Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions: A Pilot Study

Short Title: Syncope Prevention Study

Centers for Disease Control and Prevention
Clinical Immunization Safety Assessment (CISA) Project

Lead Site Principal Investigator: Emmanuel B. Walter, MD, MPH

Centers for Disease Control and Prevention (CDC) Principal Investigator: Theresa Harrington, MD, MPH&TM

CDC Sub-principal Investigator: Karen Broder, MD

NCT03533829

Version Number: 1.0
April 17, 2018

STATEMENT OF COMPLIANCE

- This trial will be conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Guideline E6-Good Clinical Practice (GCP), and the applicable guidelines and regulatory requirements from the United States (US) Code of Federal Regulations (CFR), 45 CFR Part 46.
- All study personnel with subject contact have completed Human Subjects Protection Training.

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title:	Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions: A Pilot Study
Population:	Up to 30 adolescents, 10 to 17 years of age, who will receive at least one intramuscularly administered vaccine
Clinical Sites:	One: Duke University
Study Duration:	6 weeks
Participant Duration:	1 day
Description of Study Procedures:	This is a randomized controlled open-label trial. During the study, adolescents scheduled to receive at least one IM vaccine will receive either Buzzy®, Music, or Buzzy® and Music intervention(s) in addition to standard care to evaluate the feasibility and acceptability of these interventions prior to being used in a larger study to assess the effectiveness of the interventions in preventing post-vaccination presyncope and syncope. Feasibility will be assessed according to study staff ability to successfully administer the protocol specified clinic-based interventions and per both study staff and healthcare provider responses to written feasibility assessments. Acceptability will be assessed according to the participant's self-report. In addition, baseline needle phobia and anxiety, post-vaccination pain and presyncope symptoms, and pre- and post- vaccination state anxiety will be assessed per participant written self-report to standardized survey questions.
Objectives:	**Primary Objectives (PO):** PO 1: To assess the feasibility of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents PO 2: To assess the acceptability of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents **Exploratory Objectives (EO):** EO1: To describe the proportion of adolescents with presyncope or syncope after vaccination by intervention group when Buzzy® is applied

	alone, music is played alone, or Buzzy® and music interventions are employed simultaneously EO2: To describe injection-site pain immediately after and after a brief wait period following vaccination of adolescents, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously. Injection-site pain will be measured using Wong-Baker Faces Pain Scale©. The scales ranges from 0 – 10, where a value of 0 indicates "No Hurt" and a value of 10 indicates "Hurts Worst". EO3: To describe the change in state (momentary) anxiety score in adolescents before and after vaccination, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously
Outcome Measures:	**Primary Outcome Measures (POM):** POM 1.1: The proportion of adolescents meeting each feasibility benchmark. POM 1.2: Descriptive results of feasibility survey among study coordinators POM 1.3: Descriptive results of feasibility survey among study healthcare providers POM 2: Descriptive results of study intervention acceptability surveys among study adolescents **Exploratory Outcome Measures (EOM):** EOM 1.1: The proportion of adolescents with presyncope symptoms as described in the modified Blood Donations Reactions Inventory (BDRI) after vaccination or witnessed presyncope after vaccination in the absence of a BDRI assessment EOM 1.2: Describe any post-vaccination syncope events occurring in the study population EOM 2.1: The proportion of adolescents reporting an injection site pain score ≥2, on the Wong-Baker Faces Pain Scale©, ≤1 minute following vaccination EOM 2.2: The proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, ≤1 minute following vaccination EOM 2.3: The proportion of adolescents reporting an injection site pain score ≥2, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination. EOM 2.4: The proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination EOM 2.5: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at ≤1 minute following vaccination

	EOM 2.6: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination EOM 3.1: Describe the categorical change (positive, negative, no change) in pre- and post- vaccination state anxiety EOM 3.2: Describe the numeric change (mean and range) in pre- minus post- vaccination state anxiety
Estimated Time to Complete Enrollment:	Approximately 6 weeks

1 BACKGROUND

1.1 Background

Vasovagal Syncope

Syncope is a sudden and transient loss of consciousness and postural tone that typically lasts from several seconds to a minute, followed by spontaneous recovery. Syncope is caused by a sudden decrease or brief cessation of cerebral blood flow.[1] Syncope is fairly common and more frequently occurs among females, with a peak incidence between 15 and 19 years of age.[2] Although uncommon, syncope can occur following immunization and result in serious injury.[3]

Vasovagal (neurocardiogenic) syncope is the most common form of syncope.[4] Characterized by the development of arterial vasodilation in the setting of relative or absolute bradycardia, the mechanism by which vasovagal factors lead to syncope are not well understood. In some cases, syncope may be triggered in the central nervous system. In other cases, activity at the level of baroreceptors may lead to an increase in vagal tone and sympathetic withdrawal, leading to bradycardia, hypotension, and decreased cerebral blood flow. Multiple factors have been identified as possible triggers for syncope including: fear, anxiety, pain, hunger, overcrowding, illness, fatigue, injections, venipuncture, the sight of blood, and maintaining a still upright posture for a prolonged period. Alcohol, drugs and exposure to cold or heat can also precipitate syncope. Typically, vasovagal syncope is preceded by prodromal symptoms, known as presyncope, which may involve nausea, dizziness, visual changes (e.g., spots, dimming), feelings of apprehension, pallor, yawning, diaphoresis, and feelings of warmth.

Following a syncopal event, individuals may complain of malaise, fatigue, weakness, nausea, and headache. Although vasovagal syncope is self-limited, there is a potential for harm if affected individuals fall. For example, a syncope-related fall resulting in cerebral injury and death has been reported after vaccination.[5] Rarely, syncope can be followed by a brief tonic-clonic seizure.[1] In addition to the potential for injury, syncopal episodes often prompt extensive diagnostic testing in the emergency department and can sometimes lead to hospitalization. Moreover, syncopal episodes triggered by identifiable stimuli such as needle-exposure can potentiate risk for development of more severe reactions to similar stimuli over time (e.g., blood-injection-injury phobia).[6] The median age of onset of blood-injury-injection phobia is 7-11 years.[7]

Post-vaccination syncope

The National Academy of Medicine(formerly Institute of Medicine) has concluded that evidence “convincingly supports a causal relationship between the injection of a vaccine and syncope” likely due to a vasovagal reaction.[8] Although uncommon, with an estimated rate of 1 per 1000 in the adolescent age group,[9] syncope after vaccination can lead to serious injury. An analysis of cases reported to VAERs in the 1990s described cases of syncope following immunization.[3] Reported episodes (n=697) occurred most frequently among those 10 through 18 years of age (45%), in females (58%), and within 15 minutes after vaccination (89%). Complications included tonic or clonic movements (24%) and subsequent hospitalization (10%). Reported serious adverse events associated with post-vaccination syncope included concussion, skull fracture, intracranial bleeding, cerebral contusions, and a motor vehicle collision due to syncope while driving.

Following the introduction of new vaccines for adolescents (i.e., Tetanus, Diphtheria and Pertussis (Tdap), Meningococcal (MCV4), Human papillomavirus (HPV)) between 2005-2007, the number of cases of post-vaccination syncope reported to VAERS increased, primarily among females 11-18 years of age.[10] Post-vaccination syncope has also been described in military personnel.[11] The rate of medical encounters for post-vaccination syncope was 9.7 per 100,000 immunization episodes. The rate of syncope was higher among females, declined with increasing age, and increased with increasing number of injections per immunization episode. Injuries occurred in approximately 7% of encounters for post-vaccination syncope, including head wounds, contusions, concussions, facial and clavicle fractures, and intracranial and ocular injuries.[11] Additional work has also shown that patients who experience syncopal symptoms in association with injection procedures are much more likely to be diagnosed with needle-phobia.[7,12] Moreover, emerging theories regarding acquisition of needle phobia in children describe that negative physical experiences such as syncope symptoms and pain can serve as fear conditioning events, which may contribute to the development of needle phobia.[13]

Post-vaccination vasovagal syncope and associated injuries, as well as risk for recurrent symptoms and related interference in functioning, are a public health concern that should be addressed with evidence-based preventive interventions. Although post-vaccination presyncope does not always lead to syncope, it is more common than syncope, and both are vasovagally-mediated,[11,14] and so presyncope is appropriate for use as a surrogate for syncope in prevention research. Presyncope has been used as a surrogate for syncope in syncope prevention studies in the blood donation literature. Also CDC supported a previous post-vaccination syncope prevention study at Duke and Boston University using presyncope as a surrogate endpoint for syncope.[15]

Predictors of Vasovagal Syncope

The efficiency of primary prevention of vasovagal syncope could be improved if preventive interventions could be targeted at those at greatest risk. Unfortunately, predicting risk of syncope is difficult. In blood donors, for example, pre-donation blood pressure was not associated with risk of syncope and a pre-donation elevated pulse rate has inconsistently been associated with risk of syncope,[16-18] and the best predictor, anxiety, demonstrated only a modest association.[19] Due to the challenge of accurately predicting risk, any preventive intervention would likely have to be universally applied.

Published systematic reviews and meta-analyses of interventions to prevent blood donation-related vasovagal symptoms and syncope in young donors suggest that risk factors for post-vaccination and post-blood-donation vasovagal (not volume depletion) syncope include: 1) younger (adolescents) and first time donors; 2) anxiety; 3) needle phobia; and 4) prior history of syncope from needle-related event(s).[7,11,14,16,17,20-24] Some publications also cite increases in syncope among females;[11,16,17,21,23-25] and among those with a prior history of fainting or feeling faint (due to any reason).[17,22,23] Blood donation literature also suggests that vasovagal syncope is more common among Caucasians as compared to African-Americans,[17,24] and in persons with lower body mass index (BMI) as compared to greater BMI.[16]

Current Recommendations Related to Post-Vaccination Syncope

There are no evidence-based recommendations for the primary prevention of post-vaccination syncope. However, the Advisory Committee on Immunization Practices

(ACIP) recommends that providers should take appropriate measures to prevent injuries if a patient becomes weak or dizzy or loses consciousness. Adolescents and adults should be seated or lying down during vaccination. Vaccine providers, particularly when vaccinating adolescents, should consider observing patients (with patients seated or lying down) for 15 minutes after vaccination to decrease the risk for injury should they faint. If syncope develops, patients should be observed until the symptoms resolve.[26] The effectiveness of these measures is not known. One survey found that many primary care providers were unaware of these recommendations. Other than knowledge, the most commonly reported barrier to implementing the 15-minute post-vaccination observation period was lack of clinic space.[27]

Prevention of Vasovagal Syncope

Research targeting the prevention of vasovagal syncope in blood donors may offer relevant insights for preventing post-vaccination syncope and associated injuries. However, blood donation is not an ideal model for deriving strategies to prevent post-vaccination syncope because blood donation involves a significant loss of intravascular volume, takes a longer period of time than vaccination, and only volunteers donate blood; in addition, most donors are adults ≥18 years, not among the youngest adolescents at highest risk for post-vaccination syncope.

Although several strategies have been evaluated, two have emerged as most effective in the blood donation setting: acute water loading and applied muscle tension. Review of blood donation literature indicates that consuming approximately 500 mL of water shortly before phlebotomy may help to mitigate vasovagal response to needle insertion and fainting, especially in young, first-time blood donors. Consuming water increases peripheral vascular tone by stretching of baroreceptors in the stomach wall, and is also believed to be achieved through effects on the portal venous system from ingesting a hypo-osmolalar beverage.[27-29] Water can have an effect within 15 minutes and last up to an hour. In contrast, applied muscle tension can increase venous return, and thus help maintain blood pressure. A randomized prospective study found that applied muscle tension (AMT) reduced vasovagal symptoms in blood donors by 50%, from 16% to 8% among blood donors.[22] The mechanism of action may involve a combination of factors, including increased venous return and through distraction and reduction of anxiety.[22,28] However, a systematic review and meta-analysis of interventions to reduce vasovagal reactions in blood donors found no significant reduction in vasovagal reactions among 8 AMT studies that included 3500 subjects.[21] Thus far, no single intervention has been shown to be effective for preventing vasovagal symptoms and/or syncope during blood donation in all age groups.

Unlike the blood donation literature there are limited data on effective strategies to prevent post-vaccination vasovagal syncope. Only one randomized clinical trial has assessed an interveion to prevent post-vaccination syncope. A recent Clinical Immunization Safety Assessment (CISA) randomized clinical trial (Kemper et al, ClinicalTrials.gov NCT02353390)[30] assessed the effectiveness of pre-vaccination hydration with water to prevent presyncope (used as a surrogate for syncope). Drinking some water before vaccination was not effective in preventing presyncope and by extension syncope, prompting CISA to plan evaluations of other simple interventions that could be used in busy clinical settings. The hydration study demonstrated the following as risk factors for post-vaccination presyncope among subjects 11-21 years: receiving more than one injectable vaccine; age younger than 15 years; having higher pre-vaccination anxiety levels; history of passing out or nearly passing out after a “shot” or

blood draw, and having higher levels of pain after vaccination (presumed injection-site pain).[15] These predictors may inform other strategies for preventing pre-syncope such as promoting relaxation, mitigating anxiety, and reducing immediate pain after vaccination.

1.2 Summary & Rationale

In children and adolescents, distraction and relaxation methods, such as listening to music, have shown some effectiveness in decreasing medically-related anxiety[23,31,32] and pain.[33] Further, other interventions, such as the use of a topical vapocoolant shortly before injection or the use of Buzzy® (combination vibration and cool pack applied to planned injection sites shortly before injections), have been shown to decrease injection site pain, which might play a role in decreasing injection pain-associated vasovagal symptoms.[31,32]

To identify best practices for preventing post-vaccination vasovagal syncope, we will target adolescents, a higher-risk population for post-vaccination syncope. Since post-vaccination syncope is an uncommon event, we will use presyncopal (vasovagal) signs and symptoms as a surrogate marker for syncope, as was done in the earlier CISA study. Based on our review of available blood donation literature, which does not identify one intervention with high efficacy, we plan to investigate two distinct previously unstudied interventions to prevent post-vaccination syncope through mitigation of immediate injection-site pain and anxiety. We will also assess use of a combination of these interventions.

Buzzy® | Drug Free Pain Relief is a reusable medical device designed to reduce vaccination pain [https://buzzyhelps.com/]. The Buzzy® device is applied to a targeted skin area for 30-60 seconds in order to cool/numb the area and provide vibration to desensitize pain receptors (nociceptors) prior to injection, then the device is moved just proximal to the site during injection. The device has been found to decrease pain 73% in children aged 7 years receiving Tdap in a prospective , randomized controlled trial, and the cost of the device ranges from $40 - $100 for an individual Buzzy® [https://buzzyhelps.com/store/buzzy-professional].[34]

Consumer reviews of Buzzy® are positive. As seen on Amazon.com, the ‘Buzzy Mini Personal Striped’ has received 4 out of 5 stars from 552 customers.[35] The top positive review, as designated by the Amazon website, spoke positively of the device for use with at-home injections. The top critical review noted that a two-year-old child was unreceptive to the cold features of the device (Customer Reviews). Additional web searches identified several personal blogs, mostly written by mothers who had purchased the device for their child’s injections, which were generally positive. Additionally, clinical settings have started using the device including the Shriners Hospitals for Children in Greenville, South Carolina (Shriner’s Hospitals).

Distraction has been investigated as a technique to reduce vaccination pain in children and adolescents. One systematic review identified various distraction techniques, including verbal distraction, video distraction, breathing with a toy, and musical distraction.[36] Results suggested these distraction techniques showed beneficial effects in reducing pain and distress from vaccinations.[37] An additional review focusing specifically on the utility of music in mitigating procedural pain and anxiety among youth demonstrated reduced anxiety and improved experience of pain even after controlling for covariates.[38] The effects of music on anxiety have been demonstrated across outcome measures spanning self-report, parent-report, observer-report, and

physiological functioning (Heart Rate). Moreover, based on subgroup analyses, they further concluded that passive music therapy (i.e., listening to music) may be as effective as active music therapy (i.e., working with a specified music therapist), and that music when combined with other modalities (e.g., may be more effective than when presented alone.[39] Importantly, music is a low-cost and practical intervention for use in clinical settings.[23,40] To the extent that that listening to music is an effective independent and/or adjunctive strategy in improving pain/or anxiety associated with injections, it may also help mitigate the role of these factors in the development of presyncopal symptoms.

In summary, we aim to first assess the feasibility and acceptability among adolescents of using Buzzy® alone, music distraction alone, or both Buzzy® and music distraction together to prevent post-vaccination presyncope. Results of pilot study assessments will be used to guide the development of a full study to assess the effectiveness of the most feasible and acceptable intervention.

2 STUDY OBJECTIVES

2.1 Primary Objective (PO):

PO 1: To assess the feasibility of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents

PO 2: To assess the acceptability of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents

2.2 Exploratory Objectives (EO):

EO1: To describe the proportion of adolescents with presyncope or syncope after vaccination by intervention group when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously

EO2: To describe injection-site pain immediately after and after a brief wait period following vaccination of adolescents, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously. Injection-site pain will be measured using Wong-Baker Faces Pain Scale©. The scales ranges from 0 – 10, where a value of 0 indicates “No Hurt” and a value of 10 indicates “Hurts Worst”.

EO3: To describe the change in state (momentary) anxiety score in adolescents before and after vaccination, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously

3 STUDY OUTCOME MEASURES AS RELATED TO OBJECTIVES

3.1 Primary Outcome Measures (POM):

POM 1.1: The proportion of adolescents meeting each feasibility benchmark

POM 1.2: Descriptive results of feasibility survey among study coordinators

POM 1.3: Descriptive results of feasibility survey among study healthcare providers

POM 2: Descriptive results of study intervention acceptability surveys among study adolescents

3.2 Exploratory Outcome Measures (EOM):

EOM 1.1: The proportion of adolescents with presyncope symptoms as described in the modified Blood Donations Reactions Inventory (BDRI) after vaccination or witnessed presyncope after vaccination in the absence of a BDRI assessment

EOM 1.2: Describe any post-vaccination syncope events occurring in the study population

EOM 2.1: The proportion of adolescents reporting an injection site pain score $\geqslant$2, on the Wong-Baker Faces Pain Scale©, $\leqslant$1 minute following vaccination

EOM 2.2: The proportion of adolescents reporting an injection site pain score $\geqslant$ 4, on the Wong-Baker Faces Pain Scale©, $\leqslant$1 minute following vaccination

EOM 2.3: The proportion of adolescents reporting an injection site pain score $\geqslant$2, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination

EOM 2.4: The proportion of adolescents reporting an injection site pain score $\geqslant$ 4, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination

EOM 2.5: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at $\leqslant$1 minute following vaccination

EOM 2.6: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination

EOM 3.1: Describe the categorical change (positive, negative, no change) in pre- and post- vaccination state anxiety

EOM 3.2: Describe the numeric change (mean and range) in pre- minus post-vaccination state anxiety

4 DEFINING PRESYNCOPE AND SYNCOPE

4.1 Presyncope

For this study, the case definition of presyncope was based on review of the literature, the Blood Donations Reactions Inventory (BDRI), expert opinion, and prior experience with the hydration study.[12-14] Although there may be measurable physiological changes with presyncope (e.g., decrease in heart rate or blood pressure), there are no established cut-offs that define presyncope. Therefore, the case definition is based on subjective criteria. The case definition previously used in Oral Water Hydration to Prevent Post-Vaccination Presyncope ("Water and Vaccines Study") is below:

Sudden onset of one or more of the following symptoms or signs during the post-vaccination observation period in the clinic:

Symptoms

- Feeling lightheaded, 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 like your heart is beating fast or hard or pounding
- Feeling hot AND sweaty
- Feeling cold AND sweaty, or "clammy"
- Feeling like you are breathing fast or hard
- Feeling like you might throw up (nausea)

Signs

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

AND

- Not Syncope
- Not Due to another Cause
- Not clearly present at baseline

For the purpose of this study, presyncope will be defined as any response of self-report of "some," or "a lot," to the modified BDRI or study staff noting signs or symptoms on study documents if the subject requires medical attention and does not complete the BDRI form

Usual clinical care will be provided to any subject who develops presyncope.

4.2 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.

Usual clinical care will be provided to any subject who develops syncope.

5 STUDY DESIGN

This pilot study is a prospective, randomized, open-label clinical trial that will be conducted in adolescents (10-17 years of age) receiving at least one recommended intramuscularly administered vaccine to evaluate the feasibility and acceptability of using two different interventions that might prevent post-vaccination presyncope, and by extension syncope. The two interventions to be evaluated are 1) Buzzy® Drug Free Pain Relief which is a medical device designed to reduce vaccination pain and 2) Listening to music as a distraction technique. We will also evaluate both interventions when administered simultaneously (Buzzy® and music). We will enroll approximately 30 subjects into this pilot study. Eligible adolescents will be randomized (1:1:1) to receive one of the three above named interventions: 1) Buzzy® alone; 2) Music alone; or 3) Buzzy® and Music together to assess for feasibility and acceptability. Eligible adolescents must have an identified risk factor for the development of presyncope including being either of younger age (10-13 years) or receiving 2 or more injectable vaccines (one of which must be received intramuscularly). A minimum of 20% of adolescents enrolled across all intervention groups will be 10-13 years of age and a minimum of 20% of adolescents enrolled across all intervention groups will be 14-17 years of age. 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), the occurrence of witnessed syncope or presyncope, and presyncopal symptoms as rated by the modified BDRI. For the primary objective, we will assess the acceptability and feasibility of both interventions separately or together. For the exploratory objectives, we will assess presyncope symptoms following vaccination, post-vaccination pain, and change in anxiety from baseline for the adolescents randomized to each of the intervention groups. Using lessons learned during the Pilot, if feasible and acceptable, we will evaluate the most feasible and acceptable presyncope prevention strategy in a larger effectiveness trial.

6 STUDY ENROLLMENT AND WITHDRAWAL

Subject Inclusion and Exclusion Criteria will be reviewed at Visit 1 to assess eligibility for study participation.

6.1 Subject Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in this interventional study.

1. 10 years through 17 years of age
2. If 10 through 13 years of age, the subject must be receiving at least one vaccine delivered intramuscularly
3. If 14 through 17 years of age, the subject must be receiving at least two injectable vaccines one of which must be delivered intramuscularly
4. The parent/guardian must be willing and capable of providing written informed consent for the adolescent and the adolescent must be willing and capable of providing assent.
5. The subject must be willing to stay for the completion of all study-related activities.
6. Parent/guardian and adolescent must speak and read English by self-report

6.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in this study:

1. Receipt of investigational or experimental vaccine or medication within the previous two weeks
2. Receipt of routine injectable medication
3. Permanent indwelling venous catheter
4. Blood drawn within the past hour or scheduled for a blood draw during the post-vaccination observation period
5. Injection of medication during the past hour or scheduled for injection of medication during the observation period.
6. Cold intolerance or cold urticaria
7. Raynaud's phenomenon
8. Sickle cell disease
9. Inability to hear
10. Significant visual impairment or blindness
11. Febrile or acutely ill individuals
12. Upper arm or shoulder pain or injury
13. Adolescent or parent/Guardian is an immediate relative of study staff or an employee who is supervised by study staff.
14. Any condition that would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol

6.3 Recruitment

The 30 participants in this study will be male or female adolescents 10 to 17 years of age. Adolescents will be recruited from designated study sites affiliated with the Duke University Health System (Duke Children's Primary Care, Durham Pediatrics, and Regional Pediatrics). Adolescents will primarily be recruited at the time of well child visits.

6.4 Reasons for and Handling of Withdrawals

The following may be reasons for study withdrawal:

- As deemed necessary by the principal investigator (PI).
- Parent(s)/Legally Authorized Representative(s) (Guardian(s)) withdrawal of permission for their adolescent to participate.
- Termination of the study by the sponsor.

A parent/Guardian may withdraw permission for their adolescent to participate at any time and for any reason, without penalty. Subjects who are withdrawn from the study prior to randomization or intervention will be replaced. Subjects who are withdrawn from the study after receiving intervention will not be replaced. For subjects who received intervention, data collected prior to withdrawal in the study will be included in the study.

6.5 Termination of Study

This study may be terminated for safety concerns of the principal investigators from the Lead or Contributing sites, CDC, or participating Institutional Review Boards (IRBs).

7 STUDY SCHEDULE, PROCEDURES, & EVALUATIONS

7.1 Schedule of Events

Adolescents meeting the proposed eligibility criteria will be recruited. Written permission for the adolescent to participate will be obtained from parent(s)/Guardian(s) prior to conducting any study procedures. Assent will also be obtained from the adolescents. **Table 1** describes the proposed schedule of study visits.

Table 1: Schedule of Study Events:			
Procedure	Pre-Vaccination Day 1	Vaccination Day 1	Post-Vaccination Day 1
Informed consent / Assent	X		
Inclusion/Exclusion	X		
Demographics	X		
Medical history	X		
Concomitant medications	X		
Beverage and food intake assessment on day of vaccination	X		
Youth General Anxiety Assessment	X		
Needle phobia assessment	X		
State Anxiety assessment	X		X[1] (20 minutes)
Record/obtain physical measures (height and weight) and vital signs (blood pressure and pulse and baseline pain assessment done per standard of care)	X		X (blood pressure, pulse) (20 minutes)
Randomization	X		
Buzzy® alone, Music alone, Simultaneous Buzzy® and Music Distraction	X		
Administer vaccines (not a study procedure)		X	
Injection site pain assessment			X

			(within <1 and at 10 minutes)
Presyncope symptoms assessment			X (15 minutes)
Tolerability and Acceptability Assessment			X (20 minutes)

1. Complete prior to tolerability and acceptability assessment

Visit 1, Study Day 1 Clinic Visit Prevaccination Assessments

- Obtain parent(s)/guardian(s) permission by written informed consent
- Review and confirm study eligibility (Section 4.1 and 4.2)
- Obtain medical history
- Obtain demographic data
- Obtain concomitant medication use within 2 weeks of enrollment
- Record height and weight and vital signs (blood pressure and pulse) from the medical record. Obtain measures if not already taken and recorded at clinic intake. Record baseline pain assessment if determined as part of clinical care
- Complete beverage and food intake assessment for the day of vaccination
- Complete the needle phobia assessment
- Complete the general anxiety assessment and the state anxiety assessment
- Randomize study participant to one of the three intervention arms
- Administer assigned study intervention

Visit 1, Study Day 1 Clinic Visit Vaccination

- Vaccines administered by clinic staff (Not a study procedure)
- Vaccines administered as standard of care will be recorded by study team

Visit 1, Study Day 1 Clinic Visit Post Vaccination Assessments

- Complete the Wong-Baker Faces Pain assessment for **each arm** an injection is given in (immediately after withdrawal of the needle after the last vaccination but no longer than 1 minute after injection and at 10 (up to 15) minutes after the last vaccination). If multiple injections are given in the same arm only 1 Wong-Baker Faces Pain assessment will be performed for that arm at <1 minute and 10 (up to 15) minutes after the last injection.
- Complete the presyncope symptoms assessment modified BDRI (15 (up to 20) minutes post vaccination)
- Obtain second assessment of vital signs (blood pressure, and pulse).
- Complete the state anxiety assessment (20 (up to 25) minutes post vaccination)
- Complete the acceptability assessment (20 (up to 30) minutes post vaccination)
- Study team to complete the feasibility assessment
- Coordinator feasibility assessment
- Healthcare provider feasibility assessment

7.2 Parent/Guardian(s) Permission Process (Informed Consent)

The consent/assent process will take place in research or clinic exam rooms behind closed doors to assure privacy of the prospective participant. Study staff will be available to answer all parent/adolescent questions before and after permission is obtained. Parent(s)/Guardian(s) will be given as much time as needed after being approached about their adolescent participating in the study and needing to decide

whether or not to participate. We anticipate that the initial consent/assent discussion, including presenting the information in the consent/assent document and answering questions will take about 30 minutes. During the consent/assent process, it will be stressed that participation is voluntary and that parents can withdraw permission for their adolescent to participate at any time. Permission will not be obtained from parent(s)/Guardian(s) who do not read, who are blind, or who do not read/understand English. Parent(s)/Guardian(s) will be given a copy of the signed informed consent to take home with them. The original copy of the consent/assent will be kept in the study records and a third copy will be included in the adolescent's medical record per local requirements. Eligibility of the adolescent will also be assessed.

7.3 Overview of Study Assessments

Table 2 briefly outlines factors of interest that are potentially associated with pre-syncope or syncope. A more complete description of some of the specific measurements and questionnaires follows the table.

Table 2: Factors of Interest that are Possibly Related with Pre-syncope or Syncope

Domains of Interest	Source of Information	Information obtained
Demographics	Participant and/or parent report	Participant's gender, age, race, ethnicity, health insurance status, and country of origin
Underlying Health (Chronic or acute illness)	Participant and/or parent report Review of medical record	Medical history information: (history of pre-syncope, syncope, cardiac conditions, seizures, hypoglycemia, diabetes, headaches, prescription and over-the counter medications in preceding week, supplements in preceding week)
Physical Measures	Height and weight measurement (from medical record if obtained or measured) Temperature measurement Pulse rate measurement Blood pressure measurement Pain at baseline (anywhere)	Height, Weight and Calculated BMI Body temperature Pulse rate pre- and post-vaccination Blood pressure pre- and post –vaccination
Fatigue/ tiredness	Participant	Estimated hours of sleep the previous night Feeling tired

Hunger	Participant	Meals eaten on day of vaccination Last meal and type Last food eaten Hunger estimation
Thirst	Participant	Time/type of last beverage consumed prior to vaccination Quantification of last beverage Thirst estimation
Needle-related fear	Participant response	Needle phobia questionnaire Global question about fear of injections
Anxiety	Participant response	PROMIS anxiety rating scale pre-vaccination, and state anxiety questionnaire pre- and post-vaccination
Number of Injections	Medical record review (EHR/electronic health record or State Immunization Registry)	Number / name / site of injections administered in clinic
Pain	Participant response	Wong-Baker Faces Pain Scale score post vaccination
Past history of presyncope or syncope after injection or blood draw during the past 5 years	Participant response	Questions about past history of almost fainting or fainting and circumstance

7.4 Demographic Information, Medical History

The participant's gender, age, race/ethnicity, and country of origin will be obtained from parent/guardian report at the time of enrollment. The insurance payer status for the adolescent will be obtained from the electronic health record (EHR). The participant's medical history including: history of pre-syncope, syncope, cardiac conditions, seizures, hypoglycemia, diabetes, headaches, prescription and over-the counter medications in preceding week, supplements in preceding week will be obtained by review of the electronic health record (EHR) and will be reviewed and confirmed by the parent/guardian at the time of enrollment.

7.5 Physical Measures

Participants' height, weight and calculated BMI will be obtained at enrollment or from the clinical measurements collected at the visit. Pulse-rate and blood pressure will also be obtained at baseline either through standard of care measurements or the study team will perform these assessments if they are not otherwise available. In addition, the clinic baseline pain assessment will be recorded. Blood pressure, and pulse will also be reassessed 20 minutes post-vaccination.

7.6 Needle Related Fear

Fear of having blood drawn has been shown to be predictive of vasovagal reactions in young blood donors.[7] In blood donors fear was assessed using a global question. “How afraid are you of having blood drawn from your arm?” A similarly worded global question will be used to assess fear of vaccination. “How afraid are you of getting a vaccine (shot) in your arm?” Responses will be graded using a Likert scale: 1- not at all afraid; 2- slightly afraid; 3- somewhat afraid; 4-very afraid; 5- extremely afraid. In addition, we will use the American Psychiatric Association Severity Measure for Specific Phobia to assess needle related phobia. This assessment is a 10-item scale which specifically assesses phobia around blood, needles or injections in persons 11-17 years of age. [7,19]

7.7 Anxiety

Prior to vaccination the study coordinator will have each subject complete a questionnaire to assess generalized anxiety using the Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety short form instrument for adolescents (11-17 years) to categorize their overall degree of anxiety.[41] A *resource list* of mental health providers will be made available to parents upon request.

Participants will also complete a questionnaire specifically designed for this study to measure state anxiety both prior to and 20 minutes following vaccination. State anxiety is defined as an unpleasant emotional arousal in face of threatening demands or dangers.[42,43]

7.8 *Randomization*

Participants will be randomized (1:1:1) to receive either music intervention alone, Buzzy® alone, or combination music and Buzzy® using a permuted block randomization scheme. A minimum of 6 participants per age strata (10-13 and 14-17 years) will be enrolled across all intervention groups. 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.

7.8.1 Blinding

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

7.9 Study Interventions

7.9.1 Buzzy® Intervention

Participants randomized to Buzzy® will apply or have applied by a member of the study team Buzzy® XL Healthcare Professional as described in the package insert on the deltoid vaccination site for 30-60 seconds, then move Buzzy® proximal to 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 **(Appendix A)**. 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.

7.9.2 Music Intervention

Participants randomized to Music Distraction will be instructed to select music from a prepopulated playlist or music streaming service on an iPod, iPad, or similar device provided by the study team. Music will be played for a minimum of 3 to 5 minutes prior to vaccination over a Bluetooth speaker that can easily be transported between clinic rooms and clinics. Music will be played until the time of the pain assessment – 10 minutes following vaccination. The start and stop time of music distraction will be recorded.

7.9.3 Music and Buzzy® Combination Intervention

This intervention group will receive a combination of music therapy and Buzzy®. The music will be administered the same way as that for the music only intervention group with Bluetooth speakers playing music the subjects select from an IPad provided to them. The Buzzy® will be applied after the music intervention has begun prior to vaccination. Buzzy® will be applied as described above in Section 7.9.1. Start and stop times for both interventions will be recorded.

7.10 Immunizations Administered During Visit

Vaccines received as part of standard of care during the visit will be documented by the research staff. Documentation will include: product name and brand, lot number, site and date/time of vaccine administered during study participation.

7.11 Post Vaccination Pain Assessment

The Wong Baker Faces Pain Scale will be used to assess pain.[44] The Wong- Baker Faces Pain Scale scores pain on a 0-10 metric and shows a close linear relationship with visual analog pain scales across the ages from 11-17 years, this scale is acceptable to use on younger adolescents as well. Pain will be assessed at within 1 minute and at 10 minutes (up to 15 minutes) after vaccination for each arm in which a vaccine was received. The study coordinator will be responsible for recording pain scores after vaccination. The time for assessment will start after the last injection is received.

7.12 Presyncope and Syncope

At 15 minutes (up to 20 minutes) following vaccination, study participants will complete the BDRI. During the 20 minute (up to 25 minute) observation period, research staff will also record any observed signs (pallor, sweating, facial flush or decreased interactivity) or spontaneous subject reports of symptoms of witnessed presyncope as described in Section 4.1. Subjects who developed post-vaccination syncope as described in Section 4.2 regardless of presyncope are classified as having syncope. Usual clinical care will be provided to any subject who develops presyncope or syncope.

7.13 Acceptability

At the end of the study visit, we will survey participants about the acceptability of the intervention to which they were assigned (**Appendix B)**. Where appropriate, a Likert scale (strongly agree, agree, neither, disagree, strongly disagree) will be used to assess acceptability responses. Alternately, a yes or no response will be solicited.

7.14 Feasibility

For each participant encounter, feasibility will be assessed by determining the degree of ease the study staff member had with assuring that the participant had complying with the study interventions - Buzzy® or Music. In addition, for each participant encounter, the feasibility of study interventions will also be assessed by the provider administering vaccines to the participants. Where appropriate, a Likert scale will be used to assess feasibility responses. Benchmarks for intervention feasibility in addition to benchmarks for completion of assessments are listed in **Appendix C**. No identifiable information will be collected from either the coordinator or the provider. They will not be considered study participants.

7.15 Unsolicited SAEs

Administration of vaccine is not itself a study procedure in the study population, and thus vaccine adverse events, including presyncope or syncope, are not considered study related adverse events. If indicated, however, Vaccine-related SAEs will be reported to the Vaccine Adverse Event Reporting System (VAERS) in accordance with standard procedures. Information about such events will be included in the study data as noted on the VAERS website (https://VAERS.hhs.gov).

All serious adverse events (SAES) occurring during the period of study participation will be reported to the IRBs overseeing this study and to the CDC within 24 hours of study staff awareness of the event. Given the short duration of study participation and nature of the study, SAES would not be expected to occur in this study.

An SAE is defined as an AE that meets one of the following conditions:
•Results in death during the period of protocol-defined surveillance
•Is life-threatening (defined as immediate risk of death at the time of the event)
•Requires inpatient hospitalization during the period of protocol-defined surveillance (other than routine hospital admission for labor & delivery)
•Results in congenital anomaly or birth defect
•Results in a persistent or significant disability/incapacity
•Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8 STATISTICAL CONSIDERATIONS

In collaboration with Duke, the research team at the CDC will oversee the statistical analysis. The 30 children enrolled in this study are considered part of a pilot to assess intervention acceptability and feasibility and make adjustments in study design if necessary to guide a potential future larger study design and conduct. All data for this study will reside on a secure Duke server maintained by Duke Health Technology Solutions (DHTS). For the pilot study, 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.

8.1 Sample Size and Power Estimation

The Pilot phase of the study aims to enroll up to 30 participants. This is an acceptability and feasibility assessment and is not a powered study.

8.2 Analysis Plan

8.2.1 Study Populations

The study will enroll adolescents, female and male, ages 10-17 years, receiving at least one ACIP recommended vaccine administered intramuscularly administered. Participants will be randomized into one of three intervention groups: Buzzy® only, Music only, Buzzy® and Music together.

There will be two study populations used for data analysis in this study. These are defined below:

- Intent-to-treat (ITT) population: is defined as those subjects who are randomized and have received at least one dose of an intramuscularly administered vaccine.
- Per-protocol population: is defined as those subjects who are randomized, have received at least one dose of an intramuscularly administered vaccine, have completed study procedures including all surveys post-vaccination through the 20-minute time-period, and have no protocol violations that are likely to affect the objectives.

The primary and exploratory objective analyses will be performed in the ITT and per-protocol populations, or only the ITT population if no subject is excluded from the per protocol population. The primary and exploratory objective analyses will be performed by intervention group and age group (10-13 and 14-17), as appropriate.

8.2.2 Descriptive Statistics

Descriptive analyses will be conducted for demographic variables and for baseline characteristics (e.g., fatigue, hunger, thirst, and PROMIS score). Continuous variables will be summarized with standard descriptive statistics including means, medians, ranges, 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. Figures will be provided to evaluate the data distribution. The descriptive statistics will be analyzed in the ITT and per-protocol population, accordingly.

8.2.3 Primary Objective (PO) 1:

To assess the feasibility of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents

Primary Objective Measure (POM) 1.1: The proportion of adolescents meeting each feasibility benchmark

- Assess the proportions of those achieving each feasibility benchmark (**Appendix C**) within each intervention group and overall, as applicable. A descriptive summary of findings by age group will also be conducted, as appropriate.

Primary Objective Measure (POM) 1.2: Descriptive results of feasibility survey among study coordinators

- Assess study coordinator feasibility questionnaires for each survey question by intervention group and by age group. Percentages, means and/or medians will be presented. A descriptive summary of qualitative responses will also be presented.

Primary Objective Measure (POM) 1.3: Descriptive results of feasibility survey among study healthcare providers

- Assess healthcare provider feasibility questionnaires for each survey question by intervention group and by age group. Percentages, means and/or medians will be presented. A descriptive summary of qualitative responses will also be presented.

8.2.4 Primary Objective (PO) 2:

To assess the acceptability of using simple clinic-based interventions (Buzzy® alone, music alone, or Buzzy® and music together) to inform the development of a larger study designed to assess the effectiveness of the interventions in preventing post-vaccination presyncope in adolescents

Primary Objective Measure (POM) 2: Descriptive results of study intervention acceptability surveys among study adolescents

- Assess intervention acceptability questionnaire for each survey question by intervention group and by age group. Percentages, means and/or medians will be presented. A descriptive summary of qualitative responses will also be presented.

8.2.5 Exploratory Objective (EO) 1:

To describe the proportion of adolescents with presyncope or syncope after vaccination by intervention group when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously

Exploratory Outcome Measure (EOM) 1.1: The proportion of adolescents with presyncope symptoms as described in the modified Blood Donations Reactions Inventory (BDRI) after vaccination or witnessed presyncope after vaccination in the absence of a BDRI assessment

- Assess proportions of presyncope symptoms using the modified BDRI and/or witnessed signs/symptoms by study staff in participants after vaccination by intervention group and by age group, as appropriate.

Exploratory Outcome Measure (EOM) 1.2: Describe any post-vaccination syncope events occurring in the study population

- Report the frequency and nature of any post-vaccination syncope events in the study population. Describe the event(s) and outcomes.

8.2.6 Exploratory Objective (EO) 2:

To describe injection-site pain immediately after and after a brief wait period following vaccination of adolescents, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously. Injection-site pain will be measured using Wong-Baker Faces Pain Scale©. The scales ranges from 0 – 10, where a value of 0 indicates "No Hurt" and a value of 10 indicates "Hurts Worst".

Exploratory Outcome Measure (EOM) 2.1: The proportion of adolescents reporting an injection site pain score ⩾2, on the Wong-Baker Faces Pain Scale©, ⩽1 minute following vaccination

- Assess frequency and proportions of adolescents reporting injection-site pain score ⩾2 according to Wong Baker FACES Pain Scale©, at ⩽1 minute following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

Exploratory Outcome Measure (EOM) 2.2: The proportion of adolescents reporting an injection site pain score ⩾ 4, on the Wong-Baker Faces Pain Scale©, ⩽1 minute following vaccination

- Assess frequency and proportions of adolescents reporting injection-site pain score ⩾ 4 according to Wong Baker FACES Pain Scale©, at ⩽1 minute following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

Exploratory Outcome Measure (EOM) 2.3: The proportion of adolescents reporting an injection site pain score ⩾2, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination

- Assess frequency and proportions of adolescents reporting injection-site pain with score ⩾2 according to Wong Baker FACES Pain Scale©, at (approximately) 10 minutes following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

Exploratory Outcome Measure (EOM) 2.4: The proportion of adolescents reporting an injection site pain score ⩾ 4, on the Wong-Baker Faces Pain Scale©, at (approximately) 10 minutes following vaccination

- Assess frequency and proportions of adolescents reporting injection-site pain with score ⩾ 4 according to Wong Baker FACES Pain Scale©, at (approximately) 10 minutes following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

Exploratory Outcome Measure (EOM) 2.5: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at ⩽1 minute following vaccination

- Assess overall mean and/or median and standard deviation of adolescent's injection-site pain according to Wong Baker FACES Pain Scale©, at ⩽1 minute

following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

Exploratory Outcome Measure (EOM) 2.6: Describe average injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination

- Assess overall mean and/or median and standard deviation of adolescent's injection-site pain according to Wong Baker FACES Pain Scale at (approximately) 10 minutes following vaccination by intervention group and by age group, as appropriate. (For adolescents receiving more than one vaccine, maximum pain score will be analyzed.)

8.2.7 Exploratory Objective (EO) 3:

To describe the change in state (momentary) anxiety score in adolescents before and after vaccination, when Buzzy® is applied alone, music is played alone, or Buzzy® and music interventions are employed simultaneously

Exploratory Outcome Measure (EOM) 3.1: Describe the 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.

Exploratory Outcome Measure (EOM) 3.2: Describe the numeric change (mean and range) 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.

8.3 Data Management

The amount of data that will be collected for the proposed project will be substantial and will require a sophisticated, practical and flexible system that can accommodate different modes of data collection and several separate linked surveys. The novel Vanderbilt-designed resource developed specifically for online collection of research information, the Research Electronic Data Capture (REDCap) platform, will be used to design study forms, including the reaction forms, and short customized questionnaires to collect information from study subjects. This system will be used by Duke for data management. All electronic linkages will fulfill regulations for protection of human subjects and requirements to minimize the risk of breach of confidentiality. After initial set-up, the work load required for electronic data collection will be substantially reduced (description of REDCap resources below). _ENREF_33[45] Duke investigators have previously used the REDCap system for collection and analysis of large quantities of data. All study-related documents containing protected health information, e.g. enrollment logs, and case report forms, completed by study participants, will be maintained in secure research offices at Duke, which are accessible to research staff only.

8.3.1 Research Electronic Data Capture (REDCap)

Investigators within the NIH-funded Clinical and Translational Research Unit at Vanderbilt have developed REDCap (http://project-redcap.org/), to collect and manage data for diverse clinical and translational research studies. REDCap was designed around the concept of giving research teams an easy method to specify project needs and rapidly develop secure, web-based applications for collection, management and sharing of research data. REDCap accomplishes these key functions through use of a single study metadata table referenced by presentation-level operational modules. Based on this abstracted programming model, databases are developed in an efficient manner with little resource investment beyond the creation of a single data dictionary. The concept of metadata-driven application development is well established, and the critical factor for successful data collection lies in creating a simple workflow methodology allowing research teams to autonomously develop study-related metadata in an efficient manner. REDCap includes secure institutional data hosting and includes full audit-trails in compliance with Health Insurance Portability and Accountability Act (HIPAA) security requirements. The REDCap Consortium is comprised of 2318 active institutions. The REDCap currently supports 68,000 projects with over 89,000 users spanning numerous research focus areas across the consortium. The current project will use this software application for the design of electronic forms to collect information from study participants, to link the baseline data, sample collection date, and laboratory results in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design an analytical dataset for the analysis of the project data.

Data will be entered into the REDCap database by members of the study team, from Duke using the paper case report forms utilized to record data collected as part of study procedures. Study investigators will be responsible for assuring that all paper records are securely stored according to the requirements of their IRBs. The study investigators will be responsible for assuring the accuracy of the data entered from the paper forms into REDCap. Only the assigned identifiers will be used in REDCap. Therefore, personal health identifiers will not appear in the REDCap database.

In order to perform data cleaning and data quality assurance efficiently, numerous built-in filters and checks for consistency of the data including range and limit checks, branching logic and pull down menus to limit choices for categorical variables to a pre-specified list will be implemented and performed automatically to minimize data entry error. The data will be randomly sampled and checked against source records on a regular basis. The data and related analytical datasets will also be stored with secured password-protected computers. Coded data without personal identifiers will be made available to the CDC and transferred using a secure transfer method.

8.4 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Duke University as Task Orders in the CISA Project Contract. The Duke University PI (Emmanuel “Chip” Walter) will oversee the study. CDC staff will collaborate with the site to develop the protocol, conduct the study, ensure the study is aligned with US Department of Health and Human Services public health priorities, and analyze the data and disseminate the results. CDC will receive access to coded data not containing any directly identifying information, and lead the analysis for this study, in consultation with the study team.

9 HUMAN SUBJECTS

9.1 Human Subjects Involvement, Characteristics, and Design

Duke investigators will be responsible for submitting the protocol, informed consent (**Appendix D**), recruitment letters, flyers, and any written or verbally conveyed materials specific to this project to their institutional review boards. CDC staff will be responsible for submitting materials to the CDC for review and obtain reliance on Duke IRB.

To facilitate subject recruitment at the practices, we will request a waiver of consent and HIPAA authorization for ascertainment (identification, selection) and/or recruitment of potential subjects while recording identifiable private health information (PHI) prior to obtaining the subject's consent. This information will be obtained from review of the electronic scheduling and medical record systems in the clinics in order to determine eligibility for study enrollment. We will review only the minimum amount of information necessary to determine potential eligibility. This information will be used to recruit and screen only. Use of PHI in this manner involves no more than minimal risk to subjects and no information will leave the study sites.

Continuing reviews will be submitted to the IRBs on an annual basis. Protocol deviations or concerns about study integrity will be reported promptly to the overseeing IRB in accordance with institutional requirements.

9.2 Sources of Material

Medical history, immunization history and concomitant medication history will be obtained from the medical record and from patient report. Demographic information will be obtained from the medical record and patient report. The research staff will administer the beverage and food intake assessment, needle phobia assessment, anxiety assessment, pain assessment, presyncope symptoms assessment, repeat anxiety assessment and the tolerability and acceptability assessment to the subjects.

9.3 Potential Risks and Benefits

There is the potential risk of loss of confidentiality about information obtained as part of this study.

There is the also the potential that adolescent subjects could experience some discomfort from the intervention they are randomized to such as discomfort due to music volume or the cold sensation of the Buzzy®.

In addition, talking to or reporting about feelings of anxiety may temporarily increase a subject's awareness of this experience and increase distress.

9.4 Adequacy of Protection Against Risks

9.4.1 Protections against Risk

Every effort possible will be made to keep information about participants confidential. Computerized participant information will be kept in password protected files on secured servers. Paper case report forms will be kept in locked files belonging to the study personnel. Any publications resulting from this work will not contain any identifiable participant information.

Every effort possible will be made to minimize discomfort caused by the interventions by adjusting music volume at patient request and following the precise guidelines for using the Buzzy®.

In addition, for participants with significant anxiety, a resource list of mental health professionals will be made available upon request.

9.4.2 ClinicalTrials.gov Requirements

The project is registered on ClinicalTrials.gov. (TBD).

9.5 Human Subjects

In obtaining and documenting informed consent, the Investigator and study team will comply with the applicable regulatory requirements, Good Clinical Practices, and ethical principles. The parent or guardian must sign and date the written informed consent form prior to initiation of any study procedure.

9.5.1 Vulnerable Subjects Research

Vulnerable subjects

Children are a vulnerable research population and require additional protections when they are potential research subjects. This is a minimal risk study, involving the administration of music or Buzzy® intervention. Because this study is no more than minimal risk, the permission of only one parent/guardian will be obtained. We will also obtain the adolescents assent either verbally or in writing as necessitated by their age.

10 REFERENCES

1. Kapoor WN. Syncope. N Engl J Med 2000;343:1856-62.
2. Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC. Syncope in children and adolescents. J Am Coll Cardiol 1997;29:1039-45.
3. Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. Arch Pediatr Adolesc Med 1997;151:255-9.
4. Chen-Scarabelli C, Scarabelli TM. Neurocardiogenic syncope. BMJ 2004;329:336-41.
5. Woo EJ, Ball R, Braun MM. Fatal syncope-related fall after immunization. Arch Pediatr Adolesc Med 2005;159:1083.
6. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
7. Deacon B, Abramowitz J. Fear of needles and vasovagal reactions among phlebotomy patients. J Anxiety Disord 2006;20:946-60.
8. Medicine Io. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: The National Academies Press; 2012.
9. Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. Drug Saf 2013;36:393-412.
10. Sutherland A, Izurieta HS, Ball R, et al. Syncope, Convulsive Syncope and Traumatic Injury after Human Papillomavirus and Other Adolescent Immunizations. Pharmacoepidemiology and Drug Safety 2008;17:S172.
11. Webber BJ, Cropper TL, Federinko SP. Syncope among U.S. Air Force basic military trainees, August 2012-July 2013. MSMR 2013;20:2-4.
12. Ost LG. Blood and injection phobia: background and cognitive, physiological, and behavioral variables. J Abnorm Psychol 1992;101:68-74.
13. McMurtry CM, Pillai Riddell R, Taddio A, et al. Far From “Just a Poke”: Common Painful Needle Procedures and the Development of Needle Fear. The Clinical Journal of Pain 2015;31:S3-S11.
14. Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. Prog Cardiovasc Dis 2013;55:425-33.
15. Kemper AR, Barnett ED, Walter EB, et al. Drinking Water to Prevent Postvaccination Presyncope in Adolescents: A Randomized Trial. Pediatrics 2017;140.
16. Trouern-Trend JJ, Cable RG, Badon SJ, Newman BH, Popovsky MA. A case-controlled multicenter study of vasovagal reactions in blood donors: influence of sex, age, donation status, weight, blood pressure, and pulse. Transfusion 1999;39:316-20.
17. Graham DT. Prediction of fainting in blood donors. Circulation 1961;23:901-6.
18. Bravo M, Kamel H, Custer B, Tomasulo P. Factors associated with fainting: before, during and after whole blood donation. Vox Sang 2011;101:303-12.
19. Meade MA, France CR, Peterson LM. Predicting vasovagal reactions in volunteer blood donors. J Psychosom Res 1996;40:495-501.
20. Ditto B, France CR, Albert M, Byrne N. Dismantling applied tension: mechanisms of a treatment to reduce blood donation-related symptoms. Transfusion 2007;47:2217-22.
21. Fisher SA, Allen D, Doree C, Naylor J, Di Angelantonio E, Roberts DJ. Interventions to reduce vasovagal reactions in blood donors: a systematic review and meta-analysis. Transfus Med 2016;26:15-33.
22. Holly CD, Balegh S, Ditto B. Applied tension and blood donation symptoms: the importance of anxiety reduction. Health Psychol 2011;30:320-5.

23. Uman LS, Birnie KA, Noel M, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. Cochrane Database Syst Rev 2013:CD005179.
24. van den Berg K, Lam J, Bruhn R, Custer B, Murphy EL. Water administration and the risk of syncope and presyncope during blood donation: a randomized clinical trial. Transfusion 2012;52:2577-84.
25. Centers for Disease C, Prevention. Syncope after vaccination--United States, January 2005-July 2007. MMWR Morb Mortal Wkly Rep 2008;57:457-60.
26. Kroger AT, Duchin J, Vázquez M. General best practice guidelines for immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). 2017.
27. Wieling W, France CR, van Dijk N, Kamel H, Thijs RD, Tomasulo P. Physiologic strategies to prevent fainting responses during or after whole blood donation. Transfusion 2011;51:2727-38.
28. Hanson SA, France CR. Predonation water ingestion attenuates negative reactions to blood donation. Transfusion 2004;44:924-8.
29. Newman B, Tommolino E, Andreozzi C, Joychan S, Pocedic J, Heringhausen J. The effect of a 473-mL (16-oz) water drink on vasovagal donor reaction rates in high-school students. Transfusion 2007;47:1524-33.
30. Kemper AR, Barnett, E.D., Walter, E.B., Hornik, C., Pierre-Joseph, N., Broder, K.R., Silverstein, M., Harrington, T. Oral Hydration to Prevent Post-Vaccine Presyncope in Adolescents: A Randomized Trial. Submitted 2017.
31. Sahiner NC, Bal MD. The effects of three different distraction methods on pain and anxiety in children. J Child Health Care 2016;20:277-85.
32. Shah V, Taddio A, McMurtry CM, et al. Pharmacological and Combined Interventions to Reduce Vaccine Injection Pain in Children and Adults: Systematic Review and Meta-Analysis. Clin J Pain 2015;31:S38-63.
33. Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. Cochrane Database Syst Rev 2016:CD006911.
34. Canbulat Sahiner N, Inal S, Sevim Akbay A. The effect of combined stimulation of external cold and vibration during immunization on pain and anxiety levels in children. J Perianesth Nurs 2015;30:228-35.
35. . (Accessed 3/28/2018, 2018, at https://www.amazon.com/Buzzy-Mini-Personal-Striped-injections/dp/B004UMOWBM/ref=sr_1_fkmr0_1_a_it?ie=UTF8&qid=1522262323&sr=8-1-fkmr0&keywords=buzzy%2Bmini%2Bpersonal%2Bstripe&th=1.)
36. Uman LS, Chambers CT, McGrath PJ, Kisely S. Psychological interventions for needle-related procedural pain and distress in children and adolescents. Cochrane Database Syst Rev 2006:CD005179.
37. Birnie KA, Chambers CT, Taddio A, et al. Psychological Interventions for Vaccine Injections in Children and Adolescents: Systematic Review of Randomized and Quasi-Randomized Controlled Trials. Clin J Pain 2015;31:S72-89.
38. Klassen JA, Liang Y, Tjosvold L, Klassen TP, Hartling L. Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials. Ambul Pediatr 2008;8:117-28.
39. Kesselman A, Bergen M, Stefanov D, Goldfisher R, Amodio J. Impact of Music in Reducing Patient Anxiety During Pediatric Ultrasound. Pediatr Rep 2016;8:6349.
40. Kim J, Stegemann T. Music listening for children and adolescents in health care contexts: A systematic review. The Arts in Psychotherapy 2016;51:72-85.

41. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item Banks for Measuring Emotional Distress From the Patient-Reported Outcomes Measurement Information System (PROMIS®): Depression, Anxiety, and Anger. Assessment 2011;18:263-83.
42. Spielberger CD. Anxiety: Current trends in theory and research: Elsevier; 2013.
43. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. 1970.
44. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173-83.
45. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.