FORM-STAT-04A-01	Statistical Analysis Plan
Version 1.0	

An open label randomised controlled trial of Coolsense® versus Buzzy® versus standard care for Minimising Immunisation Pain of childhood vaccines in Older children: The MIPO Study

Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
20.04.2022	1	Xiaofang Wang		Initial release.	Not applicable.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CFS	Children's Fear Scale
CRF	Case Report Form
GCP	Good Clinical Practice
ITT	Intent-To-Treat
LOCF	Last Observation Carry Forward
LS	Least Squares
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
MedDRA	Medical Dictionary for Regulatory Activities
WHO DD	World Health Organization Drug Dictionary
VAS	Visual Analogue Scale

1. STUDY OBJECTIVES

(Protocol V4 19-07-2018)

1.1. PRIMARY OBJECTIVE

The primary objective of this RCT is to evaluate the efficacy of:

a. Coolsense® versus standard care
b. Buzzy® versus standard care

in minimising immunisation pain as assessed post procedure **by child/adolescent reported Visual Analogue Scale (VAS) Score.**

1.2. SECONDARY OBJECTIVES

Secondary objectives of RCT are:

1) To evaluate the efficacy of Coolsense® versus Buzzy® in minimising immunisation pain as assessed post procedure **by child/adolescent reported VAS Score**.

2) To evaluate the efficacy of
   a. Coolsense® versus standard care
   b. Buzzy® versus standard care
   c. Coolsense® versus Buzzy®

   in minimising immunisation pain as assessed post procedure by **Nurse VAS Score Post-Procedure**.

3) To assess the child/adolescent's level of fear/anxiety **pre-procedure by the child/adolescent using Children's Fear Scale (CFS) Score.**

4) To evaluate the efficacy of
   a. Coolsense® versus standard care
   b. Buzzy® versus standard care
   c. Coolsense® versus Buzzy®

   in minimising immunisation pain as assessed post procedure **by child/adolescent using Children's Fear Scale (CFS) Score Post-Procedure**.

5) To evaluate the efficacy of
   a. Coolsense® versus standard care
   b. Buzzy® versus standard care
   c. Coolsense® versus Buzzy®

   in minimising immunisation pain as assessed post procedure **by Nurse reported CFS Score Post-Procedure**.

6) To measure post procedure **parents perception of effectiveness and usefulness** of:
   a. Coolsense® versus standard care
   b. Buzzy® versus standard care
   c. Coolsense® versus Buzzy®

7) To measure post procedure **child/adolescent's perception of effectiveness and usefulness** of:
   a. Coolsense® versus standard care
   b. Buzzy® versus standard care
   c. Coolsense® versus Buzzy®

8) To measure **compliance** to pain minimising devices (Coolsense® and Buzzy®) and standard care.

2. BACKGROUND/INTRODUCTION

2.1. STUDY DESIGN

This is a three-armed, unicentre, randomised (1:1:1), open labelled, standard care controlled, parallel-group, superiority trial in 492 children/adolescents aged 10 to 17 years of age.

- Arm 1. Coolsense®
- Arm 2. Buzzy®
- Arm 3. Standard care (Distraction using electronic devices)

2.2. TREATMENT ARMS

Participants will be enrolled and randomised on the day of the vaccination via Redcap. Randomisation will be to Coolsense®, Buzzy® or Standard care with an allocation ratio of 1:1:1. Randomisation will be in randomly permuted blocks of variable length. An independent statistician in the Clinical Epidemiology and Biostatistics Unit (CEBU) at the Murdoch Children's Research Institute (MCRI) will provide the randomisation schedules to the Immunisation Clinic.

2.3. STUDY POPULATION

Inclusion Criteria

- All children/adolescents aged 10-17 years of age inclusive presenting with their parents/guardians to the Royal Children's Hospital Immunisation Service Drop-in Centre for immunisations.

Exclusion Criteria

- Child/adolescent with needle phobia (defined here by: fear of medical needle procedure and/or recent prior failure to vaccinate due to fear/distress of the procedure)
- Child/adolescent with Haemophilia or other bleeding disorders that require deep subcutaneous injections rather than intramuscular.
- Child/adolescent with damage to the skin at the site of injection E.g.: Overlying eczema.
- Child/adolescent with developmental or behavioural disorders that may prevent them from being able to complete a Visual Analogue Scale (VAS).

2.4. INTERVENTION

Coolsense®: Coolsense® is fully registered by the Therapeutics Goods Administration (2013) as a reusable, non-invasive hand-held device that immediately cools and numbs the skin at the site of an injection.

Buzzy®: Buzzy® is a vibrating handheld device used to help block sharp pain and provide distraction when giving injections to children. A frozen cooling pad (wings) is placed behind Buzzy® before the device is placed on the child/adolescent's arm.

Standard Care: In older children and adolescents, current standard care involves distraction with an IPAD.

2.5. SAMPLE SIZE

The study sample size will be 492 participants, randomly allocated in a 1:1:1 ratio to Coolsense® (n=164), Buzzy® (n=164) and standard care (n=164). This ensures sufficient power to support both primary outcomes. Since the study aims to assess two primary endpoints (1a. and 1.b), generalised Bonferroni-adjustment of p-values and confidence interval limits will be applied in order to warrant a global type I error probability of 5%.

a. For the primary objective - Coolsense® versus standard care:

Based on the results of our previous pilot RCT, we have powered this trial to be able to detect a difference child/adolescent reported VAS of 0.95 points between Coolsense® and standard care (equivalent to a 25% reduction from pain score in standard care - mean = 3.8). We have based our sample size estimate on a SD (Standard deviation) of 2.7. To detect a mean difference of 0.95 in VAS score post immunisation procedure (2.85-points in Coolsense® and 3.8 in standard care) with a two-sided significance level of 2.5% and power of 80% with equal allocation to these two arms would require 155 patients in each arm.

b. For the primary objective - Buzzy® versus standard care:

Based on the results of our previous pilot RCT, we have powered this trial to be able to detect a difference child/adolescent reported VAS of 0.95points between Buzzy® and standard care (equivalent to a 25% reduction from pain in standard care - mean = 3.8). We have based our sample size estimate on a SD of 2.7. To detect a mean difference of 0.95 in VAS score post immunisation procedure (2.85-points in Buzzy® and 3.8 in standard care) with a two-sided significance level of 2.5% and power of 80% with equal allocation to these two arms would require 155 patients in each arm.

Allowing for 5% loss to follow up, we will recruit 164 participants to each arm, therefore 492 in total.

2.6. STUDY PROCEDURE

All children/adolescents aged 10 to 17 years of age inclusive presenting with their parents/guardians to the Royal Children's Hospital Immunisation Service Drop-in Centre for immunisations will be invited to participate into the study. Once inclusion and exclusion criteria are assessed, participants will be enrolled and randomised on the day of the vaccination via REDCap. Data will be collected and be entered into a REDCap Software Version 6013.3 ©2016 Vanderbuilt University for analysis.

3. POPULATIONS OF ANALYSIS

Participants will be compared according to the arm to which they are randomly allocated, regardless of compliance to the device used, crossover to other arms or withdrawal from the study. This approach preserves the prognostic balance in the study arms achieved by randomisation.

4. OUTCOME VARIABLES

4.1. OUTCOMES

a. **Visual Analogue Scale (VAS) score child/adolescent reported, post procedure – primary outcome**

Child/adolescent report of pain using Visual Analogue Scale (VAS): assessment of their pain using a 10-point scale VAS following completion of the FIRST injection. The VAS is treated as a continuous variable.

b. **VAS score nurse reported, post procedure**

Nurse report of pain using Visual Analogue Scale: assessment of the child/adolescent's pain using a 10-point scale VAS following completion of the injection. The VAS is treated as a continuous variable.

c. Children's Fear Scale (CFS) score child/adolescent reported, pre and post procedure

The Children Fear Scale (CFS) is a tool used to measure fear in children undergoing painful medical procedures (McMurty et al., 2011). It ranged between 0-4, and it measures the child/adolescent's level of fear/anxiety as reported by the parent/guardian. It is assessed pre and post procedure.

d. CFS score nurse reported, pre and post procedure

As the CFS above but reported by the nurse.

e. Parent/Guardian perceptions of Effectiveness and Usefulness of randomised treatment

Assessed asking the following questions: "Do you feel the pain reducing treatment was effective?" And "Do you feel it would be useful next time your child has an immunisation?" (Yes/No/Uncertain).

The following two binary variables will be derived:

New Variable Name	Value	Formula
Effectiveness of device	= 1 (yes)	If *Technique effective*=Less Painful
	= 0	If *Technique effective*=More Painful OR No effect
Usefulness	= 1 (yes)	If *Use next time* = Yes
	= 0	If *Use next time* = No OR Uncertain

f. Child/Adolescent perceptions of Effectiveness and Usefulness of randomised treatment

Assessed asking the following questions: "Do you feel the pain reducing treatment was effective?" and "Do you feel it would be useful next time you have an immunisation?" (Yes/No/Uncertain).

The following two binary variables will be derived:

New Variable Name	Value	Formula
Effectiveness of device	= 1 (yes)	If *Technique effective*=Less Painful
	= 0	If *Technique effective*=More Painful OR No effect
Usefulness	= 1 (yes)	If *Use next time* = Yes
	= 0	If *Use next time* = No OR Uncertain

g. Compliance to randomised treatment

This will be assessed by the Nurse Immuniser based on the child/Adolescent's compliance with the device or distraction tool (IPAD). They are assessed as 1) Fully compliant, 2) Somewhat compliant or 3) Not compliant. The following binary variable will also be derived:

New Variable Name	Value	Formula
Full compliance	= 1 (yes)	If *Compliance Score* = Fully Compliant
	= 0	If *Compliance Score* = Somewhat Compliant OR Not Compliant

4.2. OTHER PARAMETERS

DEMOGRAPHY AND BASELINE

- Children/Adolescents' age, gender, presence of underlying medical conditions, vaccine administered, previous use of devices for pain minimisation, immunisation administration site.

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

The baseline and demographic characteristics of participants, as well as all the primary and secondary outcomes, will be presented for each arm using the mean, standard deviation (or medians and inter-quartile ranges for non-normal data) for continuous data and proportions for categorical data.

HANDLING OF MISSING DATA

Since it is expected that less than 5% (= drop-out rate assumed in the sample size calculation) of data is missing no imputation of missing data is planned. Therefore, outcomes will be analysed according to the available cases analysis approach.

Should the proportion of missing data be greater than 5%, multiple imputation analysis will be performed. The frequency and patterns of missing data will be examined. Multiple imputation models will be conducted separately in the three treatment arms using chained equations applied to all outcomes, including baseline measures, as auxiliary variables. Fifty imputed datasets will be generated including all randomised participants.

SUBGROUP ANALYSIS

N/A

CLASSIFICATION OF PROTOCOL VIOLATION

Protocol violations will be described in the text.

5.2. DATA ANALYSES

PRIMARY OUTCOME

The primary outcome (child/adolescent reported VAS) will be presented for each arm using the mean, standard deviation (or medians and inter-quartile ranges if not normally distributed).
Comparisons between (i) Coolsense® and Standard Care arms will be made using unadjusted and adjusted linear regression models, with the presentation of mean differences and 97.5% confidence intervals. Additionally, the 95% CI of the mean differences will be calculated as secondary analysis. The adjusted model will include the following covariates: child/adolescent gender, child/adolescent age at randomisation (in years), presence of any underlying medical condition at baseline (yes/no), previous use of any study device (yes/no). The adjusted model will also be adjusted for baseline factors that may not be balanced by the original randomisation.
Comparisons between (ii) Buzzy® and Standard Care arms will be made using unadjusted and adjusted (see covariates described above) linear regression models, with the presentation of mean differences and 97.5% confidence intervals. Additionally, the 95% CI of the mean differences will be calculated as secondary analysis.

Comparisons between (iii) Coolsense® and Buzzy® arms will be made using unadjusted and adjusted (see covariates described above) linear regression models, with the presentation of mean differences and 95% confidence intervals.

SECONDARY OUTCOMES b

The nurse reported VAS will be presented for each arm using the mean, standard deviation (or medians and inter-quartile ranges if not normally distributed).

Comparisons between (i) Coolsense® and Standard Care arms, (ii) Buzzy® and Standard Care, and (iii) Coolsense® and Buzzy® will be made using unadjusted and adjusted linear regression models, with the presentation of mean differences and 95% confidence intervals. Analogously to the primary analysis, the adjusted model will include the following covariates: child/adolescent gender, child/adolescent age at randomisation (in years), presence of any underlying medical condition at baseline (yes/no), previous use of any study device (yes/no). The adjusted model will also be adjusted for baseline factors that may not be balanced by the original randomisation.

SECONDARY OUTCOMES c AND d

Pre and post procedure child/adolescent, as well as nurse immuniser assessment of children's level of anxiety using CFS (categorical outcomes) will be presented separately by arms using proportions. Chi-square test for homogeneity will be applied to compare proportions.

A *sensitivity analysis* on child/adolescent CFS and nurse CFS (5 categories each), comparisons between Coolsense® and Standard Care arms, Buzzy® and Standard Care, and Coolsense® and Buzzy® will be made using unadjusted and adjusted (see covariates described above) linear regression models, with the presentation of mean differences and 95% confidence intervals.

SECONDARY OUTCOMES e, f, AND g

Compliance score (Fully/Somewhat/Not), both parent/guardian and child/adolescent's perception of effectiveness (No effect/Less painful/More Painful) and usefulness (Yes/No/Uncertain) will be presented separately by arms using proportions. Chi-square test for homogeneity will be applied to compare proportions.

Additionally, the derived binary variables: Full Compliance, both parent/guardian and child/adolescent's perception of effectiveness of device and usefulness will be analysed using unadjusted and adjusted GLM models with Gaussian error distribution (to avert convergence difficulties with low prevalence outcomes), linear link function and the robust variance estimator, and comparisons between treatment arms will be presented as risk differences and 95% confidence intervals for the following comparisons (i) Coolsense® and Standard Care arms, (ii) Buzzy® and Standard Care, and (iii) Coolsense® and Buzzy®. The adjusted model will include the following covariates: child/adolescent gender, child/adolescent age at randomisation (in years), presence of any underlying medical condition at baseline (yes/no), previous use of any study device (yes/no). The adjusted model will also be adjusted for baseline factors that may not be balanced by the original randomisation.

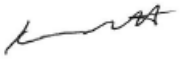
Table 1 – Summary of child/adolescent, parent and nurse reported outcomes statistical analyses

Outcomes	Statistical Model	Adjustment for covariates	Sensitivity analysis
a	Comparisons between treatment arms will be made using linear regression models, with the	- Unadjusted model - Adjusted model(1)	none

	presentation of mean differences and 97.5% confidence intervals for the following comparisons - Coolsense® and Standard Care - Buzzy® and Standard Care		
a b	Comparisons between treatment arms will be made using linear regression models, with the presentation of mean differences and 95% confidence intervals for the following comparisons - Coolsense® and Standard Care - Buzzy® and Standard Care - Coolsense® and Buzzy®	- Unadjusted model - Adjusted model[(1)]	none
c d	Chi-square test.	(SENSITIVITY ANALYSIS ONLY) - Unadjusted model - Adjusted model[(1)]	Comparisons between treatment arms will be made using unadjusted and adjusted linear regression models, with the presentation of mean differences and 95% confidence intervals for the following comparisons - Coolsense® and Standard Care - Buzzy® and Standard Care - Coolsense® and Buzzy®
e f g	Original outcomes: Chi-square test. Binary outcomes: Comparisons between treatment arms will be made using GLM models, with the presentation of Risk differences and 95% confidence intervals for the following comparisons - Coolsense® and Standard Care - Buzzy® and Standard Care - Coolsense® and Buzzy®	- Unadjusted model - Adjusted model[(1)]	none

[(1)] Adjusted by: child/adolescent gender, child/adolescent age at randomisation (in years), presence of any underlying medical condition at baseline (yes/no), previous use of any study device (yes/no). Model 2 will also be adjusted for baseline factors that may not be balanced by original randomisation

6. SIGNATURE PAGE

Signature of Principal Investigator:		Date 20-Apr-2022
Print Name	Kirsten Perret	

Signature of Trial Statistician:		Date 20-Apr-2022
Print Name	Francesca Orsini	