Control, Fludrocortisone or Midodrine for the Treatment of Orthostatic Hypotension: A Randomized Controlled Trial

Health Economics Analysis Plan

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1. A summary of the protocol

CONFORM-OH is funded by the National Institute of Health Research (NIHR) Health Technology Assessment Programme. The study is a randomised controlled trial with an embedded economic evaluation. This randomised controlled trial aims to evaluate the clinical and cost-effectiveness of the following three strategies in the treatment of Orthostatic Hypotension (OH):

- Conservative management (non-pharmacologic treatments)
- Conservative management plus Fludrocortisone
- Conservative management plus Midodrine.

OH is a common and disabling condition that significantly reduces blood pressure (BP) on standing upright [(1)]. Older people and individuals with chronic diseases are more likely to have Orthostatic Hypotension [(2-3)]. A decline in standing BP causes a decrease in perfusion in the brain, causing a range of non-specific symptoms, including dizziness, headache, nausea, fatigue and visual disturbance; at its most severe, it can cause falls and syncope (fainting) [(4)]. People with Orthostatic Hypotension have an increased risk of stroke, cognitive impairment and all-cause mortality and they can experience a significant reduction in quality of life [(5, 6,7. 8)].

There is a significant unmet clinical need due to insufficient evidence supporting Orthostatic Hypotension management [(9)]. Researchers have consistently described systematic reviews and meta-analyses of this evidence base as poor quality with current treatment recommendations based on expert opinion. They recommended more rigorous evaluation to guide clinical practice [(10-14)].

The cost of OH medication is modest, but the consequences of successful treatment and the costs of managing side effects are unknown. No high-quality economic evaluations are directly applicable to the NHS comparing these interventions. Thus, the NHS has insufficient evidence about which Orthostatic Hypotension therapy represents a good use of scarce NHS resources. The scarcity of information about the economics of Orthostatic Hypotension therapy results from the lack of evidence on the relative cost-effectiveness of Fludrocortisone and Midodrine.

The CONFORM-OH aims to provide evidence to guide the treatment of Orthostatic Hypotension.

2. Outline of economic analysis

The key objective of this economic plan is to outline how an economic evaluation will be carried out as part of the CONFORM-OH trial. It was planned that the study will include a within-trial cost-utility analysis with a longer-term model-based extrapolation to estimate the incremental cost per quality-adjusted life-years (QALYs). QALYs will be derived based on responses to the EQ-5D-5L. The rationale behind using a model-based analysis and a trial-based analysis is that the results of the within-trial study might indicate that a treatment strategy for Orthostatic Hypotension is not cost-effective. Still, it is plausible that extrapolation might change this conclusion. However, the converse can also occur, where a strategy initially found to be cost-effective becomes cost-ineffective when longer-term costs and effects are considered. Therefore, an economic evaluation model was planned to extrapolate cost and QALYs beyond the 12-month trial follow-up period. Section 4 presents further details of this analysis.

The perspective of the CONFORM trial is that of the UK National Health Service (NHS) and Personal and Social Services (PSS). Healthcare resource use will be the main cost of this economic evaluation. The economic assessment will calculate the average cost to the NHS of interventions, conservative management plus Fludrocortisone and conservative management plus Midodrine. We will also calculate the average costs of the comparator, conservative management. A sensitivity analysis will explore a broader perspective considering the price falling on individuals or their families/carers. Within the sensitivity analysis, this cost will include direct, e.g., out-of-pocket costs of any medications or therapies purchased and indirect costs such as time off, paid work and travel, and costs to the NHS.

The within-trial economic evaluation was planned to report the following economic outcomes:

- NHS cost of managing individuals with Orthostatic Hypotension over 12 months.
- Direct and indirect costs fall on individuals who suffer from Orthostatic Hypotension and their families/carers over 12 months.

- QALYs estimated based on responses to the EQ-5D-5L administered at baseline, three, six, and 12 months post-randomisation.
- The incremental cost-effectiveness ratio (ICER) is the incremental cost per QALY gained for a more effective but more costly intervention than a less costly but less effective one.

The model-based economic evaluation was planned to report the following economic outcomes:

- NHS cost of managing individuals with Orthostatic Hypotension over the estimated patient lifetime.
- Direct and indirect costs fall on individuals who suffer from O and their families/carers over the estimated patient lifetime.
- QALYs estimated based on responses to the EQ-5D-5L over the estimated patient lifetime.
- The incremental cost-effectiveness ratio (ICER) is the incremental cost per QALY gained for a more effective but more costly intervention than a less costly but less effective one.

CONFORM-OH has closed early as recruitment did not reach planned targets. This health economics analysis plan reports the originally planned Within-Trial Analysis (section 3); the plan for the economic analysis of the data given the early termination is reported in section 4.

3. Within – Trial analysis

Using the cost and effectiveness data derived from the trial allows the estimation of Fludrocortisone's cost-effectiveness compared to Midodrine and Conservative Management. The economic analysis will be an intention-to-treat (ITT) analysis.

3.1 Description of management strategies

The CONFORM protocol version 2.0 provides a more detailed description of the OH strategies. The CONFORM study is analysing the following management strategies.

- Conservative management - In this study, non-pharmacologic therapy is standard first-line care and represents the control arm of the trial.
- Fludrocortisone with conservative management -The typical starting dose will be 100 micrograms, and the highest amount used in this study will be 400 micrograms. The PI has judged participants to be frailer and may have a lower starting dose of 50 micrograms.
- Midodrine with conservative management - The recommended dose range is 2.5 milligrams three to 10 milligrams three times a day. Within this study, lower frequencies and doses may also be accepted.

The duration of follow-up for the three arms is 12 months from randomisation.

3.2 Format of the incremental analysis

Table 1 will present all analysis costs, QALYs, and the ICER. Treatments A-C do not a priori represent any of the interventions. Instead, the treatments are ordered from least costly (treatment A) to most costly (treatment C). The table assumes that treatment B is more costly and more effective than treatment A and that treatment C is more costly and more effective than treatment B. Thus, the calculation of ICERs compares treatment B to treatment A and treatment C. Should one or two treatments be more costly and no more effective (and possibly less effective), these treatments will be considered dominated and dropped from the analysis. For example, suppose treatment B is more costly and no more effective than treatment A. I. In this case, treatment A will dominate B. In this situation, the ICER would be calculated for treatment C compared with treatment A (assuming treatment C is more effective than treatment A).

Table1: Incremental cost-effectiveness of conservative management vs Fludrocortisone with conservative management vs Midodrine with conservative management

Treatment Arm	Costs	Incremental Costs	Effects	Incremental Effects	ICER
A	A				
B	B	Δ costs (B-A)	B	Δ effects (B-A)	Δ costs/Δ effects for treatment B vs treatment A
C	C	Δ costs (C-B)	C	Δ effects (C-B)	Δ costs/Δ effects for treatment C vs treatment B

3.3 Estimation of costs

3.3.1 Costs and frequency of use of services and costs

. When participants consent to enter the study, the researchers randomly allocate them into one of the three trial arms. Each of the three arms is associated with a different cost. For the within-trial analysis, we will base these costs on the interventions and healthcare services used during the 12-month follow-up period post-randomisation.

3.3.2 Costs of Interventions

Three management strategies are being evaluated as part of this study are:

- Conservative management only (non-pharmacologic treatments)
- Conservative management plus Fludrocortisone
- Conservative management plus Midodrine

Conservative management costs

We will base each form of conservative management on the data collected within the electronic case report form (e-CRF) and estimate it on an individual-participant level (micro-costing). The costs of conservative management will be a sum of every aspect, considering the mix of staffing overheads, disposable equipment, and reusable equipment.

The estimation of these costs will utilise the dummy tables presented in the Appendix, specifically Table 5.1.

We will record the length of time and the number of intervals for the conservative management interventions. The staff costs will consist of the grade of the health care professional per hour. These costs have arisen because health professionals' numbers, types, and grades will be assumed based on consultations with the research team. Total staff costs will be calculated by multiplying the cost per session by the number of sessions within a particular time horizon. The costs per session would be derived by multiplying the duration of a session in minutes by the cost of staff per minute. The cost of staff per minute will be gathered from the Unit costs of health and social care [15]. Total staff costs will allow for the average expenses per patient per arm. The total overhead costs will be calculated by multiplying the costs per session by the number of sessions. The costs of overheads will be retrieved from the Unit costs of health and social care [15].

The research team will need to confirm what reusable and consumable equipment is required for each type of conservative management. First, the cost per session will be multiplied by the number of sessions to calculate the total disposable equipment costs. Next, the disposable equipment used will be multiplied by the cost per item to calculate the total equipment costs. The cost per item would be sourced from the NHS Supply Chain website [16]. Finally, the number of reusable equipment used in a session will be multiplied by the cost per item, which will then be multiplied by the number of times equipment can be used, the life span in years, and the discount rate. This multiplication will be multiplied by the number of sessions to calculate total reusable costs.

NHS tariffs for conservative intervention will be used in sensitivity analysis, and the results compared to the micro-setting will be estimated using the methods described above.

Cost of Fludrocortisone

As described above, individuals will receive a starting dose of 10m micrograms daily; frailer patients may receive a starting dose of 50 micrograms. This decision will be based on the discretion of the clinician. Clinicians will be encouraged to titrate towards the highest clinically effective dose. As suggested by the British National Formulary (BNF), the highest dose used within this trial is 400 micrograms; however, most sites will use the maximum dose of 300 micrograms as this is the usual practice. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.2.

The unit costs of the Fludrocortisone will be derived from the BNF [17]. The BNF documents the costs per pack of Fludrocortisone and the number of tablets in a pack allowing for the cost per tablet to be calculated by dividing the number of tablets by the cost per pack. The number of tablets used per dose will be calculated by dividing the dose from the protocol by the mass of the tablet. The cost per tablet will be multiplied by the number of tablets used per dose to calculate the total daily costs. Total costs will be calculated by multiplying the total cost per day by the time horizon in days.

- cost per tablet = cost per pack/number of tablets in a pack
- number of tablets used per dose = dose from protocol/ mass of tablets
- total costs per day = cost per tablet X number of tablets used per dose
- total costs = total costs per day X by time horizon in days

In addition, the costs of the clinicians administering the therapy can be identified in the Unit costs of health and social care and NHS tariffs [15, 18]. The staff costs for administering the medication will be getting the grade of the staff, which the research team will confirm. The hourly rate of this staff will be retrieved from the Unit cost of health and social care. The research team would estimate the mean time required to administer Fludrocortisone. Staff costs per session will be calculated by dividing the

hourly staff rate by the time needed to help with the medication. Total staff costs will be calculated by multiplying staff costs per session by the number of sessions.

The estimates of the unit costs of Fludrocortisone will be added to the staff costs of administering. Total costs will be calculated for each participant, and an average cost per arm will be summarised as the average total resource use and total intervention cost per arm.

Cost of Midodrine

Participants who are randomised to Midodrine with conservative management will typically receive a starting dose of 2.5mmg TDS orally. Depending on the discretion of the clinician, lower doses and frequencies may be accepted. The maximum dose in this study is 10 mg. The costs of Midodrine will be estimated by the same method used for Fludrocortisone explained in the paragraph above, and the unit cost can be found in the BNF [19]. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.2.

3.3.3 Costs of NHS Resources

During the following-up period, participants may utilise additional healthcare resources. Examples of Primary care resources can include GP, nurse/or other healthcare professional consultations. Primary care consultations can occur in various places, healthcare providers' various places, healthcare ’providers' various places, healthcare providers' practices, the participant's home, and over the telephone (including phone calls to NHS call centres). Secondary care resource use can refer to A and E departments, outpatient visits, and hospital admissions, which could be a day or overnight.

The Health Utilisation Questionnaires are used to capture the use of primary care services, including the number of contacts with GP, nurses, and " other health professionals" "". We aim to capture all potential forms of primary care costs were captured. For example, primary care consultations may be face-to-face at the practice, at the "' 'participant's home, or by telephone. The differentiation is important as the cost of each of these varies (see below on derivation of unit costs). Secondary

care refers to visits to an A & E department, outpatient clinics and hospital admissions as a day patient or as an inpatient (inpatient admissions are defined as where the person stays at least one night in the hospital).

Healthcare resource use is associated with different unit costs, regardless of whether these resources are primary or secondary. Details of resource use of primary and secondary care will be captured using the e-CRF and follow-up Health Utilisation Questionnaires at baseline, three months, six months, and 12 months after the trial. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

The number of face-to-face or phone appointments with their GP or nurse within a specific time horizon will be extracted from the e-CRF. The cost per minute and the mean length of consultation in minutes can be removed from the Unit cost of health and Social Care [15]. The costs per consultation will be multiplied by the number of appointments within a time horizon to calculate the total staff costs per patient for each patient, thus allowing us to calculate the average staff per patient for each intervention arm. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

The ambulance service unit cost can be extracted from the NHS cost Schedule. The NHS cost Schedule lists four different types of ambulance services [18]. The average unit costs will be calculated, and the average costs will be multiplied by the number of visits within a particular time horizon to calculate the total cost of ambulance services per patient. The average cost per patient would then be calculated for each other three intervention arms. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

An average of the unit costs of the Accident & Emergency currency descriptions with the highest number of data submissions (any currency description with a number of data submissions higher than 110 will be included in the average)[18]. Accident and emergency services unit costs will be extracted from the NHS cost Schedule. The total cost will be calculated by multiplying the unit cost by the number of appointments documented in the e-CRF. The average Accident and emergency services cost will then be calculated for each of the three intervention arms. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

3.3.4 Cost of Private Services (non-NHS) Care

The cost of private services and the number of particular visits will be extracted from the e-CRF. Private services include things such as physiotherapy and acupuncture. First, the total cost for each private patient service will be calculated by multiplying the number of private service visits by the amount each patient paid for the private service they used. Then, the private costs will be grouped with the same theme. Finally, the average costs of private services for each of the three arms will be calculated. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

3.3.5 Cost of Personal Social Services

The e-CRF will allow us to determine what social benefit each participant receives. These benefits include Attendance Allowance, Pension Savings Credit, and Pensions Guarantee Credit; the cost of these benefits can be found on the the.Gov.UK website [20, 21]. These costs will be multiplied by the length of the time horizon to calculate the total cost per participant. We will then be able to calculate the average cost of benefits per intervention. A sensitivity analysis would be used to see how the cost-effectiveness would vary if we used the lowest rate compared to the highest. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.3.

The number of social service consultations a participant uses within a given time horizon can be derived from the e-CRF. The Unit Cost of Health and Social Care reports the cost of social care per hour [15]. The research team would confirm the mean time one can expect for a social service consultation. Collecting data on the mean length of time will allow us to calculate the average cost of social service intervention. The average cost of social care can be multiplied by the number of social care appointments to calculate the total cost of social care. The total social costs would allow us to calculate the average cost of social per treatment arm.

3.3.6 Time and Travel Questionnaire

The time and travel questionnaire will assist in gathering information on the cost of accessing healthcare resources relating to Orthostatic Hypotension. The questionnaire captures information about the amount of time and money the participant and a 'participant's family member or carer have spent using health care services six months after. The time and travel questionnaire are split into three sections with 12 questions.

The three sections are:

- Hospital outpatient appointments
- Hospital admissions
- GP / Nurse/Walk-in Centre visits

For each of the three sections on the questionnaire, the cost of travel and the opportunity cost in monetary terms for each study participant and the people accompanying them to the appointments will be summated, and an average will be calculated for each treatment arm. In addition, the average cost and opportunity cost will be calculated per participant and the person accompanying the appointment. The dummy tables used to estimate these costs are shown in the Appendix, Table 5.4.

Hospital Outpatients Appointments

This set of questions referred to hospital appointments. Participants who did not have a hospital appointment were told to proceed to the next section. The questionnaire captured information about the mode of transport a participant used to go to a hospital appointment to their most recent. The cost of travel to this appointment for those who used public travel will be extracted from the questionnaire; the time spent travelling to this appointment and the length of time spent at this appointment will also be collected.

The travel costs of those who arrived and used ambulance services to attend the appointment will be derived from the average unit cost of ambulance services from the NHS reference list [18]. The distance travelled to the appointment was also

recorded for the participants that travelled by car, walked or cycled. The cost per mile will be extracted from the advisory fuel rates.Gov.uk website [22]. The price per mile will be multiplied by the distance travelled to the appointment to calculate the total cost travelled by car. For those that walked and cycled, the cost of travel was not recorded. Instead, the average trip price, the average time spent travelling to an appointment, and the average time spent during an appointment per participant will be calculated for all modes of transport.

Estimates of the opportunity costs of the appointment will be calculated from the questionnaire. Participants will be asked about their main activity if they were not attending the appointment. The national median hourly wage will be calculated using the Office of National Statistics data for the participants who would have been in paid work. This hourly rate will be multiplied by the time spent travelling to and attending the appointment to calculate the opportunity cost of paid work for each employed participant. The opportunity costs of being a homemaker will be calculated by multiplying the national minimum wage, which can be found on the Gov. UK website, by the time, spent travelling to and attending the appointment [23].

A similar process will be used to calculate the opportunity cost for that hourly rate for childcare will be collected from the Coram Childcare Survey 2022; this will be multiplied by the time spent travelling to and attending the appointment [24]. The opportunity costs for caring for friends and family would be calculated using the same method mentioned above using the hourly rate of care derived from the UK Care Guide [25]. The opportunity costs of those who are retired will be calculated similarly using the state pensions, which can be found on the UK government website [26]. The student finance website will be used to provide data needed to calculate the opportunity cost of full-time education. [27].

Similar methods will be used to calculate the opportunity costs of unemployed people by deriving the average monthly allowance from universal credit [28]. The standard monthly budget for universal income varies depending on age and marital status. For this trial, we will assume participants are single and older than 25. The opportunity costs for volunteering would be calculated using information from the Office for National Statistics [29]. The Office for National Statistics will provide data on

average expenditure on recreation and culture, which will be used to calculate the opportunity costs of leisure activities.

A similar process was conducted to calculate the opportunity costs of the family member, friend or carer accompanying the study.

3.3.6 Adverse Events

Information on adverse events, AEs, and serious adverse events (SAE) will be collected via the electronic e-CRF at any time during the trial. AEs may require additional medications or hospitalisation. The cost of the AE will be estimated by calculating the cost of the action taken to resolve the AE. The three possible actions that could be taken are reducing the dose and withdrawing the Investigational Medical Product. IMP or no action. The intervention cost will be calculated as described above until the resolution is conducted for participants who had a dose reduction or no longer received their IMP; as a result, AE Reducing the dose would alter the inputs needed to calculate the intervention costs from the resolution date. The resolution date allows us to calculate the cost of AE over a specific period. A withdrawal of the IMP at a given resolution date will result in only the cost-conservative management calculated from the resolution date. For participants that did not require any action due to the AE, the intervention cost was calculated similarly to the overhead cost of the intervention section. The total cost of adverse events for each intervention will be calculated, thus allowing us to calculate the average prices.

3.3.7 Estimation of total costs

The mean total cost of each intervention group will be calculated by summing the costs of interventions, NHS resources, Private Services, Personal Social Services, Time and Travel and Adverse Events for each participant and then dividing by the number of participants included in the analysis are added together. A sensitivity analysis will be conducted for each cost input to assess the effect of high and low estimates of costs.

3.4 Effectiveness measures

The effectiveness measure for the within-trial economic evaluation will be QALYs estimated from responses to the EQ-5D-5L data. The EQ-5D-5L measures health-related quality of life (HRQoL), which the National Institute of Health and Care Excellence (NICE) recommends. This general health questionnaire considers five domains, mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression [31]. Each of the five domains has five possible responses; there are, therefore, 3125 possible health states. These responses vary in severity from no, slight, moderate, severe, or extreme problems/inability to conduct usual activities). EQ-5D-5L values are converted into health state utility for each patient at each time point, estimated from a representative sample of the UK population [32]. This process is followed by mapping the EQ-5D-5L descriptive data set onto the EQ-5D-3L value set described in the NICE guidelines using the mapping/crosswalk algorithm[31]. Finally, we will conduct a sensitivity analysis to investigate the impact of using alternative crosswalk algorithms on the ICER results.

A proxy version of the EQ-5D-5L will be included for participants who cannot self-complete the questionnaires. EQ-5D–5L data will be collected at baseline, three, six and twelve months following randomisation. With the proxy version, the caregiver is asked to rate how they think the patient would rate their health-related quality of life if they could communicate. These responses will be converted into scores using population tariffs [31]. The values from both participants and proxy values will be compared when both values are available to calculate QALY simultaneously. Following this, the variance between participant and proxy will be estimated. Where participant values are unavailable in the analysis, proxy values will be used.

The outcome data will then be converted into (QALYs) for each participant using the under-the-curve approach for baseline, three, six and twelve months. A QALY combines the quality of life and life expectancy into a single index [31]. Standard deviations, standard errors and confidence intervals will be calculated using standard formulas for each of the mean utility measures. QALYs will be calculated by summing the area under the curve (AUC), connecting the mean utility measures at each time point for all three interventions. The AUC is calculated by summing up the areas of the shapes obtained from the linear relationship between utility scores during the study period [32,33].

Baseline means utility values may be imbalanced between treatment arms. Imbalanced utilities need to be considered when the mean differential QALYs are estimated. Estimation for mean differential QALYS can be achieved using multiple regression methods[34]. This method controls for baseline utility values simultaneously, allowing for the Estimation of differential QALYs and the prediction of adjusted QALYS. The regression analysis provides unbiased estimates of differential QALYs between the trial's three arms, increasing the treatment effect's precision [35].

3.5 Cost-utility analysis

The cost-utility analysis will base on the incremental cost per QALY gained and will be presented as the incremental cost-effectiveness ratio (ICER) and can be calculated by dividing the change of the expenses by the change in effect (QALYs). The total cost and QALY will be estimated for each arm, which will then be expressed as point estimates of the mean incremental costs and effects (QALYs) and the incremental cost per QALY gained. The UK's willingness to pay is approximately £20,000 per additional QALY; thus, if conservative management plus Fludrocortisone and conservative management plus Midodrine is not dominant, the ICER is within this threshold, the interventions could be deemed cost-effective by decision-makers. A dominant intervention is an intervention with a lower cost and better health outcomes than the comparator.

3.5.1 Adjusted analysis – seemingly unrelated regression (SUR)

Both unadjusted and adjusted analyses will be performed to estimate the cost-effectiveness of conservative management plus Fludrocortisone compared to conservative management plus Midodrine compared to conservative management alone. The mean incremental costs, effects and cost-effectiveness results will be presented as point estimates.

An adjusted analysis will be carried out using seemingly unrelated regression (SUR) for all comments to estimate the costs and effects of the three interventions and their cost-effectiveness. SUR allows one to simultaneously estimate the costs and effects

for each individual, accounting for unobservable individual characteristics to affect both costs and effects, resulting in a potential correlation between two variables. Furthermore, the SUR permits the control for additional covariates such as age, baseline, severity and utility that could potentially affect costs and effects when appropriate. The covariates used in the SUR model will replicate the covariates used in the statistical analysis outlined in the Statistical Analysis Plan. We will analyse Stata using the seemingly unrelated regression command sureg (StataCorp LLC, Texas, USA).

3.5.2 Sensitivity analysis

A stochastic/probabilistic and deterministic sensitivity analysis will be conducted to characterise the uncertainty.

Stochastic sensitivity analysis

A stochastic sensitivity analysis will be conducted. Bootstrapping techniques will be utilised in this analysis [35]. (Bootstrapping can be described as the non-parametric technique used to estimate the distributions of important statistics relevant to the model, such as the ICER.[36]. Stochastic analysis would explore the potential effects of statistical imprecision of parameters used within the model on costs effects and cost-effectiveness estimates if the sampling process could be repeated many times. Random values will be selected from the cost and QALY data retrieved from the trial. When a random value is used for the bootstrap resample, it is returned to the original sample. Consequently. A bootstrapped dataset derived from the complete case data on costs and outcomes from each trial arm.

This process will be carried out many times (e.g., 1000, 5000, 10,000), creating a sample of bootstrapped mean costs and QALYs with their corresponding distributions. The bootstrapped distribution will be calculated using bootstrapped costs, QALYS, and other parametric statistics. The results from the bootstrapping will be presented as a cost-effectiveness plane to demonstrate the distribution of incremental costs and incremental effects, allowing us to identify the distribution of total incremental costs and incremental effects. The horizontal axis will represent the QALYs difference between the two interventions, and the vertical axis will represent the corresponding cost difference. The bootstrapped results will also be presented

as cost-effectiveness acceptability curves (CEACs). CEACs enable us to identify the management strategy that maximises net benefits at each willingness to pay value for additional QALYs gained) [37].

Deterministic sensitivity analysis

Deterministic sensitivity analysis will be used to assess the effect of assumptions such as dose of medications, method of conservative management and unit costs on the results using best-case and worst-case scenario analysis. A societal perspective will be used to explore the impact of patient costs on cost-effectiveness results. The results from the deterministic analysis will determine how the analysis will be performed, including one-way, two-way or multiway analysis.

To identify the primary inputs that could be changed to make Fludrocortisone and Conservative Management more or less cost-effective relative to both Midodrine and Conservative Management and Conservative Management alone.

Intervention costs

Conservative management

As mentioned before, we will use micro-costing to calculate conservative cost management. We will use sensitivity analysis to explore how low and high estimates affect the ICER. In addition, we will also investigate how the type of conservative management can influence the ICER separately. This form of analysis will be achieved by one-way sensitivity analysis. We will use higher and lower values of the intervention cost using a 95% confidence interval. Multiway sensitivity analysis will allow us to assess the impact of variation in the costs of Fludrocortisone and Midodrine.

Fludrocortisone and Midodrine

As mentioned, certain assumptions about the pharmacological interventions, such as the dose strength and the number of tablets used in a day, will be tested using

sensitivity analysis. In the sensitivity analysis, we will explore the effect of each medication's high and low estimations on the ICER.

Cost of services

As mentioned previously, the assumptions about the cost of services would be assessed using sensitivity analysis. This analysis will determine non-NHS, private healthcare, and social care resources. For each cost, we will investigate the effect of using higher and lower cost estimates on the cost-effectiveness results, and whether the ICER goes above or below the threshold. Results from the sensitivity analysis will be presented using a tornado diagram for multiple one-way sensitivity analyses for higher and lower values of service cost.

Utility values

We will use EQ-5D-5L crosswalked to the EQ-5D-3L value set in the base case analysis [31]. In sensitivity analyses, we will use alternative crosswalk algorithms (e.g., provided by van Hout et al.) and the population value set for the EQ-5D-5L to investigate the effect of these utility values on the ICER[38].

In a further sensitivity analysis, proxy values based on the degree of discordance between participants and the proxy values will be used in the sensitivity analysis. The reported proxy values will be replaced with alternative values estimated by converting the upper and lower confidence intervals of a paired t-test. This will compare the patient and proxy values into a % variation from the man score by applying that % variation of the observed score. This will mean that high and low values utilised in the sensitivity analysis will be a proxy score * (1+ x) or proxy score * (1-x), when x is the % variation.

Total costs and utility

To deal with missing costs and utility data, we will do multiple imputations in the sensitivity analysis. An ICER will be presented in addition to the base case analysis.

3.6 Handling Missing Data

Potential issues may arise when dealing with trial data, such as missing data and not adhering to the protocol. Therefore, a missing data analysis will be carried out.

This missing data analysis will primarily focus on missing data because the e-CRF and participant questionnaires are incomplete. As with most trial-based data collection, not all participants who enter the trial will complete all questionnaires and questions in each questionnaire. Therefore, missing data is expected. When we have a full trial dataset available, the imputation methods will be determined as the most appropriate, depending on the nature of the missing data.

4. Close Down Plan

4,1 Summary of Existing Economic Component

The health economics component for CONFORM-OH,-, had it been recruited to target, would have included a within-trial cost-utility analysis with longer-term model-based extrapolation. For both the within-trial and model-based analysis, the results will be reported as incremental costs, QALYs, and incremental costs per QALY gained.

The within-trial analysis cost and outcomes for the three trial intervention arms would have been based on data collected over the 12-month follow-up period. Costs were to fall on the NHS, personal social services (PSS), participants and their families. These costs were to be based upon the use of health and social services and, as part of the costs falling on patients and their families, the time and travel costs of accessing services. QALYs were to be based upon responses to the EQ-5D-5L collected from participants at baseline, three, six and 12 months.

The plan was also to use an economic model to extrapolate outcomes into the longer term. Outcomes of the model will be expressed in terms of costs to the NHS and PSS, QALYs, and incremental cost per QALY gained. The model will be structured as when there is a choice about whether or not to start medical treatment and which

medical treatment to start, and it would follow individuals for the remainder of their life. The model was to be developed per the NICE reference case [398].

4.2 Close-down Plan

Given the likely data available from the trial, we no longer propose to conduct a complete within-trial economic evaluation of the model-based analysis. As an alternative, we will use the available trial data to:

1) Provide descriptive statistics (e.g. mean, medians and appropriate measures of variance around completion rates for each health economic data collection tool (i.e. the health service utilisation questionnaire and EQ-5D-5L completed at baseline, 3, 6, 12 months)

2) Provide descriptive statistics (e.g. mean, medians and appropriate measures of variance) for each area of resource use collected at each time point and overall as part of the trial and by group.

3) Provide descriptive statistics for the EQ-5D-5L utility score and EQ-5D-VAS (e.g. mean, medians and appropriate measures of variance) at each time point and overall as part of the trial overall and by group.

4) For each trial respondent, map changes by level on the EQ-5D-5L descriptive framework for responses to the EQ-5D-5L at baseline, 3 and 6 months. There will be insufficient data at 12 months to make a similar work useful.

Analyses 1-3 are consistent with the work proposed in Section 3 of the Health Economic Analysis Plan, Version 0.2. These analyses will provide information for any subsequent evidence synthesis project (e.g., a systematic review or modelling exercise). The data will also help plan future evaluations addressing the same or similar research questions. Specifically, question 1 will provide some information as to whether the tools used can be completed by this group of people (or their proxies). Question 2 will illustrate where resources are used, which may help design future data collection tools that balance data collection against respondent burden. Questions 3 and 4 will help inform whether the EQ-5D-5L can detect any changes in health status in this group of people.

In addition to the above, we propose using the data from the trial assembled from the literature and expert opinion to conduct an early economic evaluation model. This approach is used in other healthcare contexts to help design future primary research. This element aims to identify key uncertainties and estimate, using the methods of Value of Sample Information, the sample size required for a definitive trial to address the research question. Expected value of information will be calculated.

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6. Appendix Dummy Tables

6.1Conservative Management Costs

6.1.1 Education intervention

6.1.1.1 staff

Staff		Time involved	Cost per minute	Cost per consultations	Number of Consultations	Total staff costs*	Notes
Type	Grade						
Staff member 1							
Staff member 2							
Totals							

* These are calculated

6.1.1.2 Overheads

Overhead type	Unit cost	Cost per session*	Number of sessions*	Total overhead costs*	Note
Type	Cost per minute				
Room cost					
Heat power and light					
Internet					
Print outs					
Totals					

* These are calculated

6.1.1.3 equipment disposable

Equipment item		Cost per item	Cost per session*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.1.4 equipment reusable

Equipment item/Type		Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Equipment 1									
Equipment 2									
Totals									

* These are calculated

6.1.2 Trigger avoidance

6.1.2.1 staff

Staff		Time involved	Cost per minute	Cost per Consultations	Number of Consultations	Total staff costs*	Notes
Type	Grade						
Staff member 1							
Staff member 2							
Totals							

6.1.2.2 Overheads

Overhead type	Cost per minute	Cost per session*	Number of sessions*	Total overhead costs*
Room cost				
Heat power and light				
Internet				
Print outs				
Totals				

* These are calculated

6.1.2.3 equipment disposable

Equipment item		Cost per item	Cost per session*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.2.4 equipment reusable

Equipment item	Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Equipment 1								
Equipment 2								
Totals								

6.1.3 Safe Standing

6.1.3.1 staff

Staff		Time involved	Cost per minute	Cost per Consultations	Number of Consultations	Total staff costs*
Type	Grade					
Staff member 1						
Staff member 2						
Totals						

* These are calculated

6.1.3.2 Overheads

Overhead type	Cost per minute	Cost per session*	Number of sessions*	Total overhead costs*	Notes
Room cost					
Heat power and light					
Internet					
Print outs					
Totals					

* These are calculated

6.1.3.3 equipment disposable

Equipment item		Cost per item	COST PER SESSION*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.3.4 equipment reusable

Equipment item	Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Equipment 1								
Equipment 2								
Totals								

* These are calculated

6.1.4 Physical counter–manoeuvre

6.1.4.1 staff

Staff		Time involved	Cost per minute	Cost per Consultations	Number of Consultations	Total staff costs*
Type	Grade					
Staff member 1						
Staff member 2						
Totals						

* These are calculated

6.1.4.2 Overheads

Overhead type	Cost per minute	Cost per session*	Number of sessions*	Total overhead costs*
Type				
Room cost				
Heat power and light				
Internet				
Print outs				
Totals				

* These are calculated

6.1.4.3 equipment disposable

Equipment item		Cost per item	Cost per session*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.4.4Equipment reusable

Equipment item	Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Type								
Equipment 1								
Equipment 2								
Totals								

* These are calculated

6.1.5 Fluid and salt intake

6.1.5.1Staff

Staff		Time involved	Cost per minute	Cost per consultations	Number of Consultations	Total staff costs*
Type	Grade					
Staff member 1						
Staff member 2						
Totals						

* These are calculated

6.1.5.2 Overheads

Overhead type	Cost per minute	Cost per session*	Number of sessions*	Total overhead costs*
Room cost				
Heat power and light				
Internet				
Print outs				
Totals				

* These are calculated

6.1.5.3 equipment disposable

Equipment item		Cost per item	Cost per session*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.5.4 equipment reusable

Equipment item	Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Equipment 1								
Equipment 2								
Totals								

* These are calculated

6.1.6 Compression hosiery

6.1.6.1 staff

Staff		Time involved	Cost per minute	Cost per Consultations	Number of Consultations	Total staff costs*
Type	Grade					
Staff member 1						
Staff member 2						
Totals						

* These are calculated

5.1.6.2 Overheads

Overhead type	Cost per minute	Cost per session*	Number of sessions*	Total overhead costs*
Room cost				
Heat power and light				
Internet				
Print outs				
Totals				

* These are calculated

6.1.6.3 equipment disposable

Equipment item		Cost per item	Cost per session*	Number of sessions	Total Equipment costs*
Type	Number used				
Equipment 1					
Equipment 2					
Totals					

* These are calculated

6.1.6.4Equipment reusable

Equipment item	Number used	Number of times equipment can be used	Lifespan (years)	Discount rate	Cost per item per use	Cost per session*	Number of sessions*	Total reusable Equipment costs*
Equipment 1								
Equipment 2								
Totals								

* These are calculated

6.2 Pharmacological interventions

6.2.1 Fludrocortisone

Staff Administering Fludrocortisone	Grade	Time involved	Cost per minute	Cost per Session	Number of sessions	Total staff costs*
Staff Member 1						
Staff Member 2						
Total						

* These are calculated

6.2.2 Cost of medications

Dose in Protocol	Strength of tablet according to BNF	Cost per pack	Number of tablets per pack	Frequency per day	Cost per tablet £	Number of tables used per dose	Total cost per day	Time horizon in days	Total Costs
Typical dose is 100 micrograms	100 micrograms	£8.06	30	1	£0.27	1	£0.27	365	£98.06
Starting dose 50 micrograms	100 micrograms	£8.06	30	1	£0.27	0.5	£0.13	365	£49.03
Maximal dose of 300 micrograms	100 micrograms	£8.06	30	1	£0.27	3	£0.81	365	£294.19

6.2.3 Midodrine

Staff Administering Fludrocortisone	Grade	Time involved	Cost per minute	Cost per session*	Number of sessions	Total staff costs *
Staff Member 1						
Staff Member 2						
Total						

* These are calculated

6.2.4 Medications

Dose in Protocol	Strength of tablet according to BNF	Cost per pack	Number of tablets per pack	Frequency per day	Cost per tablet £	Number of tables used per dose	Total cost per day	Number of days	Total Costs*
The typical starting dose is 2.5mg									
Maximum dose 10mg									

* These are calculated

6.3 Healthcare Resources

6.3.1 National Health Care Service

Resource	Mean length of consultation in minutes	Number of appointments	Cost per minute	Cost per Consultation	Total staff cost*	Source /Notes
GP at Practice	9.22		£4.23	£39.00		42 weeks per year. 41.4 hours per week, including direct staff costs with qualifications PSSRU 2019/20
GP on Phone	4		£3.88	£15.520		44 weeks per year, 41.7 hours per week PSSRU 2019/20, including other costs per year
Nurse at GP practice	NA		£0.73	£44		41.9 weeks per year 37.5 hours per week costs including qualifications PSSRU 2019/20,44 per hour
Nurse on the Phone	6.56		£1.19	£7.80		42 Weeks per year, 37.5 hours per week

* These are calculated

6.3.2 National Health Care Service (cont)

Ambulance service	Unit costs FY19/20	Number of visits	Total costs*	Source/ Cost
Hear and treat or refer				National cost collection 2019/20 Report
See and treat or refer				National cost collection 2019/20 Report
See and treat and convey				National cost collection 2019/20 Report
Calls				National cost collection 2019/20 Report

* These are calculated

6.3.2 National Health Care Service (cont)

Accident and Emergency	Average unit cost	Number of consultations	Total costs*	Source/ notes
Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, Category 2 Investigation with Category 4 Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, Category 2 Investigation with Category 4 Treatment Type 01 non admitted				National reference costs 19/20
Emergency Medicine, Category 2 Investigation with Category 3 Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, Category 2 Investigation with Category 3 Treatment Type 01 non admitted				National reference costs 19/20
Emergency Medicine, Category 2 Investigation with Category 1 Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, No Investigation with No Significant Treatment Type 01 non admitted				National reference costs 19/20
Emergency Medicine, No Investigation with No Significant Treatment Type 01 admitted				National reference costs 19/20
Emergency Medicine, No Investigation with No Significant Treatment Type 01 unknown				National reference costs 19/20

* These are calculated

6.3.3 Private Service

Private service	number of consultations	length of time per consultation	cost per consultation	Cost per minute of consultation	Total costs*	Source/ notes
Private hospital						
Physiotherapy						
Spa						
Acupuncture						

* These are calculated

6.3.4 Personal social service

Type of service	number of time service used per month	Frequency	Cost of social services*	Total Costs*	Sources/ notes
Pensions savings credit					
Pensions Guarantee credit					
Attendance Allowance					
Personal Independence Payment (Daily living)					
Personal Independence Payment (Mobility					
Employment and Support Allowance					
Universal Credit					
Carer's Allowance					
Other welfare Benefits					

6.3.5 Social workers and other community-based health services

Type of service	Length of time per consultation	number of consultations	Cost per consultation	Total cost*	Sources/ Notes

6.4 Time and Travel Questionnaire

6.4.1 Most recent hospital appointment

Mode of transport	Cost of fare	Distance Travelled	Time spent travelling to the appointment	Time spent at the appointment	Main Activity	Accompanied by the hospital	Main activity of the person who accompanied	Person who accompanied time spent travelling	Person who accompanied time spent at the appointment	How much did the person accompany pay for a ticket and fare	How miles did the person accompany travel

6.4.2 Hospital admission

Mode of transport	Cost of fare	Distance Travelled	Time spent travelling to the appointment	Time spent at the appointment	Main Activity	Accompanied by the hospital	Main activity of the person who accompanied	Person who accompanied time spent travelling	Person who accompanied time spent at the appointment	How much did the person accompany for a ticket and fare	How miles did the person accompany travel

6.4.3 GP/Nurse/Walk in centre visits

Mode of transport	Cost of fare	Distance Travelled	Time spent travelling to the appointment	Time spent at the appointment	Main Activity	Accompanied by the hospital	Main activity of the person who accompanied	Person who accompanied time spent travelling	Person who accompanied time spent at the appointment	How much did the person accompany pay for a ticket and fare	How miles did the person accompany travel