Statistical Analysis Plan

Study Code:	FACE
Study Title:	The Facial nerve palsy And Cortisone Evaluation (FACE) study in children: A randomized double-blind, placebo-controlled, multicenter trial
Based on protocol version and date:	Protocol version 2.3_2021-06-04
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Sponsor:	Dalarnas county council (Region Dalarna)

Reviewed and approved by Biostatistician (UCR);

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Date: 2022-07-20

Approved by Sponsor's Representative;

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Signature:

Date: 2022-07-18

SAP version:	FINAL

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1. Version History

Version	Date	Reason for Change
Draft 1.0	2022-02-24	
Draft 1.0	2022-04-13	See previous version

2. Introduction

The aim of this statistical analysis plan (SAP) is to describe details of planned presentation of the study data described to be performed by the UCR (Uppsala Clinical Research) Statistics section. The results will be presented according to the output specification (see Appendix 1 Output Shells). The UCR study biostatistician is responsible for writing the plan with necessary input from other members of the study team. A biostatistician not otherwise involved in the study together with the sponsor will approve the final version.

The SAP is based on the study protocol "CLINICAL STUDY PROTOCOL__FACE_01_version 2.3.docx"

3. Abbreviations

AE	Adverse Events
AUC	Area under the curve
CI	Confidence Interval
CKF	Center for Clinical Research, Dalarna
CRF	Case Report Form
FACE	Facial nerve palsy and cortisone evaluation in children study
FaCE-scale	Facial Clinimetric Evaluation Scale
FDI	Facial Disability Index
HB	Houce_Brackmann scale
ITT	Intention to treat
NeBoP	Clinical neuroborreliosis prediction test
PP	Per Protocol
PROMs	Patient/parent reported outcome measures
LOCF	Last Observation Carried Forward
SAE	Serious Adverse Events
SAQ	Synkinesis Assesment Questionnaire
SB	Sunnybrook scale
SD	Standard Deviation
SEM	Standard Error of the Mean
SBPS	Scandinavian Bell's Palsy Study
SUSAR	Suspected Unexpected Serious Adverse Reaction
UCR	Uppsala Clinical Research Centre

4. Background

In the Swedish pediatric populations about 5-21/100 000 children per year suffer from acute facial nerve palsy, which relates to a swollen and dysfunctional facial nerve. However, no efficient evidence-based treatment/clinical guidelines exist for these affected children. The purpose of this project is therefore to evaluate the efficacy of cortisone treatment (prednisolone) given to children with acute facial nerve palsy in a randomized placebo-controlled trial (RCT). We hypothesize that prednisolone will improve clinical outcome for children with facial nerve palsy, even after that no further spontaneous improvement is expected (12 months) by reducing inflammation and swollenness of the facial nerve.

5. Study Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this study is to evaluate the efficacy of cortisone versus placebo treatment in children with acute facial nerve palsy, measured as physician assessed recovery with the House-Brackmann grading scale.

5.1.2. Secondary Objective(s)

The secondary objectives are:

- to evaluate the total recovery rate at 1 month as compared to the total recovery rate at 12 months, in order to evaluate if prediction of recovery at 1 month is feasible and/or useful in children with acute facial nerve palsy
- to evaluate subjective symptoms and influence in daily life in children with acute facial nerve palsy
- to evaluate the safety profile for cortisone in children with acute facial nerve palsy

5.2. Endpoints

5.2.1. Primary Endpoint(s)

The primary endpoint is the total recovery rate at 12 months follow-up in the two treatment groups measured with the House-Brackmann scale.

5.2.2. Primary outcome measure

The physician performed House-Brackmann grading scale (1 is normal and 6 is total loss of function) is chosen as primary outcome measure in the FACE study, since it is a valid and easy to perform grading scale for evaluation of facial nerve function and it has most

frequently been used in previous studies. The primary outcome measure (recovery) is defined as House-Brackmann grade 1 at 12 months follow-up. The time point for the primary outcome is chosen as no further spontaneous recovery of the facial nerve function is expected after 12 months and it is used in previous studies.

5.2.3. Secondary Endpoint(s)

Secondary endpoints are:

- the total recovery rate at 12 months follow-up in the two treatment groups measured with the Sunnybrook scale.
- The Sunnybrook scale (100 is normal function and 0 is total loss of function) is another objective scale for grading the facial nerve function. It will be used as secondary outcome measure. It is validated for children, easy to perform and has been used in previous studies It correlates well to the House-Brackmann scale and has been shown to be useful for prediction of recovery in adult patients.
- the agreement between the two grading scales for facial impairment (House-Brackmann and Sunnybrook), in order to decide which grading scale has the most preferable utility and should be recommended in pediatric patients
- the total recovery rate at 1 month follow-up as compared to the total recovery rate at 12 months follow-up, measured with Sunnybrook and House-Brackmann scale (prediction).
- quality of daily life at 1 and 12 months follow-up measured with the Facial Clinimetric Evaluation (FaCE) scale and the Facial Disability Index (FDI) and at the 12 months measured with the Synkinesis Assessment Questionnaire (SAQ) and to correlate them to the physician assessed House-Brackmann and Sunnybrook grading scales .
- number of Adverse Events possibly or probably related to the study drug during the 12 months follow-up.

5.2.4. Secondary outcome measures

The physician performed Sunnybrook grading scale (100 is normal and 0 is total loss of function) is chosen as secondary outcome measure as it correlates well to the House-Brackmann scale in adult patients, is easy to perform and evaluates facial function in rest and activity. Both the House-Brackmann and the Sunnybrook grading scale are included in order to be able to evaluate agreement between them, and to decide which one has the best most preferable utility and thus should be recommended for evaluation of facial nerve palsy in children. Sunnybrook has also been used for prediction of prognosis in adult patients and will now be evaluate for prediction of recovery in pediatric patients.

Three validated child/parent assessed instruments for disease specific quality-of-life are chosen as additional secondary outcome measures for patient/parent reported outcome measures (PROMs), in order to examine and better understand facial disability (18-21).

The Facial disability index (FDI) consists of 10 different items (6 is full satisfaction, 1 is no satisfaction) divided into two domains; physical function (with composite score of -25 – 100) and social/well-being function (with a composite score of 0-100) (18).

The Facial Clinimetric Evaluation Scale (FaCE scale) includes 15 items (5 is full satisfaction, 1 is no satisfaction) in six domains and a total composite score of 0-100.

The Synkinesis Assessment Questionnaire (SAQ) includes 9 items concerning defect recovery (1 is full satisfaction, 5 is no satisfaction) and gives composite score of 0-100.

6. Study design

The FACE study is a randomized double-blind, placebo-controlled, multicenter trial. The study is a randomized two armed intervention study with several well-defined clinical outcome measures with a superiority hypothesis testing in favor for the intervention (prednisolone).
Children with acute facial nerve palsy (idiopathic or *Borrelia*-associated) will be recruited at 17 study centers during 2019-2023 and followed during 12 months. Inclusion and exclusion criteria are set.
The Principal Investigator (a pediatrician) or a co-Investigator (an Ear-Nose-Throat specialist) will be responsible for performing the objective evaluation of the facial nerve function on admission (or one day after) and at the follow-up visits 1 month and 12-months.
Study nurses will take care of parts of the study work, such as performing the one and two weeks telephone calls, collecting questionnaires from the child/parents/guardians, collecting and entering data in the CRFs and being the main contact person for the monitor.
Participants are randomly assigned to prednisolone or placebo. Content in bottles with study drug are blinded and coded after a randomization list in variable blocks without stratification. Bottles with study drug has been distributed to each study center.

Intervention:
Prednisolone 1 mg/kg (max 50 mg) per orally once daily in 10 days, given as 5 mg capsules (blinded) based on weight intervals (5 kg) up to > 50 kg.

Control:
Placebo

End of the study is defined as the 12 months follow-up visit for the last patient.

Table 1. Visit Schedule

	Screening/ Baseline	Telephone call 1 week ± 3 days	Telephone call 2 weeks ± 3 days	Visit 1 month ± 5 days	Visit 12 months ± 2 weeks
Informed consent	X				
Inclusion /Exclusion criteria	X				
Medical history	X				
Demographics	X				
Weight/length/BMI	X				
Physical examination	X				
NeBoP score	X				
House-Brackmann scale	X			X	X
Sunnybrook scale	X			X	X
Concomitant medication	X			X	X
Distribution of study medication	X				
Compliance of study medication		X	X		
Reporting of Adverse Events		X	X	X	X
Return of unused tablets				X	
Facial disability index				X	X
Facial Clinimetric Evaluation Scale				X	X
Synkinesis Assessment Questionnaire					X

7. Definition of Analysis Populations

The analysis of data will be based on different subsets according to the purpose of the analysis.

Screening failure	Patients that have been screened but have not received any investigational product, will be considered as screen failures
Withdrawals	Patients that fulfil inclusion criteria and have signed informed consent but withdrew after inclusion (before data were collected)
Intention to treat (ITT)	All randomized patients receiving at least one dose of study drug and have available data. The ITT data set will be used for the safety as well as for the efficacy endpoints
Per Protocol (PP)	The PP comprises data from all subjects randomized and treated with evaluable efficacy data, and no major protocol deviation that significantly affects the evaluability of the subject in the study. The PP will be used for presentation of the primary endpoint only.

NOTE:
Screening failures will not be included in the study database.

For participants considered lost to follow-up, the CRF will be completed up to the last visit performed. Timing of withdrawal or loss to follow-up will be presented for each group and each time point in the CONSORT flow diagram.

Criteria for withdrawal are:

- AE that precludes further continuation of treatment
- No compliance with study procedures
- The patient becomes pregnant
- Other medical to the Investigator
- Patient's decision

8. Description of statistical analysis

All variables will be presented in summary tables and/or per-patients data listings (when appropriate) within treatment group and in total. Graphical presentations may be used if necessary. Descriptive statistics are defined as frequency (%) tables for qualitative variables and as number of observations, means, standard deviations, medians, Q1, Q3, and minimum and maximum values for quantitative variables. Normality of data will be determined by visual inspection of histograms. No adjustment for covariates will be made.
All statistical tests and confidence intervals will be two-sided. The level of significance will be 5%.

8.1. Study conduct and Subject/Patient disposition

The number of patients included in the study will be presented together with the number of patients by visit (1 month, 12 months). The numbers withdrawn in total and for each pre-defined withdrawal reason, and the allocation of patients to each analysis population group will be presented in the table. Number of patients will be presented by treatment and in total.

8.2. Baseline Characteristics and Treatment Group Comparability

Demographics and baseline characteristics such as age, sex, weight, blood pressure, NeBoP test etc. will be summarized by treatment group and in total.
Continuous variables such as Sunnybrook-scale will be summarized by number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Categorical variables will be summarized in frequency tables (presenting frequencies and proportions). Medical history will be presented in a table and, if appropriate listed as a per-patient data listing. Adverse Events that occur before first treatment will be reported separately as baseline event.

8.3. Treatment Administration/Compliance

The intervention is treatment with either prednisolone (capsule Prednisolone 5 mg), 1 mg/kg once daily in 10 days or control treatment (capsule placebo) once daily in 10 days. The number of capsules is based on the child's weight and presented in the table below:

Child´s weight /kg	Number of capsules/day	Total number of capsules
5 - 9.9	2	20
10 - 14,9	3	30
15 - 19.9	4	40
20 - 24.9	5	50
25 - 29.9	6	60
30 - 34.9	7	70
35 - 39.9	8	80
40 - 44.9	9	90
>45	10	100

Capsule Prednisolon 5 mg (APL), dosage 1 mg/kg (max 50 mg) once daily for 10 days according to pre-calculated weight. All bottles include 100 capsules.

Compliance for the 10 day period:

Compliance (0-100%) = (Number of tablets actually taken x 100)/total number of capsules

Patients with treatment compliance less than 70% will be excluded from the PP analysis. Patients with 0% compliance will be excluded from ITT analysis.

8.4. Concomitant medications

Children with *Borrelia* associated acute facial nerve palsy will receive antibiotic treatment according to national guidelines.
All other concomitant medications permitted in the study will be presented in per-patient data listings and in a table by treatment group an in total. Data registered are generic/trade name, dosage, start and end date of the medication, and indication.

8.5. Primary efficacy analyses

Efficacy of cortisone treatment versus placebo will be compared between intervention group and control group at 12-months follow-up, with the outcome measured with House-Brackmann. Recovery will be defined as HB=1. Comparisons between dichotomous variables (i.e. recovered/not recovered) will be performed between groups using Chi2 (or Fisher's exact test) with risk estimate and 95% confidence interval. Mann-Whitney U-test will be used when comparing score medians for the House-Brackmann grading scale.

8.6. Secondary efficacy analyses

Efficacy of cortisone treatment versus placebo will be compared between intervention group and control group at 12-months follow-up, secondarily with the outcome measured with Sunnybrook scale. Recovery will be defined as SB=100. Comparisons between dichotomous variables (i.e. recovered/not recovered) will be performed between groups using Chi2 (or Fisher's exact test) with risk estimate and 95% confidence interval. Mann-Whitney U-test will be used when comparing score medians for the Sunnybrook grading scale or other continuous variables.
Results for continuous variables will be given as median values with interquartile range (IQR; 25th to 75th percentiles) and dichotomous data (i.e. full recovery/not full recover) as proportions with 95% confidence interval using the normal approximation approach.

8.6.1. Prediction models

Logistic regression analysis will be used to evaluate if recovery at 1 month follow-up can predict recovery at 12 months follow-up. Recovery will be defined as
HB=1
and
SB=100
at 12 months.
Multivariate models will also be performed with 1 month HB/SB scale and baseline variables. We will test if any baseline variables are independently significant together with the scale (HB/SB) at 1-month, and if they increase the predictive ability in the model.
Results will be presented as p-values, odds ratio and 95% CI. To evaluate the predictive ability, ROC curves will be constructed and number of correct classified observations will be presented together with AUC and sensitivity and specificity at the optimal cut-point.

8.6.2. Correlation and agreement

For correlations between degree of recovery measured by physician assessed grading (House-Brackmann or Sunnybrook) and child/parent assessed quality-of-life measures at 1 and 12 months follow-up visits, Spearmans's correlation will be used.

QoL will be measured with:
- Facial Clinimetric Evaluation (FaCE) scale (0-100)
- Facial Disability Index (FDI) scale, as two separate subscales Physical function (0-100) and Social/Wellbeing (0-100).
- Synkinesis Assessment Questionnaire (SAQ) scale (0-100)

Agreement between House-Brackmann and Sunnybrook grading scale will be assessed using Cohen's kappa.

8.7. Safety analyses

Adverse events (AEs) will be presented in per-patient data listings and summarized in frequency tables. A summary table will be presented with number of patients with:

- AEs
- serious AEs
- related AEs
- AE leading to discontinuation

for each treatment and in total.

Adverse events (AEs) will be presented in per-patient data listings and summarized in frequency tables by treatment and in total. AEs will be summarized as number of events and number of patients, respectively, by intensity, seriousness and relationship. SAE will be presented in a separate listing.

Safety profile will be evaluated by comparing number (%) of adverse event (AE) and serious adverse events (SEA) in each group. Difference between groups in safety profile will be compared with Chi2-test or when appropriate, Fischer's exact test.

8.8. Handling of Missing Data

Missing values where the patients have been completely recovered at the last visit will be imputed with the method of last observation carried forward (LOCF).
Other missing values where patients have not been recovered and did not complete follow-up clinic visits will be imputed using worst case last observation carried forward.

The LOCF method will be used for the primary analysis only. For secondary analyses, the complete case analysis will be applied.

In case of incomplete start dates and end dates of adverse events, the "worst case" date will be used. For example, if "December 2020" is recorded as the time of start or end of an adverse event, December 1, 2020 and December 31, 2020, will be used as start- and end-date, respectively.

The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.
For other variables, missing data will result in a reduced sample size for that parameter. A patient who withdraws prior to the last planned observation will be included in the analysis up to the time of discontinuation.

8.9. Subgroup analysis

Recovery (at 12 months) between treatment groups will be analysed in the subgroup:
-children with idiopathic facial nerve palsy or *Borrelia* associated facial nerve palsy

To predict recovery at 12 months follow-up logistic regression analysis will be used by following subgroups:

-diagnosis (*Borrelia* associated/Not *Borrelia* associated)
-treatment (Prenisolone/Placebo)
-age group (1-5, 6-10, 11-14, 15-18)
-gender (Girls/Boys)

Presentation of the results is described in section 8.6.1
Subgroup analysis for comparison between Placebo and Prednisolone at 1 and 12 month for QoL variables and HB/SB scales will be performed (see Appendix 1 table 7)

8.10. Other planned analyses

8.10.1. Quality of life

Disease-specific quality-of-life measures (FDI, FaCE scale and SAQ) will be considered as continuous variables (composite scores 0-100). Depending of the distribution, appropriate statistical method (parametric/non-parametric) will be used to compare quality-of-life between groups at 1 and 12 months follow-up visits.

9. Determination of sample size

Sample size for the FACE study is calculated on the primary outcome (i.e. number (%) of patients with total recover of the facial nerve palsy in each intervention group, measured by House-Brackmann grade 1, at 12 months follow-up). An 10% difference of the total recovery rate between groups (80% in placebo group versus 90% in prednisolone group) is an estimation from earlier non-RCT studies, interviews with children/parents (unpublished data) and a test of two independent proportions for estimation of the minimal relevant clinical improvement (MRC). To show that such a difference is significant ($p < 0.05$, two-sided test) with 80 % power, a total of 430 patients are needed. However, due to the uncertainty in the assumptions and to that a portion (10%) of patients not taking part of the study follow-up, 500 patients will be included in the FACE study (250 in each group).

10. Interim Analysis Plan

There will be no interim analysis in this study.

11. Changes in the Planned Analysis

Not applicable

12. Description of Derived Variables

Duration of AE: stop date minus onset date expressed in days

Variable	Algorithm in words	SAS Variable name
Complete recovery of palsy at month 1 according to SB scale	Healed (1) if sunnybrook scale at month 1 is 100. If sunnybrook at month 1 ≤99 then patients are considered as not healed (0)	Month1_SB_healed
Complete recovery of palsy at month 12 according to SB scale	Healed (1) if sunnybrook scale at Month 12 visit is 100. If sunnybrook at Month 12 visit ≤99 then patients are considered as not healed (0)	Month12_SB_ghealed
Complete recovery of palsy at month 1 according to HB scale	Healed (1) if HB scale at Month 1 visit =1. If HB scale at Month 1 visit >1 then patients are considered as not healed (0)	Month1_HB_healed
Complete recovery of palsy at month 12 according to HB scale	Healed (1) if HB scale at Month 12 visit =1. If HB scale at Month 12 visit >1 then patients are considered as not healed (0)	Month12_HB_healed
Compliance (%)	Compliance in % = (total number of capsules (10) minus Number of capsules remaining) * 100/10 (0% - 100%)	Compliance_pct

FaCE scale (Total score will be used)

APPENDIX B

Facial Movement Score = (((Items 1 + 2 + 3) - # valid) / 4 × (# valid)) × 100

Facial Comfort Score = (((Items 4 + 6 + 16) - # valid) / 4 × (# valid)) × 100

Oral Function Score = (((Items 11 + 12) - # valid) / 4 × (# valid)) × 100

Eye Comfort Score = (((Items 5 + 7) - # valid) / 4 × (# valid)) × 100

Lacrimal Control Score = (((Item 8) - # valid) / 4 × (# valid)) × 100

Social Function Score = (((Items 9 + 10 + 14 + 15) - # valid) / 4 × (# valid)) × 100

Total Score = (((Sum of all 15 items) - # valid) / 4 × (# valid)) × 100

valid = number of items within the domain for which an adequate response was given.

SAQ	Total Synkinesis Score: (Sum of Scores 1 to 9)/45 x 100
FDI	Will be used as subscale Physical and social/well-being function

Scoring:

Physical Function

$$\frac{\text{Total Score (questions 1–5)} - N}{N} \times \frac{100}{4}$$

N = number of questions answered

Social/Well-being Function

$$\frac{\text{Total Score (questions 6–10)} - N}{N} \times \frac{100}{5}$$

13. Description of Output

See Appendix 1: SAP FACE Appendix 1 (OS).docx

14. Statistical software

SAS version 9.4 or later. R (version 3.2.2) and SPSS (version 26) may be used.

15. References