**BELL’S PALSY IN CHILDREN: A MULTI-CENTRE, RANDOMISED, BLINDED, PLACEBO-CONTROLLED TRIAL TO DETERMINE WHETHER PREDNISOLONE IMPROVES RECOVERY AT 1 MONTH**

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LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| ABBREVIATION | TERM |
| AE | ADVERSE EVENT |
| AI | ASSOCIATE INVESTIGATOR |
| CEBU | CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS UNIT |
| CI | CONFIDENCE INTERVAL |
| CONSORT | CONSOLIDATED STANDARDS OF REPORTING TRIALS |
| CPI | CHIEF PRINCIPAL INVESTIGATOR |
| CHU-9D | CHILD HEALTH UTILITY INDEX |
| CRF | CASE REPORT FORM |
| DSMB | DATA SAFETY MONITORING BOARD |
| ED | EMERGENCY DEPARTMENT |
| FPS-R | FACES PAIN SCALE REVISED |
| GCP | GOOD CLINICAL PRACTICE |
| GMP | GOOD MANUFACTURING PRACTICE |
| HB | HOUSE BRACKMANN SCALE |
| HREC | HUMAN RESEARCH ETHICS COMMITTEE |
| ICER | INCREMENTAL COST-EFFECTIVENESS RATIO |
| ITT | INTENTION TO TREAT |
| LAR | LEGALLY ACCEPTABLE REPRESENTATIVE |
| MCRI | MURDOCH CHILDRENS RESEARCH INSTITUTE |
| NHMRC | NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL |
| PBS | PHARMACEUTICAL BENEFITS SCHEME (AUSTRALIA) |
| PEDSQL | PEDIATRIC QUALITY OF LIFE SCALE |
| PREDICT | PAEDIATRIC RESEARCH IN EMERGENCY DEPARTMENTS INTERNATIONAL COLLABORATIVE |
| PI | PRINCIPAL INVESTIGATOR |
| QALY | QUALITY ADJUSTED LIFE YEAR |
| RCH | ROYAL CHILDREN’S HOSPITAL, MELBOURNE |
| RCT | RANDOMISED, CONTROLLED TRIAL |
| REDCap | RESEARCH ELECTRONIC DATA CAPTURE |
| RR | RELATIVE RISK |
| SAE | SERIOUS ADVERSE EVENT |
| SAQ | SYNKINESIS ASSESSMENT QUESTIONNAIRE |
| SD | STANDARD DEVIATION |
| SDED | SENIOR MEDICAL DOCTOR ON DUTY IN ED  Senior is defined as a consultant except where a consultant is unavailable [e.g. overnight] in which case senior is defined as a Fellow or medical registrar. |
| SUSAR | SUSPECTED UNEXPECTED SERIOUS ADVERSE DRUG REACTION |
| TSC | TRIAL STEERING COMMITTEE |
| VAS | VISUAL ANALOGUE SCALE |

1. Study Objectives
   1. PRIMARY OBJECTIVE

To determine, in children aged between 6 months and 18 years presenting to emergency departments (ED) with symptoms of Bell’s palsy (unilateral facial nerve palsy), whether treatment with oral prednisolone (at ~1mg/kg daily for 10 days) increases the proportion of children who have complete recovery at 1 month compared with those receiving placebo, where complete recovery is defined as grade 1 on the House Brackmann [HB] scale.

* 1. SECONDARY OBJECTIVES

1. To determine the effect of prednisolone compared with placebo on:
   1. Time from randomisation to complete recovery.
   2. Emotional and functional outcomes at 1, 3 and 6 months.
   3. Pain, synkinesis and autonomic dysfunction at 1, 3 and 6 months.
2. To explore the effectiveness of prednisolone in improving recovery rates at 1, 3 and 6 months compared with placebo, and whether this varies according to age (<12 years or >12 years), time to treatment (<24h or >24h to 72h) and initial severity (HB 1 to 4 vs HB 5 and 6).
3. To compare the assessment of recovery based on:
   1. HB scoring by face-to-face assessment versus facial images (still photographs and facial video recordings).
   2. HB scoring by face-to-face assessment vs parent/guardian and participant scoring of facial recovery
   3. HB scoring vs Sunnybrook scoring.
4. To determine the effect of prednisolone compared with placebo on health service utilisation by 6 months.
5. To determine recovery at 12 months, for participants not recovered at 6 months only, based on parent/guardian and participant scoring of facial recovery.
6. Background/Introduction

The only paediatric RCT of steroid use for Bell’s palsy was conducted in 1999 by Unuvar E et al (Unuvar et al 1999) and used methylprednisolone 1mg/kg/day (equivalent to 1.25mg/kg/day prednisolone) for 10 days, then weaned over 3-5 days. Data from the PREDICT network indicate that prednisolone is the most frequently used steroid for Bell’s palsy in children, usually at a dose of 1mg/kg/day for a variable number of days (Babl et al 2017A). Prednisolone is also the most frequently used oral corticosteroid in children in Australasia for various other paediatric inflammatory conditions, with routine doses of 1-2mg/kg/day. The main adverse events associated with such short-term use of prednisolone are dose-related changes in behavior and weight gain. There is currently little evidence to assist in determining the best prednisolone dose in children in the study. In determining the dose for the study participants we: noted the adult dose of 50mg for 10 days without taper (Sullivan et al 2007); sought advice from endocrinologists and rheumatologists at Royal Children’s Hospital (RCH), Melbourne; considered the RCH guidelines recommending 1mg/kg daily for 10 days if steroids are used for Bell’s palsy (RCH 2020); and considered the ease of preparation of study drugs. With all these considerations we determined the dose of ~1 mg/kg daily (in weight-based dosing bands to a maximum of 50mg) for 10 days without taper for this study.

* 1. STUDY DESIGN

A multi-centre, randomised, triple-blinded, placebo-controlled trial of the use of prednisolone to improve recovery from Bell’s palsy at 1 month. Clinicians, participants and investigators will be blinded to treatment. Details of the methodology have been set out in a protocol paper (Babl et al 2017B).

* 1. TREATMENT GROUPS

Standard therapy for Bell’s Palsy will comprise prednisolone of ~1 mg/kg daily (in weight-based dosing bands to a maximum of 50mg) for 10 days. The intervention arm will receive this active ingredient once recruited and randomised. Patients randomised to the placebo group will be given a matching non-active ingredient. Participants will be randomly allocated between the treatment arms based on a computer generated randomsation list generated via block randomisation, with variable block size, stratified by site. Randomisation will be conducted by the pharmacy at the Royal Children’s Hospital (RCH) with each participant given a ‘study drug pack’ labelled with only their study number.

* 1. STUDY POPULATION

All participants must fulfil all the inclusion criteria and none of the exclusion criteria.

To be eligible for this study, each participant must:

* Be aged from 6 months to less than 18 years of age.
* Weigh ≥ 5 kg.
* Be diagnosed with Bell’s palsy by their treating doctor.
* Have acute onset of symptoms of Bell’s palsy for less than 72 hours prior to randomisation.
* Have written informed consent provided by the parent(s) or legal guardian. The participant, where he/she is deemed competent to provide consent, may also provide written consent.

Patients with any of the following will not be included in the study:

* Likely to be unable to complete the 1-month study assessment of Bell’s palsy symptoms. Where the participant is unable to attend the study site, the assessment can be completed via videoconferencing using skype software or other online tools.
* Previous episode of Bell’s Palsy or previously randomised into the study.
* Contraindication to prednisolone, including active or latent tuberculosis, systemic fungal infection, known hypersensitivity to prednisolone or any of the excipients in the liquid, diminished cardiac function, diabetes mellitus, peptic ulcer or chronic renal failure, multiple sclerosis, recent active herpes zoster or chickenpox.
* Use of any systemic or inhaled steroid within 2 weeks prior to the onset of symptoms.
* Current or past oncological diagnosis.
* Pregnancy.
* Breast feeding.
* Currently receiving concomitant medications in which prednisolone is contraindicated.
* Immunisation with a live vaccine within the previous 1 month.
* Requirement for a live vaccine within 6 weeks of the first dose of study drug.
* Signs of upper motor neurone VII nerve palsy (weakness of the lower half of the face only).
* Diagnosis by a medical doctor of acute otitis media concurrently or within 1 week prior to the onset of Bell’s palsy symptoms.
* Evidence of vesicles on the ear drum suggestive of herpes simplex related Ramsay Hunt syndrome.
* Known facial trauma within 1 week prior to the onset of symptoms that in the view of the clinician may have caused or contributed to facial palsy.
* Any other condition at risk of being influenced by the study treatment or that might affect completion of the study.
* Any concern regarding parent/guardian/participant ability to comply with the study protocol.
  1. INTERVENTION

For the 10-day study treatment period, participants will be assigned to receive either ~1mg/kg/day of prednisolone (dosing based on weight categories) up to a maximum of 50 mg/day or matching placebo for a period of 10 days. Randomisation will be blinded so that trial participants, the investigator team (including the facial image assessors), data management staff, data analysis staff and any other clinical staff will remain unaware of the study arm to which trial participants have been assigned. Only the central pharmacist at the RCH and the independent statistician who generated the randomisation list will be unblinded. Blinding will be undertaken to prevent ascertainment and performance biases. All participants will receive the study drug (prednisolone or placebo) orally in liquid form. The senior medical doctor on duty in the ED (SDED) or a medically qualified member of the investigator team will determine the number of milliliters of study drug required per day based on a pre-calculated weight-based table and record this on the study drug bottles. The study drug will be prescribed as a once daily dose. Prednisolone will be supplied as REDIPRED® (Prednisolone sodium phosphate oral liquid). It contains the active prednisolone sodium phosphate 6.72 mg/mL which is equivalent to 5 mg prednisolone). The placebo will be supplied by Aspen Pharmacare Pty Ltd, the manufacturer of REDIPRED to match the REDIPRED in terms of look and taste.

* 1. SAMPLE SIZE

A total of 540 participants will be enrolled and randomised in this study (approximately 270 per group).

Based on our observational data, we expect 60% of children without prednisolone to have complete recovery at 1 month. This is in line with data from a paediatric RCT which reported complete recovery without prednisolone in 72% at 4 months (Unuvar et al 1999). A study in adults found an improvement of 12% (Sullivan et al 2007) with prednisolone compared with placebo which was deemed to represent a clinically important difference between treatment groups. We therefore power our study to find an increase in the proportion with complete recovery from 60% in the placebo group to 72% in the prednisolone group. This is a conservative estimate of efficacy compared with that found in our observational pilot data which showed an increase in complete recovery at 1 month of 16% in those treated with prednisolone (75%) compared with those not receiving prednisolone (59%). To enable us to identify an increase in recovery from 60% to 72% or larger with 80% power requires a study with 244 subjects in each treatment group based on a two-sided test with α=0.05. Hence, we aim to recruit 270 per group (540 in total) to allow for 10% loss to follow-up at 1 month.

* 1. STUDY PROCEDURES

1. Presentation of a child with suspected Bell’s Palsy
2. Inclusion criteria and exclusion assessed
3. Confirmed Bell’s Palsy by SDED
4. Informed consent obtained or declined
5. If consent is obtained, randomisation using lowest numbered study pack in the appropriate strata
   * CRF assigned to patient and time point 1 (enrolment and randomisation) information including HB scores completed on the CRF;
   * Prednisolone or placebo prescribed for 10 days with first dose administered in ED
   * Optional facial imaging (video ± still photographs of standard facial expressions) will be performed and uploaded to the study database
   * The participant will take the first dose of study drug while in the ED
6. Telephone call time point 2 (Day 10-14 post randomisation)
7. Study visit at time point 3 (28 days post randomisation)
8. Study visit or telephone survey at time point 4&5 (3 & 6 months)

At the conclusion of the trial, and after the final SAP has been drafted approved and made publicly available, the data will be analysed for manuscript preparation and submission for publication.

1. Populations of Analysis

1. The primary analysis will follow the intention-to-treat principle with all participants analysed according to their random allocation irrespective of what study drug is received. Participants found to be ineligible post randomisation will be included in the analysis and will be noted as a randomisation error. The only randomised participants who will be excluded from the analysis will be participants whose parents have withdrawn consent for any of their child’s data to be used as part of this study.

2. A secondary analysis will be conducted using a complete case analysis which will only include patients with data for the outcome being analysed.

3. We will also conduct a per protocol analysis where we will exclude participants who did not receive any study drug and those who were a randomisation error (see section 4.3), along with those who withdraw permission to use their data.

1. Outcome Variables
   1. PRIMARY OUTCOME

The primary outcome of this study is whether or not the child has complete recovery of their Bell’s Palsy at 1 month (defined as grade 1 on the HB scale as determined by a treatment blinded assessor). For this outcome and all secondary outcomes, the clock starts at the time of randomisation (time point 1).

* 1. SECONDARY OUTCOMES

The secondary outcomes are:

1. Complete recovery at 1 month using the Sunnybrook scale (defined as a score of 100) assessed by the site specialist physician. Sunnybrook scale <100 will be classified as non-recovery. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
2. Complete recovery at 3 months using the Sunnybrook scale (defined as a score of 100) assessed by the site research staff. Sunnybrook scale <100 will be classified as non-recovery. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
3. Complete recovery at 3 months using the HB scale (defined as HB grade 1) assessed by the site research staff. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
4. Complete recovery at 6 months using the Sunnybrook scale (defined as a score of 100) assessed by the site research staff. Sunnybrook scale <100 is non-recovery. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
5. Complete recovery at 6 months using the HB scale (defined as HB grade 1) assessed by the site research staff. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
6. Complete recovery at 1, 3 and 6 months using the HB scale (defined as HB grade 1) assessed by the site research staff within the subgroups of age (<12 years or >12 years), time to treatment (<24h or >24h to 72h) and initial severity (HB 1 to 4 vs HB 5 and 6). This will be analysed and presented as binary data. This will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
7. Parent/guardian and participant (where aged >8 years) perception of facial nerve recovery at 1, 3 and 6 months using a lay translation of the HB scale (defined as HB grade 1). This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
8. Emotional and functional wellbeing of the participant assessed by the parent/guardian and participant using the Pediatric Quality of Life Inventory (PedsQL) and Child Health Utility 9D (CHU9D) scales and sections of the Harter scale at 1, 3, and 6 months.This will be analysed using the utility values obtained from the scales and translated into QALYs over each child's period of follow-up by using area under the curve methods.
9. Pain at 1, 3 and 6 months assessed using child assigned visual analogue scale or Faces Pain Scale Revised (for participants aged 5 and older) and using parent assigned VAS for participants at any age. Both pain scales are numbered 0-10 where no pain is a score = 0 and pain defined as score >1. The scale will be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
10. Prevalence of synkinesis at 1, 3 and 6 months assessed using the Sunnybrook scale (where no synkinesis is 1 and synkinesis is any score >1) assessed by the specialist clinician and site research staff at 1 month and the site research staff at 3 and 6 months. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
11. Prevalence of synkinesis and autonomic dysfunction at 1, 3 and 6 months assessed using the synkinesis assessment questionnaire (where no synkinesis and autonomic dysfunction is defined as a total SAQ score of 20, and synkinesis or autonomic dysfunction is any score >20), assessed by the specialist clinician and site research staff at 1 month and the site research staff at 3 and 6 months. This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.
12. Health utilisation costs assessed via CHU-9D and via capture of information from the parent/guardian/participant related to in-patient, out-patient, or ED visits and to any other health facilities including general practitioner attendance for treatment or investigation during the 6 months following randomisation.
13. Parent/guardian and participant (where aged >8 years) perception of facial nerve recovery at 12 months (outside the RCT period of 6 months) for patients not recovered at 6 months using a lay translation of the HB scale (defined as HB grade 1). This will be analysed and presented as binary data. The scale will also be analysed as a continuous variable summarised as a median (IQR) or mean (SD) depending on normality.

For all scales, we will use either median (IQR) or mean (SD) and related inferential statistics at all time points.

* 1. OTHER PARAMETERS

The following will be presented for each population (see 3. Populations of analysis: 1,2,3)

**DEMOGRAPHY AND BASELINE**

* Age (in years) – summarised as range, median (IQR) or mean (SD) depending on normality, and the number and proportion <12 years or ≥12 years in each treatment arm
* Site – number and proportion in each treatment arm
* Gender – number and proportion in each treatment arm
* Ethnicity – number and proportion in each treatment arm
* Weight in kgs – summarised as range, median (IQR) or mean (SD) in each treatment arm
* Time to treatment (onset of symptoms to commencement of treatment) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality
* Triage category in ED – number and proportion in each treatment arm
* Symptoms on presentation:
  + Side of ipsilateral facial weakness – number and proportion in each treatment arm
  + Pain scale (child reported) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality
  + Pain Scale (parent reported) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality
  + Initial severity measured using the HB scale (clinician) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality
  + Initial severity measured using the parent perception HB scale (parent) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality
  + Initial severity measured using the Sunnybrook scale (clinician) – summarised as range, median (IQR) and mean (SD) in each treatment arm depending on normality.

**SAFETY**

Adverse events will be assessed at all study time visits. In terms of adverse events relevant to the intervention, we will report adverse events within 1 month of randomisation captured at the 14 day and 1 month assessments along with any incidental information via phone calls received within this 1 month timeframe. We will present adverse events after excluding reports judged by the study team to be part of the disease process (such as facial pain) and reports clearly unrelated to disease or intervention (such as a sprained ankle). Conditions that are present at screening and do not deteriorate will not be considered AEs. Therefore, we shall only be reporting on adverse events that are unexpected and potentially intervention related.

Adverse events will be reported as the number and proportion of participants in each treatment arm with one or more adverse events and the number of adverse events in each category.

**PROTOCOL VIOLATIONS**

These will be defined as having a potential impact on the outcome for that participant.

The following events will be recorded and reported as protocol violations:

Study drug

* Did not receive any study drug
* Failed to discontinue study drug at Day 10
* Administration of the incorrect study drug

Randomised in error

* Randomised when at the point of randomisation, they were in fact ineligible or met exclusion criteria and should never have been randomised

Participants who experience a protocol violation will be excluded from the per protocol analysis.

Protocol violations will be summarised by treatment arm – number and proportion in each category.

**PROTOCOL DEVIATIONS**

These will be defined as having minimal impact on the outcome for that participant.

The following events will be recorded and reported as protocol deviations:

* Data recorded outside the specified timeframe for a study visit.
* Missed 1 or more dose of study drug
* Receipt of prednisolone outside of that specified in the protocol

The number of participants with a protocol deviation will be summarised by treatment arm as the number and proportion in each category. Participants with a protocol deviation will be included in both the ITT and the per protocol analysis.

**TREATMENT COMPLIANCE**

Compliance will be defined as the participant receiving 10 doses (i.e. 1 dose per day for 10 days to a maximum of 10 doses). Data collected at the 10–14-day timepoint will be used to check compliance.

All participants will be included in the ITT analysis regardless of compliance. Only participants who do not receive any of their assigned intervention will be excluded from the per protocol analysis (see definition of protocol violations).

Compliance will be summarised using the available data and presented by treatment arm as number of doses given and whether or not the participants had received all 10 doses.

1. Statistical Methodology
   1. GENERAL METHODOLOGY

**HANDLING OF MISSING DATA**

As detailed in the protocol, participants who were deemed to have fully recovered according to the HB scale (i.e., achieved a HB score of 1) at the 1 month visit were not required to attend the study site for the remaining study time points. For these participants, the HB score at the 3 and 6 months will be set to 1. Similarly, participants who were deemed to have fully recovered according to the HB scale (i.e., achieved a HB score of 1) at the 3-month visit were not required to attend the study site for their 6 month visit. For these participants, the HB score at 6 months will be set to 1. These data will not be classified as missing.

In a similar vein, participants who were deemed to have fully recovered according to the Sunnybrook scale (i.e., achieved a Sunnybrook score of 100) at the 1 or 3 month visit who have missing data on the Sunnybrook scale at later time points will have their Sunnybrook score at the missing time points set to 100. These data will not be classified as missing.

As we expect at least some missing data (in addition to that described above), and we suspect that the missingness will be related to the characteristics of the participants, multiple imputation will be used to handle missing data for the primary analysis of all outcomes. All outcomes (aside from the cost outcomes) will be imputed using a single (joint) imputation model via fully conditional specification. Binary variables will be imputed using logistic regression and continuous variables (including pain scores which are essentially continuous) will be imputed using linear regression, or predictive mean matching if non-normal. Baseline variables and compliance to treatment will be included as auxiliary variables in the imputation model. Imputation will be carried out separately by treatment arm, to ensure that any treatment effects are maintained, using 50 imputed datasets.

A complete case analysis will be presented as a secondary analysis.

In the reporting of study results, summaries of baseline and outcome variables will be presented using the available data (including the carried forward recovered data described above), however summaries of the completed data following multiple imputation will be presented as part the supplementary material. Inferential statistics will be presented based on the multiply imputed data, with the results from the secondary complete case analysis presented in the supplementary material.

**HANDLING OF WITHDRAWALS**

Participants who have withdrawn consent for their data and their child’s data to be included in the study will be excluded from all analyses**.**

* 1. BASELINE CHARACTERISTICS

Baseline characteristics described above will be summarised by treatment group in each population (see 3. Populations 1,2,3) using means and standard deviations (SD) or median (IQR) for continuous outcomes and number and % for categorical outcomes.

* 1. ANALYSIS OF THE PRIMARY OUTCOME

The primary outcome of complete recovery at 1 month post randomisation on the HB scale will be presented as the number and proportion in each treatment group, with a comparison between the groups presented as a difference in proportions and as odds ratio from a logistic regression model adjusted for site, with a 95% CI and p-value for the hypothesis that there is no difference between the prednisolone and placebo group (primary objective). In addition, we will present the results as Number-Needed-to-Treat (NNT) and its 95% CI.

As a sensitivity analysis, recovery at 1 month on the HB scale will be repeated assuming that all participants with missing data who have not previously been recorded as achieving complete recovery 1) have recovered, and 2) have not recovered, and using a complete case analysis. As a second sensitivity analysis, we will repeat the analysis adjusted for age (as a continuous variable), gender, baseline severity of facial nerve dysfunction (severe = HB grade 5 or 6, non severe = HB grade 1 to 4) and time to treatment (<24 vs >24-72 hours) as potentially important confounders.

* 1. ANALYSIS OF THE SECONDARY OUTCOMES

For secondary objectives 1 and 2, binary outcomes will be presented as the number and proportion with the outcome in each treatment group, with comparisons between the groups presented as a difference in proportions and as odds ratios from logistic regression adjusted for site, with 95% CIs and p-values. Continuous outcomes will be presented as median (IQR) and means (SD) within each treatment group, with comparisons made using linear regression adjusted for site presented as mean differences, 95% CIs and p-values. Time to recovery will be assessed using a Cox proportional hazards models censoring patients who have not recovered at 6 months, with results presented as a hazard ratio, with its 95% CI and p-value for the hypothesis that there is no difference between the prednisolone and placebo group.

For these secondary outcomes, we will repeat the analysis adjusted for age (<12 years or >12 years), gender, baseline severity of facial nerve dysfunction (severe = HB grade 5 or 6, non severe = HB grade 1 to 4) and time to treatment (<24 vs >24-72 hours) as potentially important confounders. We will also repeat the analysis using a complete case analysis.

Secondary objective 3, the comparison of the assessment of recovery based on HB scoring by face-to-face assessment versus facial images, HB scoring by face-to-face assessment vs parent/guardian and participant scoring of facial recovery, HB scoring vs Sunnybrook scoring will be analysed using the intra-class correlation coefficient and presented using Bland-Altman plots. This analysis will be conducted combining the data from the two treatment groups.

Secondary objective 4, comparing health service utilisation by 6 months between the intervention groups, will be assessed by the University of Melbourne Health Economics team. This will be analysed using the incremental cost-effectiveness ratio (ICER) per QALY, calculated as the mean cost difference divided by the difference in QALYs. To account for uncertainty due to sampling variation, the 95% confidence intervals for differential costs, QALYs and corresponding ICER will be calculated using bootstrap methods.

Secondary objective 5, recovery at 12 months for participants not recovered at 6 months based on parent/guardian and participant scoring of facial recovery, will be presented descriptively only, summarised as the number and percent by treatment group. This will occur outside the RCT study period which ends at 6 months.

There are no adjustments for multiplicity, hence in any presentation, publication, summary or conclusion, secondary outcomes will be explicitly stated to be secondary outcomes and results will be interpreted conservatively.

* 1. SUB-GROUP ANALYSES

As per secondary objective 2, the analysis of recovery rates according to the HB scale will be repeated according to age (<12 years or >12 years), time to treatment (<24h or >24h to 72h) and initial severity (severe = HB grade 5 or 6, non severe = HB grade 1 to 4) using the same methodology as described above.

The study is powered to compare the intervention and control groups for the trial as a whole; the study will be underpowered to determine any effect within subgroups. Given this, the results from the subgroup analyses will be reported and interpreted as exploratory only.

6. References

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