RE-PACT: Respiratory Exacerbation Plans for Action and Care Transitions for Children with Severe CP

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Respiratory Exacerbation Plans for Action and Care Transitions for Children with Severe CP	
Grant Number:	1R31HL153570-01A1	
Study Description:	This study will pilot test a just-in-time adaptive intervention to reduce severe respiratory illness, for children with severe cerebral palsy (CP). Our intervention program, called RE-PACT, delivers timely, customized action planning and health coaching when mobile text messaging with families predicts hospitalization risk is elevated. The study period will be divided into three waves: after each wave, feasibility, acceptability, and fidelity data will be reviewed against pre-defined measures of success to adjust the protocol and overcome implementation barriers.	
Objectives*:	Primary Objective:	To establish feasibility, acceptability, and fidelity of RE-PACT in 90 children with severe CP.
	Secondary Objectives:	To establish effect size of RE-PACT.
Endpoints*:	Primary Endpoint:	The primary outcomes are pre-defined measures of feasibility, acceptability and fidelity of targeting RE-PACT and/or assessments to children with severe CP
	Secondary Endpoints:	The primary clinical outcome is severe respiratory illness, defined as respiratory diagnosis requiring hospitalization. Addition secondary clinical endpoints include: total hospital days during severe respiratory illness, numbers of systemic steroid courses, systemic antibiotic courses, respiratory ED visits, and death
Study Population:	This intervention will recruit primary caregivers of children with severe CP. A total of n=90 caregivers of children with severe (GMFCS level V) CP, ages 0-17 years and cared for by a respiratory specialist or receiving daily respiratory treatments will be enrolled. Caregivers will be at least 18 years of age and have a phone capable of sending/receiving text messages. Subjects will speak English or Spanish. There are no additional demographic enrollment criteria. Participants will be recruited from pediatric complex	

	care programs at the University of Wisconsin-Madison (UW) and the University of California, Los Angeles (UCLA).
Phase* or Stage:	Behavioral Health Intervention Study
Description of Sites/ Facilities Enrolling Participants:	The two-site study takes place at clinical programs at US children's hospitals: the UW and UCLA Pediatric Complex Care Programs were each established to deliver care to children with medical complexity. Each program is comprised of primary care providers, care coordinators, and extended visit lengths, deliver comprehensive care to children with cerebral palsy. These sites have existing collaborative relationships through their participation in the CYSHCNet national research network (http://cyshcnet.org) and other federally funded initiatives, and a track record of successful productive scientific collaboration.
Description of Study Intervention/Experimental Manipulation:	The study period will be divided into three waves: after each wave, feasibility, acceptability, and fidelity data will be reviewed against pre-defined measures of success to adjust the protocol and overcome implementation barriers. This study will be conducted through a six-month randomized pilot trial. Briefly, after recruitment and baseline assessments, eligible caregiver/child dyads are randomized to intervention (I) or active control (AC). Intervention subjects receive respiratory illness action plans and weekly mobile health (mHealth) confidence surveillance. At times of low confidence or hospitalization, just-in-time action planning and coaching activities are conducted. AC subjects will receive usual comprehensive medical care and coordination. Assessments of feasibility, acceptability and fidelity, as well as clinical outcomes, will be conducted at baseline and monthly intervals for 6 months. Intervention outcomes will be evaluated at baseline (i.e., randomization) and 6 months post-enrollment, and will also include the primary clinical outcome (i.e., hospitalization for respiratory diagnosis).
Study Duration*:	24 months
Participant Duration:	6 months

1.2 SCHEMA

Total N = 90
Total by site: AFCH (45) UCLA (45)
Total by arm: Intervention (45) Control (45)
Wave 1 (10) Wave 2 (20) Wave (60)

Enrollment Period

(1-3 mon prior to T_0)

Identify potential subjects via program rosters and chart review; mail families study invitation and information.

Call families to assess interest and screen for inclusion/exclusion criteria; schedule enrollment visit if eligible and interested.

Waves 1-3 (6 months each)

Enrollment Visit (T_0)

Obtain informed consent (in-person at clinic visit or remotely via WebEx & REDCap survey); administer baseline study assessment

Randomize

Intervention Arm

- Create respiratory illness action plan
- Weekly mHealth text messages
- Monthly study assessments
- Action planning and JIT coaching
- Usual comprehensive medical care and coordination via Complex Care Program

Control Arm

- Usual comprehensive medical care and coordination via Complex Care Program

Post-enrollment Evaluation (T_0 + 6 mon)

Administer 6-month study assessment

Protocol refinement between each wave

By wave, refine Re-PACT protocol based on feasibility, acceptability, and fidelity measures:
Wave 1 – focus on onboarding/training, recruitment, data collection
Wave 2 – focus on randomization and intervention activities
Wave 3 – focus on rapid enrollment and conducting all protocol activities with high-fidelity

1.3 SCHEDULE OF ACTIVITIES

	STUDY PERIOD							
	Enroll-ment Visit	**REPACT Intervention Period**						**Final Visit**
Personnel involved	**Research Coordina-tor**	**Clinicians**						**Research Coordina-tor**
Month	0	1	2	3	4	5	6	End of Month 6
Timepoint	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7
Confirm eligibility	X							
Informed Consent	X							
Baseline Assessment	X							
6-month Assessment								X
Randomization	X							
Subject Payment	X							X
Usual comprehensive medical care and coordination via Complex Care Program		X	X	X	X	X	X	
Intervention Arm Only								
Text Msg Training	X							
Weekly mHealth text mes-sage and response		X	X	X	X	X	X	
Intervention overview		X						
Create action plan		X						
Action planning		X	X	X	X	X	X	
JIT coaching		X	X	X	X	X	X	
Monthly study assessments		X	X	X	X	X	X	

2 INTRODUCTION

2.1 STUDY RATIONALE

Respiratory illnesses, including aspiration, pneumonia, and respiratory failure, are devastating to children with severe cerebral palsy (CP). Respiratory illness is the number one cause of hospitalization and death in children with severe cerebral palsy (CP). CP is the most common motor disability in US children, and children with CP have 26x higher medical costs than those without, averaging >$1.3M per child in lifetime care costs. We define severe CP as spastic quadriplegia, i.e., no independent mobility (gross motor function classification system level V). Little progress on respiratory outcomes in CP has occurred in the last 40 years.

Severe respiratory illnesses, which we define as respiratory diagnoses requiring hospitalization, are considered potentially modifiable in CP. Families are first in line to manage these challenging events because the illness emerges at home. However, respiratory care routines are especially difficult for families in the setting of limited support to bolster knowledge, skills, and confidence. To bridge this gap, parents need clinical teams to provide the right support, at the right time, in the right context, i.e., just-in-time and adaptive.

Just-in-time adaptive interventions (JITAI) hold promise to help children with CP with respiratory illness. Our behavioral intervention, Plans for Action and Care Transitions (PACT) combined action planning with caregiver coaching and reduced all-cause hospitalizations for children with complex diseases including severe CP. Although PACT's action plans gave families just-in-time options to manage crises, plans were pre-specified, static, and did not adjust to real-time issues. To prevent severe respiratory illness in CP, responses must be dynamic, and address the wide array of contexts and comorbidities that drive these episodes. Simultaneously, clinicians and families need very simple tools that signal when they need help.

Mobile health (mHealth) approaches linked to clinical teams can easily indicate when families of children with CP experiencing respiratory illness need help. Meta-analysis of mHealth interventions suggests improved disease control in children, particularly when directed to caregivers. In early-stage studies of asthma and COPD, mHealth monitoring / response systems are associated with fewer exacerbations. We will integrate an mHealth texting solution with PACT to trigger our just-in-time adaptive intervention for severe CP. The objective of this study is to finalize a feasible, acceptable, and high-fidelity adaptive intervention, and to determine expected effect sizes for reducing severe respiratory illness for a fully powered trial. Completion of the study is necessary to subsequently conduct an adequately powered multisite efficacy trial.

2.2 BACKGROUND

Cerebral palsy (CP) is the leading cause of motor disability in childhood[8,9] and has grave respiratory consequences.[13] CP is caused by damage to the developing brain that permanently disrupts the ability to

control movement and maintain posture. Children with severe CP have spastic quadriplegia (i.e., all four extremities affected) and level V gross motor function classification system [GMFCS] (i.e., no independent mobility). Mechanisms of respiratory illness in severe CP parallel those of other neuromuscular diseases;[27] examples include respiratory muscle weakness, recurrent infections and aspiration with inflammatory fibrosis, impaired airway clearance from altered tone, upper airway abnormalities and poor chest wall compliance.[28,29] CDC estimates >$16B in lifetime cost for the children with CP born in 2000 alone.[10]

Respiratory illness is consistently the #1 cause of death and hospitalization in severe CP.4,30 Only 33% of children with CP and four co-occurring disabilities survive to age 30.[31] Respiratory illness accounts for 59% of deaths[3,4] and 25% of hospitalizations[1,7,8] in severe CP. Moreover, respiratory illness strongly predicts future episodes; respiratory hospitalization risk is 10-fold higher with a respiratory illness in the past year.[14] In fact, over 20% of hospitalizations are followed by another within 30 days and nearly 70% in the next year.[7] Hospitalizations for respiratory illness are 76% costlier8 and 2.5 times longer for children with severe CP than those without.[14] Prevention of these events is a significant need, and a key to improving quality of life and mortality.[6,13] Though the respiratory illness risk factors in severe CP are considered modifiable,14 and despite investments in respiratory care, little improvement in these outcomes has occurred in CP in 40 years.[1,2,8]

The very high utilization and specialized needs of parents of children with severe CP demands unique solutions (Box 1). In a 2007-2014 population-based child cohort with severe CP, over 91% had ≥1 hospitalization (median [IQR], 4 [2-8]).[8] Unlike children with single system disease, such as asthma, those with severe CP are 100% dependent for every activity of daily living, cannot communicate, and have subtle illness signs. Families must monitor high-acuity comorbid conditions and administer elaborate care plans despite concerns that they lack preparation and tools to deliver this sophisticated care at home.[6,13,15,32-35] Parents of children with CP articulate the need for interventions focused on crisis management and self-efficacy.[7,15,36]

Preventing hospitalization requires the opportunity for families and clinical teams to connect early enough to change trajectory.[15,16,37] Not knowing when just-in-time care is needed is a current barrier to effective action planning and health coaching in complex illnesses. Concerns may not reach clinical teams until an ED visit or hospitalization is inevitable. Families need their clinical teams to respond to early discomfort.38 In fact, a national expert panel to identify interventions to prevent hospitalization of children with complex diseases[39] concluded that enhanced access, proactive crisis planning, and support for caregiver technical skill were key strategies to lower hospital use. Prior post-discharge research confirmed that when parents were not confident that their child with chronic conditions could avoid hospitalization or ED visit, admissions and ED visits within weeks were predicted better than by other clinical or demographic indicators.[40,41] Preliminary work with a cohort including children with severe CP demonstrated that parent confidence, monitored prospectively and repeatedly by text message is feasible, acceptable and predicts hospitalization within 2 weeks. Being able to target rapid “just-in-time”, customized, clinical response to periods of low parent confidence, before respiratory illness becomes crisis, is a key advance of this research.

Preventing Respiratory Illness in Severe CP Requires Broad, Adaptive, Timely Intervention. Action planning and health coaching are effective strategies in other populations. For example, from 2003 to 2013, hospitalization rates for pediatric asthma dropped by half (from 9.6% to 4.7%), during which time asthma action plan use increased significantly.[42] A family intervention linking home-based asthma coaching to action planning significantly reduced hospitalizations in poorly controlled asthma.43 However, respiratory illness in severe CP has broad comorbid triggers, e.g., emesis, dysphagia, aspiration, seizures, among others. Simple action plans or coaching alone cannot address the breadth of respiratory illness triggers or potential responses. For example, if a parent of a child with severe CP follows an action plan directed towards bronchospasm, it would not effectively address an acute infectious lower respiratory infection. Parents of children with severe CP need action plans and coaching, but they also need an efficient direct extension to their clinical team for adaptive, just-in-time clinical response directed specifically to real-time acute problems.

The Plans for Action and Care Transitions (PACT) intervention was developed by this team to prevent hospitalizations for children with complex chronic diseases including severe CP. After integrating systematic literature review,[44] parent interviews,[38] and a national expert panel,[39] each focused on preventing hospitalization, PACT was designed to leverage evidence-based strategies from different populations: asthma action planning,[45-47] health coaching,[48-50] and feedback at our Parent Advisory Group's monthly meetings. PACT delivered action planning and coaching activities to children with diverse complex diseases, including severe CP, and a PACT RCT found 40% lower hospitalization rates for intervention vs control patients.[18]

The purpose of this study is to achieve protocol revisions and preliminary data to support a large multisite RCT to reduce respiratory illness in severe cerebral palsy. This study adapts the efficacious PACT intervention into "Respiratory Exacerbations-PACT" (RE-PACT) for children with severe CP. The proposed research is significant because the intervention targets the central, yet currently overlooked, cause of severe respiratory illness in severe CP – under-supported families managing emerging health crises at home. RE-PACT links an innovative just-in-time adaptive response to an effective intervention developed by this team. RE-PACT delivers the right care, at the right time, in the right context. The RE-PACT intervention platform has direct potential to accelerate the translation of discovery into practice by embedding a research platform within 'learning' health systems, thereby engaging clinical care and patient communities; and creating an integrative interface between research and practice. This study will establish feasibility, acceptability, and fidelity, and determine likely effect sizes of the intervention to reduce respiratory illness in severe CP. Successful completion of these objectives, will build a strong scientific foundation and necessary data, infrastructure and protocols to conduct a full-scale efficacy trial.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The proposed research will pose minimal risks to human research subjects, comparable to the risks incurred through everyday conversations, routine visits with clinic providers, and basic psychological tests. The potential risks are immediate risks (not long-term) and include: 1) mild psychological discomfort in discussing parenting, personal and family matters, including challenges and demands about caring for a child with severe disabilities, and family socio-demographics, including parental education and household income; 2) social risk by participating in the study, if their participation were to become known to anyone outside the research team; and 3) loss of confidentiality.

One potential long-term risk is that if families feel a false sense of security during an illness (e.g., from their coaching experience), they may seek care later and present with a more advanced or potentially severe acute illness. This risk is minimized however, by having clear protocols for coaches to follow to include clinical team members, and not restricting families from using their usual support channels when their child is ill (e.g., calling their provider, having an urgent visit in clinic, going to the emergency room, etc.).

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefits are immediate. All participants will receive information about their child's health status (such as care recommendations and the results of clinical tests and procedures), which may benefit families with or without concerns, and in part ameliorate the psychological risk posed by the research. Clinical information will be exchanged by oral communication between the parent and the Peds Complex Care clinical team member. The clinical team member may also communicate (orally or by MyChart) with other members of the child's clinical team (such as their pulmonologist and other specialists). Such communication is part of the standard care provided for families in the Pediatric Complex Care Program. For families enrolled in the randomized clinical trial, study staff will also share information about parent confidence with clinical providers. For example, if a parent reports low confidence that their child will avoid hospitalization in the next month, the clinical team member will share this information with other members of the child's care team to determine whether changes in care are recommended. As always, the clinical team member will discuss parental confidence, parental opinion of their child's care plans, and/or parental opinion of their child's providers with professionalism and sensitivity to patient-provider relationships. They will divulge the minimum amount of information needed to discuss the patient's health status.

The potential benefit of REPACT is that early communication will lead to early detection of crises (respiratory or otherwise) and opportunities for early intervention. It is unclear what the benefits of the RE-PACT intervention will be to study participants, but there is a potential benefit of preventing hospital and emergency department use, and improving experiences navigating the health system. There is also a potential benefit to providers in having RE-PACT help with care coordination (e.g., knowing who and when to call for respiratory health problems).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Rationale for the necessity of exposing participants to risks: If proven effective for families and providers, the proposed RE-PACT intervention has the potential to help many families and clinical systems in the future. Developing more streamlined and effective processes for real-time identification of health crises and linking families with "just-in-time" clinical interventions has the potential to improve systems of care for vulnerable children and their families, ultimately with the potential to improve health outcomes.

Summary of the ways that risks to participants were minimized in the study design: Participation in the study will be completely voluntary and participants may end their participation at any point. Participation in the study should not affect the routine medical care they receive. Clinical providers will be notified of screening results for all participants. Participants may decline to participate in any given component of the study and may decline to answer any particular question they do not wish to answer. Their participation in the study will remain confidential, with meetings between study staff and participants happening in private rooms. Written questionnaires will be labeled with a unique identifier and other identifying information will not be associated with written data. Any identifying information kept for the purposes of contacting participants will be kept secure, in REDCap, a locked filing cabinet or in a password-protected electronic file and will be destroyed when the study is complete. In the event of any adverse events, we will follow the protocols as described in the data safety monitoring plan, including notification of the PI and Co-I (UCLA site PI), clinical escalation as appropriate using the clinical staff in the respective clinic partner sites, and notification of authorities as required by law (Child Protective Services and/or law enforcement).

Justification as to why the value of the information to be gained outweighs the risks of participation in the study: This platform may prove to be adaptable to other disease states which experience acute exacerbations managed (at least in part) by families at home. Many of these improved processes are yet to be developed and tested. This study would add to the knowledge about what is effective, possibly leading to important future research and implementation efforts.

3 OBJECTIVES AND ENDPOINTS

<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th><th>JUSTIFICATION FOR ENDPOINTS</th><th>PUTATIVE MECHANISMS OF ACTION</th></tr>
<tr><td>Primary</td><td colspan="3"></td></tr>
<tr><td>To establish feasibility, acceptability, and fidelity of RE-PACT in 90 children with severe CP.</td><td>
<table>
<tr><th>MEASURES</th><th>MEASURE DETAIL</th><th>SUCCESS DEFINITION</th></tr>
<tr><td>FEASIBILITY</td><td></td><td>n=90</td></tr>
<tr><td>Recruitment</td><td>Days to enroll target, mean</td><td><14</td></tr>
<tr><td>Intervention onset</td><td>Days between randomization and “time zero” intervention activities, mean</td><td><7</td></tr>
<tr><td>Intervention time</td><td>Time logged (minutes) for action planning and for coaching activities, mean</td><td></td></tr>
<tr><td>Intervention costs</td><td>Mileage / travel costs; Personnel salary; Training; Other incurred costs, total</td><td></td></tr>
<tr><td>Intervention triggers</td><td>Number per patient (annualized); respiratory and non-respiratory focused</td><td></td></tr>
<tr><td>Data infrastructure</td><td>Data collection reliability; Coordination at UW, Data use agreements / IRBs</td><td></td></tr>
<tr><td>ACCEPTABILITY</td><td></td><td></td></tr>
<tr><td>Enrollment</td><td>Enrollment rate (# of patients enrolled / # approached)</td><td>>80%</td></tr>
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OBJECTIVES	ENDPOINTS			JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	Consent refusal	Categorized reasons for refusal			
	Loss, Drop out	Rate of drop out (active or passive) before 6 months (# drop out / # enrolled)	<10%		
	Action plan, Coaching, texting satisfaction	Do caregivers use the action plan, coaching and texting (why / why not); How could it be improved; Would caregivers recommend this to another family? (why / why not)			
	FIDELITY				
	Enrollment duration	Time (months) of participant enrollment in the study, mean	6		
	Action plan creation	# respiratory and overall action plans per patient; Action plan focus areas	≥1		
	Coaching – home or virtual visit	Success rate (# visits completed / # expected); stratify by trigger (hospitalization vs confidence rating)	>80%		

OBJECTIVES	ENDPOINTS			JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	Coaching – phone calls	Success rate (# phone calls completed / # expected); stratify by trigger (hospitalization vs confidence rating); respiratory and non-respiratory	>80%		
	mHealth texting	Response rates (# texts responded / # expected); respiratory and non-respiratory	>90%		
	Cross-over	# Patient inappropriately receiving any intervention component	0		
	Data collection	Complete entry and exit questionnaire, monthly questionnaire, chart review data (# data collection events complete / # of total data collection events)	>95%		
Secondary					
To establish effect size of RE-PACT.	Severe respiratory illness, defined as respiratory diagnoses requiring hospitalization. Respiratory diagnoses includes discharge diagnosis of any of the following: asthma, pneumonia (community or hospital acquired), bronchiolitis, influenza, upper or lower respiratory tract infection,				

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	tracheitis, aspiration pneumonia/pneumonitis, chronic lung disease, respiratory failure.		
Tertiary/Exploratory			
To explore the mediating relationships between RE-PACT and capability, opportunity, motivation (COM-B) measures.	Capability: Family Caregiver Activation in Transition Measure (FCAT)117 – mean composite score Caregiver General Self-Efficacy Scale (GSES)118 – mean composite score. Opportunity: Family Experiences with Care Coordination (FECC)119 - % top-box score for selected items Motivation: Confidence Responses mHealth texting (weekly score 1 through 10)	Blending our foundational research on preventing hospitalizations,38,39 with behavioral intervention theory,113 our conceptual model suggests that decisions to seek care (behaviors) are influenced by capability (family capacity), opportunity (health system and susceptibility), and motivation (confidence). Confidence is a modifiable expression of self-efficacy to achieve an outcome, i.e., to avoid hospitalization and manage (respiratory) crisis at home.	A theorized mechanism of RE-PACT's effect is that the combination of action planning, mHealth surveillance, and coaching, will increase caregiver capability, opportunity, motivation to manage respiratory illness in severe CP.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a pilot randomized, controlled clinical trial to establish the intervention protocol's feasibility, acceptability, and fidelity, as well as preliminary effect size data. All study participants will undergo informed consent including authorization to view the child's medical record and consent to participate in action planning, health coaching, and weekly text message surveillance.

To participate in this study, a patient must be cared for at one of two sites (University of Wisconsin/American Family Children's Hospital or UCLA/Mattel Children's Hospital) in their complex care or cerebral palsy clinical programs, and meet study inclusion criteria, which include presence of severe cerebral palsy and respiratory care needs (see **Section 5, Study Population** for details).

Following an intervention adaptation phase consisting of formative data from focus groups with primary caregivers, clinical teams and a group of national experts, this phase will employ the evidence-based Replicating Effective Program's framework for intervention adaptation and the Patient-Centered Outcomes Research Institute's standards for improving research of complex health interventions. The previously efficacious PACT (Plans for Action and Care Transitions) intervention has been adapted to prevent severe respiratory illness in children with severe cerebral palsy, and to increased dose triggers from text messages indicating a family's low confidence for their child to avoid a hospitalization in real-time. In addition, the Core Functions (standard components required for integrity) and Forms (the tailored activities to carry out the Core Functions) have been delineated. The adapted intervention is called RE-PACT, or Respiratory Exacerbation Plans for Action and Care Transitions.

RE-PACT involves action planning and health coaching to prevent and manage respiratory illness, as well as weekly text messaging surveillance of caregiver confidence for their child to avoid a hospitalization. All intervention families will receive respiratory illness action plans at study entry. Action plan content will be consistent with standard clinical care guidelines and will not differ from the recommendations of the child's clinical care team. Health coaching focuses on managing medications, understanding and responding to red flags, keeping patient-centered records, maintaining timely follow-up with primary or specialty care. Coaches focus on skill transfer to parent caregivers, achieved through structured face-to-face or virtual telehealth coaching and phone follow-up over a 2-week period. Just-in-time action planning and coaching activities are triggered by caregiver text message responses indicating low confidence (rating ≤4 on 1-10 scale) to avoid a hospitalization. The usual care, active control group will continue to receive comprehensive care coordination and medical management.

Study participants will be randomly assigned to receive usual care through the complex care clinical program, or the study intervention, RE-PACT. Random allocation will be concealed to research staff conducting recruitment and will use a 1:1 allocation with random block sizes of 2 and 4. Block randomization will be achieved with a computer-generated random number list prepared by the study

biostatistician having no clinical involvement in the trial. Randomization will be stratified by site to account for site-specific study characteristics.

RE-PACT will be run through three successively larger 6-month trials ("waves"), allowing ongoing protocol refinement according to pre-specified definitions of success for measures of feasibility, acceptability and fidelity. Each wave has a specific protocol refinement focus: Wave 1 – onboarding/training, recruitment, data collection; Wave 2 – randomization and intervention activities; Wave 3 – rapid enrollment and conducting all protocol activities with high-fidelity.

RCT participants in both groups will undergo assessments of demographic, clinical and caregiving measures reported through questionnaire and medical record review at baseline at 6 months after enrollment. Feasibility, acceptability and fidelity data will be collected through parent-report, medical record review, and research team logs monthly during the intervention, and, for control group participants, at 6 months after enrollment.

Data about research participants (children and their families) will be collected by study research assistants through electronic self-administered questionnaires or structured interviews with parents either over the phone or in person, abstraction of child medical record data by the study RAs, and (for intervention group families) through phone interactions and direct observation with health coaches in RE-PACT. Content of these assessments include parent-report questions about child and parent health, parent perceptions of child health, family socio-demographic information, care utilization, and experiences of caregiving.

Analyses will assess feasibility, acceptability, fidelity and effect size estimates (by comparing numbers of respiratory exacerbations between intervention and usual care groups). We will use pre-specified definitions of success for each of our feasibility, acceptability and fidelity measures. We anticipate being underpowered to assess the efficacy of the intervention in this pilot study, but to inform a future large RCT we will test differences between intervention and active groups in the primary and secondary clinical outcomes. For each of these measures, we will compare differences between intervention and active control group outcomes at 6 months controlling for their baselines. While we anticipate that the intervention and control groups will be similar due to random assignment, we will adjust for any variables in our analysis that are not equal between the groups given the small sample size. In addition, we will analyze for any effect of primary home language on the study outcomes, as this may affect families' ability to navigate systems of care in the U.S. To explore theoretical intervention mechanisms, we will also test the mediating effect of caregiver capability, opportunity, and motivation measures on the relationship between intervention and respiratory illness outcomes.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Rational for the study design. Conducting this pilot study will provide a high degree of certainty that the final RE-PACT protocol is feasible, acceptable and can be delivered with fidelity. This is a critical approach to designing interventions that can be integrated in diverse, real-world, settings and sustained.

Using an RCT design (i.e., with a control group who do not receive intervention) is necessary to establish effect sizes needed to adequately power an efficacy trial. The findings from this study will allow precise estimation of effect sizes to conduct a fully powered, multisite hybrid Type 2 effectiveness-implementation RCT.

Rationale for the type and selection of control conditions. The control group will be randomly assigned, allowing the study team to conclude that endpoint differences between each group are most likely due to the intervention itself.

Potential problems associated with the control group. The control group may have pre-existing respiratory action plans created during routine clinical care. In addition, the coach may have difficulty avoiding contaminating the control group by inadvertently conducting coaching activities to those not assigned to the intervention group. This risk will be minimized since action plans using the study protocol will only happen for intervention subjects, and coaching is triggered only through mHealth text responses and texting will only be set up for those assigned to the intervention.

4.3 JUSTIFICATION FOR INTERVENTION

Justification for the mode of intervention delivery. RE-PACT uses a dynamic Just-in-Time Adaptive Intervention (JITAI) design.[17] Though causes of respiratory illness in severe CP are modifiable, they are also broad and require distinct responses, even for the same child over time. RE-PACT's design addresses child and family changing needs. Managing crises with just-in-time action planning and bringing coaching directly to families breaks down barriers between home and clinical settings precisely when it matters most. This approach is innovative since we tailor the intensity of response (e.g., phone call, clinic visit, etc.) to family- and illness-specific needs. The adaptive nature of the intervention ensures it meets caregiver needs for that particular illness, whether requiring purely respiratory or a mix of respiratory and non-respiratory chronic disease management (e.g., seizures, feeding intolerance, etc.). The number and frequency of contacts is rooted in prior research using a related trial as well as feedback from families pilot-testing our texting tool. There is no minimum-acceptable participation in, or exposure to the intervention since the study is designed to assess feasibility, acceptability, and fidelity, i.e., varying rates of participation will be a relevant endpoint in itself.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, and the 6-month follow-up assessments, as shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

The participant is the caregiver of a child with severe cerebral palsy. Individuals must meet all of the inclusion criteria in order to be eligible to participate in the study:

Caregiver Criteria

- Be at least 18 years of age
- Primary caregiver to an eligible child (child criteria below)
- Speak English or Spanish well enough to be interviewed
- Have a phone capable of sending/receiving text messages

Child Criteria

- Ages 0-17 years
- Have Gross Motor Function Classification System level IV or V Cerebral Palsy
- Cared for by respiratory specialist or receive daily respiratory treatments (oxygen, ventilation, airway clearance device, medications)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Lack of interest in text messaging or coaching interactions during the study

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Reply to text messages when received at random times during daytime hours.
- Connect with an intervention coach either at home, in-person at a mutually agreeable location, by phone, or over the internet

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include child's development of needs for respiratory treatment, re-assignment to a GMFCS status that meets inclusion criteria,

acquisition of a phone capable to send/receive text messages. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment

We will recruit caregivers of children with severe CP between 0-17 years old. We will recruit a total of n=90 participants (n=45 at each site) divided across 3 waves. In each wave, there is a 1-2 month enrollment period. We anticipate approximately 80% of those screened will enroll, requiring approximately 110 individuals to be screened.

Potential participants will be identified by reviewing the clinic registries and/or EHR data using diagnostic codes for CP (ICD-10 G80-83), which contain detailed information about children and their diagnoses. We will send an "opt-out" letter that alerts families that a research study is being conducted and their child may be eligible, with a contact number to call if they wish to opt out of the research or if they wish to receive additional information or have any questions. Potentially eligible caregivers will be contacted by phone to screen for eligibility and interest.

If the research team is not notified that a family wishes to opt-out the research, the study research personnel will attempt to call the families (or meet them at an upcoming visit) to complete screening, informed consent, baseline questionnaires and random group assignment. Eligibility criteria for caregivers are detailed in **Study Population, Section 5.1-5.2**, and include being self-identified English- or Spanish-speaking caregivers of children with severe CP who have respiratory needs. CP status and additional eligibility criteria will be determined with a reliable and valid parent questionnaire and screener conducted at the beginning of initial phone contact.

Retention and Incentives

Study participants in this pilot RCT will be contacted at baseline (enrollment), monthly (for intervention subjects), and at 6 months (intervention and control groups). While we expect some degree of attrition will be inevitable, we will work to minimize attrition by sending regular follow-up post cards and phone calls requesting updates in contact information and also confirming or updating contact information when child medical records are reviewed. Moreover, participants will receive $100 on study entry and exit.

Inclusion of Women and Minorities

While we will not specifically recruit study participants based on gender, race or ethnicity, the demographics of our clinics are such that we expect parents to be predominantly women (mothers of young children brought to the clinic for care). At UCLA, families are predominantly Hispanic or Latino. Child participants will most likely be close to 50% male and 50% female. Together, we estimate approximately the demographic composition to be 35% Hispanic or Latino, 65% approximately distributed between white, non-Hispanic, African American (including a subset of Hispanic or Latino origin) and Asian, Pacific Islander, Native American, and multiracial groups combined. From the total 90

participants, we estimate 43 males and 47 females, 32 to identify as Hispanic and 58 non-Hispanic, and approximately 65 to identify as white, 9 as black, 5 as more than one race, and 11 as other (e.g., Asian, Pacific Islander, Native American, and unknown or not reported).

We also know that the majority of the Hispanic or Latino families are Spanish-speaking and will ensure that study materials are linguistically appropriate. Due to limitation of study resources, we must exclude families unable to speak English or Spanish well enough to be interviewed and receive care materials written in either English or Spanish.

We will collect demographic information about children and families as part of our data collection. While we anticipate that the intervention and control groups will be similar due to random assignment, we will adjust for any variables in our analysis that are not equal between the groups given the small sample size. In addition, we will analyze for any effect of primary home language on the study outcomes, as this may affect families' ability to navigate systems of care in the U.S.

Inclusion of Children/ Inclusion Across the Lifespan

Research participants for this study will include children and their parents or legal guardians. We propose to enroll 90 children between ages 0-17 years into this study and follow their health and health care for 6 months. This sample size and timeframe will sufficiently meet the need to establish trial protocol feasibility, acceptability, and fidelity and collect preliminary data for power calculations (it is intentionally not designed to be large enough to prove efficacy of the intervention). Although the entire proposed study relates specifically to children, we expect actual participation of children themselves to be minimal. Child-level data will be collected primarily using parent report and medical record review, with no direct child responses. Parents will be asked to provide consent for themselves and permission for their children to participate, including for the collection of child-level data. Children with severe cerebral palsy typically have functional and/or development limitations of such severity that they are not considered able to provide assent, so only parental permission will be obtained for this study, which involves minimal risk. We have the expertise and facilities to work with children of all ages and developmental abilities. Our research team includes senior researchers with pediatric clinical trials experience. Our clinical team is located at two major tertiary children's hospitals (American Family Children's Hospital / University of Wisconsin and Mattel Children's Hospital / UCLA) that specialize in delivering care to children and families facing this particular clinical condition. There is no upper age limit for parents or legal guardians to participate, and it is reasonable to expect that some older adults will be guardians for children in this study.

Justification for Inclusion of Vulnerable Subjects

Children of all ages with severe CP and see a respiratory specialist and/or use daily respiratory treatment will be included because those are the children with active disease who are most likely to have relevant fluctuations in health such that they will experience, and benefit from, intervention activities. Finally, we only have resources to recruit and interview families in English or Spanish.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The Respiratory Exacerbation Plans for Action and Care Transitions (RE-PACT) intervention has three primary activities: (1) mHealth surveillance of parent confidence to avoid hospitalization, (2) respiratory illness action planning, and (3) just-in-time adaptive coaching response triggered by low confidence or hospitalization. The theoretical basis of the intervention includes efficacy of the initial PACT trial, and prior research on preventing hospitalizations combined with behavioral intervention theory which suggests that decisions to seek care (behaviors) are influenced by capability (family capacity), opportunity (health system and susceptibility), and motivation (confidence). Confidence is a modifiable expression of self-efficacy to achieve an outcome, i.e., to avoid hospitalization and manage (respiratory) crisis at home. In our earlier work, low confidence predicted hospitalization.

Participants randomized into the intervention will receive initial T_0 intervention activities (mHealth monitoring and respiratory action plan) by phone, at clinic, or during a hospitalization within one month of enrollment.

mHealth surveillance. Upon enrollment, families will begin receiving weekly text messages asking them to rate their confidence (1-10) for their child to avoid a hospitalization in the next month.

Action Planning. The action and format are adapted from the original PACT study, and contents include (at minimum) recognizing, describing and managing the child's known contributors to respiratory illness. In step 1, objective and subjective indicators of baseline ("green"), concerning ("yellow"), and severe ("red") statuses are defined (e.g., >2 L/min of oxygen). In step 2, the specific actions caregivers should take to manage each status are defined (e.g., increase vest, albuterol, suction to q4, use oxygen up to 4 L/min).

Just-in-time Adaptive Coaching Intervention Response. Coaching is accomplished by adapting PACT, which was initially adapted from the Care Transitions Intervention® (CTI),[50] to the pediatric population. The focus is: (1) medication self-management, (2) patient-centered records maintained by families, (3) timely follow-up, and (4) "red flags" and instructions how to identify/respond to them (i.e., action plans). Face-to-face visits are typically at the family's home; however, a neutral or "virtual" (telephone) visit is an option. Coaches review the four components, elicit goals, and focus coaching activities on needs identified by families. Phone calls discuss progress toward goals. This coaching approach provides the structure for JITAI activities.

Control Group. Those participants randomized to the control group will be provided usual care through the comprehensive clinical program at their children's hospital. They will also complete pre- and post-study assessments.

6.1.2 ADMINISTRATION AND/OR DOSING

mHealth Surveillance. Text messages are programmed to be sent at random days / times to caregivers beginning the Monday after enrollment. Text messages average once weekly (Sun-Thurs) between 8AM and 9PM (local time). After 2 hours of non-response, a reminder is sent, and this is repeated up to 2 times.

Action Planning. All intervention families receive respiratory illness action plans within 1 month of study entry, and just-in-time plans are also created at times of low confidence. Plans are created in caregivers' preferred language (English, Spanish) by physician or nurse practitioner using our protocol (see intervention manual). After plans are created, teach-back is used. Copies are given to families and included in medical records. Plans are discussed at weekly clinical meetings for clarity and accuracy.

Just-in-time Adaptive Coaching Intervention Response. In the original design, coaches met families prior to a hospital discharge, conducted face-to-face visits within 72 hours and 3 phone calls within 30 days, post-discharge. Compared to the original PACT design, RE-PACT was adapted to trigger just-in-time adaptive intervention (JITAI) action planning and coaching doses when caregiver text message responses indicate low confidence. JITAI action planning and coaching doses occur within 24 hours of any text message ratings ≤4. This confidence threshold to trigger JITAI and the text prompt wording was vetted in preliminary qualitative research with families and clinicians and is based on our prospective pilot study at UW and UCLA whereby confidence ratings ≤4 predicted hospitalizations a median (IQR) 8 (2-10) days in advance. The protocol currently supports intervention coach credentials to include undergoing coach training (or equivalent, see intervention manual), and individuals can possess any university degree of higher. For example, a coach could be a care coordinator with a bachelor's degree, a physician, or other health professional.

The study feasibility, acceptability and fidelity measures are designed to quantify intervention doses, dose intensity and frequency (e.g., # of coach visits, # of action plans), and include incomplete dose administration (e.g., poor text message response rates).

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Action plans are created by study physicians or nurse practitioners using our worksheet-based protocol (see intervention manual). Plans are discussed at weekly clinical meetings for clarity and accuracy. For each enrollee, the study team will log whether (1) an action plan was created (and how many were created), (2) when they were created, and (3) whether/when each plan was reviewed with the clinical team. Spanish-speaking Action Plans will be drafted in Spanish by native-speaking Spanish clinicians or designated clinical translators.

Coaching interventionist training is based on the initial PACT protocol (see intervention manual), and includes an overview of coaching, scenarios and role-practice, mock sessions with feedback, supervisor observation with feedback, as well as weekly coaching peer discussions throughout the intervention period. The protocol currently supports intervention coach credentials to include any bachelor's degree of higher. For example, a coach could be a care coordinator with a bachelor's degree, a physician, or

other health professional. The study fidelity measures are designed to quantify coaching doses, dose intensity and frequency (e.g., # of coach visits), and include incomplete dose administration (e.g., missed coach visits / calls), etc.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Random allocation will be concealed to research staff conducting recruitment and will use a 1:1 allocation with random block sizes of 2 and 4. Block randomization will be achieved with a computer-generated random number list prepared by the study biostatistician having no clinical involvement in the trial. Randomization will be stratified by site (UW vs UCLA) to account for site-specific study characteristics. After the research team member obtains participant consent, they will telephone contact the study project manager who is independent from the recruitment process to receive the group assignment. Alternatively, it may be arranged that randomization will be built into the REDCap database by the study biostatistician.

Since this study aim is feasibility, acceptability and fidelity, there is no plan for whether/when to break randomization codes. Study and clinical team members cannot practically be blinded to treatment because only those randomized to intervention will receive text messages, specific action plans, and coaching. The need for clinical team members to create action plans and interact with coaches will identify those randomized to intervention. Presumably, the need for admission to the hospital for a respiratory illness and secondary clinical endpoints (ED visits, need for antibiotics, steroids, hospital days, and death) are less prone to observer bias. The outcome evaluator (study biostatistician) will remain blinded during analyses.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Given the nature of this pilot RCT, participant adherence measures are delineated within the primary acceptability and fidelity outcomes for the study. These include attrition, monthly self-reported action plan and coaching use, response rates to text messaging and response rates to coaching visits and follow-up phone calls.

Loss to follow-up is defined in **Section 7.3, Lost to follow-up.**

6.5 CONCOMITANT THERAPY

For this protocol, participants may use existing action plans that have been created outside the study. Action plan existence/usage will be assessed at monthly study calls and documented in the relevant Case Report Form (CRF).

6.5.1 RESCUE THERAPY

The study site will not supply rescue medication.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from any element of RE-PACT (action planning, texting, coaching), but not from the study, remaining study procedures will be completed as indicated by the study protocol.

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- If a subject is no longer a part of the complex care program at the UW or UCLA, their enrollment in the study will be discontinued.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Discontinuation/Withdrawal Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they are no longer a member of the clinical program, or if they fail to respond to 3 consecutive months of texting, or 3 monthly assessments in a row, and study staff are unable to contact the participant after at least 3 attempts.
The following actions will be taken if a participant fails to respond:

- The site will attempt to contact the participant, counsel the participant on the importance of maintaining the assigned schedule and ascertain if the participant wishes to and/or should continue the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Screening, Eligibility and Enrollment Procedures

Using clinic registry or EHR data (see **Section 5, Strategies for Recruitment and Retention**), all children with known or suspected severe CP, up to age 17 years will be identified. After sharing introductions with these identified individuals by mail and telephone, trained research personnel will begin approaching potential participants using a standardized recruitment and screening script (for use in person, virtually or by telephone) to screen eligibility and interest. The eligible participant pool will be assembled up to 3 months prior to beginning wave 1 enrollment. Screening will be used during each trial wave's recruitment period until the recruitment target is reached. Randomization/enrollment will occur at the same time as screening but can be completed up to 1 month after screening if families need additional time.

The screening questionnaires will confirm:

- Caregivers: are at least 18 years of age, are the primary caregiver to candidate child (child criteria below), speak English or Spanish well enough to be interviewed, have a phone capable of sending/receiving text messages, and are willing to send/receive text messages on their device.
    - These measures are self-reported.
- Children: are 0-17 years of age, have Gross Motor Function Classification System Level IV or V Cerebral Palsy, are cared for by respiratory specialist or receive daily respiratory treatments (oxygen, ventilation, airway clearance device, medications).
    - The Gross Motor Function Classification System (GMFCS) levels are determined by parent-report using a validated parent questionnaire.[74] The family chooses the most accurate description of their child, and this corresponds directly to their GMFCS level based on their age.
    - Need for specialty respiratory care and/or respiratory treatments is self-reported

Screening procedures continue until someone is deemed ineligible. Once deemed ineligible, the individual is thanked, and the interaction concludes. Screening results and reasons for ineligibility will be retained by study personnel.

Study Endpoint Measures and Assessment Procedures

Primary Study Endpoints - Feasibility, Acceptability, Fidelity: The specific measures and pre-specified definitions of success are listed in **Section 3**. These measures will be summarized between each of the three waves with protocol adjustments made for any measures below the definition of success.

Clinical Endpoints:

- Primary clinical outcome is severe respiratory illness, defined as respiratory diagnosis requiring hospitalization. Respiratory diagnosis includes discharge diagnosis of any of the following: asthma, pneumonia

(community or hospital acquired), bronchiolitis, influenza, upper or lower respiratory tract infection, tracheitis, aspiration pneumonia/pneumonitis, chronic lung disease, respiratory failure.[120] Field-testing assessment of this endpoint with trained research personnel at study sites demonstrated inter-rater reliability (Kappa) > 0.9.

- Secondary outcomes include: total hospital days during severe respiratory illness, numbers of systemic steroid courses, systemic antibiotic courses, respiratory ED visits, and death. Systemic corticosteroid course is defined by oral or parenteral corticosteroid prescribed for respiratory diagnosis, including hydrocortisone, prednisone, prednisolone, or methylprednisolone at least 1 mg/kg/day (or 30 mg/day) x minimum 3 days, or dexamethasone at least 0.15 mg/kg/day (or 10 mg/day) x 1 or more days. Physiologic or stress replacement doses in adrenal insufficiency are excluded. Systemic antibiotic course is defined by oral or parenteral antibiotics prescribed for respiratory diagnosis x minimum 3 days. The specific antibiotics are derived from IDSA pediatric pneumonia guidelines[121] and published literature.[122] Respiratory ED visits are any ED visits not resulting in admission and have a discharge respiratory diagnosis.

Additional Assessment Measures:

MEASURES	SOURCE	MEASURE DETAIL
Covariates		
Child and Caregiver Demographics	Survey	Child: age, gender, primary language, race/ethnicity, payer, family structure Caregiver: relationship, age, gender, language, race/ethnicity, education, health literacy,[114] income, rurality
Confounders		
Child Clinical Characteristics	Electronic health record	Organ systems affected by chronic conditions, subspecialists in past year, medical technologies used (e.g., tracheostomy, gastrostomy, etc.), duration of enrollment clinical program, numbers of ED visits and hospitalizations in past year, and respiratory treatments at time of enrollment (medications and devices)
Caregiver Strain	Survey	Caregiver Strain Questionnaire (CGSQ);[115]– mean global, objective, subjective scale scores Mental health (PHQ2)[116]
Theory / Mechanism		
Capability	Survey	Family Caregiver Activation in Transition Measure (FCAT)[117] – mean composite score Caregiver General Self-Efficacy Scale (GSES)[118] – mean composite score
Opportunity	Survey	Family Experiences with Care Coordination (FECC)[119] - % top-box score for selected items
Motivation	Text logs	Confidence Responses mHealth texting (weekly score 1 through 10)

Assessment Procedures. Feasibility, acceptability and fidelity endpoint data will be collected during each of the three waves by research personnel reviewing study logs, conducting monthly chart reviews, and

administering surveys (by telephone, in person, or sending electronic self-administered links) with caregivers randomized to intervention. For active control groups participants, feasibility of assessments will be evaluated by completion rates at study exit. Caregiver and child measures above will be recorded at baseline, endpoints will be recorded at study exit (6 months after T0). Caregiving measures, which may change as a result of the intervention, will be collected at baseline and study exit. In addition, intervention and active control caregivers will be debriefed at study exit on their experiences in the study, and asked for feedback on the strengths, weaknesses and any concerns about the protocol. Between each wave and after the third wave, clinical teams at each site will be debriefed on strengths, weaknesses, and concerns about the protocol.

Reliability of Assessment Measures. The CP GMFCS measures and all the caregiving measures have been well-documented as reliable in the literature.[11,74,115-119] We have separately established the reliability of identifying respiratory illnesses in our preliminary research (Kappa > 0.9). We will ensure reliability in data collection through direct observation, data auditing, establishing clear data dictionaries / definitions, using uniform variable definitions, and a central data repository coordinated and maintained by UW.

8.2 SAFETY ASSESSMENTS

Safety assessments are not conducted as a part of this protocol.

See **Section 10.1** for Safety Oversight Details.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, **whether or not considered intervention related. Any medical or psychiatric condition that is present or within the expected trajectory of the child's chronic condition at the time that the participant is screened will be considered as baseline and not reported as an AE.**

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **Probably Related** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

- **Potentially Related** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, report from an involved clinician, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Any medical or psychiatric condition that is present or within the expected trajectory of the child's chronic condition at the time that the participant is screened will be considered as baseline and not reported as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent. The project manager will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each monthly assessment, the research staff or caregiver self-administered questionnaire will inquire about the occurrence of AE/SAEs since the last month. Events will be followed for outcome information until resolution or stabilization.

In our consent materials, we will describe the specific procedures for handling each of the types of potential incident. These procedures will be based on those in previous projects and include:

1. The staff member who suspect or learns of any adverse event will immediately begin the adverse event case report form in REDCap.

2. The staff member who suspects or learns of any adverse event will immediately contact the project manager and PI / site PI who in turn will make an immediate judgment as to whether to report it to the authorities or whether additional action is warranted to protect the child's or participant's safety.

3. The PI will decide on a course of action, consulting with an attorney and expert consultants as necessary. This course of action will usually follow the clinic's existing guidelines and practices, with consideration of any pertinent legal or ethical issues related to it. For instance, a clinician would normally carry out child abuse reporting after it is deemed necessary. The course of action undertaken will be documented on the adverse CRF.

4. Serious adverse events (e.g., suicidal intent, child abuse reporting) will be reported immediately to the IRB and Safety Monitoring Committee, per their reporting guidelines, whereas more mild adverse events (e.g., mild distress following survey administration or coaching) will be compiled on an annual basis and reported to the IRB.

5. The Data Monitoring Committee will review all adverse event reports and determine whether additional steps are necessary (See **Section 10.1)**

6. As part of the informed consent process, study staff will provide subjects and their parent/guardian a specific name and phone number of a person to contact in case of an adverse event.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event. Adverse events meeting the guidelines for required reporting to

the IRB will be reported according to UW IRB reporting guidelines (see https://irb.wisc.edu/manual/investigator-manual/post-approval-responsibilities/reportable-events/?tab=reporting-requirements). A copy of IRB-reportable events will be sent the ICTR DMC Protocol Review Manager within the same time frame as required for reporting to the IRB. A report compiling all adverse events will be reviewed by the DMC on an annual basis.

All serious adverse events will also be reported to the NICHD according to their policy. See https://www.nichd.nih.gov/grants-contracts/process-strategies/policies/data-safety.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

1. Detection of previously undisclosed dangerous or potentially dangerous situations or occurrences. It is possible that families may disclose information to our research staff that indicates they have been or may be subject to dangerous situations. Situations or occurrences that might be disclosed to or observed by the research staff and would require the staff to complete an incident report include but are not limited to child abuse, imminent threat to self, and imminent threat to others (even though our questionnaires will not specifically ask about these issues). General procedures we will take in these situations are outlined below. Specifically, any suspected child abuse must immediately be reported to the Wisconsin Department of Child Protective Services (CPS) or Los Angeles Department of Child and Family Services (DCFS) and, if any immediate danger is possible to the child, family or other individual, to the local Police Department. The social worker on call will be notified immediately if a participant discloses suicidal ideation or domestic violence. In any adverse situation possibly related to the research study, Dr. Coller, Dr. Lerner, and the IRB will also be notified.

2. Accidental disclosure of confidential material. It is possible that despite careful procedures to protect private information, there could be accidental disclosure of confidential information. To protect against accidental disclosure, we will only use ID numbers on questionnaires and will keep any links to personal identifying information on REDCap. In the case of any breach of confidentiality we will notify the participant, PI and site-PI, and the IRB.

3. Distress experienced during or after completing research survey. It is unlikely for parents to experience distress in typical clinical encounters or when given the survey questions, and if any distress does occur it would most likely be mild and transient. However, we are attentive to the possibility that answering personal questions may be upsetting for some individuals. To protect against this distress, participants will be made aware that participation in the research study is entirely optional, has no effect on their children's medical care, that they may choose not to answer certain questions and that they may end their participation at any time. If a participant expresses distress, the research assistant will immediately notify PI / site-PI. Participants will also be given phone numbers (in the informed consent process) to contact the study PI and the IRB in case of distress during or after the study interview. In addition, on-call social workers at our clinics will be notified to help with any distress that may arise.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB following reporting guidelines (see https://irb.wisc.edu/manual/investigator-manual/post-approval-responsibilities/reportable-events/?tab=reporting-requirements). A copy of such reports will be sent to the to the Data Coordinating Center (DCC).

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

9 Statistical Considerations

9.1 STATISTICAL HYPOTHESES

- Primary Feasibility, Acceptability, Fidelity Endpoint(s): RE-PACT's primary outcomes will be analyzed descriptively, and evaluate feasibility, acceptability, fidelity using multiple approaches. Each outcome will be

assessed against our pre-specified measures of success, e.g., achieving at least 80% enrollment. By conducting iterative refinements over three waves of implementation, we expect to achieve success in all measures. We will assess all participant feedback using both quantitative and qualitative data to determine what study design changes would enhance a large-scale RCT. We will use inductive content analysis of qualitative data.

- Secondary Efficacy Endpoint(s): ***To inform a future large multisite RCT, we will test*** differences between treatment (I or AC) groups in the primary and secondary respiratory illness outcomes. Our goal with these analyses is to estimate effect sizes for the differences between groups. The primary clinical outcome is severe respiratory illness rate, defined as the total number of severe respiratory illnesses divided by the person-months over the 6 months period. The severe respiratory illness rate will be analyzed with negative binomial (NB) regression models to account for overdispersion in the count data. In the primary analysis, univariate NB regression analysis will be conducted with study arm as a predictor variable. Study site will be a stratification factor to account for stratified randomization. The observed effect size of the analysis will be quantified in terms of relative risk (RR) and reported along with the corresponding 95% confidence interval. A generalized linear mixed effects model with a logit link function and subject specific random effects will evaluate **longitudinal changes** in the severe respiratory illnesses within and between study arms. An autoregressive (AR) correlation structure will account for within subject correlations. In this analysis, presence/absence of severe respiratory illness at the monthly assessments will be the dependent variable; study arm will be included as a predictor variable, and study site as a stratification variable to account for the stratified randomization. To **investigate theoretical mechanisms**, we will test the mediating effect of caregiver capability, opportunity, and motivation (COM-B)[113] measures on the relationship between intervention and respiratory exacerbations.

9.2 SAMPLE SIZE DETERMINATION

We will enroll a total of 90 participants. Wave 1 will contain 10 participants (5 UW, 5 UCLA); Wave 2 will contain 20 participants (10 UW, 10 UCLA); Wave 3 will contain 60 participants (30 UW, 30 UCLA). Based on this team's preliminary work, eligible children average one severe respiratory illness per year and we estimate 50% of participants will experience at least one respiratory illness during the period of enrollment. We expect to be able to maintain contact and collect data from ≥90% of the participants at the final follow-up, evenly divided between intervention and control groups. We assume this sample will not be powered to establish the efficacy of the intervention; however, it will provide a sufficient sample to determine feasibility and estimate effect sizes which will be used for power calculations in the future large RCT. The following table shows the attainable power levels for detecting various differences in severe respiratory illness rates (primary clinical outcome) between study arms at the two-sided 0.05 significance level, based on a NB regression model with an overdispersion parameter of ϕ=1.0.

Attainable power levels for detecting differences in severe respiratory illness rates between arms at the two-sided 0.05 significance level based on a NB regression model, assuming a sample size of 45 subjects per arm with a missing value rate of 10% or less.

	Number of severe respiratory illnesses in intervention arm over 6-month Follow-up period				
Relative Risk (RR)	5	10	15	20	25

(Control vs. Intervention)	(λ=0.02)*	(λ=0.40)*	(λ=0.06)*	(λ=0.08)*	(λ=0.10)*
3.0	19%	29%	38%	45%	52%
4.0	31%	41%	59%	68%	75%
5.0	42%	62%	74%	83%	88%

*Severe respiratory illness rate per patient-month

Hence, large effect sizes with RRs ranging between 3.0-5.0 for comparing the severe respiratory illness rates between study arms will be detected with 19-88% power at the two-sided 0.05 significance level.

9.3 POPULATIONS FOR ANALYSES

Given that the intervention being tested requires parent adherence to recommendations to achieve success, we will use an intention-to-treat analysis approach.

While we anticipate that the intervention and control groups will be similar due to random assignment, we will adjust for any variables in our analysis that are not equal between the groups given the small sample size. In addition, we will analyze for any effect of primary home language on the study outcomes, as this may affect families' ability to navigate systems of care in the U.S.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This section outlines the statistical analysis strategy and procedures for the study. We plan to use the primary outcome data to assess the RE-PACT intervention's feasibility, acceptability, and fidelity. We anticipate being underpowered to assess efficacy using the clinical endpoints of the intervention in this pilot study. The clinical outcome endpoints will be used to develop an estimate of effect size. Categorical variables will be displayed as percentages, and continuous variables as means with standard deviations (if normally distributed) or medians with IQR (if skewed). For inferential statistics, two-sided p-values <0.05 will be considered statistically significant. A detailed Statistical Analysis Plan (SAP) describing all details of the analyses has been developed and will be finalized prior to the database lock and the analysis of the final study data.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

RE-PACT's primary outcomes will be analyzed descriptively, and will evaluate feasibility, acceptability, and fidelity. We will assess the outcomes against our pre-specified measures of success, e.g., achieving at least 80% enrollment. We will evaluate the actual vs expected performance of each intervention component (mHealth texting surveillance, action planning, just-in-time adaptive coaching intervention response) and completeness of each data collection element in intervention and active control groups. We will also determine overall positive, neutral, and negative reports of feasibility and acceptability using content analysis of qualitative data, similar to our previous intervention feedback research. We will explore any patterns if / when challenges emerge, e.g., enrollment refusal or drop out, low reported use of the intervention activities.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Clinical Outcomes. We will test differences between treatment (intervention or control) groups in the primary and secondary respiratory illness outcomes. Our goal with these analyses is to estimate effect sizes for the differences between groups which will allow precise sample size calculations for a future large-scale trial.

Primary clinical outcome is the severe respiratory illness rate, defined as the total number of severe respiratory illnesses divided by the person-months over the 6-month follow-up period. The severe respiratory illness rate will be analyzed using a negative binomial (NB) regression model to account for overdispersion in the count data. For the primary analysis, univariate NB regression analysis will be conducted with study arm as a predictor variable. Study site will be included as a stratification factor in the primary analysis to account for stratified randomization. The observed effect size of the analysis will be quantified in terms of relative risk (RR) and reported along with the corresponding 95% confidence interval.

As a secondary analysis, multivariate NB regression analysis will be performed to compare the severe respiratory illness rates between study arms. In this analysis, clinical and demographic characteristics will be included as covariates in an initial non-parsimonious model. The least absolute shrinkage and selection operator (lasso) and elastic net penalty methods for negative binomial regression models will be utilized to identify a parsimonious model with independent covariates. These methods are considered state-of-the art techniques for variable selection (Wang Z., et al. Stat Methods Med Res. 2016).

Longitudinal changes in the severe respiratory illnesses within and between study arms, will be evaluated with generalized linear mixed effects model with a logit link function and subject specific random effects. An autoregressive (AR) correlation structure will be utilized to account for within subject correlations. In this analysis, the presence/absence of severe respiratory illness at the monthly assessments will be the dependent variable, study arm will be included as a predictor variable and study site as a stratification variable to account for the stratified randomization.

Secondary clinical outcomes include total hospital days during severe respiratory illness, numbers of systemic steroid courses, systemic antibiotic courses, respiratory ED visits and death. The numbers of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits over the 6 months follow-up period will be analyzed using NB regression analyses in in a similar fashion as described above the for primary outcome. Observed effect sizes will be reported along with the corresponding 95% confidence intervals. The presence/absence of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits will be documented at the monthly assessments and longitudinal changes within and between study arms will be analyzed using generalized linear mixed effects modeling with a logit link function and patient specific random effects. The total number of hospital days over the 6 months follow-up period will be analyzed using analysis of variance (ANOVA) with study site as stratification factor. In a secondary analysis, analysis of covariance (ANCOVA) will be performed where clinical and demographic baseline characteristic will be included as covariates and the lasso method will be used to identify a parsimonious

model. Longitudinal changes in the number of hospital days per hospitalization will be analyzed using a normal mixture linear mixed effects model with patient specific random effects. The normal mixture component will be in included in the model to capture the probabilities of a hospitalization at the monthly follow-up. Parameter estimation will be performed using the Expectation-Maximization algorithm which is the standard method for parameter estimation of mixture models.

Missing values**,** e.g., due to loss of follow-up, missing monthly visits, will be evaluated by conducting a sensitivity analysis comparing the results obtained from the complete case analysis to the results obtained by imputation-based analyses. Specifically, multiple imputation (MI) will be used to impute missing values of primary and secondary clinical outcomes. For monotonic missing values data structures, we will use regression-based MI techniques. For non-monotonic missing value data structure, on the other hand, we will use Markov Chain Monte Carlo based imputation techniques.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Study confounders and covariates (see **Section 8.1** for specific measures) will be summarized and compared at baseline. Given the small sample size, we will conduct adjusted and unadjusted analyses for variables that are statistically significantly different at baseline.

9.4.6 PLANNED INTERIM ANALYSES

Iterative refinements over three waves of implementation will be conducted by reviewing feasibility, acceptability, and fidelity measures from previous waves.

9.4.7 SUB-GROUP ANALYSES

There are not planned sub-group analyses aside from the secondary analyses described above.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

We will test the mediating effect of caregiver capability, opportunity, and motivation (COM-B) measures on the relationship between intervention and respiratory illness outcomes. The mediating effects will be evaluated by conducting a multi-step analysis approach. In the initial step, NB regression analyses will be conducted to examine whether there are differences in respiratory illness outcomes (number of severe respiratory illnesses, systemic steroid courses, systemic antibiotic courses, and respiratory ED visits) between the intervention and control arm, as described in the previous section. In the next step, we will conduct a sequence of univariate analyses, by regressing each potential mediator variable (caregiver capability, opportunity, and COM-B) on the binary study arm variable. If significant associations between the potential mediator variables and study arm are detected, we will regress the respiratory illness outcomes on both the mediator variables and study arm indicator variable using ANCOVA. The

mediation effect for each potential mediator variables will then be tested using the Sobel z-test based the slope parameter estimates from the corresponding regression models.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

IRB-approved consent forms in English or Spanish (per participant preference) describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All study participants will undergo informed consent including consent to view the child's medical record. In all informed consent materials, we will make clear to potential participants that their participation is voluntary, and they may choose to leave the study at any time. Potential participants identified from the clinic registry and, following an opportunity to opt-out of further contact, their interest and eligibility will be determined through a structured screening. If a family is interested in participation, they may contact the study team or a member of the study team will contact them for informed consent. Enrollment visits will be conducted either in person or remotely (via WebEx). All consent forms will be signed electronically using a REDCap form. If a family enrolls in person, study staff will supply an iPad on which to sign the consent form. If a family chooses to enroll remotely, study staff will send the family a REDCap survey link containing the consent form. All subjects will also receive a hard copy of the consent form for their records. Informed consent materials will be provided in private spaces in both written and verbal formats, will review in detail the study design, including random assignment to the intervention and control groups, potential risks of participation, protections against risk, and the rights of human research subjects. The informed consent process will also include review and signing of the HIPAA waiver, allowing researchers to review the child's medical records. Parents will be able to decline parts of the study and still participate in other parts, and can revoke their consent at any point.

Because this research involves children with severe cerebral, it is expected that all subjects will lack capacity to give meaningful assent. Assent will not be obtained.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Wisconsin. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by University of Wisconsin research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Wisconsin.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies. It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see https://grants.nih.gov/policy/sharing.htm). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and

security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Wisconsin. After the study is completed, the de-identified, archived data will be stored at the University of Wisconsin, for use by other researchers including those outside of the study. Permission to transmit and to store data at the University of Wisconsin will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Ryan Coller, MD, MPH, Study PI	UW ICTR DMC
Gemma Warner, CCRC, MSSW, Project Manager	
Carlos Lerner, MD, MPhil, UCLA PI	

10.1.6 SAFETY OVERSIGHT

This trial collects information that is typically collected during routine care, such as perceptions of child health, demographic and clinical information, caregiving experiences, and clinical plans for health concerns. Some of this information is potentially sensitive and could pose risk to subjects if involuntarily disclosed. Therefore, we will institute the following procedures to protect subject safety:

Data and Safety Monitoring Committee. Although we anticipate the nature of our questionnaires and study design to pose minimal risk, we will plan to create a Data Safety and Monitoring Board, independent from the investigator team and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The UW Institute for Clinical and Translational Research (ICTR) has established a Data Monitoring Committee (DMC) to provide a key resource for UW-Madison investigators conducting clinical research. This DMC provides investigators services to ensure appropriate measures are in place to promote subject safety, research integrity and compliance with federal regulations and local policies for single site and multisite clinical research protocols in need of DMC review (as determined by the Principal Investigator (PI), the funding agency, the local Scientific Review Committee, or the local IRB, and for which no DMC exists).

We plan to utilize the UW ICTR Data Monitoring Committee to oversee the study across both participating sites. The DMC is supported in its mission of safety and compliance by experienced ICTR staff to provide administrative assistance, experienced members representing a diversity of backgrounds, skills and knowledge, and the use of the Research Electronic Data Capture (REDCap) tool which provides data management functionality by allowing the development of eCRFs and surveys to support data capture. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study.

The DMC members will review protocol-specific reports created by statisticians or delegates using data pulled from the REDCap data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be requested, and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator.

In providing oversight for the conduct of this study, the ICTR DMC will meet every year during the 2-year study to review all adverse events. Additional meetings may be scheduled as determined by the DMC or as requested by the PI. There are no predefined stopping points for this study. All reportable events will be submitted to the DMC and the Health Services IRB in accordance with their reporting guidelines. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

Adverse Event Protocol. The protocol for identifying and handling adverse events is outlined in **Section 8.3, Adverse Events and Serious Adverse Events** and will be revised with the DMC and included in the IRB application. Prior to the initiation of any data collection, the UW-ICTR DMC will review and approve the adverse event protocol.

10.1.7 CLINICAL MONITORING

Given the nature of the RE-PACT intervention (with plans to adapt the protocol to improve feasibility, acceptability and fidelity during 3 successive waves), the study team will monitor its own activities, as described in **Section 10.1.8, Quality Assurance and Quality Control.**

- Independent audits will not be conducted as a part of this protocol

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. All sites will follow a common quality management plan.
Quality control (QC) procedures will be implemented as follows:

Informed consent - Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data - Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity - Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations - The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study.

Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs) and clinical laboratory data will be entered into REDCap managed by the University of Wisconsin, a 21 CFR Part 11-compliant data capture system provided by the University of Wisconsin Institute for Clinical and Translational Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or entered directly from a secure self-administered questionnaires (surveys) sent from REDCap to participants.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for the duration required by the IRB and the sponsor, as required by local regulations. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.
These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.
Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the study PI. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3. Even though the final dataset will be stripped of identifiers prior to the release for sharing, we believe that with the small sample size and relative uniqueness of these conditions, there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

Data prepared for distribution under a data-use agreement will be redacted to ensure privacy of study participant identity yet allow analyses to occur by other investigators. The data-use agreement will include requirements to protect participants' privacy and data confidentiality. It will prohibit the recipient from transferring the data to other users and require that the data's security be protected by standard means and be used for research purposes only. Furthermore, we are required to honor the conditions under which we gained access to these data and will require that any applicants utilizing such data to perform data analyses per the data use agreement uphold these conditions. The method of distribution will be by request to the study PI. After a requestor completes the data-sharing agreement, requestor will receive a limited dataset mailed by CD or emailed through UW-Madison secured email systems that require users to create an account and sign-in with a username and password in order to receive and download any type of sensitive data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership, through the involved universities, have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance

QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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