Case Western Reserve University

Main Trial Protocol

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*Asterisk those items that are common across sites.

List of Abbreviations

BMI	Body Mass Index
EBP	Elevated Blood Pressure
CMSD	Cleveland Metropolitan School District
COPTR	Child Obesity Prevention and Treatment Research
IMPACT	Ideas Moving Parents and Adolescents to Change Together
WRTC	We Run This City Youth Marathon Program
YRBS	Youth Risk Behavior Survey

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1. EXECUTIVE SUMMARY

Executive Summary
Targeting Obesity and Blood Pressure in Urban Youth
Case Western Reserve University

The Case Western Reserve University COPTR project is named IMPACT (Ideas Moving Parents and Adolescents to Change Together). This protocol document describes the aims, study design, interventions, measures, and planned statistical considerations and analyses. Eligibility criteria, planned recruitment and retention strategies, and participant safety and adverse events monitoring are explained. Data capture, management and transfer procedures are delineated. We also have included the results of our formative work that consisted of focus groups, community assessments, and a pilot test of the study recruitment, intervention and measurement protocols. Lastly, a timeline for the project is displayed.

The primary aim of this 3-group randomized trial is to compare the effects of three distinct behavioral interventions on BMI in overweight/obese middle school, urban youth. Secondary aims are to: (1) evaluate the moderating effect of an enriched school environment on the impact of the child-family interventions on BMI; (2) compare the effects of the interventions on blood pressure in overweight/obese middle school students; and (3) assess the effects of the interventions on secondary outcomes related to cardiovascular risk (insulin sensitivity, lipids. CRP, fitness, body composition) and quality of life. We also will assess the costs and the cost-effectiveness of the interventions. Intermediate outcomes of the interventions on participants' diet, physical activity, sedentary behavior, and sleep will be determined and we will explore whether the impact of the interventions on relevant outcomes is influenced by selected mediating and moderating variables.

Our target population is Cleveland Metropolitan School District and public charter school students (6th-8th grade; n=360) recruited via an established BMI and BP screening program. One half of the schools will be "enriched" (participate in an innovative YMCA partnership to increase students' physical activity, and have supplemental nutrition education programs, social marketing, and navigators). The three study arms consist of: (1) SystemCHANGE (SC), a promising new behavioral approach focusing on system redesign of the family environment and daily routines (based on ecological and personal process improvement theory), (2) HealthyCHANGE (HC), a behavioral approach focusing on building skills and increasing intrinsic motivation (based mainly on cognitive behavioral theory), and (3) education-only (attention control). The intervention period is 36 months and measures are obtained at baseline, 12, 24 and 36 months. Intent-to treat analyses are planned to assess the value of our interventions as compared to education-only control to reduce BMI across a three-year study window. Our hypothesis is that both SC and HC will have greater impact than education alone on BMI.

2. SPECIFIC AIMS AND OBJECTIVES FOR MAIN TRIAL

Over 25 million U.S. children are overweight or obese[1, 2]. Cleveland has one of the highest obesity rates in the country (past studies have indicated that 42.8% of Cleveland children are overweight or obese). Cleveland is also the second poorest city in the nation. The burden of poverty and its impact on health is borne disproportionately by the region's children. Over 40% of the city's children live in poverty[3] and, in addition to the high obesity rates, past studies have noted that nearly one-third have elevated BP (EBP).

Our study focuses on both the child-family environment and the school-community environment in addressing obesity. It involves a 3-arm group randomized controlled trial of three behavioral interventions (1) HealthyCHANGE, a behavioral approach focusing on building skills and increasing intrinsic motivation (based on cognitive-behavioral theory with motivational interviewing components); (2) SystemCHANGE, an innovative behavioral approach focusing on system re-design of the family environment and daily routines (based on social-ecological and personal process improvement theories); and (3) education-only (an attention control group representing usual care referred to as Tools4CHANGE). All enrolled children and their families receive the consistent message of lifestyle change - modifying diet in accordance with a Dietary Approaches to Stop Hypertension (DASH)-like model, increasing physical activity, and decreasing sedentary behavior; however, the interventions differ markedly in approach, theoretical basis, and intensity.

Enriched school-community environments in this study refer to schools that participate in a school/community program (We Run This City [WRTC] Youth Marathon Program) that encourages physical activity in students by building their capacity to participate (walking or running) in a segment of the Cleveland Marathon, supplemented by project-supported fresh produce programs, school-wide social marketing campaigns, and trained "navigators" who facilitate participation among study participants and provide resource information to students and families. Non-enriched school-community environments are schools from the same school district that have none of these supplements to regular classroom-based health and physical education.

2.1. Primary Aims

The primary aim of this protocol is to conduct a 3 year randomized controlled trial that compares the effects of 3 distinct behavioral interventions on BMI in overweight/obese urban youth. Specifically, we will randomly assign 360 overweight or obese youth meeting eligibility criteria over two years to one of three behavioral interventions: SystemCHANGE, HealthyCHANGE, and education-only (control;Tools4CHANGE). Each intervention is described in detail below.

In addition, the study will assess the potential additive impact on BMI to be achieved by an enriched school-based intervention (We Run This City) in participants assigned to each of the three behavioral programs described above.

2.2. Secondary Aims

- Assess the effects of the interventions on cardiovascular risk factors (including BP, insulin sensitivity, lipids, CRP, body composition, biomarkers, fitness);
- Define the effects of the interventions on participants' (a) diet, (b) physical activity, (c) sedentary behavior, (d) sleep, and (e) quality of life;
- Assess the costs and cost-effectiveness of the interventions;
- Explore whether the impact of the intervention on relevant outcomes is influenced by selected (a) socioeconomic and demographic factors, (b) environmental (home, school, neighborhood) factors, (c) peer norms, and (d) personal and psychosocial characteristics of the child and parent(s)/guardians

3. BACKGROUND AND RATIONALE

Despite the explosion of childhood obesity[4, 5], treatments that provide substantial and sustainable benefits for a wide range of populations remain elusive. Many models for primary prevention of obesity have been studied, but successful templates for broad implementation are lacking[6]. Without effective preventions, it is particularly important to identify effective methods to treat the vast population of children who are already overweight or obese; without effective treatment, most will become obese adults[7-9]. Several treatment modalities have been developed and some show promise in specific populations[10-23]. However, treatments with substantial and/or sustained benefits in general populations are not known[9]. Further, many previous studies have involved non-representative samples, wide age ranges, absence of stratification by risk, and short follow-up periods- limiting their generalizability[24]. The lack of clearly effective or feasible methods to treat childhood obesity in general populations is particularly important because of the upsurge in associated co-morbidities, many increasing cardiovascular risk - including hypertension, insulin resistance, diabetes, lipid abnormalities, and sleep-disordered breathing[19,25-27].

The striking increase in childhood obesity is therefore of great concern because of the expectation that it will result in escalating morbidity and early mortality as these children mature[28-30]. Overweight children are significantly more likely to have coronary heart disease when they reach adulthood[31]. Further, because of today's childhood obesity rates, by 2035 there are expected to be more than 100,000 excess deaths from heart disease[32]. Direct medical costs of obesity in the U.S. are $147 billion[33] The data underscore the looming impact of today's obesity on tomorrow's population health and health costs.

Elevated BP (EBP) in overweight children and adolescents is an increasingly recognized epi-

demic[34-37]. Approximately 30% of overweight or obese 10-17yr olds have EBP[34, 38, 39]. Many overweight/obese youth with EBP already have other cardiovascular risk factors and evidence of end-organ damage[34,35,39-42]. Children with EBP are likely to become adults with EBP, and therefore are at increased risk for cardiovascular and renal disease[37, 43-46]. These data indicate that children with obesity and EBP are at particularly high risk, and require intervention[39]. Weight loss is a powerful tool to reduce BP in children and adults[37, 47]. A diet rich in fruits/vegetables, low-fat dairy, low-fat protein (e.g. DASH-like diet) and/or reduced sodium intake can also reduce BP, particularly in African-American adults[37, 48-51]. Combined with calorie reduction, activity, and behavioral interventions, DASH diets facilitate simultaneous reduction of BMI and BP in adults[52]. However, the most effective methods to facilitate adoption of these lifestyle changes in children are not clear, and education alone (usual care) is often ineffective[50]. This knowledge gap is particularly important because of the huge potential impact of small changes in BP- at a population level, only a 3 mm Hg reduction in systolic BP in adults can reduce mortality from stroke and cardiovascular disease by 8% and 5% respectively[37].

Racial and socioeconomic disparities in rates of obesity and its co-morbidities (including EBP) compound the issues. Although obesity has risen in all racial/ethnic groups since the early 1980s, nonwhite children are disproportionately affected[53, 54]. The reasons for higher prevalence of childhood obesity in non-white populations may involve genetic, cultural, socioeconomic, physiological, environmental factors, and interactions among these factors[55-57]. In the U.S., low socioeconomic status (SES) is a risk factor[58,59]. EBP is also more common in African-American children who are obese than in other groups[60]. Racial and socioeconomic disparities in prevalence of childhood obesity and EBP are of great concern, as they threaten to worsen already existing disparities in cardiovascular disease during adulthood. Based on high need and existing data gaps, this proposal targets an urban population (predominantly low-income, African–American) of overweight/obese youth, including half with EBP.

In spite of increasing evidence for biological contributors to obesity (including birth size, perinatal factors, breast feeding, gut flora, specific genes, and hormone-neural paths controlling appetite),[61-69] these do not account for the huge rise in childhood obesity and EBP since the 1980s. In contrast, there is strong evidence identifying several behavioral, contextual, and environmental factors as critical underpinnings of the obesity surge[70-81]. Family, school, peers, community, and policy act together (superimposed on biological predisposition) to provide the environmental contexts that shape children's energy intake and expenditure - and therefore together influence the development of obesity and its co-morbidities. The evidence that family, school, community, and policy environments are all likely contributors supports viewing childhood obesity from the perspective of a *socio-ecological model* [79, 82-84]. In this model, the child resides within several environmental systems: interpersonal (e.g. family, peers, culture), organizational (e.g. schools, churches), community (e.g., community organizations, neighborhood), and public policy[28, 82]. This model is rooted in the evidence that a single cause of the childhood obesity epidemic is unlikely, and

that processes leading to the surge of obesity probably involve combinations of factors at multiple environmental levels[85]. Accordingly, to gain traction in treating obesity, it is important to target more than one level of environmental influence. Further, it has been suggested that "small changes in one or more key factors may have large effects" overall[85]. This multilevel approach may be particularly suitable for addressing obesity and EBP, as recommended interventions for both include reduced intake, increased activity, and reduce sedentary behavior[19, 39, 70]. The multi-level approach has been effective in combating smoking and HIV, and encouraging physical activity, underscoring its potential[86-89].

Two critical levels for interventions aiming to reduce obesity and EBP in youth are the *child-family environment* (i.e. interpersonal level) and the *child-school-community environment* (i.e. organizational and community levels). Multiple factors within the *child-family environment* influence children's eating and exercise habits, and therefore may affect adoption of behaviors increasing or reducing obesity. These include (a) the child's personal characteristics (ethnicity, degree of overweight/obesity, sleep duration, presence/absence of co-morbidities, self-esteem, self-efficacy, motivation, depressive symptoms, stress, social problems, eating symptoms); (b) the parents' personal characteristics (e.g., BMI/BP status, psychosocial functioning, parenting stress, health beliefs and practices); and (c) family characteristics (e.g. socioeconomic factors, mealtime routines and problem-solving skills)[23, 90-101].The overall importance of the family is underscored by evidence that the success of child obesity intervention programs is directly related to parent involvement[102-104].

Factors in the child's school-community environment (e.g., access to healthy and unhealthy foods[104b,104c], neighborhood safety and walkability[81], venues for physical activity and social networks[104b]), together with family and peers, shape beliefs, norms and expectations about nutrition, activity, and body habits. Research indicates the potential for school environments to modify obesogenic behavior [105-107], although interventions at additional levels are likely needed to maximize potency and longevity of effect.

Interventions effectively targeting *both* the child-family environment *and* the child's school-community environment are therefore likely to be more powerful in reducing obesity and EBP than interventions addressing either alone. This may be particularly true for young adolescent[108-110]. If the fundamental message (e.g., reduce energy intake, increase physical activity, reduce sedentary behavior) is consistent across these two key environments, and if both provide opportunities to operationalize the message, there is likely to be greater impact. Yet, most previous interventions have been unimodal. In this study, we will directly address the need for multilevel approaches to childhood obesity, by targeting both child-family and school-community interventions.

4. FORMATIVE RESEARCH-- PHASE 1

4.1. Aims, Objectives, Interventions, Measurements

4.1.1. Aims and Objectives

As described in our original proposal, we have conducted or will conduct a total of four projects during the formative phase of the study. We:

1. conducted *focus groups* with children and parents to engage them as co-designers of the intervention and assessment protocols;
2. solidified our partnerships with the community to optimize parent interest and support and ensure smooth and successful integration of our study with existing programs, including the We Run This City Youth Marathon Program (part of our school-based intervention) and the BMI Screening Program partnership between the CWRU School of Nursing and the Cleveland Metropolitan School District (CMSD).
3. are collecting available *school and neighborhood level environmental data* for use in the main trial's analyses; and,
4. are conducting a *one-year pilot study* to assess feasibility and acceptability of the recruitment, intervention, and data collection protocols, as well as the impact of the interventions on the main trial's physiological and psychosocial outcomes.

Aim of Focus Groups: One of our interventions (SystemCHANGE) had been found to be successful with adults, but not yet adapted to be used with adolescents, and had primarily focused on exercise. Thus, after the initial adaptation of the intervention by the study team, we conducted a series of focus groups of parents and children, using a participatory design approach. Our goals were to: 1) identify the children's and parents' suggestions for making the intervention components culturally-appropriate for African Americans and Hispanics; 2) obtain reactions to and suggestions for refining the intervention materials and methods to ensure that they are engaging; and 3) determine age- and gender-appropriate refinements needed. We also solicited feedback on adaptations needed for the intervention's application across different families or contexts (e.g. attitudes regarding diet and exercise, barriers to healthy living and approaches that could be useful, socio-cultural influences such as family resources, home/work/school structures and schedules, etc). At the completion of these focus groups, we created an adaptive intervention that is now being tested in the pilot study.

Aim of Community Engagement: The aims of this component of the formative phase were to (a) establish a Community Advisory Board specific to the project, to conduct informational meetings with community partners, school officials, parents, and parents groups to assess community interest and perceived barriers to study recruitment and retention; (b) to solidify plans with our partners at the YMCA of Greater Cleveland and the Cleveland Metropolitan School District, who conduct the school fitness program, We Run This City, that we are integrating into the design of our study; and to work out the procedures for connecting the study to the BMI screening program that is conducted by the School of Nursing, which provides the study with its eligible population.

Aim of the Environmental (School, Community) Measures Scan: The aim of this component was to determine the feasibility of collecting and or accessing secondary sources of school and community level data that can be linked to each child in the study and to develop algorithms for creating child-specific environmental profiles based on the child's neighborhood socioeconomic status (e.g., based on income, female-headed households, education levels); school and neighborhood food environment (e.g., fast food to grocery/market ratio; classroom snacking policy, average fruits & veggie consumption and physical activity levels of school peers); safety (based on crime data and perceptions); and the built environment impacting physical activity (park, rec centers, green space). As part of this effort, we also sought to determine the feasibility of expanding the currently administered Youth Risk Behavior Survey to all CMSD schools so that school-specific norms on diet and physical activity opportunities and patterns could be accessed for use in the study.

Aims Specific to the Pilot Study: Because this was formative work, our major goal was to assess the feasibility and acceptability of the study protocols. We viewed the pilot study as an opportunity to learn more about the usefulness of our recruitment, enrollment, intervention, clinical and psychosocial measurement plans, data collection and management systems, and retention strategies. Importantly, we also wanted to assess subject engagement and satisfaction with our protocols. Process information is being carefully monitored throughout the pilot study and reflections on these data are conducted often by the study team to determine if adjustments are and will be needed (in the main trial). Our goal has been to learn as much as we can in order to make adjustments to the larger trial protocol to enhance its effectiveness, as well as assessing the role of the same moderators and impact of the interventions on the same set of mediators and physiological and psychosocial outcomes of the main trial.

4.1.2. Interventions and Measurement of the Pilot

As with the main trial, the population for the pilot were drawn from a list provided to the study team from the Cleveland Metropolitan School District (CMSD) of children who met our study criteria of being $\geq 85^{th}$ percentile on BMI and did not opt out of being contacted by the study. Letters and information on the study were mailed to parents, followed by phone calls by the study team. Among those who were interested, baseline intake assessments were scheduled

Baseline and Follow-up Assessments. Intake visits took place at the clinical research unit (CRU) at University Hospitals Rainbow Babies and Children's Hospital. Prior to any procedures, the study was fully explained using a standardized presentation designed for grade 5th literacy level and assent/consent obtained for participation in the study. After consent, baseline measures were taken, as described in later sections of this report. The child and parent are given lunch, during which time the accelerometer was given for 1 week wear, its use explained, and arrangements made for its pick-up, and the visit completed.

After the baseline visit was complete, randomization to one of the three study groups (SystemCHANGE, HealthyCHANGE, Control) took place. Data collectors were kept blind to study assignment throughout the study.

Procedures of the Pilot RCT. Those assigned to HealthyCHANGE or SystemCHANGE began their group meetings within 4 weeks of assignment. For those assigned to the usual care group, a dietitian met the family at a convenient location to provide the education intervention within 4 weeks of assignment. The behavioral intervention arms (HealthyCHANGE and SystemCHANGE) received 16 face-to-face group education sessions at 2-week intervals over an 8-month period, followed by rotating monthly face-to-face meetings or phone calls for a further 4 months. The control group received a one-hour dietary counseling session with a registered dietitian at initiation of the study and then received (or will receive) three additional contacts with study personnel approximately quarterly throughout the study year (this is in addition to the clinical assessment received by all study subjects). Two of the contacts are phone calls during which there is a general discussion reminding them of their participation in the study and checking on accuracy of home address and school attended. The third contact is a social gathering event (i.e., picnic, ball game) of small groups of families in the control group. Each intervention group included 10 children, each with at least one family member. Throughout the pilot study, we also monitor and systematically collect data associated with the fidelity of the intervention protocols.

Intervention Protocols. The pilot compares three intervention arms targeting the child-family environment: (1) SystemCHANGE (ecological and personal process improvement), (2) HealthyCHANGE (cognitive behavioral skill building), and (3) Tools4CHANGE (education only attention control group) - in achieving reduction in BMI. Each session consists of 45 minutes of behavior change content/activities consistent with the conceptual framework of the respective interventions and 45 minutes of either physical activity or diet information/activities (similar for both behavioral interventions). The child is weighed on a scale privately at each session as a method of providing feedback to participants on their progress. Each session is led by two interventionists trained in the respective intervention protocol. Parents and children are often separated to receive different content/activities during the sessions. Materials/activities addressing developmentally- and culturally-appropriate diet and physical activity and techniques for optimal management for older children and adolescents are provided. The sessions are designed to be very interactive and include cooking classes, guest chefs, and creation of photo or video presentations on healthy living by the children. A series of class attendance incentives is provided, including a “points reward system” for gifts. The 8 months of intensive face-to-face meetings is followed by 4 months of booster sessions (alternating telephone and face-to-face meetings at monthly intervals) reinforcing concepts presented in the earlier sessions.

4.2. Results from Phase 1

4.2.1 Focus Groups

Sixteen focus groups were conducted during February – April, 2011 (IRB #11-10-22). The purpose of the focus groups was to engage the children and their parents/guardians as co-designers of the study protocols. Students in the 6th, 7th and 8th grades from Cleveland Metropolitan School District who had a BMI in the 85th percentile or higher and their parents/guardians were recruited, drawn from a list of participants in the We Run This City Youth Marathon Program. Participants were invited to attend two different focus group sessions that were held one month apart. Children and their parents/guardians provided written informed assent/consent and completed demographic data during their first group session. Data were then collected in the form of information provided in round table discussions in response to open-ended questions, a structured interview guide, and graffiti art. Participants' reactions to and suggestions for improving study recruitment and retention approaches, data collection procedures, and intervention format and materials were sought. All leaders were trained; the majority of the sessions were led by persons of the same race as the participants. Data were collected using digital recordings and observer notes. A total of 16 focus group sessions were conducted: 8 each of children and parents/guardians. The children's focus groups were gender-specific. Each focus group session lasted approximately 2 hours and consisted of 8-15 participants. Adults received a $50 money order and children received a $25 money order for their participation in each session. Data were transcribed and analyzed using qualitative approaches.

The sample consisted of 45 children and 44 adults. The children had a mean age of 12.6 years (range = 11-15). 51% of the children were male; 49% were female. The children were evenly distributed among the 6th, 7th and 8th grades. 24% identified themselves as Hispanic/Latino, 64% as African-American or Black, 16% as White and 7% as mixed race. 49% of the children reported that neither parent was married. The adults had a mean age of 43 years (range = 29-85). 84% were female; 9% were male, 7% declined to identify their gender. 15% of the adult participants identified themselves as Hispanic/Latino, 2% were American Indian/Alaskan Native, 64% were African-American or Black, 18% were white, and 14% identified themselves as other.

Results indicate that parents and students (1) are interested in behavioral interventions such as those planned, (2) strongly believe that the emphasis should be on health and wellness, rather than specifically on obesity, (3) would like the method of recruitment to involve letters (with opt-out option for those wishing not to be contacted further) followed by telephone calls, (4) agreed that mixed male and female intervention groups are acceptable, and (5) want the intervention sessions to be held in convenient community venues. Parents and children had some hesitation about the 3-year commitment of the intervention component of the main study and provided ideas about how to make the interventions enjoyable, useful, and

engaging over the course of the study. Boys and girls differed in their perceptions regarding healthy living. The majority of the girls expressed that they felt healthiest when they were younger because they were thinner. Boys expressed that they felt healthiest when they were involved in organized sports. The girls described that they wanted to lose weight, whereas the boys placed a strong emphasis on both muscle and bone strength. Girls stated that they were motivated when they were on a team, training for an event, or had someone to be active with. More than half of the boys said that they were motivated by role models, performance goals and personal outlets.

4.2.2. Community Engagement

We undertook a number of different efforts to solidify our partnerships with the community to optimize parent interest and support and ensure smooth and to successfully integrate our study with existing programs, including the We Run This City Youth Marathon Program (part of our school-based intervention) and the BMI Screening Program partnership between the CWRU School of Nursing and the Cleveland Metropolitan School District (CMSD).

During the first six months of the project, we established a Community Advisory Board (CAB), which is comprised of (1) school and public health officials; (2) parent leaders (school-based); (3) parents/guardians of participant-aged children; (4) neighborhood leaders and other community stakeholders, as well as representative from both the YMCA of Greater Cleveland and the Cleveland Metropolitan School District, who serve our primary institutional partners. We have sought their opinions on methods of recruitment and engagement of families, advertising, screening procedures, retention strategies, intervention and data collection locations, perceived protocol burden, the importance or not of gender-specific intervention groups, and barriers to the above due to beliefs or perceptions.

With regard to the school-based, We Run The City (WRTC) Youth Marathon Program, we have finalized the role of the Navigator and how they will support and supplement the WRTC program in such a way to provide a natural support for IMPACT study participants to engage and stay involved with the WRTC program. Navigators will provide focused and interactive activities (on nutrition, physical activity, stress and sleep) at both the school and team level, attend training sessions at least once a week and participate with their assigned teams on race day.

In order to better understand how to retain study participants in the WRTC, we also examined program retention among overweight and normal weight children in last year's (2011) program, and conducted a series of interviews with Marathon coaches and previous WRTC participants (CWRU IRB- addendum to WRTC protocol #20100518, approved 21 August, 2011) to assess the factors that were associated with low attendance, program dropout and retention among overweight participants.

In 2011, 35% of all WRTC participants were overweight (85-94th percentile) or obese (>95th percentile), and overall, approximately 70% of WRTC participants (normal, overweight or obese) completed the training and participated on race day (note: the primary reason for program dropout is poor grades or disciplinary reasons). When comparing participation rates by weight status, the obese participants completed fewer training sessions and were slightly less likely to participate on race day than either overweight or normal weight (<85th percentile) children; however, there were no differences in training levels or program retention between overweight and normal weight participants. This leads us to believe that we will need to add additional encouragement to the obese IMPACT students who participate in the WRTC program; however, with encouragement the program should retain most of the IMPACT students.

As part of the pilot phase of the IMPACT study, we selected and interviewed 22 children from 6 different schools who participated in the 2011 WRTC program, chosen based on their weight status (60% were overweight (85th -94th %tile) and 40% obese (>95th %tile)) and the level of sustained involvement in the program (half completing more than 10 training sessions or completing more than 20 miles during the 16-week training period, and half of whom did not). We sought to better understand the factors the contributed to drop out, as well as retention among overweight and obese participants.

Surprisingly, little distinguished the overweight/obese child who completed versus did not complete the program. Regardless of whether or not they completed the program, the majority of overweight and obese participants said they joined the program to “get fit and healthy”. Encouragement from coaches and friends in the program was also an important part of the program and 85% of the students interviewed reported they had several friends on the team. Where completers and non-completers differed was in their perceptions of exercise. For example, 62% of overweight participants enjoyed running while only 33% of obese participants responded with a similar response. Overall, students enjoy WRTC, like their coach, have fun with friends, and participate in an active program that encourages a healthier lifestyle.

Other Activities: Our partners and their commitment to the IMPACT study are highlighted in a video (http://www.youtube.com/watch?v=4FKy6pKeaAY) that was produced by the Cleveland CTSC (Clinical and Translational Science Collaborative) to be shown to Dr. Francis Collins, Director of the NIH as part of a recent visit to Cleveland. The video has turned out to be an invaluable tool for sharing (and selling) the project to the local community.

Lastly, due to economic issues and a broadening scope of educational options through a school-voucher program, the number of children enrolled in the Cleveland Metropolitan School District (CMSD) has dropped significantly in the past five years. In order to ensure that we will have an adequate pool of possible students to draw from, we will need to expand the population of students that are screened for BMI, particularly from the growing number of

charter schools in the city. To this end, the CWRU Prevention Research Center for Healthy Neighborhoods (Borawski, PI), will conduct a BMI and BP screening program in interested charter schools, using the same screening protocol developed by the School of Nursing for their program with the CMSD. This will add an additional 450 children to the population of eligible students.

4.2.3. Assessment of School and Community Environmental Data

During this formative phase, we have identified four tools to be used to collect school and community environmental data. These tools are briefly discussed below.

The School Food and Beverage Audit Tool is a modified version of the food and beverage marketing and advertising too used by Samuels and Associates, commissioned by The California Endowment and the Public Health Institute[111]. The SFBA Tools will be used to assess the availability of food and beverage and healthy or un-healthy marketing on school grounds. The tool will also assess discrepancies in the school menus and what is actually served in the cafeterias, locations and availability of vending machines, the quality and availability of school dining facilities, and school stores when applicable. This training protocol is being finalized and data will be collected in May 2012.

The Neighborhood Food Environment Database (NFED) will be developed in conjunction with the Prevention Research Center for Healthy Neighborhoods (Borawski, PI) to allow us to create student-centric scores for analysis. We have begun with the identification of locations in the City of Cleveland that sell food using the Cleveland food vendor inspection database[112] as well as other sources when appropriate. We expect that we may need to add to this database as explained in more detail below.

Using Arc-GIS[113], a geographical information system software package, we will calculate a 0.25 and 0.75 mile Euclidean buffer around a participant's home and school in order to conceptualize the immediate surroundings (0.25 mile) and neighborhood food retail environments (0.75 mile buffer) respectively. The number of food retail establishments that fall within these buffers will be enumerated and used to calculate densities of facilities within a given neighborhood.

During this formative period, we have worked with local government to acquire the food vendor inspection database for the city of Cleveland, which included all vendors inspected in 2010. To establish the completeness of this dataset, we created a GIS map layer using the database, then added the CMSD schools as an additional layer. Using Arc-GIS, a mapping software package, we were able to draw a 0.25 mile Euclidean buffer around each school to identify the food retail locations. Following creation of these buffer zones and corresponding listings of food retail locations, study staff set out to "ground-truth" the actual food retail environment. Armed with maps and location addresses for several schools, staff established that identified vendors were still in operation and also noted other vendors that were not

listed. In reviewing these schools, it was found that we did not have 100% agreement for any of the six schools, and we would need to ground-truth food retail locations.

Given the vast undertaking of ground-truthing all food-retail within the city of Cleveland, we have prioritized such that we will ground-truth all food retail locations within 0.75 mile Euclidean buffer around each school and each participant's home address. Food retail locations that are identified via ground-truthing will be added to the database, allowing us to create child-centric scores related to food retail environment around the home and the school.

We will also be drawing objective social environment data from the Northeast Ohio Community and Neighborhood Data for Organizing (NEO-CANDO), a free and publicly accessible social and economic data system developed by the Center on Urban Poverty and Community Development, housed at Case Western Reserve University. NEO-CANDO will provide data on indicators including poverty, education, employment, public assistance, and crime at the census-tract level. This will allow for social and economic indices to be created for each participant based on where they live. We have already begun to download the relevant indicators from NEO-CANDO for all census tracts in the city of Cleveland, and we are currently waiting for all data from the 2010 US Census to be uploaded to NEO-CANDO (should be completed within the next several months).

Finally, the Youth Risk Behavior Survey will be utilized to capture school-specific normative data on physical activity, nutrition, and student perception of school policies in these areas. We have confirmed that the PRCHN will administer the survey in all K-8 schools within the Cleveland Metropolitan School District and all charter schools who participate in the screening program, every other year (beginning in spring 2012). This was expanded from their prior methodology of a random sampling of schools. The full district approach will allow us access to school-specific normative data on all children in the study, even if they move from their original school.

4.2.4. Results from the Pilot Study

We are conducting a one year pilot study to assess feasibility and acceptability of the recruitment, (family) interventions, and data collection protocols. Outcome measures are obtained at baseline, 4 mo, and 8 mo, with a meeting at 1 year to assess overall retention. Here are the highlights of the pilot:

- We recruited 25 overweight/obese children in the target range and 25 parents (1/child). The children were 56% female; most (88%) were African-American, with 4% each American-Indian, Caucasian, and Hispanic. Of parents, 88% receive food stamps or SNAP, and 80% reported annual household incomes under $35,000 (with 56% under $25,000).

- They were randomly assigned to the two behavioral interventions, HealthyCHANGE (n=10) or SystemCHANGE (n=10), or to education-only control (Tools4CHANGE; n=5);
- Intake visits (including assent/consent and baseline measures went very smoothly;
- We designed a responsive intervention approach;
- Intervention groups have been doing well to date (6 months into the pilot study) with good attendance and engagement;
- Data are collected using electronic data capture and management using REDCap, audio-supported, computerized (iPad) surveys for parents and children. Data collected were clean and complete;
- There was 96% retention for the 4-month follow-up visits.

4.2.5. Lessons learned from the pilot

Ties to the School Year: Because our subject pool is obtained from the Cleveland schools, we have found that it is critical for us to conduct the screening for the main trial during the school year from January through April in each of the next two years. In turn, this allows us sufficient time to conduct baseline measures on the children during the spring and summer period each year and to begin the intervention (administered via 5 cohorts of 45 children/parents each) prior to fall.

Recruitment Strategies: We believe that a major strength of our study is our ability to recruit directly from the Cleveland Metropolitan School District (CMSD) through a successful screening program administered by faculty and students from the CWRU School of Nursing. The data are turned back to CMSD, who then provide us with the list of eligible students whose parents have not opted out of further contact and their contact information. The pilot study allowed us to test the effectiveness of this screening program as our primary approach for identifying eligible participants (i.e., ≥85th percentile). The screening and eligibility process went very well. However, it was disconcerting (while not completely surprising) to find that the information on nearly half of the eligible students was no longer valid when we reached out to them. Saying that, we were extremely pleased to find that of those who we were able to contact, about a third came for the baseline assessment and consented to enroll in the intervention phase of the project. Thus, for the main trial we have made changes to our protocol to address the issue of updated information to not only ensure adequate numbers for recruitment but to ensure that more Cleveland families have the opportunity to participate. Subsequently, we have met with the school district and they will allow us to obtain updated information directly from the students during the screening process, which will significantly increase our recruitment pool and provide us with an adequate pool from which to draw our 180 subjects each year.

Measurement Protocols. Our intake and follow-up measurement protocols have been shown to work well. Although the pilot evaluation visits went very well without complaints by

participants and with full completion of data collection, we have reduced our intake protocol from 3.5 hrs to 2.5 hrs to further reduce subject burden. We learned that some of the children who had screened at or above the 85th BMI threshold for participation in the study, fell below this threshold at the actual intake baseline visit (some kids grew a lot during this 3-4 month period), and thus clarified our protocol regarding how to manage this. We have decided that they must meet the study eligibility criteria of having a BMI of $\geq$ 85th at the time of the baseline measure. We will thank families who no longer are eligible and pay them the visit incentive.

Intervention Design and Delivery. We learned from the focus groups of parents and children about the importance of making such a long intervention (3 years as required for all COPTR projects) fully engaging, fun, informative and feasible. Thus, we have designed the intervention group sessions to be very interactive and include learning games, guest chefs, group outings (e.g., wall rock climbing, sports events), PhotoVoice, and the creation of healthy living commercials. In our pilot study, these activities have been well received and create a lot of participant enthusiasm for the project and each others' success. Although we learned in the focus groups that we did not need to have gender-specific intervention sessions, we have learned in the pilot study that both parents and children prefer to be separated for much of the intervention session time (children are much more active in participation when parents are not present to hear their responses - and the parents have acknowledged this as well). We have now redesigned the sessions for "breakout time" where parents and children separate following some common time together at the beginning and end of the sessions. This change has necessitated the need for a third interventionist in some of the group sessions. We also have learned the need for ongoing incentives for engagement in the intervention meetings and thus we incorporate many "grab bag incentives" and opportunities to participate in drawings for larger prizes for attendance. Lastly, based on recent literature[114] and our pilot experiences, we have built maximum flexibility into the sequencing of our educational material and have added more individual counseling so that if participants miss intervention sessions they are not disillusioned and think that they are "too far behind to catch up." We have found this flexibility to be more acceptable to participants and important in keeping them engaged over the long intervention and study follow-up period.

Data Collection: For the pilot, we developed a fully integrated, electronic data capture system, using audio-supported iPads and the REDCap system. We were pleased to find that the system worked extremely well. Both adolescents and parents acclimated very quickly to using the IiPads, and the integration of the clinical, dietary, accelerometer and survey data into one system (REDCap) has greatly reduced the post-data collection cleaning and management, which will in turn expedite the return of the data to the RCU. Due to the ability to set ranges, skip patterns, and required responses (including refusal), the data are clean and complete, with very little missing data.

4.3. Key Recommendations for Phase 2

- Need to screen and recruit for main trial beginning in January of each of the next 2 years in order to start the last of 4-5 intervention groups by fall of each year to assure adequate intervention exposure to school-level intervention
- Need to recruit at urban schools other than Cleveland Metropolitan School District, such as Charter Schools. This is also important because of a shift within Cleveland, as children are increasingly enrolled in charter schools
- Need for a protocol for managing child change in eligibility criteria for children losing eligibility between screening and intake assessment (BMI drops below 85th %)
- Plan to get updated phone numbers of students at the time of school screening (closer to enrollment in study to reduce number of wrong phone numbers)
- Remain attentive to intervention design and subject incentives for maintaining subject participation in interventions.
- Initiate re-invigoration protocol and responsive intervention protocol for individuals/families who have missed several intervention sessions.

5. MAIN TRIAL STUDY POPULATION AND ELIGIBILITY

Potential participants will be drawn from a list provided to the study team from the Cleveland Metropolitan School District (CMSD) and participating public Charter Schools of rising 6th graders (going into the 6th grade in the fall) meeting the study criteria of a BMI $\geq$85th percentile whose parents do not opt out of being contacted by the study team. These constitute the pool from which the participants in this study will be sought, as described. Based on prior preliminary work, we expect approximately 40% of children to be identified as potentially eligible. Based on the demographics of the CMSD and Charter Schools, we expect the population for this study to include approximately 70% African-Americans, 15% white, 11% Hispanic, 3% other, and be predominantly low income.

Specifically, the CMSD schools are part of a cooperative agreement between CMSD and the Case Western Reserve University School of Nursing in which the School of Nursing provides annual standard school screenings of BMI and BP in the CMSD schools as a service. The CWRU Prevention Research Center for Healthy Neighborhoods (PI E Borawski) has recently established a similar service for charter schools within the city of Cleveland. CMSD and the participating charter schools send the screening results to the parents in a packet; for children with BMI $\geq$ 85th percentile (i.e. CDC definition of overweight or obese[70]), the letter also indicates that the child may be eligible to participate in a program focusing on health that is led by Case Western Reserve University. The letter explains that the Case project team will contact the family to explain more about the project unless the family chooses to opt out of being contacted further about the study (by telephoning or e-mailing). Following this, CMSD and participating Charter Schools will send the IMPACT team a list of eligible students whose parents did not opt out of being contacted. The IMPACT team then sends a letter and a bro-

chure to families whose children are potentially eligible and who have not opted out; the letter explains that an IMPACT team member will be contacting the family by phone in approximately 1 week to see if they are interested in learning more about the project and potential participation. An IMPACT team member will then call the family and offer more information about the study by phone or, if the family prefers, in person through meeting at a convenient place at the families' discretion to provide any further information the family wishes and to further pre-screen for eligibility (see below; this has worked well in the pilot study).

5.1. Eligibility Criteria

The Main Study inclusion/exclusion criteria are listed below, and will be ascertained through the recruitment process which begins after CMSD and Charter Schools provide contact information for families (of potentially eligible children) who have chosen not to opt out from further contact regarding the project. To be eligible for the study, a child must be a rising 6th grade CMSD or Charter School student who is found at school screenings to be overweight or obese (BMI 85th- 94th percentile or ≥ 95th percentile for age/sex respectively[70]) and whose parent(s) did not opt out.

5.2 Exclusions

The exclusion criteria for entering the trial include:

- taking medications that alter appetite or weight (e.g. glucocorticoids, metformin, insulin, Risperidone (Risperdal), Olanzapine (Zyprexa), Clozapine (Clozaril), Quetiapine (Seroquel), Ziprasidone (Geodon), Carbamazepine (Tegretol), Valproic acid (Depakote/Depakene/Depacon), Aripiprazole (Abilify), Orlistat (Xenical), Sibutramine (Meridia), Phentermine, Diethylproprion (Tenuate), Topirimate (Topamax), glitazones;
- stage 2 hypertension or stage 1 hypertension with end organ damage (left ventricular hypertrophy, microalbuminuria) as these conditions would best be treated by medication rather than lifestyle interventions[39];
- Sickle Cell Disease (makes measurement of HbA1C inaccurate);
- severe behavioral problems that preclude group participation (as reported by parent/guardian);
- child involvement in another weight management program;
- family expectation to move from the region within 1 year, or
- the presence of a known medical condition that itself causes obesity (e.g.,Prader-Willi syndrome).

ADHD medications will not be an exclusion criterion because of their widespread use in this population, but their use will be measured. Additionally, known co-morbidities such as hyperlipidemia, asthma, sleep apnea are not themselves reasons for exclusion as they represent co-morbidities commonly found in overweight/obese youth, and to exclude them

could make the population non-representative. However, their presence/absence will be considered a covariate and such children will be eligible for the program unless physical activity is precluded by their physician. Similarly, if during the course of the study, a child who was eligible on study entry develops a condition that would have been exclusionary at entry (eg begins a medication such as glucocorticoids), that child will not be excluded from the protocol but his/her new condition will be noted as a covariate.

If a family has more than one eligible child, the one with the birthday closest to a set date will be included for data collection (although others can take part in the intervention sessions). Disabilities (e.g. blindness, hearing loss) will be accommodated using the services of the FIND Lab (Full INclusion of persons with Disabilities in research), directed by MPI Moore.

Parents/guardians. The study participants will also include one index parent/guardian for each child participant. If more than one parent/guardian is available, we will ask the parent/guardian signatory (index study parent) to be the one likely to be most available to bring the child to visits. Data will be collected from this index parent/guardian. However, all parents/guardians may participate in the project, as they may attend Intervention meetings. If the index parent/guardian becomes unavailable during the course of the study (e.g. dies, moves without the child), the family will be asked to identify another index parent/guardian who would participate after signing consent. For the index parent/guardian, inclusion criteria are being the parent or guardian of an eligible child and being able to attend data collection sessions. Parents are strongly encouraged to participate in the intervention visits but it is not mandatory they participate. The intervention team will have guidelines regarding reaching out to families who are not attending the intervention visits.

5.3 Inclusion Statement

The study population consists of children who are rising 6th graders in the spring of 2012 (Cohort 1) or 2013 (Cohort 2) who were identified through the school-based screening as having BMI $\geq 85^{th}$ percentile, whose parents did not opt out of being contacted, who did not meet any of the exclusion criteria, whose parents provided consent and they provided assent to participate, and who have been randomized into the study.

6. RECRUITMENT AND RETENTION

6.1. Recruitment Tracking

Recruitment begins after CMSD and the public Charter Schools provide the project team with the parent/guardian names and contact information of all rising 6^{th} graders who (1) participated in the school BMI and blood pressure screening and who are potentially eligible for this project (i.e. BMI $\geq$ 85th percentile) and (2) parents did not opt out of being contacted.

The research team will send a letter to the homes of parents/guardians on the list provided by CMSD and participating Charter schools that briefly describes the study and states that they soon will be contacted by phone to learn more about the project. This letter will also include a brochure introducing the study. Within 2 weeks after the letter is sent to homes, trained research team members will contact the parent/ guardian of the potentially eligible children by phone to provide a basic description of the project and ask if the family is interested in learning more about the study. Study personnel will offer to present the information about the study to the parent/guardian in several ways: 1) further discussion over the phone at this time, 2) arrange to meet the parent/guardian at a convenient time and place, 3) send information through mail if family has not received. If a parent/guardian wishes to receive more time to consider participation, follow-up contact by phone or in-person will be done. If a parent/guardian expresses immediate interest in participation whether by phone or in-person, the "Pre-screening Information Sheet" will be read to them and the pre-screening questions asked to the parent/guardian.

People may also find out about the study from community and school meetings where the study is being discussed. These people can call the project office to find out if they are eligible, and the information provision system detailed above will be offered.

Because it is necessary for the research team to collect pre-screening information to determine full eligibility into the study, a "Pre-screen Information Sheet" has been developed. This "Pre-screen Information Sheet" will inform parents/guardians about the study, and what information will be collected related to their child's medical information at the time of recruitment (past medical history, illnesses, medications; see inclusion/exclusion criteria). The Pre-screen Information Sheet" will also include study contact team names and phone numbers so the parent/guardian can contact study team at any time with questions. The parent/guardian will be asked questions (pre-screening script attached) related to the presence/absence of the exclusionary criteria for study eligibility and to confirm family contact information (addresses, phone numbers, email addresses). Study consent and baseline intake visits with interested families will be scheduled for a later date in the Clinical Research Unit.

Recruitment tracking will also include standardized forms developed by COPTR (see Recruitment and Retention Tracking Protocol). In these forms, we will define number screened as the number who were found to be overweight or obese on school screenings, did not opt out of further contact by the research team, and were screened for inclusion/exclusion criteria. We define he number eligible as the number eligible for recruitment after screening. We define the number consented as the number who consented/assented to participation in the study conditional on their completion of measures required for randomization. We define the number randomized to be those who, following consent, met eligibility for randomization (ie collection of required baseline measures) and were randomized.

6.2. Recruitment of Minorities

Racial and socioeconomic disparities in prevalence of childhood obesity are of great concern, as they threaten to worsen already existing disparities in cardiovascular disease during adulthood. Based on high need and existing data gaps, our study targets an urban population (predominantly low-income, African–American) of overweight/obese youth, many with elevated blood pressure. Our recruitment targets children living in the city of Cleveland, the second poorest city in the country after Detroit. Based on the demographics of the CMSD and Charter Schools, we expect the population for this study to include approximately 70% African-Americans, 15% white, 11% Hispanic, 3% other, and be predominantly low income. The District reports that all children (100%) within the Cleveland Metropolitan School District qualify for the free and reduced lunch program.

6.3. Procedures for Obtaining Informed Consent

Families who are interested in participating and appear eligible based on pre-screening will be scheduled for a baseline visit in the CRU at which time the study will be re-explained and the consent and assent forms for participation signed. Members of the study team who are certified in Human Subject Protection will obtain informed consent for the study. The research protocol, risks and potential benefits will be discussed with the parent/guardian and youth privately. They will have time to consider participation in the research study and to have their questions fully answered. The consent and assent forms (Appendix F) will indicate that randomization and participation is entirely voluntary and that the family can withdraw at any time.

At the intake baseline visit (time 0), members of the research study team will initially explain the study using the consent and assent forms. All research study staff will be CREC certified. All questions will be answered. Inclusion and exclusion criteria will be rechecked to ensure eligibility. This includes checking weight and height to see if BMI still meets eligibility requirements at baseline as per COPTR national guidelines. If the child is eligible and the family is interested in participating, assent and consent will be obtained for participation in the full study. Rarely, children's BMI at the CRU visit will be below the threshold for eligibility (ie their BMI will be <85th percentile; this may occur if the child has grown a lot in height between their school screening and CRU visit). The consent form will specify that if the BMI criterion is not met at the baseline visit (ie BMI<85th percentile), the participant will not be eligible for participation based on national COPTR guidelines; in such rare occurrences, the family will receive the visit incentive as if they had completed the entire visit and will receive handouts discussing healthy living. The consent forms will also specify that if the screening tests indicate diabetes (FBG > 126 mg/dl) or renal disease (elevated BUN, creatinine), those children may not be eligible for the full study since other specific medications may be needed (we anticipate this to occur very rarely); however, with the family's permission, the primary care physician will be notified and referral to a specialist offered. We expect the consent

process will take about 30 minutes. The full consent/assent process plus collection of baseline data is expected to last approximately 2.5 hours. If a participant is found not to meet the eligibility criteria at the baseline visit, the family will still receive the monetary incentive and transportation and parking reimbursement.

6.4. Randomization Procedures

6.4.1. Eligible Population and Selection of the Study Sample

The study sample of 360 children will be enrolled over two years in two waves (180 in Project Year 3 and 180 in Year 4). In each of these years, between January and May, approximately 3,200 children in urban Cleveland entering the 6th grade in the upcoming Fall will be screened for BMI as part student service-learning engagement projects at Case's School of Nursing and the Case Prevention Research Center. The IMPACT project team will be provided with contact information (including parent/guardian names) for all screened students who are potentially eligible for this project (i.e. BMI ≥ 85th percentile) – excluding those children whose parents/guardians opted out of further contact. Based on our pilot work, we expect approximately 1,500 children in each of the two years will meet BMI eligibility standards for this study.

We will thus have the entire sampling frame of 1,500 eligible parent-guardian/child pairs available to us before we enroll any subjects for that year. Based on our pilot data, we expect that 20% of families will not be available for contact (due to incorrect phone numbers, etc.) so we expect to approach approximately 1200 parent/family dyads for participation in each year. We will approach subjects for participation selecting randomly from the sampling frame within four strata defined by two important criteria.

Specifically, we will first identify: (A) the child's region of residence (East Side or West Side of Cleveland – we expect approximately 50% of eligible students to fall in each region, based on current school enrollments) and (B) the child's school's enrichment status (enriched or not enriched – we expect approximately 40% of eligible students will fall in enriched schools, based on regional enrollment in the enrichment program).

The crossing of region and enrichment yields four combinations (East enriched, East not enriched, etc.) Grouping intervention sessions by region facilitates convenient access for the child and family – each of the small groups for intervention delivery will be restricted to students from the same region (so we'll have some East small groups and some West small groups, but no groups requiring students at enrollment to cross regions.) School enrichment status is a key part of some secondary analyses.

In each year, we will divide the enrollment period into four scheduling windows, each filled by contacting approximately 300 families. In each window, we will concentrate on either East or West region children and select subjects by moving down the sampling frame, after randomly

ordering the names in the initial frame within each of our four region*enrichment groups. Should our eventual acceptance rate be less than we expect, we will be able to add a fifth scheduling block in each of the recruitment years by approaching more charter schools to participate in the BMI screening program. We will review our procedures after evaluating the success of Project Year 3 recruitment so as to make appropriate adjustments to this selection procedure in Project Year 4.

6.4.2. Randomization and Assignment to Study Groups

We expect that of the 300 families approached in each of the four scheduling windows in each year, at least 45 will consent/assent to participate and will meet eligibility requirements for randomization (i.e., including BMI confirmed as ≥ 85th percentile; completion of baseline anthropometrics, BP, questionnaires [other than those declined for personal reasons], accelerometry for minimum of 4 valid days, minimum of two diet recalls [2 weekdays or 1 weekend, 1 weekday], and fasting blood tests [unless staff unable to draw blood] within one month of baseline visit) This is expected to yield approximately 180 subjects (parent-child dyads) per year for each of two years who will then be randomly and equally assigned to one of three study arms: HealthyCHANGE, SystemCHANGE, or a low-dose education-only control group, using the following approach.

We wish to ensure that three key variables (obesity status, blood pressure status, and gender) are balanced (at least in distribution) across our three study groups. These are (in order of importance from highest to lowest):

1. Baseline obesity status (BMI in 85th through 94th percentile vs. BMI ≥ 95th percentile)
2. Baseline blood pressure status: (elevated [either SBP or DBP > 90th percentile] as defined through rigorous school screening using criteria of The Fourth Report[39] or not)
3. Gender (male, female)

Each child's value on these three key stratification variables will be entered into the overall study database at the time of the baseline assessment by trained data collectors. Once a child has completed all procedures needed for randomization (described above; 6.4.2), the study coordinator (who will not be involved in data collection) will access and record a computer-generated study group assignment for a family, including the subject ID, level of each of the three minimization variables, and the randomization algorithm (note: data collectors are therefore kept blinded to participants' group assignments). The coordinator will both telephone the family to inform them about the group assignment and will send a welcome letter providing the same information, the assigned interventionist will then also contact the family to welcome them to the intervention and arrange logistics for their participation according to the protocol, and participants will be given token items branded for the study (T shirt, water bottle). .

Subjects will thus be randomly assigned to one of the three study groups using the *minimization* method[115,116] as implemented within our REDCap system. The minimization approach may be thought of as a generalization of Efron's[117] original biased coin approach, but applied to the problem of more than two treatment arms and multiple prognostic factors for stratification. We have used this method in previous clinical trials with good results. As compared to simple random assignment or to stratified randomization using the permuted blocks approach, this technique has been shown to achieve better balance between study group assignments within levels of stratification variables.[115]

The minimization technique may be less familiar than alternative structures for sequential group assignment with similar goals, such as permuted blocks or biased coin, so we provide some details here. Our three key stratification variables (BMI at two levels, BP at two levels and gender) form a set of 8 strata in the experimental design, as shown in the table below.

The first subject is randomly assigned with equal probability to a study group (SystemCHANGE, HealthyCHANGE or education-only [Tools4CHANGE].) The approach for determining subsequent subject's group assignment is determined by the minimization algorithm, and this is best illustrated by selecting an arbitrary point within the trial.

Suppose that 20 subjects have been assigned to groups so far, and we have the following distribution.

Table 6.1. Minimization Approach: Distributed by Study Group and Stratification Levels

Study Group	**BMI Percentile**		**BP Elevated**		**Gender**		**Total**
	85-94	95+	Yes	No	Male	Female	
SystemCHANGE	2	5	3	4	4	3	**7**
HealthyCHANGE	3	3	4	2	2	4	**6**
Tools4CHANGE	4	3	3	4	3	4	**7**
Total	**9**	**11**	**10**	**10**	**9**	**11**	**20**

Suppose the next patient (subject 21) has baseline BMI in the 85-94 percentile range, BP is not elevated, and gender is female. As applied to subject 21, the current balance of assignments across study groups is the range (maximum – minimum) of each column that applies to subject 21's status. For instance, in the 85-94 BMI group, we have 2, 3 and 4 assigned subjects – a range of 4-2 or 2. In the BP not elevated group, we have 4, 2, and 4 – so the range is also 2, and in the female group, we have 3, 4 and 4 subjects, so the range is 1. We calculate a weighted sum across these three range results, weighting BMI percentile at 3, BP elevated at 2, and gender at 1, based on our importance ratings. Thus, our total balance score is 3(2) + 2(2) + 1(1) = 11 at present for subjects in Subject 21's stratum. Our

job is to select the group assignment for Subject 21 that produces the smallest balance score. If two or more assignments are tied, we randomly choose between them.

Option 1: If we assign Subject 21 to SystemCHANGE, we will have the following table:

Study Group	**BMI Percentile**		**BP Elevated**		**Gender**	
	85-94	95+	Yes	No	Male	Female
SystemCHANGE	3	5	3	5	4	4
HealthyCHANGE	3	3	4	2	2	4
Tools4CHANGE	4	3	3	4	3	4
Column Range	4-3 (=1)		5-2 (=3)		4-4 (=0)	
Importance Weight	3		2		1	

Balance score is 3(1) + 2(3) + 1(0) = **9** if Subject 21 is assigned to SystemCHANGE

Option 2: If we instead assign Subject 21 to HealthyCHANGE, we have the following:

Study Group	**BMI Percentile**		**BP Elevated**		**Gender**	
	85-94	95+	Yes	No	Male	Female
SystemCHANGE	2	5	3	4	4	3
HealthyCHANGE	4	3	4	3	2	5
Tools4CHANGE	4	3	3	4	3	4
Column Range	4-2 (=2)		4-3 (=1)		5-3 (=2)	
Importance Weight	3		2		1	

Balance score is 3(2) + 2(1) + 1(2) = **10** if Subject 21 is assigned to HealthyCHANGE, and, similarly, the Balance score is 3(2) + 2(2) + 1(1) = **11** if patient 21 is assigned to Tools4CHANGE. So, Subject 21 would thus be assigned to SystemCHANGE.

Note that this minimization procedure can be generalized in several ways. It can be implemented with other (or without) importance weights, with any balancing score (for instance, standard deviations rather than ranges) and also can assign groups with varying probabilities based on the balance achieved to date (i.e. 2/3 for the study group which most improves balance and 1/6 for each of the other two groups) rather than selecting the best balance with probability one.

As described in section 12, the randomization database security settings will be specified so that, once loaded, no one on the study team will have write privileges for the algorithm, so as to prevent anticipation or subversion of the randomization process, nor will the person receiving the assignment be able to see the assignments of other participants at the time of assignment.

6.5. Techniques for Retention

The following describe the techniques that will be used to engage and retain study participants in the interventions and annual assessments throughout the 3 years of the study.

6.5.1. Overall Study Retention/Ongoing Retention

- Collect personal information of both parent/guardian and child (full name, mother's maiden name, spouse's name, address, home/work/cell phone numbers, birth dates, email addresses, child's name and grade in school). Collect/confirm contact information each time contact is made. Determine when is the most convenient day and time of day for participant to receive calls.
- Collect contact information of 3 relatives/friends who are most likely to know contact information of study participants. Ask participants to inform contacts that they were listed as possible contacts and therefore may be contacted in the future. Give participants a form that they can give to the3 relatives/friends with the study's contact information on it. Collect contact information from parent in response to the question, "Five years from now who is the one person who is mostly likely to know where you are?"
- As participants are willing, have within-arm participants exchange contact information in order to develop a buddy system so that in the event of loss of contact with any participant other participants can be encouraged to contact that member.
- Interventionists will confirm contact information each time they have contact with participant, and pass updated contact information to database managers as soon as they receive it.
- We will have a 24-hour study phone number and designated contact person for the participants if any further information is needed by the participant, or if participant cannot/does not contact the staff specific to their arm of the study.
- Send three newsletters a year highlighting staff members, stories/art from participants; things happening around town; recipes (not to include anything that would constitute "intervention.") Newsletter will be sent to all participants, addressed to "*index child* and Family". First newsletter will be sent two months after start of intervention and then q4 months until the end of the study.
- Send a Birthday card to both participant and parent; send a holiday card to participant and parent.
- Build relationships with subjects:
    - Hire and train interventionists who will develop strong positive relationship with families and who will make the intervention sessions events that families look forward to
    - Communicate effectively and maintain close communication with subjects and families. IMPACT intervention staff will stay familiar with participant family members and family situation. When talking with participants intervention staff will avoid use of medical or other scientific jargon. Use every-day language without talking down to participants.

    - Match data collectors to the same participant in each data collection wave to build and maintain interviewer/participant rapport. IMPACT staff will establish a project identity by frequently using particular language and phrases that characterize the study in a memorable way. We will use language and terminology that allows participants to easily describe the study.
    - Schedule participant visits at times convenient for them; IMPACT intervention staff will use nights or weekends to accommodate participants.
    - Be efficient in use of subject time at data collection and during intervention sessions.
    - IMPACT clinical core staff will schedule visits, and make reminder calls.
    - Attempt to match data collectors with participants based on race/ethnicity whenever possible.
    - Interventionists will make reminder calls before each face-to-face session;
    - Return phone calls promptly. All misdirected calls from participants will be forwarded to designated contact person (see 24-hour phone number and designated contact person above).
- Travel reimbursement to/from data collection
    - This can take the form of cab vouchers, bus fare, or mileage reimbursement.
    - For cab vouchers: if possible use same cab company for each participant.
    - For those using public transportation: provide passes.
    - For those participants driving themselves: Pay for parking wherever it is not free.
- Travel reimbursement to/from intervention sessions
    - This can take the form of cab vouchers, bus fare, or mileage reimbursement.
    - For cab vouchers: if possible use same cab company for each participant
    - For those using public transportation: provide passes; different types of passes will accommodate individuals and adults traveling with young children, for a day or for longer periods.
    - For those participants driving themselves: Pay for parking wherever it is not free.
- Unexpected Token gifts – t-shirts, water bottles, special annual gift, for participant and parent
    - At each face-to-face session have an inexpensive grab bag-type gift for each participant and accompanying adult (average value not more than $1).
- $50 Incentives for each child and each parent at annual data collection visit. Use credit card-type gift cards that can be used anywhere, and function like credit cards, not like debit cards.
- Protocol for tracking down lost-to-follow up (LTF) participants.
    - If phone calls result in “disconnected or no longer in use”, use all information collected and updated to locate participant. Attempt all cell phone and land line numbers given by participant. Use directory information to attempt to find new

information. Call at different times of day and different days of the week. IMPACT staff will make 5 calls attempting contact in not more than 7 days.
    - If call results in “mailbox full” response, or if otherwise unable to leave message, send letter to participant family requesting a response, and saying we were unable to contact them by phone. Continue to call at least every other day in case mailbox or messaging resolves.
    - If phone numbers are disconnected, mail letter to participant family requesting a response to last known address (include “Address Correction Requested” on the envelope so IMPACT will receive new address if known). Contact those named by participant as personal contacts and request current contact information for participant/family.
    - As in agreed-upon protocol with school system, contact school who will work with home room teacher for latest contact information.

6.5.2. Keeping Participants Engaged in the Interventions

- We have branded the study so that participants feel part of an “exclusive” group
    - Give Tshirts, waterbottles, etc with project logo
- Subjects earn points/tickets (based on attendance/participation) that are put in a lottery for larger prize such as gift cards, mp3 players, tickets to ball games, etc; for both parents and kids.
    - Grab bag “prizes” are provided at each intervention session (Items provided will cost about $1.00 and consist of items such as lip gloss, nail polish, key chains, pens/pencils, jump ropes, small balls, stress balls, and season and holiday specific items such as gloves, socks, scarves, Halloween items, Valentine) .
    - Having four large activities each year (i.e., swimming, rock climbing, sporting event tickets, bowling).
- Making the intervention sessions fun
    - Try It – in beginning of session introduce a new and interesting fruit or vegetable or exercise (i.e., yoga) method to try
- Give frequent feedback on their weight loss progress
- Cooking demonstrations
    - Have a guest chef to class
    - Provide cooking classes on a quarterly basis to help introduce new foods
    - Cooking competitions parent/child teams (could be a large activity)
    - Babysitting For families that need it, babysitting of small children will be provided at sessions to ensure participation
    - Children engaged in creative activities to display what they learn
    - Resources available for children to create “healthy” commercials, where these commercials can also be shown at their school
    - PhotoVoice – materials provided for children to develop pictorial collages of their “healthy” changes and experiences.

- Opportunity to make cooking videos as showcased on currenttv…can make their own IMPACT Youtube channel to showcase children's cooking videos

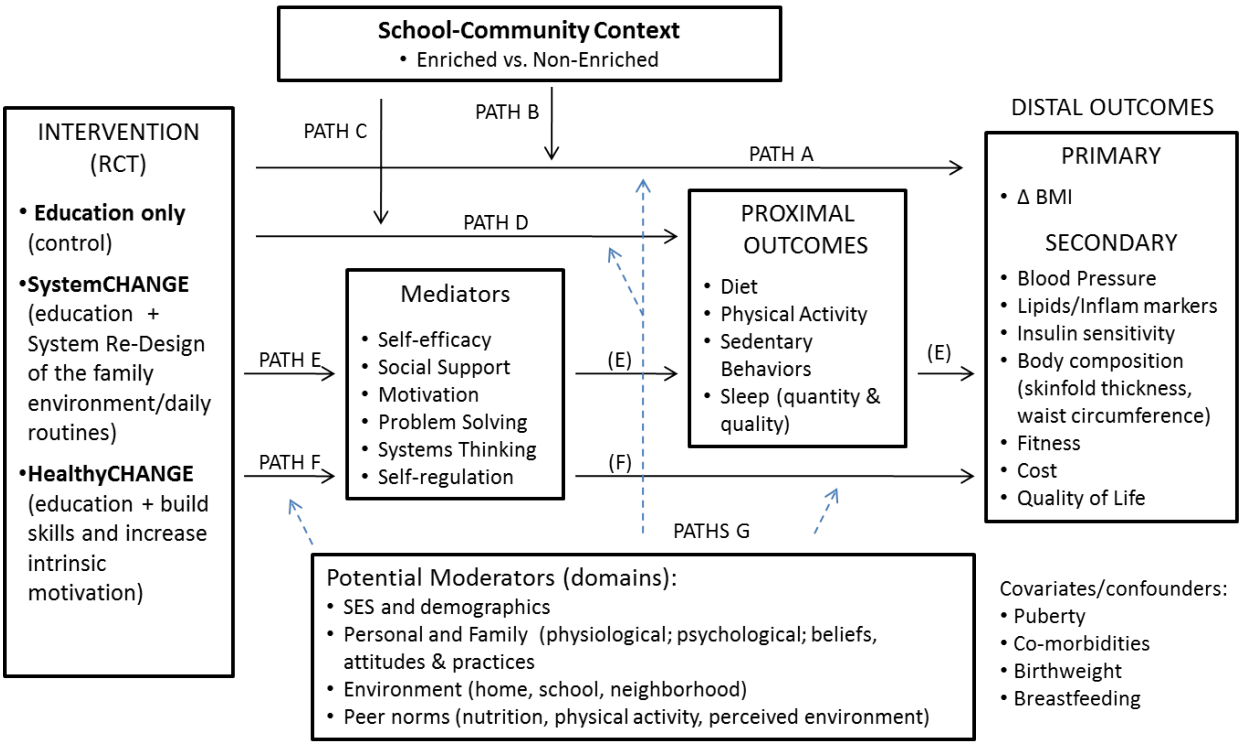
- Establishing a re-invigoration plan if attendance is not good.
  - Initiate a call to participant to see why attendance is not good.
  - Phone call day before session to assure attendance.
  - Attempt to problem solve attendance by offering, transportation, babysitting options
  - Mail information from session to home
  - Follow up phone call regarding information that was mailed.
  - Establishing a re-invigoration plan if not responding to intervention
  - Implement responsive intervention protocol
  - Provide private session with participant to go over details of what is desired from intervention
  - Special outreach to families
  - Following adverse events (hospitalization, illness, etc)
  - Following change in family situation (divorce, separation, death or bad illness in family), family move to new location, child changes schools

7. INTERVENTION

7.1. Conceptual Framework

Our study addresses obesity in urban youth by focusing on two levels of the child's environment: the child-family environment and the school-community environment. The primary goals of both the child-family interventions and the school-community program are to reduce BMI by catalyzing changes in lifestyle (diet, physical activity, sedentary behavior).

Figure 7.1: IMPACT Conceptual Framework



The proposed relationships among the major study variables and their corresponding study aims are depicted in the figure below. Our primary aim is to determine the impact of the two innovative child-family interventions (SystemCHANGE, HealthyCHANGE) when compared to an education-only approach, on reducing BMI (Path A), as well as assessing the moderating impact of an enriched school environment (Path B). That is, will the impact of the child-family interventions on BMI differ among children exposed to a supportive school environment from those who are not.

BMI and BP are termed "distal" outcomes as they likely depend on changes in other more "proximal" outcomes – dietary intake, physical activity, sedentary behaviors, and sleep. As part of our secondary aims, we will explore the impact of the child-family interventions (and the moderating impact of the enriched school environment) on these more proximal outcomes (Paths D and C, respectively, as well as secondary outcomes, including cardiovascular risk factors, body composition, cost and quality of life (also Path A).

Proposed mediators through which the interventions effect changes in both proximal and distal outcomes are: child's self-efficacy, social support, motivation and family problem-solving, systems thinking, self-regulation (Paths E and F). The mediators represent the targeted approaches of each intervention (e.g., systems thinking for SystemCHANGE, motivation for HealthyCHANGE). Lastly, we will explore potential moderators that influence the degree to which the interventions are effective including the family's socioeconomic status and demographic characteristics, personal characteristics of the child, parent/guardian, and family (including physiological and psychosocial characteristics), the child's physical and social environment (neighborhood, school, and family), and peer norms surrounding nutrition, physical activity and perceived environment (Paths G). We posit that these factors may moderate the impact of the interventions on outcomes, as well as interventions on the program-specific mediators Covariates deemed from the literature to be confounders also will be assessed.

7.2. Description of the Intervention(s)

The IMPACT study tests two innovative family-focused interventions, HealthyCHANGE and SystemCHANGE, as well as the influence of a study-enriched, school-based program (We Run This City) that provides additional opportunity and support for the four pillars of the family-focused interventions (diet, physical activity, sleep, stress management). Both the HealthyCHANGE and the SystemCHANGE groups receive comparable information regarding diet (DASH diet), physical activity, sleep and stress management. The two interventions differ in the behavior change approaches taught. The content of our education-only control group is described below in Section 8.0. An outline of the two interventions and the control group protocols is attached in Appendices A-C.

7.2.1. HealthyCHANGE

The HealthyChange intervention is a multidisciplinary family-based weight management program based in cognitive-behavioral theory with elements of Motivational Interviewing (MI) . This intervention is a modification of a hospital-sponsored program (Healthy Kids, Healthy Weight; HKHW) developed by co-PI Cuttler, co-I Ievers-Landis, and others. HKHW was modeled on family-based behavioral programs with proven efficacy[23, 102], involving12 weekly sessions conducted over the course of three months. Each session includes two separate parent and child groups focusing on food and physical activity, followed by a family (parent + child) session.

In HealthyCHANGE, we teach a set of cognitive-behavioral/MI-consistent strategies addressing diet, physical activity, sedentary behavior and sleep for children of this age group. Using interactive teaching methods and activities, we assist youth and their parents to assess their value systems regarding these target behaviors as being advantageous for meeting their short- and intermediate-term life goals, including weight management. Approaches to enhancing diet and exercise self-efficacy, problem-solving abilities, and relapse prevention skills also will be introduced. Family communication strategies are taught and reinforced throughout the sessions to support the positive enactment of home-based behaviors. The interventionists will employ MI-consistent techniques in the sessions, including asking open-ended questions, reflective listening and making affirmations and summary statements. MI will also be used to identify any barriers to children completing activity and diet logs, with parental assistance as needed. When reviewing these logs at each session, children and parents will be asked to identify areas in which to improve diet and exercise and ideas of possible solutions targeting these areas. If needed, they will be assisted to problem-solve any barriers they anticipate in implementing these solutions. We also will provide parents with tools for evaluating their children's current behaviors via daily monitoring, setting realistic small-increment goals to improve their children's health-related behaviors, and practicing positive parenting strategies using at-home behavioral assignments. Cognitive-behavioral skill development will be included in each session, beginning with weekly parental monitoring of children's diet and activity.

7.2.2. SystemCHANGE

This study will test a newly designed intervention, SystemCHANGE, which is designed to assist children and their families to focus on changing the daily systems in their lives (events, circumstances) that affect dietary intake, physical activity, and sedentary behavior. The SystemCHANGE intervention teaches people to apply a distinct set of strategies associated with the System Improvement Framework. This framework, also known as Continuous Quality Improvement (CQl) and Process Improvement, emphasizes system thinking and specifies that change is best accomplished by identifying a measurable goal, examining the system processes surrounding attainment of that goal, listing several ideas about how best to

improve the system, engaging in a series of experiments to test the best ideas to improve the process, implementing the most successful ideas based on data from the experiments, and monitoring the system to hold the gains.

In the SystemCHANGE intervention (based on systems improvement and choice architecture theories) participants are taught a set of skills to change daily routines using a set of self-designed experiments. Participants are taught about the interdependencies of their daily routines with others in their life and how to engage those individuals in redesigning family/school/work systems to promote healthier choices regarding eating, activity and sleep. Participants are taught to experiment with changes in the systems around them, rather than to try and change their personal effort or motivation for health changes. Participants are taught a set of strategies to change a system to achieve a specific goal. These strategies include identifying a chain of steps/events that comprise the system in which the desired change is to occur, counting and keeping track of data about the system process to understand it, designing and implementing short trials of possible improvement (change) solutions, evaluating success by reviewing graphically-displayed data, and making provisions for holding the gains. The SystemCHANGE intervention focuses less on individual motivation than on building habitual behavioral and change into day-to-day routines. The targeted behaviors are exercise, diet, sedentary behavior, and sleep.

The family daily routine is considered the social environment affecting this lifestyle behavior. Families are taught how to modify their immediate environment so that they succeed despite wavering motivation. A number of process improvement techniques are used, including flow charting daily routines, fishbone diagrams to identify a range of cause and effects on the desired behavior change, selection of systems-oriented vs individual motivation-oriented solutions for change, using cycles of small experiments to test their ideas for improvement, tracking objective data about cause and effect on behavior through use of Cause and Effect diaries, and family storyboards.

7.2.3. Adaptive Intervention

As recommended by the larger national COPTR Coordinating Center, we are employing an adaptive intervention design[118] to tailor our interventions to participants in the study. Participant-specific modifications to the behavioral interventions are built-in to the intervention protocols based on baseline, process, or outcome measures taken on participants over the course of the study. Explicit decision rules will be used to govern the modifications in order to ensure that the interventions are applied consistently to all participants in a respective arm and can be replicated by others. We have designed a set of decision rules for the adaptations for each of the family behavioral interventions (see Appendix D).

7.2.4. Enriched School-Community Environments

This refers to the second "level" of our multi-level intervention and refers to schools that participate in a school-community-based program (We Run This City [WRTC]; http://www.clevelandymca.org/community/marathon/index.html) that encourages physical activity in students by building their capacity to participate (walking or running) in a segment of the Cleveland Marathon, and one that receives study supplemented programming and support, provided through a special interventionist called a "Navigator". Navigators will be blinded with regard to the child's family intervention group assignment.

Each year, approximately 30 of the 65 K-8 CMSD schools register a "team" to participate in the WRTC program – approximately 85% of these schools have been engaged for multiple years. Each team is lead by a "coach", typically a physical education teacher and teams are comprised of 6-8th graders, varying in size from 10 to 50, depending upon the size of the school. This is not a program for innate athletes; rather it was originally designed to fill the gaps in physical education within the CMSD curriculum. Typically, 30-40% of the WRTC participants are overweight or obese and most have never run or walked for fitness in the past. The teams are created each December-January and training begins at the end of January. All students run/walk at least 25 miles prior to the mid-May Rite Aid Cleveland Marathon and then finish their training with one of three options: (1) run the remaining 1.2 miles, completing a total of 26.2 miles (distance of a marathon) by combining training miles and race miles); (2) run/walk the 10k (6.2 miles); or (3) run the ½ Marathon (13.1 miles). Last year, over 850 CMSD students participated (45% in 1.2; 45% in the 10k and 10% in the half-marathon).

Starting in the 2012-2013 school year and the 2012 WRTC season, the IMPACT study will begin supplementing the WRTC teams and schools with additional programming and support through the study-supported Navigators. For each of the WRTC schools, the Navigators will work to promote healthy lifestyle behaviors among the entire student body through the following: 1) display of health-oriented social marketing campaign materials that complement the same materials that are distributed in both HealthyCHANGE and SystemCHANGE; 2) conduct of four, school-wide activities during each school year (2 in the fall, 2 in the spring) aimed at the four pillars of the study (nutrition, physical activity, sleep and stress reduction). A summary of the different levels of school-based programming is provided in Appendix E.

In addition, program efforts will extend directly to the WRTC Youth Marathon team at each respective school. These activities will be conducted in collaboration with the WRTC Marathon Coach; a member of the school staff. IMPACT personnel will work closely with the YMCA to provide trainings for the coaches on best practices for encouraging and motivating overweight children for sustained participation in physical activity, as well as receiving additional information from their assigned Navigator for programmatic support during trainings, assisting coaches to improve tracking of student progress, supporting IMPACT

student participation and working to motivate study participants by modeling healthy behaviors. Therefore, the Navigator will participate in marathon training activities at least twice per month (schedule permitting), will assist the coach in monitoring IMPACT participant conditioning patterns, and organize monthly contests that include small prizes for the “runner of the Month”.

Non-enriched school-community environments are schools from the same school district that do not participate in the WRTC program and have none of these supplements to regular classroom-based health and physical education.

7.2.5. Intervention Dose

Each non-control, study participant will receive 36 months of one of the two child-family interventions. SystemCHANGE and HealthyCHANGE participants will have intensive face-to-face group meetings at 2-week intervals over the first 12 months (24 sessions of 90 minutes in length), followed by rotating monthly face-to-face meetings or phone calls for a further 24 months. Description of the control intervention is included in the next section.

Approximately half of the respondents will have up to three years of the school-community enrichment exposure. Due to the transient nature of many CMSD students and the changes in WRTC schools each year due to school closings and teacher transfers, exposure to the school-level intervention will be assessed as an accumulative exposure over a year’s time. IMPACT students will be assigned a monthly “exposure score” based on (1) whether they were in a WRTC school and if so, (2) their exposure to IMPACT support activities. Each 30 days IMPACT students will be given a score using the following metric: (0) not in a WRTC school, (1) in a WRTC school but either no programming was conducted that month or the child did not participate (not enrolled in WRTC), (2) in a WRTC school and either attended a IMPACT supported activity or was enrolled in the program and high participation (attending 75% or more of the scheduled activities). These monthly status scores will be summed for an annual exposure, with a range from 0-36.

We will communicate with each subject/family approximately q2 weeks during the first year, and approximately monthly thereafter. Vigilant inquiries about home address changes and school changes throughout the study by assigned study interventionists and data collection personnel have been written into our study retention plans.

7.3. Process and Fidelity Measures

7.3.1. Process Measures

Process measures will focus on intervention delivery and receipt as well as the process surrounding recruitment, scheduling, data collection, retention efforts, and processes associated with intervention personnel (see Table 7.1. below).

Table 7.1. Process Measures – Case Western Reserve University

1. Family Intervention Delivery

- Bi-monthly weight of child
- Baseline BMI
- Baseline binge eating score
- Participants needing travel by cab for intervention visits
- # of sessions scheduled (face-to-face and phone)
- Dates each session held
- # sessions held (face-to-face and phone)
- Topics covered
- Features of responsive intervention activated – which features and face or phone follow-up according to protocol

2. Family Intervention Receipt

- # of sessions attended – child and parent
- # of phone sessions attended
- Reasons for missing sessions
- Session length
- Session number
- Features of responsive intervention received - which features and face or phone follow-up
- Subject evaluation of individual sessions
- Course evaluation

3. Family Intervention Enactment

- Experiments (#, topic, target behavior, systems-orientation, use of storyboard/diary)
- Goals # identified, # met, diary (days of food and activity recorded, freq and min of PA, # fruits and vegs intake, sodium intake recorded)

4. School-based Intervention Delivery

- School name
- Dates each activity conducted
- Time each activity conducted
- Activity audience (entire school, middle school students, WRTC team)
- Number of students in attendance (estimate)
- Number of staff/teachers in attendance (estimate)
- # of IMPACT students in attendance
- IMPACT participant name
- Location of activity (Gym, cafeteria, classroom, other)
- Activity leader (Navigator, WRTC Coach, Other Health Prof., Other)
- Activity name
- Activity #
- Target behavior of activity (diet, PA, sleep or stress)

5. School-based Intervention Receipt

- # of school activities attended – child
- # of Marathon team-specific activities attended – child
- Activity length
- Activity topic
- # of face-to-face discussions with child outside of marathon activities.

6. Navigators (school-based)

- Number trained
- Gender
- Race
- Other demographics of Navigators – discipline, experience, etc

- Documentation of initial training, retraining and bi-weekly supervision – time, topics
- Time spent by Navigators
    - School-based intervention delivery
    - WRTC Coach Support
    - Intervention activity preparation
    - Travel to school/YMCA
    - Other contacts/follow-up with participants
- Training/retraining/supervision meetings

7. Family Interventionists

- Number trained
- Gender
- Race
- Other demographics of interventionists – discipline, experience, etc
- Documentation of initial training and retraining – time, topics
- Time spent by interventionists – intervention delivery (face-to-face and phone)
    - Intervention preparation
    - Intervention travel
    - Other contacts/follow-up with participants
    - Training/retraining/supervision meetings

8. Recruitment

- Size of population – # of children in population, #children screened, number study eligible, reason for non-eligibility
- # to be approached for participation (qualified on first screen)
- # reached
- # agreeing to come to CRU
- # ineligible on second screen and why
- # coming to CRU
- # consenting
- Reasons for refusal
- # of people assigned to arm
- Cohort number
- Number in the cohort

9. Scheduling & Retention for CRU visits

- # attempts to reach the participant after parent/guardian expresses interest in participating (ie includes busy signals, no answers)?
- # phone calls to the participant to schedule visit?
- # needing to be rescheduled (and breakdown: cancel, no show, etc)
- # participants answering or returning our calls for the 4th and 9th day of wearing the Accelerometer
- Days for return of accelerometer after call on last day of wear?
- Reminder calls: # per scheduled visits
- # participants needing cabs

10. Study Data Collection Procedures

- # of parents and children declining to use the iPad and preferring to do the questionnaire via paper
- # children using headphones versus reading questions on the iPad
- Time to complete visit (and its components)
- # calls to complete all the diet recalls/evaluation visits
- # of assessment visits within window

11. Retention

- # of children moving away from area
- # of children moving within area
- # of children changing school (and which school moved to)
- Number of children choose to withdraw from study (and reason)

7.3.2. Fidelity Measures

In addition to process measures, a plan has been developed to capture the five important components of intervention delivery: fidelity, dose delivered, dose received, program design and reach. These measures are outlined in the table below.

Table 7.2: Fidelity Measures: Case Western Reserve University

Part I: 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

Fidelity	Fidelity Construct	Data Collection Method	Completed By	Timing of Data Collection
Intervention Component #1: Family-Based				
Family Intervention Component	Content and quality of messages	Family Intervention Session Audit Forms	Intervention manager	First 4 sessions, then random 30% of sessions
	Adherence to intervention protocols	Family Intervention Session Audit Forms	Intervention manager	First 4 sessions, then random 30% of sessions
		Interventionist Session Checklists	Interventionists	At each session
	Interventionist Training: Standardized training	Interventionist Training Checklists	Intervention Trainer (PI/PD)	After initial interventionist training & annually
		Interventionist Training Evaluation Survey	Interventionists	After initial interventionist training & annually
	Interventionist skill acquisition and competency	Family Intervention Session Audit Forms	Intervention manager	First 4 sessions, then random 30% of sessions
	Interventionist delivery: Number and length of sessions delivered	Family Intervention Session Audit Forms	Intervention manager	First 4 sessions, then random 30% of sessions
		Interventionist Session Checklists	Interventionists	Each session
		Interventionist Time Log (Participant Contacts)	Interventionists	After each participant contact (phone or face-to-face)
	Interventionist attrition rates Special	Administrative data base	Intervention Trainer (PI/PD)	Annually

	interventionist training and re-training	Field notes of PI	Interventionists	Annually
Intervention Component #2: School/Community-Based				
Community Intervention Component	Content and quality of messages	School-based Intervention Activity Audit Forms	School Intervention Coordinator or Community and Data Core Manager	Attend and observe first school-wide activity and first WRTC training, then audit random 30% of sessions.
	Adherence to protocol	School-based Intervention Activity Audit Forms	School Intervention Coordinator or Community and Data Core Manager	Attend and observe first school-wide activity and first WRTC training, then audit random 30% of sessions.
		School-based Intervention Activity & WRTC Training Session Checklists	Navigators	After each school-wide or WRTC activity.
	Navigator Training: Standardized training	Navigator Training Checklists	School Intervention Coordinator or Community and Data Core Manager	After initial Navigator training & annually
	Navigator skill acquisition and competency	Navigator Training Evaluation Survey	Navigator Trainer Navigator	After initial Navigator training & annually
		School-based Intervention Activity Audit Forms	School Intervention Coordinator	First school-wide activity and WRTC training, then random 30% of sessions
	Navigator delivery: Number and length of sessions delivered	School-based Intervention Activity Audit Forms	School Intervention Coordinator	Attend and observe first school-wide activity and first WRTC training, then audit random 30% of sessions.
		School-based Intervention Activity & WRTC Training Session Checklists	Navigators	At each school activity and/or WRTC training session
		Navigator Time Log (WRTC Coach & Participant Contacts)	Navigators	After each WRTC Coach & participant contact
	Navigator attrition rates	Administrative data base	Navigator Trainer (PI/SIC/C&D	Annually

			Manager)	
	Special Navigator training and re-training	Field notes of PI	Navigators	Annually
Part II: Dose Delivered: The amount of intervention that was delivered; could include, but not limited to, number and length of sessions implemented				
Dose Delivered	**Dose Delivered Construct**	**Data Collection Method**	**Completed By**	**Timing of Data Collection**
Intervention Component #1: Family-Based				
Family Intervention Component	Subject Attendance	Participant Intervention Process Forms	Interventionists	Each Session
	Number and length of sessions implemented	Family Intervention Session Audit Forms	Intervention manager	First 4 sessions then random 30% of sessions
		Interventionist Time Logs (Participant contacts)	Interventionists	After every subject contact
		Participant Intervention Process Forms	Interventionists	Beginning of every session
	Adherence to protocol	Interventionist Session Checklists	Interventionists	After every session
		End-of-Session Evaluations	Participants	End of every session
Intervention Component #2: School/Community-Based				
Community Intervention Component	Subject Attendance	School-based Intervention Activity Process Forms	Navigators	Each Session
	Number and length of activities, implemented, and WRTC training sessions attended.	School-based Intervention Activity Audit Forms	School Intervention Coordinator	Attend and observe first school-wide activity and first WRTC training, then audit random 30% of sessions.
		Navigator Time Logs (WRTC Coach & Participant contacts)	Navigators	After each WRTC Coach & participant contact
	Content and quality of messages	School-based Intervention Activity Process Forms	Navigators	At the beginning of each activity
	Adherence to protocol	School-based Intervention Activity & WRTC Training Session Checklists	Navigators	At each school activity and/or WRTC training session
		End of WRTC Season Evaluation	WRTC Coaches, and team members inclusive of IMPACT Participants	End of WRTC Marathon season (annually)

PART III: Dose Received: The amount of intervention that was received; could include, but not limited to, participant engagement, and intervention messages or materials received				
Dose Received	**Dose Received Construct**	**Data Collection Method**	**Completed By**	**Timing of Data Collection**
Intervention Component #1: Family-Based				
Family Intervention Component	Subject Attendance Family Attendance	Participant Intervention Process Forms	Interventionists	Each Session
	Content and quality of messages, Number and length of contacts	Family Intervention Session Audit Form	Intervention manager	First 4 sessions, then random 30% of sessions
	Participant engagement	Participant Intervention Process Form	Interventionists	Beginning of every session
	Participant satisfaction behavioral change	Participant Behavioral Logs	Participants	At each session
		Participant Experiment Logs	Participants	At each session
		End-of-Session Evaluation	Participants	After every session
		End-of-Study Evaluation	Participants	Annually and End of Study
Intervention Component #2: School/Community Based				
Community Intervention Component	Subject Attendance	School-based Intervention Activity Process Forms	Navigators	Each session
	Content and quality of messages, Number and length of contacts	School-based Intervention Activity Audit Forms	School Intervention Coordinator	Attend and observe first school-wide activity and first WRTC training, then audit random 30% of sessions.
	Participant engagement	School-based Intervention Activity Process Forms	Navigators	Each session
	Participant satisfaction	End of WRTC Season Evaluation	WRTC Coaches, and team members inclusive of IMPACT Participants	End of WRTC Marathon season (annually)
Part IV. Program Design: The assessment of non-specific treatment effects, could include, but not limited to participant satisfaction with, feasibility, and costs of intervention				
Program Design	**Program Design Construct**	**Data Collection Method**	**Completed By**	**Timing of Data Collection**
Intervention Component #1: Family-Based				

Family Intervention Component	Participant satisfaction with program components	End-of-Session Evaluation	Participants	After each session
		End-of-Study Evaluation	Participants	Annually and at end of study
	Interventionist time to prepare and travel to deliver intervention	Interventionist Time Log (Non-participant Contacts)	Interventionists	After every contact
Intervention Component #2: School/Community-Based				
Community Intervention Component	Participant satisfaction with program components	End of WRTC Season Evaluation	IMPACT participants	End of WRTC Marathon season (annually)
	Navigator time to prepare and travel to deliver intervention	Navigator Time Logs (Non-participant Contacts)	Navigator	After each activity
Part V. 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)				
Reach	**Reach Construct**	**Data Collection Method**	**Completed By**	**Timing of Data Collection**
Intervention Component #1: Family-Based				
Family Intervention Component	Representation (eligible, consented)	Recruitment Logs	Recruiter	Ongoing
	Attendance, participation, completion, attrition, & engagement by race, gender, school, intervention group, BP status, and obesity level	Participant Intervention Process Form	Interventionists	Every session; group analysis reviewed quarterly by PIs
		Clinical Data	Data collectors Data manager	Annually and end of study
Intervention Component #2: School/Community Based				
Community Intervention Component	Representation, (eligible, consented)	Recruitment Logs	Recruiter	Ongoing
	Attendance, participation, completion, attrition, and engagement.	School-based Intervention Activity Process Forms	Navigators	Every session; group analysis reviewed quarterly by PIs
				Annually and end of study

7.4. Unblinded Process MeasuresT

The following is the list of process variables where unblinding for aggregation by study arm or cohort is requested by the Case Western Reserve study site.

Table 7.3: Unblinded Process Variables: Case Western Reserve University

Variables	When	Aggregation Level		Purpose
		Arm	Cohort	
Family Intervention Delivery				
# of sessions scheduled (face-to-face and phone)	Monthly	X	X	Assure comparable attention across study arms and cohorts.
# of sessions actually held	Monthly	X	X	
Topics covered in sessions (to be coded)	Monthly	X	X	
Activation of responsive intervention (which features and # of face-to-face or phone follow-up sessions)	Monthly	X	X	Assure comparable delivery of responsive intervention protocol across study arms and cohorts.
# subjects needing cab transportation for intervention visits	Quarterly	X	X	Assure comparable access to interventions across study arms and cohorts.
Family Intervention Receipt				
# of sessions attended by child and by parent	Monthly	X	X	Assure comparable attention across study arms and cohorts.
# of phone calls attended by child and by parent	Monthly	X	X	
Reasons participants miss sessions	Quarterly	X	X	Problem-solve possible issues regarding intervention receipt by arm or cohort.
Session length and number	Quarterly	X	X	Assure comparable attention across study arms and cohorts.
Features of responsive intervention received (which features and # of face-to-face or phone follow-up sessions)	Monthly	X	X	Assure comparable receipt of responsive intervention protocol across study arms and cohorts.
Subject evaluations of individual sessions	Monthly[1]	X	X	Problem-solve intervention receipt issues by arm and cohort.
Course evaluations	Annually	X	X	
Family Intervention Enactment				
Experiments (#, topics, target behaviors, systems orientation)	Quarterly		X	Within SystemCHANGE arm only. For comparison by cohort to monitor/assure subject receipt of key intervention components
Use of storyboard	Quarterly		X	As Above
Goals (# identified, # met)	Quarterly		X	HealthyCHANGE arm only. . For comparison by cohort to monitor/assure subject receipt of key intervention components

Diary Completion	Quarterly		X	Comparison of rates of completion within each arm to assure comparable delivery and receipt across both arms.
Community Intervention Delivery and Receipt				
Child Marathon participation status	Monthly	X	X	Assure comparable receipt of school intervention across arms and cohorts.
Interventionist Information				
# of interventionists	Quarterly	X	X	Assure comparable number of interventionists across arms and cohorts.
Interventionist gender, age, race, discipline, experience, other demographics	Annually	X	X	Assure comparable expertise levels, as well as race and age match across arms and cohorts.
Interventionist training/ retraining (time, topics)	Quarterly	X	X	Assure comparable interventionist expertise across arms and cohorts.
Interventionists time spent in delivery, travel, participant follow-up	Quarterly	X	X	Assure comparable subject-interventionist contact time across arms and cohorts.
Participant Recruitment and Retention				
# participants assigned	Monthly	X	X	Assure comparable intervention group size across study periods.
# of children moving out of city	Monthly	X	X	Assure comparable access to interventions across arms and cohorts.
# of children moving within the city	Monthly	X	X	
# of children changing school	Monthly	X	X	Assure comparable access to school intervention across arms and cohorts.

[1] Data will be gathered at the end of each face-to-face session, but aggregated results will be reviewed on a monthly basis.

8. CONTROL CONDITION - Tools4CHANGE

In contrast to the behavioral arms, youth with their parent(s)/guardian randomized to the education-only group will have one 60-minute face-to-face meeting at initiation of the study with a dietitian who is also trained in recommendations for exercise and sedentary behavior. The dietitian will review the goals of the Tools4CHANGE intervention pertaining to diet, physical activity, and sedentary behavior described above. The dietitian will provide individual Dash diet meal plan and review food groups and serving sizes. The family will be given several handouts and booklets (5^{th}-6^{th} grade level) that provide written documentation of the recommended guidelines and useful suggestions. The family will also be given tools to guide gradual increase in physical activity and reducing sedentary behavior with the goals described. The importance of family involvement will be reviewed.

After the initial 60-min session, participants in this group will receive three other contacts with study personnel approximately quarterly in each of the study years (this is in addition to the annual clinical assessment received by all study participants). Two of the contacts will be phone calls during which there will be a general discussion reminding them of their

participation in the study and checking on accuracy of home address and school attended. The third contact will be a social gathering event (i.e., picnic, ball game) of small groups of families in the control group.

9. MEASUREMENTS

9.1 Methods

9.1.1. Primary Outcome (BMI) and Other Anthropometric Measures

Primary Outcome – BMI

BMI - Background and Rationale. The measure used as the primary outcome variable of all four COPTR trials is body mass index (BMI). BMI assesses body weight adjusted for height and is correlated with percent body fat as assessed by dual energy x-ray absorptiometry[119-121]. When calculated using measured anthropometrics BMI is highly reliable. BMI has demonstrated clinical validity in its associations with type 2 diabetes mellitus[122; 123], hyperinsulinemia[124], blood pressure and hypertension[120; 125; 124], adverse lipoprotein profiles[124-126] and early atherosclerotic lesions[127; 128] among children and adolescents. Importantly, BMI can be assessed easily in clinical and public health settings and is generally accepted and well understood.

BMI – Objective. The objective of the BMI measures is to provide a precise and accurate measure of the impact of the intervention on relevant aspects of body size in the children studied in COPTR.

BMI – Methods. All consented index children in the COPTR study have weight and height measured at the beginning and end of the intervention (36 months) and at two common interim time points (12 and 24 months). All baseline anthropometric data will be collected prior to randomization. Weight and height are measured with the participant in light clothing without shoes. 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. BMI is calculated as weight in kilograms divided by the square of height in meters.

All height and weight measurements are collected by trained and certified staff. COPTR will use a “train the trainer” model. Each field center will designate one or more “Master Trainers” who participate in a central training organized by the RCU at the University of North Carolina at Chapel Hill on April 16-18, 2012. These Master Trainers are responsible for training and certifying the data collection staff at their center.

Table 9.1 Anthropometric Common Measures by Research Center				
Anthropometric Measure	Case	Minnesota	Stanford	Vanderbilt
Index Child				
Weight	x	x	x	x
Height	x	x	x	x
Waist circumference	x	x	x	x
Triceps skinfolds	x	x	x	x
Other Children				
Weight	--	x*	x†	--
Height	--	x*	x†	--
Waist circumference	--	--	x†	--
Triceps skinfolds	--	--	x†	--
Other Adults				
Weight	x	x*	x	x
Height	x	x*	x	x
Waist circumference	--	--	x	x
Triceps skinfolds	--	--	--	x
* Minnesota: All children and adults in household. † Stanford: Only study eligible children				

Other Anthropometric Secondary Outcomes

Anthropometric secondary outcomes differ by site as detailed in Table 9.1. Variables measured in the index child at all sites include waist circumference and triceps skinfold. All sites are measuring height and weight in at least one adult family member of the index child and some sites are measuring siblings. Secondary outcomes that will be calculated from anthropometry in at least one site include BMI z-score, waist-to-height ratio (WtHR), and percent body fat.

Other Anthropometrics: Background and Rationale. BMI z-scores provide a method for evaluating the weight status of children adjusted for age and gender. The measure is commonly used in clinical practice to track body size trajectory. However, several authors have cautioned against the use of BMI z-scores for research using longitudinal designs citing concerns that their use could result in spurious differences between groups[129; 130]. One reason for this problem is that children at the extreme ends of the BMI distribution require substantially greater changes in weight than their thinner counterparts for the same change in z-score. Also because the BMI z-score curves were constructed using only data between the 3rd and 97th percentiles, the CDC recommends extreme caution when using the growth curves outside this range[131]. Finally, Berkey et al. noted that the difference between z-scores reflect larger differences in BMI in older compared to younger children. For these reasons

the COPTR investigators have chosen to study BMI z-score as a secondary rather than a primary outcome.

Abdominal adiposity is associated with metabolic risk factors in children[132-135] although evidence to date suggests that anthropometric measures tend to only moderately predict visceral fat[136; 137]. Waist circumference is a feasible non-invasive measure of abdominal fatness for community-based assessments of children. It has also been shown to be sensitive to change in response to prevention interventions[138].

Waist-to-height ratio (WtHR) is a simple index that has recently received increased interest from investigators[139]. After the age of four years, waist and height appear to simultaneously increase during childhood and adolescence[140]. Thus, WtHR could provide a practical estimate of adiposity that could be consistently applied to a wide range of age groups. Recently Browning et al. published a systematic review of waist to height ratio as a screening tool for cardiovascular and diabetes-related outcomes[139]. In their examination of 13 cross-sectional studies in children they found that waist-to-height ratio compared favorably with waist circumference and BMI. In a cross-sectional study of 1,511 youth 8 to 17 years of age McMurray et al. found that waist circumference performed well as a predictor of insulin resistance in boys but not girls[141]. Better performance was observed when waist circumference was divided by height, producing an index that was highly associated with insulin resistance in both genders and over a range of ages. Kahn et al. and Savva et al. have suggested a WtHR cut point of 0.49 to distinguish high and low levels of risk, however, McMurray et al. suggest that a WtHR of 0.54 may result in fewer misclassifications. WtHR can also be analyzed in the continuous form[140-142]. COPTR can provide an opportunity to further evaluate this index using both cross-sectional and longitudinal designs.

Triceps skinfold thickness is a measure of subcutaneous fat and is a component of equations used to predict percent body fat. COPTR investigators are using data from the NHANES study to develop a prediction equation for percent body fat that uses triceps skinfold along with other anthropometric variables collected in COPTR (height, weight and waist circumference) together with demographic variables to predict percent body fat (see section 4.8. in RCU protocol). Equations were developed in children in the age ranges being studied by Case Western and Stanford. Preliminary work indicates that this equation has an R^2 of over 0.8. Unfortunately estimates of percent body fat from DEXA are not available in children less than 8 years of age in NHANES. Therefore Vanderbilt and Minnesota will estimate percent body fat in younger children in their study using the prediction equation created by Dezenberg (R^2=0.95 as compared to DEXA, Model SEE=0.46) using data from White and African American 4 to 11 year old children[143]. This method has been shown to have higher validity across subgroups than other equations[144; 145] and has been validated in 3 to 8 year old White and Hispanic children.

Obesity has been shown to cluster in families such that having obese parents increases the risk of obesity in children[146-148]. This clustering is due to both shared environment and genetic factors. The collection of anthropometric variables in the families of the index children in COPTR provides an opportunity to examine longitudinal changes within families in the family members and to assess any impact of the intervention on family members.

Other Anthropometrics - Objective. The anthropometric secondary outcomes are assessed to provide a richer understanding of the changes in body size characteristics associated with the COPTR interventions.

Other Anthropometrics - Methods. Waist circumference and triceps skinfolds will be measured at the beginning and end of the intervention (36 months) and at two common interim time points (12 & 24 months). Measurement details have been determined with guidance from the 2007 NHANES anthropometry procedures manual (Centers for Disease Control, 2007, (http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf). 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 using a Lange skinfold caliper (or a Harpenden caliper if the measurement exceeds capacity of the Lange skinfold caliper) in the midline of the posterior aspect (back) of the arm, over the triceps muscle, at a point midway between the lateral projection of the acromion process of the scapula (shoulder blade) and the inferior margin (bottom) of the olecranon process of the ulna (elbow). Skinfolds are measured to the nearest 0.1 mm.

9.1.2. Common Demographics, Moderators, Mediators and Secondary Outcomes

<u>Demographics, Moderators and Mediators</u>

Background and Rationale. Self-reported information will be collected from COPTR index children and other household members by obtaining responses to written or verbalized questions. Although we refer to “questionnaires”, as discussed in the methods section below, several methods are used to collect these data, and only a minority of the data is collected through the use of paper questionnaires. The information obtained is used to describe the study population or as a confounder, mediator, moderator or secondary outcome of intervention effects.

In general, the mediators chosen for measurement are targeted by the intervention, are expected to change as a result of the intervention and to result (directly or indirectly) in change in BMI. In COPTR, each Field Site's intervention is unique and many of the mediator variables are site-specific because they serve as explanatory constructs for the site-specific theoretical model. A moderating variable is defined as a variable that could influence the primary or secondary outcomes because the variable interacts with the intervention to change

study outcomes. In other words, the intervention affects people differently, depending on their status on the moderator variable. These variables are evaluated at the beginning and the end of the intervention, and in some cases as interim measurements.

Objective. The purpose is to describe the characteristics of participants, to determine possible mediators and moderators of intervention effects and to study secondary outcomes that are impacted by the intervention.

Table 9.2 Characteristics of questionnaire administration by Field Sites

	Field Sites			
	Case Western	Minnesota	Stanford	Vanderbilt
Administration Location	Clinic	Home	Community center, Home, or Clinic	Community center
Administration Format	Interviewer administered	Interviewer administered	Interviewer administered (child) and mix of interviewer and self-administered (parent)	Interviewer administered
Data collection format	Computer	Computer	Paper Computer	Computer
Languages	English Spanish	English Spanish	English and Spanish (parents) and English (child)	English only in pilot; English and Spanish in main trial
Respondent	Parent or primary adult caregiver and participating child	Parent or primary adult caregiver	Parent(s) or primary adult caregivers and participating child	Parent or primary adult caregiver

Methods. The demographic, household, mediators and moderators survey is administered to parents/primary caregivers of the participating child and/or to the participating child. Table 9.2. summarizes the location where the questionnaire will be administered and administration format in each site. To accommodate the sample being studied some sites administer questionnaires in Spanish.

Table 9.3 lists the questions used to collect common questionnaire data and shows which sites are collecting each item. All of the common survey questions are not administered at all Field Sites. The source of the 55 common questions and the responses are listed in Table 9.4. There will be four common measurement time points – baseline, 12 months, 24 months and 36 months. All common data collection will occur between May 2012 and February 2017. All baseline data collection will occur prior to randomization. Measurement data collectors are not intervention staff unless data are collected prior to randomization.

Table 9.3 Common Demographics, Moderators and Mediators by Site					
Construct	**Item**	Case	Minnesota	Stanford	Vanderbilt
Household Configuration	For all children and adults living in your household, please tell me:				
	Gender,	X	X	X	
	Birth date, or age	X	X	X	
	Relationship to the participating child.	X	X	X	
Child's date of birth	Child's date of birth	X	X	X	X
Child Sex	What is this child sex?	X	X	X	X
Child Ethnicity	Is this child Hispanic, Latino/a or of Spanish origin?	X	X	X	X
Child Race	Which of the following best describes your child?	X	X	X	X
Parent Ethnicity	Are you Hispanic, Latino/a or of Spanish origin?	X	X	X	X
Parent Race	Which of the following best describes you?	X	X	X	X
Parent Country of Birth	In what country were you born?		X	X	X
Child Country of Birth	In what country was this child born?		X		X
Years Parent Lived in USA	How many years total have you lived in the United States?		X	X	X
Employment Status	What is your employment status?	X	X	X	X
Marital Status	What is your current marital status?	X	X	X	X
Access to Car	Is there a car that you can use whenever you need to?	X	X		X
Frequency of Speaking English at Home with Family	How often do you speak English at home with your family? (Choose one.)		X	X	
	If you do not always speak in English at home with your family, what languages do you speak the rest of the time?	X	X		
WIC	Do you participate in WIC? WIC stands for Women, Infants, and Children, a Federal assistance program.	X	X		X
Food Stamps/ SNAP	Does anyone in your household receive food stamps or SNAP? SNAP stands for	X	X	X	X

	Supplemental Nutrition Assistance Program.				
Unemployment/ Social Security/ Disability	Does anyone in your household receive Unemployment, Social Security, or Disability Benefits?	X	X	X	
Education Completed	What is the highest degree or level of school that you have completed?	X	X	X	X
	What is the highest degree or level of school that your child's other parent living in the household or adult caregiver living in the household has completed?	X	X	X	X
Child Care	In a usual week, how much time does this child spend being cared for by someone other than parent/guardian?				
	in your own home		X	X	X
	in someone else's home		X	X	X
	in childcare center/after school program		X	X	X
Household Income	What was your total household income from all sources before taxes last year? By "household", we mean that you should report the combined income of everyone in your home.	X	X	X	X
Child Health Insurance	Is your child covered by a health insurance plan?	X	X	X	
	Which type of plan are they covered by?	X	X	X	
Free or Reduced Price Breakfast or Lunch	Does any child in your household receive free or reduced price breakfast or lunch at school?		X	X	
Maturation Status	Has your daughter started having her menstrual period?	X		X	
	When did she have her first menstrual period?	X		X	
Breastfeeding/ Pregnancy Risk	Did <this child> breastfeed for more than a month?	X	X		X
	How old was <this child> in months when he/she first received a bottle of formula, cow's milk, water, juice, tea, or cereal at least once a day?	X	X		X
	How much did this child weigh at birth?	X	X		X
	Did a doctor say that <you/birth mother>	X	X		X

	had diabetes when pregnant with <this child>?				
	Did a doctor say that <you/birth mother> had hypertension (high blood pressure) when pregnant with <this child>?	X	X		X
Food Security	"The food that (I/we) bought just didn't last, and (I/we) didn't have money to get more." Was that often, sometimes, or never true for (you/your household) in the last 12 months?	X[3]	X	X	X
	"I/we couldn't afford to eat balanced meals." Was that often, sometimes, or never true for (you/your household) in the last 12 months?	X[3]	X	X	X
	In the last 12 months, since (date 12 months ago) did (you/you or other adults in your household) ever cut the size of your meals or skip meals because there wasn't enough money for food?	X[3]	X	X	X
	How often did this happen --almost every month, some months but not every month, or in only 1 or 2 months?	X[3]	X	X	X
	In the last 12 months, did you ever eat less than you felt you should because there wasn't enough money to buy food?	X[3]	X	X	X
	In the last 12 months, were you ever hungry but didn't eat because you couldn't afford enough food?.	X[3]	X	X	X
TV & Media	How many working TVs do you have in your home?	X[1]	X	X	
	Is there a working TV in the room where <this child> sleeps?	X[1]	X	X	X
	Is there a computer in your home?	X[1]	X	X	X
	Is there a computer in the room where <this child> sleeps?	X[1,2]	X	X[2]	X
	Is there a video game player in your home?	X[1]	X	X	
	Is there a video game player in the room where <this child> sleeps?	X[1]	X	X	X
	Do you have Internet access in your home?	X[1]	X		
	On an average WEEK day, how many		X		X

	hours does <this child> watch TV?				
	On an average WEEKEND day, how many hours does <this child> watch TV?		X		X
	On an average day, how many hours does <this child> play video or computer games, or use a computer for something that is not school work? (Include activities such as Play Station, Xbox, hand held video games, computer games, and the Internet.)		X		X
Food Norms	During the past seven days, how often did your family eat breakfast together?		X		X
	During the past seven days, how often did your family eat lunch together?		X		X
	During the past seven days, how often did your family eat dinner together?		X		X
Weight Status	How would you classify your own weight?	X	X	X	X
	How would you classify <this child's> current weight?	X	X	X	X

1 – The TV/Media questions for Case are derived from a group of embedded scale questions
2 – Case and Stanford uses the term “desktop” computer in their question.

3—Case questions are embedded into a survey and are not administered as an interview.

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
Household Configuration	For all children and adults living in your household, please tell me:		Developed
	Gender,	Male; Female	
	Birth date or age	MMDDYYYY; __ __ yrs	
	Relationship to the participating child.	Mother; Father; Stepmother; Stepfather; Other male CG, (list); Other female CG, (list)	
Child's date of birth	Child's date of birth	MMDDYYY	Developed
Child's sex	What is this child's sex?	Male; Female	HHS data standards[220]
Child Ethnicity	Is this child Hispanic, Latino/a, or of Spanish origin? (Choose all that apply.)	No, not of Hispanic, Latino/a or Spanish origin; Yes, Mexican American, Chicano/a; Yes, Puerto Rican; Yes, Cuban; Yes, Another Hispanic, Latino/a or Spanish origin	HHS data standards[220]
Child Race	Which of the following best describes your child? (Choose all that apply.)	American Indian or Alaskan Native Asian; Black or African American; Native Hawaiian or Pacific Islander; White; Other (please describe)	U.S. Census, 2010
Parent Ethnicity	Are you Hispanic, Latino/a, or of Spanish origin? (Choose all that apply.)	No, not of Hispanic, Latino/a or Spanish origin; Yes, Mexican American, Chicano/a; Yes, Puerto Rican; Yes, Cuban; Yes, Another Hispanic, Latino/a or Spanish origin	HHS data standards[220]
Parent Race	Which of the following best describes you? (Choose all that apply.)	American Indian or Alaskan Native Asian; Black or African American; Native Hawaiian or Pacific Islander; White; Other (please describe)	U.S. Census, 2010
Parent Country of Birth	In what country were you born?	USA; Mexico; Somalia; Laos/Thailand/Vietnam; Other (please describe)	Marin Acculturation Scale
Child Country of	In what country was this child	USA; Mexico; Somalia; Laos/Thailand/Vietnam;	Modified Marin Acculturation

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
Birth	born?	Other (please describe)	Scale
Years Parent Lived in USA	How many years total have you lived in the United States?	_ _ yrs	Marin Acculturation Scale
Employment Status	What is your employment status?	Working full time; Working part time; Not working for pay	Developed
Marital Status	What is your current marital status?	Married or living as married; Single	Developed
Access to Car	Is there a car that you can use whenever you need to?	Yes and I drive; Yes but I don't drive; No	Developed
Frequency of Speaking English at Home with Family	How often do you speak English at home with your family? (Choose one.)	Never; Sometimes; About ½ the time; Most of the time; Always	Marin Acculturation Scale
	If you do not always speak in English at home with your family, what languages do you speak the rest of the time?	*Free text*	
WIC	Do you participate in WIC? WIC stands for Women, Infants, and Children, a Federal assistance program.	Yes; No; Don't know	Developed
Food Stamps/ SNAP	Does anyone in your household receive food stamps or SNAP? SNAP stands for Supplemental Nutrition Assistance Program.	Yes; No; Don't know	Developed
Unemployment/ Social Security/ Disability	Does anyone in your household receive Unemployment, Social Security, or Disability Benefits?	Yes; No; Don't know	Developed
Education Completed	What is the highest degree or level of school that you have completed? (Choose one answer.)	6th grade (elementary school) or less; 7th - 8th grade (attended some middle school/junior high); 9th - 12th grade (attended some high school); High school graduate (received diploma or the equivalent, GED for example); Completed some college credit, (or technical school) but no degree; Technical degree; Associate's degree; College degree; Master's, Professional, or Doctoral	Modified U.S. Census, 2010

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
		degree	
	What is the highest degree or level of school that your child's other parent living in the household or adult caregiver living in the household has completed? (Choose one answer.)	6th grade (elementary school) or less; 7th - 8th grade (attended some middle school/junior high); 9th - 12th grade (attended some high school); High school graduate (received diploma or the equivalent, GED for example); Completed some college credit, (or technical school) but no degree; Technical degree; Associate's degree; College degree; Master's, Professional, or Doctoral degree	Modified U.S. Census, 2010
Child Care	In a usual week, how much time does this child spend being cared for by someone other than parent/guardian…		Developed
	in your own home?	0 Hours; 1-10 Hours; 11-20 Hours; 21-30 Hours 31-40 Hours; 41+ Hours	
	in someone else's home?	0 Hours; 1-10 Hours; 11-20 Hours; 21-30 Hours 31-40 Hours; 41+ Hours	
	in childcare center/after school program?	0 Hours; 1-10 Hours; 11-20 Hours; 21-30 Hours 31-40 Hours; 41+ Hours	
Household Income	What was your total household income from all sources before taxes last year? By "household", we mean that you should report the combined income of everyone in your home.	$14,999 or less; $15,000 - $24,999; $25,000 - $34,999; $35,000 - $49,999; $50,000 - $74,999; $75,000 - $149,999; $150,000 - $199,999; $200,000 or more; Don't know; I prefer not to answer	Developed
Child Health Insurance	Is your child covered by a health insurance plan?	Yes; No; Don't know	
	Which type of plan are they covered by?	Medicaid, Medicare, CHIP, state funded, or other federally funded; Private - through work or purchased individually; Military; Other,	

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
		type unknown; Don't know	
Free or Reduced Price Breakfast or Lunch	Does any child in your household receive free or reduced price breakfast or lunch at school?	Yes; No; Don't know	Modified from TAAG2
Maturation Status	Has your daughter started having her menstrual period?	Yes; No; Don't know	Developed
	When did she have her first menstrual period?	MMYYYY	Developed
Breastfeeding/ Pregnancy Risk	Did <this child> breastfeed for more than a month?	Yes; No; Don't know	Schwarz et al. [210]
	How old was <this child> in months when he/she first received a bottle of formula, cow's milk, water, juice, tea, or cereal at least once a day?	_ _ mos.	Schwarz et al. [210]
	How much did this child weigh at birth?	_ _ lbs _ _oz	Schwarz et al. [210]
	Did a doctor say that <you/birth mother> had diabetes when pregnant with <this child>?	Yes; No; Don't know	Schwarz et al. [210]
	Did a doctor say that <you/birth mother> had hypertension (high blood pressure) when pregnant with <this child>?	Yes; No; Don't know	Schwarz et al. [210]
Food Security	"The food that (I/we) bought just didn't last, and (I/we) didn't have money to get more." Was that often, sometimes, or never true for (you/your household) in the last 12 months?	Often true; Sometimes true; Never true; Don't know; Refused	USDA (Bickel, [211]
	"I/we couldn't afford to eat balanced meals." Was that often, sometimes, or never true for (you/your household) in the last 12 months?	Often true; Sometimes true; Never true; Don't know; Refused	USDA [211]
	In the last 12 months, since (date 12 months ago) did (you/you or other adults in your household) ever cut the size of your meals or skip meals because there wasn't enough money for food?	Yes; No; Don't know; Refused	USDA [211]

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
	How often did this happen --almost every month, some months but not every month, or in only 1 or 2 months?	Almost every month; Some months but not every month; Only 1 or 2 months; Don't know; Refused; Not asked	USDA [211]
	In the last 12 months, did you ever eat less than you felt you should because there wasn't enough money to buy food?	Yes; No; Don't know; Refused	USDA [211]
	In the last 12 months, were you ever hungry but didn't eat because you couldn't afford enough food?.	Yes; No; Don't know; Refused	USDA [211]
TV & Media	How many working TVs do you have in your home?	*text*	Derived from Borzekowski[212], ; Robinson[138],; Robinson et al.[213]
	Is there a working TV in the room where <this child> sleeps?	Yes No	
	Is there a computer in your home?	Yes No	
	Is there a computer in the room where <this child> sleeps?	Yes No	
	Is there a video game player in your home?	Yes No	
	Is there a video game player in the room where <this child> sleeps?	Yes No	
	Do you have Internet access in your home?	Yes, No, Don't Know	
	On an average WEEK day, how many hours does <this child> watch TV?	None Less than 1 hour per day 1 hour per day 2 hours per day 3 hours per day 4 hours per day 5 or more hours per day	Schmitz et al.[214]
	On an average WEEKEND day, how many hours does <this child> watch TV?	None Less than 1 hour per day 1 hour per day 2 hours per day 3 hours per day 4 hours per day 5 or more hours per day	Schmitz et al.[214]
	On an average day, how many hours does <this child> play video or computer games, or use a	None Less than 1 hour per day 1 hour per day	Modified Schmitz et al.[214]

Table 9.4 Source and Response Sets of Questionnaire Common Measures			
Construct	**Item**	**Response Options**	**Source**
	computer for something that is not school work? (Include activities such as Play Station, Xbox, hand held video games, computer games, and the Internet.)	2 hours per day 3 hours per day 4 hours per day 5 or more hours per day	
Food Norms	During the past seven days, how often did your family eat breakfast together?	0 times 1-2 times 3-4 times 5-6 times 7 or more times	Developed
	During the past seven days, how often did your family eat lunch together?	0 times 1-2 times 3-4 times 5-6 times 7 or more times	Developed
	During the past seven days, how often did your family eat dinner together?	0 times 1-2 times 3-4 times 5-6 times 7 or more times	Developed
Weight Status	How would you classify your own weight?	Very Underweight Underweight Normal Overweight Very Overweight	Modified Birch et al.[215]
	How would you classify <this child's> current weight?	Very Underweight Underweight Normal Overweight Very Overweight	Modified Birch et al.[215]

A “train the trainer” model is used to prepare staff to collect questionnaire data. Each Field Site designates two or more “Master Trainers” who participate in central trainings conducted by the RCU at the University of North Carolina at Chapel Hill on April 16-18, 2012. These Master Trainers are responsible for training and certifying the data collection staff at their Field Site. To be certified, Master Trainers attends the central training, reads the protocol and manual of procedures, complete the questionnaire and administer the questionnaire. The data collectors are certified by a Master Trainer who will describe the data collection process, insure that the protocol and manual of procedures are read and observe the questionnaire being administered to a volunteer.

Secondary Outcomes: Accelerometry

Background and Rationale. Physical activity (PA) will be measured objectively using a commercially available ActiGraph GT3X+ (all youth). For parents and other adults GT3X+ accelerometers (Vanderbilt) or GT3X accelerometers (Minnesota) will be used. (ActiGraph, Pensacola, FL). The rationale for using ActiGraph is that among currently available devices it provides consistent and high quality data supported by feasibility, reliability, and validity testing in children and adults.

ActiGraph monitors have been used in numerous studies to assess PA in children[149-152]. The validity of the ActiGraph has been examined in several studies involving children aged 2 to18 years. ActiGraph has been validated using direct observation[153-155], doubly labeled water (DLW)[156; 157] (, indirect calorimetry[158-162] and other accelerometers[159; 154] as reference methods. Correlations between ActiGraph counts and observed activity was moderate to high (r = 0.52-0.77) in older ActiGraph models (Hands, 2006; Kelly et al., 2004; Sirard, 2005) and higher in a newer ActiGraph (GT1M) model and when using more advanced algorithms (Choi et al., 2010). Although the validity of ActiGraph GT3X and GT3X+ models in populations including children has not be reported, it is expected to be at least as high or higher than the GT1M and older ActiGraph models.

The GT3X+ and GT3X contain electronic motion sensors consisting of piezo-electric sensors that generate an electric charge in response to a mechanical force, thus, acceleration. They do not respond to constant acceleration. Their major advantage is that no power supply is required, except for data storage, resulting in a considerable reduction in the size and weight of the device. Both monitors provide activity counts, vector magnitude, and inclinometry data. Other data calculated by the ActiGraph manufacturer-provided software includes activity intensity levels, energy expenditure (METs) and number of steps.

The GT3X+ collects data in the raw format at a pre-defined sample rate from 30 to 100 Hertz (Hz). When collecting data at 40 Hz, the battery life is stated to be 13 days and the data memory lasts for 16 days. The GT3X has the ability to collect 1-second epoch data for at least 7 days. The GT3X does not have adequate data storage capacity to collect raw data for multiple days.

Accelerometry technology is still improving and mathematical models to predict PA and PA-related energy expenditure are being developed. We expect these advances to continue. Thus, COPTR investigators will collect raw acceleration data in the index child that could be used to measure physical activity and sedentary behavior using both currently existing algorithms and new algorithms/approaches that emerge during the study (next 6 years). Table 9.5. summarizes the specifications of the GT3X devices.

Table 9.5. Specifications of the GT3X devices		
Specifications	**GT3X+**	**GT3X**
Transducer	Tri-axis, solid state accelerometer	Tri-axis, solid state accelerometer
Dynamic Range	+/- 3G	+/- 3G
Dimensions	4.6cm x 3.3cm x 1.5cm	3.8cm x 3.7cm x 1.8cm
Capacity	16 Days (Raw data at 40 Hz)	16MB or 400 Days (60 sec epoch)
Battery Life	13 Days (Fully Charged at 40 Hz)	20 Days (Fully Charged)
Weight	19 g	27 g
Resolution	12-bit A/D conversion; 1.46 mG (Raw Data)	12-bit A/D conversion; 1.46 mG (Raw Data)
Sample Rate	30Hz-100 Hz	30 Hz

Limitations of accelerometry. Accelerometers are the best currently available relatively simple and precise device for objectively assessing physical activity and sedentariness. However, they do not provide information on types of activities, nor can they be used to assess lifestyle activities such as raking and shoveling, static activities such as bicycling and weight lifting, and aquatic activities such as showering and swimming. These limitations may be addressed as new algorithms emerge during the course of the study. Other limitations are related to use and application of collected data in device-specific arbitrary counts (PA counts) or more comparable approach of using acceleration (m/sec^2) to summarize accelerometry data.

Objective. Accelerometry monitoring will provide an objective measurement of the amount and patterns of physical activity and sedentary behavior.

Methods. Accelerometry data on children and parent (Minnesota and Vanderbilt) will be collected at four common data collection time points – baseline, 12 months, 24 months and 36 months. All baseline accelerometer data will be collected prior to randomization. The GT3X+ will be set to 40-Hertz frequency and the GT3X will be set to 1-second epoch.

The index children in the study will wear the GT3X+ monitor on the right hip for seven complete days (including while sleeping and naptime) except during water activity (e.g., bathing, swimming, showering). The responding parent in Minnesota and Vanderbilt will also wear the GT3X and GT3X+ monitor, respectively for seven days on their right hip. A consensus has been reached that the monitoring period should include two weekend days and five weekdays. In some cases, participants may be able to provide only 6 days of data, which is acceptable. If the participant does not wear the activity monitor for four days, it may be necessary to have the participant wear the monitor again in order to get valid data. The valid wear time criteria (minimums) are 4 days (3 weekdays and 1 weekend day) of at least 6 hours of awake time with 33% non-zero epochs per hour. For some participants,

accelerometer data for the 2 wears will be combined in order to meet the minimum wear time criteria.

Any major updates in the ActiLife software version used during the trial will be made as a collaborative decision by the Diet and Physical Activity Working Group. If a change does occur, it will be on the same calendar day for all Field Sites. Regular (minor) updates in the ActiLife software will be done by each Field Site as they are released by ActiGraph. The Accelerometer Manual of Procedures will be updated only after major updates in the ActiLife software (e.g. Version 6.0 to Version 7.0).

COPTR will use a "train the trainer" model. Each field center will have at least two activity monitor master trainers who will participate in a central in-person training organized by the RCU at the University of North Carolina at Chapel Hill on April 16-18, 2012. Following part 1 of the training session, the master trainers will wear the accelerometer for at least 8 hours. The certification process requires the master trainer to successfully initialize, download and transfer accelerometer data. The master trainers will train and certify additional research staff at their site. Data collectors/staff do not initialize or download accelerometer data until after they have been trained and certified.

Secondary Outcomes: Dietary Assessment

Background and Rationale. The 24-hour recall is the most widely used method to assess diet in studies of populations, and is used in national food consumption surveys such as the NHANES. This method allows assessment of all foods, beverages and dietary supplements consumed during the 24-hour period obtained – typically beginning with the first item consumed the previous day. The 24-hour method, which can be performed face-to-face or by telephone, has been validated in lean and obese individuals[163; 164]. In face-to-face interviews, the use of visual aids such as food models, food portion booklets and measuring utensils improves the accuracy of estimation of quantities consumed[165]. For telephone interviews, visual aids and instructions are often mailed to subjects[166]. In addition, with a trained interviewer, they are relatively quick and easy to administer. An important strength of the 24-hour recall method is that it allows comparison of groups of individuals by demographic variables such as age, gender, race/ethnicity or geographic region. Another strength is that the 24-hour recall (Nutrition Data Systems for Research or NDSR) has been used to generate Healthy Eating Index scores, and thus to assess dietary quality[167]. The main limitations of capturing quantitative dietary intake information by use of 24-hour recalls are: 1) the variability in day-to-day dietary intakes; 2) reliance on subject memory; and 3) the potential of over or underreporting of intakes. To compensate for these possible limitations, interviewers typically capture data on more than one day of the week which includes both weekdays and weekend days, and use the USDA 5-step multi-pass method[165].

Objective. The purpose of performing dietary intake assessment is to capture quantitative nutrient information on all the foods, beverages and dietary supplements that study subjects consume. The dietary intakes are analyzed for: volume of food, total energy, macronutrients, micronutrients, water, dietary fiber, added sugars and specific food groups. We will also examine glycemic load, dietary energy density, nutrient adequacy ratios, and dietary pattern and quality. Examples of diet quality indices used in children are shown in Table 9.6.

Table 9.6. Examples of dietary quality indices used in children

Citation	Subjects			Diet Assessment	Group/Index	Methods
	N	Sex	Age			
Daniels, EJCN, 2009[168]	1,810	m/f	2y	24 hr recall	Diet Diversity score(DDS-10g) - FAO (score 1-9)	Cross-sectional: 1 pt per 10g of a each food group or 1 pt for 1g oil.
Feskanich, JAmDietAssoc, 2004[169]	16,452	m/f	9-14y	132 item FFQ	Youth HEI- 13 components (score 0-100)	Modified HEI and compared to YHEI (Note: YHEI not strongly related to energy intake).
Freedman, JNutr, 2010[170]	17,311	m/f	≥2y	24hr recall	HEI-2005: 12 dietary components	NHANES ('01-'04) data- 3 part model (they create) based on Tooze 2- part model[219] in >1000 subjects.
Guenther, JAmDietAssoc, 2008[171]	8,650	m/f	≥2y	24 hr recall	HEI-2005	NHANES ('01-'02) compared HEI-2005 assessed validity through 4 methods (concluded valid).
Kennedy, JNutr, 2007[172]	3,164	m/f	24-71 mo	24 hr recall	Diet Diversity Score (DDS) – 10 food group & DDS-10g	Filipino Nutrition Database. DDS summed unique food groups for score. DDS-10g required minimum amounts (see: Daniels, 2009).
Manios, JAmDietAssoc, 2009[173]	2,287	m/f	2-5y	24 hr recall + weighed records + food diaries	HEI- 10 component	Weighed records were used in nurseries and recalls or diaries were used outside nurseries. Summed individual scores- used quartiles of the scores for analysis.
Steyn, Public Health Nutr, 2006[174]	2,200	m/f	1-8y	24 hr recall	DDS- following FAO guidelines Food Variety Score (FVS) (Score 0-45)	Secondary analysis of NFCS in South Africa. 1 24 hr recall by caregivers. Also used nutritional adequacy ratio and mean adequacy ratio.
Serra-Majem, EJCN, 2003[175]	3,166	m/f	6-24y	24 recall +16 item FFQ	KIDMED- Mediterranean diet measure (Score: -3 to 12)	Assessed diet from Spanish children has high, med, low KIDMED.
Kranz, JAmDietAssoc, 2006[176]	5,437	m/f	2-5y	24 recall	Created new- RC-DQI	Continuing Survey of Food intakes by individuals (1994-1996, 1998) components chosen based on My Food Pyramid, ADA, and APA recommendations (Nutrient-based)
Hurley, JNutr, 2009[177]	317	m/f	11-19	131 item- youth/ adolescent FFQ	Compared HEI and YHEI	Compared the indices to body composition and found HEI better correlated with body composition and disease risk.
LaRowe, JAmDietAssoc, 2010[178]	135	m/f	2-5	24 hr recall	My Food Pyramid	Great Lakes Inter-Tribal Council Head Start programs- baseline data from HCSF intervention.
Cheng, JNutr, 2010[179]	376	m/f	6-8y	3-day weighed record	Nutritional Quality Index (NQI)- Density measure RC-DQI- nutrient based	German Cohort

Methods. Dietary Intakes will be measured using 24-hour recalls that are conducted on two weekdays and one weekend day per study time-point using NDS-R version 2012. Any update in the NDS-R version during the trial will be made as a collaborative decision by the Diet and Physical Activity Working Group. If a change does occur, it will be on the same calendar day for all Field Sites with one caveat. Participants who have already completed 1 or 2 recalls in the old version of NDS-R will have their remaining recalls conducted using the same older version of NDS-R such that all 3 recalls are collected using the same version of NDS-R.

Dietary assessment data will be collected at baseline, and 12, 24 and 36 months during the study. All baseline dietary assessment data will be collected prior to randomization. Table 9.11 summarizes the specific data collection plans for each Field Site. To avoid collecting days with similar foods, recalls should not be conducted on consecutive days. In addition, in order to capture variability of food supplies in the home, all three recalls should not occur within a seven day period. The third recall needs to be collected more than one week after the first recall. All three recalls must be collected within 30 days. This is a hard deadline. While the goal is to collect three dietary recalls per participant, it is possible that a limited number of participants at each Field Site may only have two dietary recalls completed within the 30 day window. All efforts will be made to obtain a minimum of two recalls (1 weekday and 1 weekend) for each participant. All dietary intakes (i.e., food, and beverages including water~~)~~ will be collected. For Diet Recall of young children, those responsible for child feeding (e.g. parents, daycare providers) will be the reporter. Details of the procedures to be used in dietary assessment are in the COPTR Manual of Procedures for Dietary Assessment.

COPTR will use the “train- the- trainer” model. Each field center will have two diet master trainers who will participate in a central in-person training organized by the RCU at the University of North Carolina at Chapel Hill on April 16-18, 2012. Following the training session, the master trainers will complete two dietary recalls for certification by the RCU. The master trainers will train and certify additional research staff at their site. No diet recalls will be conducted until after the trainer has been trained and certified.

Table 9.7. Site specific 24 hour dietary recall data collection plans				
	Case	**Minnesota**	**Stanford**	**Vanderbilt**
Number of recalls	3	3	3	3
# weekdays	2	2	2	2
# weekends	1	1	1	1
Recaller	Child & parent	Parent & day care provider	Child & parent	Parent & day care provider
How collected (1st, 2nd, 3rd)	In-person Telephone Telephone	In-person In-person/Telephone In-person/Telephone	In-person Telephone Telephone	Telephone Telephone Telephone
Announced/ Unannounced	Announced	Announced	Unannounced	Announced
Language administered	English, Spanish	English, Spanish	English, Spanish	English, Spanish
Use of Portion Size Devices	Food Booklet	Food Booklet	Food Booklet	Food Booklet & Measuring Utensils

Secondary Outcomes: Blood Pressure

Background and Rationale. Elevated blood pressure (BP) in overweight children and adolescents is an increasingly recognized epidemic[180-183] (. Many overweight/obese youth with elevated BP already have other cardiovascular risk factors and evidence of end-organ damage[184-186; 182; 187; 183] Children with elevated BP are likely to become adults with elevated BP, and therefore are at increased risk for cardiovascular and renal disease[180; 188-191]. These data indicate that children with obesity and elevated BP are at particularly high risk, and require intervention[185]. Weight loss is a powerful tool to reduce BP in children and adults[180; 192]. A diet rich in fruits/vegetables, low-fat dairy, low-fat protein (e.g. DASH-like diet) and/or reduced sodium intake can also reduce BP, particularly in African-American adults[180; 193-195; 209]. Combined with calorie reduction, activity, and behavioral interventions, DASH diets facilitate simultaneous reduction of BMI and BP in adults[196]. However, the most effective methods to facilitate adoption of these lifestyle changes in children are not clear, and education alone (usual care) is often ineffective[193]. This knowledge gap is particularly important because of the huge potential impact of small changes in BP[180]. Therefore, blood pressure will be obtained for all participants from the two COPTR sites (Case Western Reserve University and Stanford University) testing interventions to treat overweight and obesity.

Objective. We will determine if interventions to reduce overweight and obesity reduce blood pressure. In addition we will use the 3-year longitudinal data to examine risk factors and correlates of blood pressure changes over time in children and adolescents.

Methods. An automated blood pressure measurement device (OMRON HEM-705-CP or OMRON HEM-705-CPN Digital Blood Pressure Monitor) and a standardized procedure for the measurement of blood pressure and pulse will be utilized, as specified in the Blood Pressure Manual of Procedures (MOP). The design and operation of the OMRON HEM-705-CP and the OMRON HEM-705-CPN Digital Blood Pressure Monitor are based upon the combined principles of compression of the brachial artery under an elastic, inflatable cuff and estimation of the systolic and diastolic blood pressure levels by oscillometric methods.

Blood pressure and pulse will be measured at four data collection time points – baseline, 12 months, 24 months and 36 months. All baseline blood pressure and pulse measurements will be collected prior to randomization. Blood pressure measurement must be conducted early in the visit and not following potentially stressful exam components such as the blood drawing. Before measurements commence participants are offered the opportunity to visit a restroom or bathroom. The participant should not have smoked or had any caffeine within the last 30 minutes prior to the blood pressure determinations.

Blood pressure measurements will be taken using the right arm. Participants should sit quietly for 4-5 minutes before the first measurement is taken. Seated, resting blood pressure and pulse are measured three times at each evaluation visit. The first reading will be discarded and the average of the second and third measurements will be used in analysis.

The OMRON HEM-705-CP and the OMRON HEM-705-CPN are automated devices. The data collector determines and places the correct size cuff on the participant's arm, pushes the button on the device and waits for the output. All readings will be recorded to the nearest integer.

COPTR uses a “train the trainer” model. Each Field Site designates two or more “master trainers” who participate in central trainings organized by the RCU at the University of North Carolina at Chapel Hill, NC from April 16 to April 18, 2012. The designated master trainers are responsible for training and certifying the data collection staff at their center. For certification, the data collector is observed by the trainer. The participants must include 5 or more children requiring varying cuff sizes. The trainee must correctly select the appropriate cuff size and demonstrate consistent compliance with the MOP to be certified. No blood pressure and pulse measurements will be taken until after the data collector has been trained and certified.

<u>Secondary Outcomes: Biomedical Measures</u>

Background and Rationale. Hyperinsulinemia/insulin resistance is a risk factor for future Type 2 diabetes, and is associated with increased blood pressure, adverse lipid profiles and increased body fatness in children and adolescents[124; 197; 198], and weight loss is associated with improved insulin sensitivity among adolescents[199]. Thus, insulin resistance serves both as a direct indicator of a significant risk factor and as a biochemical marker of metabolically-

significant adiposity and changes in adiposity. Increased fasting insulin concentration is an appropriate marker of insulin resistance for this study.

Fasting insulin concentrations can also be combined with fasting glucose concentrations using a number of algorithms, including the HOMA and QUICKI, among others, to generate indices. However, all of these calculated measures of insulin resistance appear to be highly correlated with fasting insulin concentrations in non-diabetic subjects[200]. The Stanford group have recently confirmed this with their own data from the 8-10 year old African-American girls in Stanford GEMS (correlations of .98-.99). However, because a fasting glucose will also be collected, the Field Sites will be able to examine each of these combination indices. Fasting glucose will also be collected to identify children with previously undiagnosed type 2 diabetes (fasting glucose ≥ 126 mg/dl) and to identify children who will be referred for further evaluation by their primary care medical provider (fasting glucose ≥ 110 mg/dl) according to Field Sites clinical monitoring protocol.

Adverse lipid profiles are risk factors for cardiovascular diseases and increased BMI is associated with increased total cholesterol, LDL-cholesterol, and triglycerides and lower HDL-cholesterol concentrations[125; 201; 124; 202; 203]. Thus, lipid measures also serve both as direct indicators of a significant risk factor and as a biochemical marker of metabolically-significant adiposity and changes in adiposity.

High levels of C-reactive protein (CRP) is a marker for inflammation. CRP prospectively assesses the risk of atherosclerotic complications, may be a mediator of vascular injury and is strongly related to obesity[204]. In adults, higher body mass index (BMI) levels are associated with higher CRP concentrations. Some clinicians are starting to use CRP levels when assessing risk for cardiovascular disease. Using cross-sectional data from the National Health and Nutrition Examination survey 1999-2000, Ford found significant associations between CRP levels and BMI in children 3 to 17 years of age[205]. CRP levels were also associated with age and systolic blood pressure, but BMI had the strongest association.

Unexplained elevated levels of alanine Aminotransferase (ALT) has been liked with adiposity and may be a marker for nonalcoholic fatty liver disease (NAFLD) in adolescents and adults[206; 207]. Researchers have found a close association between metabolic syndrome, insulin resistance, elevated ALT levels and NAFLD in overweight/obese children and adolescents[206; 208].

Objective. We will determine if the COPTR interventions to reduce overweight and obesity change cardiovascular risk factors measured in blood. In addition we will use the 3-year longitudinal data to examine the risk factors and their correlates over time.

Methods. Blood specimens are collected at baseline, 12 months and 36 months at the two Field Sites testing interventions to treat overweight and obesity – Case Western Reserve University and Stanford University. All baseline blood specimen samples are collected prior to

randomization. All common blood specimens are analyzed by the Northwest Lipid Metabolism and Diabetes Research Laboratories (NWRL). The biomedical measures analyzed in the index child are Hemoglobin A1c (HbA1c), Glucose, Total Cholesterol, LDL-cholesterol, HDL-cholesterol, Triglycerides, high-sensitivity C-reactive protein (hs-CRP), Insulin and Alanine Aminotransferase (ALT). Salivary DNA will be obtained from the child at the year 1 visit with additional consent/assent (not yet submitted to IRB); families who decline provision of DNA will still be able to continue in the study. This approach is based on our experience that consent for DNA can take substantial time and may intimidate some families who may decline to participate in the study if DNA is collected at baseline

Fasting status will be confirmed prior to blood draw. A trained phlebotomist at each site is responsible for the blood collection. However, a data collector might have the responsibility for mailing the blood specimens to the NWRL. All specimen samples will be frozen to allow for batch shipment. The assays and quality control for each measurement is described below.

HbA1c

The measurement of the relative proportion of hemoglobin subclasses and calculation of the HbA1c levels are performed by an NGSP-certified auto-analyzer (G-8 Tosoh, Biosciences, Inc.) using non-porous ion exchange high performance chromatography to achieve rapid and precise separation of stable HBa1c from other hemoglobin fractions. The system calibration is maintained using two point calibration reagents. A set of quality control samples are analyzed twice daily. The acceptance allowance for quality control is + 0.1% variance from the target value for the low level, and + 0.2% variance from the target value for the high level. The inter-assay CVs for the low and high quality control samples are 0.9% and 0.6%, respectively.

Glucose

Analysis of fasting and post glucose intake samples is performed enzymatically on a Roche Hitachi Modular P chemistry autoanalyzer. This instrument executes the glucose hexokinase method described by[216-218] and recognized as the most specific method for the determination of glucose. Quality control samples with normal and high glucose levels are used for monitoring glucose assay performance. The inter-assay CV is <3%. Lyophilized samples at two different glucose concentrations are used to monitor possible analytical drift.

Lipid Profile

Measurements of total plasma cholesterol in plasma, cholesterol in the lipoprotein fractions and triglycerides are performed enzymatically on the Roche Modular P autoanalyzer using methods standardized to the Centers for Disease Control and Prevention Reference Methods. Determination of HDL-cholesterol is performed after precipitation of apo B-containing particles by dextran sulfate Mg2+. LDL-cholesterol is calculated by the Friedewald equation. This approach for measuring LDL-CH is clinically reliable if the measurements of total CH, HDL-CH and triglycerides are performed with a high level of accuracy and precision. However, the

Friedewald equation for the estimation of LDL-CH is inaccurate when triglycerides are >400 mg/dl. In this case, a complete lipoprotein separation by ultracentrifugation which allows quantitation of the individual lipoprotein classes is performed using the Lipid Research Clinics Beta Quantification procedure.

Quality control materials (BCL-Low, BCL-High (Biocell Laboratories) and L1-Medium (In-house prepared fresh frozen pool) are used at the beginning and at the end of each run.

The inter-assay CVs are consistently <1.5% for total cholesterol and triglycerides and <2% for HDL cholesterol.

Long-term Drift: A large quantity of two lyophilized quality control materials was acquired from Bio Rad for lipids. Values for each analyte were assigned by analyzing the samples daily for at least two weeks to achieve a minimum of 50 values. The mean of all the values constitutes the target value for each analyte. These materials are stored at -70°C and analyzed monthly to monitor for analysis drift. Actions are taken if the values are consistently above or below the 2 SD limit on two consecutive months.

C-Reactive Protein

Levels of C-reactive protein (CRP) in plasma are measured immunochemically on a nephelometer autoanalyzer (BNII). The reagents are obtained from Siemens Inc. This high sensitivity method is based on polystyrene particles coated with monoclonal antibodies specific to CRP which form immunocomplexes with CRP in plasma samples.The intensity of the scattered light in the nephelometer is directly proportional to the concentration of CRP which is determined versus dilutions of a standard of a known CRP concentration. The method is standardized against the IFCC/BCR/CAP reference preparation.

Insulin

The Insulin assay is a two site immuno-enzymometeric assay performed using Tosoh 2000 auto-analyzer. The assay is calibrated to WHO IRP 66/304 standard. The assay has a sensitivity level of 0.5 uU/mL and the standard curve linearity is up to 330 uU/mL. A set of high, medium and low insulin level controls are included in each batch of samples to monitor assay performance. The inter assay CVs for Low, Medium and High insulin level controls are 2.8%, 2.5% and 2.0% respectively. The assay has high specificity as cross- reactivity with Human C-peptide, intact Proinsulin, split (32, 33) Proinsulin and Des (64,65) proinsulin is 0%, 2 %, 2.6% and 39.8 % respectively. A Reference Interval for apparently healthy donors has been established at <17.0 uU/mL. The laboratory has participated in external proficiency evaluation program by the College of American Pathologists (CAP). Additionally, the laboratory has participated in the ADA sponsored Insulin Standardization workshops in 2007 and 2011. In the 2007 insulin standardization workshop this assay was reported as top performer with high sensitivity and specificity. Most recently, in 2011, ADA Insulin standard prepared and target level assigned by IDMS reference method was distributed to the laboratories. The ADA criteria of individual laboratory performance was set at up to 15.5% measurement bias from the

assigned target level. Using the current insulin assay our laboratory achieved a bias less than 8.5%.

Alanine Aminotransferase (ALT)

This assay is performed on a Roche Double Modular P Analytics automated analyzer using Roche Diagnostics reagents. L-alanine reacts with alphaketoglutarate in the presence of ALT to form pyruvate and Lglutamate. NADH is then added to the pyruvate in the presence ofLDH to form L-lactate and NAD+. The rate of NADH oxidation to form NAD+ is directly proportional to the rate of pyruvate formation indicating ALT activity. The rate of decrease in absorbance at 340nm due to the formation of NAD is directly proportional to the rate of pyruvate formation and proportional to the ALT activity of the sample. The normal reference ranges for adults are: 17–67U/L (Male) and 13–50U/L (Female).

9.1.3. Site-Specific Mediators, Moderators and Secondary Outcomes.

Background and Rationale. Self-reported information will be collected from COPTR index children and other household members by obtaining responses to written or verbalized questions. Although we refer to “questionnaires”, as discussed in the methods section below, several methods are used to collect these data, and only a minority of the data is collected through the use of paper questionnaires. The information obtained is used to describe the study population or as a confounder, mediator, moderator or secondary outcome of intervention effects.

As shown in our conceptual framework, our study will examine a comprehensive list of both mediators and moderators. First, our theoretical framework assumes that our two family-based interventions, SystemCHANGE and HealthyCHANGE will have an impact on BMI via two different sets of **mediators** – first, a set of cognitive mediators that are tied to the targeted approach of each intervention (systems thinking for SystemCHANGE, motivation for HealthyCHANGE) tat we hypothesize will influence the proximal outcomes of diet, physical activity, sleep and stress, which in turn (also mediators themselves) will impact more distal, physiological outcomes (i.e., BMI, blood pressure, fitness levels, cardiovascular risk). Proposed cognitive mediators include: child’s self-efficacy, social support, motivation and family problem-solving, systems thinking, self-regulation.

A **moderating** variable is defined as a variable that could influence the primary or secondary outcomes because the variable interacts with the intervention to change study outcomes. In other words, the intervention affects people differently, depending on their status on the moderator variable. These variables are evaluated at the beginning and the end of the intervention, and in some cases as interim measurements.

There is strong evidence identifying several behavioral, contextual, and environmental factors as critical underpinnings of the adolescent obesity[70-81]. Family, school, peers, community, and

policy act together (superimposed on biological predisposition) to provide the environmental contexts that shape children's energy intake and expenditure - and therefore together influence the development of obesity and its co-morbidities. These factors are not only likely to have an independent impact on BMI outcomes, but also are likely to moderate the impact of the interventions themselves..

Our list of potential moderators have been carefully selected based on the literature, our own work and the psychometric properties of the measurements themselves. These include: the family's socioeconomic status and demographic characteristics, personal characteristics of the child, parent/guardian, and family (including physiological and psychosocial characteristics), the child's physical and social environment (neighborhood, school, and family), and peer norms surrounding nutrition, physical activity and perceived environment. We posit that these factors may moderate the impact of the interventions on outcomes, as well as interventions on the program-specific mediators Covariates deemed from the literature to be confounders also will be assessed.

Objective. The purpose is to describe the characteristics of participants, to determine possible mediators and moderators of intervention effects and to study secondary outcomes that are impacted by the intervention.

Methods. The demographic, household, mediators and moderators survey is administered to parents/primary caregivers of the participating child and/or to the participating child. Table 9.2. summarizes the location where the questionnaire will be administered and administration format in each site. To accommodate the sample being studied, we are administering the surveys in both English and Spanish

The following table (Table 9.8.) outlines the list of site-specific mediators, moderators, covariates and self-reported secondary outcomes that will be considered in our study.

Table 9.8. Case Western Reserve University Site-Specific Mediators, Moderators and Secondary Outcomes*

Construct	Respondent	# Questions
Treatment Self-Regulation Questionnaire	Child	6
Brief scale for sedentary equipment in the home	Child	9
Brief scale for physical activity in the home	Child	14
Active Where? Survey – Rules for TV	Child	8
Parental Monitoring Scale	Child	6
Social Support and Exercise Survey	Child	10
Self-efficacy scale for physical activity barriers	Child	4

Modified Rosenberg Self-Esteem Inventory	Child	6
Center for Epidemiological Studies Depression Scale for Children	Child	20
Neighborhood environment walkability scale – Safety scales	Child	13
Youth Risk Behavior Survey physical activity	Child	3
Modified activity questionnaire	Child	10
Active Where? Survey – Active transportation to school	Child	2
Active Where? Survey – Food scale	Child	18
Active Where? Survey – Rules for eating	Child	12
Child Food Security Survey	Child	9
School wide food practices scale	Child	7
Social support and eating habits survey	Child	20
Children's self-efficacy for eating habits survey	Child	15
Modified -Youth Eating Disorder Examination Questionnaire	Child	3
Family Ritual Questionnaire – dinnertime subscale	Child	7
Sleep evaluation questionnaire (SEQ)	Child	10
Adolescent sleep wake scale (ASWS)	Child	28
Pediatric Daytime Sleepiness Scale	Child	8
Perceived Stress Scale	Child	10
Systems Thinking Scale	Child	16
Index of Self-Regulation	Child	7
Impact of weight on quality of life (IWQOL)	Child	27
PACER Test	Child	1
Brief scale for sedentary activity equipment in the home	Parent	9
Brief scale for physical activity equipment in the home	Parent	14
Active Where? Survey – Rules for TV	Parent	8
Child Behavior Checklist – social problems subscale	Parent	7
Center for Epidemiological Studies Depression Scale	Parent	20
Family Assessment Device	Parent	12
Neighborhood environment walkability scale – Safety scales	Parent	13
Active Where? Survey – Active transportation to school	Parent	2
Active Where? Survey – Rules for eating scale	Parent	12

The Child Feeding Questionnaire	Parent	31
Obstructive Sleep Apnea screen	Parent	8
Systems Thinking Scale	Parent	20
The Stress Index for Parents of Adolescents	Parent	34
Family Health History	Parent	20
Maternal History	Parent	5
Medical History	Parent	9

*The Health Utilities Index (child, 40 items) is also under consideration by the OPCTR consortium for addressing cost-effectiveness.

Site-Specific Secondary Outcomes

In addition to the secondary outcomes outlined in the common measures section, we will also assess the following secondary (proximal) outcomes:

Sedentary Behavior will be assessed primarily using 1-week accelerometer data at each evaluation point, as described, and supplemented by MAQ [221]questions about TV, video, and leisure computer fine (expressed as hr/d).

Sleep. Quality and Quantity of sleep will be assessed with the Sleep Evaluation Questionnaire (SEQ)[222]; the Adolescent Sleep Wake Scale (ASWS)[223] and the Pediatric Daytime Sleepiness Scale [224].

Fitness Assessment. A standard shuttle run test (in which the child runs between two markers) will be performed according to standard protocols[138,152-154].

9.2. Quality Control (common and site-specific)

The overall goal of quality assurance is to assure complete, precise and accurate date. This is accomplished through monitoring the quality of the data collected and training and certification of the staff who collect the measurements. Biannually the RCU provides the DSMB Quality Assurance tables for the common measurements and site specific measurements.

9.2.1. Quality Control - Primary Outcome (BMI) and Other Anthropometric Measures

Ten percent (10%) of the measurements (height and weight) that compose the primary outcome (BMI) and the other anthropometric measurements (waist circumference and triceps skinfold) are measured by two different data collectors. Ideally one of the data collectors is a Master Trainer. The method used to select the 10% sample is site specific and is incorporated into the site's data management system to track who requires the second measurer. Duplicate

measures are recorded to confirm inter-rater reliability, but the first data collection staff's measurements will be used in the analysis. To be acceptable, the absolute difference between the calculated values by the two data collectors must be less than 0.5 cm for height, 0.3 kg for body mass, 1 cm for waist, and no larger than 2 mm if the skinfold is less than 10 mm or greater than 10% if the skinfold is 10 mm or larger. If a data collection staff's agreement on a measurement (height, weight, waist circumference or skinfold) is outside this range in more than two out of ten individuals, then he/she must complete retraining.

Range checks are built into the data management system to prevent the collection of erroneous data. The 2003-2010 NHANES was used to determine age and gender-specific range checks for the anthropometric variables. Range checks are set so that participants with extreme and erroneous values are brought to the attention of the data collection staff for scrutiny.

The bounds for range checks in the baseline data collection vary by center since the anthropometric eligibility criteria for enrollment of index children vary.

9.2.2. Quality Control – Common Mediators, Moderators and Secondary Outcomes

The demographic variables are collected via questionnaires along with additional mediator variables (e.g. food security, tv and media). The survey collection, review and editing procedures are site specific. The RCU monitors for missing and out of range values on the common questions across the Field Sites.

Physical activity is measured by accelerometry. Because activity levels change daily and the test retest relationships would be low, participants are not asked to wear the activity monitor twice for quality control. In addition, an interview is not a good quality control check since it does not provide the necessary data for a comparison, and thus are not used for quality control. The RCU monitors and reports the amount of data (e.g. the number of valid days, number of re-wears). The valid wear time criteria (minimums) are 4 days (3 weekdays and 1 weekend day) of at least 6 hours of awake time with 33% non-zero epochs per hour. For some participants, accelerometer data for the 2 wears will be combined in order to meet the minimum wear time criteria.

The dietary interviewer reviews and edits the 24-hour dietary recall as soon as possible after its administration. During editing, special attention is paid to NDS-R Missing Foods, Priority Notes and all other Notes. Full quality assurance must be conducted on at least 10% of recalls. The quality assurance checks include ensuring information is entered correctly in header tab, meal information window, food tab and trailer tab. In the header tab the goal is to make sure information is filled in correctly (e.g. ID, Date of intake, Site ID). The meal information window should have meals in order by time and the eating and activity codes entered correctly. The quality assurance checks in the food tab include checking that foods entered correctly, amounts match code, missing foods and priority notes are resolved. Recalls

that have issues that need to be resolved are put into the FIX project. All data must be cleaned and missing foods, or priority notes must be resolved before the output file is run and sent to the RCU on a quarterly basis. All missing foods are discussed at diet interviewer staff meetings. There will be quarterly reviews of data entry issues and shared user recipes to standardize the data entry process across all sites.

In SAS or other statistical package a quality assurance report is run to generate for each record total energy, percent kilocalories from fat, fruit servings, vegetable servings and grams of fluid. Ranges are set for school aged children and preschool aged children. Records with values beyond the cutoff points below are printed and checked.

	School Aged Samples	Preschool Samples
Total Energy	<500; >2500	<250; >1200
% kcal from fat	<25%; >45%	<25%; >45%
Fruit Servings	>3	>2
Vegetable Servings	>3	>2
Grams of Fluid	<300; >2000	<200; >1500

To protect against erroneous blood pressure and pulse measurements, computer entered data can be deleted and reentered as needed. Since the blood pressure and pulse measurement are collected using an automated device, end digit preference (e.g. 0 or 5) should not be an issue. Also, the OMRON blood pressure device does not require calibration. The RCU will calculate the correlations between the 2nd and 3rd blood pressure and pulse measurements within an individual.

All biomedical samples are sent to the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington (Seattle, WA, USA) for analysis. The laboratory participates in the Center for Disease Control and Prevention (CDC) lipids standardization program and is the Central Lab for several NIH sponsored studies. Standard procedures are implemented to ensure high quality data analysis and monitor for long term drift. See section 9.1.3.4. for specific quality assurance details for each lab measure.

9.2.3. Quality Control - Site-Specific Mediators, Moderators and Secondary Outcomes

The site specific mediators, moderators and potential covariates/confounders that are highlighted in our conceptual framework are, for the most part, collected via audio-supported electronic data collection, where respondents have the options to read the questions or have them “read” to them. Audio files for the surveys have been prerecorded and attached to each corresponding question. Participants may use this feature throughout the entire survey, or on specific questions they might not understand or having difficulty reading. Those who prefer to have the questions read to them are given a set of reusable headphones. The headphones are sanitized after each use.

The nature of the electronic-based survey allows researchers to program a variety of additional quality control measures. Each survey question required a participant to provide an answer before moving on to the next question. If the participant feels uncomfortable answering or refuses to answer a question, they are given the choice, “I prefer not to answer”.

Skip patterns are employed throughout the surveys to eliminate the confusion and/or burden of being asked questions not applicable to the participant. In the rare event that internet connectivity is an issue, all survey data will be collected through paper-and-pencil surveys. Designated members of the research staff will be responsible for entering survey data directly into REDCap once internet connectivity becomes a non-issue.

Triggers have also been employed in various sections of the survey to notify study staff in the event that a participant’s depression score, binge eating score, or sleep score require follow-up from a clinician. If a child or parent reaches a clinical threshold for depression, binge eating or sleep, an email will be sent to a member of the research staff indicating that a threshold has been reached by the participant. No names or any identifiable information will ever be included in the email, only that a threshold was reached and follow-up with a clinician is required.

At the end of each data collection day results from the participant surveys will be downloaded to a secure server, quickly reviewed and then imported into REDCap. Before REDCap accepts the import, data quality checks are enacted to ensure that value ranges, variables names, etc match the database formatting and are linked to the correct participant. If the import passes the data quality check, overview of all of the data being submitted is displayed and confirmation is required from the Data Manager. If the data quality check fails, a summary of what went wrong is displayed so that appropriate actions can be taken to address the problem. This process will eliminate possible data transcription error, improving data quality.

In the rare event that internet connectivity is an issue, all survey data will be collected through paper-and-pencil surveys. Designated members of the research staff will be responsible for entering survey data directly into the electronic survey once internet connectivity becomes a non-issue. Survey responses entered by a member of the research staff will be verified by another member of the research staff to decrease the likelihood of transcription error.

Other data not obtained by a survey, such as interviews and lab results, will be directly entered into REDCap. Much like the participant surveys, REDCap is programmed with a variety of data quality checks. All fields require a response and skip patterns prevent unnecessary questions. Data validations are used to ensure data is entered in the correct format, such as dates and times and data ranges are used to flag abnormal data at the time of entry.

REDCap also provides additional data quality protections that will be used throughout the duration of the study. To ensure that REDCap users have access only to data and information that they are supposed to have within the application, user privileges are utilized within the

system. Each user is assigned their own account, and their user account will only have access to REDCap databases assigned by the data manager or that they themselves have created for a different study in which they are involved.

User privileges are also granular on the project level and can be modified within any of the study database by the data manager. The data manager will automatically be given full rights to everything within each database and is responsible for granting other members of the research staff access to the project and assigned each user a set of privileges based on their role in the study. Within each study database, there are user controls to limit access to various functionality and modules, such as being able to export data, to enter data, to add or modify database fields or survey questions, to build or run reports, to modify user privileges, to view the logging records, etc.

The creation of data access groups to help segregate users and the data they enter. Research staff will be placed into data access groups according to their role in the study and will only be able to access records created by someone within the same group.

REDCap also maintains a built-in audit trail that logs all user activity and all pages viewed by every user, including contextual information (e.g. the project or record being accessed). The Logging page allows such users to view or export the entire audit trail for that project, and also to filter the audit trail in various ways based upon the type of activity and/or user. The built-in audit trail in REDCap allows administrators to be able to determine all the activity and all the data viewed or modified by any given user.

9.3. Measurement Schedule

Data collection will occur at four time points: baseline (time 0), 1 year after the intervention begins, 2 years after the intervention begins, and 3 years after the intervention begins.

Visits are planned to be conducted at a Clinical Research Unit (UH Dahms Clinical Research Unit (DCRU) or MetroHealth Medical Center (CRU). An unlikely event may result in data collection occurring over the phone, in the home or community if family is unable to make it to the CRU locations or after the family leaves the visit some data is found to be missing. Meetings have been conducted with staff of both CRUs regarding the overall project. Data will be collected by the research study team, assisted by CRU staff (nurses, dietitian, diet techs). All personnel collecting data will be CREC-certified and, for specific anthropometric measures (height, weight, skin-fold thickness, waist circumference), certified as proficient by the COPTR Coordinating Center (UNC). All data will be collected with parent/guardian and participant in private. Questionnaire and interview-based data will be obtained by private interview and, for some questionnaires, by audio-assisted survey software (Qualtrex). Data will be entered directly into a laptop or iPad[225].

10. PARTICIPANT SAFETY AND ADVERSE EVENTS MONITORING

10.1. Potential Risks and Protection against Risks

10.1.1. Potential Risks

Potential risks include loss of privacy and confidentiality, but we will take great care to maintain privacy and confidentiality. There may be pain/discomfort or bruising and a small chance of infection with venipuncture, but we will offer LMX or EMLA cream and venipuncture is performed by skilled nurses. There is the potential for stigmatization due to weight status; however, measurements are taken in private and all results are reported privately in a sensitive and culturally appropriate manner. If baseline questionnaires indicate symptoms suggestive of depression or suicidal ideation or an eating disorder, the results will be reviewed with Dr. Landis, Ph.D. (co-investigator, licensed clinical psychologist, #5331) who will consult with the youth and/or parent/guardian to determine whether the youth or parent/guardian is in need of a referral for further evaluation and treatment. Potential risks arising during the study could involve development of new co-morbidities associated with obesity itself and/or worsening of elevated blood pressure (EBP). These are discussed under Safety Monitoring Plan below

10.1.2. Protections Against Risk

Children with stage 1 hypertension (found on CMSD or Charter School screening) who would otherwise meet inclusion criteria are potentially eligible to enroll in study if an evaluation shows that the hypertension is essential/primary in origin and is not associated with target organ damage (Left ventricular hypertrophy).Children with secondary hypertension and/or target organ damage require different management including antihypertensive drug therapy. Families of children found to have stage 1 hypertension at school screening will be advised to schedule an appointment with a hypertension physician at UH Rainbow, MHMC, or The Cleveland Clinic Foundation. At these appointments, history, physical examination, urinalysis, echocardiogram, and renal ultrasound will be performed, as recommended in standard medical practice[39]. These evaluations would not be paid through the study as they represent standard of care for children with confirmed hypertension and are regularly covered by commercial insurance. If the child's evaluation suggests essential/primary hypertension, the child will be eligible and proceed with the CRU visit as described. The child would still need to have a renal function panel to fully ensure normal renal function and electrolyte balance; this is unlikely to be abnormal if all other tests are normal and will be drawn as part of baseline visit to avoid an extra blood draw. The consent will specify that for such children indication of renal dysfunction on baseline blood tests will preclude participation (see below).

Results of height, weight, BMI status, BP, and lab tests that screen for comorbidities / cardiovascular risk factors will be reported to families by letter (and families will be called if results exceed thresholds defined.

The consent form will specify that if the screening tests indicate diabetes (FBG $\geq$ 126 mg/dl) or, renal disease [elevated BUN, creatinine]), those children may not be eligible for the full study since other specific medications may be needed; however, with the family's permission, the primary care physician will be notified and referral to a specialist offered. If the tests show other abnormalities, impaired glucose tolerance (fasting glucose >110mg/dl), liver function tests 2 or more times normal, cholesterol >200mg/dl, triglycerides >135mg/dl, LDL-C >130mg/dl, HDL-C <35mg/dl), the family will be informed by letter and they will be referred to their primary care physician so that evaluation can be arranged can be arranged; however, these children remain eligible for the study. If they do not have a primary physician, we will provide a list of potential physicians.

Each study participant will be assigned a unique identifier for tracking purposes, which will be stored in a locked cabinet in locked office. The code which will match study participant to the unique identifier will be stored in a locked file cabinet in a secured room. Access to the code will be restricted to authorized study personnel identified (Study Coordinators, PI's). Participant tracking information will be stored on a password database. Data will be entered and stored in a secure computer database. Original paper forms and all paper copies will be stored in locked cabinets (separate from the locked cabinet in which codes matching study participants to identifiers are kept) in a secured room. Access to the computer and backup copies of the data will be controlled so that unauthorized use of the computer, destruction of data, or breach of confidentiality will be prevented. Staff will be instructed to avoid discussing any study subject with persons who are not part of the research team.

10.2. Potential Benefits

The study may benefit participants by increasing their knowledge of healthy lifestyle, and potentially increasing their fitness and general health, and reducing their weight. If successful, the program may improve family interaction and child self-efficacy. In addition, children found to have a co-morbidity will be referred for medical attention. Eligible families who are interested and want to take part but cannot, as enrollment is completed, will receive informational material and will be informed about community resources to achieve a healthy lifestyle. The potential benefits to participants' families are also increased knowledge about healthy lifestyle.

10.3. Safety Monitoring Plan

10.3.1. Level of risk

We believe that the risks associated with participation in this protocol fall in the low risk classification. The procedures to be performed include history/physical examination, questionnaires, ultrasound, exercise, and venipuncture.

10.3.2. Mechanism of safety monitoring

We have developed a set of action items to prompt follow up action in order to ensure the safety of participants and to optimize their medical care. While the interventions in this study are not invasive, we believe that it is important and ethical to ensure that an abnormal physical finding, lab value or diagnostic test is appropriately followed up. These will be reviewed by the PIs or their authorized designee after each visit.

If the standard questionnaires completed at any of the visits suggest depression, suicidal ideation, or eating disorder, the results will be reviewed with Dr. Landis, Ph.D. (co-investigator, licensed clinical psychologist, #5331)) who will consult with the youth and/or parent/guardian to determine whether the youth or parent/guardian is in need of a referral for further evaluation and treatment. If baseline assessment suggests sleep apnea [164,177], the child will be recommended for a sleep study and, depending on the result, may be suggested to their primary physician to see ENT or Sleep clinic. If baseline tests indicate an abnormality (e.g. liver function tests more than 2 x normal; elevated lipids), the child will be referred to their primary care physician (or, if physician and/or parent prefer, to an appropriate specialist), Response to non-emergent treatment and disease-related events will be coordinated and mediated through the participant's primary care physician. If the participant does not have a primary care physician, every effort will be made to facilitate care within our healthcare systems. If during the course of the study, participants show evidence to suggest a new or worsening complication of obesity (e.g., polyuria/polydipsia), appropriate tests will be performed (e.g. glucose) and treatment instituted if needed. If a child with normal BP at baseline develops elevated BP during the study, the child will have 2 repeat BP assessments within 2 weeks; It these BP measurements confirm stage 1 or 2 hypertension, Dr. Vogt (co-I) will arrange for prompt evaluation with a Pediatric Hypertension specialist. Children with Stage 1 essential/primary hypertension without target organ damage who are participating in the study will be followed regularly by the pediatric hypertension specialist who did their initial evaluation prior to study enrollment. If at any point after baseline, the child develops Stage 2 hypertension, further evaluation and drug therapy will be initiated by the hypertension specialist. Participants started n antihypertensive medications will be able to continue in the study so as to continue to observe their BMIs and other outcomes.

10.3.3. Reporting of Adverse Events.

The reporting of adverse events experienced by study participants meets the important purpose of providing the mechanism for reporting the occurrence and severity of adverse events to the study group and the NIH.

Definition. An adverse event is any untoward medical occurrence experienced by a study subject. An event can be any unfavorable and unintended sign, symptom, laboratory abnormality, or disease associated with study participation.

Classification. Monitoring of adverse events requires that they be classified as to seriousness, expectedness, and potential relationship to the study intervention, which then drives the reporting process. In the COPTR studies, adverse events should be rare, and monitoring should be commensurate with risk, which is minimal. Adverse events will be recorded for the duration of participation in the study.

A serious adverse event (SAE) is one that: (a) Results in death, (b) Is life-threatening, (c) Requires inpatient hospitalization or prolongation of existing hospitalization, (d) Results in persistent or significant disability/incapacity, or (e) Is a congenital anomaly/birth defect in the offspring of a participating parent/adult or teen.

An event definitely, probably, or possibly related to the study procedure is one that follows a reasonable temporal sequence from the time of study participation, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Data collection procedures for adverse events. Events are recorded by the field center staff, including the date and time (if relevant) of occurrence, description, severity, frequency/duration, outcome/resolution, potential relationship to study participation, and action taken with respect to study participation, as specified in the data elements forms. For those participants in the intervention groups, they will be asked at every visit if they have been hospitalized since the last session.

Reporting procedures for Serious Adverse Events (SAEs). If classified as serious, unexpected, and possibly, probably or definitely related to study participation, reports will be forwarded electronically to the RCU within 4 working days of learning of the event. The RCU will report any such events to the NHLBI and the DSMB Chair as soon as possible, but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15 calendar days.

Reporting procedures for events not classified as serious. If not classified as serious, unexpected, and possibly, probably or definitely related to study participation, reports will be reported annually or twice-annually to the RCU according to the meeting schedule of the DSMB. The RCU will report these events to NIH and the DSMB.

Adverse Events (AEs) aka non-serious adverse events (Non-SAEs). If classified as unexpected, and possibly, probably or definitely related to study participation, will be reported annually or twice-annually to the RCU according to the meeting schedule of the DSMB. The RCU will report these events to NIH and the DSMB.

The site investigators or designees will report all adverse events to the local IRB according to local IRB policies.

Serious Adverse Events and Adverse Events data elements forms. SAEs and AEs will be collected systematically at all regularly scheduled data collection visits. SAEs and AEs will be queried at the end of the data collection visit (preferably) but at least after measurement of height and weight, to prevent unnecessary unmasking of data collectors at that visit.

The accompanying forms will be used for querying and recording SAEs and AEs. Some sites may collect this information using paper-and-pencil methods and others may use direct computer data entry. All will be via interview (not self-administered). For each participant, SAEs will be queried first, followed by queries for AEs.

The same forms (data elements) will be used for adult and child SAEs and very similar data elements will be used for collection of AEs.

SAEs and AEs reported between scheduled data collection visits will be designated as such (see item on form) and use the same format. However, these will be reported separately from those collected at regularly scheduled data collection visits, to minimize the potentially misleading results from having differing opportunities for reports in different intervention groups (e.g., more contact with treatment group participants, and thus more opportunities to learn of adverse events).

As noted on the forms, Principal Investigators or their designee(s), and not data collectors, shall make determinations regarding expectedness and relatedness of SAEs and AEs to study participation, at the time they are identified and reported. These will be reported to the DSMB and the DSMB may also make their own determinations at the time of their review.

10.4. Informed Consent Documents

10.4.1. Description of the informed consent process

Families who are interested in participating and appear eligible based on pre-screening will be scheduled for a baseline visit in the CRU at which time the study will be re-explained and the consent and assent forms for participation signed. Members of the study team who are certified in Human Subject Protection will obtain informed consent for the study. The research protocol, risks and potential benefits will be discussed with the parent/guardian and youth privately. They will have time to consider participation in the research study and to have their questions fully answered. The consent and assent forms (attached) will indicate that randomization and participation is entirely voluntary and that the family can withdraw at any time.

10.4.2. Informed Consent Documents

See APPENDIX F for Informed Consent documents

11. STUDY DESIGN, STATISTICAL CONSIDERATION AND ANALYSIS PLAN

11.1 Study Design

IMPACT is an individually randomized group trial with three study groups (SystemCHANGE [SC], HealthyCHANGE [HC], and active education-only control.) Subjects (n = 360 patients and their families) will be randomized equally to these three study groups with half of the patients entering in Project Year 3 and the remaining half in Project Year 4. Outcome measures will be assessed at baseline, and then at approximately 12, 24 and 36 months after randomization.

11.2 Primary Research Question and Hypothesis

Our primary analysis assesses the value of our interventions (SystemCHANGE [SC] and HealthyCHANGE [HC]) as compared to education-only control (Tools4CHANGE) in terms of reducing the BMI of overweight/obese urban youth, across a three-year study window. Our hypothesis is that both SC and HC will have greater impact than education alone on BMI.

11.3 Primary Outcome

Our primary outcome is a derived outcome - specifically the changes (slopes) in BMI alone over the three-year window, with outcomes multiply imputed for patients without BMI values post-baseline to permit a true "intent to treat" comparison. Our primary analysis compares HC to Control and SC to Control, collapsed across levels of the school-community enrichment exposure.

11.4 Primary Analysis

11.4.1. Statistical Model and Approach

The primary analysis will be an intent-to-treat comparison across all 360 subjects providing baseline BMI and randomized to a study arm (120 subjects in each of SC, HC and control.) BMI values will be measured at baseline, 12, 24 and 36 months, and our primary outcome is a derived value - specifically the annualized slope in BMI across the study period.

Our primary analysis addresses the impact of both SC and HC as compared to Control patients in terms of mean BMI reduction. The statistical model for our primary outcome (BMI slope for subject j) follows.

$$\text{BMI Slope}_j = \beta_0 + \beta_1 \text{BMI at Baseline}_j + \beta_2[\text{Intervention} = \text{SC}]_j + \beta_3[\text{Intervention} = \text{HC}]_j$$

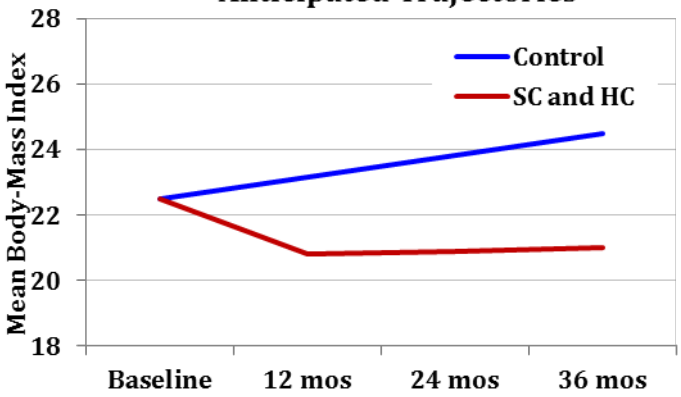
across subjects *j* = 1, 2, ..., 360. Using this model, we test $H_0: \beta_2 = \beta_3 = 0$ using an appropriate F test with two degrees of freedom for our primary analysis. Note that we will account for (what we anticipate to be modest) clustering within intervention small groups (*n* ≤ 12 students per small group) and within schools (*n* = 7.2 students per school on average) through modeling the small groups and schools as levels of nested random effects in our primary analysis.

All other planned comparisons, including comparisons of the SC and HC groups to each other (see Section 11.8), comparisons of the enriched vs. non-enriched school-community environments (see Section 11.6), and the interaction of our interventions with enrichment are not primary, and are thus described later in Section 11.

11.4.2. Assumptions with Justification

Anticipated Effects. We anticipate a non-linear effect of our interventions over time, as shown at right. However, our primary analysis focuses on changes over time, expressed in the form of linear regression slopes, because our ability to estimate non-linear relationships with baseline and three follow-up assessments is weak. Our primary analysis will therefore be somewhat conservative in assuming a linear change over the three year period. Note that as part of our secondary analyses, we will consider the impact of this decision – fitting models that look at comparisons limited to particular spans of time, in particular, fitting slopes that use only the data from baseline and 12, then 24, then 36 months.

Figure 11.1. CWRU COPTR Anticipated Trajectories



Control Group. We anticipate an approximately linear relationship with a positive (increasing) slope between BMI and time for our control group. The strength of the evidence to support an increasing relationship in overweight and obese subjects as they move from age 11 to age 14 is quite strong across both sexes, in fact well-established.

The strength of the evidence to support an assumption of no substantial non-linear relationship is moderate – clearly the patterns observed in somewhat related previous cohorts (for instance, the control patients in Savoye et al[226] and in Savoye, et al[227] have not been described as substantially non-linear, and analyses have been conducted for these studies assuming linearity.

We expect the slope in our control group to be approximately +0.8 kg/m^2 per year, based in part on the results observed in Savoye [227] (24 month control group change from baseline of 1.9 kg/m^2), and on a careful examination of slopes in CDC percentiles, which show a similar result. Examining the confidence intervals at various time points (6, 12 and 24 months) provided in Savoye 2011 suggests a standard deviation of approximately 0.4 kg/m^2 based on the 12 month data. Boys in our sample will have a BMI of at least 20.2 at study entry, while girls will have a BMI of at least 20.8 (85th percentile or higher.) From CDC age-percentile data (modified 10/16/2000) we would expect the following distribution at 11 years old:

Table 11.1. Expected Distribution of 85th percentile or higher among baseline boys and girls

11 year old	85th	90th	95th	97th
Boys	20.2	21.2	23.2	24.8
Girls	20.8	22.0	24.2	25.8

This implies that our baseline sample (assuming equal numbers of boys and girls) would likely have a mean between 22 and 23, with a standard deviation near 2. At 3 years, we thus anticipate a mean BMI in our control group near 25 (on the basis of our anticipated increase in BMI over three years) with a somewhat larger standard deviation – perhaps between 2.5 and 3 kg/m^2. A review of our pilot data within the COPTR project suggests nothing to invalidate our assumptions here, although after 4 months and a small pilot sample, it is difficult to evaluate the magnitude of change, we continue to believe that the control group will, on average, show increases in BMI close to that which we have assumed.

Treatment Effects. We expect a non-linear shape to the association of BMI with time in our treatment groups, with a larger effect at the start of the study (especially in year 1) and some reduction in the size of this effect (as compared to baseline) in years 2 and 3. We anticipate a decline in BMI of about 1.8 kg/m^2 in our HC and SC intervention groups in year 1. In years 2 and 3, we anticipate a leveling off to a more modest decline or perhaps a slight rise (we assume a flat linear relationship in the second two years in what follows.) The evidence to support an expectation of a non-linear effect, leveling off after year 1, is modest. The Savoye et al study[227], for instance, saw a substantial reduction in the size of the observed effect after the most intensive part of the treatment was completed. We have seen similar results in our studies among adults.

We anticipate a decline in BMI of about 1.8 kg/m^2 in our HC and SC intervention groups in year 1. In years 2 and 3, we anticipate a leveling off – while we would be happy to simply hold the gains in BMI in this period, we expect a small rise, with a smaller slope than will be observed over this time in the control periods. We expect the lowest BMIs to be observed at the end of year 1 – roughly age 12. We anticipate a mean BMI near 21 for our HC and SC patients at the three year time point, with a larger standard deviation than in our control group – perhaps 4 kg/m^2.

While we expect the largest effect to occur in the first year, the trend towards rising BMIs in the control group suggests that the largest difference in raw BMI (not change in BMI) between groups will be at 36 months. Again, a review of our pilot COPTR data suggests nothing to invalidate our assumptions, although given the small pilot size, we did not focus on the magnitude of loss in the experimental group after just 4 months.

11.4.2. Missing Data

For our primary analysis, we assume missingness at random for the purposes of multiply imputing annualized slope values for those patients who do not have a BMI value recorded after baseline, incorporating the nested groups (small delivery groups for the intervention as well as the student's school) as random effects in our imputation model. We intend to complete imputations for primary analysis by directly imputing the derived outcomes (the slopes) and, then, in secondary analyses (see Section 11.8), imputing the individual values at missing time points, then deriving the slopes. We anticipate that this distinction will have little impact in this case.

11.5. Detectable Difference, Sample Size and Power

Our primary analysis involves a two-tailed ($\alpha = 0.05$) comparison of SC vs Control and HC vs Control using an F test with two degrees of freedom and the linear model in Section 11.4.1.

In our sample size calculations, we anticipate a modest design effect of 1.25. This modest design effect is reasonable, given the small number of subjects (≤12) in each of the interventional study groups, the small number of subjects (average = 7.2) within each baseline school-community environment and because we anticipate only mild clustering effects on BMI slope within these groupings.

We based our initial assessment of a minimum clinically meaningful effect size on our review of the literature, and our prior work. Our expectations for average BMI results across participants within each study group are summarized in the table below, which matches the trajectories shown in Figure 11.1.

Table 11.2. Expectations for Average BMI Results

Group	Baseline	12M	24M	36M	Annualized BMI Slope
Control	22.5	23.17	23.83	24.5	0.67
HC	22.5	20.8	20.9	21.0	-0.44
SC	22.5	20.8	20.9	21.0	-0.44

Such an effect would naturally be quite large if observed across the trial, and so instead we selected our sample size to provide sufficient power to detect a smaller effect. Specifically, we identify a mild-to-moderate effect size for our two degree of freedom comparison,

corresponding to a Cohen's f^2 value of 0.065, in comparing either HC (or SC) to education-only controls in terms of our primary outcome (BMI slope.) A Cohen's f^2 value of 0.065 corresponds to the effect size observed in a linear model for BMI slope using group assignment as predictor that accounts for just over 7% ($R^2 = 0.061$) of the variation in BMI slopes, after accounting for baseline BMI. Note that Cohen's f^2 is $R^2/(1-R^2)$, and that Cohen identified medium effect sizes at 0.15 and small effect sizes at 0.02, so our effect of 0.065 is appropriately described as mild-to-moderate.

As noted, we then conservatively assume 20% attrition across our 360 subjects across the 36 month study window, where such attrition pertains to subjects who will be completely lost to follow-up (in terms of outcome measurement) after baseline, i.e. those patients whose BMI slope will need to be imputed using only baseline BMI information. Our intent to treat analysis will use imputation of the BMI slopes across all 360 subjects. To account for this attrition in our power calculation, we further dilute our anticipated effect size (again conservatively) by a full 20%, from $f^2 = 0.065$ down to $f^2 = 0.052$, which corresponds to a linear model with incremental $R^2 = 0.05$ attributable to group assignment, although we expect the actual impact of imputation to be substantially smaller than this.

Our sample includes 360 subjects, with 120 enrolled in each of our three intervention arms. We next describe the effective sample size after accounting for these rather conservative estimates of attrition and clustering. All enrolled patients (120 per arm) will have outcome information (imputed or not) past baseline. Applying a design effect of 1.25 yields an effective sample size which may be as small as 96 patients per intervention arm. So, assuming an effective sample size of 96 patients per intervention arm, we describe two illustrative calculations related to power concerns.

First, we performed calculations based on a linear model and ANOVA-style F test (with 2 and 285 degrees of freedom - based on our effective sample size of 96 subjects per study group) and a two-tailed $\alpha = 0.05$ significance level to compare HC to control and SC to control, assuming a modest effect size diluted 20% by imputation so that our Cohen's $f^2 = 0.052$.

Using the pwr library in the R statistical software language, we conclude that an effective sample size of 288 subjects - 96 per arm - yields just over **94**% power to detect an effect of size Cohen $f^2 = 0.052$, which corresponds to an incremental R^2 of approximately 5% for the joint effect of our interventions as compared to control on BMI slope, after adjusting for baseline BMI, accounting for 20% loss of information due to missingness, as accounted for by imputation.

With 90% power, an F test based on our effective sample size could detect an effect as small as that represented by a Cohen f^2 of 0.044, corresponding to an incremental R^2 for the intervention of 4.2%. With 80% power, this test could account for Cohen f^2 as small as 0.034, which corresponds to an incremental R^2 of 3.3%, and so this is consistent with our ability to detect mild-to-moderate effect sizes with our sample size.

In a perhaps more familiar and simpler "worst case" calculation, an independent-samples t test restricted to our smallest effective sample size of 96 patients in any two of the intervention arms (say, HC and control) has **93**% power to detect a difference (α = 0.05, two-tailed) in mean slope corresponding to an effect size of Cohen's d = 0.50. Again, we believe this result, though acceptable, clearly understates our true power, since it assumes our worst case scenario regarding clustering will occur, and that the incorporation of BMI at baseline data as a covariate will not aid in our assessment of the intervention.

11.6. Analysis for Possible Effect Modifiers

11.6.1. Studying Enrichment Exposure

In studying school-community enrichment's effect on BMI and its impact (via interaction effects) on our conclusions with regard to our interventions, we plan additional analyses which are only briefly sketched here. The main complicating factor is potential confounding, due to the fact that while children within each school will be randomized to each intervention, the environments themselves are assigned (without randomization) at the school level. This makes the exposure assessment part of an observational study.

As a means of accounting for this potential exposure selection, we will use propensity scores to design the observational study. Specifically, we will follow the approach of Rubin[228] and Rosenbaum[229,230] by estimating a propensity score for enrichment across all patients, using available covariates. Next, we will compare the distributions of propensity scores across the two enrichment exposures, within and across intervention arms, without using outcome information. Should substantial selection bias be present, unadjusted regression models for our outcomes would be inappropriate, and we will apply propensity score weighting and/or matching to adjust comparisons until we obtain exposure groups that are appropriate for fair comparisons via regression analysis. Weighting approaches are likely to be more useful in this setting given the relatively modest sample sizes (180 patients in each enrichment group.)

Once we have either verified that the enriched and unenriched groups are comparable in terms of baseline covariates or made them comparable via propensity weighting or matching, will we then fit linear models to account for both intervention (operationalized as SC/HC vs. Education to improve power) and exposure (Enriched/Not) effects and their interaction on our derived primary outcome, followed by our secondary outcomes. In these analyses, we will again account for missing data via multiple imputation, and clustering via modeling the small groups and schools as levels of nested random effects, and, in case exposure selection pressures not accounted for by our propensity scores remain a concern, we will complete formal sensitivity analyses (Rosenbaum [229,230)] to assess the necessary amount of hidden bias required to invalidate our conclusions.

11.7. Analysis for Possible Effect Mediators

AS shown in our conceptual model of the study (Figure 7.1) and in our table of moderators and mediators (Table 9.8.), we have conceptualized and will be obtaining measures of several possible mediating variables. Our analysis of effect mediators is currently under development. This work will continue as we move toward the completion of the main study under the guidance of the COPTR Mediation and Moderation Team, at which point these analyses will be further refined.

11.8. Secondary Hypotheses and Analyses

If significant, the primary comparison described in Section 11.4.1 will be followed (in secondary analyses) by one degree-of-freedom pre-planned comparisons of HC to Control and SC to Control, adjusting for multiple comparisons. In further analyses, analogous models will be fit to: [1] compare HC to SC directly, [2] incorporate additional covariates into our comparisons for purposes of adjustment and [3] describe the impact of our interventions on the slope of blood pressure and other outcomes. These models form our analytic framework for questions related to the comparative effectiveness of our interventions, collapsed across enrichment exposure.

The simple intervention model described in Section 11.4.1 does not permit the effect of the interventions to vary substantially based on baseline levels of BMI. This assumption seems unlikely, and so we will expand our analytic structure using the following model:

$$\begin{aligned}\text{BMI Slope}_j = {} & \beta_0 + \beta_1 \text{BMI at Baseline}_j + \beta_2[\text{Intervention} = \text{SC}]_j + \beta_3[\text{Intervention} = \text{HC}]_j \\ & + \beta_{12}\text{BMI at Baseline}_j[\text{Interv.} = \text{SC}]_j + \beta_{13}\text{BMI at Baseline}_j[\text{Interv.} = \text{HC}]_j\end{aligned}$$

across subjects *j* = 1, 2, ..., 360, and where the interaction terms permit differential effects on BMI slope for each intervention, depending on baseline BMI. We will include baseline BMI elements as described above in all primary analyses, and investigate the impact of this decision (and also consider the inclusion of other covariates) in secondary analyses to assess the stability and sensitivity of our conclusions.

While we anticipate a non-linear effect of our interventions over time, as shown in Section 11.4.2, our primary analysis focuses on changes over time, expressed in the form of linear regression slopes, because our ability to estimate non-linear relationships with baseline and three follow-up assessments is weak. In secondary analyses, we will consider the impact of this decision – fitting models that look at comparisons limited to particular spans of time, in particular, after 12 months, then at 24 and finally at 36 months without inclusion of intermediate values.

In keeping with the broader plans across COPTR sites, we will need to thoroughly investigate the properties of all fitted models. As at other sites, this will involve the usual diagnostic

approaches looking at predicted values, residual plots, and so forth. We will also adopt the simulation approach to model-checking recommended by Gelman and Hill[231] where we use the fitted model to simulate new outcomes and then compare these results to what we have observed.

Secondary outcomes of special interest include changes in blood pressure (for which analogous approaches to those taken for BMI change will apply), and a major secondary analysis will assess the potential additive impact on BMI and BP changes achieved by exposure to an enriched school-based intervention (We Run This City) which will be observed in approximately 40% of study participants (see Section 11.6).

Robustness, Sensitivity and Stability of Conclusions. As noted above, we plan multiple secondary analyses to check for the robustness of our conclusions in light of differing analytic decisions. These include a set of potential *imputation* assumptions (imputing our derived outcome directly vs. imputing individual BMI values before deriving the outcome, as well as assessing whether the data can be properly assumed to be MCAR or [more likely] MAR) and assessing whether interaction of other covariates with baseline BMI should be incorporated into our imputation models, assumptions about *linearity* of our key outcomes (the use of BMI slopes as our principal outcomes, rather than time-specific BMI values, adjusted for earlier values, and the potential inclusion of regression splines a la Harrell[232], the inclusion or exclusion of *covariates* in our models, including baseline BMI and interaction terms, and the use of multiple propensity score *weighting and matching* approaches in our observational study of enrichment exposure.

11.9. Additional Analysis

We plan a cost-effectiveness analysis of these interventions, but the details of that work are still evolving, as we work with our project economist and the larger COPTR project. We have planned for an economic analysis from the beginning of our project, however, and in consultation with our economist, have identified important variables on which we are collecting data in order to conduct the economic analysis, such as interventionist preparation and contact time with subjects and health services utilization by subjects.

12. DATA MANAGEMENT & QUALITY CONTROL

12.1. Common Database (Data Capture and Data Audits)*

The COPTR Data Center was designed after extensive discussions with representatives from all of the sites to provide a secure, easy, and effective set of tools for submitting Common Measures to a central repository for the consortium. Each of the four Field Sites has a site-specific data system for conducting the daily tracking and data collection.. The COPTR Data Center does not dictate how those disparate site systems are designed or used. Instead, the

Data Center provides a set of web-based tools for sites to upload completed Common Measures to the central repository at the RCU.

Field Sites collect a subset of the Common Measures following the protocols and manual of procedures (MOPs) for those common measures. The common measure subsets for each Field Site differ slightly but the MOPs and protocols defining the measurement/collection procedures are identical. The recruitment data elements identified for submission to the RCU are identical at each Field Site. Each Field Site submits the current collection of common measures quarterly and the recruitment and retention data monthly to the RCU to be included in the central data store of the Consortium. Variables collected at only one Field Site are not transferred to the RCU.

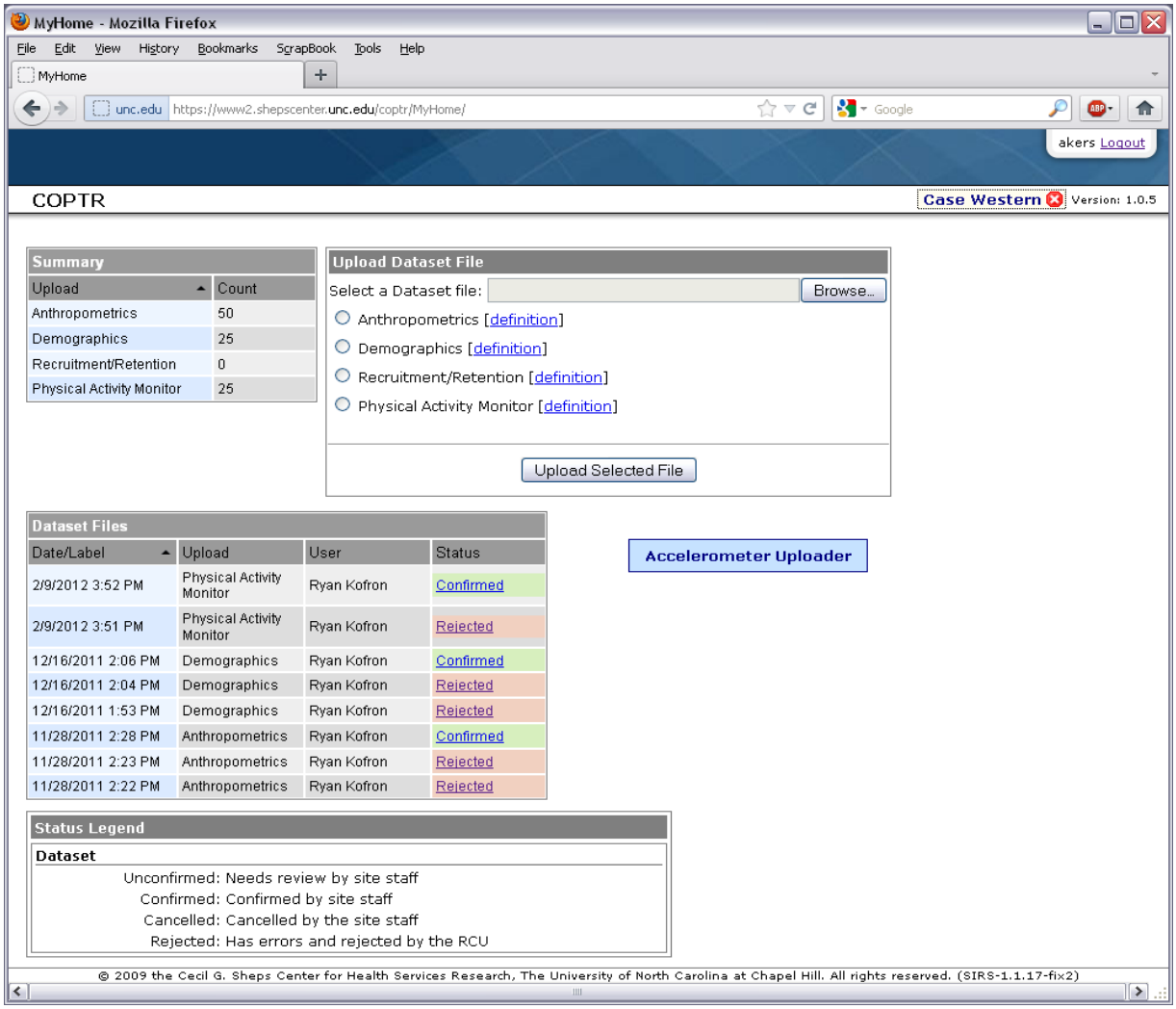
One or more representatives from each Field Site have been designated as members of the Data Capture Working Group. These representatives contributed to the design of the Data Center tools and continue to contribute to improved functionality of the Data Center site. These representatives also serve as the primary contacts at a Field Site when the RCU notices irregularities with the submitted data.

The RCU data transfer system utilizes a restricted access website to provide encrypted transfer of data files containing common measures (measurements collected at more than one Field Site) to a central data repository at the RCU. Each Field Site will have one or more project staff authorized to have access to the Data Center website. An individual at a site must receive authorization from the site's PI prior to getting an assigned Data Center userid and password. Field Site staff login to the Data Center via the following URL: http://www.shepscenter.unc.edu/coptr

After successful authentication, the user will land on the "MyHome" page of the affiliated Field Site. Access is restricted according to Field Site affiliation and defined roles. An authorized staff for a Field Site only has permission to work within that site's defined workspace. Some RCU staff are authorized to work across all Field Sites' workspace. Figure 12.1 is a screenshot of the Case Western MyHome space.

On this MyHome page, a Field Site user (e.g. Case Western user) will see two sections that give real-time information on successful uploads and attempts. The top left box provides a Summary of the data records by type that have been uploaded to the Data Center and Confirmed by any of the site's authorized users. The Dataset Files box just below the Summary box provides more detailed information on each upload attempt. Authorized site users always have access to these status displays. Furthermore, authorized RCU users can see the status displays of all four Field Sites, providing an opportunity for RCU staff to monitor upload processes and provide assistance when errors are displayed. In addition to the MyHome displays, the Data Center system has extensive error logging available to RCU staff to troubleshoot any problems encountered. Last, to the right of the Summary box are the tools for uploading data sets.

Figure 12.1 Screenshot of the MyHome space



12.1.1. Uploading Data to the RCU

The COPTR Capture Working Group decided to use file upload facilities versus web data entry forms for submitting site data to the Data Center. To upload a data set, the user will Browse his/her local file space for the desired CSV file, select the corresponding type by clicking on the appropriate radio button (e.g. Anthropometrics, Demographics, etc.), then click “Upload Selected File”. The upload process evaluates the incoming data file, looking for the required unique identifiers, the correct site ID, and comparing the field names, data types, and data values according to the predefined “definition”. (The “definition” files are available to read via the “definition” links.) If any required data check fails, the RCU rejects the incoming file and reports the reasons to the user. The user can then correct those issues and upload the file again. If all required data checks pass, the incoming file is held with “Unconfirmed” status and the user is presented a report on the number of new records and number of modified records found in this incoming file. This report provides the user an opportunity to confirm that those

numbers are as s/he expects. If the numbers are as expected, the user can “Confirm” the upload and the process is complete. Otherwise, the user can “Cancel” the upload then investigate the issues offline and attempt the upload again at another time.

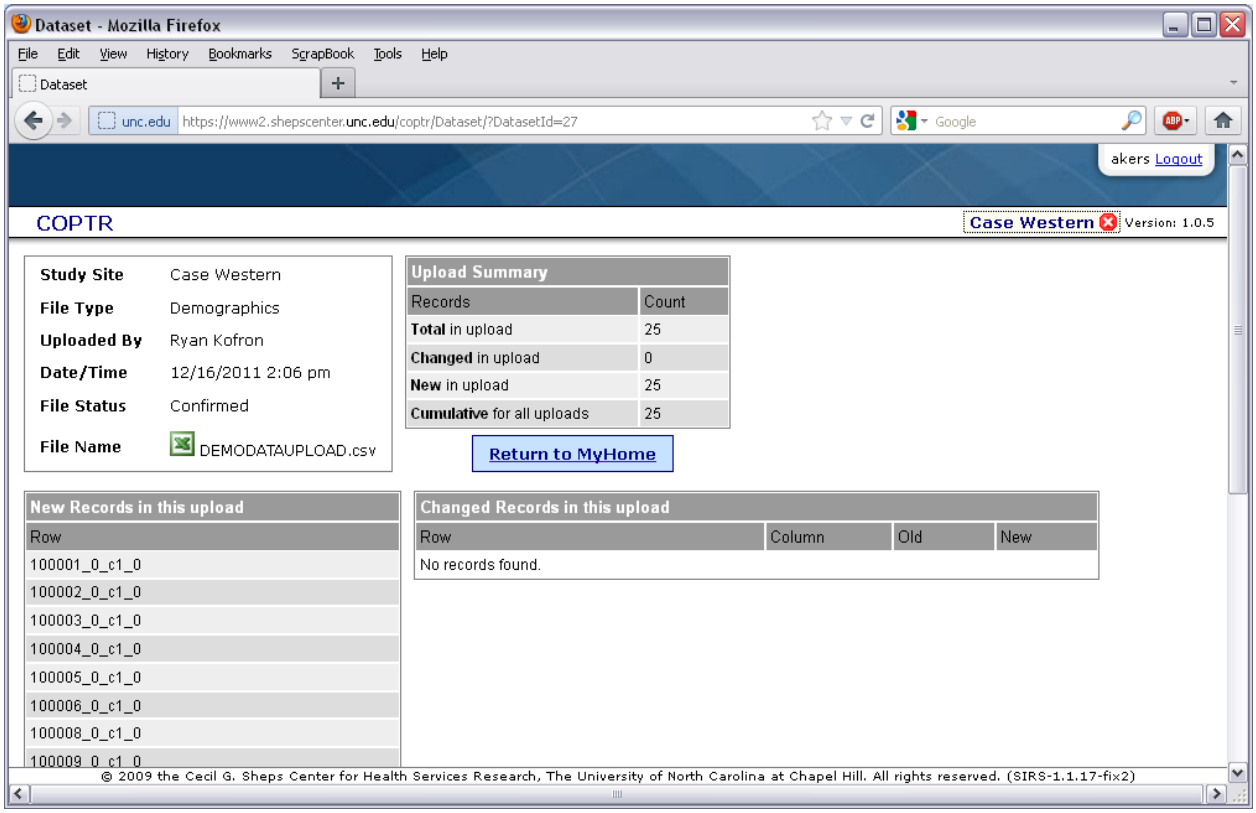
The next section on the screenshot in Figure 12.1 shows a running log of the dataset upload activities for the site. The log shows the date and time of each upload attempt, the type of upload, the user performing the upload, and the status of that upload attempt. Clicking on a “Confirmed” link in the Status column loads more detailed information about the confirmed upload. Figure 12.2 shows the details of a confirmed Demographics upload from Case Western. The more detailed information includes the local File Name of the uploaded file, the Upload Summary, and the unique identifiers of the New Records that were included in that file. In addition, if there were records uploaded that were intended to update or correct data that had previously been uploaded to the RCU Data Center, details of those changes would be listed in the right hand table labeled “Changed Records in this upload”. Changes to data fields in existing records are made by matching the unique record key of an existing record with that of an incoming record then accepting the new incoming record as the most up-to-date. (The older record is kept for reference. It is not overwritten.)

The Data Center is designed with three objectives in mind:

1. Promote the submission of the highest quality data to the RCU for future use of the Common Measures;
2. Provide an upload facility that is efficient and easy to use from the individual site’s perspective;
3. Give the users enough information and flexibility to track progress and correct problems with Common Measures submissions.

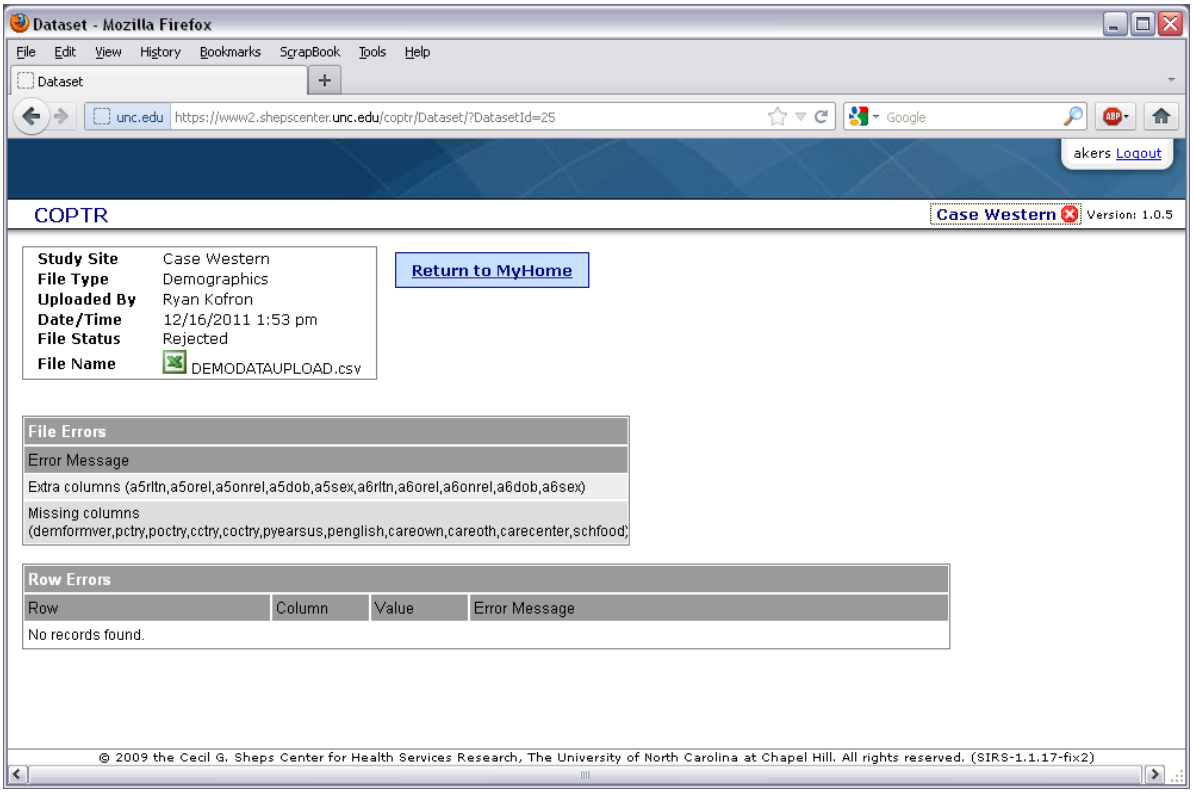
To that end, all data uploads with the exception of the accelerometer GT3X or AGD uploads, follow the same general model: organize your data to fit the approved definition, upload a CSV file via the website, confirm the upload or correct the errors and try again. Figures 1-3 illustrate the information provided and assistance with identifying and correcting problems prior to the RCU accepting data.

Figure 12.2 Screenshot of a confirmed demographics upload



Clicking on a “Rejected” link in the Status column will load more detailed information about a file with data that did not match the required criteria for acceptance in the Data Center. Figure 12.3 below shows the details of a rejected Demographics upload. Again, the local File Name is displayed along with Date/Time and Uploaded By user. The File Errors box in this example indicates that an upload was attempted that contained extra fields that the RCU was not expecting (first message). Also, the second message indicates there are fields or columns missing in the upload that are required as Demographics Common Measures. If there had been any data type mismatches or data values out of range, error messages would be presented in the “Row Errors” box.

Figure 12.3 Screenshot of a rejected demographics upload



12.1.2. Authoritative ID File – Study Arm

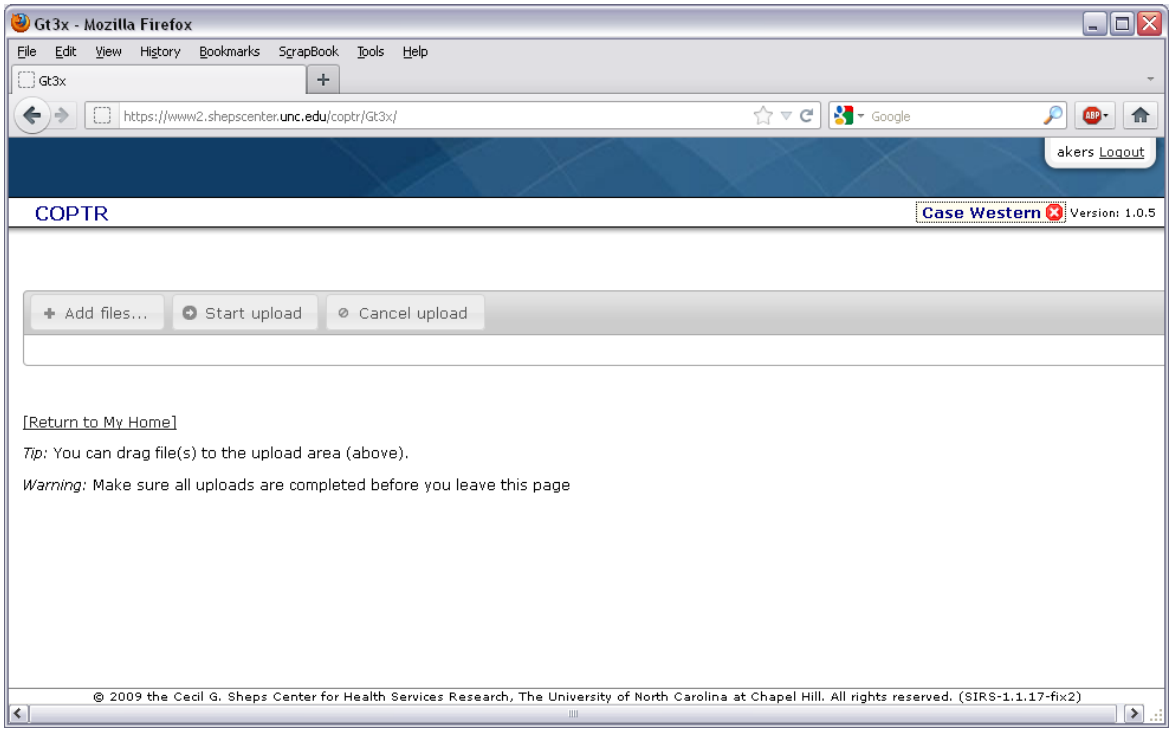
The RCU Data Center requires one of the data uploads to be the authoritative source for Index Child IDs. Having an authoritative “master” list of Index Child IDs allows the RCU to prevent orphan records from being introduced in any of the other data uploads. The consortium has designated the Study Arm upload to be this source. As such, a Study Arm record for an Index Child must be uploaded to the RCU before any other Common Measure records are accepted into the Data Center. The Index Child IDs in other data uploads (e.g. Anthropometric, Demographic, etc.) are verified against the RCU’s Study Arm records prior to accepting the data records. Data records that do not have a matching Index Child ID in the RCU’s Study Arm data are rejected to prevent orphan records from being introduced into the Data Center.

12.1.3. Accelerometer Data

Accelerometer data on an individual consists of two distinct parts: a Physical Activity Monitor (PAM) record, and recorded data from the ActiGraph device (GT3X or AGD format). The RCU requires sites to upload the PAM record of the pair prior to uploading the matching GT3X or AGD file. The steps for uploading PAM records follows the same steps described above for other data uploads. However, the steps for uploading GT3X or AGD files are different because

of the difficulties introduced in handling these large files. (We are anticipating the average size of these files to be around 200MB.) After successfully uploading and confirming PAM records, the user clicks the “Accelerometer Uploader” button shown in Figure 12.1. The user is then presented with a screen similar to Figure 12.4 below. The user can then queue up one or more GT3X/AGD files for upload either by clicking “Add files…” or by dragging files from local file space into the upload area. Clicking “Start upload” will begin uploading the queued files in the order they are shown. Each GT3X/AGD file is verified against the uploaded PAM records to ensure a PAM record exists for a GT3X/AGD file before allowing the upload to proceed. This verification allows the RCU to accurately link a PAM record to an incoming GT3X/AGD file. The user must make sure all queued uploads are completed before leaving this web page.

Figure 12.4 Screenshot of the accelerometry file upload screen



Uploaded GT3X and AGD files are not automatically analyzed at the RCU. The files are simply stored in a file system for later use. Each site is responsible for analyzing GT3X and AGD files for completeness prior to uploading to the RCU Data Center.

12.2. Site-Specific Database (Data Capture and Data Audits)

12.2.1. Surveys/Self-Report Data

Surveys will be administered to each participant during scheduled assessment days. Most surveys will be administered to participants electronically on iPads using a web-based survey application known as Qualtrics and some will be administered in person; if a participant says s/he is uncomfortable with the computer based system, in-person interviewing will be performed. Qualtrics has SAS 70 Certification and meets the rigorous privacy standards imposed on health care records by the Health Insurance Portability and Accountability Act (HIPAA). All Qualtrics accounts are hidden behind passwords and all data is protected with real-time data replication. All data collected electronically through Qualtrics will be stored on Qualtrics' server. No survey data will ever be stored directly on the iPad. No identifiable information will ever be stored on in the survey or on Qualtrics' server. Data will be linked to each participant by a unique ID number. Data will be transferred from Qualtrics to the REDCap database on a regular basis. After data has been successfully transferred from Qualtrics to the REDCap database, it will be removed from Qualtrics' server.

In the rare event that internet connectivity is an issue, all survey data will be collected through paper-and-pencil surveys. Designated members of the research staff will be responsible for entering survey data directly into REDCap once internet connectivity becomes a non-issue. Paper-and-pencil surveys will be stored in a secure location—a locked filing cabinet—at the clinical research unit where it was collected. Only key research staff will have access to this filing cabinet.

12.2.2. Anthropometric Data

Anthropometric data collected by research staff will be directly entered into REDCap through iPads during each visit. No data will ever be stored directly on the iPad. No identifiable information will ever be stored on this database. Data will be linked to each participant by a unique ID. A Manual of Operations will detail all procedures related to the protocol. It will include detail on participant recruitment, data collection, database usage, and data management. Study personnel roles and responsibilities, as well as access rights to the data will also be specified. All results will be reported in aggregate only and at no time will individuals or identifiable groups be described. Data quality will be monitored by random inspection of the completed forms by the data manager and any problems detected will be discussed with the PIs. Data entry and/or data collection personnel will receive standardized training; if the inspections indicate errors or drift, re-training will occur.

12.2.3. Study Databases

Data collected for this study will be stored on three independent REDCap databases. REDCap is a secure, web-based application for building and managing online surveys and databases,

supported by the university's Clinical and Translational Science Collaborative. All three databases will be hosted on the CWRU REDCap server, which is imperative for the PIs and their designated staff (CWRU, UH and Metro employees) to have access to the databases. Throughout the duration of the study, members of the research team will require quick, immediate access to the database, from different locations. This can only be accommodated by the CWRU's REDCap system because it allows the database administrator to assign usernames to any individual, regardless of their place of employment. Moreover, the system permits different access levels for each research staff member, dependent upon the access needs. Some members of the research staff will be granted permission to access, enter or change data into each database. Others may be given read-only access. Select individuals will have the permission to download/export data from REDCap. These individuals will be determined by the PIs of the study.

Recruitment Database: Prior to recruitment into the pilot study, the Cleveland Metropolitan School District and Charter Schools will provide the PIs will the contact information of all eligible students for the study (rising 6th graders who were screened and parents did not opt out of contact). This population will form the basis of the recruitment database. This database will store contact information (e.g., address, phone) and the process and outcomes of the recruitment process (e.g., dates contacts, result of call, whether additional information was sent, whether they came to a parent information meeting, date of initial assessment). No other data will ever be stored in this database. The database will only be used to record information related to the recruitment of participants, which will be used to report to NHLBI and the DSMB. Upon enrollment in the study, contact information for study participants will be transferred to the second database, the personal information database. Upon completion of all required reporting to NHLBI and the DSMB, the recruitment database will be destroyed.

Personal Information Database: The Personal Information Database will be used to store all identifiable information recorded on each enrolled study participant. This database will be used to store all identifiable information, including phone numbers, addresses, birthdates and tracking and scheduling information regarding assessment and group intervention dates. Intervention fidelity data (e.g., sessions attended) will also be stored in this database. A unique participant ID will be assigned to each participant and stored in this database. This is the only place where a participant's name will ever be linked to study ID. No other study data will be stored in this database. Only key members of the research staff who will require access to this database will be granted access. Most members of the research staff with access to this database will only have permission to add information. Select individuals, as determined by PIs of the research study, will be granted permission to download/export data from REDCap to a secure, password protected computer. All downloaded datasets will require password protection and will not be allowed to leave the designated computer.

Process, Tracking and Fidelity Database: All data related to contacting participants, attendance, and data collected during interventions will be directly entered into a REDCap database stored on Case Western Reserve University's server (see Data Processing). It is

imperative that CWRU's REDCap be used to store the data since the research team is comprised of both UH and CWRU staff who will require convenient and immediate access. No Identifiable information will ever be stored on this database. Each participant will be assigned a unique ID. This unique ID will be used to link the participant with the data.

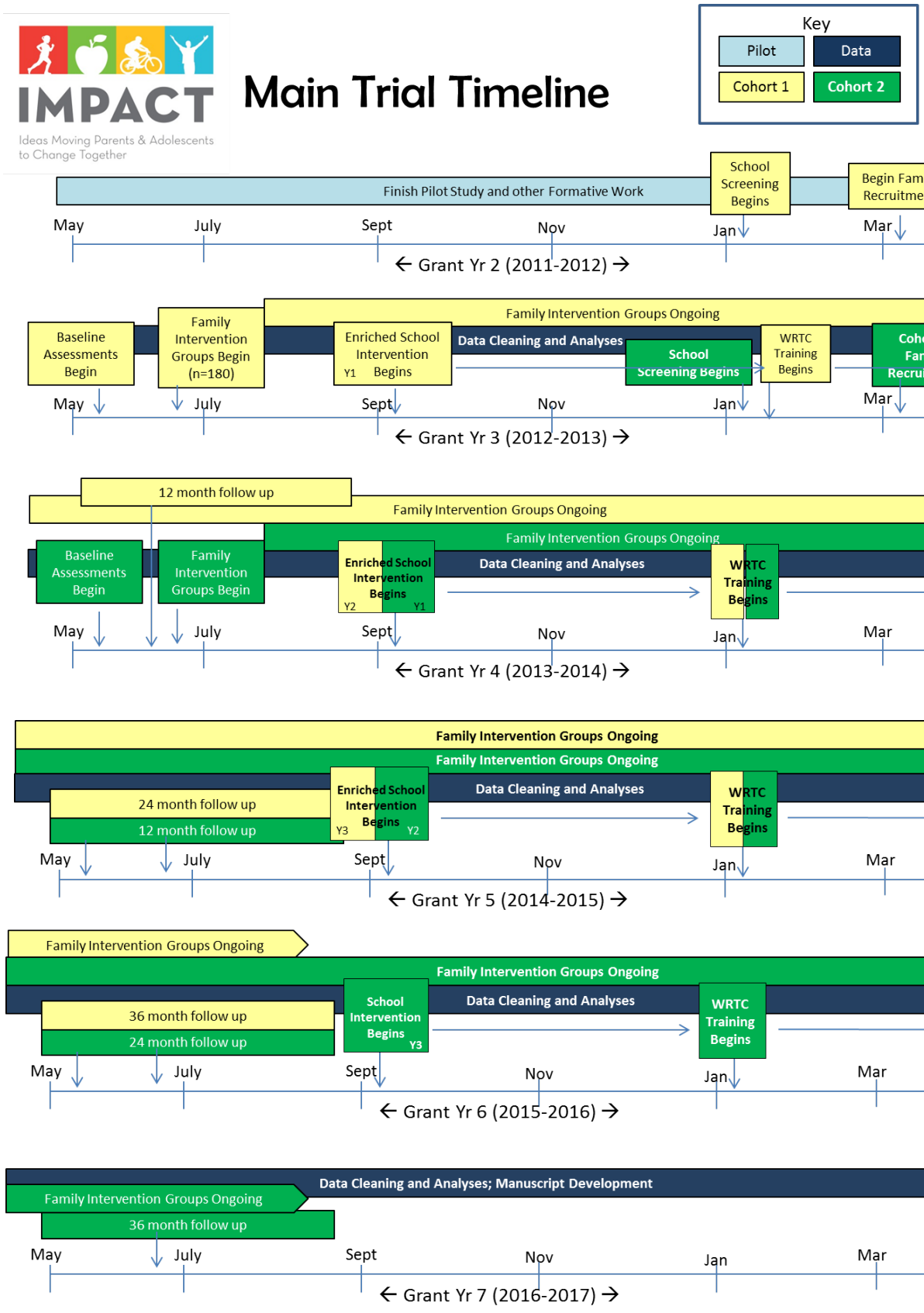
De-identified Database: All data collected during the scheduled assessments (e.g., collected via interview, survey, assessment) will be directly entered into a REDCap database stored on Case Western Reserve University's server (see Data Processing). It is imperative that CWRU's REDCap be used to store the data since the research team is comprised of both UH and CWRU staff who will require convenient and immediate access. No Identifiable information will ever be stored on this database. Each participant will be assigned a unique ID. This unique ID will be used to link the participant with the data.

In order to accurately assess hypertension risk according to NHLBI standards and determine BMI percentile according to the CDC's, birthdates and data collection dates must be collected. This information is required to properly assess blood pressure and BMI status for this age population. Other than these two dates, no identifiable information will ever be stored on this database. Each participant will be assigned a unique ID. This unique ID will be used to link the participant with the data.

Each member of the research staff requiring access to the REDCap database will be assigned a unique user ID and password. User-rights will be established for all research staff requiring access to this REDCap database. User-rights will be determined by PIs and based and database access needs. Most members of the research staff with access to this database will only have permission to add information. Select individuals, as determined by PIs of the research study, will be granted permission to download/export data from REDCap to a secure, password protected computer. All downloaded datasets will require password protection and will not be allowed to leave the designated computer.

For final analyses of the resulting de-identified database, in keeping with modern practice, Dr. Love (project statistician and co-investigator) and Mr. Thomas (statistical programmer) will use a variety of statistical software packages, including R (for basic and complex graphical work, implementation of new methods, model fitting, and some data management) and Stata (for some model-fitting, multiple imputation and data management tasks.) Main analyses of an appropriately cleaned and locked master database will be conducted in the final project year. In addition, the statistical analysts will be responsible for responding to all requests for analyses of the local data that come forth from the RCU or DSMB.

13. SITE SPECIFIC TIMELINE



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