HEALTH ECONOMICS ANALYSIS PLAN

Estimation of the Cost and Cost-Effectiveness of Carbamazepine for Metaphyseal Chondrodysplasia type Schmid (MCDS)

Analysis plan v1.0

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Abbreviations

BIA	Budget Impact Analysis
CEAC	Cost Effectiveness Acceptability Curve
CUA	Cost Utility Analysis
DCE	Discrete Choice Experiment
ER	Endoplasmic reticulum
EQ-5D-Y	EuroQol Five Dimension Youth
HEAP	Health Economics Analysis Plan
HRQoL	Health-related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
MCDS	Metaphyseal Chondrodysplasia type Schmid
MI	Multiple Imputation
NICE	National Institute of Health and Care Excellence
NHS	National Health Service
NMB	Net Monetary Benefit
PedsQL	Paediatric Quality of Life Inventory
QoL	Quality of Life
PSA	Probabilistic Sensitivity Analysis
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality Adjusted Life Years
SD	Standard Deviation
STM	State Transition Markov Model
WP	Work Package
WTP	Willingness to Pay
UK	United Kingdom

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Summary of the economic evaluation analysis plan

The aim of this part of the MCDS study is to evaluate the cost and cost-effectiveness of carbamazepine for patients with Metaphyseal Chondrodysplasia type Schmid (MCDS). To do this a cost-effectiveness and budget impact model will be developed.

The model used in this analysis will be based primarily on the MCDS trial (Formally entitled: *Repurposing of Carbamazepine for the treatment of skeletal dysplasia*), clinical pathway based on clinician input, and relevant data from the literature. The model will address the questions: ***"Is introducing carbamazepine cost-effective compared to surgical and pain management alone for the treatment of MCDS?"*** and, ***"What is the net budget impact of adopting carbamazepine for the management of MCDS?"*** over a 5-year timeframe.

Data for this analysis will come from multiple sources including the MCDS Trial, the literature, and a cohort preference elicitation exercise that also runs concurrently with the trial. The analysis of quality-of-life questionnaires (EQ-5D-Y scores) and use of health services completed by participants taking part in the trial will be utilised. Cost values will be based on National Health Service (NHS) and Personal Social Services (PSS) perspective (converted to Euros for other jurisdictions). The model will provide estimates of costs of treatment over a patient's lifetime, information of lifetime costs and QALYs will be brought together in an incremental analysis that compares the strategy of using carbamazepine versus current practice/standard care. Here the extra cost of the carbamazepine strategy compared to standard care will be estimated as is any extra QALYs that will be produced. These are brought together to provide the incremental cost per QALY gained (a measure often called an incremental cost effectiveness ratio or ICER). To address other forms of uncertainty such as conflicting opinions and how large an impact a particular event has on quality of life a technique called deterministic sensitivity analysis will be used. To reflect statistical imprecision a technique called probabilistic sensitivity analysis (PSA) will be used.

The second work package will involve conducting a Budget Impact Analysis (BIA). This is a forecast of rates of use (or change in rates of use) with their consequent short and medium-term effects on budgets to help health service managers plan changes that result from the introduction of a new technology. To do this, the analytical framework must be determined. The most important components to understand for a jurisdiction when constructing a BIA are the eligible population, the potential use of the technology in the care pathway, and the budget holder cost perspective and time horizon.

BACKGROUND

Metaphyseal Chondrodysplasia Schmid Type (MCDS)

Metaphyseal chondrodysplasia type Schmid (MCDS) is a rare autosomal dominant skeletal dysplasia affecting <1/100,000 of the population. It can affect both male and females. It is a very rare form of short-limbed dwarfism that is characterised by disproportionate short stature and long bone deformities.

The knowledge of this rare disease is based upon clinical expertise and the literature (i.e., case reports of affected patients). Patients usually present after age 2 years with short stature, waddling gait and varus or valgus deformity of the knees. The greatest disability stems from the tendency to develop hip (coxa vara) and knee deformity, which causes **chronic pain and the need of long-term analgesia**.

Even though there is no evidence of decreasing life expectancy, MCDS is a condition that has a debilitating effect on the patient's whole life, as it limits normal everyday activities. The available data in the literature suggest that height deficit usually exceed three standard deviations (-3SD) below the normal average, and it can be very variable with a reported range form -7SD to -3.6SD, in a single case height was at -1.2 SD. (1, 2) Adult height varies between 135 and 160 cm.

MCDS is caused by heterozygous mutations in the *COL10A1* gene. (3, 4) Collagens are structural proteins of connective tissues (i.e. bone, tendons, cartilage), and collagen type X is produced in the cartilage by chondrocytes in the hypertrophic stage. (5)

Carbamazepine in MCDS

Type X collagen, a protein encoded by *COL10A1* and expressed exclusively by hypertrophic chondrocytes in the cartilage growth plate of growing bones (6). Mutations in *COL10A1* cause the autosomal dominant skeletal dysplasia in MCDS (3, 4). Mutant type X collagen molecules miss-fold during protein synthesis and increase the endoplasmic reticulum (ER) stress in hypertrophic chondrocytes. The occurrence of increased ER-stress ultimately results in a significant reduction in bone growth, with associated severe skeletal abnormalities.

Pharmacologically targeting, using carbamazepine (CBZ), the misfolding of mutant type X collagen and/or the resulting ER stress is an attractive therapeutic avenue for MCDS. CBZ is routinely used in paediatric care for the treatment of epilepsy and neuropathic pain. It has a well-known safety profile.

MCDS Therapy Trial

This is a two-stage open label phase I/II trial (Figure 1). The aim of the MCDS therapy trial is to evaluate the effect of carbamazepine on patients with a diagnosis of MCDS with confirmed *COL10A1* pathogenic mutation. There is currently no specific treatment for patients with MCDS, and patient care is based only on the management of symptoms. CBZ effects on patients with MCDS have never been investigated.

The MCDS trial will evaluate the effect of CBZ on growth and bone alignment. The trial plan to recruit 40 participants who have not yet reached bone maturity. The trial is divided into a

first dose finding stage and a second treatment stage. Baseline data will be collected in the first year of the trial on all patients before starting administration of CBZ to allow comparison of pre and post treatment characteristics in everyone.

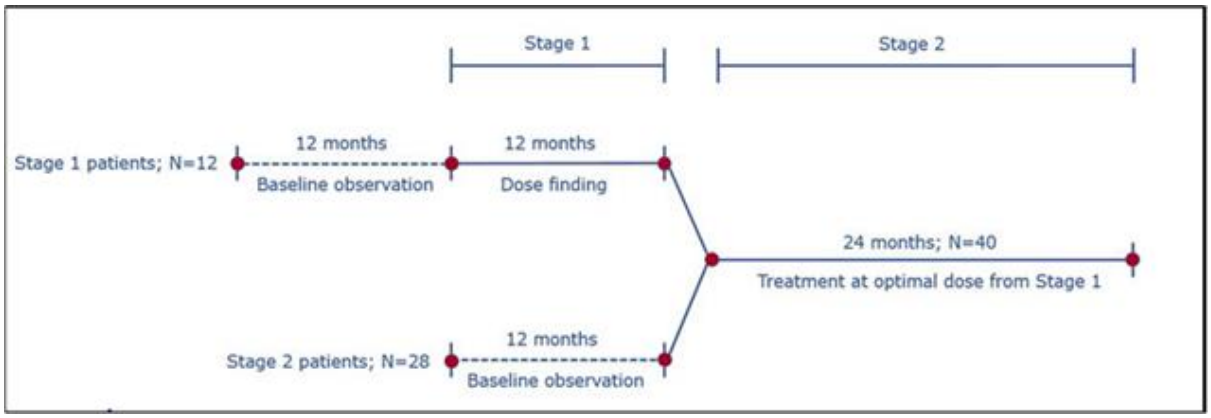

Figure 1: Overview of MCDS Therapy Clinical Trial

For the Health Economics Analysis Plan (HEAP), we will utilise data from the treatment stage of the trial, which seeks to:

- evaluate the efficacy of CBZ for the treatment of children with MCDS who are walking but have not yet reached skeletal maturity/open epiphyses (i.e., height in patients; pain perception as measured by Paediatric Quality of Life Inventory (PedsQL) Pediatric Pain Questionnaire (a specific module of PedsQL); health related quality of life as measured by PedsQL and EQ-5D-Y

Questionnaires and assessments are carried out every 3 months for 2 years in the MCDS trial.

The costs to the NHS will depend on the use of NHS services. They will then receive the intervention and consequent appointments related to that, as well as unscheduled visits to NHS providers (in acute or primary care) which may or may not be related to the condition of interest in this study (MCDS). All costs required for the economic analysis are illustrated in the tables included in Appendix A.

Data will be collected on resource use in the following cost areas:

- Intervention (Medication) costs
- Inpatient/Day-case costs
- Outpatient costs
- Primary and other community care costs

Use of **surgical interventions to manage the condition will be captured on the CRF over the whole follow-up** period. These will be reported descriptively as the type and proportion of participants experiencing an event per three-month period from baseline until the end of study follow-up.

Responses to the EQ-5D-Y descriptive components will be reported in tabular form and responses will be converted into health state utilities using the recommended scoring algorithm available at the time of trial analysis for the UK. Currently, the only value set is for the Slovenian general population.(7) Any updated on EQ-5D-Y development will be monitored and updated accordingly. (8) Changes in HRQoL, based on responses to the EQ-5D-Y, will be compared across time points.

See Appendix A for the dummy tables from the trial-based data analysis and a cost-consequence balance sheet analysis approach.

Use of Discrete Choice Experiment (DCE)

As part of the health economics work package, an online Discrete Choice Experiment (DCE) of patient/parent preferences with be conducted. This will uncover how patient/parents value selected attributes of treating MCDS. The DCE will collect socio-demographic and clinical data from patients and/or their parents/guardians. It will also conduct the EQ-5D-Y quality of life measure.

Based on systematic reviews, qualitative survey, and pilot work (2022), the attributes with levels in the DCE are: patient activities of daily living, reduction in pain severity, gain in height in adulthood, treatment preventing life-threatening complications, treatment causing a severe adverse effect affecting Quality of Life (QoL) permanently and irreversibly, and average out-of-pocket expenses (per year) for treatment.

The attributes and levels from the DCE do consider probabilities around improving QoL. Together with MCDS trial data, this could help create threshold analysis linking any benefits from CBZ in the trial with patient and parent preferences from the DCE.

COST EFFECTIVENESS MODEL OVERVIEW

An economic model will be developed to understand the costs and health outcomes associated with CBZ for patients with (MCDS) compared with current practice over a patient's lifetime. The consequences will be measured in terms of Quality Adjusted Life Years (QALYs). The model will be based on the MCDS trial and clinical expert opinion. It will be supplemented with inputs from the literature where necessary.

Model overview

Decision problem

It is currently unclear whether using CBZ presents a more cost-effective way of managing young patients with MCDS. The aim of analysis is therefore to evaluate the cost-effectiveness of CBZ versus standard care for over the estimated lifetime of patients treated using an economic evaluation model. The model will be developed using TreeAge Pro® (Williamstown, MA, USA) software package.

Target population

The model will be based on a hypothetical cohort of young patients, with equal proportions of male and females, undergoing either CBZ treatment or current treatment options. The mean starting age will be based on the MCDS trial. This target population is chosen as it is compatible with the population of the MCDS trial.

Comparators

The evaluation will compare CBZ vs current management for pain relief.

Perspective

The base-case model will consider all costs and health effects from the NHS and Personal Social Services perspective which means that productivity lost through illness or costs incurred directly by the patients will not be modelled. This perspective is consistent with the NICE reference case for economic evaluations

Time Horizon

According to the NICE reference case, the time horizon of economic evaluations has to be long enough to reflect all important differences in costs or outcomes. Therefore, in order to fully capture the benefits of the interventions, a lifetime horizon (average life expectancy for the starting age) will be applied.

Discounting

The recommended discount rate in the UK is 3.5% per annum. It will be applied for both costs and benefits. All costs in the analysis are expressed in the last complete financial year at the time the analysis is conducted.

Model structure

A long-term state transition Markov model (STM) will be used to explore clinical pathway of patients. This methodology is particularly useful for diseases that continue or increase over time, where events can occur more than once and where the probability of an event changes depending on the time since a previous event (9), as is the case in MCDS. The initial clinical pathway is set out in Appendix B.

The outline structure of the model is shown in Figure 2 and 3 (Below). All patients in the model are children with MCDS. The model is divided into two separate 'arms' – **(1) treatment with carbamazepine**, and **(2) patient management based on current practice**.

Carbamazepine 'arm' (Figure 2)

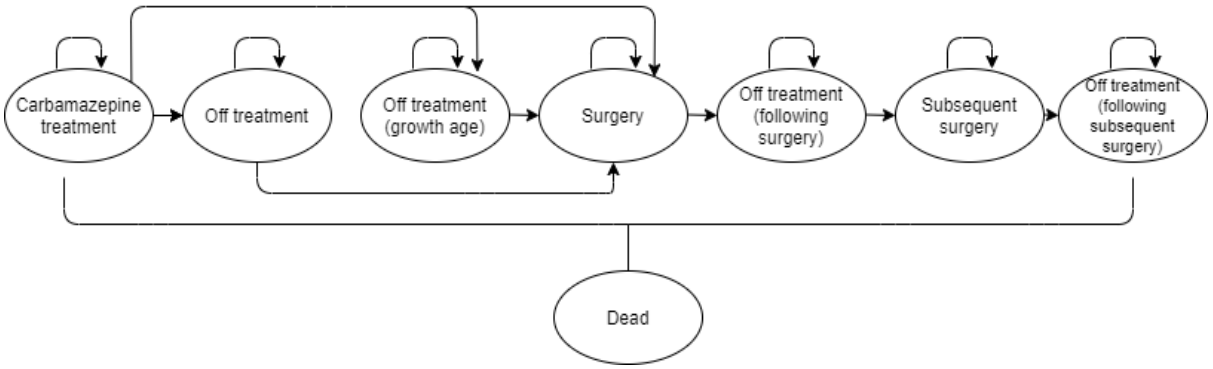

Figure 2: Carbamazepine treatment arm of the model

This is the first health state that patients will occupy in the model, i.e. **'Carbamazepine treatment'** – all patients will be in this health state during the first 'time cycle'. Within this health state, patients may experience a clinical complication related to the medication (or not), and they may also die due to general background mortality (a miniscule risk but still needs to be considered for all patients regardless of health state). At the end of the first time cycle, patients may continue treatment (in which case they would re-enter the **'Carbamazepine treatment'** health state and experience a new possibility of these same events occurring), they may discontinue treatment due to issues such as lack of adherence or serious complications (**'Off treatment'**), they may discontinue treatment due to the fact that their final growth age has been reached **['Off treatment' (growth age)**] or alternatively they may progress directly to receive surgical intervention ('**Surgery'**).

The second time cycle of the model will then begin with a particular percentage of patients still on carbamazepine treatment, i.e., having re-entered the **'Carbamazepine treatment'** health state, and a certain percentage of patients in each of the other health states in the model [**'Off treatment'**, **'Off treatment (growth age reached)'**, and **'Surgery']**. For patients in the **'Off treatment'** health state, patients are now no longer on CBZ treatment. They once again may survive or die and they may also progress to receive surgical treatment (if required, due to ongoing pain etc.). Alternatively, they may remain off treatment, in which case they would re-enter the **'Off treatment'** health state at the end of the next time cycle. For patients in the **'Off treatment (growth age reached)'** health state, patients are also no longer on CBZ and the model pathways are the same, i.e. patients may survive or die and they may progress to surgical treatment or remain off treatment. Note: patient can be on CBZ again after surgery.

For those patients who have progressed to surgical intervention, they enter the **'Surgery'** health state. Patients in this health state will undergo surgery for their condition (most likely

guided growth surgery but could be osteomy of limb-lengthening). Patients may then either survive or die due to background mortality, and they may experience a clinical complication related to the surgery or not. Patients may then either exit the **'Surgery'** health state by progressing to a health state called **'Off treatment following surgery'**, or they may require an immediate revision surgery (in which case patients re-enter the **'Surgery'** health state and undergo another procedure, which may be guided growth or osteotomy). A maximum of two revision procedures will be modelled for those patients who require revision surgery. Revision surgeries, if required, are assumed to take place immediately following an unsuccessful prior surgery. For patients who have undergone a successful surgery (or who have had the maximum number of unsuccessful revision surgeries), they will enter the **'Off treatment following surgery'** health state. In this health state, patients can either survive or die and they can either progress to a subsequent surgical treatment or not. Where patients progress to a subsequent surgical treatment, they enter the **'Subsequent surgery'** health state. In this health state, the possibility of surviving/dying and experiencing an adverse event or not are again considered. Additionally, the possibility of requiring up to two revision procedures is again considered. From here, patients will enter the **'Off treatment following subsequent surgery'** health state, which is the final health state in the model. Patients will remain in this health state unless they die.

Current practice 'arm' (Figure 3)

With current practice, all patients in the model begin in a **'No treatment'** health state. These patients have MCDS but are not undergoing any active treatment for their condition. Patients may either survive or die in this health state and may experience an adverse clinical event (i.e., sufficient pain) which necessitates a surgical intervention, or they may not. If patients do not experience an adverse clinical event, they will re-enter the **'No treatment'** health state in the subsequent cycle. If they experience an adverse clinical event, patients will enter a **'Surgery'** health state.

In the **'Surgery'** health state, patients (Most likely guided growth surgery, but could be osteomy of limb-lengthening). From here, patients may either survive or die, and experience an adverse clinical event related to surgery or not. Depending on the success, or otherwise, of surgery, patients will either undergo immediate revision surgery (in which case they re-enter the **'Surgery'** health state) or they enter an **'Off treatment'** health state. If patients re-enter the **'Surgery'** health, the same pathways as described previously are followed with up to two possible revisions being modelled. If patients enter the **'Off treatment'** health state, they will either survive or die and progress to a further surgical intervention or not. If patients don't require a further surgical intervention, they will remain in the **'Off treatment'** health state. If patients do require further surgery, they will enter a **'Subsequent surgery'** health state. In the **'Subsequent surgery'** health state, patients can either survive or die, experience an adverse event related to surgery or not, and require a revision surgery or not. If patients require a revision surgery, they will re-enter the **'Subsequent surgery'** health state, and follow the same pathways as described previously. Once again, a maximum of two revision procedures will be modelled. Where patients have a successful subsequent surgery (or where the maximum number of revisions has been reached), they will enter an **'Off treatment**

following subsequent surgery' health state where they will remain for the duration of the model, unless they die.

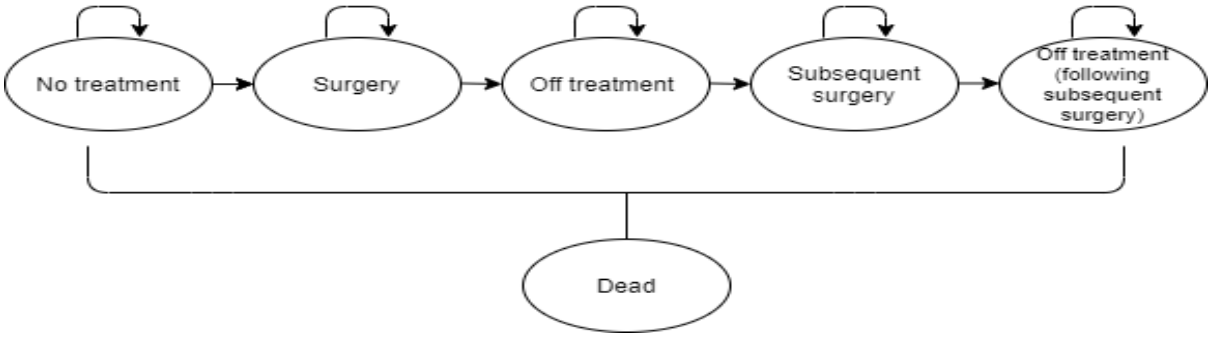

Figure 3: Current practice arm of the model

In both arms, the **dead** state will be included in the model as an absorbing state. Transition probabilities to this state will be assumed to be independent of severity and treatment history and are derived from age/sex specific UK life tables. These data will either come from the trial or from the literature as data from the trial may be imprecise due to the relatively small number of participants for what is expected to be an uncommon event.

Note: Therapies such as physical & heat therapy and analgesics will be considered in the model for treating complications and managing patients. It is likely that we will need to consider their use amongst patients currently **'off treatment'**. However, it is likely they will be considered from a cost standpoint only, i.e., they will be assumed not to impact clinical outcomes, but we acknowledge that such therapies can improve HRQoL dramatically.

Cycle length

Model cycle can be defined as the time spent in each health state. Based on the review of clinical pathway and data availability, the chosen cycle length will be equal to one year.

Half-cycle correction

As one year is a relatively long cycle length, it is important to highlight the fact that it is unclear when the transitions occur within the cycle. In order not to bias the analysis in any direction, it can be assumed that, on average, transitions will occur about half-way through the cycle. To account for this, a half-cycle correction will be made by assigning half of the reward (costs and/or consequences) in each state. This adjustment has been recommended by good practice guidelines for economic modelling.

Model inputs

Where possible, the model will be populated with the patient level data from the MCDS trial. Otherwise, inputs will be obtained from targeted literature searches, national routine data sources and clinical expert opinion. Table 1 below illustrates the types of inputs required for the model.

Table 1: Model Inputs

Clinical inputs			
Transition Probabilities	**Definition**	**Value**	**Reference/Details**
Carbamazepine arm			
Starting on CBZ			
- Off Treatment	probability of going off treatment		Expert Opinion/MCDS Trial
- Off treatment (growth age)	probability of going off treatment due to growth age		Expert Opinion/MCDS Trial
- Surgery	probability of having surgery		Expert Opinion/MCDS Trial
Surgery to off treatment	probability of going off treatment following surgery		Expert Opinion/MCDS Trial
Off treatment to Subsequent surgery	probability of having subsequent surgery		Expert Opinion/MCDS Trial
Subsequent surgery to off treatment	probability of going off treatment following subsequent surgery		Expert Opinion/MCDS Trial
Current practice arm			
Starting on no treatment			
- Surgery	probability of having surgery		Expert Opinion/MCDS Trial
- Off treatment	probability of going off treatment after surgery		Expert Opinion/MCDS Trial
Off treatment to Subsequent surgery	probability of having subsequent surgery		Expert Opinion/MCDS Trial
Subsequent surgery to off treatment	probability of going off treatment following subsequent surgery		Expert Opinion/MCDS Trial
Costs	**Definition**	**Value**	**Reference/Details**
State/Event			
Carbamazepine arm			
Carbamazepine	The annual costs associated with MCDS and being on CBZ		BNF/MCDS Trial/Literature
Off-treatment	The annual costs associated with MCDS but not being on any specific treatments		MCDS Trial/Literature

Off-treatment (growth age)	The annual costs associated with MCDS being off-treatment, CBZ, because patient has reached growth age		MCDS Trial/Literature
Surgery	The annual costs associated with MCDS after undergoing surgery and being on CBZ for that year		MCDS Trial/Literature
Off-treatment (following surgery)	The annual costs associated with MCDS after being off-treatment, CBZ, following surgery		MCDS Trial/Literature
Subsequent surgery	The annual costs associated with MCDS after undergoing subsequent surgery		MCDS Trial/Literature
Off-treatment (following subsequent surgery)	The annual costs associated with MCDS after being off-treatment, CBZ, following subsequent surgery		MCDS Trial/Literature
Dead	The cost of last year-of-life care (UK)		From the literature
Current practice arm			
No treatment	The annual costs associated with MCDS but not being on specific treatments		MCDS Trial/Literature
Surgery	The annual costs associated with MCDS after undergoing surgery for that year		MCDS Trial/Literature
Off treatment	The annual costs associated with MCDS after surgery but not being off any specific treatments		MCDS Trial/Literature
Subsequent surgery	The annual costs associated with MCDS and undergoing subsequent surgery		MCDS Trial/Literature
Off-treatment (following subsequent surgery)	The annual costs associated with MCDS being off treatment following subsequent surgery		MCDS Trial/Literature
Dead	The cost of last year-of-life care (UK)		From the literature
Intervention costs		**Cost**	
Carbamazepine	Annual cost of using CBZ		BNF – MCDS Trial
Guided Growth (8-plates)	Day-case		NHS Reference costs HD24D - Non-Inflammatory, Bone or Joint Disorders, with CC Score 12+
Osteomy			NHS Reference costs HD24D - Non-Inflammatory, Bone or

	Inpatient		Joint Disorders, with CC Score 12+
Limb-lengthening	Inpatient		NHS Reference costs HD24D - Non-Inflammatory, Bone or Joint Disorders, with CC Score 12+
Utility	**Definition**	**Value**	**Reference/Details**
Carbamazepine arm		**Utility**	**Reference/Details**
Carbamazepine	Utility value whilst on CBZ		MCDS Trial
Off-treatment	Utility value not on any specific treatments		MCDS Trial
Off-treatment (growth age)	Utility value off treatment due to reaching growth age		MCDS Trial
Surgery	Utility value associated with MCDS after undergoing surgery		MCDS Trial
Off-treatment (following surgery)	Utility value associated with MCDS following surgery but not on any specific treatment		MCDS Trial
Subsequent surgery	Utility value associated with MCDS after undergoing subsequent surgery		MCDS Trial
Off-treatment (following subsequent surgery)	Utility value after being off-treatment, CBZ, following subsequent surgery		MCDS Trial
Current practice arm			MCDS Trial
No treatment	Utility value associated with MCDS but not being on specific treatments		MCDS Trial
Surgery	The annual costs associated with MCDS after undergoing surgery for that year		MCDS Trial
Off treatment	Utility value associated with MCDS after surgery but not being off any specific treatments		MCDS Trial
Subsequent surgery	Utility value associated with MCDS and undergoing subsequent surgery		MCDS Trial
Off-treatment (following subsequent surgery)	Utility value associated with MCDS being off treatment following subsequent surgery		MCDS Trial

Incremental cost-effectiveness (ICER) analysis

Using the trial-based analysis, the joint estimates of costs and effects will be combined in an incremental analysis between two strategies and presented as the point estimate of mean incremental cost-effectiveness ratio (ICER) for CBZ versus current practice. The ICER will be calculated as difference in costs divided by difference in effects (QALYs) between the two arms. The main outcome of the analysis will therefore be reported as incremental cost per QALY gained in using CBZ when compared to current standard of care.

Sensitivity analysis

Deterministic sensitivity analysis

Several one- and multi-way sensitivity analyses will be conducted to investigate the impact of varying key assumptions and/or parameter values used in the base-case analysis. By varying one or a few values at a time, it will be possible observe their individual impact on the model results. The results of these sensitivity analyses will be depicted in a tornado diagram to identify main inputs that could be altered to make CBZ strategy, more or less cost-effective relative to current treatment strategy and presenting the results for different time horizons.

Probabilistic sensitivity analysis

In a probabilistic sensitivity analysis, rather than assigning a single value to each parameter, specific distributions, selected based on the nature of each variable, will be assigned to the parameters for which this is feasible and appropriate. Each time the model is run or simulated, values for each parameter will be randomly selected using the process called Monte Carlo simulation. The aim of this is to translate the imprecision in each input variable into a measure of uncertainty in overall cost-effectiveness.

The input parameters of the model will be based on the MCDS data set where multiple imputations (MI) will be performed for missing data. These data will be used to parameterise uncertainty surrounding the joint incremental costs and effects which is presented graphically as confidence ellipses on the incremental cost-effectiveness plane. Ranges and distributional assumptions for input parameters will be based on the MCDS trial data. We will assign gamma distributions for costs and beta distributions for utility data. We will also calculate correlations between the coefficients of cost and utility for the variables included in the time-to-event and logistic regression analyses using Cholesky decomposition and assigned multi-normal distributions to these parameters in the model to account for uncertainty in the estimated transition probabilities.

This form of analysis will also allow estimation of the probability of the treatment being cost-effective given the current societal willingness to pay threshold. This will be graphically illustrated by a Cost Effectiveness Acceptability Curve (CEAC). The CEAC for the model-based analysis will summarise the impact of uncertainty using Monte Carlo simulation where the model is analysed very many times, e.g., 10,000 times with a random value from its assigned distributions for each input parameter chosen each time.

BUDGET IMPACT ANALYSIS OVERVIEW

The budget-impact model estimates the economic impact (change in healthcare expenditure) of introducing carbamazepine for the treatment of MCDS in UK, German and Italian healthcare markets. The target population in the model is patients with a diagnosis of MCDS with confirmed *COL10A1* pathogenic mutation. There is currently no specific treatment for patients with MCDS, so the model will consider costs associated with using CBZ compared with current methods of managing symptoms. These methods include physical therapy and surgical management. The size of the eligible population is estimated using an incidence approach (plus the prevalent population in the first year of the analysis). Costs are calculated and presented for two scenarios - with and without the introduction of carbamazepine - over a time horizon of up to ten years. More specifically, the steps used to model the budget impact of introducing carbamazepine in these health care markets for the treatment of MCDS are:

- *Defining the scope and perspective of the Budget Impact Model*
  Analysis at national level, inclusion of comparators, inclusion of costs
- *Estimating the size of the eligible population*
  Total population in each country
- *Estimating the market share*
  Including all relevant treatment comparators in a current scenario without carbamazepine and a scenario with carbamazepine using its anticipated market uptake
- *Calculating the percentage of the target population on each treatment comparator per year -Based on the incidence of the disease, and market shares and treatment durations for each treatment*
- *Estimating the costs associated with all included treatments based on their market share - Administration and monitoring costs, adverse event costs, concomitant treatment costs*
- *Calculating the results of the Budget Impact Model based on default input values or those defined by the user*

For this MCDS project, the BIA will be conducted in Excel software. We will be looking at the UK, Germany and Italy. For this HEAP, we will look at the UK situation and shall be taking an NHS perspective.

In designing a BIA, there are a number of steps involved – 1) characterise and identify eligible population 2) current market share of treatments 3) Market share with CBZ 4) Total costs comparing current scenario with CBZ scenario and 5) Establishing 5-year costs.

Step 1: Characterise population

Eligible Population:	**Value**	**Source**
UK population		ONS
Population growth rate		ONS
The prevalence of MCDS in the UK		Beacon
Total number of patients newly diagnosed with MCDS per year (Incidence)		Beacon
Total number of patients with confirmed *COL10A1* pathogenic mutation (considered for treatment with carbamazepine)		Beacon
Percentage of patients with MCDS who currently receive surgical and non-surgical management		Beacon
Percentage of patients with MCDS who receive treatment who are treatable with carbamazepine		Beacon
Percentage of patients with MCDS who are at an age where carbamazepine would be effective		Beacon
Percentage of patients who cease using CBZ		
Total eligible population		

Step 2. Current Market share (Current Scenario)

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Number of eligible patients					
Guided-growth surgery					
Osteotomy					
Limb lengthening surgery					
Analgesics only					
Physical therapy only					
Total (100%)	**100%**	**100%**	**100%**	**100%**	**100%**

Step 3. Introduction of Carbamazepine (CBZ scenario)

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Number of eligible patients					
Carbamazepine					
Guided-growth surgery					
Osteotomy					
Limb lengthening surgery					
Analgesics only					
Physical therapy only					
Total (100%)	**100%**	**100%**	**100%**	**100%**	**100%**

Step 4. Total costs associated with new and existing medicines

Treatment-related and Condition-related Costs	Current	CBZ scenario
Treatment costs		
Supportive care costs		
Adverse events costs		
Diagnostic and monitoring costs		
Primary care costs		
Secondary care costs		
Total costs		

Step 5. 5-year costs

	Year 1	Year 2	Year 3	Year 4	Year 5
Current					
CBZ					

References:

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APPENDIX A: MCDS Trial data capture and analysis

Table 2: Medication costs associated with MCDS Trial

Type of Cost	Description	Unit of measurement	Units used	Cost (£) per unit	Price Year	Source
Medication	Carbamazepine	Dose per day	Days x dose per day			BNF
Concomitant Medication	e.g., analgesics					BNF
Total cost ∑" Units used" x ∑" Cost(£) per unit" (standardised Price Year) per participant						

Table 3: Inpatient/day case costs

Type of Cost	Description	Unit of measurement	Units used	Cost (£) per unit	Price Year	Source
Accident and Emergency visit(s)	Reason associated with visit	Per visit				NHS Reference costs
Inpatient stay	Osteomy Limb-lengthening surgery					NHS Reference costs
Day case stay(s)	Guided growth					NHS Reference costs
Total cost ∑" Units used" x ∑"Cost(£) per unit" (standardised Price Year)		Per participant				

Table 4: Outpatient Costs

Type of Cost	Description	Unit of measurement	Units used	Cost (£) per unit	Price Year	Source
Outpatient episode	Reason associated with visit	Per new visit				NHS Reference costs
Outpatient episode	Reason associated with visit	Per follow-up visit				NHS Reference costs
Total cost ∑"Units used" x ∑"Cost(£) per unit" (standardised Price Year)		Per participant				

Table 5: Primary and Community Care Costs

Type of Cost	Description	Unit of measurement	Units used	Cost (£) per unit	Price Year	Source
GP Surgery visit	Reason associated with visit	Per new visit				Personal Social Services Research Unit, Unit costs of health and social care
GP home visit	Reason associated with visit	Per follow-up visit				Personal Social Services Research Unit, Unit costs of health and social care
GP Phone call	Reason associated with visit					Personal Social Services Research Unit, Unit costs of health and social care
Physiotherapist (Community based)	Reason associated with visit					Personal Social Services Research Unit, Unit costs of health and social care
Practice nurse/district nurse at home	Reason associated with visit					Personal Social Services Research Unit, Unit costs of health and social care

Practice nurse/district nurse phone call	Reason associated with visit					Personal Social Services Research Unit, Unit costs of health and social care
Total cost ∑" Units used" x ∑"Cost(£) per unit" (standardised Price Year)		Per participant				

Table 6: EQ-5D-Y and QALYs

Score	**MCDS Patients on Carbamazepine**
Baseline EQ-5D-Y	
95% CI or credible interval	
3-month EQ-5D-Y mean (SD) score	
95% CI or credible interval	
6-month EQ-5D-Y mean (SD) score	
95% CI or credible interval	
1-year EQ-5D-Y mean (SD) score	
95% CI or credible interval	
2-year EQ-5D-Y mean (SD) score	
95% CI or credible interval	
QALYs (unadjusted)	
95% CI or credible interval	
QALYs (adjusted)	
95% CI or credible interval	

Table 7: Mean costs for MCDS trial group

	£ Mean Costs (SD) 6 months	£ Mean Costs (SD) 1-Year	£ Mean Costs (SD) 2-Year	£ Mean Costs (SD Total)
Carbamazepine				
Analgesics				
Inpatient costs				
Outpatient costs				
Primary and Community Care Costs (GP visit etc.)				
Total primary care costs				
Total secondary care costs				
Total NHS costs				
Total NHS and social care costs				

Table 8: Mean scores (SD), mean differences, and p-values

Domains	Baseline	1 year	Mean Change (p-value)	2 years	Mean Change (p-value)
Height in patients (cm)					
Pain Score (PEDSQL)					
QOL (PedsQL)					
EQ-5D-Y (MCDS Trial)					

Table 9: Cost-consequence balance sheet after 2-years

COSTS	**£**			
NHS perspective - **On Carbamazepine**				
CONSEQUENCES	**Height in patients (cm)**	**Pain Score (PEDSQL)**	**QOL (PedsQL)**	**EQ-5D-Y (MCDS Trial)**
Mean score difference (SD) from baseline				
p-value				

Table 10: Cost-Utility Analysis (patient)

				Probability that intervention is cost-effective for different threshold values for society's WTP for a QALY			
Treatment	**Cost (£)**	**QALYs**	**ICER**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
Carbamazepine							
Control							

Table 11: Cost-Utility Analysis (proxy)

				Probability that intervention is cost-effective for different threshold values for society's WTP for a QALY			
Treatment	**Cost (£)**	**QALYs**	**ICER**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
Carbamazepine							
Control							

APPENDIX B: Care Pathway

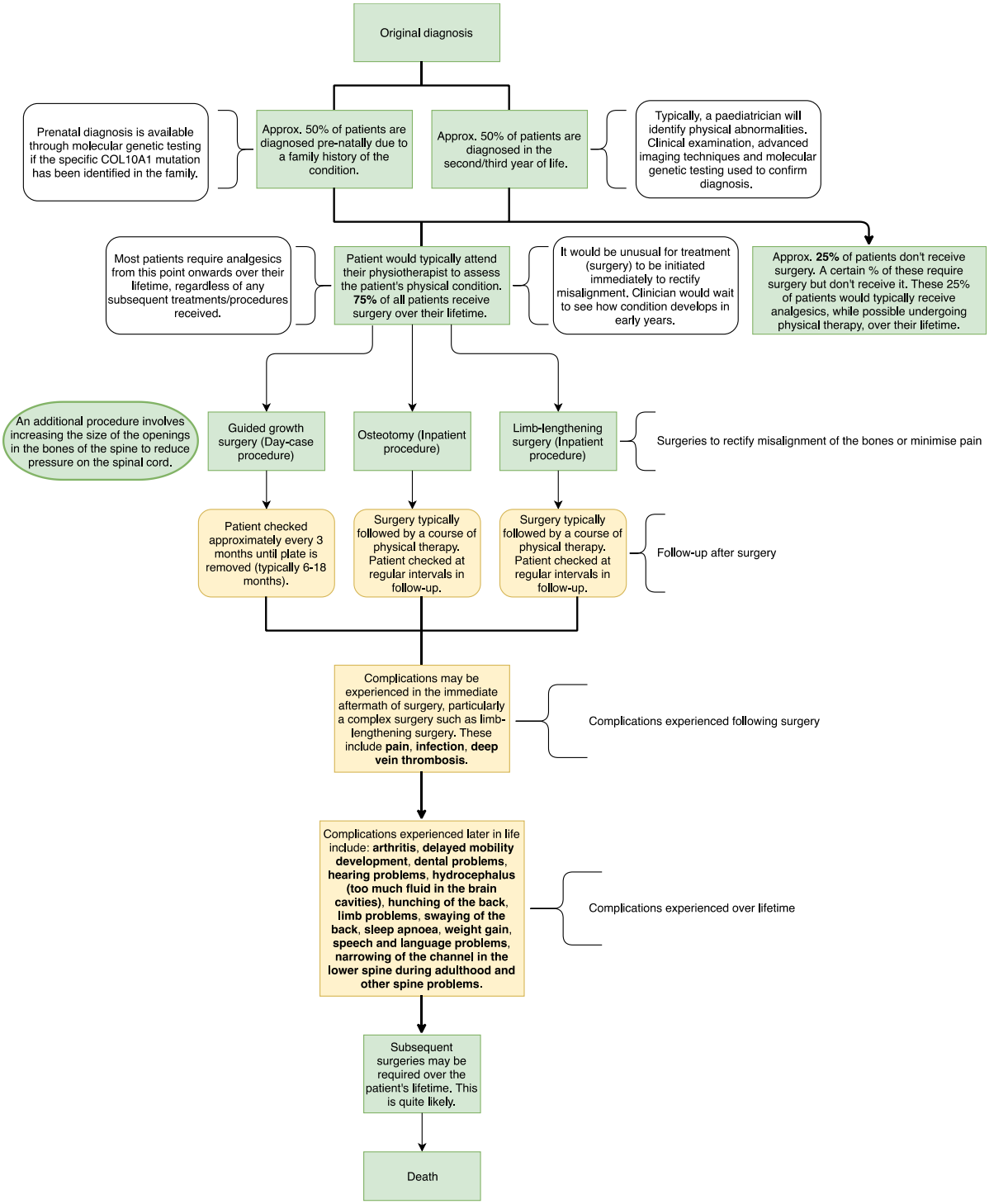

Figure 4*:* Care Pathway