Planning for Real World Impact

Methods, models, & frameworks for planning pragmatic research.

August 11: 8am - 6pm MDT

August 12: 7:30am - 4:30pm MDT

Breakfast Session

Early Career Investigator Consultations

1. Brian Anderson, MD, MSc
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2. *Title: Pragmatic Trial of Psilocybin Therapy in Palliative Care*

Objective of the study:
This will be the first multi-site double-blind randomized controlled clinical trial (N=80) to evaluate the efficacy, safety and implementation of administering psilocybin therapy to distressed terminally-ill adults in real world outpatient palliative care settings. The trial will evaluate the efficacy of psilocybin therapy, compared to an active control, primarily in treating demoralization, but also in addressing secondary outcomes such as depression, anxiety, quality of life, and, in a sub-set of participants, chronic cancer-related pain. Importantly, this trial will evaluate how clinicians with prior experience administering psilocybin therapy in legal research settings can effectively train palliative care clinicians, with no prior experience with psilocybin therapy, to administer the intervention.

Significance:
Demoralization is a clinically significant and measurable form of existential distress characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life. Demoralization is associated with physical symptom burden and poor quality of life, and it is highly prevalent (13-53%) among patients with serious medical illness (e.g., advanced cancer, AIDS, ALS, etc.). In some patients, demoralization occurs independently of major depressive disorder (MDD), and in cancer patients, demoralization can be more strongly associated with a desire for hastened death than is MDD. No medications have an FDA indication for the treatment of demoralization, and no FDA-approved medications have been reliably shown to improve demoralization. There exist psychotherapies that have been especially designed for the treatment of demoralization, hopelessness, and despair in palliative care patients, but none have demonstrated efficacy when compared to an active control condition. And yet, in early-phase, explanatory trials the experimental medication, psilocybin, when combined with psychological support (henceforth referred to as "psilocybin therapy"), has shown promise in addressing demoralization and distress in patients with serious medical illness (e.g., cancer or long-term AIDS survivors), demonstrating between-group standardized effect sizes in clinical outcomes on the order of 0.8 in two double-blind RCTs. However, over the last 20 years, only a total of 110 patients with serious medical illness across 4 studies have been administered psilocybin therapy in clinical research. Moreover, much remains to be learned on the administration of psilocybin to a diverse population of palliative care patients. Participant expectancies may have significant effects on clinical outcomes because treatment allocation is unlikely to be adequately masked when psilocybin is compared to an inactive control. And to date, all psilocybin clinical trials have been conducted as explanatory trials within psychiatric research settings with limited generalizability, and not as pragmatic trials in real world clinical settings.

3. *Specific Aims:*
1) Primary clinical outcome: Psilocybin therapy (vs control) will lead to a significantly greater reduction in demoralization at 1-week and 6-8 weeks post drug in patients with a broad spectrum of terminal diagnoses in palliative cate settings.
2) Implementation outcome: We will evaluate the feasibility and fidelity with which palliative care clinicians can learn psilocybin therapy through apprenticeship and close supervision from clinicians with experience administering this intervention in research settings.
3) Secondary clinical outcomes: Psilocybin therapy (vs control) will lead to significantly greater improvements in depression, anxiety and quality of life at 1-week and 6-8 weeks post drug.

4) Exploratory clinical outcome: In a subset of participants with chronic cancer-related pain at enrollment, psilocybin therapy (vs control) will lead to a clinically meaningful standardized effect size in measures of pain 1-week and 6-8 weeks post drug.

4. This is my main question for the consultation: What frameworks would be most appropriate for assessing the implementation of teaching psilocybin therapy to palliative care clinicians in real world clinical settings?

5. The trial is partially funded by philanthropy. I plan to apply for a K23 at NCCIH (PA-20-205) and the NPCRC Kornfeld Scholars Program to support my effort on the trial.

6. Key question: What types of pragmatic study designs, methods, or measures would be best for testing my hypotheses?

Colorado Pragmatic Research in Health Conference
Pragmatic Research Early Career Investigator Consultation Opportunity

Project Title:

Using the positive deviance approach to establish evidence-based best practices in pediatric care escalation: Identifying and studying high performing hospitals

Applicant:
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Brooke Dorsey Holliman, PhD

Target funding agencies
CHCO RI Research Scholar Award (September 2020)
AHRQ K08 (February 2021)

Challenges and key question
Selecting the appropriate pragmatic research planning framework (e.g., RE-AIM/PRISM, EPIS, others)
Specifically, in aim #2 I hope to evaluate the implementation of rapid response systems so that, once I establish best practices from the science in the rest of the grant, I am prepared to develop and test a new intervention prospectively in the next step in my research program.

A. Specific Aims

Over *** children and adolescents hospitalized admitted to an acute care (non-ICU) unit in the United States require transfer to an ICU each year [***citation***]. These patients have a nearly 3x increased risk of death during their hospitalization and longer average ICU length of stay than other critically ill children [10-12]. Each emergent transfer from acute care units to ICUs for immediate initiation of life-sustaining interventions adds an additional $99,773 in post-hospitalization costs compared to non-emergent transfers occurring earlier in the deterioration process [14]. For transfers following a cardiopulmonary arrest on an acute care unit, the odds of post-arrest survival decrease by 23% compared to those in an ICU [15], and overall survival rates improve as a higher proportion of resuscitations occur in ICUs compared to acute care units [16]. Rapid Response Systems (RRSs) aim to improve these outcomes by assisting acute care clinicians with early identification of critical illness and facilitation of effective intervention. My past research showed that RRSs are present in 100% of hospitals that care for children, although there is substantial RRS variation between hospitals [7]. In that multisite survey study, we identified associations between specific RRS components and perceived improvement in patient outcomes, however these components were only used in a subset of hospitals. Additionally, many respondents felt their current RRS over-identified risk of deterioration and led to unnecessary resource utilization. The true effect of RRS variation on RRS-related patient outcomes like emergency ICU transfer, cardiopulmonary arrests outside the ICU, and in-hospital mortality is unknown, however, because no prior studies have collected or evaluated objective, multisite, RRS-related patient outcomes. Without this critical multisite study, the existing evidence-base guiding RRS development and implementation is weak and devoid of defined best practices [17-19] despite the significant cost and institutional support provided to RRSs in hospitals across the country [***citation***]. Importantly, comparison of published, single site RRS reports suggest significant variation in RRS-related patient outcomes that highlights a substantial opportunity associated with improved knowledge of RRS effectiveness and implementation. To fill this gap in knowledge, it is critical that we evaluate the effect of RRS variation on patient outcomes to define best practices that will inform the development of effective, disseminatable interventions designed for implementation.

The objective of this proposal is to establish best practices in pediatric care escalation using the positive deviance approach by (1) characterizing existing hospitals by their RRS-related patient outcomes and (2) identifying practices associated with top performance and successful implementation. Our central hypothesis is that—although the published evidence is weak in aggregate—there are unidentified practices at top performing hospitals that will inform the future development and implementation of effective, disseminatable RRSs.

I am well positioned to accomplish the objectives of this proposal. I have preliminary data and collaboration commitments through the Pediatric Research in Inpatient Settings (PRIS) Network that will facilitate multisite study. Under the direction of my primary mentor, Dr. Amanda Dempsey, I have surrounded myself with a mentorship team comprised of experts who will ensure my success, including members of the PRIS Executive Council as well as experts in the field of care escalation. This team will facilitate my development of necessary skills in biostatistics, qualitative and mixed methods, dissemination and implementation science, and leadership of multisite research. To accomplish the objectives of this proposal, I propose a multi-method strategy using the positive deviance approach with the following specific aims:

Aim 1: To (a) characterize hospitals that care for children by their RRS-related patient outcomes and (b) evaluate associations between these outcomes and RRS characteristics. I will compare patient outcomes between PRIS hospitals to identify high performing 'positive deviants' using rates of emergency ICU transfer, cardiopulmonary arrests, and in-hospital mortality among acute care patients adjusted for hospital

type and acuity. I will then evaluate associations between these adjusted outcomes and specific RRS components identified in my recent national survey of PRIS hospitals [7].

Aim 2: To use qualitative methods to generate additional hypotheses about practices that allow for top RRS performance and implementation. I will interview bedside nurses and physicians from 'positive deviant' and 'negative deviant' hospitals to identify practices that allow them to achieve top performance and evaluate facilitators and barriers of successful RRS implementation guided by the *** framework.

I will apply the findings of this proposal to my immediate next step of applying RRS best practices to the development and implementation of an evidence-based intervention in my subsequent AHRQ K08 application. Ultimately, this will allow me to accomplish my long-term career goal of becoming an independently funded pediatric hospitalist researcher focused on improving the quality of care for hospitalized children who are deteriorating through the dissemination of best practices, development of evidence-based interventions, and use of pragmatic trials to test the implementation of these interventions in real-life, inpatient settings.

MEHTA, POOJA

I am requesting consultation regarding **Aim 1a** of my AHRQ K08 proposal. Specifically, the use of the analytic deliberative model for stakeholder engagement (versus should I use a user-centered design approach)?

As background, here are my aims (much abbreviated):
We hypothesize that interventions to improve habit formation including a medication action plan and *MedVenture* can increase treatment adherence in adolescents with EoE. Thus, the overall goal of this proposal is to determine the effect of our habit-targeting interventions on medication adherence in adolescents with EoE using an adaptive trial.

Aim 1: Optimize two novel EoE self-management interventions targeting habit formation that can be used in the clinical setting (aim 1a) and home setting (aim 1b).

1a. Create a "Habit Action Plan" that can be used in clinical practice for adolescents with EoE. With the input of adolescents with EoE, their parents, behavior change experts, psychologists, gastroenterologists, and nurses with expertise in EoE, we will create a Habit Action Plan specific to adolescents with EoE that incorporates habit formation and planning rather than symptom control.

1b: Perform beta testing of *MedVenture* – a home-based mobile health tool we designed to improve habit formation and medication adherence – in adolescent patients with EoE.

Aim 2: Conduct a pilot adaptive trial using both interventions from Aim 1 (Habit Action Plan and *MedVenture*) using a sequential, multiple assignment, randomized trial (SMART) design. A SMART not only allows for the testing of each individual intervention (the Habit Action Plan and *MedVenture*) but also tests the effects of sequential interventions and identifies possible tailoring variables to improve adherence. We will use the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework, to measure feasibility, acceptability, the effect of each intervention on medication adherence, and EoE disease outcomes.

Excerpt from "Approach" – I apologize that it is in draft form.

1a. Create a "Habit Action Plan" that can be used in clinical practice for adolescents with EoE.

Rationale: Action Plans are a type of behavioral change technique in which a person outlines actions needed to reach one or more goals, chooses measurable and attainable action steps to achieve the goal(s), and identifies who is responsible for each action step including who will support him/her. Action plans to promote better medication adherence frequently rely on symptom management however newer research suggests that medication adherence can best be improved if interventions focus on behavior change and creating a medication-taking habit (REF systematic review). In Aim 1a, we will create a Habit Action Plan in which we encourage medication taking through planning and habit formation rather than focusing on symptoms.

Pilot Data: From February 2018 to March 2020, we performed a cross-sectional study of 117 children between 5-18 years old with EoE which sought to 1) determine adherence rates among children with EoE, 2) describe factors related to adherence, and 3) determine the association between adherence and EoE symptoms. Adherence rate was determined based on self-reported number of doses taken in the last week over the total number of prescribed doses per week. Subjects completed the Pediatric Eosinophilic Esophagitis Symptoms Score V2.0 (PEESS) – a validated measure of EoE symptomatology, a disease history and demographics questionnaire, and the "Medication-Taking Checklist" (MTC). The MTC is a study-specific clinical tool designed to assess behaviors associated with medication-taking. It was informed by health-behavior theory (REF paper 16-19) and was modified with the input of patients, physicians, psychologists, and nurses with expertise in EoE and medication adherence. We found that adolescents (N=57 adolescents out of N=117 children total) had lower adherence rates than younger children (76.2 ± 24.5% versus 88.0 ± 18.7%, *P*=.005). Adherence rates were not associated with PEESS scores (*P*=NS) but instead, strongly correlated with the MTC score (Pearson's r of 0.65, *P*<.001 for child-reported adherence and Pearson's r of 0.74, *P*<.001 for parent-reported adherence). Additionally, we found that nearly

Medication-Taking Checklist (Child-report)	Association with child-reported adherence (Pearson r)	P-value	Medication-Taking Checklist (Parent report)	Association with parent-reported adherence (Pearson r)	P-value
Total Score	0.65	<.001	Total Score	0.74	<.001
Individual items			Individual items		
Takes swallowed steroids "as instructed"	0.56	<.001	Takes swallowed steroids "as instructed"	0.69	<.001
Takes swallowed steroids when difficulty swallowing	0.11	.21	Takes swallowed steroids when difficulty swallowing	0.18	0.058
Takes swallowed steroids when feeling well	0.54	<.001	Takes swallowed steroids when feeling well	0.65	<.001
Takes swallowed steroids even when very busy	0.45	<.001	Takes swallowed steroids even when very busy	0.63	<.001
Takes swallowed steroids on school days	0.59	<.001	Takes swallowed steroids on school days	0.62	<.001
Takes swallowed steroids on weekends/holidays	0.51	<.001	Takes swallowed steroids on weekends/holidays	0.68	<.001
Takes swallowed steroids when something unexpected happens	0.52	<.001	Takes swallowed steroids when something unexpected happens	0.52	<.001
Takes swallowed steroids when traveling	0.40	<.001	Takes swallowed steroids when traveling	0.57	<.001
Makes plans for when he/she will take swallowed steroids	0.35	<.001	Makes plans for when he/she will take swallowed steroids	0.38	<.001

Table 1: Correlation of Medication-Taking Checklist (MTC) to EoE adherence rates

every item on the MTC was significantly associated with both child and parent-reported adherence (**Table 1**).

Study Design and Participants: In Aim 1a, we will use the MTC as the foundation for our Habit Action Plan. Figure 2 depicts the organization of Aim1a and how it fits into the greater study design.

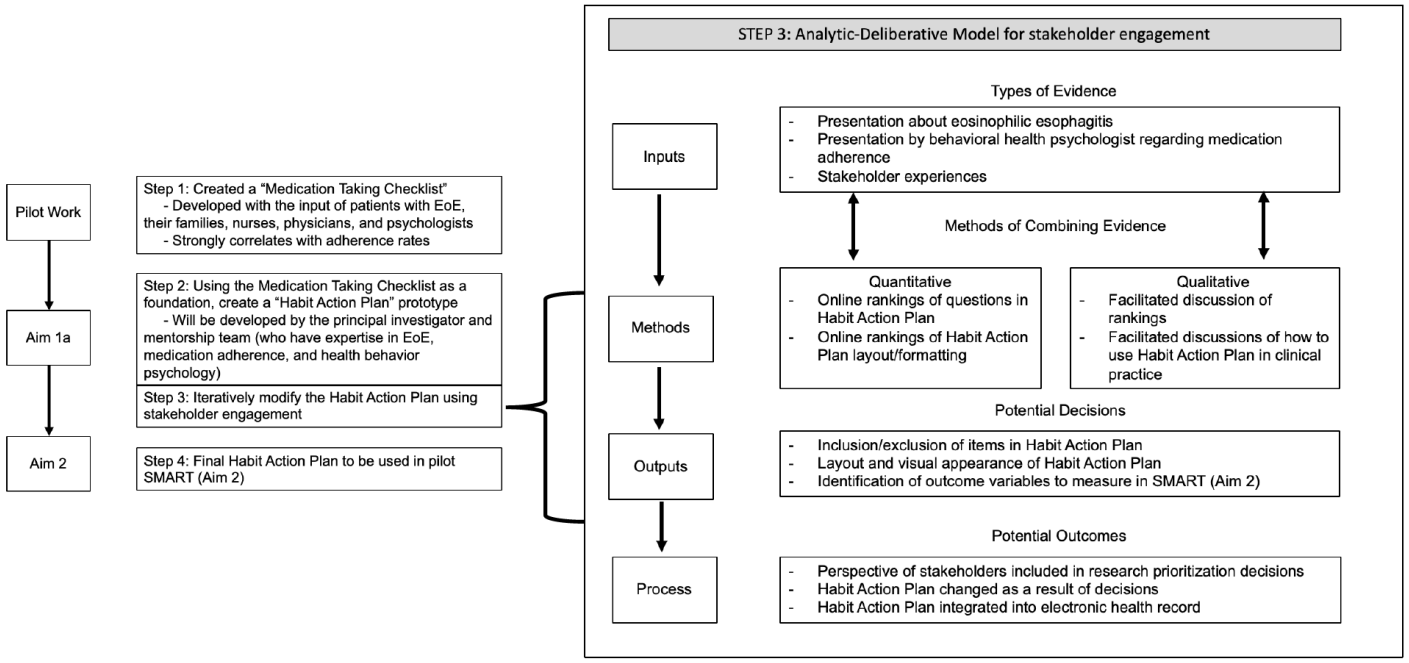

Figure 2: Study design for Aim 1a including description of stakeholder engagement methodology.

We will create a stakeholder panel to modify our Habit Action Plan. Stakeholders are defined as "individuals, organizations or communities that have a direct interest in the process and outcomes of a project, research or policy endeavor." (REF: 22707880) Since patients with EoE can be cared for by both allergists and gastroenterologists, our stakeholder panel will consist of experts in both fields. Because research in other fields has shown that difficulty integrating action plans into the electronic health record (HER) has limited the uptake of action plans, we will also include EHR specialists as stakeholders (REF). The stakeholder panel will consist of 3 adolescents with EoE, their caregivers, 2 pediatric gastroenterologists, 2 allergists, 1 nurse and 1 medical assistant specializing in pediatric gastroenterology, 1 nurse and 1 medical assistant specializing in pediatric allergy, 2 psychologists, and 2 EHR specialists. To recruit stakeholders, parents and patients will be approached in the Gastrointestinal Eosinophilic Diseases Program multidisciplinary clinic at the Children's Hospital Colorado. Stakeholders who are health care providers or hospital staff will be approached via email based on their expertise. Participating stakeholders will be given a $30 gift card as compensation for their time.

Data Collection, Management, and Analysis: We will use Analytic Deliberative Model for stakeholder engagement (22707880) (Figure 2). We will ask members of the stakeholder panel to 1) review the Habit Action Plan prototype, 2) suggest changes to the prototype, and 3) recommend outcomes to be assessed in the future SMART trial (Aim 2). All stakeholders will be emailed monthly updates with links to questionnaires eliciting feedback on the Habit Action Plan prototype and suggestions for outcome measures to be included in the SMART. There will be at least 4 monthly meetings with the stakeholder panel to review questionnaire responses and also engage in facilitated discussions. The meetings will be face-to-face and/or via Zoom. All meetings will be recorded for those who could not attend. Facilitated discussions will be led by Dr. Bethany Kwan (one of the PI's primary research mentors who has extensive experience in stakeholder engagement). After each meeting, the PI will email updates and decisions made to the entire stakeholder panel. Stakeholders will be encouraged to email the PI or meet with the PI separately if there is additional feedback.

Feasibility:

Potential Limitations/Alternative Approaches: Give the ongoing COVID-19 pandemic, we may have limited ability to recruit patients and families in person. The Gastrointestinal Diseases Program is doing multidisciplinary clinics via telehealth including research recruitment. We will offer all meetings virtually as well as in-person in order to account for potential impacts of COVID-19.

Deliverable: Aim 1a will result in the creation of a Habit Action Plan that will be used as an intervention in the pilot SMART (Aim 2). Aim 1 will also result in 1 manuscript about the creation of the Habit Action Plan.