**PROTOCOL TEMPLATE: INTERVENTION STUDY (CLINICAL TRIALS)**

| | |
|---|---|
| Title: | **Evaluating an eHealth solution for screening in pediatric care** |
| Short Title | Evaluating eHealth solution for screening |
| Drug or Device Name(s): | N/A |
| FDA IND | N/A |
| Regulatory Sponsor: | N/A |
| eIRB Number | IRB 20-017351 |
| Protocol Date: | 1 December 2021 (Last approved by IRB on 3 February 2022) |
| Amendment 1 Date: | Amendment 3 Date: |
| Amendment 2 Date: | Amendment 4 Date: |

**Sponsor**
National Institute of Child Health and Human Development (NICHD)

**Study Principal Investigator** (multicenter study with CHOP PI responsible)
Nancy Kassam-Adams, PhD
Children's Hospital of Philadelphia
Roberts Center for Pediatric Research - 2716 South Street, 13th floor (13-291)
Philadelphia PA 19146
Office 215-590-3118
email: adamsn@email.chop.edu

**Site Principal Investigator - University of Kentucky**
Meghan L. Marsac, PhD
800 Rose Street, MN 472
Lexington, KY 40536
Office: 859-323-3850
email: meghan.marsac@uky.edu

## TABLE OF CONTENTS

**Table of Contents** ..... **ii**
**Abbreviations and Definitions of Terms** ..... **iv**
**Abstract** ..... **v**
**Table 1: Schedule of Study Procedures** ..... **vii**
**Figure 1: Study Diagram** ..... **viii**

**1 BACKGROUND INFORMATION AND RATIONALE** ..... **1**

1.1 INTRODUCTION ..... 1
1.2 NAME AND DESCRIPTION OF INVESTIGATIONAL PRODUCT OR INTERVENTION ..... 2
1.3 RELEVANT LITERATURE AND DATA ..... 2
*1.3.1 Background and rationale* ..... *2*
*1.3.2 Measures addressing primary and secondary study aims* ..... *3*
1.4 COMPLIANCE STATEMENT ..... 5

**2 STUDY OBJECTIVES** ..... **5**

2.1 PRIMARY OBJECTIVE (OR AIM) ..... 5
2.2 SECONDARY OBJECTIVES (OR AIM) ..... 5

**3 INVESTIGATIONAL PLAN** ..... **6**

3.1 GENERAL SCHEMA OF STUDY DESIGN ..... 6
*3.1.1 Screening & Baseline Research Assessment* ..... *6*
*3.1.2 Study Treatment Phase* ..... *6*
*3.1.3 Follow-up* ..... *7*
3.2 ALLOCATION TO TREATMENT GROUPS AND BLINDING ..... 7
3.3 STUDY DURATION, ENROLLMENT AND NUMBER OF SITES ..... 7
*3.3.1 Duration of Study Participation* ..... *7*
*3.3.2 Total Number of Study Sites/Total Number of Subjects Projected* ..... *7*
3.4 STUDY POPULATION ..... 8
*3.4.1 Inclusion Criteria* ..... *8*
*3.4.2 Exclusion Criteria* ..... *8*

**4 STUDY PROCEDURES** ..... **8**

4.1 SCREENING & BASELINE RESEARCH ASSESSMENT ..... 8
4.2 STUDY TREATMENT PHASE ..... 9
4.3 FOLLOW-UP ..... 9
4.4 SUBJECT COMPLETION/WITHDRAWAL ..... 10

**5 STUDY EVALUATIONS AND MEASUREMENTS** ..... **10**

5.1 SCREENING AND MONITORING EVALUATIONS AND MEASUREMENTS ..... 10
*5.1.1 Medical Record Review* ..... *10*
5.2 EFFICACY EVALUATIONS ..... 10
*5.2.1 Diagnostic Tests, Scales, Measures, etc.* ..... *10*
5.3 SAFETY EVALUATION ..... 11

**6 STATISTICAL CONSIDERATIONS** ..... **11**

6.1 PRIMARY ENDPOINT ..... 11
6.2 SECONDARY ENDPOINTS ..... 12
6.3 STATISTICAL METHODS ..... 12
*6.3.1 Baseline Data* ..... *12*
*6.3.2 Efficacy Analysis* ..... *12*
6.4 SAMPLE SIZE AND POWER ..... 13

**7 STUDY INTERVENTION** ..... **14**

7.1 DESCRIPTION ..... 14
*7.1.1 Treatment Compliance and Adherence* ..... *15*
**8 SAFETY MANAGEMENT ..... 15**
8.1 CLINICAL ADVERSE EVENTS ..... 15
8.2 ADVERSE EVENT REPORTING ..... 15
**9 STUDY ADMINISTRATION ..... 15**
9.1 TREATMENT ASSIGNMENT METHODS ..... 15
*9.1.1 Randomization* ..... *15*
*9.1.2 Blinding* ..... *15*
*9.1.3 Unblinding* ..... *15*
9.2 DATA COLLECTION AND MANAGEMENT ..... 15
9.3 CONFIDENTIALITY ..... 17
9.4 REGULATORY AND ETHICAL CONSIDERATIONS ..... 18
*9.4.1 Data and Safety Monitoring Plan* ..... *18*
*9.4.2 Risk Assessment* ..... *18*
*9.4.3 Potential Benefits of Trial Participation* ..... *19*
*9.4.4 Risk-Benefit Assessment* ..... *19*
9.5 RECRUITMENT STRATEGY ..... 19
9.6 INFORMED CONSENT/ASSENT AND HIPAA AUTHORIZATION ..... 19
*9.6.1 Waiver of HIPAA Authorization* ..... *20*
9.7 PAYMENT TO SUBJECTS/FAMILIES ..... 21
**10 PUBLICATION ..... 21**
**11 REFERENCES ..... 22**
**Appendix ..... Error! Bookmark not defined.**

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | | |
|---|---|---|
| AE | | Adverse event |
| AUC | | Area under the curve (in ROC analyses) |
| CPSS-5 | | Child PTSD Symptom Scale for DSM-5 |
| eScreen | | Game-based online screening system under development at CHOP |
| HRQoL | | Health=related quality of life |
| NICHD | | National Institute for Child Health and Human Development |
| NIH | | National Institutes of Health |
| NRSI | | Numerical Rating Scale for Pain Intensity |
| PPPM | | Parents Postoperative Pain Measure |
| PROMIS | | Patient-Reported Outcomes Measurement Information System |
| PTS | | Posttraumatic stress |
| PTSD | | Posttraumatic stress disorder |
| PTSS | | Posttraumatic stress symptoms |
| ROC | | Receiver Operating Curve |
| SCD | | Sickle cell disease |
| STTR | | Small Business Technology Transfer |
| | | |
| | | |
| | | |

## ABSTRACT

Context:

A significant minority of ill or injured children experience pain or posttraumatic stress symptoms (PTSS) that interfere with recovery and may indicate a need for follow-up care from the health care team. Many of these phenomena are best reported via children themselves, yet there is currently no practical validated means to screen and monitor children after hospitalization or a medical event, and connect results of screening to follow-up care. The "eScreen" system is being developed as part of an NIH-funded Phase II STTR project, and will encompass a game-based system for children, parent messages and dashboard, and integration of eScreen findings into the electronic health record. Prior work by our team established concurrent validity of eScreen-delivered measures compared to validated research measures of pain and posttraumatic stress, in a single assessment for research purposes.[1] The current project will further evaluate several key components of the system (game-based child screening, parent messages / dashboard) as these are used by children and parents over a 6 week period.

Objectives:

The primary objective of the current prospective validation study is to evaluate predictive validity of eScreen measures of pain and PTSS during children's at-home use of the eScreen system to predict ongoing symptoms or problematic recovery at 6 weeks.

The secondary objective, addressed via randomized assignment of participants to usual care plus eScreen versus usual care, is to evaluate the impact of using the eScreen system on factors related to parents' management of child symptoms and recovery.

Study Design:

This study is a randomized controlled trial that will examine validity of eScreen measures (primary aim) and assess the impact of the eScreen system on parent management (secondary aim). At T1, after baseline assessment (questionnaires), children will be randomized to the usual care plus eScreen (eScreen) or usual care alone (Usual Care) groups. In the eScreen group, children will use the game-based screening component and parents the parent information component for 6 weeks. All participants will complete follow-up research assessments by phone, online, or mail at T2 (6 weeks) and T3 (12 weeks). Following their T3 research assessment, child participants in the Usual Care group will be provided with the option to play the game and invited to provide feedback on the game if they wish.

Setting/Participants:

We will enroll up to 10 child-parent pairs in a pilot phase and then enroll a cohort of 300 children (and one parent per child) recently treated for illness or injury at CHOP or Kentucky Children's Hospital inpatient or outpatient services.

Inclusion criteria: a) age 8 – 17 years, b) treated or admitted for injury or illness event that occurred within the past month, c) child has regular access to a compatible (IOS or Android) tablet at home, d) parent has an internet-capable smartphone and can receive text messages on that phone OR has email account that can receive messages about child status, and e) the child and parent read or understand English well enough to consent / assent to participation and complete study tasks (e.g., checklists, use of screening system).

Exclusion criteria: a) index event is an injury due to family violence.

Study Interventions and Measures:

The study intervention includes two key eScreen system components:

- A child screening component: a set of brief screening measures (of pain, PTSS, functional recovery) for children age 8 to 17, delivered within a game played multiple times per week on a compatible (IOS or Android) tablet, and
- A parent information component: weekly messages sent to parents (via text or email) that summarize child ratings and include a link to an online dashboard with additional personalized information for parents.

Participants will be randomized to usual care plus eScreen or to usual care alone, in a 2-to-1 ratio.

The primary study endpoints employ validated measures of ongoing symptoms / problematic recovery: pain (NRSI rating), pain interference (PROMIS Pain Interference T score) and PTSS (CPSS-5 scores) at T2 (6 weeks post-baseline). Reflecting our primary aim of prediction, the primary study endpoints are not participant scores on these measures, but rather the results of ROC analyses; i.e. the area under the curve (AUC) for eScreen pain score predicting pain and pain interference and the AUC for eScreen PTSS score predicting PTSS.

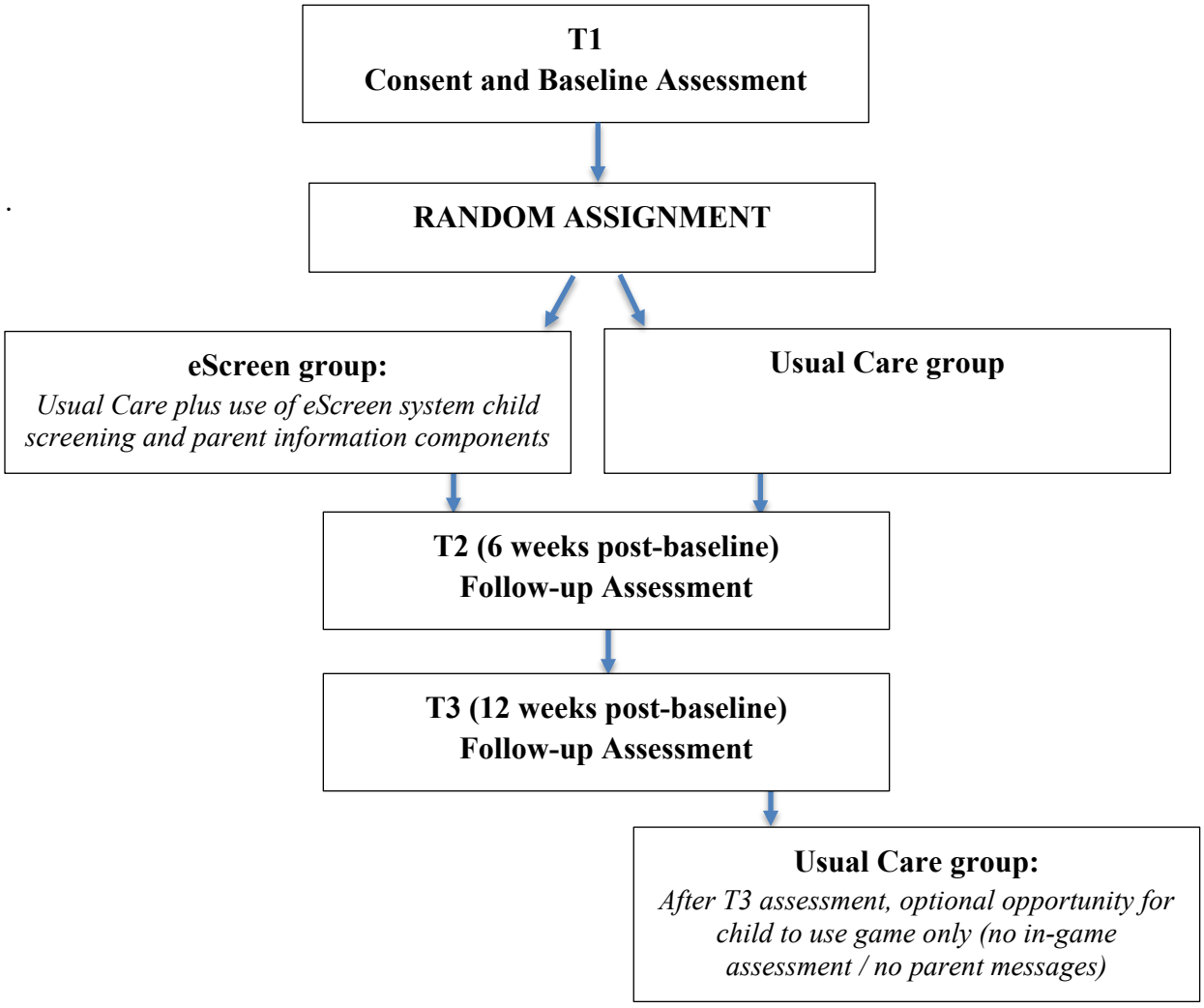
The secondary study endpoint relates to the potential impact of the eScreen system on parent management of child symptoms and recovery. We will compare eScreen and Usual Care groups on parent ratings at T2 of the extent to which they (a) have received the information they needed to take care of their child after leaving the clinic or hospital, and (b) have felt confident in taking care of their child (related to their illness / injury) in this 6 week period.

## TABLE 1: SCHEDULE OF STUDY PROCEDURES

| **Study Phase** | **Screening and Baseline** | **Intervention (use of eHealth tools at home)** | **Follow-up (phone, online, or mail)** | | |
|---|---|---|---|---|---|
| **Visit Number** | **T1** | | **T2** | **T3** | **post-T3 (optional)** |
| Informed consent / assent | X | | | | |
| Review inclusion / exclusion criteria | X | | | | |
| Demographics / medical history | X | | | | |
| Complete study questionnaires | X | | X | X | |
| Randomization | X | | | | |
| eScreen group:<br>Use eScreen system (child screening and parent information components) | | X | | | |
| Usual Care group:<br>**Optional** use of game & feedback on game | | | | | X |

.

## FIGURE 1: STUDY DIAGRAM



# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Undetected and unaddressed persistent pain and post-traumatic stress symptoms are major modifiable factors in suboptimal outcomes after child illness or injury. No solution exists for monitoring child self-reported pain, traumatic stress, or functional recovery after hospital or clinic discharge. Our team's NIH-funded STTR project proposes to address this critical, systemic problem by focusing on the gap between current approaches for identifying child pain and PTSS post-discharge, and the unmet needs of recently ill or injured children, their families, health care providers, and health systems.

Our long-term vision encompasses an integrated screening and intervention system with child, parent, provider, and health system integration points. The eScreen system will proactively deliver regular screening questions to children, collect child and parent data, and connect parents with timely resources via automated follow-up messaging. The child screening component is embedded in an episodic game, promoting user engagement and measurement fidelity. Screening will be repeated at regular intervals to identify children with symptoms or problems, such as persistent/impairing PTSS or pain, that may warrant attention by parents or the health care team. Ultimately, raw, aggregate, and derived data collected by the system can be made available to external systems via a set of application program interfaces (APIs) that utilize industry-standard protocols, maximizing flexibility in how data may be integrated into clinical practice, analytics systems, or care management platforms.

Funded via a prior Phase I and current Phase II STTR grant from NICHD, Radiant is the small business developing this system, with CHOP and UK as research partners. Overall research aims for Phase II are to evaluate the extent to which eScreen measures delivered via a mobile game-based system:

(a) serve as valid indicators of pain, posttraumatic stress symptoms (PTSS), and functional recovery, compared to gold standard (but resource-intensive) means of assessment,

(b) can detect concerns that may warrant follow-up care, i.e. that parents, providers, and insurers need to identify or monitor, and

An additional research aim is to determine whether use of the eScreen system can improve adherence with follow-up care and parent / health system awareness and detection of post-discharge pain, PTSS, and delayed recovery in pediatric patients.

In keeping with these research aims, in a prior study (IRB-16-013517) we demonstrated solid validity for eScreen measures presented in a game-based context compared to validated research measures for pain and posttraumatic stress[1]. The current study will evaluate predictive validity of eScreen measures, and evaluate the impact of using the eScreen system on parents' information (i.e., meeting their information needs regarding child recovery and care) and confidence regarding management of child symptoms and recovery. Future studies will address the impact of making eScreen findings available to the health care team.

## 1.2 Name and Description of Investigational Product or Intervention

The study intervention includes two key components of the eScreen system:

- A child screening component delivered in this study on a compatible (IOS or Android) tablet - A set of brief screening measures for children age 8 to 17, delivered within a game played by the child (ideally multiple times per week over the course of at least 6 weeks), and
- A parent information component delivered in this study via text or email messages plus a dashboard that can be accessed online via any internet-connected device or computer - Messages sent to parents (at least weekly) that summarize child ratings and include a link to an online dashboard with additional personalized information for parents.

See further details on eScreen screening measures in Section 1.3.2 and on the eScreen system and components in Section 7.

## 1.3 Relevant Literature and Data

### 1.3.1 Background and rationale

Undetected and unaddressed persistent pain and post-traumatic stress symptoms are major modifiable factors in suboptimal outcomes after child illness or injury. For example, in the first 3 months post-injury 40 - 50% of injured children have delays in functional recovery[2], over >50% have pain that interferes with functioning[3], and up to 40% report impairment from posttraumatic stress symptoms (PTSS).[4] Accreditation standards from The Joint Commission help ensure that assessment and management of pain receive attention during clinic visits and hospital care[5], but pain is often not systematically assessed or managed once a child is discharged home.[3,6]

No solution exists for monitoring child self-reported pain, traumatic stress, or functional recovery after hospital or clinic discharge. While structured approaches to detecting and addressing pain and PTSS among children have shown promise[7,8], their widespread implementation in health care settings is hindered by a number of challenges. One challenge is timing: even when admitted, many pediatric patients are released home after a brief hospital stay. Systemic issues (health care incentive structures, limited information exchange) have also presented hurdles. Recent shifts in health care financial models, systems of care, and e-Health approaches present new opportunities to incorporate tools, such as the screening system being developed in this project, that increase the effectiveness and value of care and improve patient satisfaction.

Our team's NIH-funded STTR project proposes to address this critical, systemic problem by focusing on the gap between current approaches for identifying child pain and PTSS post-discharge, and the unmet needs of recently ill or injured children, their families, health care providers, and health systems. We are developing an integrated screening system that takes advantage of advances in e-Health and developmentally-appropriate engagement strategies, as well as a shifting economic landscape that provides health systems with incentives for optimizing short- and long-term patient outcomes and for meaningful use of health information technology. Stakeholders interviewed in Phase I noted the paucity of reliable and actionable monitoring data in the post-discharge period (particularly in pediatrics), and

the absence of (gold standard) child self-report outcomes for pediatric patients to enhance predictive analytics.

Developmental considerations and child self-report

Middle childhood into adolescence is a key period for children's development of self-management and social-emotional skills needed to manage physical and emotional symptoms, cope with challenges, and solicit support from others when needed.[61] An acute medical event such as injury or illness event challenges children's growing capabilities and represents an opportunity for parents and providers to intervene and support the child's development of critical competencies for this and future challenges. In this age range, child self-report is the gold standard for assessing pain, PTSS, and health-related quality of life. [8-10] A large body of research, including work by our team, has established that it can be difficult for parents to accurately assess their child's acute pain and PTSS.[11,12] Thus direct screening of school-age children is optimal but requires validated, developmentally appropriate methods such as those in the eScreen system.

Using e-Health tools and engaging game mechanics for repeated screening post-discharge

Digital screening tools and interventions are made increasingly feasible by the fact that the vast majority of US families have access to online e-Health tools via tablet or phone. Across our target age range of school-age children and adolescents, online activity is widespread and increasing: 26% of 8-10 year olds and 45% of 11-14 year olds have their own personal smartphone or tablet; 73% of 8-10 year olds go online at least weekly and 29% spend > 1 hour per day online, and 95% of 11-14 year olds are online at least weekly and 52% spend >1 hour per day online.[13] Children in this age range are motivated to play electronic games for a variety of reasons, including fun, mastery, competition, and managing emotions. Game mechanics (i.e., avatars. feedback, levels, digital rewards like points and badges) are linked to increased usage and adherence in e-Health tools.[14] Our system *directly engages school-age children and adolescents in screening* via an e-Health tool directly embedded in a child-friendly game experience.

In summary, the scientific premise of this study and the overall project is that (a) gaps in parent, provider, and health system ability to monitor children's post-discharge pain, traumatic stress, and functional recovery impede optimal follow-up care, and (b) a novel game-based experience can address these gaps via practical, valid assessment of key child-reported indicators**.**

### 1.3.2 Measures addressing primary and secondary study aims

Background is presented here for measures addressing primary and secondary study aims. More information on study measures is in Section 5 and in the Appendix.

**eScreen measures**

In this study, these eScreen measures will be delivered to the child on a compatible (IOS or Android) tablet.

**eScreen Pain Screener** This measure is a visual analog scale designed for delivery on a mobile device by adapting key elements of existing validated pain measures[15] and adding personalization features. In our prior study, the eScreen Pain Screener was highly correlated (r =.86 - .92) with, and evidenced strong agreement with, two validated pain measures. The

measure appears on screen as a visual analog 'slider' with a movable marker; the width and color intensity increased from bottom to top. The face of the child's avatar (i.e. selected by the child in the eScreen system) anchors the lower and upper ends of the slider with a 'no pain' and a 'most pain' facial expression, respectively. On-screen instructions state "The bottom of this scale is no pain, and the top is the most pain you can imagine. Slide the marker to show how much pain you feel right now." The child uses their finger on the touch screen to slide the virtual marker.

**eScreen PTSS Screener** The Acute Stress Checklist for Children 6-item Short Form (ASC-6) was developed as a short form of the Acute Stress Checklist for Children (ASC-Kids) [16]. Across multiple samples, it has demonstrated concurrent validity with severity of symptoms as assessed via the full-length ASC-Kids checklist (correlations from .88 to .92) or a structured clinical interview (correlations of .61 - .62).[16] In our prior study, scores on the ASC-6 presented within the eScreen system were strongly correlated with a validated PTSS measure (r=.67); a positive PTSS screen was associated with significantly higher PTSS severity.

**eScreen Functional Recovery Screener** Our team developed a single item screener "Would you say you are all the way back to normal from the injury / illness?" (Response options = Yes, completely; Partway or Somewhat; Not at all) to assess a child's global perception of their recovery. Across multiple samples, responses on this item have shown significant associations with validated full-length measures of health-related quality of life, such as the Physical, Emotional, and Social functioning scales of the PedsQL.

In the eScreen system, the PTSS and functional recovery screeners are delivered on a mobile device with the child's avatar appearing on each screen. The child uses the touch screen to select a response to each item.

**Research measures**

**Numerical Rating Scale for Pain Intensity (NRSI)** The NRSI is a verbally-administered pain evaluation in which children are asked to rate their pain by choosing a number from 0 to 10 "that best tells us how much you are hurting, where 0 = no pain or hurt and 10 = the most or worst pain/hurt." The NRSI has demonstrated strong convergent validity with other measures of pain intensity in children age 7 to 18 across multiple studies,[17,18] as well as sensitivity to change over time.[17] Child and parent-proxy-report versions will be used in this study; the child report version will be used in analyses of the primary endpoint.

**PROMIS pediatric pain interference scale** The PROMIS Pain Interference Scale is a brief measure that assesses interference by pain on children's daily activities (interference on physical, psychological, and social functioning) during the past 7 days. The Pain Interference Scale has demonstrated construct validity in assessing clinically meaningful interference from pain and in detecting change over time. Child and parent-proxy-report versions will be used in this study; the child report version will be used in analyses of the primary endpoint.

**Child PTSD Symptom Scale for DSM-5 (CPSS-5)** The CPSS-5 includes 20 items assessing posttraumatic stress symptoms aligned with the DSM-5 criteria for posttraumatic stress disorder (PTSD), rated by the child on a 5-point Likert scale, scored as 0 to 4.[19] The DSM-5 update of the CPSS builds on the well-validated DSM-IV version,[20,21] and has

demonstrated strong internal consistency, test-retest reliability, convergent and discriminant validity in initial evaluations.[19]

The **Parent Information and Confidence scale** was developed at CHOP to assess the extent to which parents feel prepared for the care of their ill or injured child after hospital or clinic discharge. Items in the measure have been used in prior studies by our team. [22,23]

### 1.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

Primary study objective: Examine ability of eScreen system to identify patients with clinically-relevant problems (pain, pain interference, PTSS symptoms and related impairment) in the 6 weeks after a medical event or hospital discharge.

Secondary study objective: Examine impact of eScreen system (vs usual care) on factors related to parents' management of child symptoms and recovery in this 6 week period.

### 2.1 Primary Objective (or Aim)

The primary objective of the current study is to evaluate predictive validity of eScreen measures during children's at-home use of the eScreen system, for prediction of ongoing symptoms or problematic recovery at 6 weeks: pain, pain interference, PTSS, impairment from PTSS.

### 2.2 Secondary Objectives (or Aim)

The secondary objectives are to examine the impact of the eScreen system (vs usual care) on factors related to parents' management of child symptoms and recovery in this 6 week period.

- (a) parent perceptions that they have the information they need to care for their child's illness or injury, and
- (b) parent confidence in their ability to manage their child's care.

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

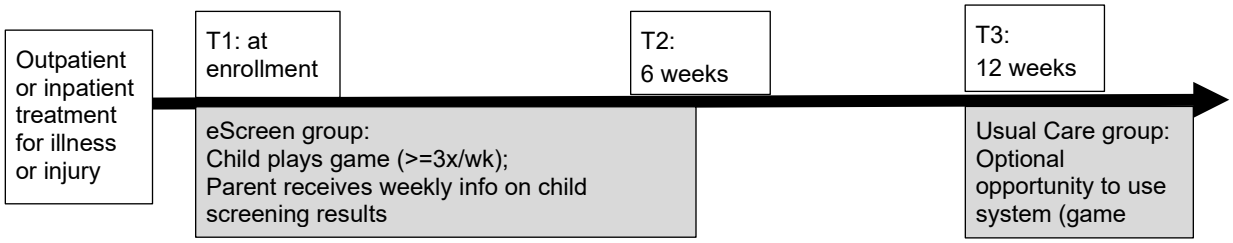
This study is a randomized controlled trial examining validity of eScreen measures (primary aim) and assessing the impact of the eScreen system on parent management (secondary aim).

Pilot of study procedures: Before we begin enrollment for the randomized trial, we will enroll up to 10 child-parent pairs at each site in a pilot phase to allow a "dry run" of study procedures. We will implement study procedures (other than randomization) described below, and conducting procedures consistent with assignment to the intervention arm ("usual care plus eScreen"). We will not include pilot phase cases in any analyses of effectiveness.

We will recruit a cohort of 300 children (and one parent per child) recently treated for illness or injury at CHOP or Kentucky Children's Hospital inpatient or outpatient services.

Participants will be randomly assigned to usual care plus eScreen ("eScreen group") or usual care alone ("UC group"). Analyses addressing the primary study aim will use data from the eScreen group; analyses addressing the secondary aim will compare eScreen and UC groups. We have powered our study to answer our primary aims within our eScreen group.

**Figure 2. Research assessments for both groups (above timeline) & eScreen system use / actions (below timeline)**




### 3.1.1 Screening & Baseline Research Assessment

Research staff will examine clinic schedules and inpatient admission records daily to identify potentially eligible patients. Research staff will approach parents to describe the study, review eligibility criteria, and invite their and their child's participation. We will obtain parent consent, followed by child assent, for study participation before any other research assessments are administered. After consent / assent is obtained, children and parents will complete baseline research assessments (see Table 2 in Section 5), and will then be randomized to the eScreen or Usual care group.

### 3.1.2 Study Treatment Phase

Over the next 6 weeks, children in the eScreen group will be asked to play the game at least 3 times per week. Each instance of game play includes an embedded eScreen assessment of current pain, PTSS and functional recovery. The system will provide templated weekly

messages to parents regarding their child's ratings of pain, PTSS, and functional recovery, with links to more information as appropriate.

### 3.1.3 Follow-up

Follow-up research assessments will take place at T2 (6 weeks post-T1) and T3 (12 weeks post-T1) via phone, online, or mailed questionnaires – see Table 2 in Section 5.

After completion of their T3 assessment, children in the Usual Care group will be provided with sign-in information and offered the opportunity to play the game (without eScreen measures). We will include a modified TAM questionnaire to allow us to collect additional pilot data on their satisfaction with the game).

Follow up research assessments for subjects at both sites will be completed by study teams at CHOP or UK.

## 3.2 Allocation to Treatment Groups and Blinding

We will prepare a set of sealed files (sealed envelopes or a virtual / digital analog), with appropriate numbers for the eScreen condition and for Usual Care. Each file will contain directions for either: a) proceeding with the eScreen system or b) proceeding with the Usual Care condition.

We will randomize in blocks (2-to-1 ratio of eScreen to Usual Care within each block). Randomization files will be prepared at CHOP and released in blocks at each of the two study sites. As each participant is enrolled, and after completion of baseline measures, research staff will open the next available file and proceed with the designated activity.

Participants, as well as research staff conducting the baseline assessment visit, cannot be blinded as to study condition. Research staff conducting the T2 and T3 follow-up assessments will be blinded to the family's study condition. These staff will not have access to study tracking sheets that indicate condition, and will not participate in meetings in which case allocation is discussed. Questionnaires regarding acceptability of the eScreen system will be administered separately for those families in the eScreen condition.

## 3.3 Study Duration, Enrollment and Number of Sites

### 3.3.1 Duration of Study Participation

The study duration per subject will be up to approximately 12 weeks, with (a) one brief screening / baseline assessment, (b) for the eScreen group only: intermittent involvement (using eHealth tools at home) over a 6 week period, and (c) two brief follow-up research assessments at approximately 6 weeks and 12 weeks post-baseline.

### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at 2 investigative sites: CHOP and the University of Kentucky.

Recruitment will stop when approximately 300 randomized child-parent pairs are enrolled. It is expected that approximately 300 randomized child-parent pairs will need to be enrolled to produce 127 evaluable families for completer analysis.

## 3.4 Study Population

We will enroll children (and one parent per child) at CHOP or KCH (N=300 child-parent pairs ; plus up to 10 child-parent pairs in a pilot phase) who meet the following criteria.

### 3.4.1 Inclusion Criteria

- Child age 8 – 17 years
- Child treated or admitted for injury or illness event that occurred within the past month
- Child has regular access to a compatible (IOS or Android) tablet at home
- Parent has an internet-capable smartphone and can receive text messages on that phone, OR has email account that can receive messages about child status
- Child and parent read or understand English well enough to consent / assent to participation and complete study tasks (e.g., checklists, use of screening system)

### 3.4.2 Exclusion Criteria

- Index medical event is injury due to family violence.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

## 4.1 Screening & Baseline Research Assessment

Research staff will approach parents to describe the study, review eligibility criteria, and invite their and their child's participation. We will obtain parent consent, followed by child assent, for study participation. We will document consent/assent via RedCap or on paper. Consent / assent will include child and parent agreement that, if assigned to the eScreen group, the child will be asked to sign in and play the eScreen game at least 3 times per week for 6 weeks. (Children may play more often, and beyond the 6 week time frame if they choose.)

At enrollment (T1), before randomization, children and parents will complete baseline research assessments (see Table 2 in Section 5). Following baseline assessments, study staff will open a file to reveal the condition to which the child is assigned. Those randomized to the eScreen group will then receive sign-in instructions for the mobile / online interface, practice signing in, and begin to play the eScreen game. (Parents will be introduced to these procedures so they can assist their child if needed.)

We will make every effort to approach parents and children in person to obtain consent / assent and initiate study procedures. In cases where an eligible participant / parent is missed at the hospital or clinic and during periods when we are unable to conduct in-person enrollment for public health reasons, we may obtain consent / assent (via REDCap or telephone) when staff are not present with the family. (See Section 9.6) After consent / assent are obtained, we will administer baseline (T1) study questionnaires verbally or online for parent and child. Following completion of T1 assessments, study staff will open a file to

reveal the condition to which the child is assigned. Those randomized to the eScreen group will then receive sign-in instructions for the mobile / online interface. We will also offer to schedule a phone call at a convenient time for the family to answer any questions about the sign-in process and encourage children to practice signing in and begin to play the eScreen game. (Parents will be introduced to these procedures so they can assist their child if needed.)

### 4.2 Study Treatment Phase

Over the next 6 weeks, children in the eScreen group will be expected to play the game at least 3 times per week, and will able to play the game more often if they want to. Reminders to parents will encourage children to play at least 3 times per week.

Each instance of game play will include an embedded eScreen assessment of current pain, PTSS and functional recovery (unless the child has completed this assessment within the past 24 hours).

For the eScreen group, the system will provide templated weekly messages (weeks 1 to 6) to parents regarding child pain, PTSS, and functional recovery. Design of message timing and delivery mode is based on lessons from stakeholder interviews in Phase I. Message content and specific screening algorithms are derived from our team's prior studies. Parent messages (sent via text or email per parent preference) will include information drawn from evidence-based resources on pain and PTSS, with links to more information as appropriate.

The research team will provide parents at CHOP and UK with a study-specific CHOP email and phone number which they can use to alert the team of any technical difficulties with the system.

### 4.3 Follow-up

For both study groups, research assessments at T2 (6 weeks post-T1) and T3 (12 weeks post-T1) will repeat baseline measures and also assess pain interference and impairment from PTSS – see Table 2 in Section 5. Additional outcomes will be gathered from parents at T3 and abstracted from medical records and each hospital's Trauma Registry (for injured children).

At the completion of each research assessment, all participants will be provided with a message about talking with their primary care provider if they have any concerns about physical or emotional recovery. Depending on context of measure administration, this will be delivered verbally by study staff and/or as a written message at the end of self-administered questionnaires in the REDCap system. Additionally, when a T2 or T3 research assessment indicates that a child is currently experiencing high pain or may meet symptom criteria for posttraumatic stress disorder, we will inform parents and suggest that they check in with their child and consider contacting their child's doctor.

After completion of their T3 assessment, children in the Usual Care group will be provided with sign-in information and offered the opportunity to play the game. For this group, we

will not administer eScreen in-game assessments. We will ask about the child's perceptions of game use – via a modified TAM questionnaire.

Study teams at CHOP and UK will complete the follow up research assessments for CHOP and UK subjects.

## 4.4 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study protocols. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety, or for administrative reasons. It will be documented whether or not each subject completes the study.

# 5 STUDY EVALUATIONS AND MEASUREMENTS

## 5.1 Screening and Monitoring Evaluations and Measurements

### 5.1.1 Medical Record Review

Variables that will be abstracted from the medical record:

- Age
- Gender
- Race
- Ethnicity
- Medical diagnos(es) for this admission or ED/outpatient visit
- For injured children, date and mechanism / circumstances of injury
- For children with a medical event (other than injury), date of onset and circumstances of current complaint
    - e.g., for children with SCD, date of onset and any circumstances related to onset of pain crisis or other medical event that precipitated their specialty care or ED visit or their admission

## 5.2 Efficacy Evaluations

### 5.2.1 Diagnostic Tests, Scales, Measures, etc.

Measures used in analyses of primary and secondary study objectives are in **bold** in Table 2. More detailed information about each of these measures is presented in Section 1.3.2. Other measures are used to assess sample descriptives or covariates, or are used in exploratory analyses. Timing of each assessment is also presented in Table 2.

**Table 2. Study measures by reporter, mode of delivery, and time point.**

| Measure | Construct | Reporter | In-game* | Assessments* | | |
|---|---|---|---|---|---|---|
| | | | | T1 | T2 | T3 |
| Demographic & health form | Demographics and child health / health utilization | Parent** | | X | | |
| **eScreen pain screener: Analog** | **Current pain intensity** | **Child** | **X** | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **pain scale** | | | | | | |
| **eScreen PTSS screener: ASC- 6** | **Current traumatic stress symptoms** | **Child** | **X** | | | |
| **eScreen functional recovery screener: "Back to Normal"** | **Current functional recovery** | **Child** | **X** | | | |
| **Numerical Rating Scale (NRSI)** | **Current pain intensity** | **Child** | | **X** | **X** | **X** |
| Colored Analogue Scale | Current pain intensity | Child | | X | | |
| **PROMIS Pediatric Pain Interference** | **Impact of pain on functioning - past wk** | **Child / Parent**** | | | **X** | **X** |
| Parent Post-op Pain Measure (PPPM) | Current pain intensity | Parent* | | X | X | X |
| PROMIS Sleep Disturbance Short Form | Sleep problems (covariate) | Child / Parent** | | X | X | X |
| **Child PTSD Symptom Scale for DSM5 (CPSS-5)** | **Traumatic stress symptoms & impairment from these symptoms** | **Child** | | **X** | **X** | **X** |
| PTSD Checklist for Children – Parent Report (PCL-C/PR) – adapted for DSM5 | Traumatic stress symptoms & impairment from these symptoms | Parent** | | X | X | X |
| Pediatric Quality of Life Inventory (PedsQL-C & -P) Acute Version | Functional recovery / Health-related quality of life - past wk | Child / Parent** | | X | X | X |
| Health and Recovery Questionnaire | Health status & follow-up care *** | Parent** | | | X | (X) |
| **Parent Information / Confidence Questionnaire** | **Management of child health & recovery** | **Parent** | | | **X** | **X** |
| Technology Acceptance Model (TAM) questionnaire (eScreen group only) | Perception of eScreen system utility & acceptability | Child / Parent | | | X | |
| Modified Technology Acceptance Model (TAM) questionnaire (Usual Care group only – *optional* with game play after T3) | Perception of game and acceptability | Child | | | | *optional* after T3 |
| * Timing of assessments: T1 = at enrollment in hospital / clinic; T2 = 6 wks post-T1; T3 = 12 wks post-T1; plus, for eScreen group only: In-game assessment at T1 and at each subsequent game session<br>** Parent reporting on child symptoms / functioning<br>*** Health and Recovery Questionnaire admin at T2, but if T2 is missed will admin at T3 | | | | | | |

## 5.3 Safety Evaluation

This is a minimal risk study. There is no known physical risk for subjects of completing measures of pain or stress symptoms, nor in using a prototype screening system.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Primary Endpoint

The primary study endpoints employ validated measures of ongoing symptoms / problematic recovery: pain (NRSI rating), pain interference (PROMIS Pain Interference T score) and PTSS presence and related impairment (CPSS-5 scores) at T2 (6 weeks post-baseline).

Reflecting our primary aim of prediction, the primary study endpoints are not participant scores on these measures, but rather the results of ROC analyses; i.e. the area under the curve (AUC) for eScreen pain score predicting pain and pain interference and the AUC for eScreen PTSS score predicting PTSS symptom presence and related impairment.

## 6.2 Secondary Endpoints

The secondary study endpoint relates to the potential impact of the eScreen system on parent management of child symptoms and recovery. We will compare eScreen and Usual Care groups on parent ratings at T2 of the extent to which they (a) have received the information they needed to take care of their child after leaving the clinic or hospital, and (b) have felt confident in taking care of their child (related to their illness / injury) in this 6 week period.

## 6.3 Statistical Methods

We will first conduct descriptive analyses of key variables, examine missing data, and consider whether the distribution of any key study variables warrants alternative, non-parametric analyses. All primary study analyses use child self-report measures; we collect additional parent-report measures of some variables for use in later exploratory analyses.

### 6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### 6.3.2 Efficacy Analysis

**Primary endpoint**

*Hypothesis: Results of eScreen-delivered in-game assessments will predict ongoing symptoms / problematic recovery at T2 (6 weeks post-baseline), i.e. in ROC analyses, good to excellent AUC (≥ .80) for prediction of problems as follows: eScreen pain score predicting pain (NRSI ≥ 6) and pain interference (PROMIS pain interference T score ≥ 65); eScreen PTSS score (ASC-6) predicting PTSS (significant PTSS indicated by CPSS-5 symptom endorsement) and impairment from PTSS symptoms (impairment endorsed on CPSS-5).*

Analyses: In ROC analyses, we will estimate AUC as a global indicator of predictive efficiency of eScreen results in detecting children with clinically meaningful ongoing symptoms or problematic recovery. We will then calculate sensitivity and specificity for dichotomous indicators predicting presence of these problems using cutoff scores based on results of prior studies:

- eScreen pain indicator (pain score ≥ 6) predicting pain and pain interference (NRSI / PROMIS scale);
- eScreen PTSS indicator (ASC-6 ≥ 6) predicting PTSS and related impairment (CPSS-5);
- eScreen functional recovery indicator predicting reduced HRQoL (PedsQL-C score < 70).

After primary analyses with a priori cutoffs, we will use results of ROC analyses to examine potential adjustments to cutoff scores for eScreen-delivered measures to optimize prediction

of problems. Given the system's aim to detect children whose ongoing symptoms or problematic recovery might otherwise be missed (to allow parents and providers to further assess and respond in a timely manner) the goal for eScreen cutoff scores is to optimize sensitivity while maintaining reasonable specificity.

**Secondary endpoint**

*Hypothesis: At T2, compared to the Usual Care group, the eScreen group will demonstrate higher parent information and confidence in managing child symptoms and recovery.*

Analyses: All analyses comparing groups will be conducted first on an intent-to-treat basis. We will calculate Cohen's d as the between-group difference in summed parent information / confidence ratings, standardized by the pooled SD for the groups.

Exploratory analyses:

We have already examined concurrent validity in a prior study, but will conduct exploratory analyses in this new sample to determine the association between scores on brief child-report measures delivered via the eScreen system and scores on validated measures administered by trained research staff at the closest available research assessment.

After primary study analyses above, we will examine the ability of the eScreen measures to predict the same outcomes at a more distal point (T3: 12 weeks post-baseline).

We will also examine whether eScreen performance varies by child sex, age, race/ethnicity, or socio-economic status.

In exploratory analyses to better understand eScreen performance, we will examine a) the association of eScreen measures with sleep disturbance, parent-reported medication usage, new medical concerns, and service utilization, b) the potential impact of relevant child history (prior injury or illness, hospital admission, trauma exposure) on eScreen performance, and c) prediction of parent-reported outcomes (pain / pain interference, PTSS / impairment, HRQoL).

Results of these exploratory analyses will inform future development and deployment of the eScreen system.

## 6.4 Sample Size and Power

Precision of estimates / power considerations:

Sample size is driven by planned analyses to address the primary study objective. We will randomize up to 300 child-parent dyads, with 2/3 randomized to the eScreen condition, and 1/3 to usual care.

Analyses for the primary study objective utilize data only from participants assigned to the eScreen condition. We will estimate the area under the curve (AUC) and calculate sensitivity and specificity for prediction of recovery problems. The precision of these estimates depends on N and the proportion who demonstrate the (problem) outcome of interest, i.e., interference from pain or PTSS.[114,115] We estimate this proportion from prior

studies with injured children that suggest 40-50% have delays in functional recovery,[50] ≥40% have impairment from PTSS[47], and >50% have pain that interferes with functioning post-discharge.[45,46] With an analyzable sample of at least 85 children, if 50% have the outcome of interest, the 95% CI for an AUC of .80 will be ± .10. Our anticipated evaluable sample for these analyses is based on projected retention from the point of consent through intervention completion 9use of the eScreen system) and completion of follow up assessments.

Analyses for the secondary study objective use data from participants assigned to both conditions in order to estimate effect sizes (between-group differences). An analyzable sample (for completer analyses) of 85 (in eScreen group) compared to 42 (UC group) will enable us to detect between-group differences in proportions as small as 23% (i.e. 50% vs 73%), and a medium effect size (Cohen's d of .49) for between-group differences in mean scores on continuous measures, both with 80% power ($\alpha \leq .05$).

# 7 STUDY INTERVENTION

## 7.1 Description

The study intervention includes two key components of the eScreen system: a child screening component and a parent information component.

Child screening component

This component will be delivered via a game played on an iOS or Android tablet. Each instance of game play includes an embedded eScreen assessment of current pain, PTSS and functional recovery, unless the child has completed this assessment within the past 24 hours.

Design of the eScreen game leverages "idle game" mechanics to create a cyclical game experience that supports the overall goal of engaging children in game play, and delivering screening questionnaires directly to children repeatedly for several weeks. Over the period of 6 weeks, children are expected to play the game (and rate symptoms and feelings) at least 3 times per week, and they will be able to play the game as often as they want to. Reminders to parents will encourage children to play at least 3 times per week.

Parent information component

The system will provide templated weekly messages for parents in weeks 1 to 6 regarding child pain, PTSS, and functional recovery. Messages will be sent to parents at least weekly, via text or email, with brief updates summarizing child ratings. Each message will include a link to an online dashboard with additional personalized information for parents, and links to evidence-based resources on pain or PTSS as appropriate. Parents may access the dashboard from any internet connected device or computer.

The design of message timing and delivery mode is based on lessons from stakeholder interviews in Phase I. Message content and specific screening algorithms are derived from our team's prior studies.

### 7.1.1 Treatment Compliance and Adherence

The use of online, eHealth tools makes it possible to accurately track many aspects of child and parent use of each intervention component. Electronic data / metadata collected by the eScreen system (child screening component and parent information component) will include responses to screening items (child ratings), when and whether a parent clicks a link in a text message, as well as a date / time stamp for each participant interaction with the system.

# 8 SAFETY MANAGEMENT

## 8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

## 8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

# 9 STUDY ADMINISTRATION

## 9.1 Treatment Assignment Methods

### 9.1.1 Randomization

Participants will be randomized to eScreen or Usual Care groups (2:1 ratio) after baseline assessment is complete. See Section 3.2 for randomization procedures.

### 9.1.2 Blinding

Given the nature of the intervention to be evaluated, it is not possible for participants or research staff conducting the baseline assessment visit to be blinded as to study condition. Research assistants conducting the T2 and T3 follow-up assessments will be blinded to the family's study condition.

### 9.1.3 Unblinding

Not applicable.

## 9.2 Data Collection and Management

Data will be collected via written and electronic questionnaires completed by child and parent participants, or administered verbally by research staff. Electronic data (coded, not identifiable to Radiant) will be gathered during participants' use of mobile device-delivered eScreen system tools and stored in a database hosted on the Radiant server. Existing records

will yield medical information about the index child's diagnoses, clinical pain ratings, and treatment.

Identifiable information linking individual subjects to their PHI (i.e., the master list) will be stored electronically in a password-protected file. The study dataset will not include identifiable information.

For enrollment or administration of research measures, when an in-person meeting is not possible, or based on the family's preference and convenience, we will offer families the option of a telephone or virtual meeting (e.g. at the CHOP site, meeting virtually via CHOP's Webex account).

Each site, CHOP and Kentucky, will utilize online REDCap questionnaires hosted at CHOP that will allow online data entry by participants or research staff. Each site will also offer paper copies of each research questionnaire, in case of internet connectivity issues at the time of the research assessment, or if a family requests that questionnaires be mailed to them. Data collected via paper questionnaires will be entered by research staff into an electronic database, and maintained via a secure, password-protected database at each site. Data entry screens will contain range and logic checks to minimize data entry errors. The PI will monitor data accuracy and identify ways to resolve any problem areas.

CHOP and Kentucky study staff will receive identifiable information from both sites to facilitate completion of follow up assessments. This information will be shared between sites via CHOP's secure systems.

De-identified data will be shared between sites via secure systems such as CHOP's Sharefile. All study data, at both CHOP and Kentucky, will be maintained for at least 6 years post study completion at CHOP and for at least 5 years at Kentucky, per institutional policy.

Security:

Database security will be assured at the server, application, table and entry screen levels. Disaster recovery procedures will guard against loss of data.

Electronic data / metadata collected by the eScreen system (child screening component and parent information component) will include responses to screening items (child ratings), whether a text or email message is successfully delivered, and when and whether a parent clicks a link in a text or email message; as well as automated collection of IP address and date / time stamp for each participant interaction with the system. These data will be captured in the custom software application (the prototype screening system) and stored in a relational database that is hosted externally at Radiant Creative, LLC (Radiant), our study partner, developer of the screening system prototype, and Business Associate of CHOP. All such data will be coded and not identifiable to Radiant Creative LLC. If Radiant and the CHOP/UK study team need to communicate about a specific case in order to troubleshoot technical difficulties, we will use the Case ID (i.e. if a text message fails delivery, Radiant will alert the study team – using the Case ID - so that the team can contact the parent to confirm we have correct contact information for message delivery).

Via Radiant, the relational database will be stored on a fully-managed, secured, HIPAA-compliant web server. Study data on this server will be stored in a relational database that utilizes encrypted fields. Database read/write privileges will be strictly controlled via an access control layer. At the application layer, data will be protected via a role-based access system and robust authentication requirements. All data access via the application layer will be recorded in a persistent audit log. All code will be tested regularly for brute force, XSS, SQL injection and other vulnerabilities. Any identified vulnerabilities will be remediated within 24 hours. At the server layer, data will be protected by continuous backup, a robust firewall, and pro-active server management practices. At the host layer, data will be protected in physically locked cabinets and on-premises site access security protocols.

Study data stored from this external server will be transferred to CHOP personnel via secure FTP website. FTP site access will require a unique username/password combination, and each investigator will be granted a single account. Data will be made available on the FTP site for a limited time (typically 24 hours or less). Security-focused FTP account management practices will be required (e.g., nontrivial password requirements, password reset every 60 days, etc.)

## 9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Study staff at CHOP and Kentucky will receive identifiable information from the both sites in order to complete follow up research assessments.

Participants' identities will be disguised by a unique identification number which will appear on all interview and questionnaire materials instead of their name. The identification numbers will be linked with participant names only in password-protected electronic documents.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP or UKentucky) before sharing a limited dataset (PHI limited to dates and zip codes).

The participant consent process will inform participants that de-identified data will be archived in appropriate data archives or repositories, in keeping with NIH Data Sharing policies. De-identified data from this study will be added to the Prospective studies of Acute Child Trauma & Recovery (PACT/R) Data Archive.

We will ask participants if they would like to be added to a list of future "testers" who may be invited to participate in later stages of evaluating the screening system under development. Name and contact information (parent contact information for children) for this list of potential future testers will be kept separate from study data, and will not be connected to any participant's study data.

## 9.4 Regulatory and Ethical Considerations

### 9.4.1 Data and Safety Monitoring Plan

This is a multi-site, low risk study. Each site will maintain their own full data sets. De-identified data will be shared between sites for the purpose of summarizing results. Dr. Nancy Kassam-Adams, as the PI, will be responsible for monitoring the safety of study participants and complying with all reporting requirements. She will report any adverse events to the CHOP IRB in accordance with CHOP IRB policies. Dr. Marsac will promptly report any adverse events to Dr. Kassam-Adams for reporting to CHOP IRB. Dr. Kassam-Adams will also be responsible data accuracy, security, and validity.

Linda Fleisher, PhD, MPH, Associate Research Professor at Fox Chase Cancer Center with more than 20 years of experience in development and assessment of eHealth interventions, will serve as the Data Safety Monitor. She will meet every six months with the PI and Study Coordinator. During these meetings, the team will review participant demographic characteristics, expected versus actual recruitment, retention to follow-up, and any ethical, quality assurance or regulatory issues that have arisen. Dr. Fleisher will also review any concerns about participant distress associated with the study that might not qualify as an adverse event. She will make recommendations, as needed, regarding changes to the study protocol.

### 9.4.2 Risk Assessment

Risks are not greater than minimal.

The risk of ongoing distress created by the research procedures is extremely low. Completing questionnaires about pain symptoms or traumatic stress reactions could be distressing for some children or for their parents. However it is not likely that answering questions about one's symptoms or recovery after illness or injury will create additional distress beyond that which is already present. Empirical data regarding research participants' evaluation of similar studies of child and parent acute reactions to trauma indicates a very low risk of emotional distress for participants.[116] Children and parents will be able to discontinue the study at any time if they become uncomfortable.

Protections against risk:

Our recruitment procedures are sensitive to child medical status and family well-being. We determine whether the child's medical status warrants a delay in approaching the family for study recruitment by reviewing the medical chart and/or asking the child's primary nurse if the child is able to complete the necessary study tasks prior to approaching the family.

If indicated, Drs. Kassam-Adams (clinical psychologist) and Winston (pediatrician) at CHOP or Dr. Marsac (clinical psychologist) at U Kentucky will work with the respective hospital's social work team to make appropriate referrals for further psychosocial support for a child or parent. Research consent forms contain standard language to inform children and parents of potential reporting of abuse or other safety concerns.

### 9.4.3 Potential Benefits of Trial Participation

There may be no direct benefit to participants. However, children in the eScreen group may enjoy engaging with the game-like aspects of the eScreen system, and may benefit from rating their post-injury or illness traumatic stress or pain symptoms. There is a body of research that indicates that disclosing traumatic stress responses is likely to be therapeutic.[82] In addition, children who are troubled by post-injury or illness symptoms but who have not sought help may benefit from being identified and referred for assistance through their participation in this study.

Indirect, societal benefits for the broader population of injured and ill children and their parents and health care providers include the opportunity to develop, and ultimately make broadly available, a screening system that would facilitate optimal care to promote children's emotional and physical recovery after injury and illness.

### 9.4.4 Risk-Benefit Assessment

The very low risk of emotional distress for participants is balanced by the protections built into the study protocol, and the importance of improving screening and care in the aftermath of pediatric injury and illness.

## 9.5 Recruitment Strategy

Research staff will examine clinic schedules and inpatient admission records daily to identify potentially eligible patients, and approach parents to describe the study, review eligibility criteria, and invite their and their child's participation. We will obtain parent consent, followed by child assent, for study participation. At enrollment / consent, we will collect multiple methods of contacting families (multiple phone numbers, email addresses, etc) and ask permission to reach parents via text if needed to remind or schedule study-related follow-up calls.

## 9.6 Informed Consent/Assent and HIPAA Authorization

Prior to enrolling patients, study staff will review the electronic medical record to determine potential eligibility of the parent and child before obtaining consent; we have requested a Waiver of HIPAA authorization for this screening process only.

Study staff will then approach parents and children, describe the study, provide time for parents and children to ask any questions and consider their decision. Staff are trained to explain the consent form to the subjects thoroughly, emphasizing their freedom to choose to participate or not in this study as well as emphasizing the fact that the subjects' healthcare will not be affected by their decision.

Study staff will enroll eligible participants, and obtain combined informed consent / assent and HIPAA authorization / assent before administering research interviews with children and parents/legal guardians.

Families will be asked to provide electronic signatures on a tablet computer utilizing the REDCap interface. Consent/assent and HIPAA authorization will be obtained by research team members. Families will be able to read, digitally sign their name, which will be

logically associated with the participant, and will receive an signed copy of the Study Consent for their files. Families who are unable to access the necessary technology to provide an electronic signature will give verbal consent. In this case, study staff will sign the documentation of verbal consent form via REDCap and provide the families with a copy of the verbal consent form for their records.

We will offer paper consent/assent forms as a back-up in case of internet connectivity issues at time of consent. Signed paper consent/assent forms will be scanned and the digital copy saved on a secure server at CHOP or UK, respectively. Once digital copies are saved, paper consent forms will be destroyed in a manner consistent with institutional policy for confidential documents.

In cases where a non-legal guardian (e.g., grandparent) is identified as the child's primary caregiver and meets all other study eligibility criteria, we will obtain parental (legal guardian) consent for youth participation, in addition to verbal parental approval for the non-legal guardian to participate in the caregiver role.

We will make every effort to approach parents and children in person to describe the study and invite their consent / assent and participation. In cases where an eligible participant / parent is missed at the hospital or clinic (e.g. study team is unable to approach them at a convenient time for the family), and during periods when we are unable to conduct in-person enrollment for public health reasons, we will contact the parent using contact information that is in the medical record or that we have obtained from the parent in an initial brief contact while at the hospital / clinic. In that case, we will describe the study, via telephone or in a virtual meeting with the family, and obtain consent / assent via REDCap.

We will prioritize obtaining consent / assent via REDCap. In cases where eligible participants enrolled via telephone are unable to access necessary technology we have requested a waiver of documentation of consent in order to obtain verbal consent / assent. Study staff will complete documentation of verbal consent / assent via REDCap for the study records.

### 9.6.1 Waiver of HIPAA Authorization

We have requested a waiver of HIPAA authorization only for the process of screening medical records to identify potentially eligible participants. Prior to enrolling patients, study staff will review the electronic medical record to determine potential eligibility of the parent and child before obtaining written consent and HIPAA authorization.

This waiver of authorization satisfies the following criteria:

(A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals. We have a plan to protect the identifiers from improper use and disclosure; to destroy the identifiers at the earliest opportunity consistent with conduct of the research; and the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

(B) The research could not practicably be conducted without the waiver or alteration, and
(C) The research could not practicably be conducted without access to and use of the protected health information. We would not be able to identify potentially eligible patients without this waiver.

### 9.6.2 Waiver of Documentation of Consent

We have requested a waiver of documentation of consent to obtain verbal consent in cases when participants are enrolled over the phone and unable to access the necessary technology to consent via REDCap.

This waiver of documentation of consent satisfies the following criteria:

(A) The procedures being consented to verbally involve no procedures for which written consent is normally required outside of the research context. Study staff will review the consent form and all relevant study materials over the phone, and families will receive a copy of the verbal consent form for their records;
(B) The research could not be practicably conducted without the waiver of documentation of consent. In cases where participants are unable to access their email during virtual study enrollment, we may miss out on enrolling eligible patients without this waiver. The waiver of documentation of consent will allow us to enroll patients with limited technology capabilities over the phone;
(C) The research could not practicably be conducted without the access and use of protected health information.

## 9.7 Payment to Subjects/Families

Payment in appreciation for completion of research assessments: We will provide child and parent participants with thank you gifts in the form of prepaid cards potentially totaling $100 per family across T1, T2, and T3 assessments. We will provide child participants with an incentive valued at $10 (T1), $20 (T2), and $20 (T3), and parent participants with an incentive valued at $10 (T1), $20 (T2), and $20 (T3).

Payment in appreciation for use of eScreen system: For the eScreen group, in order to encourage full use of the system being tested, we will provide incentives to parents for their own use of the eScreen system and their encouragement of their child's use of the system during the 6 weeks after T1. For each week in which the child completes in-game assessments on at least 3 days and the parent clicks through to the information portal, $5 will be added to this amount, for a total additional incentive valued at $0 to $30 provided to the parent at T2. An additional brief weekly message to parents will inform them of the status of this incentive as of that point.

# 10 PUBLICATION

This research will be reported in peer-reviewed presentations and publications.

## 11 REFERENCES


1. Kassam-Adams N, Kohser KM, J, Winston F, Marsac M. Evaluating the acceptability and validity of assessing pain and posttraumatic stress symptoms in an adaptable eHealth system for school-age children. *Clinical Practice in Pediatric Psychology.* 2019;7(1):9-19.
2. Ding R, McCarthy M, Houseknecht E, et al. The health-related quality of life of children with an extremity fracture: A one-year follow-up study. *Journal of Pediatric Orthopedics.* 2006;26:157=163.
3. Gill M, Drendel AL, Weisman SJ. Parent satisfaction with acute pediatric pain treatment at home. *The Clinical journal of pain.* 2013;29(1):64-69.
4. Kassam-Adams N, Palmieri PA, Rork K, et al. Acute stress symptoms in children: Results from an international data archive. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2012;51(8):812-820.
5. Fein JA, Zempsky WT, Cravero JP, et al. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics.* 2012;130(5):e1391-e1405.
6. Zisk R, Frey M, Medoff-Cooper B, MacLaren J, Kain Z. The squeaky wheel gets the grease: Parental pain management of children treated for bone fractures. *Pediatric Emergency Care.* 2008;24(2):89=96.
7. Kramer DN, Landolt MA. Characteristics and efficacy of early psychological interventions in children and adolescents after single trauma: a meta-analysis. *European Journal of Psychotraumatology.* 2011;2:24.
8. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *The Journal of Pain.* 2008;9(9):771-783.
9. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes.* 2007;5:1.
10. Nader K. Assessing traumatic experiences in children. In: Wilson J, Keane T, eds. *Assessing Psychological Trauma and PTSD*. New York: Guilford Press; 1997.
11. Chambers C, Reid C, Craig K, McGrath P, Finley G. Agreement between child and parent reports of pain. *Clinical Journal of Pain.* 1998;14(4):336-342.
12. Kassam-Adams N, Garcia-España J, Miller V, Winston F. Parent-child agreement regarding children's acute stress: The role of parent acute stress reactions. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45 1485-1493.
13. Lauricella AR, Cingel DP, Blackwell C, Wartella E, Conway A. The mobile generation: Youth and adolescent ownership and use of new media. *Communication Research Reports.* 2014;31(4):357-364.
14. Baranowski T, Buday R, Thompson DI, Baranowski J. Playing for real: video games and stories for health-related behavior change. *Am J Prev Med.* 2008;34(1):74-82.
15. McGrath P, Seifert C, Speechly K, Booth J, Stitt L, Gibson M. A new analogue scale for assessing children's pain: An initial validation study. *Pain.* 1996;64:435-443.

16. Kassam-Adams N, Marsac M. Brief practical screeners in English and Spanish for acute posttraumatic stress symptoms in children. *Journal of Traumatic Stress.* 2016;29(6):483-490.
17. Page MG, Katz J, Stinson J, Isaac L, Martin-Pichora AL, Campbell F. Validation of the numerical rating scale for pain intensity and unpleasantness in pediatric acute postoperative pain: sensitivity to change over time. *Journal of Pain.* 2012;13(4):359-369.
18. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain.* 2009;143(3):223-227.
19. Foa E, Asnaani A, Zang Y, Capaldi S, Yeh R. Psychometrics of the Child PTSD Symptom Scale for DSM-5 for trauma-exposed children and adolescents. *Journal of Clinical Child & Adolescent Psychology.* 2018;47(1):38-46.
20. Foa E, Johnson K, Feeny N, Treadwell K. The Child PTSD Symptom Scale: A preliminary examination of its psychometric properties. *Journal of Clinical Child Psychology.* 2001;30(3):376-384.
21. Meyer R, Gold J, Beas V, Young C, Kassam-Adams N. Psychometric evaluation of the Child PTSD Symptom Scale in Spanish and English. *Child Psychiatry Hum Dev.* 2015;46(3):438-444.
22. Marsac M, Hildenbrand A, Kohser K, Winston F, Li Y, Kassam-Adams N. Preventing posttraumatic stress following pediatric injury: A randomized controlled trial of a web-based psycho-educational intervention for parents. *Journal of Pediatric Psychology.* 2013.
23. Marsac M, Kassam-Adams N, Hildenbrand AK, Kohser K, Winston FK. After The Injury: Initial evaluation of a web-based intervention for parents of injured children. *Health Education Research.* 2011;26(1).