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

Short Title: Presyncope/Syncope Prevention Study (PS^2)

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

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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
Population:	Up to 340 adolescents, 10 through 14 years of age, who will receive at least one intramuscularly administered vaccine
Clinical Sites:	One: Duke University
Study Duration:	18 months
Participant Duration:	Up to 2 hours
Description of Study Procedures:	This is a randomized controlled trial. During the study, adolescents scheduled to receive at least one intramuscular (IM) vaccine will receive either a combined intervention (vibration and cool pack device plus an electronic game) versus usual care to evaluate the efficacy and acceptability of the intervention in preventing post-vaccination presyncope and syncope. Efficacy will be assessed per participant written self-report to standardized survey questions regarding presyncope symptoms and the occurrence of presyncope/syncope in addition to changes in participant's self-report of pre- versus post-vaccination state anxiety, and post-vaccination pain. Acceptability will be assessed according to the participant's self-report.
Objectives:	**Primary Objectives (PO):** 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. **Secondary Objectives (SO):** 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. SO 2: To compare with control (usual care) injection-site pain after vaccination in adolescents, when Buzzy® and the electronic game intervention are used. SO 3: To assess acceptability of Buzzy® and the electronic game intervention among adolescents. **Exploratory Objectives (EO):**

	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. EO 2: To assess for factors associated with post-vaccination presyncope in adolescents in the control and intervention groups.
Outcome Measures:	**Primary Outcome Measures (POM):** POM 1: Proportion of adolescents with presyncope or syncope after vaccination in the intervention and usual care groups. **Secondary Outcome Measures (SOM):** SOM 1.1: Categorical change (positive, negative, no change) in pre- and post- vaccination state anxiety. SOM 1.2: Numeric change (mean and 95% confidence interval (CI)) in pre- minus post- vaccination state anxiety. SOM 2.1: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at ≤ 1 minute following vaccination. SOM 2.2: Proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination. SOM 2.3: Proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination. SOM 2.4: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination. 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. 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. SOM 3: Proportion of adolescents reporting positive and negative perceptions about their vaccination experience will be determined for each survey item. **Exploratory Outcome Measures (EOM):**

	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. EOM 2: Descriptive results of factors associated with post-vaccination presyncope and syncope using the primary and alternate case definitions for presyncope.
Estimated Time to Complete Enrollment:	13 months

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] Although uncommon, syncope can occur following immunization and result in serious injury.[2]

Vasovagal (neurocardiogenic) syncope is the most common form of syncope.[3] 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.[3]

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.[4] 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).[5] The median age of onset of blood-injury-injection phobia is 7-11 years.[6]

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.[7] Although uncommon, with an estimated range of 1.3 - 5 per 1000 in the adolescent age group,[8,9] syncope after vaccination can lead to serious injury. An analysis of cases reported to Vaccine Adverse Event Reporting System (VAERS) in the 1990s described cases of syncope following immunization.[2] 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.[6,12] 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] 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 broadly 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).[6,11,14,16,17,20-24] 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 stretches baroreceptors in the stomach wall which reflexively increases peripheral vascular tone, and temporarily decreases vasovagal-mediated hypotonia; this vasovagal tone mitigating response is also believed to be achieved through effects on the portal venous system from ingesting a hypo-osmolar beverage.[27-29] Water can have an effect within 15 minutes after ingestion 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 intervention 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 within the preceding 5 years, 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 reducing immediate pain after vaccination in addition to promoting relaxation and reducing anxiety around the time of vaccination.

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] 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 and anxiety in children aged 7 years receiving DTaP in a prospective, randomized controlled trial.[33] Likewise, in a separate prospective, randomized controlled trial of 497 employees receiving influenza vaccine, those randomized to use Buzzy® prior to vaccination reported less pain.[34] Another prospective, open-label randomized trial in 50 children between the ages of 3 and 18 demonstrated the Buzzy® lowered child-reported pain but did not impact child-reported anxiety or how much pain the child expected.[35]

In children and adolescents, relaxation methods, such as listening to music, have shown some effectiveness in decreasing medically-related anxiety[23,31,32] and pain.[36] In particular, 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 tasks (e.g., blowing bubbles, party blowers, etc.), and musical distraction.[37] Results suggested that breathing tasks and musical distraction showed beneficial effects in reducing pain and distress from vaccinations in children younger than 12. Video distraction demonstrated beneficial results in reducing distress in children and adolescents. [38] An additional review focused specifically on the use of iPads with video games or cartoons as a distraction to reduce the parent’s perception of their child’s pain and distress during vaccinations. This study found that the parents of the children using iPads perceived significantly lower levels of fear and anxiety in their children than those in the control group.[39] The use of iPads as a distraction tool also improved parental satisfaction with pain reduction practices used for their child.

In a recent pilot study we evaluated the feasibility and acceptability of two simple office-based interventions aimed at reducing presyncope symptoms among adolescents receiving vaccines (Walter et al, ClinicalTrials.gov NCT03533829). Adolescents receiving one or more vaccines (at least one administered intramuscularly) were randomized to use Buzzy® prior to vaccination, choose music from a streaming internet music service to listen to prior to and during vaccination or to do both. Both interventions were found to be acceptable and feasible. However, neither intervention required ongoing and active engagement of the adolescent during the vaccination process, and hence, may ultimately be less effective at distraction and reducing anxiety than an intervention requiring more active participation.[23] In this study, we aim to pair

Buzzy® with a distraction tool or technique that requires more active participant involvement.

1.2 Summary

To identify best practices for preventing post-vaccination vasovagal syncope, we will target younger adolescents, a population that we have identified as having a higher risk for post-vaccination presyncope and 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 literature, which does not identify one intervention with high efficacy, we plan to investigate the combination of two interventions designed to prevent post-vaccination syncope through mitigation of immediate injection-site pain and anxiety, both factors that we have identified as occurring more frequently among adolescents with post-vaccination presyncope. In summary, we aim to assess the acceptability and efficacy among adolescents of using a paired intervention that includes Buzzy® to reduce injection site pain and a simple electronic game employed as an active distraction to prevent post-vaccination presyncope.

2 STUDY OBJECTIVES

2.1 Primary Objective (PO):

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):

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.

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

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

2.3 Exploratory Objectives (EO):

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.

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

3 STUDY OUTCOME MEASURES AS RELATED TO OBJECTIVES

3.1 Primary Outcome Measures (POM):

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

3.2 Secondary Outcome Measures (SOM):

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

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

SOM 2.1: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at ≤ 1 minute following vaccination.

SOM 2.2: Proportion of adolescents reporting an injection site pain score ≥ 2, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination.

SOM 2.3: Proportion of adolescents reporting an injection site pain score ≥ 4, on the Wong-Baker Faces Pain Scale©, ≤ 1 minute following vaccination.

SOM 2.4: Mean injection-site pain scores on the Wong-Baker Faces Pain Scale© at (approximately) 10 minutes following vaccination.

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.

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.

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):

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.

EOM 2: Descriptive results of factors associated with post-vaccination presyncope and syncope using the primary and alternate case definitions for presyncope.

4 DEFINING PRESYNCOPE AND SYNCOPE

4.1 Presyncope

For this study, the case definition of presyncope was based on review of the literature, an amended Blood Donations Reactions Inventory (BDRI) which was used in previous studies including the CISA Hydration Study, expert opinion, and prior experience with the CISA 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 CISA hydration study to Prevent Post-Vaccination Presyncope ("Water and Vaccines Study") is outlined below and will be used as the primary definition of presyncope in this study:

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:*

<u>Symptoms</u>

- 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)

<u>Signs</u>

- 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.*

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 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.

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 14 years of age
2. The subject must be receiving at least one vaccine delivered intramuscularly
3. 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.
4. The subject must be willing to stay for the completion of all study-related activities.
5. Parent/guardian and adolescent must speak and read English by self-report
6. Parent/guardian must be willing to let their child select an electronic game to play during the study

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. Significant visual impairment or blindness
10. Significant auditory impairment or deafness
11. Febrile(>38.0°C) or acutely ill individuals
12. Upper arm or shoulder pain or injury
13. Has the subject had video game-induced seizures?
14. Adolescent or parent/guardian is an immediate relative of study staff or an employee who is supervised by study staff.
15. 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 340 participants in this study will be male or female adolescents 10 to 14 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 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 research site, CDC, or participating Institutional Review Board (IRB).

7 STUDY SCHEDULE, PROCEDURES, & EVALUATIONS

7.1 Schedule of Events

Adolescents meeting the proposed eligibility criteria will be recruited and if enrolled the subject could spend up to two hours in the clinic. Written permission for the adolescent to participate will be obtained from parent(s)/guardian(s) prior to conducting any study procedures. Written or verbal assent, depending on the age of the adolescent, will also be obtained. **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		
PROMIS Pediatric Anxiety Short Form	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 usual care)	X		
Randomization	X		

Simultaneous Buzzy® and electronic game intervention or usual care	X		
Administer vaccines (not a study procedure)		X	
Injection site pain assessment			X (within 1-3 and at 10 minutes)
Presyncope symptoms assessment			X (15 minutes)
Acceptability Assessment			X (20 minutes)

[1] Complete prior to 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 one week 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 two study arms
- Administer assigned study intervention if randomized to that group

Visit 1, Study Day 1 Clinic Visit Vaccination

- Vaccines administered by clinic staff (Not a study procedure)
- Vaccines administered as usual 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 within 1 minute (up to 3) after last 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 1-3 minutes and 10 (up to 15) minutes after the last injection.
- Complete the presyncope symptoms assessment modified BDRI (15 (up to 20) minutes post vaccination)
- Complete the state anxiety assessment (20 [up to 25] minutes post vaccination)
- Complete the acceptability assessment (20 [up to 30] minutes post vaccination)

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. After initial discussion of the study, parent(s)/guardian(s) will be given as

much time as needed to decide whether or not to give permission for their child to participate in this study. 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
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, prescription and over-the counter medications in preceding week, supplements in preceding week)
Physical Measures	Height, weight, pulse rate and blood pressure measurements (from medical record if obtained or measured, otherwise measured by study staff) Pain at baseline (from medical record)	Height, weight and calculated BMI Pulse rate and blood pressure Pain assessment at baseline
Fatigue/ tiredness	Participant response	Estimated hours of sleep the previous night Feeling tired
Hunger	Participant response	Last food eaten Hunger estimation
Thirst	Participant response	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 Pediatric Anxiety Short Form 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, and race/ethnicity will be obtained from parent/guardian report at the time of enrollment. The participant's medical history including: history of pre-syncope, syncope, cardiac history, seizures, hypoglycemia, diabetes, prescription and over-the counter medications in the preceding week, and supplements in the preceding week will be obtained by review of the electronic health record (EHR) and will be reviewed and confirmed with 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 from the clinical measurements. Height, weight, pulse rate, and blood pressure measurements will be performed by the study team if they are not otherwise available. In addition, the clinic baseline pain assessment will be recorded.

7.6 Needle Related Fear

Fear of having blood drawn has been shown to be predictive of vasovagal reactions in young blood donors.[6] 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 which will have a range from 0, which indicates not at all afraid, to 5 which indicates 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. [6,19]

7.7 Anxiety

Prior to vaccination the study coordinator will have each subject complete a questionnaire to assess generalized anxiety using the Patient Reported Outcome Measurement Information System (PROMIS) Pediatric Anxiety Short Form v2.0 8a instrument for adolescents (11-17 years) to categorize their overall degree of anxiety.[40]

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.[41,42]

7.7.1 Risk Mitigation Procedure

If the subject scores into the severe category for anxiety measured from the PROMIS Pediatric Anxiety Short Form, the subject's score and answers will be shared with the subject's primary care physician.

7.8 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.

7.8.1 Blinding

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

7.9 Study Interventions

7.9.1 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 **(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.

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.

7.9.2 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.

7.10 Immunizations Administered During Visit

Vaccines received as part of usual 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.[43] The Wong- Baker Faces Pain Scale scores pain on a 0-10 metric with 2 point intervals and shows a close linear relationship with visual analog pain scales across the ages from 11-17 years and is acceptable for use with younger adolescents as well. Pain will be assessed at 1 minute (up to 3 minutes) 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 15 minute (up to 20 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. 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 to survey questions will be solicited.

7.14 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 or results in prolongation of existing inpatient hospitalization (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

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.

8.1 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.

8.2 Analysis Plan

8.2.1 Study Populations

The study will enroll adolescents, female and male, ages 10-14 years, receiving at least one ACIP recommended vaccine administered intramuscularly. Participants will be randomized into either of the two groups: intervention (vibration and cool pack device [Buzzy®] and an electronic game) or the control (usual care).

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

- Modified Intent-to-treat (MITT) population: is defined as those subjects who are enrolled, randomized into the study, and received an intramuscular 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 all study procedures, and have no protocol violations that are likely to affect the objectives.

The primary and exploratory objective analyses will be performed in the 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.

8.2.2 Descriptive Statistics

Descriptive analyses will be conducted for demographic variables and for baseline characteristics (e.g., fatigue, hunger, thirst, needle fear and phobia, and an anxiety rating scale score). 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. The descriptive statistics will be analyzed in the MITT and Per-protocol populations.

8.2.3 Primary Objective (PO 1):

The primary objective is 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. The proportion of adolescents with presyncope or syncope after vaccination will be compared between the control and intervention groups using a chi-square test.

8.2.4 Secondary and Exploratory Objectives

Secondary Objective (SO 1):

The first secondary objective is to compare the change in state anxiety score for adolescents before and after vaccination in the control group to the intervention group. 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-Haenszal 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 Objective Measure (SO 2):

The second secondary objective is to compare the change in injection-site pain after vaccination of adolescents in the control group to the intervention group. 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.

Secondary Objective Measure (SO 3):

The third secondary objective is to assess the acceptability of the intervention among the adolescents based on their positive or negative responses for each survey item. The groups will be compared for each survey item using a chi-square test.

Exploratory Objective (EO 1):

The first exploratory objective is 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, after vaccination will be compared between the control and intervention groups will be compared using a chi-square test.

Exploratory Objective (EO 2):
This exploratory objective is 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. 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.

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 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).[44] All study-related documents containing protected health information, e.g. enrollment logs, case report forms, memory aids 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 directly into the REDCap database by members of the study team. 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, as appropriate. 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 may receive access to coded data not containing any directly identifying information.

9 HUMAN SUBJECTS

9.1 Human Subjects Involvement, Characteristics, and Design

Duke investigators will be responsible for submitting the protocol, informed consent (**Appendix B**), 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 Duke's IRB on an annual basis. Protocol deviations or concerns about study integrity will be reported promptly to the overseeing IRB in accordance with institutional requirements. CDC staff will be responsible for submitting materials to the CDC for review and obtain reliance on Duke IRB.

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 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 annoyance or movement limitation due to the electronic game 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.

One potential benefit includes less injection site pain due to administration of Buzzy® on the subject's arm. Adolescents may also be distracted from the vaccination by playing the electronic game.

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 allowing patients to play a game of their choosing from a predetermined list and following the precise guidelines for using the Buzzy®.

In addition, for participants with significant anxiety, the study team will notify the health care provider caring for the participant.

9.4.2 ClinicalTrials.gov Requirements

The project is registered on ClinicalTrials.gov. (NCT04772755).

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 Buzzy® and an electronic game 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. Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. Arch Pediatr Adolesc Med 1997;151:255-9.
3. Chen-Scarabelli C, Scarabelli TM. Neurocardiogenic syncope. BMJ 2004;329:336-41.
4. Woo EJ, Ball R, Braun MM. Fatal syncope-related fall after immunization. Arch Pediatr Adolesc Med 2005;159:1083.
5. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
6. Deacon B, Abramowitz J. Fear of needles and vasovagal reactions among phlebotomy patients. J Anxiety Disord 2006;20:946-60.
7. Institute of Medicine, Committee to Review Adverse Effects of Vaccines, Stratton KR, Clayton EW. Adverse effects of vaccines: evidence and causality: National Academies Press Washington, DC; 2012.
8. Gasparini R, Bonanni P, Levi M, et al. Safety and tolerability of bivalent HPV vaccine: an Italian post-licensure study. Human vaccines 2011;7:136-46.
9. Zimmerman RK, Nowalk MP, Lin CJ, et al. Randomized trial of an alternate human papillomavirus vaccine administration schedule in college-aged women. Journal of women's health 2010;19:1441-7.
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. 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.
34. Redfern RE, Micham J, Seegert S, Chen JT. Influencing Vaccinations: A Buzzy Approach to Ease the Discomfort of a Needle Stick-a Prospective, Randomized Controlled Trial. Pain Manag Nurs 2018.
35. Redfern RE, Chen JT, Sibrel S. Effects of Thermomechanical Stimulation during Vaccination on Anxiety, Pain, and Satisfaction in Pediatric Patients: A Randomized Controlled Trial. J Pediatr Nurs 2018;38:1-7.
36. 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.
37. 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.
38. 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.
39. Shahid R, Benedict C, Mishra S, Mulye M, Guo R. Using iPads for distraction to reduce pain during immunizations. Clin Pediatr (Phila) 2015;54:145-8.
40. 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.
41. Spielberger CD. Anxiety: Current trends in theory and research: Elsevier; 2013.
42. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. 1970.
43. 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.
44. Influenza activity--United States and worldwide, 2007-08 season. MMWR Morb Mortal Wkly Rep 2008;57:692-7.

Appendix A – Buzzy® instructions

CLEANING:

Buzzy® is a reusable medical device that should be thoroughly cleaned and reprocessed following your facility's infection control protocol for non-critical equipment. All accessories must be cleaned and disinfected with your facility's disinfecting wipes or method used to reprocess non-critical equipment such as stethoscopes or patient monitors. Do not autoclave. Do not immerse in liquid.

BATTERIES:

When battery power is getting low, Buzzy® will emit short spurts of vibration upon initial activation. Please refresh your Buzzy® with new batteries. Buzzy's batteries will last at full strength about 20 hours. For best pain relief, replace batteries when vibration weakens. Unscrew the back using a philips head screwdriver to remove back panel. Buzzy® is powered by 2 alkaline AAA batteries. Remove batteries if Buzzy® is not being used for extended period of time.

TROUBLESHOOTING:

When used with care, Buzzy should last years. If Buzzy is dropped repeatedly, however, the metal that holds the batteries in place can bend. If Buzzy fails to function after a fall, try pinching battery clip in to restore contact.

HOW TO ORDER /ADDITIONAL INFORMATION:

Please visit our website buzzy4painrelief.com for a complete list of FAQ's, other pain management tips, how-to videos, accessories, replacement parts, and more!

GUARANTEE:

Previous medical history and intrinsic physiologic differences may make Buzzy® less effective for some people. If not completely satisfied, return within three months to place of purchase for a full refund, or contact us at the address below.

MMJ Labs
322 Sutherland Place
Atlanta, GA 30307, U.S.A.

buzzy4painrelief.com info@mmjlabs.com

877.805.2899

US Patented British Patent No. 2455695
RM-1910, 1248-064-5002-00, 1248-064-5001-00

Type B Applied Part

Buzzy®

DRUG FREE PAIN RELIEF

Developed by a physician, Buzzy® is a reusable device for minor aches and pains.

Healthcare Buzzy® for professional/clinical use. Reusable pain relief product intended for multiple users. Thoroughly clean and disinfect Buzzy® and its accessories between patients following your facility's infection control protocol for reprocessing non-critical equipment.

buzzy4painrelief.com

Clinical Use Rev. 08.18.14

DIRECTIONS FOR USE:


Attach Frozen Wings to Back of Buzzy

Immediately before use, remove the Wings from the freezer and attach behind Buzzy® on the hook. Activate by firmly pressing button on top of Buzzy®. Press once for constant vibration, twice for intermittent vibration. Press a third time to turn Buzzy® off.

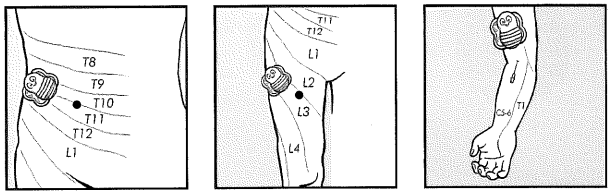
Buzzy® has an energy saving automatic shut-off after 3 minutes of constant use. Simply press the button on top of Buzzy® to reactivate vibration.

Buzzy comes with a silicone Comfort Strap to hold Buzzy in place on extremities. **1.** Loop the Comfort Strap around the arm, passing one end through the slit in the other. **2.** Hold the slit and pull the other end through until the desired tension is reached, then release the slitted end. **3.** To lock the Comfort Strap in position, release the tension from the long end. **4.** To release, simply pull gently on the short end and the Comfort Strap will fall away.

Use Buzzy® only on clean, unbroken skin. Buzzy's stripes, or bottom end should be closest to the procedure, and Buzzy's head and switch farthest away.

Tip: For best results, center Buzzy's bigger rounded end directly next to the pain.

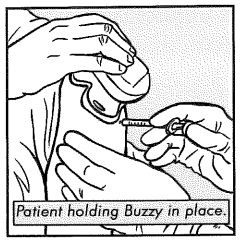
Buzzy PLACEMENT:



Buzzy's physiologic blockade works best when placed "between the brain and the pain" in the same nerve area as the pain. On arms and shoulders, nerves run from fingers to shoulders to the spine. For the chest and back, the nerves run from the center of the chest or stomach horizontally to the back. On the thighs, the nerves run diagonally from the inner thigh around to the back to the spine.

For children: For best results, let children hold Buzzy® in advance for familiarity, and let them choose whether or not to use the ice pack.

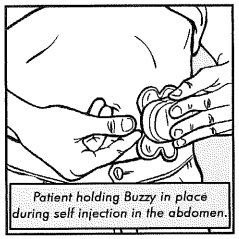
For shots: Switch on to activate the vibration, and then place Buzzy® on the site of the shot. Leave for 15 seconds for surface shots - 60 seconds for deeper injections. Immediately before cleaning the site, move Buzzy® proximal (closer to the head) to the pain location, and press in place throughout cleaning and giving the shot.


Patient holding Buzzy in place.


Parent holding Buzzy in place while comforting child.

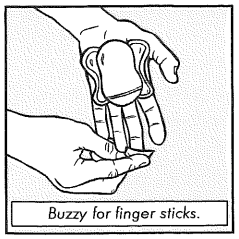
For children who get their shots sitting up, a parent can put an arm around the shoulders to hold Buzzy® for them.

For injections in the stomach: Place Buzzy® lateral to the shot (i.e., belly button, the shot, and then Buzzy®.

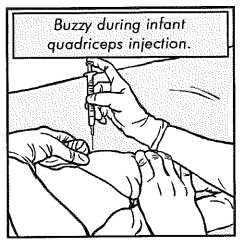

Patient holding Buzzy in place during self injection in the abdomen.

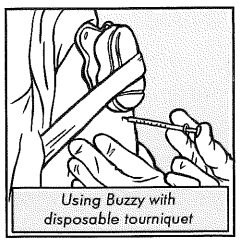
For Aches and Pains:
Apply directly to sore muscles for maximum of 10 minutes. Hold in place or attach with strap. Buzzy® has an energy saving automatic shut-off after 3 minutes of constant use. Simply press the button on top of Buzzy® to reactivate vibration.

For finger sticks or splinter removal: Switch on to activate the vibration, and then press Buzzy® on the palm with the bottom end toward the finger. Leave in place throughout cleaning and doing the procedure.


Buzzy for finger sticks.

For burning or itching: Like any cold and warm therapy application, Buzzy® can be helpful for burning or itching. For insect bites or medications that cause burning or itching, take frozen Wings and massage the vibrating Buzzy®/Wings combination directly on the site. Rub or press in place until the area feels better. Do not place Buzzy® directly on a thermal burn.

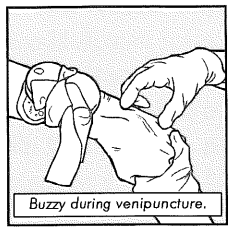

Buzzy during infant quadriceps injection.


Using Buzzy with disposable tourniquet

FOR NURSES:

Press Buzzy® with the heel of your hand, leaving the thumb and forefinger to bunch skin for the shot. Leave Buzzy in place during the procedure. Once procedure is completed, secure Buzzy in one hand and release strap with other hand.

For IVs or phlebotomy:
Switch on to activate the vibration, and then place Buzzy® proximal (above) to the pain location. Press in place or tuck under tourniquet before immediately cleaning and obtaining access. Pass any tourniquet through slot to secure Buzzy® to arm. Do not put directly on site of access.


Buzzy during venipuncture.

INDICATIONS FOR USE:

Controls pain associated with injections (venipuncture, IV starts, cosmetic procedures) and the temporary relief of minor injuries (muscle or tendon aches, splinters and bee stings). Also intended to treat myofascial pain caused by trigger points, restricted motion and muscle tension.

Fold Wings and STORE IN FREEZER. Wings must be frozen solid for best effect.

Healthcare Buzzy comes with reusable, clear blue gel wings and a silicone Comfort Strap. Thoroughly clean and disinfect between patients and refreeze Wings after each use. Follow your facility's infection control protocol for cleaning non-critical equipment between patients.

WARNINGS: For intended use only • Direct or prolonged application of ice could vasoconstrict or alter lab values.

CONTRAINDICTATIONS: Do not use in the presence of unexplained calf pain. Consult a physician. • This device should not be used over swollen or inflamed areas or skin eruptions. • Do not place directly on a thermal burn • Do not use ice pack with underlying sensitivities to ice or cold (e.g. Sickle Cell Disease, Reynaud's Disease).

CAUTIONS: Store in a cool, dry place.

ICE WINGS:

Wings will stay frozen 10 minutes at room temperature. For best pain relief, the Wings must be frozen solid to avoid absorbing vibration.

Thoroughly clean and disinfect between patients and refreeze after each use. Follow your facility's infection control protocol for cleaning non-critical equipment between patients.

Tip: For long procedures or for medications that burn or sting, prepare additional Wings.

Store folded Wings in freezer. Gel inside Wings is a non-toxic, safe, food-grade product that may deteriorate if not stored properly.

Note: To transport, place the Wings between the Cold-To-Go bag blue ice inserts (sold separately), or between 2 commercial cold packs (sold separately) to maintain frozen temperature.

COMFORT STRAP:

Our Comfort Strap is a reusable, single-handed tourniquet, smooth and pinch free. To use, **1.** Loop the Comfort Strap around the arm, passing one end through the slit in the other. **2.** Hold the slit and pull the other end through until the desired tension is reached, then release the slitted end. **3.** To lock the Comfort Strap in position, release the tension from the long end. **4.** To release, simply pull gently on the short end and the Comfort Strap will fall away.

Appendix B – Informed Consent Form

Duke University Health System

Consent to Participate in a Research Study
Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions

CONCISE SUMMARY

This is a research study to test a strategy designed to prevent fainting (syncope) or symptoms that might occur before fainting (presyncope) in adolescents 10 through 14 years of age who are receiving at least one injected vaccine.

Adolescents in this study will be randomly assigned (like flipping a coin) to one of two groups. Adolescents in Group 1 will select an electronic game to play and have a vibrating cooling device (like a small ice pack) named Buzzy® placed on the arm/s where they will receive their shot/s. Adolescents in Group 2 will receive usual care. They will not choose and play an electronic game and Buzzy will not be applied on the upper arm at the time of vaccination. Adolescents will answer questions about whether they have a fear of needles, if they have anxiety before or after the vaccine injection, how they feel after vaccination, if they have pain from the needles. Adolescents will also be asked about their vaccination experience, and those in Group 1 will be asked about the electronic game and Buzzy.

Only minor risks are expected from this study. Your child may feel slight discomfort from the vibration and coolness of the Buzzy®. Your children may also experience some uneasiness answering some of the questions.

If you are interested in learning more about this study, please continue reading below.

We are asking you to allow your child to take part in a research study because they are scheduled to have a routine vaccine. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. Please ask the study doctor or study staff to explain anything that you do not clearly understand. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if your child is taking part in another research study.

Dr. Emmanuel Walter will conduct the study and it is being funded by the Centers for Disease Control and Prevention (CDC). The sponsor of this study, the CDC, will pay Duke University to perform this research, and these funds may pay part of Dr. Walter's salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to have your child participate, Dr. Walter will be your child's doctor for the study. He will be in contact with your child's regular health care provider while your child is in the study and afterwards, if needed.

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WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see how well a strategy designed to prevent fainting or symptoms related to fainting following vaccination works in children 10 through 14 years of age who are receiving one or more injected vaccines. Our strategy is to apply a cold, vibrating device named Buzzy® on their arm/s where they are getting their shot/s just prior to and during the shot/s. If your child is in this group, they will also play an electronic game for 5 minutes prior to, during and after their shot/s. In this study, we will look at whether applying Buzzy® on the arm and playing an electronic game versus usual care makes people feel better during and after receiving vaccinations. Those receiving Buzzy® and the game will have Buzzy® applied to the arm for 30-60 seconds prior to vaccination and during the vaccination. The electronic game will be played for about 5 minutes before vaccination, during vaccination, and for a minimum of 1 minute and up to 15 minutes following vaccination.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 340 children will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?

If you agree for your child to be in this study, you will be asked to sign and date this consent form. Your child must also agree to participate in the study. We will also ask your child if he/she agrees to participate, and if 12 years or older, we will ask him/her to sign this form.

A member of the study staff will ask you questions regarding your child's health (including medical history and current medications). The medical history is obtained to make sure that your child is healthy and is eligible to participate. If your child is not eligible, he/she will not be enrolled, and no further procedures will be done.

Your child will be randomly assigned (like flipping a coin) to one of 2 groups:

Group	Strategy	What is involved
1	Buzzy® + electronic game	Wear Buzzy® on arm just prior to and during shot/s and play an electronic game 3-5 minutes prior to, during, and 1-15 minutes after vaccination
2	Control	This intervention group will receive usual care during vaccination.

Your child will have an equal chance of being assigned to each of the groups. Regardless of which group your child is assigned to, he/she will receive the usual standard of care for vaccinations, including monitoring for about 20 minutes after being vaccinated.

FOR ALL PARTICIPANTS:

All participants will be asked about their medical history, current health status, recent sleep, and about the last time they ate or drank. We will also ask questions about fear of shots, pain, and anxiety. In

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addition, we will measure temperature, weight, height, pulse rate and blood pressure if not already measured by the clinic staff before receiving shots. All subjects will be monitored for about 20 minutes after the vaccination, also called the wait period. Your child will also be provided with the CDC's Advisory Committee on Immunization Practices guidance that they may choose to sit or lie down during the post-vaccination wait period.

FOR PARTICIPANTS ASSIGNED TO THE BUZZY® + ELECTRONIC GAME GROUP:
In addition to the activities that occur for all participants, those who are assigned to the Buzzy® + electronic game group will be asked to play an electronic game on an iPad provided by the study team. They will play the electronic game for 3 to 5 minutes prior to vaccination, during their vaccination, and for 1-15 minutes following vaccination. Buzzy® will be applied on their upper arm/s near the area where they will get their shot/s for 30-60 seconds prior to getting their shots. Buzzy® will be moved further up on their upper arm during the actual vaccine injection. If getting shots in both arms, Buzzy® will be applied on both upper arms before and during the injection.

HOW LONG WILL MY CHILD BE IN THIS STUDY?
If you agree for your child to take part in this study, your child's involvement may last for up to two hours.

You can choose to have your child stop participating at any time without penalty or loss of any benefits to which you or your child are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your study doctor first.

WHAT ARE THE RISKS OF THE STUDY?
Your child is receiving vaccinations today as part of their routine care and not as a part of this study. Your child's health care provider will explain the risks related to the vaccines to you before your child is vaccinated.

As a result of your child participating in this study, they are at risk for the following side effects. You should discuss these with the study doctor and your child's regular health care provider if you choose. There may be some temporary discomfort associated with wearing Buzzy® on the arm as it applies a cold sensation, like wearing an ice pack, and vibrations to the arm. There are few known risks to interacting with an age-appropriate electronic game, and these may include fatigue or boredom.

Your child may also experience some uneasiness from answering some of the questions. These questions will be asked verbally by study staff or in a written format.

There is also the potential risk of loss of confidentiality about information obtained as part of this study. Please see below for additional information regarding confidentiality.

There may be risks, discomforts, or side effects that are not yet known.

Duke University Health System

Consent to Participate in a Research Study
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ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There might be no direct benefit to your child for participating in this study, especially if your child is randomized to the usual care group. However, it is possible that participation in this study could decrease your child's chance of fainting or feeling faint after vaccination. There is also a possible benefit of decreased pain associated with vaccination due to the cold and vibration mechanism of Buzzy®. We hope that in the future the information learned from this study will benefit other children.

WILL MY CHILD'S INFORMATION BE KEPT CONFIDENTIAL?
Participation in research may involve some loss of privacy. We will do our best to make sure that information about your child is kept confidential, but we cannot guarantee total confidentiality. Your child's personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. If questionnaires suggest that your child is having considerable anxiety, we will inform your child's health care provider. Your child's personal information may also be given out if required by law.

As part of the study, results of your child's study-related procedures may be reported to CDC and its affiliates. In addition, your child's records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives and affiliates of the CDC, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your child's research record, they may also need to review your child's entire medical record.

The study results will be retained in your child's research record for six years after the study is completed, or until your child reaches the age of 21, whichever is longer. At that time, either the research information not already in your child's medical record will be destroyed or information identifying your child will be removed from such study results at DUHS. Any research information in your child's medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your child's name or other personal information will not be revealed. If the results from this study are published, you may receive notification of this by letter.

Some people or groups who receive your child's health information might not have to follow the same privacy rules. Once your child's information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share your child's private information with anyone not involved in the

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Consent to Participate in a Research Study
Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions

study, the federal law designed to protect your child's health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

This study is supported by the Centers for Disease Control and Prevention (CDC). Because of this support, your study information is protected by a Certificate of Confidentiality.

With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2) you have consented to the disclosure, including for your medical treatment; or
3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.
Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your child's routine medical care, including copayments and deductibles. Routine medical care services are those that your child would have received for his/her condition if he/she were not participating in this research study.

WHAT ABOUT COMPENSATION?
You will be reimbursed with a $40 ClinCard for your expenses related to your child's participation (parking, gas, and time).

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that your child is injured as a result of his/her participation in this research study. However, there is no

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Consent to Participate in a Research Study
Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions

commitment by Duke University, Duke University Health System, Inc., or your child's Duke physicians to provide monetary compensation or free medical care to your child in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Walter using the pager number at (919) 970-5720 during regular business hours, after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

Your decision to allow your child to be in this study is voluntary. You may choose not to have your child be in this study, or, if you agree to allow your child to be in the study, you may withdraw your child from the study at any time. If your child withdraws from the study, no new data about your child will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study.

If such an adverse event occurs, we may need to review your child's entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor. We may want to have an investigator assess your child.

Your decision for your child not to participate or to withdraw your child from the study will not involve any penalty or loss of benefits to which he/she are entitled, and will not affect their access to health care at Duke. Your child can still get vaccinated today, regardless of whether or not you agree to participate in the study. If you decide to withdraw your child from the study, we ask that you notify any member of the study team during the visit or you can contact Dr. Walter in writing and let him know that your child is withdrawing from the study. His mailing address is Duke Vaccine and Trials Unit, 2608 Erwin Road, Suite 210, Durham, NC 27705.

The study doctor or sponsor may withdraw your child from this study for any reason at any time even without your consent. This could occur, for example, if the study doctor decides that it is in your child's best interest.

We will tell you about new information that may affect your child's health, welfare, or willingness to stay in this study.

A description of this clinical trial will be available on https://www.clinicaltrials.gov/ as required by U.S. Law. This Web site will not include information that can identify you or your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Duke University Health System

Consent to Participate in a Research Study
Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Emmanuel Walter using the 24 hour pager number at (919) 970-5720.

For questions about you and your child's rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to my child and me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree for my child to be in this study, with the understanding that I may withdraw my child at any time. I have discussed the study with my child, who agrees to be in the study. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Parent or Legal Guardian	Date	Time
_____	_____	_____
Signature of Subject (if 12 years or older)	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time