Centers for Disease Control and Prevention

Clinical Immunization Safety Assessment (CISA) Project

Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions

Short Title: Presyncope/Syncope Prevention Study (PS)

NCT # (NCT04772755)

Statistical Analysis Plan

Version 1.0 (10.7.2021)

October 7, 2021

1 Introduction

This document describes the statistical procedures that will be utilized for the CISA protocol Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions that was approved on March 4, 2021. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was developed prior to any data being collected in order to avoid bias. Any subsequent changes that occur to the study protocol warranting changes to the analysis procedures will be documented in the SAP (both draft versions (0.X) and the final version (X.0). Table 1 below will be used for tracking of changes to the SAP. In this study adolescents 10 through 14 years of age are randomized 1:1 to either the intervention or control group: 1) intervention (Buzzy® and electronic game); or 2) control (usual care).

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.1	24 June 2021	NA
1.0	07 October 2021	NA

2 Protocol objectives

2.1 Primary Objective (PO)

a) PO 1: To assess if simultaneous use of a vibration and cool pack device (Buzzy®) (reduces injection site pain) and an electronic game (simple active distraction intervention) before and during IM vaccination reduces risk for presyncope or syncope after vaccination in adolescents *Research hypothesis: The Buzzy® and electronic game intervention will be at least 50% effective at reducing risk for post-vaccination presyncope or syncope compared with control.*

2.2 Secondary Objectives (SO):

a) SO 1: To compare with control (usual care) the change in state anxiety score in adolescents before and after vaccination, when Buzzy® and the electronic game intervention are used.

b) SO 2: To compare with control (usual care) injection-site pain after vaccination of adolescents, when Buzzy® and the electronic game intervention are used.

c) SO 3: To assess acceptability of Buzzy® and the electronic game intervention among the adolescents.

2.3 Exploratory Objectives (EO):

a) EO 1: To assess if using Buzzy® and an electronic game before and during IM vaccination reduces risk for presyncope or syncope after vaccination using alternate case definitions for presyncope.

b) EO 2: To assess for factors associated with post-vaccination presyncope in adolescents in the control and intervention groups.

3 Study Outcome Measures

3.1 Primary Outcome Measures (POM):

a) POM 1: Proportion of adolescents with presyncope or syncope after vaccination in the intervention and usual care groups.

3.2 Secondary Outcome Measures (SOM):

a) SOM 1.1: Categorical change (positive, negative, no change) in pre- and post- vaccination state anxiety.
b) SOM 1.2: Numeric change (mean and 95% CI) in pre- minus post- vaccination state anxiety.
c) SOM 2.1: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at ≤ 1 minute following vaccination.
d) SOM 2.2: Proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination.
e) SOM 2.3: Proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination.
f) SOM 2.4: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination.
g) SOM 2.5: Proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination.
h) SOM 2.6: Proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination.
i) SOM 3: Proportion of adolescents reporting positive and negative perceptions about their vaccination experience will be determined for each survey item.

3.3 Exploratory Outcome Measures (EOM):

a) EOM 1: Proportion of adolescents with presyncope or syncope after vaccination in the intervention and usual care groups using the alternate case definitions for presyncope.
b) EOM 2: Descriptive results of factors associated with post-vaccination presyncope and syncope using the primary and alternate case definitions for presyncope.

4 Study Design

4.1 Study Description

This study is a prospective, randomized clinical trial that will be conducted in adolescents (10 through 14 years of age) receiving at least one recommended intramuscularly administered vaccine to evaluate the efficacy and acceptability of using two different, simultaneously administered interventions that might prevent post-vaccination presyncope, and by extension syncope. The two interventions to be evaluated together are Buzzy®, which is a medical device designed to reduce vaccination pain, and an electronic game. We will evaluate both interventions when administered simultaneously (Buzzy® and electronic game). We will enroll approximately 340 subjects into this study. Eligible adolescents will be randomized (1:1) to either the intervention or control group: 1) intervention (Buzzy® and electronic game); or 2) control (usual care) to assess for acceptability and efficacy. Detailed data will be collected and described from study participants including demographics, medical history, baseline anxiety, and needle phobia. Participants will be observed for 20 minutes following receipt of vaccines and reassessed for post-vaccination anxiety, immediate and subsequent post-vaccination pain (within 1 minute and at 10 minutes), and the occurrence of witnessed syncope or presyncope, and presyncopal symptoms as rated by the modified BDRI. For the primary objective, we will assess the efficacy of the intervention to decrease presyncope symptoms or signs as compared to usual care. For the secondary

objectives we will assess the pre- and post-vaccination anxiety score, the immediate post-vaccination injection-site pain score, and the acceptability of the intervention. For the exploratory objectives we will assess the efficacy of the intervention to decrease presyncope symptoms or signs as compared to usual care using alternate case definitions for presyncope and we will assess factors associated with post-vaccination presyncope.

4.2 Study Interventions

a) Buzzy® and Electronic Game Intervention

Participants randomized to Buzzy® and the electronic game will apply or have Buzzy® applied by a member of the study team. Buzzy® XL Healthcare Professional will be applied as described in the package insert on the deltoid vaccination site for 30-60 seconds. Then, the Buzzy® will be moved proximal to the injection site keeping Buzzy's® switch/head toward the brain or spine during injection. The procedures for applying Buzzy® are consistent with the procedures on the package insert If vaccines are given in more than one arm, Buzzy® will be placed on both arms with the assistance of the study coordinator. Buzzy® will be removed from the vaccination site(s) following vaccination. The start and stop time of Buzzy® placement will be recorded. If more than one vaccination is given in a single arm only one Buzzy® device will be applied per package instructions.

For the electronic game, participants will be instructed to select a game from a prepopulated list of games on a tablet provided by the study team. The game will be played for a minimum of 3 to 5 minutes prior to vaccination, throughout the procedure and for a minimum of 1 minute and up to 15 minutes after vaccination.

Although preferable for participants to remain in the same exam room during the post-vaccination observation period, participants may have to shift rooms during the post-vaccination observation period. The participant will be provided with the guidance (derived from the Advisory Committee on Immunization Practices (ACIP) General Best Practices Guidelines for Immunization)[26] that they may choose to sit or lie down during the post-vaccination wait period. Movement from room to room or if the patient decides to stand should be noted by the study staff. No instruction will be provided to the participant regarding sitting or standing unless the participant starts to exhibit signs of presyncope.

b) Control Group

This intervention group will receive usual care during vaccination. Usual care will include not receiving the Buzzy® and electronic game combination intervention and will also consist of the patient waiting in the exam room for 20 minutes post-vaccination. The participant will also be provided with the ACIP guidance that they may choose to sit or lie down during the post-vaccination wait period. Although preferable for participants to remain in the same exam room during the post-vaccination observation period, participants may have to shift rooms during the post-vaccination observation period. Movement from room to room should be noted by the study staff.

4.3 Sample Size and Power Estimation

The study has approximately 82.0% power to reject the null hypothesis of no difference in the proportion of adolescents with presyncope or syncope after vaccination in the intervention (vibration and cool pack device [Buzzy®] and an electronic game) group compared to the control (usual care) group based on a two-side alpha 0.05 chi-square test with N=160 per group. This assumes that the proportion of adolescents with presyncope or syncope after vaccination will be 25% in the control group and 2-fold lower (12.5%) in the intervention group.[15] This assumption is based on a review of the literature and expert opinion. We plan to enroll approximately 340 adolescents for this study with the assumption of a 5% drop out rate, thus providing at least 160 subjects per group to have approximately 82% power.

4.4 Randomization

Participants will be randomized (1:1) to receive either Buzzy® and electronic game or the control using a permuted block randomization scheme. A minimum of 170 participants will be enrolled in the intervention group and 170 in the control group. The project statistician at Duke University will generate randomization schemes, which will be uploaded to REDCap. The randomization schedule will not be available to the study staff, so the next randomization allocation will not be known before randomization occurs. Following confirmation of study eligibility criteria during Visit 1, participant randomization will be through REDCap with treatment allocation recorded on the CRF.

4.5 Blinding

Study staff and subjects will not be blinded to treatment arm assignments.

4.6 Definitions

a) Presyncope

The case definition of presyncope was based on review of the literature, an amended Blood Donations Reactions Inventory (BDRI).

Primary definition: Sudden onset of one or more of the following symptoms (reported as “a little bit”, “somewhat” or “a lot”) or signs during the post-vaccination observation period in the clinic:

Symptoms

- Feeling like you might “pass out” or faint
- Feeling dizzy, like the room is spinning
- Feeling weak
- Feeling like your face is getting red and warm (or hot), like blushing or flushing
- Noticing any change in your vision, like spots or flickering lights, tunnel vision, or loss of vision
- Experiencing ringing in your ears, decreased hearing, or sounds seem far away
- Feeling lightheaded
- Feeling like your heart is beating fast or hard or pounding
- Feeling hot or sweaty
- Feeling cold or “clammy”
- Feeling like you are breathing fast or hard
- Feeling like you might throw up (nausea)

Signs

- Pallor
- Sweatiness
- Facial flush
- Decreased interactivity (decreased level of arousal or responsiveness)

AND

- Not syncope
- Not due to another cause
- Not clearly present at baseline

In exploratory analyses we will employ two alternate case definitions for presyncope.

Alternate definition 1: Sudden onset of one or more of the above symptoms (reported as “somewhat” or “a lot”) or signs during the post-vaccination observation period in the clinic.

Alternate definition 2: Sudden onset of one or more of the following symptoms limited to feeling like you might pass out, dizziness, weakness, or lightheadedness symptoms (reported as “a little bit”, “somewhat” or “a lot”) or signs during the post-vaccination observation period in the clinic.

b) Syncope

Syncope (fainting) that occurs in an otherwise healthy person after receipt of a vaccine or during venipuncture is usually attributed to vasovagal syncope, and may occur alone (simple syncope) or may be associated with tonic-clonic movements (convulsive syncope, anoxic seizure).12,13 For the purposes of this study, we have defined syncope as: Any sudden and brief loss of consciousness or postural tone after vaccination from which recovery is spontaneous and is not attributed to another cause (e.g., anaphylaxis). For purposes of this study, cases counted as syncope must occur during the post-vaccination observation period.

5 Statistical Considerations / Parameters of Analysis

5.1 Data Collection and Storage

Data will be handled according to the Duke Vaccine and Trials Unit SOP (DVTU M010) and captured on paper CRFs and entered into the REDCap database. All data for this study will reside on a secure Duke server maintained by Duke Health Technology Solutions (DHTS). A database will be developed and a dataset without personal identifiers will be made available to the CDC for analysis purpose. All analyses will be performed using SAS version 9.4.

5.2 Analytic Issues

No adjustments will be made to the alpha level (two-sided alpha=0.05) for the study objectives described below.

The primary and exploratory objective analyses will be performed in the Modified intent-to-treat (mITT) and Per-protocol populations, or only the mITT population if no subject is excluded from the per protocol population. No adjustments will be made to the alpha level (two-sided alpha=0.05) for the study objectives described below.

6 Analysis Populations

6.1 Modified Intent-to-treat (mITT):

Defined as those subjects who are enrolled, randomized into the study, and received an intramuscular vaccine.

6.2 Per-Protocol population:

Defined as those subjects who are randomized, have received at least one dose of an intramuscularly administered vaccine, have completed all study procedures, and have no protocol violations that are likely to affect the objectives.

7 Baseline data and flow chart

7.1 Presentation of Baseline Data

The following baseline information will be presented by treatment group: age, ethnicity, race, insurance status, fatigue, hunger, thirst, needle fear and phobia, and a generalized anxiety rating scale score, syncope history. Continuous variables will be summarized with standard descriptive statistics including

means, medians, 95% CI, and standard deviations. Categorical variables will be summarized with frequencies and percentages. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted. These descriptive statistics will be presented for the mITT and Per-Protocol populations.

7.2 Flow Chart

The number of enrolled participants and participants in the mITT and Per-protocol populations will be presented in a flow chart by treatment group.

8 Analysis of study objectives

8.1 Primary Objective (PO1)

To assess if simultaneous use of a vibration and cool pack device (Buzzy®) and an electronic game before and during intramuscular vaccination will reduce risk for presyncope or syncope after vaccination in adolescents. This information is collected in CRF forms: “Buzzy® Form”, “Electronic Game Form”, “Presyncope or Syncope Form (EVENT FORM)”, and “Post Vaccination Questions” (Modified BDRI (PostVax)). The proportion of adolescents with presyncope or syncope as determined by the modified BDRI or witnessed presyncope or syncope after vaccination will be compared between the control and intervention groups using a chi-square test.

- *Research hypothesis: The Buzzy® and electronic game intervention will be at least 50% effective at reducing risk for post-vaccination presyncope or syncope compared with control.*

  This objective will be assessed using a chi-square test with the alpha level set at 0.05 (2-sided).

8.2 Secondary Objectives

1. **Secondary Objective (SO1):** To compare the change in state anxiety score for adolescents before and after vaccination in the control group to the intervention group.

   This information is collected in CRF Forms: “Youth Momentary Anxiety Checklist (YMAC)” and “Anxiety – Youth - 11-17.” The categorical change in the anxiety score (positive, negative, and no change) in pre- and post- vaccination state anxiety will be presented by group in a tabular format. A comparison of the two study groups will be made using a Mantel-Haenszel statistic (row mean scores difference with standardized midranks scores [modified ridit scores]). Descriptive statistics (e.g., mean, 95% CI, min, max) of the pre- minus post- vaccination state anxiety will be presented by group and compared using Mann-Whitney U/Wilcoxon rank-sum test.

   Secondary Outcome Measure SOM 1.1: Categorical change (positive, negative, no change) in pre- and post- vaccination state anxiety.

   - Assess frequency and proportions of adolescents reporting a categorical change (positive, negative, no change) in their overall score for anxiety according to state anxiety questionnaire, before and after vaccination, by intervention group and age group, as appropriate.

   Secondary Outcome Measure SOM 1.2: Numeric change (mean and 95% confidence interval (CI)) in pre- minus post- vaccination state anxiety.

   - Assess overall mean score and standard deviation of adolescents’ anxiety scores according to state anxiety questionnaire, before and after vaccination, by intervention group and by age group, as appropriate.

2. **Secondary Objective (SO2):** To compare the change in injection-site pain after vaccination of adolescents in the control group to the intervention group. This information is collected in CRF forms: “Post-Vaccine Form” and “Wong-Baker Faces Pain Scale.” The following four outcomes will be compared between groups using a chi-square test or a logistic regression model to control for covariates:
   - The proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination
   - The proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination
   - The proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination
   - The proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination.

   Descriptive statistics (e.g., mean, 95% CI, min, max) of injection-site pain scores on the Wong-Baker Faces Pain Scale© at ≤ 1 and minute and at (approximately) 10 minutes following vaccination will be presented by group and compared using Mann-Whitney U/Wilcoxon rank-sum test.

3. **Secondary Objective (SO3):** To assess the acceptability of the intervention among the adolescents based on their positive or negative responses for each survey item. A descriptive breakdown of the responses will be presented in tabular format. This information is collected in CRF form “Buzzy® and Electronic Game Acceptability Scale”:

   1. How much did you like having Buzzy® on your arm(s) during the shot(s)? (Disliked very much; Disliked a little; Neither liked or disliked; Liked a little; Liked very much; Not Sure)
   2. How difficult or easy was holding or having Buzzy® held on your arm during the shot(s)? (Very difficult; Somewhat difficult; Neither difficult nor easy; Somewhat easy; Very easy; Not Sure)
   3. How comfortable or uncomfortable was Buzzy® on your arm(s) during the shot(s)? (Very uncomfortable; Somewhat uncomfortable; Neither comfortable nor uncomfortable; Somewhat comfortable; Very comfortable; Not Sure)
   4. Did the cold temperature of Buzzy® bother you? (No; Yes; Not Sure)
   5. Did the vibration of Buzzy® bother you? (No; Yes; Not Sure)
   6. If you had the choice would you like to use Buzzy® again when receiving shots? (No; Yes; Not Sure)
   7. Write below anything else you want us to know about your experience with Buzzy®. (free text)
   8. How much did you like playing a game during the shot(s)? (Disliked very much; Disliked a little; Neither liked or disliked; Liked a little; Liked very much; Not Sure)
   9. How difficult or easy was it to select and play the game? (Very difficult; Somewhat difficult; Neither difficult nor easy; Somewhat easy; Very easy; Not Sure)
   10. How comfortable or uncomfortable were you playing a game when receiving shots? (Very uncomfortable; Somewhat uncomfortable; Neither comfortable nor uncomfortable; Somewhat comfortable; Very comfortable; Not Sure)

11. If you had the choice would you like to play a game again when receiving shots? (No; Yes; Not Sure)
12. Write below anything else you want us to know about your experience with playing a game. (free text)

8.3 Exploratory Objectives

1. **Exploratory Objective (EO1):** To assess if using Buzzy® and an electronic game before and during intramuscular vaccination will reduce risk for presyncope or syncope after vaccination using alternate case definitions for presyncope.

   The proportion of adolescents with presyncope or syncope, using the two alternate case definitions for presyncope described in Section 4.6, after vaccination will be compared between the control and intervention groups using a Chi-square test.

2. **Exploratory Objective (EO2):** To assess for factors associated with post-vaccination presyncope in adolescents in the control and intervention groups.

   This objective will be conducted using the primary and alternate case definitions for presyncope described in Section 4.6. A logistic regression model with select covariates (e.g., demographic data, hunger, thirst, fear, phobia, anxiety level, pain) will be used to evaluate factors associated with post-vaccination presyncope and syncope. The relative risk and associated 95% confidence interval will also be reported.