG would have preferred to see an analysis using multiple imputation allowing for missing data on BI use in the previous 6 months to be missing not at random. However, in the absence of a comprehensive exploration of the impact of missing data, the ERG prefers the original analysis, in spite of its limitations, in which patients with missing BI use in the previous 6 months were categorised as "BI unsure". Therefore, the ERG has not incorporated the revised regression analysis into its preferred base-case.

In response to the question, *"Could 'usage of BIs in the previous 6 months' reflect any other markers that may have not been explicitly modelled (such as time since diagnosis, or disease severity)?",* the company has pointed out that the utility regression accounts for disease severity through the inclusion of ICSI and ICPI scores and provides information on the relationship between time since diagnosis and bladder instillations in the previous 6 months. They conclude that usage of BIs in the previous 6 months does not reflect time since diagnosis as suggested.

The ERG accepts that the utility regression accounts for the possibility of confounding due to disease severity, although ICPI and ICSI and considered in separate regression and therefore they are not controlled for simultaneously. The ERG also accepts that that time since diagnosis is not predictive of BI usage in the previous 6 months and therefore differences in time since diagnosis alone is unlikely to account for the decrement observed. However, the ERG notes that given the observational design of the utility survey, the utility decrement attributable to BI usage may relate to other unknown or unmeasured confounding variables that have not been adjusted for in the regression. As the company states it their Technical Engagement Response Form, *"it is not possible to conclude a cause/effect relationship between bladder installations and quality of life from this cross-sectional survey".*

Given the ERG's concerns regarding the company's utility regression, and the lack of any head-to-head comparative data demonstrating that treatment with BIs causes greater disutility than treatment with PPS, the ERG is not confident that it is reasonable to apply the utility decrement attributable to BI usage within their preferred base-case. Therefore, the ERG's preferred base-case analysis continues to use the regression provided in the original CS, without the coefficient for BI usage (model identified as "Twopm 1" in Table 86 of the CS), which is in line with the technical team's preliminary scientific judgement (Issue 5). However, a scenario analysis including the utility decrement from the company's original analysis of the survey data, which included regression coefficients for BI usage (model identified as "Twopm 2" in Table 86 of the CS), has been provided in section 3.2 to demonstrate the sensitivity of the cost-effectiveness results to this parameter.

Table 5: Studies reporting utility values for UTI identified in the systematic review by Bermingham et al. (2012)

First author, year	Population with UTI	Comparator population	Method used to derive utilities	Utility without UTI	Utility with UTI	Difference
Ellis and Verma 2000[11]	Adult women with symptomatic UTI, N=47 Mean age = 32 (±12) Male = 0%	Healthy age-matched controls, N=71 Mean age = 34 (±13) Male = 0%	EQ-5D (mapped from SF-36)	0.922	0.724	0.202
Abrahamian 2011[12]	Adult women with symptomatic UTI *N* = 139 Median age = 29 (IQR 18 – 40) Male = 0%	Population norms from 1998 National Survey of Functional Health Status of non-institutionalized general United States population	EQ-5D (mapped from SF-36)	0.584	Treatment susceptible: 0.560 Treatment resistant: 0.565	Treatment susceptible: 0.024 Treatment resistant: 0.019
Ernst 2005[13]	Adult women with cystitis *N* = 146 Mean age = 34 (± 12) Male = 0%	Utility 7 days post UTI in those with clinical cure	QWB (using VAS)	0.82	0.68	0.14
Maxwell 2009[8]	Older adults living in care homes *N* = 514 N with UTI = 18 (3.5%) Mean age = 80.5 (± 8.4) Male = 28%	Older adults living in care homes without UTI N = 496 (96.5%)	HUI2 using Canadian valuation	0.49	0.40	0.09

First author, year	Population with UTI	Comparator population	Method used to derive utilities	Utility without UTI	Utility with UTI	Difference
Vogel 2002,[9] Vogel 2011[15] and Zebracki 2010[16]	Adults with spinal cord injury *N* = 415 (238 with UTI, 42 with severe UTI and 134 without UTI) Mean age = 30.9 (±5.3) Male = 63% Time since SCI = 16.6 years (±6.2) Aetiology of SCI: Trauma 89% Medical 9% Other 2% Tetraplegia: 54%	Patients from the same population without UTI	SF-12 values mapped to EQ-5D by Bermingham 2012 using patient level data provided by Vogel et al.	0.831	0.782 for UTI 0.738 for severe UTI	0.049 for UTI 0.093 for severe UTI
Haran 2005[10] and Lee 2008[17]	Individuals with SCI predominantly living in the community who had participated in a trial of antiseptics for UTI, with absence of current symptoms of a UTI N = 305 (138 with UTI and 167 without) Mean age = 44 (± 14) Male = 83%	Values obtained at 6 months in those who did not develop a UTI are compared to values obtained at the time of UTI in those who developed a UTI.	SF-36 data were mapped to SF-6D SF-12 data mapped to SF-6D	0.68 0.70	0.58 0.60	0.10 0.10

EQ-5D, EuroQol 5 Dimensions; HUI-2, Health-utilities index -2; UTI, urinary tract infection; SF-6D, short-form 6 Dimensions; QWB, quality of well-being scale; VAS, visual analogue scale

2.5 Modelled costs and resource use (Issue 7)

In the company's original base-case analysis it was assumed that BIs would be given every week for 4 weeks, followed by every 4 weeks thereafter. This frequency of BIs is assumed to apply life-long in those having BIs, as those who discontinue treatment with first-line PPS or first-line BIs are assumed to switch to second-line BIs and no discontinuation rate is applied to second-line treatment.

In the ERG's preferred base-case, it was assumed that patients would switch to 6 weekly dosing of BIs after 1 year for first line BIs and that dosing of second-line BIs would be six-weekly as it was not possible to change the frequency of dosing over time. This was based on advice from clinical experts that indicated that the time between doses would be extended to the maximum that could be tolerated and that this could be as long as 2-3 months between doses for some patients.

The ERG has considered the additional evidence provided by Consilient which takes the form of a survey of clinical experts. Nine out of 10 clinical experts responded to the question *"In your experience, what is the average length of time between bladder instillations that the majority of patients with IC//BPS can be successfully managed on?"* One clinical expert indicated 3-4 weeks, four indicated monthly or 4-weekly, one indicated 6 weekly, and three indicated longer than 6 weeks (2-6 months, 4 to 12 weeks, 3 months). In response to the question *"What percentage of patients can go longer than 4 weeks?"* the responses ranged from less than 10% to 75%. In response to the question, *"What percentage of patients are unable to be managed with 4 weekly instillations and require more frequent treatments?"* the responses ranged from 10% to 30%.

The ERG also notes that the company's analysis of HES data (Appendix O of the CS) shows that the frequency of BIs decreased over time (Table 80 of the CS) with 0.6 BIs per month reported for both outpatients and inpatients 13-24 months post diagnosis. This is equivalent to an average period of 7.2 weeks between BIs. As described in section 2.4, the ERG were unable, in the limited time available, to reconcile the data from the HES analysis presented in Appendix O of the CS with the spreadsheet provided in Appendix H of the company's response to the technical engagement. Therefore, the ERG would require further explanation regarding the differences between these two datasets before accepting the figures from the analysis. However, on face value, the figures seem supportive of the ERG's assumption of 6 weekly BIs beyond the first year.

Overall, the ERG believes that the evidence provided by Consilient is consistent with its assumption of 6 weekly BI administrations in the long-term. However, the ERG accepts that there is significant variation in practice with a proportion of clinicians appearing to adhere to the four-weekly treatment

regimen in the majority of their patient cohort, and a proportion appearing to favour less frequent administrations in the majority of their patient cohort. The ERG notes that it is difficult to use the clinical expert survey presented by the company to determine a more accurate estimate of the average dosing regimen as the company has not used a formal elicitation framework.

The ERG also notes that the ICERs provided in Table 2 and Table 6 of the company's Technical Engagement Response Form assume 4 weekly BIs. The updated cost-effectiveness analyses provided by the company are therefore inconsistent with the technical team's preliminary scientific judgement which stated that it is preferable to model 6-weekly administration of second line bladder instillations and first line bladder instillations after the first year.

3 ERG additional analyses

The exact changes to the ERG's previous base-case model required to implement the additional analyses described below are detailed in Appendix 1.

3.1 ERG's updated preferred base-case

The ERG's updated preferred base-case incorporates the outputs of the ERG's NMA analysis described in sections 2.1 and 2.2. To do this, the ERG used the CODA samples for the predictive distribution of the absolute response rates. These were generated by combining the treatment effects model described in section 2.1 with the baseline response model, described in section 2.2. The summary statistics for the predictive distribution of the absolute response rates are provided in Table 2 above. The CODA samples were incorporated into the PSA and the PSA was run for 10,000 simulations to generate stable estimates of incremental costs and QALY. However, in order to run the ERG's preferred base-case using the PSA version of the model, it was necessary to fix the regression parameters for the utility regression as the variance-covariance matrix for the utility regression excluding BI usage were not available to the ERG. Therefore, the ERG's revised base-case analysis probably underestimates uncertainty about the ICER.

In addition, the ERG also revised their analysis of the time to discontinuation data from Hanno et al. (1997) to consider deaths during follow-up as censored outcomes rather than discontinuations. This was in line with the technical team's preliminary scientific judgement as set out in the draft technical report (Issue 4, page 9 of draft technical report). The updated survival model parameters are provided in section 2.4.

The ERG's updated preferred base-case does not include the company's revised utility regression which was generated after excluding patients with missing data on BI usages in the previous 6 months. Instead it includes the utility regression incorporated in the ERG's previous base-case which excluded the variable for BI usage. Therefore, this analysis excludes any utility decrement directly attributable to BI usage (see section 3.2 for an exploratory analysis using the company's original regression).

It can be seen from the results presented in Table 6 that revising the time to discontinuation survival function to treat deaths during follow-up as censored events rather than discontinuations had minimal impact on the deterministic ICER for the comparison against BI. In contrast, using the mean absolute response rate from the ERG's NMA had a large impact on the deterministic ICER for the comparison against BIs increasing it to [redacted]. The ICER was [redacted] in the ERG's revised base-case, which used the outputs from the PSA and incorporated the CODA samples from the ERG's NMA. The ERG notes that the spread of incremental QALYs on the cost-effectiveness plane (Figure 4) covers a wide

range, with PSS being dominated by BI in 45.5% of PSA samples. This reflects the large uncertainty in the relative effectiveness of PPS and BIs when using the ERG's NMA outputs shown in Table 2.

Table 6: Results for PPS versus BI including ERG's revised base-case

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
1 = ERG's original preferred base-case (Table 28 of ERG report) – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-
2 = 1+ revised time to discontinuation curve (deaths censored) - deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-
3 = 2+ mean absolute response rates from ERG's NMA – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-
ERG's revised base-case: **4 = 2+ absolute response rates based on CODA samples from ERG's NMA – probabilistic**					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-

Figure 4: [redacted]

Figure 5: [redacted]

It can be seen from the result presented in Table 7 that revising the time to discontinuation survival function so that deaths during follow-up are treated as censored events rather than discontinuations also had minimal impact on the deterministic ICER for the comparison against BSC.

For the comparison against BSC, the ICER was similar to the ERG's previous base-case with the ERG's revised base-case having an ICER of [redacted] per QALY when incorporating the CODA samples from the ERG's NMA.

The variability in incremental costs and QALYs from the PSA for the comparison of PPS versus BSC are shown in Figure 6. There is a considerable variability in both costs and QALYs across the cost-effectiveness plane with PPS dominated by BSC in 34.6% of PSA samples.

Table 7: Results for PPS versus BSC including ERG's revised base-case

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
1 = ERG's original preferred base-case (Table 29 of ERG report) – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-
2 = 1+ revised time to discontinuation curve (deaths censored) - deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-
3 = 2+ mean absolute response rates from ERG's NMA – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-
ERG's revised base-case: **4 = 2+ absolute response rates based on CODA samples from ERG's NMA – probabilistic**					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-

Figure 6: [redacted]

Figure 7: [redacted]

3.2 ERG's additional exploratory analyses

Table 8 presents results for the exploratory sensitivity analysis using the company's original utility regression which results in a decrement of [redacted] for patients having BIs compared to those having PPS, and applied to all patients having first or second line BIs. It can be seen that the model results are

particularly sensitive to changes in this parameter because the inclusion of the decrement for BIs results in QALY gains of [redacted] compared to QALY gains of [redacted] when the decrement is excluded. However, this analysis demonstrates that the mean ICER is above £30,000 even if accepting that BI usage results in a utility decrement of [redacted] as proposed by the company.

The ERG notes that the ICER in this exploratory scenario analysis is higher than those presented in Tables 2 and 6 of the company's Technical Engagement Response Form, which range from [redacted]. It should be noted that the company's revised model does not incorporate the ERG's preferred assumption that the frequency of BIs should decrease after 1 year to once every 6 weeks. Instead, the company's revised analyses all incorporate 4 weekly BI administrations in the long-term. In the ERG's previous exploratory analyses (section 5 of the ERG report) reducing the frequency of BIs from 4 weekly to 6 weekly in the long-term increased the company's base-case ICER from [redacted], which would bring the company's revised ICERs up to a level similar to that reported in Table 8 for the scenario including the company's original utility regression.

Table 8: Exploratory scenario for PPS versus BI

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
4 = ERG's revised base-case (Scenario 4 in Table 7 which uses the utility regression excluding coefficient for BI usage from the original CS) – probabilistic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-
5 = 4 but with utilities based on company's original regression analysis – probabilistic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BI	[redacted]	[redacted]	-	-	-

5 OVERALL CONCLUSIONS

The company presented additional information from a new clinical expert survey to support their preferred assumptions around the frequency of BIs in current clinical practice. The ERG considered that the additional evidence was consistent with its assumption that patients would receive 6 weekly BIs in the long-term, although the ERG accept that there appears to be variation in clinical opinion regarding the optimum long-term dosing frequency.

The company also reported the clinical experts' opinion on the likelihood of patients on BSC achieving a response. The ERG consider that the estimates of the expected response rate provided both by the ERG's clinical experts and the company's survey of clinical experts are reasonably consistent with the response rate achieved in the ERG's meta-analysis of the placebo response rates in the PPS RCTs (15.5%).

The ERG also notes that the company's revised cost-effectiveness analysis used a higher response rate for BSC (18.9%) because it was informed by both the response rate in the two Uracyst® (BI) RCTs which were in the broader BPS population, and the response rate in the PPS RCTs which were in the more relevant IC/BPS population. In the absence of an external estimate for the response rate following treatment with BSC in clinical practice, the ERG considered it preferable to use the response rate based on the data from the placebo arms of the PPS RCTs in the economic model.

The company also reported the clinical experts' opinions on the durability of any response achieved on BSC. However, in the absence of any evidence on the long-term response rate in patients having BIs and PPS, the ERG preferred to use their original assumption that the response to treatment was equally durable in both groups.

The company provided an updated utility regression of their patient survey data, in which they excluded from the analysis patients with missing data on BI usage in the previous 6 months (i.e. they performed a complete case analysis). The ERG considered that this analysis was less robust than the analysis previously presented in which those with missing BI usage data were categorised as "BI usage unsure". Nevertheless, the ERG would prefer it if the company would perform analyses using multiple imputation assuming not missing at random as well as missing random to account for the missing data on BI usage within the previous 6 months rather than performing a complete case analysis.

The company provided additional evidence, from a published systematic review, on the utility decrement attributable to UTIs in an attempt to provide a rationale for there being a difference in utility

between those with and without BIs in the previous 6 months. However, the ERG noted that comparing the utility decrement of UTI with the utility decrement for previous BI usage is flawed because it implicitly assumes that all patients having BIs are experiencing UTI symptoms continuously from one BI administration to the next. The ERG attempted to summarise the available data on the incidence of UTIs in patients having BIs, PPS or BSC and noted that it was generally low. Therefore, the ERG does not believe that the incidence of UTIs in patients having BIs is a plausible reason for there being a utility decrement associated with BI treatment.

The company provided an NMA comparing the response rate in PPS, BIs and BSC. However, the company has used a technically incorrect approach to characterising uncertainty about the absolute responses to each treatment in their NMA. The ERG has provided a revised NMA, which has been incorporated into the ERG's revised base-case cost-effectiveness model. In the ERG's revised NMA, the baseline response rate is based only on the PPS RCTs in the IC/BPS population and this baseline response model is combined with a treatment effect model for PPS and Uracyst®. For PPS versus BSC, the evidence from the ERG's baseline response and NMA analysis has minimal impact on the ICER, increasing it marginally from [redacted] (deterministic) to [redacted] (probabilistic). For PPS versus BIs, the evidence from the same models has substantially increased the ERG's preferred ICER from [redacted] (deterministic) to [redacted] (probabilistic). The ERG notes that the PSA results presented here ignores additional uncertainty in the ICER because the ERG was unable to include the regression coefficients and uncertainty about them for the utility regression in the PSA.

The ERG also provided a scenario analysis using their revised base-case analysis, which incorporates the ERG's NMA results, and combines this with the company's original utility regression. This demonstrates that the ICER is extremely sensitive to the utility decrement associated with BI usage, although the mean ICER remained marginally above £30,000 even when including the company's original decrement for BI usage.

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7 APPENDICES

Appendix 1: Changes made to the ERG's previous base-case model

Change 1 – incorporating survival analysis for time to discontinuation where deaths are censored

Sheet 'ERG_survival_curve has been replaced with 'ERG_survival_curve_deaths_censr'.

This revised sheet contains the data for the time to discontinuation survival analysis when assuming that patients who died were censored instead of being counted as having discontinued. The outputs of the analysis using this updated dataset are linked to cells F120, F125, F126, F131 and F132 of the "Model inputs" sheet (via cells J120:J128). This ensures that the ERG's updated survival analysis is used when the cell named "T2TD_ERG_flag" is set to 1 on the "ERG options sheet".

Change 2 – incorporating the ERG's NMA outputs in the deterministic analysis

A named cell called "ERG_NMA_switch" has been added to the ERG options sheet (cell B32). When this is set to 1, cells J22 to J24 of the 'Response and Utility data' sheet, which set the response rates in PPS, BIs and BSC respectively, are set equal to cells U3, V3 and T3 of the new "ERG_CODA_NMA" sheet. These cells provide the mean response rate from the CODA samples for PPS, BIs and BSC respectively. Please note that these values are fed through into the 'Model input' sheet only after the "CLICK TO APPLY DEFUALT VALUES TO MODEL" button on the "CONTROL" sheet has been activated.

Change 3 - incorporating the ERG's NMA outputs in the deterministic analysis

The CODA samples for the predictive distribution of the absolute responses are stored in cells T8:V10007 of the new "ERG_CODA_NMA" sheet. This array has been named "CODA_in_array".

New VBA code has been added to the 'PSAsimulations()' subroutine which implements the PSA.

The following lines have been added to store the array of CODA samples;

```
Dim CODA_array As Variant
If NumSim > 10000 Then
NumSim = 10000 'max CODA samples so max PSA runs.
End If
ReDim CODA_array(1 To NumSim, 3) 'ERG  new
CODA_array = Range("CODA_in_array").Offset(0, 0).Resize(NumSim, 3).Value 'ERG new
```

In addition, the following lines have been added within the loop which goes through each iteration of the PSA to allow one row of the CODA samples to be used to populate the efficacy estimate of the 'Model inputs' sheet for each PSA iteration;

```
If Range("ERG_NMA_switch").Value = 1 Then
```

```
    Range("bsc_efficacy").Value = CODA_array(1, sim)
    Range("elmiron_efficacy").Value = CODA_array(2, sim)
    Range("blad_efficacy").Value = CODA_array(3, sim)
End If
```

When running the PSA with the CODA samples from the ERG's NMA, the utility regression inputs were fixed at the midpoint estimates by setting cells J25:J32 of the "PSA – ICSI data" sheet equal to cells J50:J57 of the "Response & utility data" sheet. This was because the ERG did not have access to the variance-covariance matrix for the regression excluding BI usage which is also included in the ERG's preferred base-case.

Pentosan polysulfate sodium for treating bladder pain syndrome: A Single Technology Appraisal: second addendum prepared after technical engagement

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

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Contributions of authors

Sarah Davis and Kate Ennis extracted and presented the results incorporating the PAS described in this addendum.

CONTENTS

List of tables

Abbreviations

BI	Bladder instillations
BSC	Best supportive care
ICER	Incremental Cost Effectiveness Ratio
NMA	Network meta-analysis
PAS	Patient Access Scheme
PPS	Pentosan polysulfate sodium
PSA	Probabilistic sensitivity analysis
QALY	Quality-Adjusted Life Year

1 ERG additional analyses incorporating PAS

This addendum provides the results presented in section 3 of the first addendum to the ERG report but with the application of the patient access scheme (PAS) discount provided to the ERG on the 4th of June. The PAS is a simple discount to the list price of [redacted]. In addition, Appendix 1 of this addendum provides an additional table of ICERs requested by NICE on 3rd of June with the PAS applied.

1.1 ERG's updated preferred base-case

See section 3.1 of the first addendum to the ERG report for a description of the ERG's preferred base-case. Results when including the PAS are provided in Table 1 and Table 2.

It should be noted that the QALY gains for PPS vs BI in the ERG' revised base-case (Table 1, scenario 4) are [redacted] with a 95% Credible Interval (CrI) of [redacted] to [redacted]. If the incremental costs were considered fixed at their mean, then the CrI around the QALYs would give an ICER range of £74,269 to £103,560. This indicates that there remains considerable uncertainty around the mean ICER despite running 10,000 PSA iterations. The mean QALYs gained for PPS vs BI in scenario 3, which used mean NMA outputs was [redacted], which is why the ICER is higher in scenario 3 than scenario 4 indicating the importance of using the CODA samples to obtain a true estimate of the mean ICER in this comparison.

Table 1: Results for PPS versus BI including ERG's revised base-case (including PAS)

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
1 = ERG's original preferred base-case (Table 28 of ERG report) – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£65,301**
BI	[redacted]	[redacted]	-	-	-
2 = 1+ revised time to discontinuation curve (deaths censored) - deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£65,299**
BI	[redacted]	[redacted]	-	-	-
3 = 2+ mean absolute response rates from ERG's NMA – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£100,309**
BI	[redacted]	[redacted]	-	-	-
ERG's revised base-case: **4 = 2+ absolute response rates based on CODA samples from ERG's NMA – probabilistic**					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£86,502**

BI	[redacted]	[redacted]	-	-	-

Table 2: Results for PPS versus BSC including ERG's revised base-case (including PAS)

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
1 = ERG's original preferred base-case (Table 29 of ERG report) – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£73,383**
BSC	[redacted]	[redacted]	-	-	-
2 = 1+ revised time to discontinuation curve (deaths censored) - deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£73,257**
BSC	[redacted]	[redacted]	-	-	-
3 = 2+ mean absolute response rates from ERG's NMA – deterministic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£73,257**
BSC	[redacted]	[redacted]	-	-	-
ERG's revised base-case: 4 = 2+ absolute response rates based on CODA samples from ERG's NMA – probabilistic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£72,355**
BSC	[redacted]	[redacted]	-	-	-

1.2 ERG's additional exploratory analyses

The ERG's additional exploratory analysis examining the impact of using the ERG's preferred assumptions but with the company's original regression analysis is described in section 3.2 of the first addendum to the ERG report. The results for this scenario when incorporating the PAS are provided in Table 3.

Table 3: Exploratory scenario for PPS versus BI (including PAS)

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
4 = ERG's revised base-case (Scenario 4 in Table 7 which uses the utility regression excluding coefficient for BI usage from the original CS) – probabilistic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£86,502**
BI	[redacted]	[redacted]	-	-	-
5 = 4 but with utilities based on company's original regression analysis – probabilistic					
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£24,000**

BI	[redacted]	[redacted]			

Appendix 1 Additional tables requested by NICE on 3rd with PAS applied

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BIs) - Patient Access Scheme (PAS) included

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (includes median response rates from company's NMA and PAS)	**Addresses issues 2 and 4 plus new evidence on issue 1**	**£11,282**	
1. Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	£44,898	+£33,616
2. 6-weekly administration for second line BIs and first line BIs after first year	Issue 7	£21,299	+£10,017
3. Combined changes 1 and 2 (remove BI usage covariate + 6-weekly BIs)	Issue 7 and 5	£84,763	+£73,481
4. **ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)**	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	**£86,502**†	**+£75,220**

† this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs

Table 1b: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BSC) - Patient Access Scheme (PAS) included

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (includes median response rates from company's NMA and PAS)	**Addresses issues 2 and 4 plus new evidence on issue 1**	**£73,838**	
5. Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	Not relevant	
6. 6-weekly administration for second line BIs and first line BIs after first year	Issue 7	Not relevant	
7. **ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)**	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	**£72,355**†	**-£1,483**
† this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs			

Table 2: Detailed results for company updated base-case (PPS vs BSC) – incorporating PAS

Option	Costs	QALYs	Inc. costs	Inc. QALYs	ICER (per QALY gained)
PPS	[redacted]	[redacted]	[redacted]	[redacted]	**£73,838**
BI	[redacted]	[redacted]	-	-	-

Correction to Table 1a in 'ERG addendum post TE with PAS'

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BIs) - Patient Access Scheme (PAS) included

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (using the Bucher method and including PAS)	Addresses issues 2 and 4	**£9,952**	
Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	£34,059	+£24,107
6-weekly administration for second line BIs and first line BIs after first year	Issue 7	£19,081	+£9,129
Combined changes 1 and 2 (remove BI usage covariate + 6-weekly BIs)	Issue 7 and 5	£65,301	+£55,349
ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	**£86,502**[†]	**+£76,550**
[†] this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Pentosan polysulfate sodium for treating bladder pain syndrome

1. Summary of the technical report

1.1 This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: June 2019

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. Scientific judgments that have been updated after engagement are highlighted in **bold** below.

1.3 In summary, the technical team considered the following:

- For both base-case analyses:
  - **An indirect treatment comparison using the ERG's Bayesian network meta-analysis is preferable to the Bucher method used in the company's updated model (see Issue 1)**
  - A lifetime horizon in the economic model is appropriate (see Issue 2)
  - It is preferable to use the ERG's time-to-discontinuation datatset (but with deaths excluded from being 'failures' in the analysis) and a log-normal extrapolation (see Issue 4)
  - It is preferable not to include 'previous use of bladder instillations in the past 6 months' as a covariate in the utilities regression (see Issue 5).
- For the analysis of pentosan polysulfate sodium compared to best supportive care:
  - It is not appropriate to assume that utilities and costs of non-responders who move onto best supportive care are maintained after the initial 6-month response check (see Issue 6)
  - Length of any response in the best supportive care arm should not be limited to 12 months (see Issue 3)
  - **The estimated response rates to BSC should be based on the placebo arms of the pentosan polysulfate sodium trials (see Issue 3).**
- For the analysis of pentosan polysulfate sodium compared to bladder instillations:

- It is preferable to model 6-weekly administration of second line bladder instillations and first line bladder instillations after the first year (Issue 7).

1.4 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved (see Table 2):

- Methodological limitations of the clinical trials informing the economic model (such as different reported outcomes and small sample sizes)
- Age of available evidence (clinical trials providing evidence about pentosan polysulfate sodium were published between 1987 and 2003).

1.5 Based on the available analyses and **with the patient access scheme applied**, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of **£86,502 per QALY gained** for the analysis compared to bladder instillations (see Table 1a), and an ICER of **£72,355 per QALY gained** for the analysis compared to best supportive care (see Table 1b). The technical team notes that there is substantial uncertainty associated with these estimates due to outstanding uncertainties in the evidence base.

1.6 The technology is unlikely to be considered innovative (see Table 3).

1.7 Some stakeholders highlighted that interstitial cystitis/bladder pain syndrome (with Hunner's lesions and/or glomerulations) affects women more frequently than men. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal (see Table 3).

2. Key issues for consideration

Issue 1 – Indirect treatment comparison

Questions for engagement	• Mindful that there are challenges with all approaches for comparing pentosan polysulfate sodium with bladder instillations, which is the best indirect treatment comparison to use in this appraisal (an indirect treatment comparison using a Bayesian network meta-analysis or the Bucher method)?
Background/description of issue	To compare pentosan polysulfate sodium (PPS) with bladder instillations (BIs), the company used an indirect treatment comparison (ITC). Uracyst was the only bladder instillation that was suitable for indirect comparison with PPS via placebo. Meta-analysed data from two Uracyst trials were compared to meta-analysed data from four PPS trials using the Bucher method of ITC (an adjusted ITC method which retains the original randomisation of patients). The company highlights several challenges with the ITC: • Differences in trial populations: PPS trials were in people with interstitial cystitis/bladder pain syndrome who have Hunner's lesions and/or glomerulations (IC/BPS; the population in the NICE scope) whereas Uracyst trials were in people with bladder pain syndrome (BPS) • Differences in placebos: PPS was compared to an oral placebo whereas Uracyst was compared to a placebo instillation • Differences in the timings of outcome measurement • Differences in definition of Global Response Assessment[1]. The ERG accepts that, in order to satisfy the NICE scope, an ITC of PPS and Uracyst is necessary. The ERG highlights Bayesian network meta-analysis (NMA) as an alternative to the Bucher method of ITC. Although the ERG acknowledges that neither method is ideal, it prefers a Bayesian NMA to the Bucher method because:

[1] The Global Response Assessment (GRA) is a standardised outcome in IC/BPS to capture response. It is scored from 0–7, and a score of 6 or 7 is classified as moderately improved or markedly improved, respectively.

	• The Bucher method generates unrelated estimates of treatment effects from separate meta-analyses, whereas a Bayesian NMA uses all of the data to estimate heterogeneity (which the ERG considers to be preferable) • As implemented, the Bucher method assumes that the sample estimate of the effect of PPS compared to Uracyst follows a normal distribution, which is an unnecessary approximation.[2]
Why this issue is important	The effect of the limitations with the ITC are unknown. However, these challenges greatly increase the uncertainty in the estimates of treatment effect. Because the results from the ITC are included in the economic model, this also leads to uncertainty in the cost effectiveness estimates.
Technical team preliminary scientific judgement and rationale before engagement	The technical team consider that the challenges with performing an ITC greatly increase the uncertainty in the estimates of treatment effect. To acknowledge some of this uncertainty, the best possible methods for ITC should be used. On this basis, the technical team prefer a treatment comparison using a Bayesian NMA.
Summary of comments	Comments from company The original submission used the Bucher method whilst recognising the considerable heterogeneity between trials. Neither the Bucher method nor a Bayesian NMA are ideal for comparing PPS and bladder instillations in this submission. The company's updated base-case used the Bucher method, however, they also submitted a scenario using a Bayesian NMA incorporating the following: • The same clinical data as considered in the original submission • A random-effects model (both a fixed effect and a random effects model were explored) • A vague Gamma prior distribution to model between-study precision (1/sd^2) • Analyses conducted on the logit scale to obtain relative risk estimates • Model fit determined using the deviance information criteria (DIC)

[2] The technical report that was originally released for engagement has been corrected for factual inaccuracies within these statements. The statements in the original technical report were:

- The Bucher method maintains treatment effect estimates from separate meta-analyses, whereas a Bayesian NMA incorporates all the data into estimating a common random treatment effect (which the ERG considers to be preferable)
- As implemented, the Bucher method assumes that the sample estimate of the effect of PPS compared to Uracyst follows an approximately normal distribution; the ERG considers that this assumption may not hold.

	Comments from British Association of Urological Surgeons The view of the technical team preliminary scientific judgement and rationale suggesting using the Bayesian network meta-analysis method is reasonable. Comments from ERG The ERG agrees that neither method deals directly with differences in populations and placebo treatments in the studies. However, the ERG highlight the following considerations about the company's updated approach: • It is preferable to use a Bayesian NMA • The company have misinterpreted NICE Decision Support Unit Technical Support Document 2; the use of a gamma prior distribution is not justified • The ERG is content with using a weak prior distribution for the between study standard deviation over the range 0 to 2 • The ERG prefers to use the predictive distribution for the effect of treatment in a new study as the estimate of treatment effect • A random effects model is appropriate because the ERG expect heterogeneity between studies • The ERG prefers to estimate the absolute response to each treatment based on separate baseline and treatment effect models
Technical team judgement after engagement	The company submitted a revised model which included a scenario incorporating a Bayesian NMA for comparing PPS with BI which increased its base-case ICER (with patient access scheme applied) from £9,952 (Bucher method) to £11,282 (Bayesian NMA). The ERG identified methodological limitations with the company's NMA approach, and preferred their own Bayesian NMA. The technical team consider that the ERG preferences address the corrections required in the company's analysis.

Issue 2 – Time horizon in economic model

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 3 – Modelled response rate

Questions for engagement	• Based on a meta-analysis, the company assume 16% of patients would respond to best supportive care with no intervention. Is this assumption reasonable? • The company assume that any response in patients receiveing best supportive care would not last more than 12 months. Is this assumption appropriate?
Background/description of issue	The company notes that response rates in the placebo arms of the PPS trials were high (the meta-analysis estimates a reported response in 16% of the placebo arm). The company considers that the high response rates in the placebo arms are a likely result of participation in the clinical trial and do not reflect response rates under best supportive care (BSC) in clinical practice. It considers this to be conservative against PPS, and that high placebo response rates would lead to an underestimation of the effectiveness of PPS. The company attempts to account for this by limiting duration of response to 12 months in the best supportive care (BSC) arm of the model. The ERG's clinical experts advise that in clinical practice, they would expect a response in 20-30% of patients on best supportive care (implying that the response rates estimated from the meta-analysis are in fact conservative). The ERG considers that the placebo response rates may be explained by regression to the mean, where the variability of the condition over time means there is a natural improvement of symptoms after a 'flare-up' which is unrelated to any intervention. Any regression to the mean present in the placebo arms of the clinical trials would also be present in the PPS and Uracyst arms of the trials, and so should not be adjusted for. The ERG highlight that in the company's model, the relative response to treatment of PPS compared to BIs depends on the rate of response for best supportive care (BSC). This is because the response rates are calculated by multiplying the relative risks estimated by the meta-analyses with the BSC response rate, meaning the absolute difference in treatment effect becomes greater with increasing BSC response. Therefore, the ERG considers that the high response rate in the placebo arm is likely to favour PPS (rather than leading to the effect being underestimated, which is the company's interpretation).

	Without further evidence of a plausible difference in duration in response, the ERG does not consider the company's approach of limiting response in the placebo arm to 12 months to be appropriate. In its base-case analysis of PPS compared to BSC, the ERG assumes that BSC response rates do not recede over time.
Why this issue is important	Assumptions about relative treatment effect that favour the technology may add uncertainty to the cost-effectiveness estimates. The effect of assuming the same durability of response in all treatment arms increased the company's original base-case ICER (which was based on list price) by around [redacted] in the analysis of PPS and BSC.
Technical team preliminary scientific judgement and rationale before engagement	In an analysis using relative risks, a high response rate in the BSC arm would favour PPS, which increases uncertainty in the cost-effectiveness results. Any regression to the mean present in the BSC arm is likely to be present in the PPS and BI arms and therefore does not support an assumption of shorter durability of response in the BSC arm than the PPS and BI arms. In the absence of evidence suggesting differences in durability of response, it is acceptable to assume that BSC response rates (based on the placebo response rate from the meta-analysis) do not recede over time.
Summary of comments	<u>Comments from company</u> The company sought the view of clinical experts to validate the results of the meta-analysis. The result of the meta-analysis (that 16% of people would respond to best supportive care) appears to be broadly in line with the views of clinical experts.The experts indicated that between 0 and 30% of people would experience symptom resolution and up to 50% might have some level of symptom improvement if managed with BSC alone. However, all the experts agreed that the symptom improvement/resolution would be short-lived. The company's experts indicated that these patients are unlikely to receive either PPS or BI until their symptoms deteriorate or return. The consensus of the experts was that the durability of response to BSC ranged from <3 months to 1 year. The company considered it is therefore conservative to assume a response to BSC to last 12 months. The company's economic model assumes that people will only be considered for PPS or BI when BSC no longer sufficiently manages their symptoms. The company considers that it is unrealistic to expect to see long-lasting symptom improvements in people being sub-optimally managed with BSC. The company assert their original assumption, that the duration of response to BSC would be limited to 12 months, is valid and conservative. However, they have incorporated into their base-case the ERG's preference that response to BSC does not recede over time.

	Comments from British Association of Urological Surgeons Placebo effects are variable. Larger placebo-controlled drug trials have shown an average placebo effect of 35%. The 16% modelled by the company seems a little low (would be in the lower range of expected estimates). However, as this data is based on meta-analysis, an assumption of 16% response to best supportive care with no intervention would appear reasonable to use. Placebo affects are usually shorter-lived, therefore from a clinical perspective it would be reasonable to assume the effects would not last beyond 12 months. Comments from ERG The ERG highlight that the company's original submission used data from the placebo arms of the PPS trials, whereas, in their updated analysis the placebo arms from the Uracyst trials were also included. The company's revised cost-effectiveness analysis used a higher response rate for BSC (18.9%). The ERG considers that the estimate of the response rate to best supportive care (BSC) used in the cost effectiveness analysis should be based only on the data from the placebo arms of the PPS capsule studies (16%), which was the approach used in the company's original submission. Also, the company estimated the response to BSC within the same analysis as the treatment effects model. The ERG highlight the following problems with the company's updated approach: • The company is unable to quantify the absolute response to BSC in clinical practice using evidence other than from the available clinical trials (which have methodological limitations) • An estimate of the absolute response to BSC in clinical practice is required in order to estimate the absolute responses to treatment with PPS and BI • It is not necessarily true that the baseline response in the target population is comparable to a simple summary of the baseline response in the available clinical trials • It is problematic to include the placebo arms from both the PPS and BI studies as the patient populations and placebo treatments are different for each treatment. The ERG instead prefers the following approach: • Separate baseline and treatment effects models to ensure that the information in the baseline model does not affect the relative treatment effects model

	• Generate the baseline response as the predictive distribution of the baseline response in a new study using a random effects model • The ERG's estimate of the baseline response based on the predictive distribution for the response in a new study was 15.5% compared to the company's estimate of 16% in the original submission and 18.9% as reported in the company's updated analysis
Technical team judgement after engagement	The technical team consider this issue to be partially resolved. The company have incorporated the ERG's preferred assumption on the duration of response to BSC in their revised base-case. The technical team agree with the ERG's conclusion and the company's updated model that the response to BSC does not recede over time. However, the technical team also note that the company's estimate of the response rate to BSC is higher than the ERG's preference. The technical team agree with the ERG's estimate of the baseline response, and consider that the ERG have accounted for problems within the company's updated approach.

Issue 4 – Time to treatment discontinuation

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 5 – Utilities associated with use of bladder instillations

Questions for engagement	• The company assume a utility decrement (a reduction in quality of life) of around [redacted] associated with the use of BIs. Is this assumption appropriate? • Could 'usage of BIs in the previous 6 months' reflect any other markers that may have not been explicitly modelled (such as time since diagnosis, or disease severity)?
Background/description of issue	Utility values were derived from Interstitial Cystitis Symptom Index (ICSI) scores collected in the Sant et al. (2003) trial, which were mapped to EQ-5D data. Utilities were estimated as a function of ICSI, usage of BIs in the previous 6 months and age. The regression coefficient for 'received a BI in the past 6 months' was applied to all patients having BIs in the model. The company highlights that the inclusion of a coefficient for having had a BI in the previous 6 months leads to a utility decrement associated with receiving a BI. The company justifies this on the grounds that BIs are invasive and

	associated with adverse effects. A result of the company's modelling is that the utility score of non-responders having BSC is [redacted] than the utility score of patients having second-line BIs (even though a proportion of these patients achieve response). The ERG notes that a large driver of the PPS QALY gain comes from the decrement applied to people having first-line BIs. The ERG is concerned that the difference in utility detected in the patient survey may reflect baseline patient characteristics rather than being treatment specific. The ERG notes that previous treatment with PPS was not included as a covariate in the mapping model, and therefore do not know whether a similar decrement associated with PPS should be applied. The ERG highlights the possibility that [redacted] In its base-case, the ERG did not include previous BI usage as a covariate in the utilities model. The technical team notes that the utility decrement appears to be a key driver of the analysis comparing PPS with BIs. The technical team questions whether usage of BIs in the previous 6 months could be a proxy for another driver not captured in the model (such as time since diagnosis or disease severity).
Why this issue is important	In the analysis of PPS compared to BIs, using the ERG's preferred utility regression (omitting previous BIs as a covariate) increased the company's original ICER (which was based on list price) by around [redacted] . In the analysis of PPS compared to BSC, omitting previous BIs as a covariate decreased the company's original ICER by around [redacted] .
Technical team preliminary scientific judgement and rationale before engagement	The technical team consider that there is not enough evidence to tell whether the 'usage of BIs in the previous 6 months' disutility captured by the patient survey would be relevant to the full survey population. Because BIs are an outpatient procedure, the technical team considers that any disutility caused by BIs is likely to be shortlived. Without further evidence, 'usage of BIs in the previous 6 months' should not be included as a covariate in the utility regression model, in line with the ERG preferred assumption.
Summary of comments	Comments from company The company maintain that their use of a utility decrement associated with BIs is appropriate. The company provided evidence in support of its use from clinical experts and a systematic review (Bermingham, 2012) of the impact of UTIs on health-related quality of life. The company suggest that this evidence shows that BIs are associated with an increase in the likelihood of UTIs and that individuals with UTIs have significantly lower quality of life compared to those without UTIs. The company calculated an average utility difference in people with UTIs of 0.10 from the 6 studies

	included in the review. Patient case studies provided by the company also suggest that UTIs in people with IC/BPS may have a bigger impact on quality of life than UTIs in the general population. The company explored 2 alternative approaches to handle missing data in relation to the survey responses about BI usage in the previous 6 months. The first approach was to impute a value of zero for the missing data. However, the company do not consider this an appropriate approach as the respondents who did not complete the survey question were found to have [redacted] compared with those who reported no BI use. The company's preferred approach is to exclude respondents with missing data for the question on previous BI use. The company consider that their updated analysis accounts for disease severity, age of the patient and other potential confounding variables. They also do not consider that usage of BIs in the previous 6 months could reflect time since diagnosis as no statistically significant relationship was found in the logistic regression model. <u>Comments from British Association of Urological Surgeons</u> It would be uncommon for BIs to cause a permanent effect on quality of life. Although a sub-set of patients cannot tolerate the catheter insertions, this would be reason to stop the instillations leading to only a temporary effect on quality of life. As BIs are generally second-line therapy, this treatment may represent patients with a slightly worse disease severity compared to patients whose symptoms are managed with tablet medication. <u>Comments from clinical experts</u> Although BIs are more invasive than PPS, the utility decrement is likely to be minimal as patients will tolerate the inconvenience if symptoms improve. Also, PPS is inconvenient to administer and some patients can self-administer BIs at home. However, bladder instillations require more daycase resource and nursing time. It is generally the catheter insertions that are associated with UTIs but in this case the treatment would be stopped so the effect on quality of life would be temporary. Stopping treatment leads to any gains going away and symptoms returning and in clinical practice responses are checked typically at 3 months rather than 6 months. In general, BIs are given as second-line after tablet medication has been tried and so this may represent people with a slightly worse disease severity.

	Comments from ERG The ERG does not accept the company's use of a utility decrement associated with BIs for the following reasons: • The company's model assumes that all patients who had BIs also experienced UTIs, however, the model does not explicitly capture incidence data to support this • The model also does not explicitly capture incidence data to support the company's assumption that UTI symptoms were ongoing from one BI administration to the next • Because of this, it is not reasonable to compare the utility decrement for UTI versus no UTI with the utility decrement for having BI versus not having BI • The company submission includes only 1 trial of PPS (6.6%) versus placebo (3.4%) and 1 trial of BI (3%) versus placebo (3.1%) that reported UTI incidence • Clinical advisers reported that the risk of UTIs following BIs remains low at around 1-5% and that they are easily treated with antibiotics • Clinical advice on the incidence of UTIs provided to the company during the Advisory Board meeting are in line with the low rate reported in the BI versus placebo trial • The company's analysis of HES data for the incidence of UTIs is not based on a randomised comparison therefore confounding variables are not accounted for • The company have not provided robust evidence for an increased risk of UTIs in patients having BIs compared to treated with either PPS or BSC • It is difficult to judge the relevance of the utility estimates from the studies in the systematic review provided by the company as several studies include patients with significant comorbidities, only 3 used the EQ-5D, and 1 included a potentially confounded control population with a short time-frame. The ERG highlighted concerns regarding the handling of missing data for the BI use in the previous 6 months variable. The company's assertion that there are [redacted] suggests that data are not missing at random. The company's approach of excluding patients with missing data from the analysis could potentially bias estimates. For this reason, the ERG considers that he company's revised regression does not adequately account for the missing data. The ERG would have preferred an analysis using multiple imputation allowing for missing data. However, as its preferred

	approach has not been fully explored, the ERG prefers the company's original analysis of the survey in which missing data is categorised as 'BI unsure', despite its limitations. The ERG consider that 'usage of BIs in the previous 6 months' should not be included as a covariate in the utility regression model, in line with the technical team's preliminary judgement.
Technical team judgement after engagement	Considering the uncertainties associated with attributing a utility decrement to the use of BIs, the technical team prefer the regression based on the company's original survey analysis but without the coefficient for BI usage.

Issue 6 – Utilities associated with response

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 7 – Modelled costs and resource use

Questions for engagement	• In clinical practice, what is the frequency of BI administrations? • In clinical practice, what proportion of patients would be admitted through inpatient services for IC/BPS?
Background/description of issue	The company modelled disease-related costs associated with disease severity as captured by ICSI. The ERG's clinical experts confirmed that people with poorer disease control were likely to incur greater resource use, but that this was more likely to be through outpatient services than inpatient services. The company had modelled admission to specialist wards for a proportion of patients. The ERG considers that these admissions may not necessarily be related to IC/BPS. Because of this, the ERG considers that disease-related costs may have been overestimated in the model. The company modelled weekly administrations of first-line BIs for the first 4 weeks, and 4-weekly administrations after this point (also applied to all second-line BIs). Based on clinical expert advice, the ERG preferred to model 6-weekly administrations of BIs after the first year of first-line instillations, and for all second-line BIs.

Why this issue is important	In the analysis of PPS compared with BIs, the ERG's preferred approach of modelling a 6-weekly administration of second line BIs and first line BIs after the first year increased the company's original base-case ICER (which was based on list price) by around [redacted].
Technical team preliminary scientific judgement and rationale before engagement	Based on the ERG's clinical expert input, it is preferable to model 6-weekly administration of second line BIs and first line BIs after the first year. Resource use and associated costs captured in the model should be disease related; the technical team would like to see more evidence supporting assumptions made about hospital admissions (especially with regards to the distribution of patients treated through inpatient and outpatient services).
Summary of comments	Comments from company The company highlight that the manufacturer's recommend administration of BIs typically weekly for 4 weeks then increased to once every 4 weeks. Further advice from clinicians suggested that the dosing frequency of BIs in clinical practice varies according to an individual patient's needs. However, the company considered the clinical expert advice was broadly consistent with the manufacturer's recommendations. They also note that the effect of BI wanes over time and that extending the interval between doses may have an adverse impact for patients. The company model assumes a dosing regime of once every 4 weeks, rather than weekly, for when patients change bladder instillations; the company considers this to be conservative. The company considered that IC/BPS is a long-term chronic condition that required long-term treatment and that limiting the course of treatment to 6 months is related to a more general BPS population or those with a transient condition. The company agree that the majority of resource use would be incurred in an outpatient setting, however, a small percentage of patients will require inpatient care as indicated by a clinical expert and analysis of HES data. Comments from British Association of Urological Surgeons It is estimated that at least 50% of patients with BPS may progress to bladder instillations with treatment being individualised according to the individual patient needs. As there is no guideline consensus, typical regimen administrations for BI consist of induction treatment once weekly for 4-6 weeks followed by maintenance treatment once monthly for 4-6 months. After 6 months the patient is reviewed and most would stop treatment.

	A minimal proportion of patients would be admitted through inpatient services for IC/BPS as this is a chronic condition most commonly encountered in the outpatient setting. It is uncommon but patients may access inpatient services if they have experienced a complication following an investigation. Comments from clinical experts Bladder instillations are administered weekly for the first month and then monthly after this. Treatment is generally continued until 6 months if symptoms improve, however, for those experiencing UTIs the treatment is reviewed and stopped at that point. A small proportion of patients (5-10%) will require continued BI treatment but this will be at increased intervals to around 4 treatments in a year. The number of patients requiring inpatient care is minimal and usually only when they have experienced a complication after an investigation and before commencing treatment. Generally, the overall number of patients treated for IC/BPS is relatively small. Comments from ERG The ERG highlight the variation in the responses provided by the company's clinical experts regarding the frequency of BI doses, and notes that the company did not use a formal elicitation framework for the clinical expert survey. The ERG also notes that the company's analysis of HES data requires further explanation, as it seems to indicate that the frequency of BIs decreased over time and equated to an average of 7.2 weeks between BIs. The ERG note that in the company's model frequency of BI administrations is assumed to continue indefinitely. Overall, the ERG believes that the evidence provided by the company is consistent with its assumption of 6 weekly BI administrations in the long-term.
Technical team judgement after engagement	Based on the ERG's critique of the evidence, the technical team prefer to model 6-weekly administration of second line bladder instillations and first line bladder instillations after the first year.

3. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and are not included in the Technical Report comments table provided. Analyses presented in Tables 1a and 1b **incorporate the patient access scheme discount** for pentosan polysulfate sodium.

The technical team considers that there is substantial unresolved uncertainty associated with the cost-effectiveness results presented in Tables 1a and 1b (see Table 2).

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BIs)

The company's updated base-case includes the following NICE technical team preferred assumptions:

- Incorporated a lifetime time horizon in the model (Issue 2)
- Time to discontinuation based on the ERG's time-to-discontinuation dataset (which included deaths as discontinuations whereas the technical team would have preferred deaths to have been censored) and a log-normal extrapolation (Issue 4)

Table 1a outlines the cumulative effect of all NICE technical team preferred assumptions on the company's updated cost-effectiveness estimate.

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (using the Bucher method and including PAS)	Addresses issues 2 and 4	**£9,952**	
Utilities regression without covariate for 'usage of BIs in the previous 6 months'	Issue 5	£34,059	+£24,107
6-weekly administration for second line BIs and first line BIs after first year	Issue 7	£19,081	+£9,129
Combined changes 1 and 2 (remove BI usage covariate + 6-weekly BIs)	Issue 7 and 5	£65,301	+£55,349
ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)	Addresses issues 5 and 7 with additional modifications for issues 4 and 1	**£86,502**[†]	**+£76,550**
[†] this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs			

Table 1b: Technical team preferred assumptions and impact on the cost-effectiveness estimate (PPS vs BSC)

The company's updated base-case includes the following NICE technical team preferred assumptions:

- Incorporated a lifetime time horizon in the model (Issue 2)
- BSC response rates do not recede over time (Issue 3)
- Deaths censored from treatment discontinuation in line with ERG's censoring rules, and extrapolated using a log-normal distribution (Issue 4)
- Utility scores and costs return to baseline for non-responders who move onto BSC (Issue 6)

Table 1b outlines the cumulative effect of all NICE technical team preferred assumptions on the company's updated cost-effectiveness estimate.

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case (using the Bucher method and including PAS)	Addresses issues 2, 4 and 6 plus new evidence on issues 1 and 3	**£76,213**	
ERG's revised preferred ICER (includes CODA samples from ERG's NMA and minor correction to discontinuation curve)	Addresses issue 5 with additional modifications for issues 4 and 1	**£72,355**†	**-£3,858**
† this ICER is based on 10,000 PSA samples whereas the other ICERs in this table are based on midpoint parameter inputs			

Table 2: Outstanding uncertainties in the evidence base[3]

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Quality of clinical evidence for pentosan polysulfate sodium	The marketing authorisation for PPS is based on 4 randomised controlled trials published in the USA comparing PPS with placebo in people with IC/BPS (Sant et al., 2003; Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987). The ERG considers that 3 of the studies (Parsons et al., 1993; Mulholland et al., 1990; Parsons and Mulholland, 1987) were of good methodological quality. However, it advises that results from Sant et al. (2003) should be interpreted with caution due to uncertainty about allocation concealment and numbers of patients withdrawing from treatment.	The effect of the limitations of the evidence base is unknown. However, the limitations increase parameter uncertainty in the economic model, and increase uncertainty in the cost-effectiveness estimates. Because of the concerns with concealment and sample size in the Sant et al. (2003) study, it may be useful to see analyses

[3] The draft technical report released before engagement included 'Pairwise meta-analysis underlying the indirect treatment comparison' as an outstanding uncertainty in the evidence base. Following engagement, the ERG have advised that the methodological limitations with the meta-analysis are sufficiently discussed in Issue 1.

	The European Public Assessment Report (EPAR) highlights that prospective sample sizes were not calculated for 3 of the trials, and that the target sample size for the Sant et al. (2003) was not met. The ERG notes that this may lead to potential issues with study power. The ERG also highlights that there is some author commonality between all 4 trials, and that there have not been any independent studies validating the results of the trials. Global Response Assessment (GRA) was an outcome in 3 of the PPS trial, but definitions of GRA and follow-up times differed between trials. All 4 PPS trials reported non-visual analogue scale (non-VAS) pain outcomes, although assessment methods and follow-up times also varied between trials. The ERG considers that the trials comparing Uracyst to placebo (which were included in the indirect treatment comparison; see Issue 1) were of moderate to low quality.	based on a meta-analysis excluding this study.
Subsequent treatments	In the company's model, people starting second-line treatment with BIs are assumed to stay on treatment for the rest of the model horizon. Patients are assumed to cycle through different BIs until they achieve a response. Costs and utilities for subsequent BIs are based on the mean response rate to first-line BIs (rather than being modelled explicitly). The ERG highlights that it has not seen evidence to support the assumption that the cumulative effect of subsequent BIs would be equivalent to response to first-line BIs. The ERG were not clear whether some patients may transition to BSC over time, rather than staying on BIs indefinitely. However, the ERG could not estimate the size and direction of any potential bias introduced by the modelling of subsequent treatments.	The size and direction of any potential bias introduced by the modelling of subsequent treatments is unknown. However, this potential bias increases uncertainty in the cost-effectiveness results.

Table 3: Other issues for information

Issue	Comments
Time horizon in economic model (Issue 2)	The company's base-case analysis assumed a 20-year time horizon. However, the NICE reference case states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. The ERG therefore considered that a lifetime horizon would be more appropriate. **Following technical engagement, the company updated its base-case to incorporate a lifetime time horizon in the economic model.**
Time to treatment discontinuation (Issue 4)	In the company's model, time to PPS treatment discontinuation was informed by a meta-analysis from Hanno et al. (1997) and extrapolated using an exponential distribution. The ERG considered that the model may overestimate lifetime costs for patients, and that the discontinuation rates for BIs lack face validity. The company do not consider it appropriate to include deaths as a reason for discontinuation as this results in double counting deaths in the cost-effectiveness model. The ERG agreed and updated their survival analysis to reflect this. The ERG noted that it is not possible to separate out some of the other reasons for discontinuation because of the way the data are reported. **Comments from the British Association of Urological Surgeons considered the technical team's judgement to be reasonable in that the ERG's alternative survival dataset is less subject to bias and is preferable.** **Following technical engagement, the company has incorporated the ERG's revised time to treatment discontinuation analysis in their revised base-case. The technical team accepts the ERG's updated survival analysis to treat those who died as censored at the time of death and their use of a lognormal extrapolation.**
Utilities associated with response (Issue 6)	The ERG disagrees with the assumption in the company's model that [redacted] for non-responders who move onto BSC. The ERG instead prefers to assume that non-responders who have BSC second-line return to their baseline level of utility (and costs associated with this). **Following technical engagement, the company accepted the ERG's comments and have updated their model to incorporate the assumption that utility scores and costs**

	return to baseline for non-responders who move onto BSC (the ERG preferred approach).
Population in economic model	The population in the NICE scope is adults with bladder pain syndrome characterised by either glomerulations or Hunner's lesions with moderate to severe pain, urgency, and frequency of micturition. The Uracyst studies (and accompanying meta-analysis) informing the modelled response rates were conducted in people with BPS; study inclusion criteria did not require evidence of either Hunner's lesions or glomerulations. The population modelled to receive bladder instillations therefore deviates from the population in the NICE scope. The ERG also highlight that people would not receive a confirmed diagnosis of IC/BPS until after first-line oral therapies including analgesics and antihistamines. The modelled population is therefore based on people who did not respond to initial interventions; the ERG advises that cost-effectiveness results should not be extrapolated to earlier positions in the treatment pathway.
Comparators	Comparators in the NICE scope are BIs in people for whom they are suitable, or established clinical management without BIs. The company did not include locally prepared BIs (also known as bladder cocktails) because of heterogeneity in the different combination, infrequent use and lack of available data. The company excluded 3 studies of BIs from the indirect treatment comparison because they did not contain the relevant comparator needed to construct a network; the ERG agrees that these exclusions are appropriate. The technical team are aware that there may be interventions used in the treatment BPS that have not been included in the company submission. The company modelled the efficacy of BIs based on Uracyst (one type of BI); other instillations (such as intravesical DMSO) were not apppriate for use in an indirect treatment comparison. The technical team note that the company submission mentions laser surgery but that this treatment was not included in its searches. However, the ERG's clinical expert indicates that data of the effectiveness of laser surgery in people with Hunner's lesions may not be in the public domain. **Following technical engagement, the company have clarified that laser surgery is an additional treatment that can be performed at any point in the treatment pathway and is not an alternative to treatment with PPS or BIs.** The technical team are also aware that pelvic

	floor exercises have been shown to effective in the treatment of BPS. The ERG's clinical experts advise that physiotherapy/pelvic floor exercises are unlikely to be used as standalone treatment for IC/BPS.
Stopping rule	The marketing authorisation states that response to treatment with pentosan polysulfate sodium should be reassessed every 6 months. In case no improvement is reached 6 months after treatment initiation, treatment with pentosan polysulfate sodium should be stopped. In responders pentosan polysulfate sodium treatment should be continued chronically as long as the response is maintained.
Implementation of company model	The ERG highlighted a number of errors in the company's original model (relating to the VBA code). Correction of these errors increased the company's original base-case ICER (which was based on list price) by [redacted] in the analysis compared to BIs and by [redacted] in the analysis compared to BSC. **This issue was resolved in the company's updated model after technical engagement.**
Age-related utility decrements	The company's model assumes that utilities are constant over time. The ERG prefers to apply age-related decrements to the utilities. Given a lifetime horizon (see Issue 2), the technical team consider that it is appropriate to model age-related utility decrements. **In the analysis submitted after engagement, the company included age in the utility mapping regression.**
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	The company and a clinical expert highlighted that IC/BPS affect women more frequently than men. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

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