1 APPENDIX G- Economic Evaluation of Interventions used in the Treatment of Bedwetting in Children

1.1 Introduction

Although health economics is considered as part of the review for every clinical question, only certain questions are prioritised for original economic evaluation. Given the lack of published evidence assessing the cost-effectiveness of different interventions used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The decision modelling presented here was developed in close collaboration between the health economist, NCGC technical team and GDG members.

1.2 Methods

1.2.1 Model overview

The analysis set out to evaluate the comparative cost-effectiveness of different intervention sequences used in the treatment of bedwetting in children. A multistate Markov model was created using TreeAge Pro 2008[1] to capture the potentially recurrent nature of bedwetting. It was built to reflect transitions between a set of mutually exclusive health states, namely bedwetting and not bedwetting. The consequences of a given treatment strategy and sequence are reflected as a set of possible transitions between health states over a series of discrete time periods, called cycles. Movement between the various health states is governed by transition probabilities which are derived from the systematic review of clinical effectiveness data.

Health states in the model are defined by whether or not a hypothetical patient is experiencing bedwetting. It is assumed that all patients begin in a state of bedwetting and that over the course of the time spent in the model they will face transition probabilities that determine whether they continue bedwetting or when they stop bedwetting.

Definitions of response and recurrence of bedwetting used here are the same as previously defined in the guideline. A complete or full response means that a child has achieved at least 14 consecutive nights dry or a 90% reduction in bedwetting. A partial response refers to at least a 50% reduction in bedwetting. And 'success' has been defined as the achievement of at least 12 consecutive months of sustained dryness following a response to treatment or spontaneous cure without treatment.

The time horizon for the analysis is 13 years, modelling patients from the time they enter at age 7 years until they reach age 20. This was considered sufficiently long enough to capture all relevant costs and benefits associated with competing intervention sequences. We followed the methods of the NICE reference case[2] therefore an NHS and PSS costing perspective was taken, such that only direct medical costs to the NHS are included. All costs were measured in current (2009) UK pounds. Outcomes were measured in terms of quality-adjusted life-years (QALYs) gained. In order to scale future costs and health benefits to their present value, costs and benefits were discounted

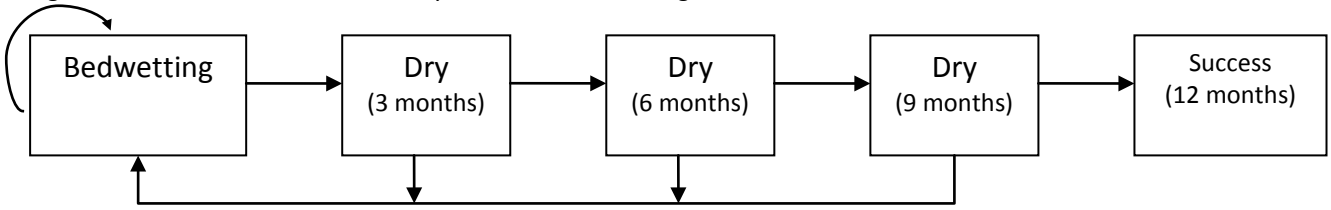
at a rate of 3.5% per annum[1]. The performance of alternative treatment sequences was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness.

A probabilistic sensitivity analysis was undertaken to test the robustness of the results against the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 20,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals.

1.2.2 Natural History Model

A natural history Markov model of bedwetting was built to reflect the natural progression towards achieving dryness that most children follow without treatment. The health states modelled assume that all children enter the model with bedwetting and every three months they face a probability of becoming spontaneously dry (i.e. stop bedwetting) without treatment. Figure 1 shows a schematic of the natural history model.

Figure 1: Schematic of Natural History Model for Bedwetting



There are several key assumptions to this natural history model. First, in order to reach a cure, called 'success,', patients must progress first through each of the other health states (i.e. dryness at 3 months, 6 months and 9 months). During each intermediate 3-month interval, patients face a risk of bedwetting recurrence. The risk of bedwetting recurrence is thought to be related to both age and time spent already dry, however, data to support the former was not available beyond the age of 9.5 years and nothing was available to support the latter. Therefore the risk of recurrence was assumed to be constant from 7.5 years onwards and was independent of time spent dry. When a person experienced a recurrence of bedwetting, they were assumed to return to the initial bedwetting state and work their way towards 'success' again as though they had never been dry before. Finally, once they reach 'success' at 12 months, they are no longer subject to any risk of bedwetting recurrence.

[1] Discounting is a technique used to reflect the present value of a cost or a health benefit that will occur at some future date. Because there is an opportunity cost to spending money now and there is a desire to experience health benefits now rather than in the future, discounting gives future costs and health benefits less weight compared to present costs and benefits.

1.2.3 Model Comparators

The interventions compared in the model are those that would be considered for patients who have already been advised on the importance of regular toileting, healthy fluid intake and reward systems for agreed behaviour. The interventions modelled in the analysis include the enuresis alarm, desmopressin, imipramine, combined enuresis alarm and desmopressin and combined desmopressin and anticholinergic. Enuresis alarm and desmopressin are the most commonly used treatments for bedwetting in the NHS currently. Imipramine is prescribed, but far less commonly. The combinations of enuresis alarm and desmopressin and desmopressin and anticholinergic are not widely used currently, but the clinical evidence review showed them to be effective. However, as they are combination treatments, they are also more costly and therefore the GDG needed to see evidence of cost-effectiveness. Among the interventions included in the clinical evidence review, the interventions mentioned here have the largest evidence base and were among those shown to be more effective than no treatment.

Two specific interventions that were effective in one or both of the network meta-analyses were combined retention control training and enuresis alarm and combined dry bed training and alarm. These were excluded from the economic analysis despite evidence of their effectiveness compared to no treatment because they were no better than the enuresis alarm alone. Furthermore, it was unclear what actually constituted retention control training and there were serious GDG concerns over the punitive elements of dry bed training.

The clinical evidence review identified data to suggest that a response or non-response to one intervention may affect the likelihood of response to another intervention offered subsequently. This means that in thinking about a treatment pathway, it cannot be assumed that treatment effects of different interventions are independent from one another. Because this assumption could not be made, treatment comparators needed to be modelled as intervention sequences. Therefore, interventions have been grouped into logical and clinically relevant sequences and the analysis was interested in identifying the most cost-effective sequence.

The baseline strategy (no treatment) was populated with data relating to an untreated population of children with bedwetting. Running the model estimates outcomes over a specified time period. By applying cost and utility weights we estimated mean costs and QALYs per patient over the entire time period. To compare the impact of treating the same population with a pre-defined sequence of interventions, relative treatment effects from the systematic review of clinical evidence were applied for each intervention to the baseline estimates in the natural history model. With the relative treatment effects applied, the model would calculate the total costs and total QALYs per patient for each intervention sequence.

It was assumed that only single interventions would be used in first line treatment: enuresis alarms, desmopressin and imipramine. Possible second line interventions included the same three considered in the first line as well as combination therapy with desmopressin and alarm. It was also assumed that combined therapy with alarm and desmopressin would only follow first line treatment with either enuresis alarm or desmopressin, but not imipramine. Only pharmacological interventions were considered as possible third and even fourth line interventions: imipramine, desmopressin and combined desmopressin and anticholinergic. A combination of desmopressin and anticholinergic was assumed to only come after a trial of desmopressin on its own.

Treatment sequences always end with a pharmacological intervention (imipramine, desmopressin or combined desmopressin and anticholinergic) and this reflects their use as a longer term treatment option in clinical practice. The GDG felt that enuresis alarms are not considered an acceptable option for long term therapy because in their experience patients often grow tired of them and are less inclined to adhere to treatment. The way that pharmacological interventions work to manage bedwetting is fundamentally different from conditioning interventions like enuresis alarms and this difference makes them acceptable interventions for longer term use.

Altogether, 23 different sequences were modelled and compared back to a baseline arm of no treatment:

1. No treatment
2. Alarm – Imipramine
3. Alarm – Alarm+Desmopressin – Imipramine
4. Alarm – Alarm+Desmopressin – Desmopressin
5. Alarm – Desmopressin - Imipramine
6. Alarm – Desmopressin
7. Alarm – Alarm+Desmopressin – Desmopressin – Desmopressin+Anticholinergic
8. Desmopressin – Imipramine
9. Desmopressin – Alarm – Imipramine
10. Alarm – Imipramine – Desmopressin
11. Desmopressin
12. Alarm – Desmopressin – Desmopressin+Anticholinergic
13. Desmopressin – Alarm – Desmopressin
14. Alarm – Imipramine – Desmopressin – Desmopressin+Anticholinergic
15. Desmopressin – Alarm – Desmopressin or Desmopressin+Anticholinergic
16. Imipramine – Alarm – Desmopressin
17. Desmopressin – Alarm+Desmopressin – Imipramine
18. Imipramine – Desmopressin
19. Desmopressin – Alarm+Desmopressin Desmopressin
20. Desmopressin – Desmopressin+Anticholinergic

21. Desmopressin – Alarm+Desmopressin – Desmopressin or Desmopressin+Anticholinergic

22. Imipramine – Alarm – Desmopressin – Desmopressin+Anticholinergic

23. Imipramine – Desmopressin – Desmopressin+Anticholinergic

1.2.4 Modelling intervention sequences

The model assumes that patients will either respond completely or partially or not respond to treatment within an initial 3-month cycle. Patients who do not respond at all (non-responders) move on to the next intervention in the sequence. Those who experience a partial response to the treatment are assumed to undergo a second 3-month trial of the treatment. If they still have not experienced a complete response at the end of this second 3-month trial, they are assumed to move on to the next intervention in the sequence.

Those who experience a full response to the treatment in either the first or second 3-month cycle are assumed to discontinue treatment for 1 week at the end of the cycle and will face an immediate intervention-associated risk of bedwetting recurrence. These risks are derived from the clinical evidence and are specifically associated with the intervention received.

If they experience a recurrence of bedwetting in the following cycle they will resume treatment for a further cycle. If they experience a recurrence after two cycles, they are assumed to move on to the next treatment in the sequence. Complete responders who do not experience a recurrence of bedwetting after the following two cycles are assumed to enter a dry (no bedwetting) state and face an intervention-associated risk of relapse at 3 months and 6 months. If no recurrence of bedwetting occurs, modelled patients are assumed to enter the natural history model at the relevant time-dependent health state and face the natural risk of recurrence until they reach 'success' at 12 months. For example, if a person treated with an alarm has responded to treatment and sustained that response after 3 months and then 6 months, they would enter the natural history model health state of 9 months dry.

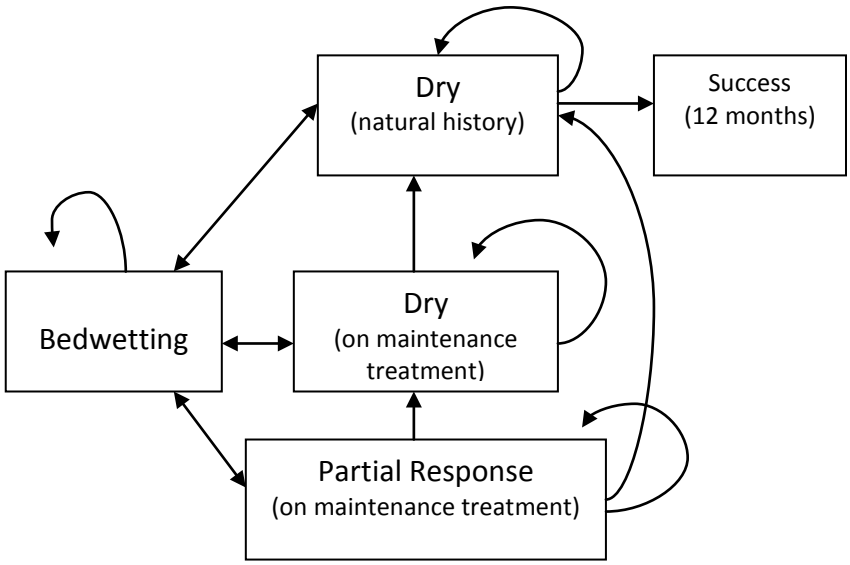
When a patient experiences a recurrence of bedwetting at 3 or 6 months after a complete response to a given treatment, it is assumed that 10 percent will abandon treatment altogether and the remaining 90 percent will be split between those going back to the treatment that worked last and those trying the next intervention in the sequence. However, once a complete responder has entered the natural history model, if bedwetting recurs, they will not resume any treatment and are assumed to enter the bedwetting state in the natural history model and will progress towards 'success' under natural, no treatment, assumptions. Using the example above, if the same responder enters the natural history model at 9 months dry, but then experiences a recurrence of bedwetting (according to the natural risk of recurrence), they would enter the bedwetting state and progress towards 'success' based on the natural history model outlined in 1.2.2 and Figure1.

The GDG felt that for children who have not responded to one or more interventions, the objective of treatment changes slightly. In the first and second instances, the goal of treatment is to achieve a full response that ideally translates into a sustained response at 3, 6 and 9 months and then 'success' at 12 months following the discontinuation of active treatment. However, when patients achieve a full response but experience a repeated recurrence of bedwetting, the goal of treatment

becomes one of maintaining dryness even if that means maintaining active treatment. Additionally, whereas in the first and second line treatments, partial response is not considered an acceptable outcome, in the third line partial response represents an acceptable improvement and must be taken into account.

In order to deal with partial responders and those patients who are dry on treatment but regularly experience a recurrence of bedwetting once it is withdrawn, a longer term approach has been modelled for interventions used in the third line (and in second line where there is no third line) treatment. Therefore, two additional health states, 'responders on treatment' and 'partial responders on treatment' were created to capture the ongoing maintenance costs of prescriptions and monitoring as well as the differentiated utility weights attached to time spent in these categories. The assumption is that most patients will ultimately achieve sustained dryness off treatment, but until then, the objective is to minimise the burden bedwetting imposes on the child and their family. A schematic of the Markov health states corresponding to this longer term maintenance treatment situation is presented in Figure 2.

Figure 2: Schematic of maintenance therapy for pharmacological interventions used late in the treatment of bedwetting



With regard to the resumption of treatment after a recurrence of bedwetting in this longer term treatment scenario, it is assumed that patients who experience a recurrence immediately (within 1 week following initial success) will face a decreasing likelihood of resuming treatment following each recurrence. After the first recurrence, 100 percent will resume the same treatment. After the second, 95 percent will resume and 5 percent will move on to no treatment (in the natural history model). After the third recurrence, 90 percent resume and 10 percent withdraw and so on until in the end, a maximum of 5 percent resume treatment following each recurrence of bedwetting.

1.2.5 Baseline Risk

In the vast majority of cases, children will become spontaneously dry without ever undergoing treatment for bedwetting. Because of this natural trend towards dryness, it seemed to be a good baseline comparator against which to assess the cost-effectiveness of all other interventions. In

order to do this, it was necessary to find data with which to calculate the baseline probability of achieving dryness in the absence of treatment. Effectiveness for all the comparators are then calculated within the model by multiplying the relative treatment effect figures from the systematic review by the baseline probabilities.

Epidemiological studies of bedwetting were identified as part of the clinical evidence review and were included as potential data sources for the spontaneous cure rate for bedwetting. A 15% annual spontaneous cure rate is the figure most commonly quoted in studies included in the clinical review and is based on work by Forsythe and Redmond from 1974 [3]. It was unclear what methodology the authors used to calculate this figure and so alternative sources of data were sought. A recent study by Butler and Heron [4] used data from the Avon Longitudinal Study of Parents and Children to determine the prevalence of nocturnal enuresis and infrequent bedwetting among children at various ages between 4 and 10 years. The data was considered optimal because it was from a contemporary UK longitudinal study, used a clear methodology and allowed for the calculation of spontaneous cure and recurrence of bedwetting rates at different time points. Prevalence estimates of infrequent bedwetting and nocturnal enuresis and standard errors reported in the study as well as the composition of each relative to the previous time point are presented in table 1.

Table 1: Prevalence (standard error) of infrequent bedwetting, nocturnal enuresis and dry categories and composition in relation to previous time point.

Current health state Health state at previous time point	Age (months)				
	54	65	78	91	115
Dry	**0.7**	**0.778**	**0.804**	**0.846**	**0.903**
Dry		0.636404	0.716364	0.7614	0.823536
IB		0.123702	0.078792	0.079524	0.074046
NE		0.017894	0.00804	0.005076	0.005418
IB	**0.216 (0.0042)**	**0.162 (0.0039)**	**0.156 (0.0039)**	**0.128 (0.0037)**	**0.082 (0.0031)**
NE		0.026568	0.02028	0.014464	0.01025
IB		0.079866	0.071916	0.067456	0.040672
Dry		0.055566	0.06396	0.04608	0.031078
NE	**0.084 (0.0028)**	**0.06 (0.0025)**	**0.04 (0.0021)**	**0.026 (0.0018)**	**0.015 (0.0014)**
NE		0.04098	0.02848	0.017472	0.00885
IB		0.01362	0.00936	0.006786	0.0045
Dry		0.0054	0.0022	0.001742	0.00165

IB, infrequent bedwetting defined as <2 wet nights per week; NE, nocturnal enuresis defined as >2 wet nights per week

In the calculation of transition probabilities, we lumped together data for infrequent bedwetting and nocturnal enuresis. The model was fundamentally interested in the transition from bedwetting with any frequency to dry and vice versa. Table 2 presents the prevalence estimates (in bold) of infrequent bedwetting and nocturnal enuresis combined at each of five time points between ages 4.5 and 9.5 years. Also presented in table 2 are estimates of the composition of bedwetting and dry categories in relation to the previous time point. These figures, derived from those in table 1, were used to define the movement of children between the three different categories and also for calculating transition probabilities for the natural history model.

Table 2: Prevalence of bedwetting (NE and IB combined) and dry categories and composition in relation to previous time point.

Current health state Health state at previous time point	Age (months) 54	65	78	91	115
Dry	**0.7**	**0.778**	**0.804**	**0.846**	**0.903**
Dry at previous time point		0.636	0.716	0.761	0.824
Wet at previous time point		0.142	0.087	0.085	0.079
Bedwetting	**0.3**	**0.222**	**0.196**	**0.154**	**0.097**
Wet at previous time point		0.161	0.130	0.106	0.064
Dry at previous time point		0.061	0.066	0.048	0.033

Prevalence estimates in bold; composition in plain text

The values in table 2 were used to calculate the point estimates of 3-month transition probabilities of becoming dry without treatment for bedwetting using the following methods.

It was assumed that between 7.5 years (91 months) and 9.5 years (115 months) of age, approximately 7.9% of children will become dry without treatment and 6.4% will remain in a bedwetting state. Assuming the rate of becoming dry is constant over the whole time period, then the monthly rate can be calculated using the following formula:

$$\begin{aligned} Monthly\ rate &= -\frac{\ln(p)}{t} \\ &= -\frac{\ln\left(\frac{0.064}{0.154}\right)}{(115-91)} \\ &= 0.0364 \end{aligned}$$

Where: p= the proportion of patients that did not become dry over time period t.

This was then converted from a monthly rate to a 3-monthly transition probability using a standard formula:

$$\begin{aligned} \Pr obability\ of\ \ achieving\ \ \ dryness\ in\ 3\ month\ cycle &= 1-e^{-rt} \\ &= 1-e^{-0.0364\times 3} \\ &= 0.1035 \end{aligned}$$

Where: r=rate; t=time period

The probabilities thus calculated are presented in Table 3 along with beta distribution parameters used in the probabilistic sensitivity analysis.

The same study [4] and formula were used for the calculation of the 3-month probability of experiencing a recurrence of bedwetting, presented in table 4.

For data addressing children over the age of 9.5 years, a good quality, Hong Kong epidemiological study by Yeung [5] was used. The authors used the results from 16,512 questionnaires to evaluate the prevalence of primary nocturnal enuresis amongst 5 to 19 year olds from different areas in Hong Kong. The GDG felt that although it would be ideal to have prevalence data exclusively from the UK, in its absence, the Yeung study was well conducted and figures were unlikely to differ

extremely from those that might be found amongst children in the UK. Therefore, Yeung data from age 10 to 15 was used to calculate baseline risk for the rest of the model. Because the data relating to adolescents between 15 and 19 showed an increase in the prevalence of bedwetting, a trend not found elsewhere, it was assumed that the likelihood of becoming dry at age15 was constant until age 20 when the model terminated. The transition probabilities derived using Yeung's data are presented in Table 3 along with the beta distribution parameters used in the probabilistic sensitivity analysis.

Table 3: 3 month probabilities of becoming dry without treatment

Age (years)	Point Estimate	Distribution	Distribution parameters	Source
4.5	0.1561	Beta distributions were applied to prevalence estimates reported in study (and summarised in table 1) and then each random sample was used to calculate a different point estimate using aforementioned formulae for each Monte Carlo simulation		Butler[4]
5.5	0.1161			Butler[4]
6.5	0.1319			Butler[4]
7.5	0.1035			Butler[4]
10	0.0471	Beta	α=4.7124 β=95.2876	Yeung[5]
11	0.0174	Beta	α=1.7421 β= 98.2579	Yeung[5]
12	0.0634	Beta	α= 6.3376 β= 93.6623	Yeung[5]
13	0.0107	Beta	α= 1.0658 β= 98.9341	Yeung[5]
14+	0.0369	Beta	α= 3.6912 β= 96.3087	Yeung[5]

Table 4: 3 month probabilities of bedwetting recurrence

Age (years)	Point Estimate	Distribution	Distribution parameters	Source
4.5	0.0243	Beta distributions were applied to prevalence estimates reported in study (and summarised in table 1) and then each random sample was used to calculate a different point estimate using aforementioned formulae for each Monte Carlo simulation.		Butler[4]
5.5	0.0181			Butler[4]
6.5	0.0119			Butler[4]
7.5+	0.0032			Butler[4]

1.2.6 Treatment Effectiveness

1.2.6.1 Complete response to treatment

Effectiveness data used to parameterise the model are summarised in table 5 and are taken from the results of the network meta-analysis described and presented in Appendix F or derived from the results of the systematic review of clinical evidence (Chapters 7-20). Effectiveness estimates

for interventions used first line are taken from the network meta-analysis results for the bedwetting only population.

Table 5: Relative treatment effects, point estimates and distribution parameters

Variable	Point Estimate	Distribution	Distribution parameters	Source
Odds Ratios of first line interventions compared to no treatment				
Enuresis alarm Desmopressin Imipramine	11.42 26.42 2.643	For PSA, the 20,000 simulated output odds ratios from the NMA were used.		NMA, see appendix F
Odds Ratios of interventions used in treatment resistant patients				
Following a partial or non-response to desmopressin				
Desmopressin compared to no treatment	1.349	log normal	mean = -0.346 se = 1.136	Austin [6] (2008)
Desmopressin+Alarm compared to first line alarm	1.252	log normal	mean = 0.194 se = 0.269	Gibb [7]; Vogt[8]
Desmopressin+Anticholinergic compared to desmopressin following non-response to desmopressin	3.0	log normal	mean = 0.365 se = 1.212	Austin [6]
Following a partial or non-response to alarm				
Desmopressin+Alarm compared to Desmopressin+Alarm following non-response to desmopressin	3.143	log normal	mean = 0.916 se = 0.677	Vogt[8]

NMA – network meta-analysis

The GDG felt that there may be a relationship between age and effectiveness of different interventions, but there was no data identified in the clinical review to support this. In the absence of such data, it was assumed that intervention effectiveness was independent of age and therefore constant. Thus, even though the baseline probability of getting dry without treatment varied with age, the relative effect of different interventions was assumed to be the same and was applied as such.

To calculate the absolute probability of response to first line treatment, the odds ratios of a given intervention compared to no treatment from the network meta-analysis was converted into a relative risk and applied to the baseline risk. For example, the absolute risk of treatment response with alarm compared to no treatment (baseline risk) at the age of 10 years was calculated using the following formula:

$$Absolute\ risk = baseline\ risk \times relative\ risk$$

where:

$$\begin{aligned} \text{Re}\,lative\ risk &= \frac{odds\ ratio}{\left(1 - baseline\ risk \times \left(1 - odds\ ratio\right)\right)} \\ &= \frac{11.42}{\left(1 - 0.0471 \times \left(1 - 11.42\right)\right)} \\ &= 7.66 \end{aligned}$$

$$Absolute\ risk = 0.0471 \times 7.66$$
$$= 0.36$$

Therefore, the absolute probability of becoming dry with alarm treatment at age 10 years is approximately 36%.

For treatment effects not measured in the network meta-analysis, odds ratios from direct comparisons were taken from the clinical review and applied in the model in the same method as above. For example, if a study compared desmopressin to alarm, the absolute risk of response with desmopressin would be calculated using the odds ratio from the comparison and the absolute risk of response with alarm as the baseline risk.

Some limitations of the data informing the treatment resistant treatment effect estimates should be pointed out. First, the data informing the relative effect estimate of repeat desmopressin following a non- or partial response to first line desmopressin was derived from a study by Austin[6], in which combined desmopressin and placebo was compared directly to combined desmopressin and tolterodine over the course of 1 month in a population with a mean age of 10.5 years. 1 month was a much shorter length of treatment than in other studies used to inform the effectiveness parameters, but the GDG felt comfortable including it as most people will see results on a pharmacological intervention fairly quickly. In addition, the relative effect estimate for desmopressin following a non- or partial response to desmopressin was linked back to no treatment by using the formula identified above and a baseline risk of 0.0471 which corresponds to the likelihood of becoming dry without treatment at the age of 10 years. The GDG also felt that it was reasonable to assume treatment equivalence between tolterodine and oxybutynin as they are both antimuscarinic drugs, therefore the data from Austin[6] for combined desmopressin and tolterodine was used to inform parameters for a combined desmopressin and anticholinergic intervention.

Second, there was some variation in the definition of response in the studies used to inform the treatment resistant effectiveness parameters. For example, Gibb [7] defined response as the achievement of 28 consecutive nights dry and Vogt[8] defined response as the achievement of less than 3 wet nights in 1 month.

Finally, there was no data to inform the effectiveness of imipramine following a non- or partial response to desmopressin, alarm or combined desmopressin and alarm. Therefore, the effectiveness of imipramine as a second and third line treatment was assumed to be the same as it was in first line treatment.

For the deterministic analysis, the median point estimates from the network meta-analysis of children with bedwetting only were used. For the probabilistic sensitivity analysis, instead of fitting a distribution around the median point estimate and sampling randomly from it, the 20,000 simulated odds ratios from the network meta-analysis were used. This preserves the joint posterior distributions from the network meta-analysis and incorporates all uncertainty and any correlation of treatment effects.

1.2.6.2 Partial response to treatment

The model assumed that patients undergoing treatment would experience a full response or not a full response in the first instance, and the probabilities governing this distinction have been

summarised above in table 5. However, based on the clinical review, not experiencing a full response did not mean that no improvement was observed or that with more time a full response could not be achieved. Some patients who did not experience a full response still experienced a 50% reduction in their bedwetting compared with baseline and this was defined as a partial response. For pharmacological interventions used as longer term treatment, a partial response represented a discrete health state with its own utility weight used to inform the calculation of QALYs. For other interventions, probabilities of achieving at least a partial response were used in the model to determine which hypothetical patients continued on with a treatment for a further 3-month course.

Table 6 presents the probabilities of experiencing a partial response by intervention. These probabilities were derived from the studies reporting partial response and are conditional upon a full response having not been achieved. For example, a proportion of patients were expected to fully respond to treatment with alarm, as outlined in section 1.2.6.1. Of the patients who did not fully respond, 25.93% of them were expected to experience a partial response, and 74.07% (=1.00 - 0.2593) were expected not to respond at all.

Table 6: Probability of a partial response conditional on not having achieved a full response

Variable	Point Estimate	Distribution	Distribution parameters	Source
Enuresis Alarm	0.2593	beta	$\alpha = 6.74$ $\beta = 19.26$	Ng[9]
Desmopressin	0.1818	beta	$\alpha = 3.82$ $\beta = 17.18$	Ng [9]
Desmopressin+Alarm	0.4167	beta	$\alpha = 4.58$ $\beta = 6.42$	Ng [9]
Imipramine	0.7160	beta	$\alpha = 4.30$ $\beta = 1.70$	Tahmaz[10]
Desmopressin+Anticholinergic	0.3333	beta	$\alpha = 5.00$ $\beta = 10.00$	Austin [11]

All of the studies informing this parameter [9,10], with the exception of Austin [11] were undertaken in a treatment naïve population. However, because partial response was not an outcome reported in all studies, particularly not in many of the studies undertaken in treatment resistant populations, the conditional probabilities of a partial response presented in table 6 were applied to their respective interventions regardless of changes in probabilities of complete response. For example, Vogt [8] reported probabilities of full response for combined alarm and desmopressin in a treatment resistant population, but did not report probabilities of partial response. Although the treatment effect estimates for a full response with combined alarm and desmopressin are different from those observed in Ng [9], the likelihood of achieving a partial response conditional on not having achieved a full response is assumed to be the same.

1.2.6.3 Recurrence of bedwetting

Another important element of treatment effectiveness captured in the model relates to the achievement of a sustained response. This was built into the model by looking at the absolute risks of bedwetting recurrence presented in relevant RCTs identified in the systematic review. Much of the data was not in a readily usable form in that it had recurrence data for different time points and defined recurrence in slightly different ways. The model ultimately required recurrence data at

two time points, 1 week and 3 months after stopping treatment. Data from relevant RCTs included in the clinical review were used to calculate the probabilities presented in table 7 of bedwetting recurrence at each of these time points, and the methods are described below.

Table 7: Probability of experiencing a recurrence of bedwetting following a full response to treatment

Variable	Point Estimate	Distribution	Distribution parameters	Source
Enuresis alarm				
Recurrence at 1 week	0.0373	Beta	α = 5.03 β = 129.95	Nawaz[12], Fielding [13], Ng [9]
Recurrence at 3 months	0.1202		α = 4.08 β = 29.85	
Recurrence at 6 months	0.2704		α = 46.78 β =126.21	
Desmopressin				
Recurrence at 1 week	0.2500	beta	α = 3.75 β =11.25	Stenberg [14]; Ng[9]
Recurrence at 3 months	0.4167		α = 4.58 β =6.42	
Desmopressin+Alarm[††]				
Recurrence at 1 week	0.1560	beta	α = 2.96 β =16.04	Ng [9]
Recurrence at 3 months	0.2299		α = 3.65 β =12.23	
Imipramine				
Recurrence at 1 week	0.3555	beta	α = 3.56 β =6.45	Wagner[15]; Tahmaz [10]
Recurrence at 3 months	0.7021		α = 7.02 β =2.98	
Desmo+Anticholinergic[†]				
Recurrence at 1 week	0.2500	beta	α = 3.75 β =11.25	Assumption
Recurrence at 3 months	0.4167		α = 4.58 β =6.42	

 Austin (2008) does not report relapse for desmo+placebo or desmo+tolterodine; therefore, relapse for repeated desmo and for desmo+anticholinergic is assumed to be the same as for desmo in first line.

To calculate the risk of bedwetting recurrence among children treated with alarm, data from several studies reporting recurrence of bedwetting at 3 months [13], [12], [9] and 6 months [13], [12],[15], [16] were used. Meta-analysing the alarm treatment arms of these trials at each time point showed that 15.3% of complete responders had relapsed by 3 months and 38.2% by 6 months. In the absence of data available at earlier time points following the end of treatment, it was assumed that approximately one quarter of patients who relapse in the first 3 months after treatment would do so in the first week. Therefore, 3.73% of patients are assumed to relapse within 1 week, 12.02% between 1 week and 3 months and 27.04% between 3 and 6 months, leading to a cumulative probability of relapse of 38.2%.

To calculate the risk of bedwetting recurrence among children treated with desmopressin, data from Stenberg [14] and Ng [9]were used. Stenberg showed that one-third of successfully treated patients experience a recurrence of bedwetting within 2 weeks of discontinuing treatment. Ng gave recurrence figures at 4 and 12 weeks after stopping treatment and showed that 43.75% and

56.25% of complete responders had experienced a recurrence of bedwetting at each time point, respectively. These figures were plotted on a graph in Microsoft Excel as cumulative probabilities and then fitted with a logarithmic trend line. The trend line indicated that approximately 25% of all patients who had experienced a full response would experience a recurrence of bedwetting within one week of stopping treatment. This represents approximately 44% of the total 56.25% of full responders that are likely to experience a recurrence of wetting by the end of three months following treatment (0.25/0.5625 = 0.44). With a cumulative probability of recurrence at 3 months of 56.25%, this means that a further 41.67% of patients will experience a recurrence between 2 weeks and 3 months after stopping treatment.

To calculate the risk of recurrence among children treated with imipramine, data at 3 months post treatment from Tahmaz [10] and Wagner [15] were used. A meta-analysis of the imipramine trial arms from these studies showed that 80.8% of complete responders had experienced a recurrence of bedwetting by 3 months. Assuming, as with desmopressin, that 44% of all patients who experience a recurrence of bedwetting by 3 months would do so by 1 week, patients face a 35.55% risk of recurrence at 1 week and a further 70.21% between 2 weeks and 3 months.

To calculate the risk of bedwetting recurrence among children treated with combined alarm and desmopressin, data at 4 and 12 weeks following the end of successful treatment was available from Ng[9]. The Ng study showed that 25% of full responders would experience a recurrence of bedwetting by 4 weeks and 35% by 12 weeks. Again, if 44% of all patients experiencing a recurrence at 3 months do so by 1 week (as assumed for desmopressin and imipramine), then 15.6% of patients can be expected to experience a recurrence by 1 week and a further 22.99% by 3 months.

Recurrence of bedwetting data for combined desmopressin and anticholinergic was unavailable and therefore it was assumed that recurrence following a successful course of this intervention follows the same pattern as for desmopressin alone. Additionally, there was no data on recurrence among treatment resistant populations, thus a pragmatic approach of assuming the same risk of relapse as in first line was taken.

1.2.7 Cost Data

Costs were applied differentially in the model depending on what intervention a patient was offered and whether the intervention was newly initiated or part of ongoing management. Costs were separated in this way because for all interventions unit costs and NHS staff costs differ depending on whether the intervention has been newly initiated or if it is ongoing. For example, when enuresis alarms are prescribed for the first time, the total cost is that of the device itself plus three follow-up visits with a community nurse specialist. Because it is assumed that patients will hold on to their alarm going into the second cycle (that is, if they are using it again) the only cost included is that of replacement batteries and no ongoing follow-up. Although it is unlikely that the NHS will be purchasing replacement batteries on an ongoing basis, GDG members indicated that when they prescribe an alarm for the first time, they often will give patients the alarm, and two sets of batteries.

Unit costs of the interventions (e.g. alarm devices and prescription drugs) are presented in table 8, broken down by costs incurred in the first treatment cycle and subsequent cycles.

Table 8: Unit costs of interventions

Intervention	Cost (first 3 months)	Cost (maintenance cycles)	Source
Enuresis alarm	£52.17	£0.72	NHS Supply Chain[17]
Desmopressin (tablets)	£128.17	£137.32	BNF 2009[18]
Alarm + Desmopressin (tablets)*	£128.89	£138.04	
Alarm + Desmopressin (tablets)†	£189.49	£138.04	
Desmopressin (tablets) + Anticholinergic	£197.77	£197.77	BNF 2009[18]; PCA 2008[19]
Imipramine (by age in years)			BNF 2009[18]; Health Survey for England 2007[20]
7	£3.33	£3.33	
8	£3.92	£3.92	
9	£5.29	£5.29	
10	£6.08	£6.08	
11	£6.17	£6.17	
12+	£6.29	£6.29	

*cost of combined alarm and desmopressin after alarm alone

†cost of combined alarm and desmopressin after desmopressin alone

There is always the risk that equipment will break, but in the absence of data to inform how often this might happen, it was assumed in the base case that no breakage will occur and thus no replacements will need to be provided. This assumption was tested in a one way sensitivity analysis wherein 100% of alarms would need to be completely replaced.

The cost of desmopressin has been calculated to reflect the average cost of desmopressin for the treatment of bedwetting. Based on dose-escalation studies identified in the clinical review, some patients will respond to initial low doses of desmopressin, but many will need to increase their dose in order to see a response. In the study by Schulman [21] patients were titrated from 0.2 mg to 0.6 mg of desmopressin depending upon their response. By the end of the 8 week trial, 86.9 percent of patients had been titrated to the maximum dose of 0.6 mg and 12.12 percent had been titrated to 0.4 mg. Since a maximum dosage of 0.4 mg (or 240 micrograms for melts) is licensed in the BNF for the treatment of bedwetting, this study shows that 99 percent of patients will have reached a maximum dose of 0.4 mg. This figure was considered quite extreme and unlikely to be the case in clinical practice, therefore the GDG proposed a more conservative estimate that was fed into the modelling. It was assumed that in the first cycle (first 3-month trial of treatment) all patients will start on a dose of either 0.2 mg (tablet) or 120 micrograms (melt) for two weeks. At the end of two weeks, one-third of patients will continue on this lower dose and two-thirds will increase to the higher dose, 0.4 mg (tablets) or 240 micrograms (melt) for the remainder of the cycle. The effect of this assumption was explored in a sensitivity analyses.

The cost of imipramine is also a weighted average, and here it varies by age. Based on the methods outlined in an RCT [15] wherein imipramine was evaluated, it was assumed that patients below 32 kg would receive a daily dose of 25 mg and patients above 32 kg would receive 50 mg. The proportions of patients above and below 32 kg were derived from frequency distributions of childhood weights listed in the Health Survey for England 2007[20].

The cost of treatment with combined alarm and desmopressin therapy is dependent in part on what treatment has come previously in the sequence. If, for instance, alarm treatment alone has come before, then it is assumed only the additional cost of desmopressin and extra batteries are required. However, if desmopressin therapy alone is the treatment immediately prior, then not only would the cost of further courses of desmopressin be required, but the cost of a new enuresis alarm would also be incurred.

The cost of anticholinergics was calculated as the weighted average of oxybutynin and tolterodine, using the Prescription Cost Analysis (PCA) 2008[19] to identify the relative usage of each drug within the relevant dosage in the UK. Based on the figures listed in the PCA, the average cost of a daily dose of anticholinergic used in the treatment of bedwetting is 51.15% of the cost of oxybutynin and 48.85% of tolterodine.

NHS staff costs make up the other element of intervention costs. Because no published data on resource use could be identified from the literature, resource use figures summarised in table 9 are based upon the expert opinion of the GDG and unit costs were taken from published costs of health care professional time[22].

Table 9: NHS staff costs

Consultation Type	Health Professional	Time (minutes)	Unit cost per minute	Cost
Assessment				
Initial Assessment	Community Nurse Specialist	45	£1.23	£55.50
Reassessment for new intervention		20	£1.23	£24.67
Reassessment following repeated non-response	Consultant	30	£2.38	£71.50
Follow-up	Community Nurse Specialist	15	£1.23	£18.50
Maintenance				
Pharmacological interventions (excl Imipramine)	GP	5 per 6 months	£2.30	£11.50
Imipramine	GP	12 per 3 months	£2.30	£26.91

Resource use estimates based on GDG opinion; Unit costs from PSSRU[22]

It was assumed that all patients are first assessed by a community nurse specialist, a cost common across all intervention sequences and thus not contributing cost differences between strategies. In the first 3-month treatment cycle of any new intervention, 2 or 3 follow-up visits with a community nurse specialist, for pharmacological interventions and enuresis alarm respectively, are assumed to take place. A reassessment with the community nurse is assumed to take place whenever patients move on to the next intervention in the sequence. If patients do not achieve a full response or experience repeated relapse of bedwetting following successful treatment, they are eventually referred on to a consultant for reassessment.

Costs included during cycles spent in longer term desmopressin and combined desmopressin and anticholinergic treatment include 6-monthly monitoring visits to the GP. In the case of imipramine, the BNF[18] states that patients must undergo a 'full examination' before further courses of

imipramine can be offered. Therefore, for imipramine, the cost of 3-monthly GP consultations has been included.

Total costs of treating bedwetting were comprised of the unit costs of interventions, costs of assessments, reassessments and follow-up with health care professionals, and any costs of monitoring for longer term pharmacological treatment. Table 10 summarises the total 3-monthly costs of each intervention depending on whether it is the first 3 months of a new treatment or a subsequent 3-month course with an ongoing treatment.

Table 10: Total 3-monthly costs of interventions

Intervention	Cost (first 3 months)	Cost (maintenance cycles)	Sources
Enuresis alarm	£107.67	£0.72	NHS Supply Chain[17]; PSSRU costs[22]
Desmopressin (tablets)	£170.92	£143.07	BNF 2009[18]; PSSRU costs[22]
Alarm + Desmopressin (tablets)*	£171.64	£143.79	
Alarm + Desmopressin (tablets)†	£250.74	£143.79	
Desmopressin (tablets) + Anticholinergic	£240.52	£203.52	BNF 2009[18]; Prescription Cost Analysis 2008[19]; PSSRU costs[22]
Imipramine (by age in years)			BNF 2009[18]; Health Survey for England 2007[20]; PSSRU costs[22]
5	£45.97	£30.22	
6	£45.97	£30.22	
7	£46.08	£30.33	
8	£46.67	£30.92	
9	£48.04	£32.29	
10	£48.83	£33.08	
11	£48.92	£33.17	
12+	£49.04	£33.29	

*cost of combined alarm and desmopressin after alarm alone
†cost of combined alarm and desmopressin after desmopressin alone

1.2.8 Utilities (health-related quality of life)

1.2.8.1 Child Utility Weights

No published utility data for children with bedwetting could be identified in the literature. However, it is important to measure health gains in a generic and non-condition specific way such that comparisons can be made across different health programmes and policies using a common measure (e.g. cost per QALY gained), therefore we looked for alternative options.

During guideline development, several methods to value quality of life with and without bedwetting were attempted. The GDG looked at other chronic childhood conditions, including asthma, eczema, hyperactivity, neurological disability and constipation. Other urological conditions in adults – female urinary incontinence, overactive bladder, urinary tract infection - were surveyed as well. A study by Guest and others [23] explored the cost-effectiveness of interventions used to treat paediatric faecal impaction in England and Wales. In this study, the authors developed an algorithm (which they did not describe in detail) to translate adult utility scores for constipation into childhood utility scores for constipation. The utility weight attached to a child with faecal impaction was 0.7 and to a healthy child was 0.94.

Another method considered was using the Health Utilities Index Mark 2 (HUI2) [24] instrument to make assumptions about the health-related quality of life of children with bedwetting. The HUI2 is the only preference based multi-attribute health-related quality of life instrument specifically developed for use with children. It consists of seven dimensions (sensation, mobility, emotion, cognition, self care, pain and fertility (optional), each of which has between three and five levels. The levels range from "normal functioning for age" to "extreme disability." For the purposes of

valuing a health state of associated with bedwetting, the fertility dimension was not considered here.

A limited number of possible HUI2 scores were considered likely for the average child with bedwetting. Bedwetting was thought most likely to affect the dimensions of emotion (which accounts for issues of fretfulness, anger, anxiety and depression) and self care (which encompass issues of eating, bathing, dressing and toileting normally for age). Table 11 gives examples of HUI2 health state descriptions and associated utility weights that might be appropriate for bedwetting.

Table 11: HUI 2 Health scenarios potentially describing bedwetting

HUI2 Health States	Utility weights
A Normal' on all dimensions*	1.000
Normal' on all dimensions, except	
B Occasionally fretful, irritable, angry, anxious or depressed	0.926
C Occasionally fretful, irritable, angry, anxious or depressed AND Eats, bathes, dresses or uses toilet independently with difficulty	0.896
D Eats, bathes, dresses or uses toilet independently with difficulty	0.968
E Often fretful, irritable, angry, anxious or depressed	0.799
F Often fretful, irritable, angry, anxious or depressed AND Eats, bathes, dresses or uses toilet independently with difficulty	0.773

*6 HUI 2 dimensions: sensation, mobility, emotion, cognition, self-care, pain

It would be ideal to have data from patients with bedwetting, but in the absence of this, a next best alternative was found. Based on the utility weights from HUI2 summarised in table 11 and benchmarks provided from examples of other childhood conditions, such as constipation, a utility weight of 0.896 (HUI2 state C in table 11) has been used in the base case. This figure is in line with the assumption that, for children, bedwetting is not as bad a faecal impaction (0.7) but is not as good as normal health (1.00). Thus the QALY gain attributed to getting dry is 0.104 (1.00-0.896 = 0.104).

Two other aspects of utility to consider for bedwetting are the difference between being dry off treatment and being dry whilst on ongoing treatment, and the difference between regular bedwetting and experiencing a partial response to treatment. If the utility weights are attached to health states – bedwetting or not bedwetting – then the same weight should be attached to being dry whether on or off treatment. However, the fact that whenever treatment is withdrawn (which is for at least one week every three months) the patient might go back to wetting might be reasonable justification for applying a slightly lower utility weight to being dry only whilst on ongoing treatment. The patient representatives on the GDG also felt strongly that there was a difference between being 'cured' (i.e. dry without treatment) and being dry on treatment, as there are certain inconveniences associated with remembering to take medicines, avoiding excessive fluid intake before bed, taking certain precautions when going on holiday, etc. On that basis, in the base case, a utility gain of 0.03 has been applied to being dry whilst on ongoing pharmacological treatment, as this is the difference between the utility weight attached to bedwetting (0.896) and

the utility weight attached to HUI2 health state B (0.926) described in table 11. The effect of this is tested in sensitivity analysis by assuming it is the same as simply being dry.

For partial responders, a partial response means that the patient experiences an overall reduction in his/her wet nights, but does not achieve complete dryness. Does this improvement in bedwetting represent a substantive improvement in quality of life? Or is 'wet sometimes' the same as 'wet often'? In the base case, it has been assumed that there is a slight improvement in quality of life attached to experiencing a partial response whilst on active treatment. This improvement is equal to half of the utility gain associated with becoming dry on active treatment. The effect of this assumption was also tested in sensitivity analysis.

All of the utility weights applied in the model are summarised in table 12.

Table 12: Utility weights

Health State	Point estimate	Distribution	Distribution parameters	Source
Patient				
No bedwetting	1			Expert opinion
Bedwetting	0.896	beta	α=52.39 β=6.07	Expert opinion
No bedwetting on treatment – utility gain	+0.03			Expert opinion
Partial response on treatment - utility gain	+0.015			Expert opinion
Carer				
No bedwetting	0.92	beta	α=2.09 β=0.182	Kind[25]
Bedwetting – utility decrement	- 0.045			Egemen[26]

1.2.8.2 Parent or Carer Utility Weights

As outlined in the NICE reference case[2] the perspective on clinical outcomes should be all direct health effects, whether for patients or for other people, principally carers. A single health-related quality of life study by Egemen [26] was identified from the literature and had used the Short-Form Health Survey (SF-36) Questionnaire to compare the quality of life of mothers of children with nocturnal enuresis with the quality of life of mothers of children without nocturnal enuresis. The study was carried out in Turkey, making it partially applicable to the UK and this guidance.

The patient level data from Egemen was generously shared with the NCGC such that it could be fed into the health economic modelling. An algorithm[27] from researchers at the University of Sheffield's Health Economics and Decision Science unit allowed for the translation of SF-36 data into usable SF-6D utility weights. The US version 1 (modified) algorithm was chosen based on the particular version of the SF-36 questionnaire Egemen and his colleagues used and was executed in SPSS [28]. We used SF-6D, a generic preference-based single index measure of health, to generate utility scores to apply to time spent in health states in the model.

The utility scores thus calculated were used to estimate the carer's utility decrement due to bedwetting. The mean difference between the utility score of mothers of children with bedwetting

(0.688) and the utility score of mothers of children without bedwetting (0.733) is 0.045 (95% CI -0.104, 0.014). This means that if a child or young person's bedwetting is successfully treated, in addition to the child's QALY gain, the carer will experience an average gain of 0.045 QALYs over one year. Because the study was carried out in Turkey, and there may be differences between quality of life among adult women in Turkey compared to the UK, the utility difference identified in the study was used in conjunction with UK specific quality of life data available from a study by Kind[25]. Kind found that women between 25 and 44 years of age reported a mean utility weight of 0.92. In the same study, men between 25 and 44 years also reported a mean utility weight of 0.92. Therefore, it was assumed that 0.92 would be a reasonable utility weight to attach to parent and carer health states wherein their child was not currently bedwetting. To reflect health states when their child was bedwetting, the 0.045 QALY loss identified in Egemen [26]was subtracted from 0.92. These figures are summarized in table 12 along with the utility weights of the children.

It was assumed that if a child or young person is dry whilst on treatment, the carer will experience this as a carer of a child without bedwetting (0.92). Similarly, if the child or young person has only had a partial response to treatment and therefore still has some wet nights, the carer will experience this as a carer of a child with bedwetting (-0.045). The effect of including parent and carer utility weights was tested in a sensitivity analysis by removing them and assessing cost-effectiveness of intervention sequences purely based upon QALY gains to the children.

1.2.9 Computations

The model was constructed in TreeAge Pro 2008 and was evaluated by cohort simulation. All patients start the first cycle experiencing bedwetting and in each cycle, they face the age-dependent probabilities of becoming dry without treatment. Each 3-month cycle the cohort spends in a bedwetting or dry state is counted.

Total QALYs were calculated from the above information as follows. Each 3-month cycle, the time spent in each health state of the model was weighted by the utility for that state. The QALYs per cycle were then discounted to reflect time preference. QALYs during year one were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

$$Total\ discounted\ QALYs = \sum_{t=1}^{i} \frac{Q(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; Q(t) = QALYs in cycle t; r = discount rate

Total costs were calculated from the above information as follows. Each cycle, the time spent in each state of the model was multiplied by the costs for that state. The costs per cycle were then discounted to reflect time preference. Costs during year one were not discounted. The total discounted costs were the sum of the discounted costs per cycle.

$$Total\ discounted\ costs = \sum_{t=1}^{i} \frac{C(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; C(t) = costs in cycle t; r = discount rate

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in

QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold, the result is considered to be cost-effective. If both costs are lower and QALYs are higher, the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost and then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

It is also possible to re-express cost-effectiveness results in terms of net benefit at a particular cost-effectiveness threshold. For strategy X, this was calculated as

$$Net\ Benefit(X) = (QALYs(X) \times D) - Costs(X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D=threshold

The decision rule then applied is that the strategy with the greatest net benefit is the cost-effective option at that threshold. That strategy is expected to provide the highest number of QALYs at an acceptable cost

Results are also presented on the cost-effectiveness plane where the total cost and total QALYs are plotted for each treatment sequence. The no treatment strategy is always located at the origin. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio, the value of which is labelled.

1.2.10 Sensitivity analysis

In addition to the probabilistic sensitivity analysis run to take account of uncertainty around the input parameters, various other sensitivity analyses, where one or more inputs were varied, were undertaken to test the robustness of model assumptions and data sources. First, a scenario analysis in which alarm based treatment sequences were removed was undertaken to identify the most cost-effective strategy for children for whom alarm is unsuitable due to personal or familial circumstances. Next, a series of one-way sensitivity analyses were run in the deterministic analysis in order to see how variation in key parameters, such as treatment effect estimates, recurrence rates and utility weights, affects the overall results. Then, the effect of changing assumptions about utility weights applied to partial and full response whilst on treatment was tested as was the complete removal of parent and carer utilities from the analysis. The assumption about 100% of patients resuming treatment following a recurrence of bedwetting after treatment was relaxed to 50% and 75%. The model was rerun with new costs for desmopressin, assuming that 100% of patients required the highest dose. In another sensitivity analysis, the cost of alarm was doubled in order to assess cost-effectiveness of alarm-based strategies if all alarms prescribed would need to be replaced at least once over the course of treatment. And finally, the model was also rerun to test cost-effectiveness of intervention sequences if they started from age 5 instead of age 7 years.

1.3 Results

1.3.1 Deterministic Analysis

Results of the basecase deterministic analysis are presented in table 13 in order of increasing total cost per patient. The health gain to children and their parents/carers is presented in terms of total QALYs for each treatment sequence as well. Also presented are estimates of the total proportion of patient who would have achieved sustained dryness of at least 12 months by the age of 20 years.

Table 13: Basecase deterministic analysis results

Treatment sequence	Total cost (£)	Total QALYs	Proportion achieving a 12-month response
No Treatment	£0	19.738	93.28%
Alarm - Imipramine	£195	19.927	97.12%
Alarm - Alarm+Desmopressin - Imipramine	£237	20.005	98.54%
Alarm - Alarm+Desmopressin - Desmopressin	£240	20.014	98.57%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£252	20.019	98.70%
Alarm - Desmopressin - Imipramine	£265	19.976	97.94%
Alarm - Desmopressin	£266	20.008	98.58%
Desmopressin - Imipramine	£281	19.940	97.47%
Desmopressin	£291	20.001	98.38%
Desmopressin - Alarm - Imipramine	£292	19.975	97.88%
Alarm - Imipramine - Desmopressin	£299	19.976	98.21%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£313	20.024	99.04%
Desmopressin - Alarm - Desmopressin	£328	20.015	98.77%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£339	19.992	98.71%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£341	20.024	99.01%
Desmopressin - Alarm+Desmopressin - Imipramine	£357	20.004	98.52%
Imipramine - Alarm - Desmopressin	£364	19.944	98.02%
Desmopressin - Desmopressin+Anticholinergic	£373	20.031	99.08%
Desmopressin - Alarm+Desmopressin - Desmopressin	£380	20.017	98.74%
Imipramine - Desmopressin	£388	19.933	97.68%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£392	20.027	99.01%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£406	19.960	98.54%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£470	19.962	98.47%

Table 14 presents the results of the incremental analysis after dominated and extendedly dominated strategies have been removed.

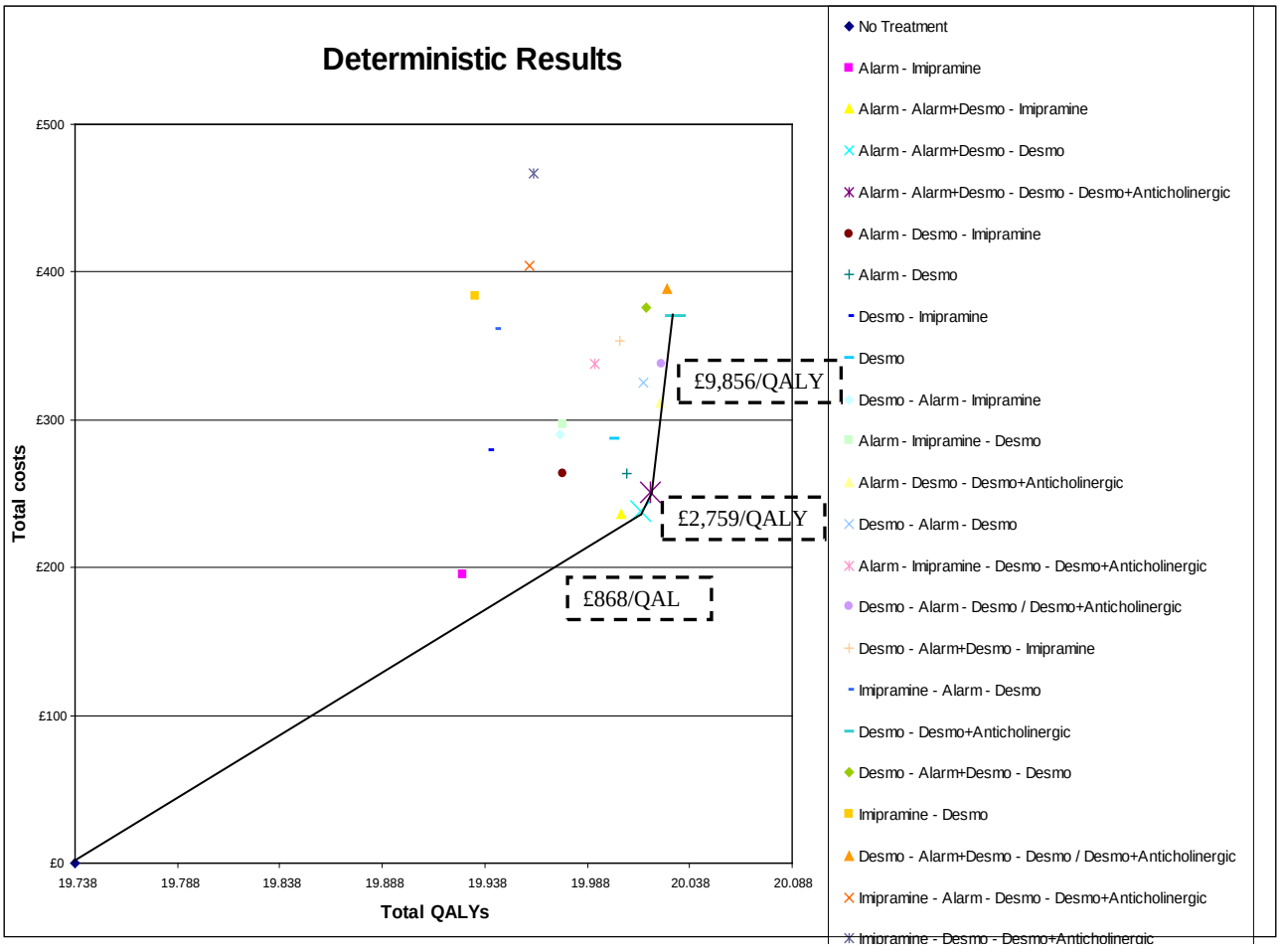
Table 14: Incremental analysis of basecase deterministic results with dominated and extendedly dominated sequences removed

Treatment sequence	Incremental Cost (£)	Incremental Effect (QALYs)	ICER (£/QALY)
No Treatment	£0		
Alarm - Alarm+Desmopressin - Desmopressin	£240	0.276	£868

Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£252	0.004	£2,759
Desmopressin - Desmopressin+Anticholinergic	£373	0.012	£9,856

These results in table 13 are represented graphically in a cost-effectiveness plane in figure 3.

Figure 3: Basecase deterministic results on the cost-effectiveness plane



Intervention sequences represented by coordinates to the left of the lines are not considered cost effective. These treatment sequences are said to be dominated, as they are both more costly and less effective than intervention sequences connected by the lines.

In the basecase deterministic analysis the least effective, but also the least expensive strategy is offering no treatment. Costlier than this, but also generating an additional 0.276 QALYs, is alarm – alarm+desmopressin – desmopressin producing an ICER of £868. The ICER associated with adding combined desmopressin and anticholinergic to the end of this sequence is £2,759. The most effective and cost-effective treatment sequence in the basecase was desmopressin – desmopressin+anticholinergic, with an ICER of £9,856 compared to alarm – alarm+desmopressin – desmopressin – desmopressin+anticholinergic. All treatment sequences using imipramine were dominated or extendedly dominated from the deterministic analysis.

1.3.2 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis was run for 20,000 simulations. In each simulation, the total cost and total QALYs were calculated for each treatment option. The net benefit was also calculated and based on the net benefit, the most cost-effective strategy identified. The results of the probabilistic sensitivity analysis are summarised in table 15 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Table 15: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold= £20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£514	19.922	£397,929	0.0%
Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%
Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£346	19.997	£399,592	5.6%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Desmopressin - Alarm - Desmopressin /	£373	20.001	£399,647	5.8%

Desmopressin+Anticholinergic				

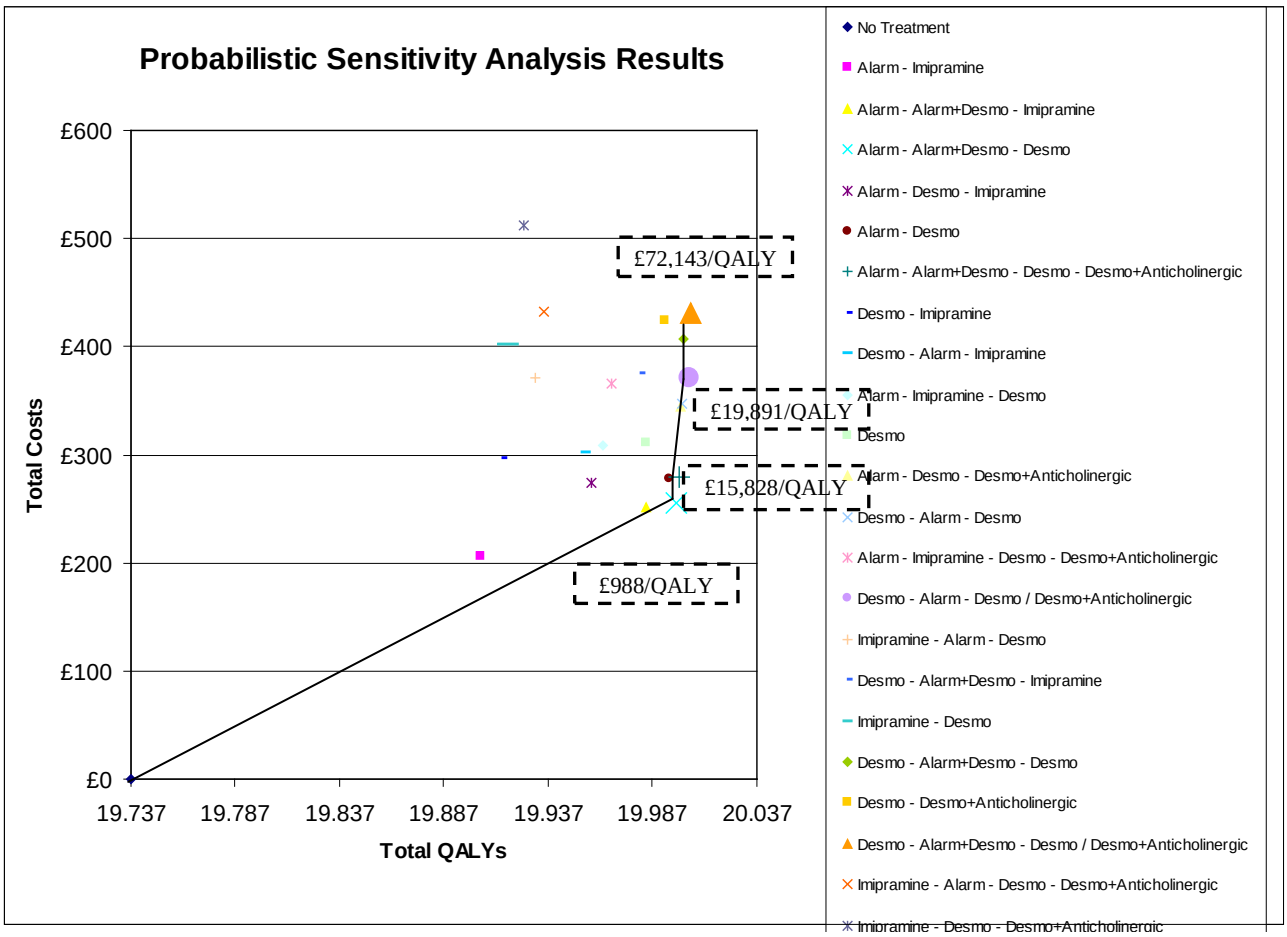
The results of the incremental analysis in the probabilistic model are also presented in table 16.

Table 16: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	£61	20.00183	0.00084	£72,143

The results presented in table 15 are represented graphically in a cost-effectiveness plane in figure 4.

Figure 4: Basecase probabilistic sensitivity analysis results on the cost-effectiveness plane



Intervention sequences represented by coordinates to the left of the lines are not considered cost effective. These treatment sequences are said to be dominated, as they are both more costly and less effective than intervention sequences connected by the lines.

The incremental analysis based on the mean PSA results indicate that alarm – alarm+desmopressin – desmopressin with and without the addition of anticholinergic at the end are very likely to be cost-effective treatment sequences at a willingness to pay threshold of £20,000 per QALY gained. The strategy of desmopressin – alarm – desmopressin / desmopressin+anticholinergic was ruled out through extended dominance in the deterministic analysis and desmopressin – alarm+desmopressin – desmopressin / desmopressin+anticholinergic was dominated. In the PSA, desmopressin – alarm – desmopressin / desmopressin+anticholinergic is more effective and more costly than alarm - alarm+desmopressin – desmopressin – desmopressin+anticholinergic, with an ICER just under the £20,000 per QALY gained threshold. Finally, desmopressin – alarm+desmopressin – desmopressin / desmopressin+anticholinergic was the most effective sequence, but its very high cost compared to desmopressin – alarm – desmopressin / desmopressin+anticholinergic generates a very high ICER of £72,143, well over the £20,000 per QALY gained threshold. Again, all treatment sequences using imipramine were dominated or extendedly dominated from the probabilistic analysis.

The incremental analysis of the mean costs and QALYs does not fully capture the uncertainty in the results of the PSA. For this, we look to the statistic for the probability that a given strategy is most cost-effective at a specified willingness to pay threshold, in this case £20,000 per QALY gained. Based on these estimates, presented in table 15, no sequence has a probability greater than 20% of being optimal and each of the rest having a probability of less than 16%. Even the strategy with the greatest probability of being optimal (desmopressin – desmopressin+anticholinergic) is dominated in the incremental analysis. The uncertainty reflected in these results is likely caused by the substantial uncertainty in model inputs, such as treatment effectiveness and health state utilities. The results demonstrate how any variation in these inputs could lead to a different conclusion about relative cost-effectiveness.

1.3.3 Results when alarm-based strategies are removed

If all treatment sequences using alarm either alone or in combination with desmopressin are removed from the analysis, probabilistic results indicate that initial treatment with desmopressin alone and followed by combined desmopressin and anticholinergic is the most cost-effective treatment strategy with an ICER of £12,422 compared to initial and longer term desmopressin alone.

Table 17: Incremental analysis of strategies when alarm-based strategies are removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.737		
Desmopressin	£314	£314	19.984	0.247	£1,272
Desmopressin - Desmopressin+Anticholinergic	£426	£112	19.993	0.009	£12,422

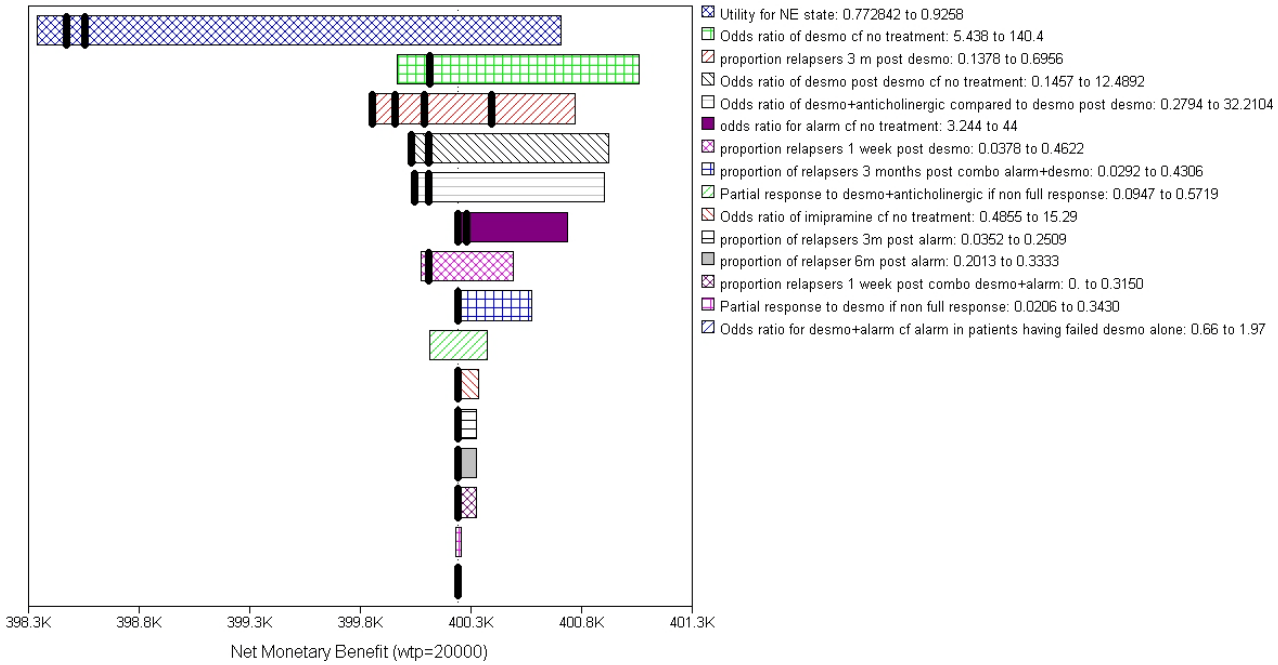
1.3.4 Sensitivity analyses

All results presented in the following sections are generated from probabilistic modelling. In each, an assumption made in the basecase was tested and the model rerun probabilistically producing new mean costs and QALYs.

1.3.4.1 One-way sensitivity analysis of key parameters

A series of one-way sensitivity analyses were run in the deterministic analysis in order to see how variation in key parameters, such as treatment effect estimates, recurrence rates and utility weights, affects the overall results. Figure 5 presents a tornado diagram which visually summarises how variation in inputs affects the net monetary benefit of different treatment sequences at our £20,000 per QALY threshold.

Figure 5: Tornado diagram of key parameters: treatment effect estimates, recurrence rates and utility weights



The figure is called a tornado diagram because the bars are arranged in order, with the widest bar at the top and the narrowest at the bottom. Each bar represents a one-way sensitivity analysis and the dotted vertical line represents the point estimate used in the deterministic base case. The widths of the bars represent the range of expected net monetary benefit values at a threshold willingness to pay of £20,000 per QALY. A wide bar, such as the one for the utility weight attached to experiencing bedwetting, indicates that the variable has a large potential effect on the results. The bolded lines on some bars represent a threshold value at which optimal treatment sequences change.

The threshold diagram indicates that the greatest uncertainty arises from the utility weight attached to bedwetting. If the utility weight attached to bedwetting is less than 0.78, then a sequence of alarm followed by combined alarm and desmopressin and then desmopressin with the possible addition of anticholinergic is optimal. However, if it is greater than 0.788, then desmopressin followed by combined desmopressin and anticholinergic is optimal.

Uncertainty around particular desmopressin parameters, including its effectiveness compared to no treatment as either first or second line intervention and its probability of producing a sustained response as measured by risk of recurrence at 1 week and 3 months, also seem to drive variation in the results. In terms of the effectiveness, the odds of responding to desmopressin must be greater than 39 times that of success without treatment in order for desmopressin followed by combined desmopressin and anticholinergic to be optimal. If less than 39, alarm – alarm+desmopressin – desmopressin – desmopressin+anticholinergic is likely to be the best option. Risk of relapse at 3 months seems particularly important to the determination of optimal strategies, with the optimal strategy being desmopressin – alarm – desmopressin/desmopressin+anticholinergic if risk of relapse is less than 31% and alarm – alarm+desmopressin – desmopressin – desmopressin+anticholinergic being optimal between 49% and 57%. Finally, if the odds of responding to desmopressin following an initial non-response or partial response to desmopressin compared to no treatment are less than 2.58, then the sequences of alarm – alarm+desmopressin – desmopressin with or without the addition of an anticholinergic are likely to be optimal. Desmopressin followed by combined desmopressin+anticholinergic are optimal if the odds ratio is over 2.58.

1.3.4.2 Utilities of partial and full response on longer term treatment

When it is assumed that a partial response to maintenance therapy with a pharmacological intervention such as imipramine, desmopressin or combined desmopressin and anticholinergic is no better than experiencing bedwetting and that a full response to maintenance therapy is as good as being dry without treatment, the relative cost-effectiveness of treatment sequences changes. Non-dominated and non-extendedly dominated strategies under these revised assumptions are presented in table 18.

Table 18: Incremental analysis of strategies when utility of a partial response equals the utility of bedwetting and utility of dry on treatment equals the utility of being dry

Treatment sequence	Total cost (£)	Incremental Cost (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.737		
Alarm - Alarm+Desmopressin – Desmopressin	£256	£256	19.997	0.260	£983
Alarm – Desmopressin	£278	£22	20.002	0.005	£4,400
Desmopressin - Alarm – Desmopressin	£348	£70	20.013	0.011	£6,400
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£371	£23	20.016	0.003	£7,800

In this particular sensitivity analysis, strategies beginning with desmopressin appear more cost-effective than they do in the basecase. This is due to the fact that desmopressin is very effective at getting children dry and keeping them that way whilst desmopressin is maintained. If being dry whilst on treatment provides the same health gain as achieving sustained dryness off treatment, then it is unsurprising that treatments like desmopressin perform better.

1.3.4.3 Excluding parent/carer utilities

The non-dominated and non-extendedly dominated incremental results of the analysis wherein quality of life gains among parents/carers are excluded are summarised in table 19. When only QALYs accruing to the children are counted, alarm – alarm+desmopressin – desmopressin is the most cost-effective strategy under the £20,000 per QALY threshold. The addition of combined

desmopressin and anticholinergic and the end of that sequence is both more effective and more costly, with an ICER of £24,400 per QALY gained. And the sequence desmopressin – alarm+desmopressin – desmopressin / desompressin+anticholinergic, which had an ICER well beyond the £20,000 per QALY threshold in the basecase, more than doubled to £150,100 in this scenario.

Table 19: Incremental analysis of strategies when parent/carer utilities are removed

Treatment sequence	Total cost (£)	Incremental Cost (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		10.212		
Alarm - Alarm+Desmopressin – Desmopressin	£256	£256.00	10.393	0.181	£1,414
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£280	£24	10.394	0.001	£24,400
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£431	£151	10.395	0.001	£150,100

1.3.4.4 Structural assumption regarding resumption of treatment following relapse

In the base case, it was assumed that 100% of children would resume treatment following a recurrence of bedwetting after 1 week of discontinuing treatment. When this assumption was relaxed and only 50% or 75% of children resumed treatment following a relapse, the cost-effectiveness of alarm – alarm+desmopressin – desmopressin did not change substantially. At 50% resumption the ICER was £1,020 compared to no treatment; at 75%, the ICER was £997 per QALY gained. At 50% resumption, alarm – alarm+desmopressin – desmopressin – desmopressin+anticholinergic was dominated by alarm – alarm+desmopressin – desmopressin. At 75% it had an ICER of £23,100 compared to alarm – alarm+desmopressin – desmopressin. All other treatment sequences were ruled out through dominance or extended dominance in this sensitivity analysis.

1.3.4.5 100% require high dose of desmopressin

In the base case, it was assumed that 75% of children would increase their dosage of desmopressin from 0.2 mg in the first two weeks to 0.4mg in the following weeks. The results of the probabilistic sensitivity analysis when it is assumed, instead, that 100% of children would require the higher dose of desmopressin are presented in table 20.

Table 20: Incremental analysis of strategies when 100% of children taking desmopressin require the higher dose

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.737		
Alarm - Alarm+Desmopressin - Desmo	£274	£274	19.998	0.261	£1,048
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£299	£26	20.000	0.002	£12,900
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£404	£104	20.004	0.004	£26,050
Desmopressin - Alarm+Desmopressin -	£473	£70	20.005	0.001	£69,700

Desmopressin / Desmopressin+Anticholinergic					

Based on these results, if 100% of children required the higher dose of desmopressin, the treatment sequence alarm – alarm+desmopressin – desmopressin with or without the addition of an anticholinergic to desmopressin at the end, is still cost effective, as in the base case. However, the strategy desmopressin – alarm – desmopressin / desmopressin+anticholinergic which may be considered cost-effective in the base case (ICER=£19,891) is now over the £20,000 per QALY threshold with an ICER of £26,050. Therefore it seems clear that the cost-effectiveness of this particular strategy is sensitive to proportion of patients requiring the higher dose of desmopressin.

1.3.4.6 100% alarms need to be replaced

In the base case, it was assumed that no alarms would require replacement due to malfunction or breakage. This is likely to be an underestimation of the likelihood that alarms will need to be replaced in at least some instances over the course of between 3 and 6 months of treatment and possibly more if patients resume following a recurrence of bedwetting. To see how sensitive the base case results are to this assumption, a sensitivity analysis was run wherein all alarms would need to be replaced at least once, thus doubling the unit cost of alarms. The results of this sensitivity analysis are presented in table 21.

Table 21: Incremental analysis of strategies if 100% of alarms needed to be replaced once

Treatment sequence	**Mean cost (£)**	**Incremental Cost (£)**	**Mean QALYs**	**Incremental QALYs**	**ICER (£/QALY)**
No Treatment	£0		19.73834		
Alarm – Alarm+Desmopressin - Desmo	£284	£284	19.99948	0.26114	£1,086
Alarm - Alarm+Desmopressin - Desmopressin – Desmopressin+Anticholinergic	£308	£24	20.001	0.00152	£15,789
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£400	£92	20.00552	0.00452	£20,442
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£459	£59	20.00643	0.00091	£64,615

Based on these results, if 100% of alarms needed to be replaced, the treatment sequence alarm – alarm+desmopressin – desmopressin with or without the addition of an anticholinergic to desmopressin at the end, is still cost effective, as in the base case. However, the strategy desmopressin – alarm – desmopressin / desmopressin+anticholinergic which may be considered cost-effective in the base case (ICER=£19,891) is now slightly over the £20,000 per QALY threshold with an ICER of £20,442. Therefore the results in the basecase do not appear to be very sensitive to the assumption made about alarm replacement. Even if all alarms needed to be replaced at least once, an overly pessimistic assumption about their likely durability, the same strategies are likely to be cost-effective.

1.3.4.7 Using a starting age of 5 years

When the hypothetical cohort includes children from the age of 5 years, the relative cost-effectiveness of alarm – alarm+desmopressin – desmopressin does not change substantially

compared with the basecase where only children over the age of 7 years were included. However, all other strategies considered cost-effective in the base case become not cost-effective, each having an ICER of well over the £20,000 per QALY threshold. The non-dominated and non-extendedly dominated strategies are presented in table 22.

Table 22: Incremental analysis of strategies when starting age is 5 years

Treatment sequence	Total cost (£)	Incremental Cost (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		22.19181		
Alarm - Alarm+Desmopressin - Desmopressin	£241	£241	22.38413	0.19232	£1,254
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£260	£19	22.38467	0.00054	£35,556
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£354	£93	22.38579	0.00112	£83,304
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£410	£57	22.38581	0.00002	£2,835,000

1.4 Discussion

The aim of this analysis was to evaluate which sequence of interventions was the most cost-effective for the treatment of children with bedwetting. 22 sequences permutations comprised of alarm, imipramine, desmopressin, combined alarm and desmopressin and combined desmopressin and anticholinergic were compared, as was a baseline comparator of no treatment.

1.4.1 Summary and interpretation of results

Although both the deterministic and probabilistic analyses were presented to the GDG, greater emphasis was placed on the results emerging from the probabilistic analysis. The probabilistic analysis better reflected the considerable uncertainty around the estimates of treatment effect derived from the network meta-analysis and around the utility values attached to model health states. The differences between the results of the deterministic and probabilistic reflect the importance of this uncertainty and demonstrate how it might be driving the results.

Mean results of the basecase probabilistic analysis indicate that a treatment sequence comprised of alarm followed by combined alarm and desmopressin, and then desmopressin with or without the addition of an anticholinergic if desmopressin alone does not produce a full response is very likely to be cost-effective given a willingness to pay threshold of £20,000 per QALY gained. A sequence starting with desmopressin and then proceeding to alarm followed again by desmopressin if it worked before or desmopressin and anticholinergic if it did not may also be cost-effective, with an ICER of £19,891, just under the £20,000 per QALY threshold. It is worth pointing out that the incremental QALY gain between these strategies amounts to approximately 1.68 days, reflecting the broadly similar efficacy between modeled sequences. And the same sequence, but with combined alarm and desmopressin instead of alarm alone following initial desmopressin was marginally more effective but also more expensive, giving it an ICER of £72,143, which is well over the threshold. Treatment sequences that included imipramine were never found to be cost-effective.

The GDG considered that the differences between intervention sequences were relatively small and the probabilistic results indicated substantial uncertainty around the mean cost and benefit estimates. Small changes to the model inputs appears to result in substantial changes to the conclusions about modelled sequences' relative and overall cost-effectiveness. The GDG was concerned that alarms, despite their cost-effectiveness, may not be an appropriate intervention for all children. There may be circumstances identified during assessment that make the alarm an unsuitable intervention and other options need to be considered. To help with decision making in this type of situation, an analysis was undertaken wherein all alarm based strategies were removed. For this group of children, a strategy of starting and maintaining desmopressin with or without the addition of an anticholinergic until sustained dryness is achieved is considered cost-effective.

A series of sensitivity analyses were undertaken to test some of the assumptions feeding into the model and none of these affected the cost-effectiveness of the sequence alarm followed by combined alarm and desmopressin and then desmopressin alone compared to no treatment. However, there was some substantial variation in the relative cost-effectiveness of some of the more effective and expensive options.

A series of one-way sensitivity analyses indicated that the results and conclusions about desmopressin followed by combined desmopressin and anticholinergic were senstivitive to changes in effectiveness parameters for desmopressin, both as a first and second line treatment. Uncertainty in these same parameters was built into the probabilistic sensitivity analysis and have likely contributed to the different results between deterministic and probabilistic base case analyses as well as the lack of confidence around which treatment sequence is most cost-effective.

If the assumption is made that bedwetting is bedwetting and dry is dry, then a partial response to ongoing treatment is no better than no response and a full response to ongoing treatment is the same as a sustained response off treatment. In this scenario, a treatment sequence of desmopressin followed by alarm and then by desmopressin or combined desmopressin and anticholinergic is very likely to be cost-effective. Without real data to inform the utilities of these different health states, it is difficult to know whether this scenario or the basecase scenario is a better reflection of reality.

The NICE reference case specifies that all health outcomes, whether for patients or parents and carers, should be taken into account. The basecase analysis included the potential quality of life gain for parents and carers if their child were to achieve temporary or sustained dryness. In a sensitivity analysis, these health benefits were excluded to assess the cost-effectiveness of intervention sequences if there was no health gain accrued to parents and carers. In this scenario, only alarm followed by combined alarm and desmopressin and then by desmopressin alone was cost-effective. The addition of combined desmopressin and anticholinergic at the end of this sequence generated an ICER of £24,400, which is over the £20,000 per QALY threshold.

In the basecase it was assumed that 100% of children who experienced a recurrence of bedwetting within 1 week of discontinuing treatment following a full response would resume treatment, either with the same intervention that had worked before or with the next intervention in the sequence. In a sensitivity analysis, this assumption was relaxed to 50% and 75% and results showed that only the sequence alarm followed by combined alarm and desmopressin and then by desmopressin alone was cost-effective.

The proportion of patients increasing to a higher dose of desmopressin was assumed to be 75% in the base case, but in a sensitivity analysis, this proportion was increased to 100%. The cost-effectiveness of the sequence desmopressin followed by alarm and then followed either by desmopressin or combined desmopressin and anticholinergic (depending upon the initial response to desmopressin) was pushed over the £20,000 per QALY threshold using this alternative assumption, but just barely (£20,050). The GDG felt that the true proportion may lie somewhere in between 75% and 100%, and given the rather small change in the results between the base case and this scenario, they felt that the strategy beginning with desmopressin was likely to be cost-effective and should still be considered an acceptable treatment sequence.

The GDG also expressed some concern over the assumption made regarding the resilience of alarms, arguing that they do sometimes require new sensors and/or complete replacement during the course of treatment. A sensitivity analysis demonstrated that even if every alarm prescribed was replaced with a brand new one, strategies starting with alarm, and followed by combined alarm and desmopressin and then desmopressin alone or with the addition of an anticholinergic are still cost-effective in the treatment of children with bedwetting.

Finally, in the basecase, treatment only commenced for hypothetical patients at the age of 7 years. In actuality, some children may seek treatment starting at the age of 5 years. When the model is rerun from the age of 5 years, the same treatment sequences as in the base case are included in the incremental analysis, however the ICERs for all strategies except for alarm followed by combined alarm and desmopressin and then desmopressin alone are greater than £20,000 per QALY gained and therefore unlikely to be cost-effective.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn.

First, the effectiveness data available from the studies did not allow for the differentiation of treatment effectiveness by age. Therefore, in the absence of evidence that interventions are more or less effective in different age groups, it was assumed that the relative treatment effect of interventions was constant regardless of age.

Second, the availability of utility data to inform the estimation of QALYs was lacking. In the absence of this crucial input, the GDG used health state scenarios from the Health Utilities Index Mark 2 to estimate possible utility weights to apply to bedwetting. Utility weights derived from the exercise were assumed to be constant across all age groups with bedwetting, although in reality there may be additional utility decrement associated with more severe bedwetting or bedwetting that persists into adolescence.

Thirdly, there was no data available to estimate health care resource use associated with bedwetting or treatment for bedwetting. The estimates of resource use are an important part of calculating costs linked to different interventions. In the absence of this data, the GDG estimated likely resource use based on their experience from both a clinician and patient perspective.

The analysis did not take account of possible costs or QALYs losses associated with adverse events such as accidental overdose with imipramine or hyponatreamia with desmopressin. These were excluded for the reason that they are extremely unlikely to occur if medications are taken correctly.

The NICE guide to the methods of technology appraisal[2] states that costs borne by patients and carers that are not reimbursed by the NHS or PSS should not be included in either the reference or non-reference case analyses. As a result, costs to the family of children with bedwetting were not explicitly considered as part of the cost-effectiveness analysis presented here. However, The GDG felt that the substantial costs borne by the family as a result of frequent bedwetting should be considered and reflected in the guideline recommendations. Families coping with a child with bedwetting have the extra financial burden of frequently washing and replacing bed linens and night clothes as well as the potential depreciation of washing machines and mattresses. The successful treatment of the bedwetting could generate a real savings to the family. The potential savings to families lends further support to the recommendation to actively treat children and young people who experience bedwetting and even supports the idea that treatment should be initiated at an earlier age, such as at 5 years.

1.5 Conclusion

Overall, the results indicate that treating bedwetting is very likely to be cost-effective compared to not treating. But as for which particular intervention sequence is most cost-effective, the substantial uncertainty prevents one from drawing any definitive conclusions. In terms of treatment options, the least cost, non-dominated strategy was consistently initial treatment with alarm followed by treatment with combined alarm and desmopressin if alarm alone does not produce a sustained response and then followed by ongoing desmopressin alone until sustained dryness is achieved. The addition of an anticholinergic to desmopressin at the end of this sequence may be cost-effective, but there is some uncertainty about this. A sequence of initial desmopressin may be cost-effective when followed by alarm alone and then by desmopressin or combined desmopressin and anticholinergic, but again, there is considerable uncertainty in the incremental effectiveness. However, in the situation where an alarm is unsuitable, initial treatment with desmopressin with the addition of an anticholinergic if desmopressin alone does not produce a full response is likely to be cost-effective.

1.5.1 Implications for future research

Further research in the areas where there is little to no evidence would be useful to inform future economic evaluations in this area. Assessment of the impact bedwetting and treatment of bedwetting has health-related quality of life among children and possibly their families would be useful for the estimation of QALYs. Research into the effectiveness of interventions by age would be useful to determine what age to initiate treatment and with what intervention. Assumptions had to be made in the absence of this evidence and it is unclear to what degree results might change if this data were available.

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