STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

Protocol Title	Recovery after Stress Toolkit (RESET) Trial
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TABLE OF CONTENTS

ABBREVIATIONS

ABBREVIATION	DEFINITION
DSMB	Data and Safety Monitoring Board
SAP	Statistical Analysis Plan
ITT	Intent-To-Treat Population
PP	Per-Protocol Population
CSR	Clinical Study Report
PTSS	Post-Traumatic Stress Symptoms
CBT	Cognitive Behavioral Therapy
CPSS	Child PTSD Scale

1. PREFACE

This SAP describes the planned analysis and reporting for the Recovery after Stress Toolkit (RESET) Trial.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. PURPOSE OF SAP

This SAP is important for the following reasons: (1) to ensure that data collected in the study are adequate to address the study hypotheses; (2) to prevent ad hoc decisions in analyzing study data; and (3) to prospectively identify a timeline and structure for completion of study analyses.The planned analyses identified in this SAP will be included in future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in subsequent versions.

2.1 SAP VERSION HISTORY

After a version of an analysis plan is approved for use in a study (for example, by a Data Safety Monitoring Board or study Principal Investigator), any subsequent changes to the SAP require a subsequent version of the SAP to be released. Each such subsequent version of the SAP must explicitly summarize all changes made in each SAP revision since the initially approved version. This section of the SAP contains that summary. All previous approved SAP versions must be archived and should be easily accessible for review if needed.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to compare the effect of cognitive behavioral therapy (CBT) delivered via telehealth to usual care among children with post-traumatic stress symptoms. We hypothesize that CBT will decrease symptoms compared to usual care.

3.1.2 Secondary Objectives

Secondary objectives are to demonstrate that CBT delivered via telehealth is feasible and acceptable.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary outcome is post-traumatic stress symptoms (PTSS) as measured by the Child PTSD Scale (CPSS) at approximately 10 weeks post randomization. The CPSS will be provided by both parents and children. Children have a tendency to underreport their symptoms, and parents don't always notice their children's symptoms. As a result, the primary outcome of 10 week CPSS score will be calculated as the sum of the maximum of each individual question response across parent/child question dyads. If either the parent or child is missing the response for a given question, the only response available will be utilized. There is a precedence for this approach in the field.

3.2.2 Secondary Endpoints

The secondary outcome is CPSS at approximately 6 months post randomization.

3.2.3 Exploratory Outcomes

Key exploratory endpoints include: PROMIS-psychological stress; PROMIS-SF depression; SCARED (measure of anxiety).

We will also look at child and parent report CPSS at 10 weeks and 6 months post randomization.

The following tables include all outcomes collected for the study. Note that only

the ones mentioned above will be analyzed in the primary manuscript for the project.

Table 1: Study Measures			Timing of Assessment †				
Construct	Questionnaire	# of Items	T1 1 week post-injury	T2 1 month post-injury	Weekly during intervention	T5 10 weeks post-randomization	T6 6 months post-randomization
Psychological Health							
Screener	Acute Stress Checklist for Kids (ASC-Kids)	10	C	C			
Primary Outcome	Child PTSD Scale (CPSS)	24	B	B	C	B	B
Comorbid Psychological Health and Coping	Children's Post-Traumatic Cognitions Inventory (CPTCI) SF	10	C			C	
	Screen Child Anxiety and Related Emotional Disorders (SCARED)	41	C			C	
	PROMIS Scale – Anger SF	5	B			B	B
	PROMIS Scale – Anxiety SF	8	B			B	B
	PROMIS Scale – Depression SF	8	B			B	B
	PROMIS Scale – Psychological Stress SF	8	B			B	B
	PROMIS Scale – Physical Stress SF	8	B			B	B
	Connor-Davidson Short Form	10	C			C	
	Traumatic Events Screening Inventory (TESI)	24	C			C	
	COVID-19 Life Impact (Child)	1	C				
	Vanderbilt ADHD Diagnostic Rating Scale (VADRS)	40	P			P	
Physical Health							
	PROMIS Scales: Global Health[117]	7	B			B	B
	PROMIS Scale – Sleep	26	P			P	P
HRQoL							
	PedsQL4.0[118]	15	P			P	P
End of treatment surveys							
	System Usability Scale (SUS)	10				B	
	Satisfaction survey	33				B	
† C= CHILD REPORT, P=PARENT REPORT, B=BOTH PARENT AND CHILD							

Table 2: Family Study Measures		# of Items	Timing of assessment			
Construct	Questionnaire		T1 1 week post-injury	T2 1 month post-injury	T5 10 weeks post-randomization	T6 6 months post-randomization
Demographics	Parent demographics form	8	P			
Social Support	Social supports	10	P			
Family Functioning	McMaster FAD [120]	12	P			
Parent Psychological Health	PROMIS Adult Self-Report Profile 29 v2[121]	29	P		P	
	COVID-19 Exposure and Family Impact Survey (CEFIS)	37	P			
	PTSD Checklist-DSM 5[122] (PCL-5)	20	P		P	

3.2.4 SAFETY OUTCOMES

Given the nature of the intervention we do not anticipate adverse events (AEs).

Serious Adverse Event (SAE): A serious adverse event (SAE) for this population is an adverse event that:

- results in death; or

- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

SAEs are collected according to our standard database form (see "AE_form_5-1-23.docx" form rc_aesae).

4. STUDY METHODS

4.1 Overall Study Design and Plan

RESET is a prospective, randomized, multicenter trial of pediatric patients who experienced a traumatic injury and developed post-traumatic stress symptoms (PTSS). Subjects were randomized to one of two study groups to receive either (1) 8 sessions of cognitive behavioral therapy (CBT) or (2) usual care. The main research question is whether CBT reduces PTSS symptoms relative to usual care at 10 weeks post randomization.

4.2 Selection of Study Population

Candidate children are screened at the time of hospitalization for traumatic injury, and then again at one month post discharge, with the latter screening determined whether they had sufficient PTSS to qualify for the study. Those who qualified with sufficient PTSS and consented to participate in the study were randomized to CBT or usual care.

4.3 Method of Treatment Assignment and Randomization

Randomization of children eligible after the second screen was conducted using permuted blocks with equal allocation to each arm stratified by center (UU, UT, CI) and age group (8-11yrs, 12-16yrs). The randomization protocol was developed by the statistical team and implemented via REDCap.

4.4 Treatment Masking (Blinding)

Blinding was not possible due to the nature of this behavioral therapy intervention.

5. SAMPLE SIZE DETERMINATION

Goal enrollment is 53 children per group (106 total). This will provide 80% power

at a 0.05 significance to detect an effect size of 0.5.

The following table indicates sample sizes per group and total sample size for our 2 arm study under different combinations of correlation and effect size. With a correlation between baseline and follow-up CPSS measurements of 0.55, and an expected large effect size of 0.5, we would have 80% power at a 0.05 significance level to detect this difference with 45 subjects per group (90 total). Expecting a loss-to-follow-up (LTF) rate of 15%, we would need to enroll 53 subjects/group or 106 total. These calculations are based on an ANCOVA model, and were conducted in PASS v 16.0.6.

Table 3. Sample size calculations for different combinations of within subject correlations and effect sizes.

			Sample Size		Sample Size Adjusted for LTF	
Correlation	Effect Size	Adjusted SD	N/Group	Total N	N/Group	Total N
None	0.35	1.00	130	260	153	306
0.4	0.35	0.92	110	220	129	258
0.55	0.35	0.84	90	180	106	212
None	0.50	1.00	64	128	75	150
0.4	0.50	0.92	53	106	62	124
0.55	0.50	0.84	45	90	53	106

6. ANALYSIS POPULATIONS AND STUDY SUBJECTS

6.1 ANALYSIS POPULATIONS

The following analysis populations are planned for the studies:

- **Intent-to-Treat Population (ITT):** The ITT population includes all patients who are randomized. All randomized subjects are included and analyzed according to their randomization assignment. The ITT population will be used for the primary analysis.
- **Per-Protocol Efficacy (PP):** The PP population includes all patients in the Efficacy Population who received the therapy that they were randomized to and then completed the CPSS at approximately 10 weeks post randomization. For the CBT arm we require at least 4 of the 8 therapy session(s) to qualify.

6.2 STUDY SUBJECTS

Potential participants are identified by initial EHR review close to the time of injury. From there, selected inclusion and exclusion criteria are further evaluated via EHR in a preliminary fashion (see below under "Baseline Screening"). Those meeting criteria based on initial EHR review are contacted when possible in an attempt to fully evaluate

eligibility. Once eligibility is confirmed and families agree, they are asked to complete baseline surveys one week post injury, including the Child PTSD Symptom Scale (CPSS), see Figure 1a below.

Regardless of one week CPSS score, families who are eligible at the baseline screening and complete one week surveys are contacted at one month after injury to again complete the CPSS. Those with combined parent/child CPSS ≥ 11 at one month after injury are considered for participation in the main trial. After eligibility confirmation, parents and children are approached for consent/assent and randomization (Figure 1b).

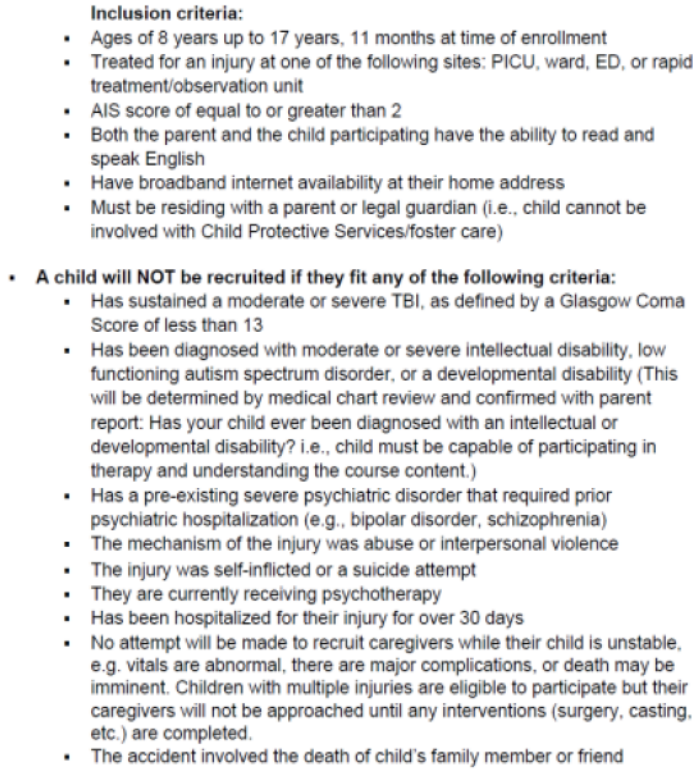


Figure 1a-b. Recruitment and randomization of participants.

Figure 1a. Consort diagram – Baseline enrollment

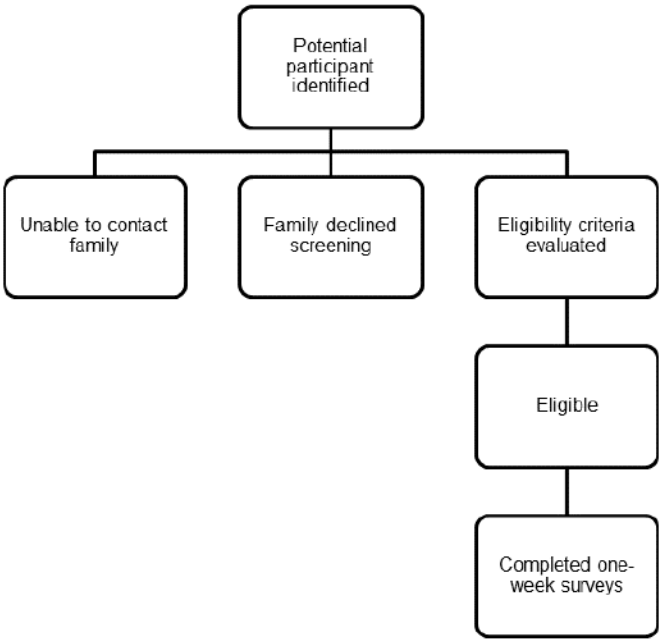
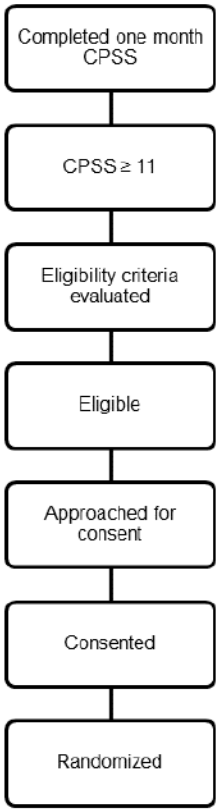


Figure 1b. Consort diagram – Main study enrollment



7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 Analysis Software

All analysis will be performed using SAS® Software version 9.4 or later whenever possible. Other software packages, including R, STATA and StatXact®, may be used for particular specialized procedures.

7.2 Methods for Withdrawals, Missing Data, and Outliers

We do not expect an issue with loss to followup in our study. Since CPSS is defined as the maximum of the child and parent scores, then in the event that one of either a child or parent score is missing, the other will be used. This affords some protection from missingness for our primary outcome. However, we do expect that there will be outliers in terms of when the CPSS was collected. Given that this is a smaller study, we plan to include all available measurements. We will summarize the extent of mistimed measures in our study and check for differences by treatment arm.

MI will be implemented for our ITT analysis if there is notable missingness in 10 week CPSS or an imbalance in missingness between treatment arms.[1] MI is particularly useful if there are auxiliary variables that are highly correlated with both the study outcomes and risk of missingness. We will include the following auxiliary variables: child and parent measures (Tables 1-2) and patient demographic factors (Table 3).

In the event that MI is used, we will generate 20 imputed data sets which contain imputed values of the primary CPSS outcome (if R is used, we will use the mice package). The imputation model will include the outcomes and all predictor variables including the randomized treatment assignment, auxiliary variables and the baseline level of CPSS.

We plan to include all CPSS post therapy follow-up measures, regardless of timing. At the time of writing (3/31/23) we have 4 subjects prior to 10 weeks (59-65 days) in the CBT arm (none in usual care) and 8 subjects after (78-96 days) in the CBT arm and 1 subject after (105 days) in the control arm due to an issue with REDCap programming that sent the post-therapy assessment at the finish of therapy instead of 10 weeks. The REDCap issue was corrected. Since more subjects come after the window in the CBT arm this introduces an anticonservative bias. We will handle this in two ways: adjusting for time since randomization as a continuous variable in our analysis (primary strategy) and dropping these kids from our analysis (secondary strategy). The downside to our primary strategy is that it assumes that recovery is consistent over time. In reality, it's likely that more recovery happens earlier, so that this would be a conservative approach (but if more recovery happened later, then this would potentially be anticonservative). Another downside is that reviewers will have a difficult time understanding our rationale – but it is defensible and potentially takes an

anticonservative bias and makes it conservative. The downside to the secondary strategy is a loss of power.

7.3 Multicenter Studies

Since randomization was stratified by center we will account for center in our analyses as a covariate or stratification variable (the same applies for age group).

7.4 Multiple Comparisons and Multiplicity

As there is a single primary endpoint for this study (10 week CPSS), adjustment for multiple comparisons will not be required for the primary analysis. Similarly, multiple comparison adjustment is not required for the main secondary endpoint as a single main secondary comparison of CPSS at 6 months has been defined.

All other analyses will be considered exploratory. Hence, analyses of additional endpoints will be performed on a comparison-wise basis unless the writing committees for specific manuscripts define multiple comparison adjustments during the publications process. Reports from this trial should, whenever appropriate, note the nature of endpoints reported (primary vs. secondary vs. exploratory) as well as relevant multiplicities of comparisons.

7.5 Planned Subgroups, Interactions, and Covariates

Randomization was stratified by center and age group, and thus center and age group will be included as covariates in our analyses as mentioned above.

Planned subgroup analyses include sex, age group, and injury severity.

Cut off for enrollment was 11+, but we will conduct an exploratory analysis using 15+.

<u>Future publications will explore the following questions:</u>

Exploratory questions include whether children's pre-injury psychological health (anxiety and depression) and parent PTSS symptoms at time of injury will modify the treatment effect. Thus, we will plan to examine these questions through interactions.

Another exploratory research question is the relationship between PTSS symptoms and children's and caregivers' pre-injury psychological adjustment and

family function. This question will be evaluated by examining these variables in exploratory models.

8. STUDY SUBJECTS

8.1 Disposition of Subjects and Withdrawls

All subjects who provide informed consent will be accounted for in this study. The frequency and percent of subjects in each population, study withdrawls, subgroups, and major protocol deviations will also be presented.

8.2 Protocol Deviations

We will summarize the number and % of subjects overall and by center with minor and major protocol deviations. See "Recovery After Stress Toolkit - ReSeT _ REDCap.pdf" form "rc_protocol_deviation" for a list of deviations.

8.3 Inclusion and Exclusion Criteria

The number and percent will be presented for subjects meeting each Inclusion and Exclusion Criteria. Generally, it is expected that the overall percentage will be 100% for inclusion and exclusion criteria, except when waivers are granted or when data review indicates that inclusion or exclusion criteria have been violated.

9. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

9.1 Demographics

Table 3: Demographics	
Child	
Sex	
Age	
Race/ethnicity	
Grade in school	If summer – last completed grade
Co-morbidities (ADHD, anxiety, depression, learning problems) Does your child have any illness that needs lots of doctor visits such as asthma or diabetes? Has your child been hospitalized in the past year?	Requires treatment – yes/no Yes/no
Family	
Number of adults in the home	Bottom level is 1 = if greater than 1 – Is there a second parent in the home?

Number of children in the home including the injured child	Bottom level is 1
Respondent relationship to child	List – mother, father, grandmother, grandfather, aunt, uncle, other relative, non-relative guardian or foster parent
Family income	Slider bar?
Respondent education	Grade school, high school, some college, college or greater
Insurance	None, Medicaid/CHIP, Private, Military
Marital status	Married, partnered, never married, divorced
Respondent race/ethnicity	

9.2 Measurement of Treatment Compliance

The CBT arm consists of 8 therapy sessions, and we will summarize the distribution of sessions completed as n (%).

10. EFFICACY ANALYSES

10.1 Analysis of Primary Outcome

The primary analysis will test the null hypothesis:

H_0: There is no difference in mean 10 week CPSS score between the CBT and usual care arms.

The alternative hypothesis is:

H_1: There is a difference in mean 10 week CPSS score between the CBT and usual care arms.

Rejecting the alternative hypothesis in the ITT population, along with a positive improvement in 10 week CPSS for CBT relative to the usual care arm, will be considered to be a successful demonstration of efficacy.

The model used to complete the primary analysis is a generalized linear regression model with an outcome of 10 week CPSS score and predictors that include an indicator for treatment group, baseline (one month) CPSS score, time since randomization, site and age group. The coefficient for treatment group will answer our primary efficacy question regarding whether 10 week CPSS score differs between CBT versus usual care arms. Adjustment for the baseline CPSS score provides the structure of an analysis of covariance (ANCOVA) to improve

statistical power.[2] Time since randomization will be included as a continuous variable to control for a technical redcap issue (see Section **7.2**). Site and age group are included since they were stratification variables used in the randomization protocol.

Regression diagnostics will include plotting residuals vs fitted values to assess linearity, the square root of the standardized residuals vs fitted values (ie "Scale-Location) to assess variance homogeneity, qq plot to assess normality, and standardized residual vs leverage to assess for outliers. The choice of outcome model will depend on the distribution of the CPSS score, which will be visualized using a histogram and density curves stratified by treatment arm. Provided the CPSS score distribution is sufficiently symmetric, we will use a normal outcome model. If the regression assumptions are not reasonably met, we will consider alternative models such as gamma or lognormal, or a tobit model if there are notable floor and/or ceiling effects.[3]

As a sensitivity analysis, we will repeat the above model excluding time since baseline, and also excluding the CBT subjects that had a CPSS score collected after 12+ weeks.

If there is an issue with treatment adherence, we will use an instrumental variables approach to estimate treatment effects under different treatment doses. The advantage of this approach over a per-protocol analysis is that it enables us to analyze patients according to their randomized assignment.

We will also examine the efficacy of CBT treatment in subgroups consisting of sex, age group and injury severity by including interactions between the indicator for CBT versus usual care and sex, age group and injury severity (where each interaction will be assessed in a separate model). Each interaction model will answer the question of whether the efficacy of CBT treatment differs by the subgroup, and it will also provide the efficacy estimates within each subgroup level.

10.2 Analysis of Secondary Outcomes

For analysis of the 6 month CPSS time point, which will assess persistence of the treatment effect between the CBT and usual care groups, we will use restricted maximum likelihood estimation[4] under a generalized linear mixed model. We will again adjust for the same variables as described above for the main efficacy analysis, except that time will be coded as binary (10 weeks vs 6 months). The primary efficacy evaluation will be performed using an interaction between the CBT versus usual care group indicator and time. We will adjust for 1 month baseline CPSS in this analysis.

10.3 Analysis of Exploratory Outcomes

Similar analysis approaches will be used for the separate child and parent CPSS scores, and the other exploratory outcomes described previously. As the non-CPSS exploratory outcomes are not assessed at the 1 month time point, but they are available at 1 week after injury, we will use this 1 week time point as our baseline measure.

As an exploratory analysis, we will repeat the primary and secondary analyses within the subgroup of kids who have a CPSS score of 15+.

11. REFERENCES

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