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ORIGINAL RESEARCH ARTICLE

The Cost Effectiveness of Licensed Oromucosal Midazolam (Buccolam®) for the Treatment of Children Experiencing Acute Epileptic Seizures: An Approach When Trial Evidence is Limited

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Abstract

Background In the UK, two treatment options are used for acute epileptic seizures in the community—rectal diazepam and unlicensed buccal midazolam. In practice, the former is rarely used, with unlicensed buccal midazolam being widely recommended and prescribed by physicians. In September 2011, Buccolam® (licensed midazolam oromucosal solution) became the first medicine to receive a Paediatric-Use Marketing Authorization (PUMA) and it is indicated for the treatment of prolonged, acute, convulsive seizures by caregivers in the community for children (aged 6 months to <18 years) diagnosed with epilepsy. The approval process for a PUMA product differs from other marketing authorization processes and may be based upon small population subsets and may not, in some cases, require new safety or efficacy data to be generated; a similar situation to that seen for orphan drugs. This can lead to challenges when conducting economic evaluations.

Objective The aim of this study was to assess the cost effectiveness of Buccolam® for children with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures occurring in the UK community setting.

Design and Perspective A hybrid model was developed according to a UK payer perspective. The model included a time-to-event simulation for the frequency and location of occurrence of seizures, along with a decision-tree model that assessed the treatment pathway when a seizure occured. The model compared treatment with Buccolam® with standard care in the community (95 % unlicensed buccal midazolam and 5 % rectal diazepam) or either treatment alone. The model was informed by data from a variety of sources, including clinical effectiveness estimates, and costs based on published UK data, using 2012–13 prices, where possible. To determine current practice and real-world effectiveness, a Delphi panel and a survey of parents of children with epilepsy were conducted.

Results Buccolam® showed a reduction in costs of £2,939 compared with standard care, £14,269 compared with rectal diazepam alone and £886 compared with unlicensed buccal midazolam alone. Increases of 0.025, 0.082 and 0.013 quality-adjusted life-years, respectively, were also seen. Buccolam® remained dominant across a range of scenario analyses.

Conclusion This model demonstrates the possibility of constructing a thorough economic case when trial or real-world data are not available. The results of the model show Buccolam® to be cost saving compared with rectal diazepam due to a reduction in the need for ambulance callouts and hospital stays, and compared with unlicensed buccal midazolam, through reduced drug costs and wastage.

Key Points for Decision Makers

- Buccolam® is cost saving from a UK healthcare perspective.
- Treatment with Buccolam® results in fewer seizures requiring an ambulance to be called or the child to be hospitalized compared with either rectal diazepam or unlicensed buccal midazolam.
- For products that have been approved through the PUMA process, economists may need to think about alternative data collection where trial data are not available.

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1 Introduction

Buccolam® (midazolam oromucosal solution) is indicated for the treatment of prolonged, acute, convulsive seizures in children, and it may be administered by parents or carers in a community setting if a child has been diagnosed with epilepsy [1]. It was the first product to receive a Paediatric-Use Marketing Authorization (PUMA), which has a different approval process to other marketing authorizations. The PUMA process was designed to stimulate the development of paediatric-use drugs that are appropriately authorized, while ensuring that children are not subjected to unnecessary clinical trials.

In many disease areas, children are currently treated with medication licensed and formulated for adults and subsequently dose-adjusted for use in a paediatric setting. The PUMA process is designed to address this issue and enable children to receive child-specific, innovative, licensed medications. However, from reimbursement and associated pharmacoeconomic perspectives, the PUMA process presents a challenge. The approval of a medicine can be based on small population subsets and may not, in some cases, require new safety or efficacy data to be generated. This situation mirrors the data limitations seen for orphan drugs, which often require data to be based upon small populations or population subsets.

Convulsive status epilepticus is the most common neurological emergency that occurs in childhood, with an incidence of between 17 and 23 per 100,000 children per year [2], and is associated with epilepsy later in life and cognitive and behavioural impairments [3]. In Europe, 130,000 new cases of epilepsy are diagnosed each year among children and adolescents (an incidence rate of 70 per 100,000) [4]. Incidence is particularly high during the first year of life and the likelihood of developing the condition subsequently decreases during childhood [5].

The primary treatment for children with epilepsy is antiepileptic drug therapy, which is used to prevent seizures [6]. In spite of this treatment, 48 % of patients with epilepsy experience breakthrough seizures, some of whom will require a regular prescription for rescue medication [7]. An established relationship also exists between the length of these breakthrough seizures and subsequent health outcomes for the patient. Longer seizures are associated with an increased risk of subsequent prolonged seizure activity, memory deficits and learning difficulties [8], as well as a greater impact on healthcare resources, should patients require more intensive medical assistance [9–12]. Consequently, prompt treatment with rescue medication is an important aspect of care for children experiencing prolonged, acute, convulsive seizures. However, treatment provides a particular challenge, as prolonged seizures often occur in the community setting, where children will be in their normal daily routine rather than in a healthcare facility.

In the UK community setting, two treatments have traditionally been used for prolonged, acute, convulsive seizures in children—rectal diazepam and unlicensed buccal midazolam. Rectal diazepam, which until recently was the only licensed treatment, is rarely used by parents and carers; this is due, in part, to carer concerns about the route of administration and concerns around loss of dignity during rectal delivery [13–15]. Medications that can be administered by the oromucosal route are more socially acceptable and are preferred to rectal diazepam by patients, parents and non-family carers [14].

As a result, unlicensed buccal midazolam has been widely recommended by physicians; this must be ordered as a 'special' according to the UK regulatory framework. 'Special' products can be defined as "unlicensed medicinal products manufactured for human use which have been specially prepared to meet a prescription ordered for individual patients without the need for the manufacturer to hold a marketing authorization for the medicinal product concerned" [16]. The General Medical Council recommends that an unlicensed medication should only be prescribed when no licensed alternative that would meet the patient's needs is available [17].

To gain approval from the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) to use Buccolam® within its licensed indication in Scotland and Wales, ViroPharma developed submission dossiers that included the demonstration of clinical and economic effectiveness. In constructing the pharmacoeconomic case for these submissions, which required cost–utility analyses, an unintended consequence of the PUMA process became apparent. It was found that there was a paucity of comparative evidence, and the requirement to minimize trials involving children limited the data that was collected to support the assessment of efficacy and real-world effectiveness. Therefore, an alternative approach to data collection was required. This involved a parent/carer survey and elicitation of clinician opinion via a Delphi panel to support the cost–utility modelling. The submissions to the SMC and AWMSG both resulted in the advice to accept Buccolam® for use within its licensed indication in Scotland and Wales, respectively [18, 19].

In this study, we present the economic model populated with the Welsh data assessing the cost effectiveness of Buccolam® for those paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures occurring in the community setting [19]. A comparison with the results obtained in the Scottish model is presented as part of the discussion.

2 Methods

2.1 Overview

A cost–utility model was developed from the perspective of the National Health Service (NHS) in Wales. The model was designed to estimate the clinical outcomes from a prolonged, acute, convulsive seizure occurring in the community setting, and capture the associated resource and health-related quality of life (utility) implications. Clinical experts advised that very young babies would be treated exclusively in a hospital setting with rectal diazepam. In addition, parents and carers can only administer treatment with Buccolam® in the community to those patients who have a diagnosis of epilepsy; therefore, febrile seizures were considered outside of the scope of this evaluation.

Efficacy and effectiveness inputs were derived from the literature and commissioned research projects, including parent/carer and clinician surveys. Costs for events were taken from published reference-cost sources, and utility values were elicited from clinicians. Model outputs were expressed in terms of direct costs in British Pound Sterling, using 2012–13 prices, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs).

The analysis was designed to address UK cost-effectiveness requirements, accounting for only direct resource usage. Implications from a broader societal perspective, such as carer utility, were excluded from the analysis. The model had a 6-year time horizon because this is the shortest period in which the shelf life of Buccolam® (18 months) and that of unlicensed buccal midazolam (2 years) coincide; this allowed a comparison of the wastage costs of the two treatment pathways. Extending the time horizon further would have no effect on the ICER because mortality is assumed to be the same for all treatments and therefore was not included in the model. A 1-year time horizon is also presented to allow analysis of short-term impacts. Costs and health benefits were discounted at an annual rate of 3.5 %. The model structure and assumptions were validated with UK clinicians who took part in the Delphi panel process and those advising on the submission.

2.2 Model Structure

The model compared treatment with Buccolam® with standard care (unlicensed buccal midazolam, the treatment most often used in Wales, or rectal diazepam) and with each medication separately. Clinical experts emphasized that treatment with unlicensed buccal midazolam results in a large amount of drug wastage, which substantially increases the overall acquisition cost [11]. This wastage is caused by buccal midazolam being supplied in bottles containing multiple doses. Each patient requires multiple bottles to have access to the medication in numerous locations. As a result, much of the medication is not used before the end of its shelf life. In order to fully capture the costs associated with the different treatments, an estimation of drug wastage was necessary.

The model, therefore, had two components: a discrete-event simulation that estimated the frequency and location of occurrence of prolonged seizures and a decision tree that assessed the treatment pathway when a child had a seizure. By estimating the frequency and location of prolonged seizures the discrete-event simulation enabled the estimation of both drug wastage and the probability that rescue medication was not present when a seizure occurred. The decision tree enabled the costs and health consequences following a prolonged seizure to be estimated.

Figure 1 shows the decision tree constructed for this analysis. This was repeated each time a child experienced a prolonged seizure and had the following key chance nodes:

- Whether medicine was available for parents or caregivers to administer.
- If treatment was attempted by the parent or caregiver and whether it was successfully administered.
- If treatment was given, whether the seizure lasted less or more than 10 min.
- Whether the care plan recommended giving a second dose in the community setting when the seizure lasted more than 10 min.
- If the seizure lasted less than 10 min, whether the child had a repeat seizure.
- If an ambulance was called:
  - whether the ambulance staff were able to administer treatment;
  - whether the patient was taken to hospital and, if so, whether the patient was then admitted as an inpatient;
  - if the patient was admitted as an inpatient, whether the patient was then admitted to an intensive care unit/high-dependency unit.

The discrete-event simulation model determined the frequency of seizures and drug wastage for unlicensed buccal midazolam compared with Buccolam®, using the results of the survey of parents of children with epilepsy. Figure 2 shows the simulation model structure and the inputs used. The model simulated 5,000 patients for each treatment to minimize stochastic error and to provide an appropriate level of certainty in the ICER. For each of the 5,000 patients in the simulation, the frequency, location of seizures and the initial store of drugs at each location were simulated at the start of the model. The availability of treatments at each location was then adjusted by the occurrence of seizures within the model

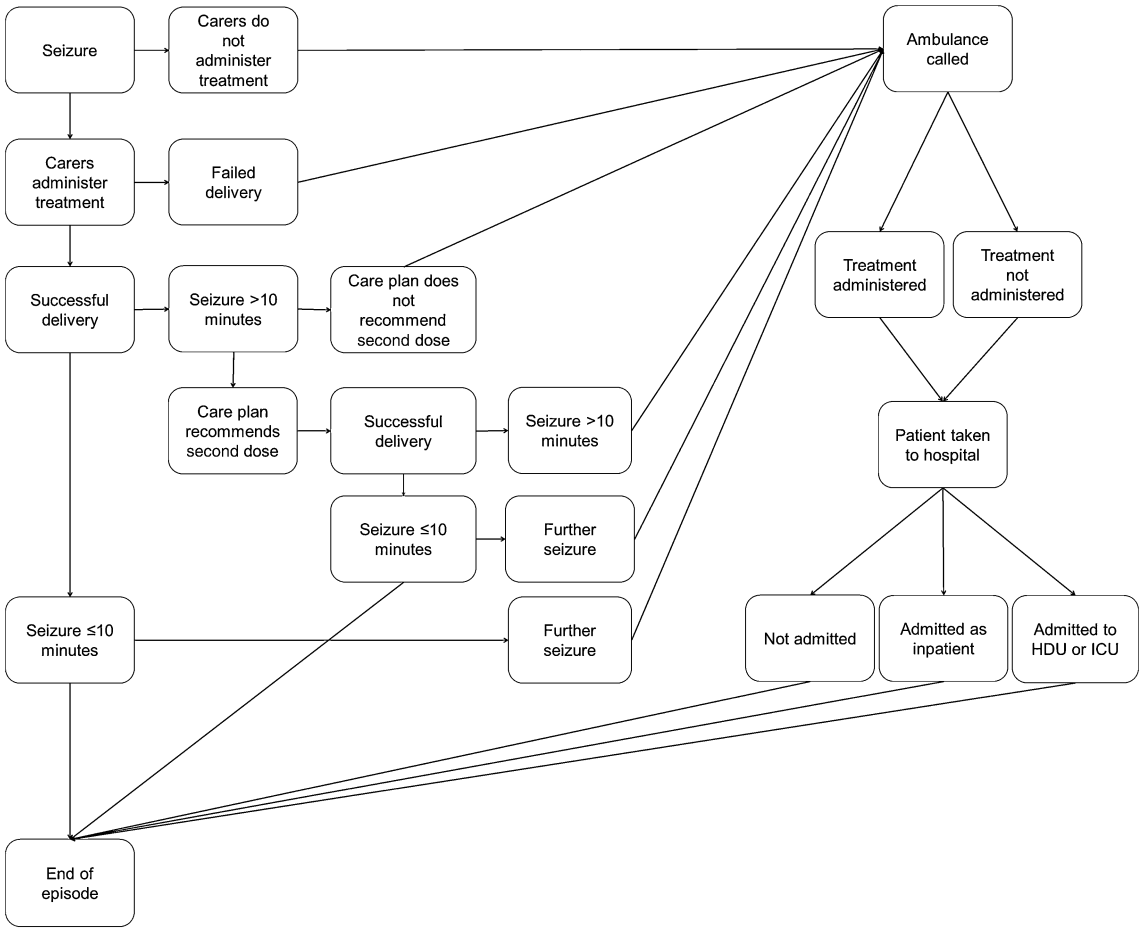

Fig. 1 Decision-Tree Model Structure. The decision-tree model assessed the treatment pathway when a child had a seizure and was repeated each time a child experienced a prolonged seizure. *HDU* high-dependency unit, *ICU* intensive care unit

time horizon. In each location, when a seizure occurred, the model then checked whether medication was available. If it was available, one dose was used for the seizure; if medication was not available, then the carer was unable to administer treatment.

To account for wastage, if the model had reached the time at which drugs were disposed of due to product expiry, the value of the disposed products were calculated and new products were ordered as replacements. If, however, all the medication in one location was used, new products were reordered and for simplicity it was assumed that there would be no wastage at this location throughout the duration of the model. The wastage from each simulation was collated to provide average wastage over the model time horizon.

2.3 Efficacy Data

The economic model used efficacy data for buccal midazolam and rectal diazepam, relating to the duration of seizures, the probability of seizure cessation and the occurrence of further seizures upon receipt of rescue therapy. These data were taken from the clinical trial reported by McIntyre et al. [20], which was the only published pseudo-randomized, controlled trial with the correct comparators, conducted in a European context and with a large number of patients (see Table 1). The other data available were from trials that were either small, such as the one conducted by Scott et al. [10], or situated in a context that is significantly different to Wales, such as the trial by Mpimbaza et al. [21], which was performed in Uganda. The meta-analysis by McMullan et al. [22] was not used because the results were significantly affected by the inclusion of the Mpimbaza et al. trial. Assumptions around the relative efficacy of Buccolam® compared with rectal diazepam were varied in a scenario analysis.

2.4 Collection of Effectiveness Data

There is a paucity of published data describing the frequency of seizures and the outcomes of prolonged seizures. Therefore, it was necessary to conduct two data-collecting

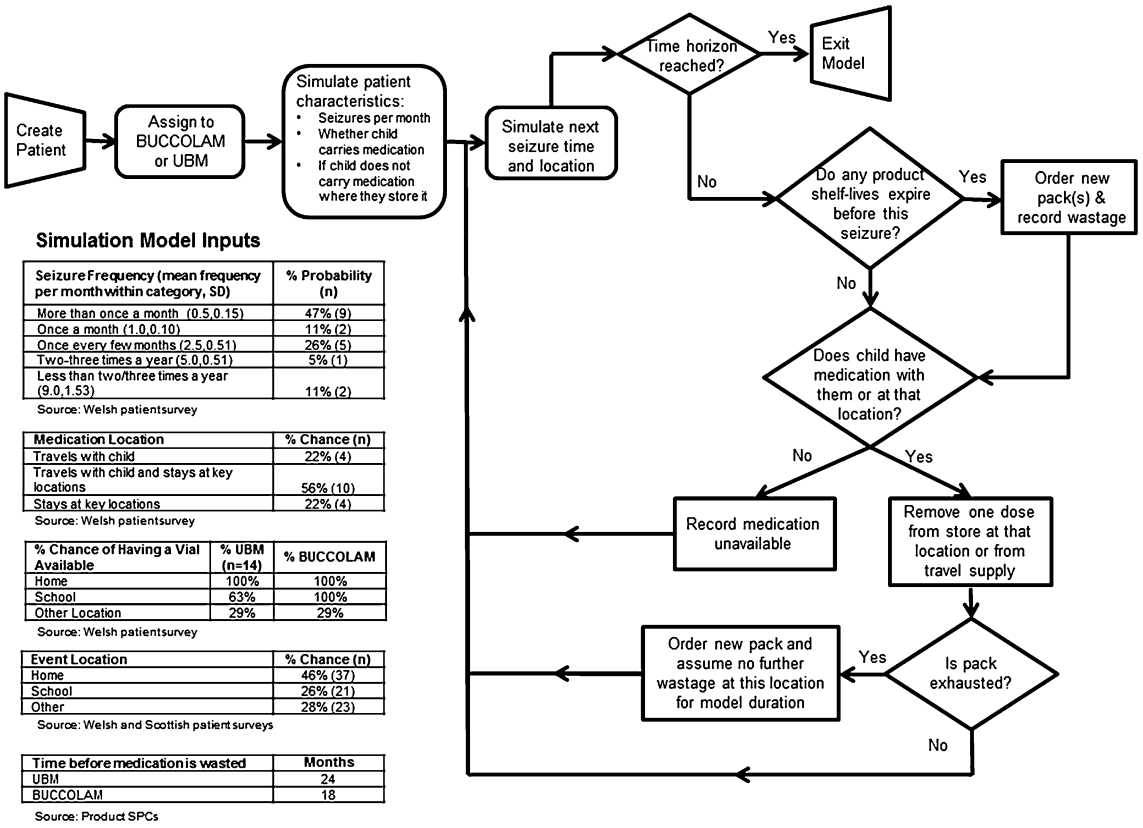

Fig. 2 Simulation Model Structure. The discrete-event model estimated the frequency and location of prolonged seizures. This information was used to estimate drug wastage and the probability that rescue medication was not present when a seizure occurred. *SD* standard deviation, *UBM* unlicensed buccal midazolam

exercises to help inform and populate the economic model: a survey of parents of children with epilepsy and a Delphi panel audit of clinicians [13, 23].

The survey of parents of children with epilepsy was performed in conjunction with Epilepsy Wales and Epilepsy Action Cymru to elicit data on the frequency, location of occurrence and average length of seizures as well as other descriptive aspects of epilepsy. The survey consisted of 31 questions and was open to anyone with children aged between 3 months and 18 years, with a diagnosis of epilepsy and experiencing convulsive seizures with durations of more than 5 min. Nineteen responses were collected anonymously and used solely in the simulation of the treatment of seizures. A similar survey was conducted in Scotland, which received 43 responses; results from this survey were consistent with the results of the survey conducted in Wales and were used to supplement the Welsh results in the simulation of seizure locations.

A modified Delphi process was performed to elicit data from 5 clinical experts. The Delphi survey was designed to take place in two sequential stages: (i) a questionnaire was mailed electronically to each expert for completion; and (ii) a panel meeting was held. The responses to the Round 1 questionnaire were collated and presented to the experts before the meeting to enable them to review the group's responses. The panel meeting was used to review the responses to the questions for which consensus had been achieved and to try to establish consensus where there had been a divergence of opinion in Round 1. The experts involved covered a range of geographical areas in Wales and included a consultant paediatric neurologist, clinical nurse specialist working in epilepsy, senior university lecturer in clinical neurology, consultant in emergency medicine and lead pharmacist in neurosciences. The results of the Delphi process informed the probabilities used within the effectiveness analysis, the choice of comparators and the assumptions behind wastage within the model.

Despite the limited trial and disease history data originally available, this additional primary data collection allowed the construction of a cost–utility model with appropriate data. Table 1 includes the data used within the model as well as the sources of these data.

Using data from the survey of parents of children with epilepsy, the patient simulation estimated that carers would more frequently be unable to treat patients if they were using unlicensed buccal midazolam rather than Buccolam®. Additionally, the survey results indicated that parents often have one or two bottles of unlicensed buccal midazolam.

Table 1 Model parameters

Parameter	Buccolam®	UBM	Rectal diazepam[a]	References
Transition probabilities				
Carer cannot administer treatment	5 %	6 %	5 %	Patient survey [23]
Failed delivery resulting in ambulance callout	3.5 %	4 %	5 %	Delphi survey [13]
Probability of seizure >10 min	35 %	35 %	59 %	McIntyre et al. [20]—most representative of UK population
Probability of further seizure	14 %	14 %	33 %	
Admitted as inpatient				
Following ambulance callout (single seizure)	10 %	10 %	10 %	Delphi survey [13]
Following ambulance callout (multiple seizure)	100 %	100 %	100 %	Delphi survey [13]
Admitted to ICU following admission as inpatient	2 %	2 %	2 %	Delphi survey [13]
Utilities				
Baseline utility for 1 cycle (30 days)[b]	0.0583	0.0583	0.0583	Delphi survey [13]
Disutility over 1 cycle—seizure no ambulance	−0.0003	−0.0003	−0.0003	
Disutility over 1 cycle if seizure >10 min or repeated but not admitted	−0.0014	−0.0014	−0.0014	
Disutility over 1 cycle if seizure >10 min or repeated, admitted	−0.0044	−0.0044	−0.0044	
Disutility over 1 cycle if seizure >10 min or repeated, ICU	−0.0057	−0.0057	−0.0057	
Costs				
Drug	£87.00 per pack	£82.38 per bottle + £20 sourcing fee per prescription	£1.81	British National Formulary [26]; NHS [25]
Average ambulance cost per incident—applied once when an ambulance is called	£229.61			NHS Reference Costs [27]
A&E cost if admitted as an inpatient—applied once when an ambulance is called and the patient is admitted	£114.01			NHS Reference Costs [27]
A&E cost if not admitted as an inpatient—applied once when an ambulance is called and the patient is not admitted	£91.47			
Admitted as inpatient: weighted average 'cost of non-elective inpatient cost if no CC and with CC'	£548.61			
ICU or HDU: weighted average cost	£1,269.78			

[a] At the time of developing the model, ambulance staff in Wales were only allowed to administer rectal diazepam

[b] A baseline utility of 0.0583 over 30 days is equivalent to a utility 0.71 over 1 year; i.e. 71 % of full health

A&E accident and emergency, *CC* complications and comorbidities, *HDU* high-dependency unit, *ICU* intensive care unit, *NHS* National Health Service, *UBM* unlicensed buccal midazolam

Each bottle contains 4 doses; however, due to the product presentation, the multiple doses within each bottle cannot be split between different locations. In contrast, Buccolam® is provided in packages of 4 pre-filled syringes enabling medication to be stored at multiple locations. Therefore, if Buccolam® is prescribed, it would be more likely that rescue medication is stored at the location of the seizure.

The patient simulation estimated that unsuccessful treatment delivery by carers would be more frequent with unlicensed buccal midazolam than Buccolam®. The Delphi panel findings supported this result. For the Delphi questionnaire, failed delivery was defined as either delay in preparation, a delay in administration or an incorrect dosage that resulted in an ambulance needing to be called out [13]. Clinicians estimated that failed delivery and ambulance callout would occur more often with unlicensed buccal midazolam, which requires the correct dose to be drawn up into a syringe at the time of seizure. Administration of Buccolam® is likely to be easier and the dosing more likely to be correct because it is presented in pre-filled syringes, which contain the correct dose. In addition, the clinicians estimated that failed delivery would also occur more frequently with rectal diazepam compared with oromucosally administered Buccolam®—rectal treatment

delivery can be compromised by fecal incontinence, which can be associated with a seizure [15].

Data collected from clinicians and parents in Wales indicated that 5 % of patients were treated with rectal diazepam and 95 % were treated with unlicensed buccal midazolam in a community setting [13, 23]. This has, therefore, been defined as standard care for Wales. In the hospital setting, 32 % of patients received rectal diazepam administered by paramedics and 68 % received unlicensed buccal midazolam [24]. In the base case, patients were allocated to the standard care treatment pathway.

2.5 Costs

Costs were taken from published sources and have been updated since the submission to the AWMSG to use the most recent tariff (see Table 1). The updated cost of unlicensed buccal midazolam in England and Wales was £82.38 per bottle, with a £20 sourcing fee per prescription for ordering a special [25], each bottle containing 4 doses according to manufacturer instructions (cost per dose of £25.60 when one bottle is ordered per prescription and £23.10 when two bottles are ordered). Buccolam® was less expensive, with an average cost of £87.00 for four syringes (£21.75 per dose), while the cost of rectal diazepam was approximately £1.81 per dose [26].

The cost of hospitalizations and ambulance callouts was obtained from NHS reference costs for 2011–12 [27].

2.6 Quality of Life

None of the clinical trials, including the one published by McIntyre et al. [20], captured quality of life data. In part, this is likely due to the short, intense nature of the event, which means that it is not feasible to capture responses from the patient during a seizure. Therefore, an alternative approach was necessary to quantify the quality of life implications of seizures, as required for submissions to the AWMSG and SMC.

As an exploratory analysis, indicative utilities were taken from a EuroQoL five-dimensions (EQ-5D) survey of clinicians in Wales who were asked to value the health states on behalf of patients [13]. Clinicians were asked to estimate the quality of life of patients both during, and shortly after a seizure. The clinicians estimated that, in addition to having epilepsy, approximately 20 % of patients are cognitively impaired; these patients would have a lower baseline health-related quality of life. For this reason, clinicians estimated the utility decrements resulting from seizures of different levels of severity for cognitively impaired patients also. The resulting utility values used within the model can be found in Table 1.

2.7 Sensitivity Analyses

To test the data inputs, a range of deterministic sensitivity analyses was carried out by varying key inputs and assumptions. One-way sensitivity analyses were performed by varying each parameter within its likely range. Where possible, the 95 % confidence intervals of the parameter distributions were used to construct the lower and upper bounds. For the parameters for which it was not possible to calculate confidence intervals the lower and upper bounds were constructed by varying the parameters by ±30 %.

To construct the model with the data available, a number of assumptions were necessary. Scenario analyses were undertaken to determine the sensitivity of the results to the key assumptions. The assumptions and the scenario analyses are shown in Table 2, which also outlines a threshold analysis that was undertaken. To test the sensitivity of the model to the price of Buccolam®, the price of a pack of 4 pre-filled syringes was increased, using threshold analysis, until treatment with Buccolam® was no longer cost saving.

A probabilistic sensitivity analysis (PSA) was performed in which parameters were assigned a probability distribution and were varied simultaneously. The analysis was run 10,000 times, using a Monte Carlo simulation method.

3 Results

Base case estimates for the model results are shown in Table 3. Over the 6-year time horizon, compared with standard care, treatment with Buccolam® resulted in a cost reduction of £2,939 and an increase in health-related quality of life by 0.025 QALYs. When compared with rectal diazepam treatment alone, the only licensed comparator, treatment with Buccolam® resulted in a cost reduction of £14,269 and an improvement of 0.082 QALYs. When compared with unlicensed buccal midazolam treatment alone, treatment with Buccolam® resulted in a cost reduction of £886 and an improvement of 0.013 QALYs (see Table 3).

Threshold analysis showed that for Buccolam® to no longer be cost saving compared with standard care, the price of Buccolam® would need to be £227 (for 4 syringes), considerably higher than the average cost of £87. Figure 3 illustrates the one-way sensitivity analysis undertaken using the model. There are no parameters for which variation has the potential to result in treatment with Buccolam® not being cost saving compared with standard care, and Buccolam® remained dominant in all 4 of the scenario analyses. Changing the assumption concerning the efficacy of Buccolam® and unlicensed buccal midazolam relative to rectal diazepam to non-inferior had the most negative effect on the cost effectiveness of Buccolam®.

Table 2 Scenario and threshold analyses

Scenario	Assumption to be varied	Alternative assumption explored in scenario analyses
Scenario Analyses		
1	Unlicensed buccal midazolam is kept for 24 months in all locations. Buccolam® has a shelf life of 18 months	Unlicensed buccal midazolam has a shelf life of 3 months when opened in all locations
2	Each bottle of unlicensed buccal midazolam contains only 4 doses (syringes are not re-used)	Each bottle contains 6 doses as syringes are re-used
3	Only one bottle of unlicensed buccal midazolam is ordered per prescription	Two bottles are assumed to be ordered per prescription
4	Buccolam® and unlicensed buccal midazolam are more efficacious than rectal diazepam, as supported by the data in McIntyre et al. [20]	In line with recommendations from European regulatory agencies, the efficacy of Buccolam® and unlicensed buccal midazolam is considered non-inferior rather than superior to rectal diazepam
Threshold Analysis		
Base case:		**Variation:**
Price for a pack of 4 pre-filled syringes of Buccolam® is £87 [26]		Cost of a pack of 4 syringes increased until Buccolam® is no longer cost saving

However, even in this scenario, treatment with Buccolam® resulted in an expected saving of approximately £326 over 6 years due to reduced wastage and ambulance costs. The results of the scenario analyses can be seen in Table 4.

Figure 4 shows the results of the probabilistic sensitivity analysis comparing Buccolam® with standard care. For the substantial majority of iterations, the results indicate that treatment with Buccolam® is both cost saving and has an incremental QALY gain. Treatment with Buccolam® is cost saving in 99 % of iterations. Buccolam® was cost effective at the thresholds of £20,000 and £30,000 per QALY in 100 % of iterations.

4 Discussion

These economic analyses suggest that treatment with Buccolam® is cost saving compared with standard care. In Wales, these savings are largely the result of reductions in drug acquisition, ambulance and inpatient admission costs. The reduction in drug acquisition costs is the result of the lower price of Buccolam® compared with the tariff rate for buccal midazolam as an unlicensed 'special' and decreased drug wastage. The reduction in ambulance costs is the result of an increase in successful administrations compared with unlicensed buccal midazolam (due to its supply in pre-filled syringes) and rectal diazepam (due to the mode of administration). Clinicians predicted that it would be easier for carers to administer Buccolam® in the community setting because (i) packs would be split and individual doses would be stored in more locations; and (ii) the delivery mechanism would reduce the likelihood of treatment failure. The reduction in inpatient admission costs is primarily achieved through a decrease of repeat seizures, which result in ambulance callouts and subsequent hospital admissions, compared with treatment with rectal diazepam.

The analysis for Scotland followed a similar methodology. Data were collected through a modified Delphi approach and a survey completed by parents/carers of children with epilepsy. The cost-effectiveness model incorporated in the SMC submission had a very similar structure to the Welsh model combining a discrete-event simulation and a decision tree. However, it was populated by the results of the Scottish data collection exercises. Similar to the clinicians in Wales, those in Scotland estimated real-world effectiveness advantages for Buccolam® compared with both rectal diazepam and unlicensed buccal midazolam. Accordingly, the analysis carried out for Scotland reached similar conclusions, indicating a cost saving with Buccolam® of £2,046 compared with unlicensed buccal midazolam (£341 over a 1-year time horizon) and a cost saving of £8,516 compared with rectal diazepam (£1,512 over a 1-year time horizon) [18]. Differences between the Welsh and Scottish results are driven by increased drug costs for the unlicensed comparator off-tariff and decreased hospitalization and ambulance reference costs.

Prevention of hospital admission through the prompt use of Buccolam® could help to prevent further seizures and the onset of status epilepticus. Depending on healthcare and societal factors, this could lower the costs associated with status epilepticus. Unfortunately, no comprehensive data on the costs of status epilepticus in children and adolescents are available and only limited data are available in adults. A recent population-based study in adults showed that 24.4 % of epilepsy-associated hospital costs in Germany are due to status epilepticus, with a mean

Table 3 Base case results—discounted

	Buccolam®		Standard care		Patients treated only with RD		Patients treated only with UBM		Incremental Buccolam® vs standard care		Incremental Buccolam® vs RD		Incremental Buccolam® vs UBM	
	1 Year	6 Year	1 Year	6 Year	1 Year	6 Year	1 Year	6 Year	1 Year	6 Year	1 Year	6 Year	1 Year	6 Year
Drug costs	£320	£1,823	£345	£2,068	£29	£161	£390	£2,332	−£25	−£245	£291	£1,661	−£70	−£509
Ambulance costs	£1,348	£7,618	£1,429	£8,080	£2,217	£12,531	£1,388	£7,846	−£82	−£462	−£869	−£4,913	−£40	−£228
A&E treatment costs non-admitted	£325	£1,839	£301	£1,703	£421	£2,381	£340	£1,921	£24	£136	−£96	−£542	−£14	−£82
Inpatient admission costs	£1,502	£8,489	£1,903	£10,759	£3,279	£18,536	£1,513	£8,554	−£402	−£2,270	−£1,777	−£10,047	−£11	−£65
ICU or HDU admission costs	£64	£362	£81	£459	£140	£790	£64	£365	−£17	−£97	−£76	−£428	£0	−£3
Total costs	**£3,559**	**£20,130**	**£4,060**	**£23,070**	**£6,086**	**£34,399**	**£3,696**	**£21,016**	**−£501**	**−£2,939**	**−£2,527**	**−£14,269**	**−£137**	**−£886**
QALYs	**0.685**	**3.763**	**0.680**	**3.738**	**0.670**	**3.681**	**0.682**	**3.749**	**0.004**	**0.025**	**0.014**	**0.082**	**0.002**	**0.013**

A&E accident and emergency, *HDU* high-dependency unit, *ICU* intensive care unit, *QALYs* quality-adjusted life-years, *RD* rectal diazepam, *UBM* unlicensed buccal midazolam

hospitalization cost of €8,347 ± €10,773 per patient [28]. The potential cost savings are not considered in the current model but, if included, could further increase the cost savings achieved with Buccolam®.

Broadening the model to include a societal perspective would further enhance the benefit associated with treatment with Buccolam®. If parent/carer utility was included in the analysis, then the incremental improvement seen as a result of treatment with Buccolam® would increase due to the expected reduction in more severe seizures (seizures lasting longer than 10 min and/or requiring hospital treatment), which would likely lead to reduced parental/carer anxiety.

Conventional data to support the pharmacoeconomic value of Buccolam® were scarce. In part, this was a result of the reduced requirement for new data in the PUMA process, but it was also due to the nature of the condition being treated. In addition, as noted by Strzelczyk et al. [28], the costs incurred by status epilepticus are often neglected in costing studies. The aim of treatment with rescue medications is for parents and carers to treat the child in the community setting and elicit a faster response, which mitigates complications and reduces the need for ambulance callouts. Because of the setting of the event, it would be extremely challenging to study this intervention in a clinical trial or observational study. Accurately recording the number of seizures occurring in the community, their duration and whether an ambulance was required would be difficult to carry out prospectively in an unbiased manner.

As a result, alternative methods were needed to capture, as accurately as possible, the relative effectiveness of Buccolam® compared with unlicensed buccal midazolam and rectal diazepam. It was necessary to collect data retrospectively and use a Delphi process to determine a consensus from clinicians.

While the best efforts were made to obtain data from other sources, we recognize that there are limitations to these. Most notably these relate to the adapted nature of the Delphi panel process, the number of parents/carers responding to the survey and effectiveness data being taken from a single trial in which the patients were aged 3 years or older.

In addition, the valuation of acute health states is difficult, particularly in the case of epilepsy. First, at the time of the event, patients are not able to complete questionnaires, nor is it thought ethically appropriate for patients to be surveyed during their recovery. Second, many patients included in the economic evaluation are young children under the age at which standard tools can be applied; for instance, the EQ-5D-Y, the youth version of the EQ-5D, is intended for children aged 5–12 years. Although utilization of parent proxy surveys would be preferable, in this instance it was felt that clinician surveys would provide sufficient information to estimate utilities for the purposes of this exploratory analysis.

While there seems unanimous consensus among clinicians that treatment with Buccolam® would result in an improvement in the quality of life of patients [13], little evidence is available to quantify this due to current limitations in methodologies, and further research is therefore required. Existing quality of life instruments are unsuitable for valuing acute seizures, which makes the quantification of quality of life benefits difficult. In addition, having clinicians, rather than patients or parents/carers, complete the questionnaires is not optimal, as this method can be prone to bias. Given that the available evidence suggests that treatment with Buccolam® is cost saving, these factors have minimal impact on the economic decision; however, the difficulty in obtaining robust utility data should be considered in future research.

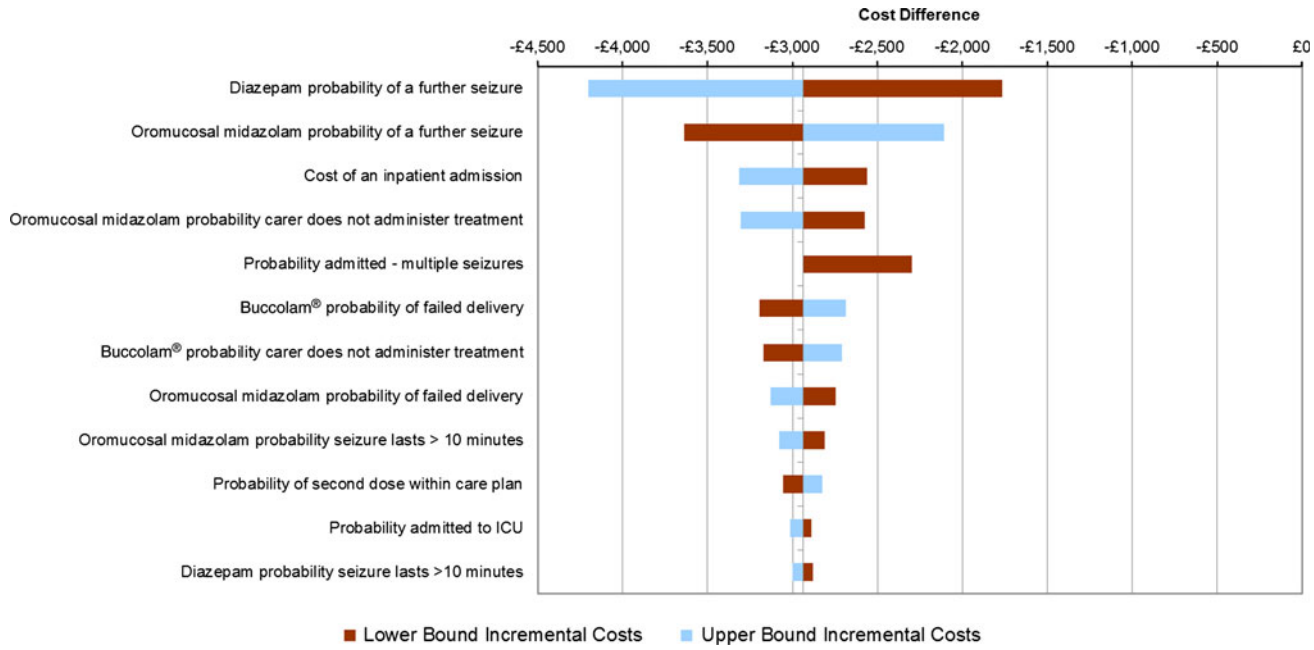

Fig. 3 Tornado Diagram Presenting Key Model Drivers. The tornado diagram presents the cost difference per patient associated with introducing Buccolam® when each of the model parameters is varied within reasonable limits. *ICU* intensive care unit (includes both intensive care unit and high-dependency unit)

In spite of the challenges, the methods used were deemed sufficiently rigorous to support health technology assessment submissions to the AWMSG [19], as outlined above, and, using a similar approach, to the SMC [18]. Both agencies have subsequently issued advice, approving Buccolam® for use within its licensed indication.

The model is based on UK costs and treatment patterns; however, the results are likely to be relevant to countries with a similar healthcare system and societal values. In particular, the comparison with rectal diazepam might be easily applied to other Western countries. Research on societal attitudes to rectal treatment would need to be conducted to generalize further. Subsequent research and economic models have been developed for different European healthcare systems; these have broadly used the approach outlined above, with adaptions to account for variation of treatment practices and medication costs. In the models developed so far, Buccolam® has remained dominant over comparator treatments as a result of the reduction in seizures lasting longer than 10 min, and the associated health and cost outcomes.

Table 4 Scenario results—discounted

Treatment strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Scenario 1: Unlicensed buccal midazolam shelf life 3 months when opened instead of 24 months					
Buccolam®	£20,126	3.763	−£4,547	0.025	Dominant
Standard care	£24,673	3.738			
Scenario 2: Each bottle contains six doses as syringes are re-used instead of 4 doses					
Buccolam®	£20,137	3.763	−£2,336	0.025	Dominant
Standard care	£22,473	3.738			
Scenario 3: Two bottles are assumed to be ordered per prescription instead of one					
Buccolam®	£20,130	3.763	−£2,753	0.025	Dominant
Standard care	£22,884	3.738			
Scenario 4: In line with recommendations from European regulatory agencies, the efficacy of Buccolam® and unlicensed buccal midazolam is considered non-inferior rather than superior to rectal diazepam					
Buccolam®	£36,038	3.731	−£326	0.050	Dominant
Standard care	£36,364	3.681			

ICER incremental cost-effectiveness ratio, *QALYs* quality-adjusted life years

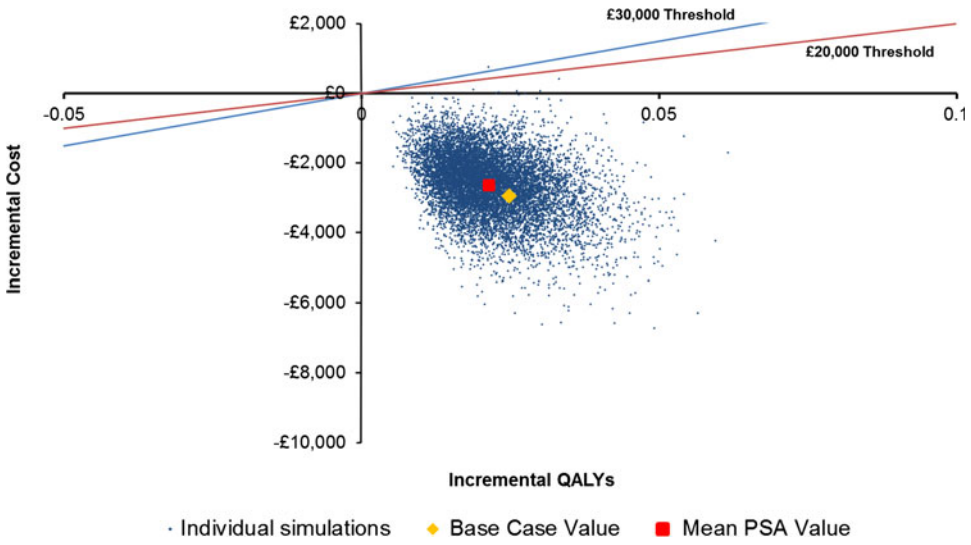

Fig. 4 Cost-effectiveness acceptability plane. The cost-effectiveness acceptability plane presents the difference in costs and quality-adjusted life-years with the introduction of Buccolam® sampling each model parameter within its distribution. Points in the south-east quadrant indicate that Buccolam® is cost saving and improves quality of life. Points in the north-east quadrant indicate that Buccolam® costs more and improves quality of life. *PSA* probabilistic sensitivity analysis

5 Conclusions

This example shows that it is possible to assemble a thorough economic case even when inputs to the decision are not available from trials or real-world data. An alternative approach to data collection combined with a cost-effectiveness model supported the pharmacoeconomic case for Buccolam®, giving patients with high unmet need access to this new treatment.

Sensitivity analysis shows that the model results for the cost effectiveness of treatment with Buccolam® are robust. Treatment with Buccolam® remains dominant (cost saving, with improved quality of life) in all scenario analyses performed.

As PUMA authorizations become more frequent, more medications will be authorized for children where there is frequently high unmet need. As a result of the new review process, pharmacoeconomic practitioners may need to use additional data gathering instruments and techniques, as adopted in this study, to demonstrate the value of these treatments.

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