

COPTR Preparation for Primary Analysis

INTRODUCTION

Determination of the effect of an intervention on the primary outcome is usually the most important analysis in a randomized trial. Therefore, the COPTR investigators have carefully specified the statistical analysis plans for the primary outcome for each of the 4 field site studies. Analysis plans were reviewed and approved by the DSMB in April, 2012 as a part of the review of the study protocols. More recently, the COPTR investigators have taken additional steps to ensure full and detailed specification of variable definitions and the analytic plans that will be used in the final analyses.

The process undertaken involved the simulation of data in which the final primary outcome analysis could be rehearsed. The variables to be used in the analysis and imputation of missing data (when applicable) were defined and constructed. Analytic code was written independently by investigators at study sites and the RCU, analyses were conducted using simulated data, and results were compared. If differences were identified the code from the RCU and the site were compared by an independent programmer and adjudicated. Following this process, the results from the study sites and from the RCU were, for practical purposes, identical.

This primary outcome analysis rehearsal has served as a vehicle to expose detailed decisions and adjustments that needed to be made in analysis plans. The Steering Committee acknowledges that ideally every aspect of the primary analysis would be established before the study begins. However, our protocols, while detailed, did not address every nuance of the analysis and the imputation of missing data. In addition, there can be unanticipated changes in study implementation that invoke refinement of the data analysis plan. It is important to note that, at the time of this report, masking remains firmly in place. All personnel at the sites, including the site statisticians, signed written statements masking them to all analyses by arm.

To support full transparency, we have prepared a summary of the adjustments, clarifications and specifications made to statistical analysis plans during the course of this project (section A), followed by the final revised analysis plan (section B). Revisions to the analysis plans approved in April of 2012 are shown as tracked changes. The descriptions address only the primary analysis and, unless relevant to the revised analysis, we have removed from the text below details related to assumptions, power calculations, and secondary and sensitivity analyses. Deletions were not tracked, but the removal of this type of text is denoted by 3 stars (***)�.

The plans shown below were endorsed by the Steering Committee with 5 votes in favor and one abstention. The NHLBI abstained because of concerns about the Vanderbilt change in the primary outcome test. More details on this discussion are shown below in Section 4 and in the addendum.

The preliminary work on the primary analysis done by the COPTR investigators was more extensive than that usually conducted in trials. The construction of simulated data and the implementation of planned analyses exposed details and concerns that otherwise may not have been addressed until after the blind was broken. We are confident that the expanded process of preliminary analyses conducted by the COPTR investigators will expedite the time required to move the COPTR primary outcomes analyses to full publication.

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A2: Summary of adjustments, clarifications and specifications

- The primary analysis will not include a random effect for ECFE cohort membership.
At the time the original SAP was approved by the DSMB, it was our intention that consistent and identifiable cohorts of families would attend a series of Early Childhood and Family Education (ECFE) classes together over the duration of the intervention. This component of the NET-Works intervention did not materialize as intended. ECFE participation was lower than expected and there are not identifiable or consistent groups of families that attend these classes.
- The primary analysis will include a random effect for Family Connector (FC) assignment
It was observed that the home visit component of the NET-Works intervention was delivered to N=257 out of N=265 intervention group families by 7 family connectors. Because it is possible that characteristics of particular FCs may be related to BMI outcomes of the families to which they are assigned, we determined that it would be prudent to model this potential source of dependency in the primary outcome.
The decision to omit the random ECFE term and estimate a random FC term was made after study recruitment was complete and sample size was therefore fixed.
- Family Connector specification
The method for coding the Family Connector was not previously specified. Seven FCs delivered the home visit intervention component to 257 of the 265 treatment group families. Each of these 257 families will be assigned to a FC group based on the primary FC with whom they worked. Treatment group families that did not participate in the home visit intervention component, and all control group families, will be assigned to their own n=1 FC group.
- Multiple imputation specifications
We indicated previously that variables from the analytic model as well as auxiliary variables and interactions would be used in the imputation model. We have now specified a list of 9 candidate auxiliary variables and decided not to include interactions. We also provide more specificity regarding the number of datasets to be imputed (minimum 20) and the principles guiding decisions about the imputation process.

B2: Revised Analysis Plan

2.1. Study Design

The study is an individually randomized group trial. Families will be randomized equally to the NET-Works intervention or a control group. The NET-Works intervention duration is thirty-six months. Outcome measures will be assessed at baseline and at 12, 24 and 36 months post-randomization.

2.2. Primary Research Question and Hypothesis

Specific Aim 1

To evaluate the effects of a three-year multi-setting parent-targeted randomized controlled intervention on the primary outcome, child BMI, compared to a standard primary care-only intervention among low income ethnic minority two to four year old children who are at or above the 50th percentile of BMI for age and gender.

Hypothesis 1: Children in the multi-setting parent-targeted intervention will have a lower BMI at 24 and 36 months, compared with children in the standard primary care only control group.

2.4. Primary Analysis

2.4.1. Statistical model and approach

The primary analysis will test whether NET-Works participants have lower BMI at 24 and 36 months relative to comparison participants. We will use data from all randomized participants (intent to treat approach) to estimate two mixed models in which 24 or 36 month BMI values are predicted from randomized treatment group with age group at baseline, sex and BMI at baseline as covariates, and a random intercept for family connector (u_{0j}):

$$\text{BMI}_{ij} = \gamma_{00} + \gamma_{01}\text{NET-Works}_j + \gamma_{20}\text{3yo}_i + \gamma_{30}\text{4yo}_i + \gamma_{40}\text{female}_i + \gamma_{50}\text{BMI baseline}_i + [u_{0j} + e_{ij}].$$

We will conclude that NET-Works was efficacious if the γ_{01} parameter in both mixed models is statistically significant and negative, meaning that BMI is significantly lower among NET-Works children than comparison children.

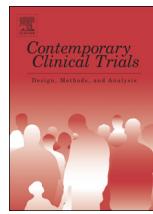
A source of dependence lies in the family connector (FC) assignment. Seven family connectors delivered the home visit component of NET-Works to intervention families. To the extent FC assignments were intended to be culture-specific, and FCs may vary slightly in their manner of delivering intervention content to the families with whom they work, dependence may be introduced through common FC assignment. As such, it will be important to account for dependence in BMI introduced through FC assignment.

Each of the families will be assigned to a FC group based on the primary FC with whom they worked. Treatment group families that did not participate in the home visit intervention component, and all control group families, will be assigned to their own n=1 FC group following the method of Esserman et al. (2012).

2.4.3. Missing data including level of attrition, loss to follow-up, and missing data treatment

The primary analysis will be conducted using multiply imputed data. We plan to use fully conditional specification to impute sporadically missing followed by 12, 24 and 36 month monotonically missing BMI values. We anticipate imputing a minimum of 20 datasets based on the observed missingness to date in post-baseline BMI values but may upwardly adjust this number to ensure adequate power (Graham et al., 2007). The imputation model will include the

primary analytic model covariates (child gender, child age at randomization, baseline BMI, treatment group) as well as auxiliary variables. Candidate auxiliary variables include child race / ethnicity, primary parent education, highest parental education, household income, family connector, parent BMI and 12m, 24m and 36m BMI. Some of the candidate auxiliary variables may be culled in consideration of factors such as the ratio of complete cases to estimated parameters and the degree of correlation with the outcome (Hardt et al., 2012). All analytic model covariates will have been documented prior to randomization with no missing values. Candidate auxiliary variables, excepting post-baseline BMI values and family connector, will have been measured at baseline with minimal missing values. The imputation model parameters may need to be calibrated in a manner that departs from the aforementioned expectations (i.e., number of imputations, number of iterations between datasets, number and coding of auxiliary variables). Model calibration will be informed by extant literature and guided by sensitivity analyses to arrive at a stable imputation model. The significance of the combined treatment parameter will not be a consideration in guiding imputation model decisions.



NET-Works: Linking families, communities and primary care to prevent obesity in preschool-age children

Nancy E. Sherwood ^{a,*}, Simone A. French ^{b,1}, Sara Veblen-Mortenson ^{b,1}, A. Lauren Crain ^{a,2}, Jerica Berge ^{c,3}, Alicia Kunin-Batson ^{a,2}, Nathan Mitchell ^{b,1}, Meghan Senso ^{a,b,1,2}

^a HealthPartners Institute for Education and Research, 8170 33rd Ave. S., Mail stop 2111R, PO Box 1524, Bloomington, MN 55440-1524, USA

^b Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, West Bank Office Building, 1300 South Second St., Suite 300, Minneapolis, MN 55454, USA

^c Department of Family Medicine and Community Health, University of Minnesota, 717 Delaware St SE, Ste 454, Minneapolis, MN 55414, USA



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ABSTRACT

Obesity prevention in children offers a unique window of opportunity to establish healthful eating and physical activity behaviors to maintain a healthful body weight and avoid the adverse proximal and distal long-term health consequences of obesity. Given that obesity is the result of a complex interaction between biological, behavioral, family-based, and community environmental factors, intervention at multiple levels and across multiple settings is critical for both short- and long-term effectiveness. The Minnesota NET-Works (Now Everybody Together for Amazing and Healthful Kids) study is one of four obesity prevention and/or treatment trials that are part of the Childhood Obesity Prevention and Treatment (COPTR) Consortium. The goal of the NET-Works study is to evaluate an intervention that integrates home, community, primary care and neighborhood strategies to promote healthful eating, activity patterns, and body weight among low income, racially/ethnically diverse preschool-age children. Critical to the success of this intervention is the creation of linkages among the settings to support parents in making home environment and parenting behavior changes to foster healthful child growth. Five hundred racially/ethnically diverse, two-four year old children and their parent or primary caregiver will be randomized to the multi-component intervention or to a usual care comparison group for a three-year period. This paper describes the study design, measurement and intervention protocols, and statistical analysis plan for the NET-Works trial.

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1. Introduction

Nearly one-third of preschool-age children are overweight or obese [1]. Racial/ethnic minority and lower socioeconomic

status children are at even greater risk for obesity [2]. The preschool years provide a unique window of opportunity to establish healthful eating and physical activity behaviors [3]. Given the complex etiology of childhood obesity, multi-level, multi-setting interventions are critical for effectiveness [4]. Interventions that directly engage parents and impact the home environment are needed given that the largest obesity prevention interventions have been school-based with limited parental involvement [5–9]. One strategy to more effectively engage parents in obesity prevention efforts is to consider the types of organizations and community-based programmatic initiatives utilized and valued by parents. Integrating strategies that promote healthy eating and activity patterns into settings where parents already spend their time could lead to the development of interventions with high potential for

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* Corresponding author at: HealthPartners Institute for Education and Research, 8170 33rd Ave. S., Mail stop 2111R, Bloomington, MN 55425, USA. Tel.: +1 952 967 7303.

E-mail address: nancy.e.sherwood@healthpartners.com (N.E. Sherwood).

¹ Tel.: +1 612 626 8594.

² Tel.: +1 952 967 7303.

³ Tel.: +1 612 626 3693.

dissemination and sustainability. Three examples include public health nurse home-visiting, community-based parenting classes, and pediatric primary care.

Public health nurse home-visiting programs provide health and psychosocial-related services to at-risk pregnant women and young mothers [10–15]. National early childhood parent education programs also offer home-visiting models [16,17]. Recently, the nurse home-visiting model was evaluated for obesity prevention in infants in a randomized controlled trial [18,19]. The Parents As Teachers Program also evaluated a parent-targeted home-based intervention to increase child fruit and vegetable intake [20]. Results suggest home-visiting holds promise for obesity prevention.

Community parenting classes are also widely available and appeal to parents of preschool-age children from diverse backgrounds. Parenting classes promote child school readiness through building parenting skills and social support networks. Healthful food choices, active play, and screen time topics align well with parenting class curriculum and could be readily incorporated into existing parent-focused community-based programs.

Primary care is a third important setting through which parents of preschool-aged children may be reached [21]. Primary care providers are influential sources of health information who can help parents promote and reinforce child behaviors related to healthful eating, activity patterns, and body weight. The primary care setting represents a unique intervention opportunity for direct, parent-focused child obesity prevention [21].

In addition to these well-established systems, the neighborhood environment provides resources that can enhance or detract from parent efforts to support optimal child growth [22–26]. Without access to these resources, parents face significant barriers to adopting eating and activity-related behavioral intervention messages. Thus, obesity prevention interventions need to identify and connect parents to existing neighborhood resources.

The goal of the Minnesota NET-Works (Now Everybody Together for Amazing and Healthful Kids) study is to integrate home, community, primary care and neighborhood intervention strategies to prevent obesity among ethnically diverse preschool-age children. The NET-Works trial is one of two unique prevention trials that are part of the Childhood Obesity Prevention and Treatment Research (COPTR) consortium, a National Heart, Lung, and Blood Institute (NHLBI)- and National Institute of Child Health and Human Development (NICHD)-sponsored collaborative effort to develop and test novel approaches to prevent or treat childhood obesity. Each field center is testing distinct interventions with unique populations and eligibility criteria, but share a core set of common measures and protocols. This paper describes the NET-Works trial study design, measurement and intervention protocols, and statistical analysis plan.

2. Materials and methods

2.1. Trial design overview

NET-Works is a two-arm, randomized controlled trial to test the efficacy of a multi-setting, multi-component intervention approach to preventing obesity among racially/

ethnically diverse preschool age children. The NET-Works intervention includes four main components: 1) a pediatric primary care brief counseling intervention; 2) a home-based intervention delivered by NET-Works family connectors to support parents in making changes in the home environment and parenting practices to promote healthful eating and activity patterns; 3) community-based parenting classes designed to parallel the home-based intervention curriculum and provide social support to participating parents; and 4) linkages to neighborhood and community resources to support parents in promoting healthful eating and activity patterns for their children. Five hundred parent/child dyads will be randomized to either the NET-Works intervention or a usual care comparison condition and followed for three years. Participants will be assessed at baseline and annually. The primary hypothesis is that children randomized to the NET-Works intervention will have lower BMI at two and three years post-randomization relative to usual care comparison group children. BMI is the primary outcome across all four COPTR trials. Recruitment for the trial began in July 2012 and will be completed in December 2013, with the final three year follow-up data collected in December 2016.

2.2. Study setting and population

The target population for NET-Works is racially/ethnically diverse preschool children and their parent or primary caregiver. To reach the intended population, NET-Works has partnered with 12 primary care clinics and three managed health care systems that serve diverse populations with respect to race, ethnicity and income. Over 18 months, 500 families will be recruited, enrolled and randomized to the intervention or to the usual care comparison group. Administrative databases and centralized electronic scheduling systems at the partner clinics provide data needed to target recruitment efforts on two-to-four year old children residing in certain zip code areas. The clinics have recent data from preventive care visits available for calculation of child body mass index (BMI) percentile to focus recruitment efforts on children who are potentially BMI-eligible for the study.

2.3. Eligibility criteria and exclusions

Eligibility criteria are assessed on a telephone screening call and confirmed in person at the first data collection home visit. A child and his or her parent or primary caregiver are eligible for the study if: 1) the child is between ages of two and four years of age; 2) the child has no medical problems that would preclude study participation as determined by the primary care physician; 3) does not use any medications that would affect the child's growth; 4) the child's BMI is greater than or equal to the 50th percentile according to CDC age and sex reference standards with no upper limit [27]; 5) the family's income is below \$65,000 per year; 6) the child's parent agrees to participate in the study and does not plan to move out of the state in the next three years; 7) the parent or primary caregiver is willing and able to complete the evaluation measures and participate in intervention activities if assigned to the active intervention group; and 8) the parent or primary caregiver speaks either English or Spanish.

2.4. Recruitment

Recruitment procedures are adapted from those used in our previous pediatric primary care-based obesity prevention intervention trials. Administrative databases and centralized electronic scheduling systems at three partner health care organizations will provide data needed to target families of two–four year old children whose BMI percentile is at or above the 50th percentile for age and gender. Clinic liaisons obtain approval from each child's pediatrician to send a study invitation letter to the parent or primary caregiver. A list of physician-approved potentially eligible children is shared with the NET-Works recruitment team. NET-Works sends the parent or primary caregiver a study invitation letter from the pediatrician and researchers. Approximately five working days later, NET-Works recruitment staff follows up by phone to provide more information, asks additional screening questions, and assesses parent/primary caregiver's interest in the study. If the parent/primary caregiver is interested and the child appears to be eligible, a home visit for eligibility confirmation, consent, and data collection is scheduled. The purpose of this initial home visit is to: 1) explain and discuss the study, and begin to develop rapport with parents; 2) measure the index child's height and weight to confirm eligibility; 3) obtain informed consent; and 4) begin the process of collecting baseline data. Based on our pilot study experience we anticipate that the majority of the participating parent/caregivers will be female. We also anticipate recruiting a significant number of Hispanic families as well as non-Hispanic White, African American, and multi-race participants.

2.5. Randomization

Prior to the start of recruitment and enrollment, the study statistician created 6 blocked randomization schedules, one for each age group (2, 3, 4) by gender (M, F) stratum, that equally allocated children to the NET-Works intervention or the usual care comparison group in blocks of 10 to ensure equivalent study group size. Parent–child dyads will be randomized to treatment and control conditions after completion of all baseline measures, including data eligibility requirements established by the COPTR consortium. Data eligibility requirements include valid height and weight measurement, a minimum of one weekday and one weekend day NDS-R previous day dietary recall and four days of valid accelerometry data (see below for details regarding measurements). The study coordinator will randomly assign the participant to the condition shown in the next available slot in the stratum-appropriate pre-defined randomization schedule. The investigators and all assessment staff will remain blinded to experimental assignment until after the final follow-up assessments are completed.

2.6. NET-Works intervention

The social ecological model provides an overarching framework for the intervention. The SEM recognizes multiple levels of influence on a behavior [28]. Fig. 1 illustrates the multiple levels of influence on child eating and physical activity behaviors, which influence body weight. The NET-Works intervention reaches into the home and family environment to

influence parent behaviors and attitudes to support changes in the home that affect food availability, family meals, television viewing, and active play. Each intervention component is situated in community settings where parents and children already live their lives. The intervention is expected to be effective in part through taking advantage of the settings that families already inhabit, and through coordination across settings to reinforce and link the messages, resources and feedback families receive about healthful food choices, physical activity, and body weight for their child. A neighborhood-based model will be more likely to enhance class participation, reduce transportation needs/costs, allow the local community resources to be accessed more easily, and foster outside-of-class interpersonal connections among parents for enhanced social support.

2.6.1. Intervention components implementation overview

The intervention curricula across each component (home visiting, parenting classes, neighborhood environment, pediatric primary care) were developed and refined during the pilot phase of the COPTR consortium. The intervention is implemented by trained research staff including a family connector who conducts the home visiting and connector check-in calls and attends the parenting classes, and a parent educator who conducts the community parenting classes that are based on the early childhood parenting class model and were developed in partnership with ECFE in Minneapolis and St. Paul. The home visiting and parenting classes share a common set of underlying curricula that includes skills building around general parenting behaviors and the specific content behaviors targeted by the intervention (e.g., healthful snacks, family meals, physical activity). The family connector meets parents and children in their own home, tailoring the intervention messages and strategies to best fit with the resources and motivations of parents. The family connector provides a one-on-one approach to synergize with the skills and strategies implemented in a group format in the NET-Works community parenting classes. Both home visiting and parenting classes directly connect parents to food and physical activity resources that already exist in their neighborhood ("community links"). Primary care providers bolster these messages with parents during annual well-child visits. Table 1 provides an overview of the intervention components, including the frequency and timing of each component and the target behavioral goals and parenting strategies to support goal achievement.

2.6.2. Home visiting

The goal of the home visiting is to help parents develop parenting skills, set goals related to child healthful eating, active play and reduced television viewing, and provide support for sustaining and building on these behavior and home environment changes. The dose for the home visiting intervention component is one visit per month for each of the three years. The family connector builds a collaborative, partnership-based goal setting process for parents to facilitate child behavior change. Facilitation of the home visits is modeled on Motivational Interviewing, an approach designed to help individuals explore and resolve ambivalence about behavior change in a non-confrontational manner. Home visiting includes a goal setting process guided by the family connector, healthful action activities to create norms

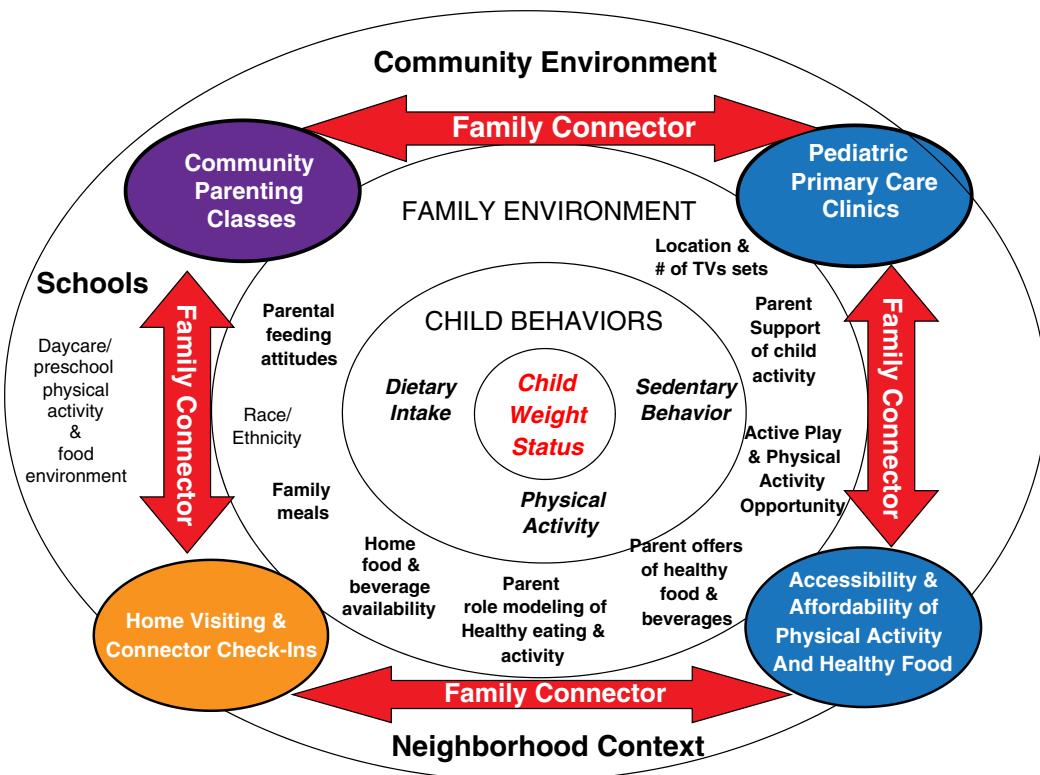


Fig. 1. Socioecological model for obesity prevention.

and skills related to the targeted behaviors, and resources for links in the community to support healthful behaviors. Family connectors also check in with participants to review progress on goals and provide support in between home visits. Family connector check-in contacts can be conducted over the telephone or via email. Family connectors have weekly supervision sessions with a licensed mental health provider with expertise in Motivational Interviewing to review progress with each participant, problem solve regarding any challenges that arise, and ensure adherence to the intervention protocol.

2.6.3. Parenting classes

The parenting classes are designed to work synergistically with the home visiting curriculum. The parenting class and the home visiting curriculum both include topics that address parenting skills development, the home food environment, healthful eating, family meals, television viewing limits, active play, and goal setting. The parenting class provides a group format where parents can share their experiences, gain support from other parents and learn from each other. The curriculum is research-based and facilitated by a trained parent educator. The dose for the parenting class component is 12 classes per year for each of the three years. The curriculum in years 2 and 3 will build upon and deepen the topics introduced in year 1, and will address parenting and developmental issues as children progress from ages 2–7 years of age. Parent educators also participate in weekly supervision sessions to ensure adherence to the intervention protocol.

2.6.4. Neighborhood and community initiatives

The purpose of the neighborhood and community intervention component is to increase access to, and use of, healthful food, physical activity, and school readiness resources available in the neighborhood communities where study participants live. Parents are directly linked with resources in their neighborhood through both the parenting classes and the family connector home visits. For example, through the parenting classes, parents take a group field trip to a local grocery store to practice shopping skills. Community initiatives implemented with the family connector include conducting a walkability assessment of the family's neighborhood. The family connector reviews neighborhood food and physical activity resources with the parent at each home visit, and encourages them to use these resources to support their home and behavior changes. The community links include one school readiness community activity (e.g., a library visit) to promote developmental parenting, sustain parent interest, and provide active support for whole child development. Four community links will be included in the parenting class and home visiting curriculum each year of the intervention.

2.6.5. Primary care

The primary care provider is an influential connection for parents. In NET-Works, the primary care provider delivers key messages around parent behaviors for shaping, reinforcing and sustaining healthful child eating and physical activity behaviors and body weight. To support providers in delivering key messages to parents during well child visits, a brochure was developed in partnership with the participating clinic systems.

Table 1

Overview of intervention components, targets, and parenting strategies.

Intervention component	Staff person	Frequency
Home visits	Family connector	12 visits per year
Connector check-ins	Family connector	4 phone or email contacts
Parenting classes	Parent educator	A 12 class series each year
Pediatric primary care	Primary care provider	Initial well child visit intervention Annual well child visit check-in
Intervention targets across components		
Physical activity & active play		Aim for ≥60 min per day
Screen time		Aim for <2 h per day
Sweetened beverages (including juice)		Aim for <4 oz per day
Portion size		Serve child size portions
Eating out		Aim for eating out once a week or less
Family meals		Aim for ≥5 per week
Breakfast		Eat breakfast everyday
Fruit and vegetable intake		Aim for ≥5 servings per day
Snacks		Aim for ≤1 treat per day
Parenting strategies promoted across components		
Model		Set rules and routines
Nurture		Be a good example Give attention, praise and encouragement Reinforce positive actions Communicate and respect each other
Guide		Set limits Offer choices
Shape		Use rewards and consequences Find healthy solutions together Develop healthy habits
Network		Use your community Ask for help when you need it

The brochure is used by the primary care provider to converse about child BMI percentile and strategies parents can use to promote their child's healthful eating and activity patterns. The NET-Works family connector will also provide information about progress on intervention goals to the primary care provider on an annual basis to reinforce continuity and integration of intervention messages. The primary care intervention links with the community parenting classes and home visiting to deliver consistent intervention messages over a sustained time period.

2.6.6. Intervention component integration

Linkages across the intervention components are created in several ways with the family connector playing a key role in this connectivity. Specifically, in addition to conducting home visits, family connectors facilitate participant entry into parenting classes and also attend parenting classes. Attending parenting classes allows the family connector to be knowledgeable about the parenting class content and the experience their assigned participants are having during class. This information informs the goal setting that family connectors and parents work on during home visits. Family connectors also serve as the liaison between parents and primary care

providers. The home visits and parenting classes also incorporate connections to community resources for physical activity and healthy eating as described above.

2.7. Usual care comparison group

The usual care comparison group will receive the primary care provider component described above, and quarterly newsletters with information about their child's general health and wellness and school readiness.

2.8. Participant timeline, assessments, and measures

Data collection takes place in the home setting at baseline, 12, 24, and 36 months by trained and certified, bilingual English and Spanish research specialists, blinded to experimental assignment. At 6, 18, and 30 months, a brief telephone survey is conducted. Participants receive a total of \$50 in gift cards for each set of measurement visits (baseline and each subsequent annual assessment) and a \$5 gift card for each brief telephone survey. Data collectors are trained by the investigators and, for COPTR consortium common measures, by the Research Coordinating Unit (RCU) according to standardized protocols. COPTR uses a train-the-trainer model. "Master Trainers" who participate in a central training organized by the RCU are responsible for training and certifying the data collection staff at their field center. Data collectors must demonstrate high inter- and intra-rater reliability prior to data collection.

2.8.1. Primary outcome measure – common measure

Body mass index (BMI) is the primary outcome measure of all four COPTR trials. Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in meters. Weight and height are measured with the participant in light clothing without shoes using the common COPTR protocol. Weight is measured to the nearest 0.1 kg using research precision grade, calibrated, digital scales and height is measured to the nearest 0.1 cm using a free-standing or wall mounted stadiometer (Seca Corp., Hanover, MD).

2.8.2. Secondary outcomes – common measures

2.8.2.1. Anthropometrics. Waist circumference and triceps skinfolds are measured for all index children and weight and height are measured for other children and adults in the household. Weight and height for adult and child household members is measured using the above described approach. Waist is measured to the nearest 0.1 cm just above the uppermost lateral border of the right ilium using a Gulick II tape measure, model 67020. The triceps skinfold is measured to the nearest 0.1 mm using a Lange skinfold caliper. For quality control, 10% of the anthropometric measurements are measured by two different data collectors.

2.8.2.2. Dietary assessment. Dietary intake is measured using 24-hour recalls conducted on two weekdays and one weekend day using NDS-R software. Dietary recalls are collected in-person or over the telephone in English or Spanish. The Food Amounts Booklet is used by the respondent to estimate portion sizes. Recalls are not conducted on consecutive days, do not occur within a seven day period, and are collected within 30 days. The

adult responsible for child feeding reports the child's intake. Quality assurance checks are conducted on at least 10% of the dietary recalls according to NDS-R standard protocols. Previous day dietary recalls have been shown to be a valid measure of dietary intake among children [29].

2.8.2.3. Physical activity. Accelerometry data are collected on all index children using the GT3X + monitor. The GT3X + monitor is worn on the right hip for seven complete days (including while sleeping and naptime) except during water activity (e.g., bathing, swimming, showering). The index parent also wears a GT3X or GT3X + monitor for seven days on the right hip. The ActiGraph GT3X + and the GT3X devices measure acceleration in three individual orthogonal planes using a vertical axis, horizontal axis and a perpendicular axis. The GT3X + is set to collect data at a 40-Hz frequency and the GT3X is set to collect data in 1-second epochs. The valid wear time criteria (minimum) are four days (three weekdays and one weekend day) of at least 6 h of activity between 5:00 am and 11:59 pm. Accelerometry has been shown to be feasible and valid in preschool age children [30–33].

2.8.3. Moderators and mediators

2.8.3.1. Child Eating Behavior Questionnaire (CEBQ). The CEBQ measures individual differences in child eating behaviors [34]. The parent reports the child's usual eating behaviors. The eight subscales are food responsiveness, enjoyment of food, emotional overeating, desire to drink, satiety responsiveness, slowness in eating, emotional undereating, and food fussiness. The scales have high internal consistency reliability (range .72–.91) and test-retest reliability (range .52–.87). The subscales satiety responsiveness, food responsiveness, and enjoyment of food have been validated in four and five year old children using behavioral observation measures of energy intake and eating without hunger [35]. In addition to these three sub-scales, the food fussiness sub-scale is completed by parents in NET-Works.

2.8.3.2. Parent feeding styles. Parent feeding styles were measured using the Parent Feeding Styles Questionnaire [36]. Parents self-report their usual feeding practices in relation to the target child. The scale consists of 27 items that comprise four subscales: emotional feeding, instrumental feeding, prompting to eat, and control over eating. The subscales have high internal reliability (.65–.85) and test-retest reliability (.76–.83).

2.8.3.3. Family eating patterns. Frequency of family meals and eating at fast food and other restaurants are also assessed. Parents report the number of times their family ate breakfast, lunch, and dinner together during the past seven days [37]. Parents report the number of times the child ate something at a fast food restaurant during the past week and how many times the child ate something from another restaurant [38]. Parents are also asked to report how often they choose their child's meals and snacks each day.

2.8.3.4. Parent support for child PA. Parent support for their child's physical activity behaviors was measured using four questions that have been used in previous research and shown to have good internal consistency ($r = .78$) and one

week test-retest reliability ($r = .81$) [39]. Parents report the frequency with which they provide verbal encouragement to be active, watch their child play, play with their child, take them to a location to play or be active.

2.8.3.5. Parenting styles. NET-Works general parenting style measure is based on a subset of 20 items from a questionnaire developed from previously published literature on parenting styles [40]. Previous research identified four parenting styles that are related to child outcomes (authoritative; authoritarian; indulgent/permisive; disengaged/neglectful). Other research has identified two primary parenting dimensions that relate to child outcomes: warmth/responsiveness; and control. For NET-Works, items were selected to represent the following dimensions: nurturance, structure, and behavioral control.

2.8.3.6. Perceived Stress Scale (PSS). The PSS is a widely used measure of perception of stress designed for use in community samples [41,42]. Items tap how predictable, controllable, and overloaded respondents find their lives. A four-item short-form of this scale was used, which asks about thoughts and feelings in the last month and includes items such as "how often have you felt that you were unable to control the important things in your life?" Items are rated on a 5-point Likert scale ranging from 0 (never) to 4 (always). Coefficient alpha reliability for the PSS in community-based samples is .85; test-retest reliability is .85.

2.8.3.7. Parenting stress. Parenting stress is measured using the 4-item scale developed by the Fragile Families and Child Wellbeing Study [43,44], which includes the following four statements: "Being a parent is harder than I thought it would be," "I feel trapped by my responsibilities as a parent," "I find that taking care of my child(ren) is much more work than pleasure," and "I often feel tired, worn out, or exhausted from raising a family." Items are rated on a 4-point Likert scale (0 = strongly disagree to 3 = strongly agree). The sum of the four items serves as the final scale (coefficient alpha reliability = .63).

2.8.3.8. Neighborhood availability parks/playgrounds and food stores. To measure neighborhood availability of parks and playgrounds, parents are asked about the neighborhood locations that they take their child to for play. The parks and playgrounds within a one mile radius of the home are identified using a mapping program (Google Maps). Parents are asked to report the frequency of visiting each park or playground with their child during the past month. In addition, parents are asked to name the most frequent park or playground they visited during the past month with their child, and the number of times visited. Parents are asked to report their most frequent food shopping location and the distance it is from their home. These measures were developed for the NET-Works trial.

2.8.3.9. Neighborhood block audit. For NET-Works, a 23-item modified version of a previously developed block audit inventory is used [45]. Because the factor structure varied from sample to sample in previous research, a face-valid method is used to group items into categories for summary score creation. Three categories are defined: walkability/support for walking;

places to go/destinations; physical incivilities. Walkability includes the following items: sidewalks; pedestrian crossings/markings; and traffic control signals/stop signs. Places to go include the following items: nearby parks (size and available equipment); and commercial outlets. Physical incivilities include the following items: physical condition of home or apartment building; visible trash or graffiti; and condition of buildings. NET-Works focuses on preschool-age children and therefore items are weighted higher for those that assess aspects of the neighborhood that are hypothesized to be more supportive for preschool children's physical activity. For attractions the weighting scheme keeps yards, parks and other places on the same scale. For transportation the weighting scheme keeps sidewalks, traffic and places on the same scale.

2.8.3.10. Home food inventory (HFI). The home food inventory measure used in NET-Works is based on the previous research by the investigators and the broader literature on home food inventories [46,47]. A variety of HFIs have been published, most of them tailored to the particular dietary targets in the research question. In our previous research on the home food environment, the HFI was created by a series of iterative pilot studies to capture the foods and beverages targeted by the intervention, in sufficient detail to be both feasible [time to collect the data; level of detail] and informative about the amounts of specific foods and beverages in the home. For the present study, the following eight home food item categories are used: Sugar sweetened beverages; non-caloric beverages; milk; fruits; vegetables; fruit/vegetable juices; sweets; packaged snacks. Individual food items within categories are recorded as either being present or not present under the appropriate category. Each HFI is reviewed and edited for accuracy and completeness.

2.8.3.11. Perceived neighborhood environment. Parents are asked to indicate how much they agree or disagree with a series of nine statements related to perceptions about traffic density, road safety, strangers, sporting facilities, and walking safety in their neighborhood [48].

2.9. Process measures

Process evaluation measures are conducted throughout the study to assess the integrity of the intervention components (family connector home visits and check-in contacts, parenting classes, community link activities, and primary care). Integrity is described across five domains: (1) fidelity, or message quality and content; (2) dose delivered, or amount and length of intervention sessions; (3) dose received, or participant engagement and satisfaction; (4) reach, or extent to which the intervention was delivered to and received by the intended population; and (5) program design (i.e., feasibility and cost effectiveness). These domains are measured using several methods including parent surveys, intervention staff documentation forms, and coding of audio-recorded family connector home visits. Table 2 shows the process evaluation measures that are collected and described below.

2.9.1. Family connector home visiting and check-in contacts

Before conducting intervention visits and calls, intervention staff are trained and certified in intervention techniques.

Staff attendance, certification, and satisfaction with training are recorded. After each visit and interaction (i.e., home visit, phone call), contact length, type and quality of intervention messages, parent engagement, and parent-staff relationship are documented by the intervention staff person who worked with the family. Each home visit is audio recorded, with participating parent consent, and coded by independent process evaluation staff for intervention fidelity. At 6-, 18-, and 30-month time points, parents complete a telephone survey conducted by independent process evaluation staff about satisfaction with these intervention components.

2.9.2. Parenting classes and community links

Intervention staff conducting sessions and events documents attendance, session length and quality, amount of material covered, and perceived group engagement. After each session and event, participating parents complete a brief satisfaction survey. At 6-, 18-, and 30-month follow-up time points, parents complete a phone-administered satisfaction survey about these components.

2.9.3. Primary care

Primary care provider trainings are conducted before the start of the intervention. Provider attendance and satisfaction with these trainings are recorded. Well-child visit attendance for comparison and intervention families is measured at the end of each study year through electronic medical records. At baseline-, 6-, 12-, 18-, 24-, 30-, and 36-month time points, parents are asked to report attendance and content and quality of messages received at the participating child's most recent well-child visit.

2.10. Statistical analyses

2.10.1. Primary analyses

The primary efficacy analysis will test whether income racial/ethnic minority of two to four year old children who are randomized to the NET-Works program have statistically and clinically lower BMI at 24 and 36 months post-randomization relative to usual care comparison group children. Data from all randomized participants will be used to estimate two mixed models. In each, BMI at either 24 or 36 months will be predicted from treatment group (NET-Works, usual care) with age at randomization (2, 3, 4), sex (F, M) and BMI at baseline included as covariates. The NET-Works study is an individually randomized group trial, and dependence may be introduced into the BMI values of NET-Works children whose parents participate in common parenting classes over the course of the three-year intervention while there is unlikely to be dependence in the usual care group where parents are unlikely to ever interact with each other [49]. Among NET-Works children randomized to the intervention group, parenting class cohort will be treated as a random effect, and the intraclass correlation of BMI among children within cohorts will be estimated. Each usual care child will be treated as a random effect and BMI assumed independent. It will be concluded that NET-Works was efficacious if the fixed treatment group parameter in both mixed models is statistically significant and BMI is meaningfully lower (Cohen's $d \geq .30$) among NET-Works children.

Table 2

NET-Works process evaluation.

Fidelity. The extent to which the intervention is delivered as intended; quality of the intervention; how well an intervention is being implemented compared to its original design; could include, but not limited to, content & quality of messages, adherence to protocol, and intervention staff skill/training/certification.

Intervention component	Construct(s)	Data collection method	Completed by	Timing of data collection
Primary care	Content of messages received	Adherence survey	Parent	Baseline, 6, 12, 18, 24, 30 and 36 months
	Provider training attendance and satisfaction	Survey	Pediatric primary care providers	After provider training
Home visits and check-in calls	Content and quality of messages delivered/received	Documentation forms	Intervention staff	After every visit/call
	Staff training attendance, certification and satisfaction	Satisfaction survey	Parent	6, 18, and 30 months
	Content and quality of messages delivered/received	Survey	Intervention staff	After staff training
Parent class sessions and community events	Staff training attendance, certification and satisfaction	Documentation form	Intervention staff	After every class/event
	Content and quality of messages delivered/received	Satisfaction survey	Parent	After every class/event and 6, 18, and 30 months
	Staff training attendance, certification and satisfaction	Survey	Intervention staff	After staff training

Dose delivered. The amount of intervention that was delivered; could include, but not limited to, number and length of sessions implemented.

Intervention component	Construct(s)	Data collection method	Completed by	Timing of data collection
Well-child visit	Attendance	Electronic medical records	Process evaluation staff	Annually
Home visits and check-in calls	Activities completed, messages/materials delivered, attendance	Documentation forms	Intervention staff	After every visit/call
Parent class sessions and community events	Activities completed, messages/materials delivered, attendance	Documentation form	Intervention staff	After every class/event

Dose received. The amount of intervention that was received; could include, but not limited to, participant engagement, and intervention messages or materials received.

Intervention component	Construct(s)	Data collection method	Completed by	Timing of data collection
Well-child visit	Messages/material received	Adherence survey	Parent	Baseline, 6, 12, 18, 24, 30 and 36 months
Home visits and check-in calls	Engagement	Satisfaction survey	Parent	6, 18, and 3 months
Parent class sessions and community events	Engagement	Documentation forms	Intervention staff	After every visit/call

Program design. The assessment of non-specific treatment effects, could include, but not limited to participant satisfaction with, feasibility, and costs of intervention.

Intervention component	Construct(s)	Data collection method	Completed by	Timing of data collection
Well-child visit	Participant satisfaction	Adherence survey	Parent	Baseline, 6, 12, 18, 24, 30 and 36 months
Home visits and check-in calls	Participant satisfaction	Satisfaction survey	Parent	6-, 18-, and 30-month surveys
Parent class sessions and community events	Staff time to prepare and travel for delivery of intervention	Documentation forms	Intervention staff	Quarterly

Reach. The proportion of intended recipients who actually participate in an intervention; the extent to which the intervention is reaching the target population; could include, but not limited to, attendance, participation, and engagement by group (e.g. race, gender, SES, intervention group).

Intervention component	Construct(s)	Data collection method	Completed by	Timing of data collection
Well-child visit	Attendance, participation, and engagement by clinic, race, ethnicity	Similar to above measures, but examined by groups noted in previous column		
Home visits and check-in calls	Attendance, participation, and engagement by race, ethnicity	Similar to above measures, but examined by groups noted in previous column		
Parent class sessions and community events	Attendance, participation, and engagement by location, race, ethnicity	Similar to above measures, but examined by groups noted in previous column		

These analyses will be conducted using multiply imputed datasets. A fully conditional specification approach will be used for the imputation process, and will include in the imputation model all variables included in the primary analytic (scientific) model as well as interactions among them to improve the precision of the imputations. All covariates in the primary

analysis will have been measured at baseline prior to randomization and are therefore available for observed and unobserved BMI values. The random effects estimated in the primary analytic model will also be estimated in the imputation model [50]. The mechanisms that are likely to produce missing observations in the analytic dataset should result in

missing observations that are missing at random (MAR; e.g., early dropouts, busy schedule) or possibly missing not at random (MNAR; e.g., sporadic missing). The primary analytic models will be estimated from imputed datasets that assume all missing observations to be MAR. Sensitivity analyses will assess the severity of non-random missingness that would be necessary to reconsider the conclusions drawn from the primary analysis.

2.10.2. Detectable difference, sample size and power

A power analysis determined the minimum detectable standardized effect size (MDSE, Cohen's d) in BMI for NET-Works versus usual care children at 24 or 36 months post-randomization (i.e., the fixed treatment group parameter). The effective number of follow-up BMI observations was estimated separately for each treatment group by imposing assumptions about the design effect resulting from NET-Works parent-child dyads clustered within parenting class cohorts ($ICC_{PC} = .01\text{--}.03$ NET-Works, $ICC_{PC} = .00$ usual care), the design effect resulting from autocorrelation within cohorts ($r_{PC} = .30\text{--}.50$ NET-Works, $r_{PC} = .00$ usual care) and children ($r_{child} = .40\text{--}.60$) between baseline and follow-up BMI, and the proportion of children from whom BMI will be available (75–85%) (Table 3).

NET-Works dyads will be clustered within about 16 parenting class cohorts ($M = 15.6$ dyads/cohort). The clustered sample size in each treatment group ($n = 250$) was divided by the design effect introduced by clustering within parenting classes, $DEFF_{PC} = [1 + (n - 1)\rho]$, to estimate the effective number of independent dyads in each group. Next, the effective number of independent dyads was divided by the design effect introduced by cohort and child autocorrelation in BMI, $DEFF_{corr} = (1 - r^2)$, to adjust for the efficiency gain resulting from controlling for baseline BMI. In this case, $r = [np/(1 + (n - 1)\rho)]\rho_c + [(1 - \rho)/(1 + (n - 1)\rho)]\rho_s$, where n is the average number of dyads per cluster; ρ is the correlation in BMI values of different children in the same cluster at a single point in time, ICC_{PC} ; ρ_c is the cohort auto-correlation in BMI values, r_{PC} ; and ρ_s is the child auto-correlation in BMI values, r_{child} [51,52]. Finally, the NET-Works and usual care sample sizes were reduced to 75–85% of their estimated values to account for the expected number of children with a follow-up BMI. We will use a generalized Holm procedure to ensure a family-wise Type I error rate of .05 in the two mixed models, so that the treatment group parameter with the smaller p-value will be tested at $\alpha_2 = .025$, while the treatment group parameter with the larger p-value will be tested at $\alpha_2 = .05$ [53,54].

The resulting MDSEs are displayed in Table 2. Given median values for ICC and retention assumptions ($ICC_{PC} = .01\text{--}.03$, $r_{child} = .40$, $r_{PC} = .30$, and 75–85% of randomized children provide follow-up BMI data).

Table 3

Minimum detectable effect size, d , when $\alpha_2 = .025$, $ICC_{PC} = .01\text{--}.03$, $r_{child} = .40$, $r_{PC} = .30$, and 75–85% of randomized children provide follow-up BMI data.

ICC_{PC}	Follow-up BMI data		
	85%	80%	75%
.01	.286	.294	.304
.02	.296	.305	.315
.03	.307	.316	.326

.02, 80% follow-up) and conservative alpha and autocorrelation assumptions ($\alpha_2 = .025$, $r_{PC} = .30$, $r_{child} = .40$), the MDSE is $d = .305$. When $\alpha_2 = .05$, the comparable MDSE is $d = .277$. These effect sizes are in keeping with our stated goal of detecting a clinically meaningful difference ($d = .30$) in BMI between treatment groups at 24 and 36 months.

A similar approach will be utilized for the analysis of secondary endpoints.

2.11. Data monitoring and participant safety

Adverse events will be assessed systematically at each data collection visit with direct queries for all injuries, illnesses or other medical problems requiring a visit to a medical care provider and related to participation in the study. Serious Adverse Events (SAEs) are specifically monitored. Adverse events will also be recorded and evaluated when they come to the attention of study staff between the data collection visits. An independent Data & Safety Monitoring Board has been selected and reports to NIH to review study protocols and provide oversight of recruitment and study progress, data quality and completeness, and participant safety.

3. Discussion

This paper describes the study design, measurement and intervention protocols, and statistical analysis plan for the Minnesota NET-Works trial, one of the four multi-setting, multi-component childhood obesity interventions that are part of the seven-year COPTR consortium. Five hundred racially/ethnically diverse two–four year old children and their parent will be randomized to the multi-component NET-Works intervention or to a usual care control group for a three year period. The NET-Works study offers a unique opportunity to synergistically combine several single-setting interventions that have been implemented and evaluated in previous studies into a multi-component, multi-setting comprehensive integrated intervention. The intervention components include home visits, community parenting classes, community links, and primary care provider intervention. The coordination of the intervention components is facilitated by the family connector. These components will be linked with each other and with the family home environment, allowing families to receive consistent and multi-sourced messages and support for the targeted behavior and environment changes. The intervention is expected to be feasible and effective partly through taking advantage of the settings that families already inhabit, and through incorporating coordination across settings to reinforce and link the messages, resources and feedback families receive about healthful food choices, physical activity and body weight for their child.

Strengths of the NET-Works trial include the focus on preschool-age children at risk for obesity and their parents, a comprehensive evaluation protocol, the 3 year length of follow-up, and the multi-component, integrated intervention. The evaluation protocol includes measures of dietary intake, physical activity, the household food environment, the neighborhood environment, general and domain-specific parenting strategies, as well as measures of child cognitive development and novel measures of stress (i.e., hair cortisol). The comprehensive evaluation protocol will allow the impact

of the intervention to be evaluated on a wide range of outcomes, in addition to the primary focus on child BMI. Additionally, key moderators and mediators of the intervention will be explored. The NET-Works study includes detailed process evaluation measures developed in collaboration with the other COPTR sites. The process evaluation data will allow for examination of intervention fidelity, dose, and reach and the relationship between specific intervention components and study outcomes. The integration of the intervention components into existing and trusted settings where parents and children already spend time may increase the likelihood that if successful, the NET-Works intervention can be sustained and adopted widely within existing community parenting education and home visiting programs that include a national reach.

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Net-WORKS Study CONSORT Diagram

