CommunityRx-Hunger (CRx-H) Overall Statistical Analysis Plan (SAP)

NCT04171999

March 2, 2018

CommunityRx-Hunger RCT Statistical Design and Power

NIH funding will support a double-blind randomized controlled trial (N=640, 480 food insecure, 160 food secure) and qualitative research to evaluate the impact of CRx-H on adult and child outcomes. This research will fill important gaps in knowledge about how best to intervene in a hospital setting to support food insecure parents or caregivers with a hospitalized child. The study design and analytic plan incorporate best practices to ensure a robust and unbiased approach, drawing on the mixed methods and large scale clinical trials expertise of the multidisciplinary team. The CRx-H trial will be registered on clinicaltrials.gov in accordance with NIH policy. All reporting will comply with CONSORT guidelines. For each aim, we provide hypotheses.

Aim 1: Screening-based interventions target the highest-risk individuals in a population. Food insecurity screening recommended for use in the healthcare setting classifies people dichotomously as food insecure or not. But food insecurity is a dynamic and complex condition and we have found that a child's hospitalization is a triggering event for 19% of previously food secure caregivers. Healthcare systems are moving quickly to adopt a screening-based approach to intervening on food insecurity and other HRSNs, but little is known about what impact this new practice will have on food insecure people. The purpose of Aim 1 is to study the effect of a screening-based approach to delivery of the CRx-H intervention on caregiver self-efficacy and more distal caregiver and child health and healthcare outcomes.

Among caregivers of hospitalized children who screen positive for household food insecurity we will evaluate the longitudinal effects of CRx-H versus usual care on self-efficacy (primary outcome), severity of caregiver and child food insecurity, adult and child nutrition and health, and child healthcare utilization (secondary outcomes).

Hypothesis 1a. The intervention group will report higher levels of self-efficacy at 12 months compared to controls.

Hypothesis 1b. Adults in the intervention group and their children will have a higher rate of food security and nutritious intake at 12 months compared to controls and their children.

Hypothesis 1c. Children of caregivers in the intervention group will present sooner for the post-discharge follow-up visit and will have a longer interval to ER visit or hospitalization than children of control group caregivers.

RCT Strategy, Timeline, Methods, and Key Measures: After pretesting with 10 food secure and 10 food insecure caregivers, a consecutive sample of 640 caregivers of hospitalized children at Comer Children's Hospital (CCH) will be enrolled in the RCT Y1-Y3. Eligible subjects will include caregivers who are English-speaking (~95% of CCH caregivers), who live in the 16 ZIP code target region and who self-identify as a primary caregiver of a child <18 years old hospitalized in CCH's general, intensive care or transplant units. Caregivers of well newborns will be excluded as will caregivers of children expected to be hospitalized for <24 hours and >30 days (~25% and 7% of caregivers, respectively, meeting above criteria). To be eligible, caregivers must agree to receive text messages from the research team.

CCH will admit ~10K unique children during the 24 month enrollment period. Based on CCH admission data and our preliminary studies, at least 3400 caregivers of these children will meet all eligibility criteria. New admissions will be identified via the EMR by HIPAA-trained research staff. Caregivers will be consecutively approached, screened for eligibility and enrolled on the child's hospital unit within 72 hours of the child's admission. This recruitment protocol uses the same successful strategy we implemented for prior studies, including a cross-sectional study of food security in caregivers of children hospitalized at CCH (85% cooperation rate) and the CRx trial (80% completed the 1 and 3 month surveys, 71% cooperation with all 3 follow-up surveys). For the CRx trial, we approached 3034 adults and successfully screened 70% (18% refused, 12% could not be screened due to feeling unwell, sleeping or they were called to their appointment). Given the expected number of eligible caregivers (3400), a projected 70% screening rate, and a 43% food insecurity rate, we project that we will need less than 24 months to enroll the target sample of 480 food insecure and 160 food secure + 20 pretest participants (3400 eligible/24 months x 70% screened x 43% food insecure = 1023 food insecure eligible and 1357 food secure eligible caregivers).

To ensure balance of intervention groups by food security status, we will use stratified randomization to allocate subjects to usual care or CRx-H. Randomization within each strata, immediately after enrollment, will be facilitated by biostatistician K. Wroblewski, using the method of permuted blocks and the uniform random number function in Stata Version 15. A stratum will be closed for enrollment once its accrual goal has been reached.

(1) Usual Care Arm: the usual care arm will receive information in the standard "Caregiver FYI Admissions Packet" from hospital admission staff about all available retail food options in the hospital and the self-serve food pantries operated by Feed1st. In addition to food resources, this packet includes information about visiting hours, parking, hospital amenities, safety restrictions, and patient/caregiver rights and responsibilities. The Feed1st pantries are listed as a food resource for families in need of "free, nutritious food items." Signage in the Feed1st pantries include information about the Community Resource Navigator (the navigator). Usual care also includes referral to social work according to the discretion of the healthcare team.

(2) CommunityRx-Hunger (CRxH): In this arm of the study, caregivers will receive CRxH in addition to usual care. CRxH will be initiated by the navigator as part of the discharge process and will include: (a) a brief, structured educational intervention about the common problem of food insecurity in households with children and co-occurring needs, like housing, legal and financial assistance, and transportation, (b) delivery and review of a HealtheRx for nearby, vetted resources to address these needs (SNAP/WIC enrollment, food support, services to meet other basic needs), and (c) coaching on how to activate community resources and the community resource navigator, including a series of automated text messages.

All caregivers randomized to CRxH will receive, in addition to the educational component and review of the HealtheRx, an initial text message (during the discharge process) and can reply "stop" at any time to prevent additional messages. Phone numbers will be verified via text message at the time of 7 day, 30 day, 90 day, 180 day and 12 month surveys and via text message each month in between follow-up surveys. The navigator will respond to text messages within 24 hours during regular work days and within 48 hours of weekends or holidays. The frequency and content of automated text messages sent to caregivers randomized to CRxH will be more frenquent in the beginning of the intervention, decrease in frequency between 31-60 days of the intervention, and culminate in a final text at the end of the intervention at 90 days. The content of these messages is based on a text messaging experiment conducted during the the CMMI HCIA CRx study and provides proactive support from the resource navigator. The timing of these messages is informed by the Critical Time Intervention model.

Following randomization, the baseline survey will be administered in the hospital by a research interviewer blinded to the subject's study arm. All caregivers will have received usual care at the time of the child's admission and will also be blinded to the arm to which they are randomized. Discharge status of subject's child will be monitored via the EMR. For caregivers randomized to the intervention, CRx-H will be delivered in the 48 hours pre-discharge. Follow-up surveys will be conducted by telephone using computer-assisted personal interviewing (CAPI) at 7, 30, 90 and 180 days and 12 months post-discharge. To maximize retention, we will use text messaging and phone calls, if needed, monthly between surveys to verify contact information, schedule and remind participants about upcoming surveys.

We will conduct two waves of baseline and 1 week follow-up pre-testing (Y1Q2), each with 5 food secure and 5 food insecure subjects (20 total) to ensure survey quality and minimize risk of measurement and CAPI error. The baseline survey will query domains, including: facilitators and barriers (e.g., household composition, SNAP/WIC enrollment, stigma due to racial discrimination), proximal outcomes (e.g. knowledge and use of food, SNAP/WIC and other self-care resources, and communication with members of the child's healthcare team) and distal outcomes (e.g. caregiver self-efficacy, satisfaction with care, health and healthcare outcomes). Dynamic factors will be assessed at appropriate intervals.

Food security status will be measured during the study screening process by the validated 12-month recall 18-item Household Food Security Survey (HFSS) (score of <3, food secure versus score ≥3, food insecure). Severity of adult and child food insecurity at 12 months (secondary outcome), will be derived from the 18-item HFSS (primarily using the continuous score but also employing the categories defined by the USDA and also validated for severity of food insecurity). At baseline, we will assess food security in the past 12 months and past 30 days to better understand patterns of food insecurity in the immediate pre-hospitalization period. We will assess food security at 1 week using open-ended questions and at 30, 90 and 180 days using the 30-day recall 18-item HFSS to assess change over time. At 12 months, we will again assess food security using both 12 month and 30 day recall to elicit a full picture of food security since study enrollment.

The primary outcome for Aim 1, caregiver self-efficacy, will be assessed using the same measure that we used in the CRx trial. Developed using Bandura's Self-Efficacy Scale, we will ask "How confident are you in your ability to find resources in your community that help you manage your health?" Responses will be assessed on a 5-

point Likert scale ranging from “not at all confident” to “completely confident.” The pragmatic CRx intervention was delivered to an adult patient by a patient service representative or ER nurse at the time of discharge from an ambulatory care visit with no specific counseling. The CRx-H iteration is more intensive (e.g. initiated in the hospital by a navigator, ongoing support via text messaging). We therefore hypothesize that CRx-H may also promote General Self-Efficacy (a broader concept than self-care self-efficacy) and will explore this by administering the Generalized Self-Efficacy Scale (range 10-40) at baseline and at follow-up.

Secondary outcomes will also be measured longitudinally. Caregiver health will be assessed using the Medical Outcomes Study Short Form-12 (the CRx trial saw positive trends in the physical component score at 3 months). Caregiver-reported child health will be assessed with a widely used, well-validated single-item physical and mental health measure from the National Survey of Child Health. Recognizing significant limitations of self-reported nutrition assessment, we will estimate caregiver nutrition using the 2-item CUP Fruit and Vegetable Screener (FVS), and will adapt this item to elicit caregiver-reported child nutrition. Child healthcare utilization, including time to child follow-up for the post-discharge medical visit, time to and number of ER visits, and time to and total days of hospitalization will be obtained from the child’s EMR and caregiver self-report.

Analysis and Sample Size Justification: To determine the impact of the CRx-H intervention on the highest-risk group, Aim 1 analyses will focus on 480 food insecure caregivers. Descriptive statistics will be used to summarize, overall and by study arm, sociodemographic characteristics and primary and secondary outcomes at each measured time point. The mean, standard deviation, median, and inter-quartile range will be generated for continuous variables; frequency counts and percentages will be generated for categorical variables.

The main analyses will follow the principle of intent-to-treat, and include all 480 food insecure caregivers in the study arm to which they were allocated. We aim to minimize missing data by employing interviewer-administered surveys and communicating to participants the protections of a certificate of confidentiality. Using these strategies, item non-response ranged from 0-3% in our CRx trial. To avoid potential bias due to missing data, analyses will be conducted using multiple imputation with the chained equations method or inverse probability weighting to account for dropout and/or item non-response. In addition, characteristics of caregivers who complete each interview will be compared to caregivers who do not.

To fully leverage the longitudinal data, generalized linear mixed-effects models (GLMM) will be fit with particular interest in the time (baseline and 7, 30, 90 and 180 days and 12 months post-discharge) by study arm interaction. Based on this model, appropriate contrasts to test the intervention effect at specific time points (e.g., 12 months) will be constructed. These contrasts will permit examination of early versus late effects of the intervention, valuable information for future iterations of this and other parent/caregiver self- and family management interventions. GLMM can be used for continuous (e.g., food security score, amount of fruits and vegetables per day), ordinal (e.g., caregiver self-efficacy, food insecurity categories), or binary (e.g., enrollment in SNAP/WIC) outcomes. If there is a serious imbalance in baseline covariates despite randomization, those covariates will be included in the model. Latent growth curve modeling is a viable alternative to GLMM and will be explored when sufficient variability in the distributions of patterns of outcomes by time points exist (e.g., with the binary outcomes there will be a limited number of potential patterns).

Potential moderators of the intervention effect (e.g., race, sex, stigma) will also be assessed by inclusion of a moderator by study arm interaction term. Although in the CRx trial we saw no gender differences in outcomes, special consideration will be given to sex (as measured by self-reported gender) as a biological variable (moderator) and variation in intervention effects will be examined in accordance with NIH policy. In addition, based on preliminary evidence of similarity across race and ethnic groups from the CRx trial, we generally hypothesize that the intervention effect will be similar and will analyze for dramatic departures from this outcome (e.g., whether the intervention has no or negative effect among non-Hispanic white caregivers and children versus a strong positive effect among AA/B caregivers and children) through effect modification analyses such as testing of the race by intervention interaction. Also, we will seek to identify factors that mediate the relationship between the study arm and the outcome of interest. Improved understanding of moderating and mediating factors will facilitate future improvements to the intervention. For example, if the relationship between intervention effect and severity of food insecurity at time t is mediated by self-efficacy at time t-1, future improvements might focus the navigator’s messaging more explicitly on fostering caregiver self-efficacy.

Transition models will be utilized to delve deeper into the impact of the intervention on state changes in food security, enrollment in SNAP/WIC, or resource use. This model will be of the general form: logit $P(Y_{it} = 1 \mid Y_{it-1} = y_{it-1}) = X + y_{it-1} + y_{it-1}*X$ where X is the intervention group variable and Y_{it} is a binary variable for food security, SNAP/WIC status, or resource use for subject i at time t. This approach will allow us to determine the frequency of transitioning into and out of food security or use of government food support services and how the intervention

impacts on this. This model can be extended to permit ordinal outcomes such as food insecurity severity categories. We will assume a first-order Markov model but check the sensitivity of the model to this assumption and will use robust standard errors.

We will also use survival analysis methods and methods for analyzing count data (e.g., Poisson or negative binomial regression) to assess the following secondary outcomes among children: 1) time to child follow-up for the post-discharge medical visit, 2) time to and number of ER visits, 3) time to and total days of hospitalization. For example, time from discharge to first ER visit will be calculated for each subject and those who never have an ER visit will be censored at the end of study follow-up. Stratified Cox proportional hazards regression models will be fit with intervention group as the independent variable and discharge location (e.g. transplant unit, general unit) as a stratification factor, due to the potential for different underlying rates based on discharge location. The proportional hazards assumption will be checked using log-log plots of survival and Schoenfeld residuals.

For the primary outcome (self-efficacy for self-care at 12 months) a sample of 236 caregivers per arm allows for detection of an intervention group difference of similar magnitude as that found in our CRx trial (3.56 +/- 1.47 vs. 3.92 +/- 1.24). Calculations were performed under the following conditions: with nonparametric adjustment accounting for the fact that an ordinal logistic model with intervention group as the only covariate is equivalent to a Mann-Whitney U test; sample size calculation using a group allocation of 1:1; power=0.8; α=0.05. We will therefore enroll 480 food insecure caregivers to accomplish Aim 1. With this sample size, power is sufficient to see at least a 0.26 standard deviation (SD) difference in Generalized Self-Efficacy between intervention and control groups. Assuming a standard deviation of about 5 (based on US adult population norms), a 0.26 SD difference would be equal to 1.3 points.

Aim 2. A screening-based approach to intervention is particularly important when the per individual cost of intervening is high or when the intervention has low relevance for the unaffected group. In general, healthcare-based screening is costly and, to be effective, requires ongoing training, continuous quality improvement and integration with clinical and EMR workflows. In the case of highly prevalent and potentially stigmatizing conditions like food insecurity or other unmet basic needs, a universal approach to intervention may be optimal, especially if the intervention is easily scalable and relatively low cost. In the case of CRx-H, a universal approach will not only reach food insecure people but also people who are at high risk of becoming food insecure and food secure people who may be called upon to support food insecure people in their community. We see evidence from universal implementations of CRx that 40% (CRx pragmatic trial) to 49% (HCIA CRx study) of people who received the intervention used information to help others with community resource needs. In our hospital, we also see food secure parents and other caregivers enlightened to the problem of food insecurity in our community by virtue of exposure to the Feed1st pantries during their child's hospitalization at CCH.[4] Yet, physician concern about patient and caregiver satisfaction is a major barrier to intervening to address food insecurity.[24,25] The purpose of Aim 2 is to demonstrate that a universal approach to delivery of the CRx-H intervention does not diminish caregiver satisfaction with care or cause caregiver or patient harm relative to usual care.

Among **all caregivers of hospitalized children (those who do and do not screen positive for food insecurity)**, evaluate the effects of CRx-H versus usual care on caregiver satisfaction with care (primary outcome), caregiver and child health (secondary outcomes) and caregiver stigma during hospitalization (secondary outcome).

Hypothesis 2a. There will be no evidence, comparing the intervention group to controls, that CRx-H decreases caregiver satisfaction with hospital care, diminishes caregiver or child health, or promotes caregiver stigma during hospitalization.

Hypothesis 2b. Within the food secure caregiver group, those randomized to the CRx-H intervention will demonstrate a lower likelihood of becoming food insecure. In addition, they will exhibit a higher level of knowledge about food insecurity rates and support resources, more positive attitudes about welfare, and a higher likelihood of sharing resource information with others.

Strategy, Timeline, Methods, and Key Measures:

Aim 2 will utilize RCT data from both food secure and food insecure caregivers. For Aim 2, the primary outcome of interest is satisfaction with hospital care, specifically satisfaction with the discharge process. Satisfaction will be assessed 7 days post-discharge. After reviewing peer-reviewed literature as well as documentation of federal policy and payment models related to satisfaction with care, we narrowed the potential measures for assessing caregiver satisfaction to: (a) the Patient Satisfaction Questionnaire (PSQ) and (b) the Hospital Consumer Assessment of Healthcare Providers Survey (HCAHPS), and have chosen the latter. Developed and validated in 1976, the PSQ is designed for adult inpatients. HCAHPS, developed between 2002-05, was similarly designed to assess adults patients' and caregivers' experience of inpatient care. In 2015 with funding from AHRQ and

CMS, the Child HCAHPS was validated specifically to assess pediatric inpatient care. The global satisfaction and patient-provider communication sub-scales of the PSQ are the most relevant PSQ measures for our study. HCAHPS similarly assesses global satisfaction and patient-provider communication, but also specifically queries about satisfaction with the information provided at discharge, the segment of the hospital experience most likely to be affected by the CRx-H intervention. In addition, HCAHPS is being widely adopted into practice because performance on this measure informs value-based purchasing. We anticipate that the Child HCAHPS is on a similar trajectory. We selected the Child HCAHPS as our primary measure because it is targeted for pediatric hospitalizations, includes the dimension of satisfaction with discharge, and is likely to influence decision-making that could inform adoption and sustainability of the CRx-H intervention. To our knowledge, the CRx-H trial will be the first randomized trial to assess the impact of a self- and family management intervention on satisfaction with hospital care among food secure and food insecure caregivers.

Although the primary outcome will be caregiver satisfaction, measured as experience with hospital discharge, we will also examine other dimensions of caregiver experience with hospital care (e.g., communication with child's providers, overall hospital satisfaction). In addition, we will assess the Patient Satisfaction with Logistical Aspects of Navigation tool, which has been validated in a largely minority and low-income cancer patient population and assesses satisfaction with logistical support for navigating barriers to care and health-related information.

Analysis and Sample Size Justification Physician concern about patient and caregiver satisfaction is a major barrier to intervening to address food insecurity. To address this barrier, we hypothesize that neither satisfaction nor caregiver or child health will be significantly diminished among caregivers randomized to CRx-H compared to those randomized to usual care. Aim 2 analyses will include all caregivers enrolled in the trial (N=640).

We will use the analytic approach described for Aim 1, following the principles of intent-to-treat. Here, we discuss analytic issues unique to Aim 2. To facilitate ease of interpretation of the primary outcome, we will linearly rescale the composite score for the Child HCAHPS dimension of satisfaction with discharge.[59] Three possible responses for each of the five items included in this dimension will be scored as: No=1; Yes, somewhat=2; Yes, definitely=3. Scores will be transformed using the formula: $y= 100 * (x-a)/(b-a)$ where y=the transformed score, x=the original score, a=the minimum possible score and b=the maximum possible score. Transformed items will be averaged to generate the composite score (range 0-100, higher values mean greater satisfaction). Of particular interest for the non-inferiority hypothesis (H2a) will be the confidence interval for the difference (usual care - CRx-H) and whether or not the upper limit of the confidence interval exceeds the non-inferiority margin. Of note, superiority of the intervention with respect to satisfaction with care, child and caregiver health, and stigma will also be tested as this can be done without penalty. Caregiver satisfaction will be measured at 7 days post discharge and will reference the index hospitalization; no longitudinal analyses will be conducted for this outcome. Typically, analyses of HCAHPS data adjust for case-mix (age, education and general health status); this will be feasible, but given the randomized design and single-site analysis, adjustment should not necessary. To determine whether there are substantial differences in the intervention's effect on food insecure compared to food secure caregivers, the intervention by food security status interaction will be tested. As in Aim 1, we will examine for differential intervention effects on primary and secondary outcomes among racial and ethnic groups, and by sex, using effect modification analyses. Some analyses will be restricted to the food secure group (N=160) to provide a more complete assessment of the impact of the intervention on this group (e.g., changes in knowledge and attitudes about food insecurity and changes in food security over time).

The proposed sample size of 640 is sufficient based on a non-inferiority margin of 1.6 points in patient satisfaction (primary outcome), assuming group allocation 1:1, power=0.8, α=0.05, standard deviation=8 (10% of the mean in a prior study of Adult HCAHPS). The non-inferiority margin of 1.6 points is less than the difference in this domain identified between non-Hispanic white and non-Hispanic Black adults reporting satisfaction with discharge (79.3 vs 77.4). For the analysis of changes in food security status during follow-up among the food secure group, 80 caregivers per study arm will provide 80% power (α=0.05) to detect a 0.45 standard deviation difference in the food security score at a given time point.