SingHealth

STUDY PROTOCOL

PROTOCOL TITLE:

Pilot evaluation of a mobile health intervention to identify early responders to treatment in adolescent obesity as a triage approach

PROTOCOL NUMBER:

006100317

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PROTOCOL SIGNATURE PAGE

Protocol Title: Pilot evaluation of a mobile health intervention to identify early responders to treatment in adolescent obesity as a triage approach

Protocol Number: 006100317

Protocol Version/ Date: V6/ 17 April 2019

Sponsor Name: Paediatrics Academic Clinical Programme

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and Singapore Guideline for Good Clinical Practice (SGGCP).

Principal Investigator Name: : Dr Chew Chu Shan, Consultant, KKH

Principal Investigator Signature: _____ 

Date: 17/04/2019

1. BACKGROUND AND RATIONALE

Prevalence of overweight and obesity amongst Singaporean adolescents has increased from 11 to 12 per cent in 2014 in school children (1) Current numbers of adolescents who are overweight or obese are predicted increase to 148,000 in year 2025. Adolescents who are overweight or obese have a moderate to substantial risk of remaining so in adulthood and they suffer from a range of immediate and long term medical and psychosocial complications. (2, 3) In addition, obesity-related cardiovascular disease risk markers present in adolescence are predictive of obesity related morbidity present in adulthood. (4). Importantly, obese and overweight adolescents who became normal weight adults, had cardiovascular disease risk markers that were similar to those of persons who had a normal BMI consistently from childhood to adulthood (5) Overweight and obese adolescents aged 12-15 were also found to have a higher chance of having normal Body Mass Index (BMI) at adulthood compared to children and adolescents of other age groups. (5) This further highlights a golden opportunity for intervention in adolescent obesity. Adolescent obesity is also a costly chronic disease and the lifetime direct medical costs is estimated to cost S$24,000 more per adolescent relative to a normal weight child. (6) Indirect costs of obesity such as carer's loss of productivity and intangible costs such as loss of well- being further add to the burden of adolescent obesity.

The Expert Committee on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity(7) recommends a staged based approach to the management of adolescents with overweight and obesity from Stage 1-4 with increasing intensity of management in higher stages. Stage 3 is recommended for overweight and obese adolescents that showed poor response to Stage 1 and 2 or for adolescents with BMI of greater than 99th percentile. These adolescents are termed high risk obesity in our WMC program. Stage 3 interventions consist of multidisciplinary visits with frequent (up to weekly) visits for 8 or more weeks.

Although the recommendations are based on available and mounting evidence of the efficacy of these multidisciplinary interventions (8) Stage 3 program is practically challenging to deliver within KKH paediatric and adolescent weight management clinic (WMC). KKH WMC is currently a physician-led multidisciplinary clinic, which receives the majority of referral from intra-hospital department. There is a wide spectrum of patients being referred to the weight management clinic from low to high-risk obesity. Unfortunately this is taxing on the service that should be servicing mainly the high-risk patients with obesity. The challenges facing WMC are multifactorial

with patient, provider, institutional, and community barriers that affect the achievement of successful outcomes. A few barriers that we are hoping to reduce through our waitlist intervention, are as listed below. One significant institutional barrier is the high manpower resource required to run the Stage 3 multidisciplinary programme. There is also a high rate of patient attrition from stage 3 weight-management clinics and programs (9) Within WMC, our audit shows high level of dropout of 58% after the initial visit (10). KKH WMC receives the majority of referral from intra-hospital department with adolescents ranging from overweight to severely obese with or without comorbidities. However, there is difficulty in moving the overweight adolescents without comorbidities to primary care, due to a lack of trained primary care provider in management of adolescent obesity for Stage 1 program. There is also a lack of structured community services to provide regular contact for adolescents with obesity as required in Stage 1 program as well as the lack of triaged referral pathways for poor responders to primary care intervention.

In considering a structured community-based lifestyle behavioural change program, we examined several studies and recommendations (11-13), as well as the adolescents' views on the mode of intervention(14). Common barriers cited by adolescents and parents were physical accessibility of intervention programs and scheduling inconveniences (14-16) Smartphones and mobile applications, with their widespread market penetrability, offer a potentially powerful approach for addressing common barriers to health behavior change through delivering convenient, individually tailored, and contextually meaningful behavioral interventions. The American heart association has supported the role of social network as a tool in fighting childhood obesity and has suggested the use of an intervention social network for more efficient and effective use of a clinician time. The clinician could continue to serve as a resource to the patient and family by providing accurate measurement, monitoring of growth and obesity related co-morbidities but defer the bulk of the intervention to a social network experienced in the use of motivational interviewing for childhood and adolescent obesity. (17)

Multifunctional mobile applications that provide patient education with self-monitoring tools and provide counselling has been found to be the most effective in obesity treatment.(12, 13) The Kurbo program is an example of a multifunctional mobile application that was developed to aid adolescents and their families to learn healthy eating habits and weight management through the use of a mobile application with dietary self-monitoring and weekly interactive coaching sessions. Using the Kurbo app, adolescents track their food and exercise, as well as learn about healthy behaviours through games and videos. The Kurbo coaches check in with adolescents for 15 minutes once a week via video, phone or text over a 12 weeks period.

The app's data driven platform provides users with feedback via push notifications, text messages and emails. Kurbo utilizes Traffic Light Diet (18) to categorise foods into reds, yellows and greens. The Kurbo program teaches users to gradually reduce their consumption of red(high caloric) food over time instead of focusing on caloric counting which promotes disordered eating behaviours (19).The app is supplemented with weekly live coaching with a Kurbo behavioural coach. Coaches check in with the adolescents for 15 minutes once a week via video, phone or text. Health care professionals, who referred their patients, will also have access to the patient's progress through the Kurbo administrator site. Briefly, Kurbo coaching philosophy is based on a theoretical model of human support called Supportive Accountability (20) Human increases adherence through accountability to a coach who is seen as trustworthy, benevolent, and having expertise. Details about Kurbo coaching philosophy, screening, training and supervision of coaches is as attached in Appendix 1. Terms and conditions about Kurbo program is attached in Appendix 2. The program is licensed from the Stanford Packard Pediatric Weight Control Program and is currently part of the weight management program in Stanford and Florida's Children weight management clinic. There are also ongoing trials in Baystate Pediatric weight Management Program and University of Chicago on the utility of Kurbo Program. Locally, Health Promotion Board had conducted a pilot study using Kurbo Program on 80 overweight and obese children aged 8-17 years old as a school-based initiative. The pilot study showed a low drop-out rate of 19%. 65 families completed the 3 month program with a significant drop in BMI z-score by 0.26. Of this group, 90% of the children either maintained or reduced their weight. Of those who reduced their weight, 58% reduced their BMI by over 3% and 20% reduced their BMI by over 7%. Reduction of BMI z-score of more than 0.25 has been found to be clinically significant for reduction of cardiovascular risk factors. (21)

Several studies in adolescent obesity have consistently identified early treatment engagement as evidenced by attendance and initial weight loss, between 4-10 weeks, to be strongly predictive of long term weight loss (9, 26, 27) Early responders have been reported in studies varying from 60-80% (9, 27) These data support the hypothesis that a large proportion of obese adolescents can be managed in primary care with structured interventions. Identification of early treatment attendance and initial weight loss introduces a second filter to Stage 3 program. A third filter will be the identification of the severely obese adolescents as severely obese adolescents have been found to have higher risks of obesity related co-morbidities (7) with poor response to treatment (28). Early responders, who are not severely obese, can then be channelled to low risk WMC clinics which are made to simulate a primary care provider clinic with only 10-15 minutes consultation time. If the low risk clinics are found to be successful, it has potential to be implemented widely in primary care. To our knowledge, there have been no clinical program that have utilized a waitlist intervention to identify early responders in WMC as a triage approach.

We thus propose a waitlist intervention with two main components of a brief intervention by a nurse coordinator followed by the Kurbo program to identify early responders, who are not severely obese, in our WMC waitlist system. The waitlist intervention is cost effective and makes only very modest demands on the nurse clinician's time and skills, which is a strategy we have chosen deliberately. If successful, it can be implemented widely as a brief opportunistic intervention and increase the degree to which primary care providers (polyclinic nurses and doctors, general practitioners or school health services) engage with adolescent obesity interventions.

2. HYPOTHESIS AND OBJECTIVES

Primary objective will be to examine the proportion of patients triaged to the low risk WMC clinics after brief intervention by a nurse coordination and completion of 4 sessions of Kurbo Program over a 12 month recruitment period.

Secondary objectives:

1. To examine the effect of the waitlist intervention and WMC intervention on mean BMI z-score change at 3 months and 6 months.

2. To examine the feasibility of using Kurbo program as a waitlist intervention for the target population as measured by quantifying the percentage of patients offered the program who agreed to enrol.

3. To examine program fidelity as measured by the percentage of patients who complete each of the 12 sessions of online coaching by Kurbo coaches

4. To examine changes in treatment outcomes as a function of program fidelity as measured by those who complete more online coaching show greater improvements in BMI z-score

5. To examine other factors that predict poor response (parental BMI, quality of life, disordered eating and physical activity measurement) in high risk WMC

6. To examine the effects of waitlist intervention on lifestyle changes (nutrition and physical activity), quality of life and disordered eating at 3 and 6 months.

7. To examine the rate of attrition from WMC after implementation of the waitlist intervention and new model of care in WMC.

8. Examine changes in branched chain amino acid(BCAA), aromatic amino acid (AAA) and long chain acylcarnitines, insulin and second hour glucose results and fasting lipids at baseline and at month 6.

3. EXPECTED RIKS AND BENEFITS

Possible risks include inconvenience and the discomfort of weighing for the Kurbo coaching sessions, as well as during the weight management clinic appointments, may be expected.

Inconvenience of the coaching sessions by Kurbo coaches and attendance at the weight management clinic sessions may be expected. Potential benefits of participating in the research includes personal coaching from Kurbo coaches to eat healthier and exercise more as well as the tracking of weight and diet using the Kurbo application to help participants manage their weight more effectively.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

45 adolescents, aged 10-17 years old, will be recruited in KKH

4.2. Criteria for Recruitment and Recruitment Process

The clinical research coordinator will complete a trial screening form consisting of date of birth, gender, ethnic race, weight and height, main language spoken, owes a smartphone and significant medical conditions to assess eligibility. These data are to identify potential participants and the research team will ask to keep a copy of this if a person is eligible for the study but declines participation. This is to compare the characteristics of people who participate to those who do not.

4.3. Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study.

a. Overweight as defined by BMI percentile of above 90^{th} percentile
b. Age 10-17 years old in the year of referral
c. Ability to provide informed consent
d. Adolescents with a phone which is able to download the application to be used on their devices

4.4. Exclusion Criteria

Subjects meeting any of the below exclusion criteria at baseline will be excluded from participation

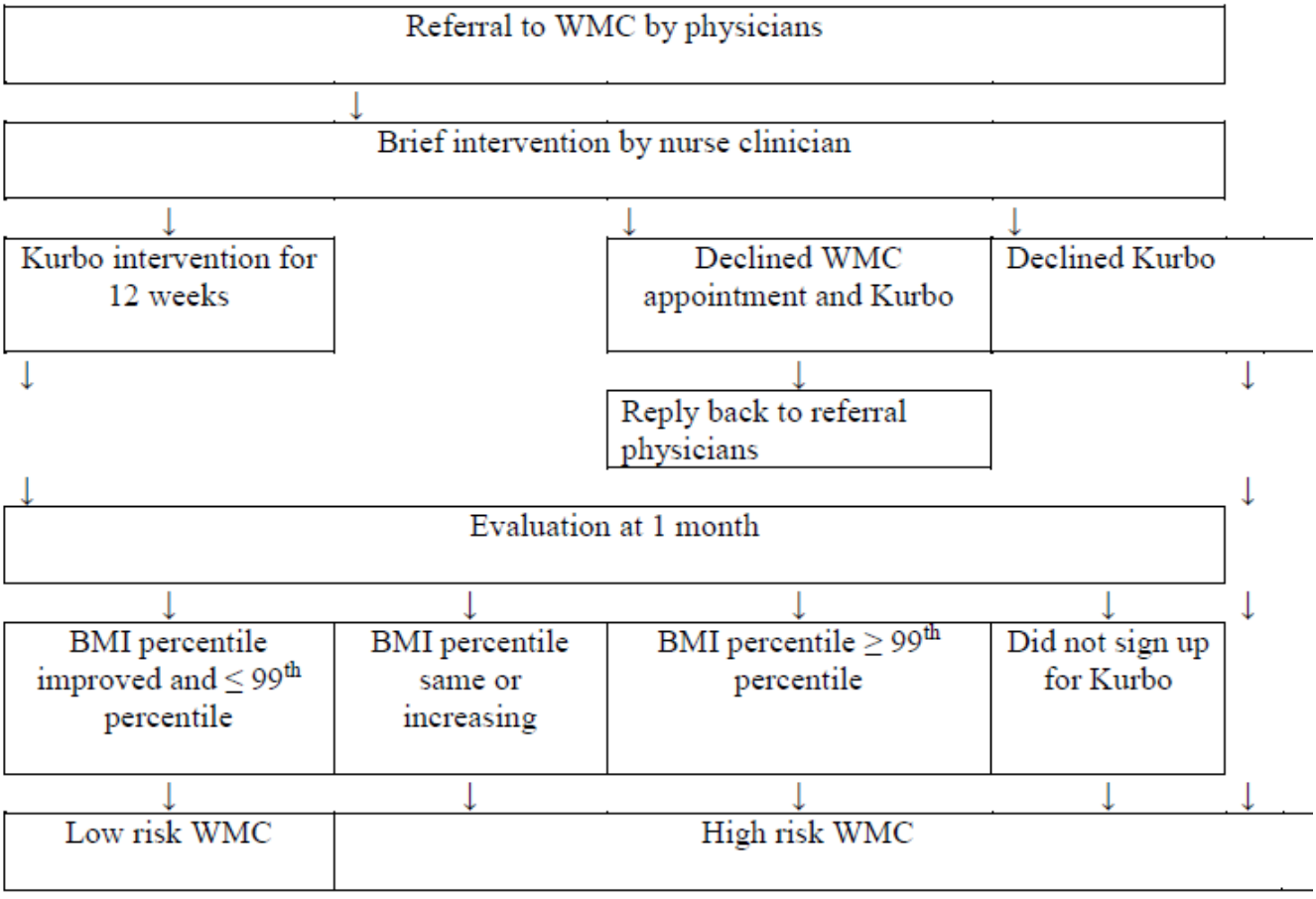
- Patients with secondary causes of obesity especially genetic syndromes e.g. Trisomy 21, Prader-Willi
- Currently participating in a weight management program
- Unable to understand and speak English sufficiently to give informed consent and complete the research assessments.

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

Children aged 10-17 years old with BMI percentile of above 90th percentile, who are referred to the WMC, will receive a brief intervention by the WMC nurse coordinator followed by introduction to Kurbo program for more detailed dietary and physical activity recommendations and implementation of behavioural changes. The patient's progress will be reviewed by the nurse clinician at one month post intervention to determine whether the BMI percentile has shown a reduction through the Kurbo Program. Patients that declined Kurbo intervention, has a BMI of more than 99th percentile or continue to have increase in their BMI percentile in Kurbo program, will be offered the high risk weight management clinic appointment for a more detailed multidisciplinary evaluation for targeted intervention. Patients that are able to engage with Kurbo intervention and showed a decrease in BMI percentile over 4 sessions of Kurbo will be offered the low risk weight management clinic.

The following section illustrates how and when the outcomes will be measured. Figure 1 depicts the flow diagram for an adolescent at the point of referral to the WMC.

Figure 1: Flow diagram of the intervention at the point of referral to WMC



Study visits and procedures

The expected duration of study involvement for each participant will be 6 months with 5 in-person visits with the study team. Table 1 depicts the study visits and measurements for each visit.

Table 1: Study visits and measurments

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Parental demographics and parental BMI	x					
Anthropometry (weight, height, waist circumference, blood pressure and body fat composition)	x		x	x		x
Peds QL questionnaire	x			x		x
Three day food diary	x			x		x
Eating Pattern Inventory	x			x		x
Evaluation questionnaire				x		
Accelerometry	x			x	x	
Fasting insulin, lipids, oral glucose tolerance test		x			x	
Plasma amino acid, long chain acylcarnitine levels and vitamin D level, calcium, magnesium,phosphate and alkaline phosphatase		x			x	

First contact (Baseline):

The research coordinator or WMC nurse coordinator will be informed at the point of WMC referral from the clinic assistants who book the patients in the system or directly from physicians who make the referral. Either the clinical research coordinator, WMC nurse coordinator or one of the investigators will establish the first contact with participant and parent. There are a few purposes to the first contact. Firstly, this is to confirm the WMC appointment. Secondly, this will enable the nurse to conduct a brief intervention and introduce Kurbo Program to both parent and adolescent. Thirdly, the first contact will be able to identify parents and adolescents who are not ready for weight management program and a reply letter to the referring doctor will be provided. In addition, the first contact will be important to obtain accurate baseline anthropometric measurement, complete questionnaires, obtain a 7 day physical activity assessment, as well as to update contact information and to establish rapport with the adolescents. Lastly, the nurse will also inform of a follow up telephone call to remind about the appointment and follow up on Kurbo program.

Visit 0 (Baseline before week 6):

The investigator will determine the eligibility of the patients. If the patient is found to be eligible and willing to participate, written consent to participate in the trial will be taken by the nurse coordinator or the clinical research coordinator. The patient's weight and height, body fat composition, waist circumference and blood pressure will be measured as per usual standard protocol or by the study team members and Co-I. Questionnaires to assess eating, quality of life and dietary recall will be administered as part of the research. Accelerometers are optional for patients and will be fitted to assess physical activity. The purpose and instructions for use of activity monitor will be explained, with a copy of the guidelines / instructions provided to all participants. During the measurement period, they will be required to complete an activity diary, providing information on activities / exercises engaged in during the measurement period. In the event the device is removed, they will be required to provide details (e,g, reason and duration) in the activity diary. As the participants will be required to wear the activity monitor throughout the day, including during school activities, a letter to the school / teacher will be provided to explain the reason for wearing the device during the study period. Participants will need to complete a 3-day food diary.

Visit 1 (preferably before visit 2):

Metabolic blood tests (HbA1C, fasting lipid panel, oral glucose tolerance test, fasting insulin level and liver function test) were collected after a minimum 8 hour fasting period together with bloods for AAA, BCAA, long chain acylcarnitines and vitamin D level, calcium, magnesium,phosphate and alkaline phosphataseand are optional for participants. Participants may choose to return the accelerometer and food diary during this visit.

Telephone call (before visit 2):

Phone call reminders of the upcoming visit will be provided by the study team member.

Visit 2 (preferably between 4-11 weeks):

Prior to the clinic visit, the nurse coordinator or clinical research coordinator will obtain a summary of the adolescent's progress in Kurbo to aid the discussion during the clinic visit. If there has been no change in the adolescent's BMI percentile after 4 sessions of Kurbo program or the adolescent had not signed up for Kurbo, the adolescent will be placed in the high risk clinic. If the adolescent had shown reduction in BMI percentile after 4 sessions of Kurbo, they will be placed in the low risk clinic. There are several key objectives to the visit. Firstly, it is to objectively measure the patient's weight and height, body fat composition, waist circumference and blood pressure. In the low risk clinic, the current clinic slots are in 15 minutes slot as the main purpose of the consult is to screen for obesity related co-morbidities and for motivational interviewing. The visit also allows the nurse coordinator to build further rapport with the adolescent. In the high risk clinic, the clinic slots are in 30 minutes slot to allow for more time to obtain a medical and psychosocial history. The weight management program for high risk and low risk WMC will be as routine care.

Current low risk WMC patients will be offered 2 monthly follow up with optional dietician and exercise physiologists counselling and exercise sessions. The high risk WMC patients will be routinely offered the standard high risk follow up protocol consisting of weekly follow up with the multidisciplinary team for 4 weeks followed by 2 weekly appointments for 2 months and monthly appointment thereafter based on clinical response.

Visit 3:(12-23 weeks)

Prior to the clinic visit, the nurse coordinator or clinical research coordinator will obtain a summary of the adolescent's progress in Kurbo to aid the discussion during the clinic visit. The follow up will be timed together with the WMC appointment to measure the patient's weight and height, body fat composition, waist circumference and blood pressure as well as administration of the questionnaire. Accelerometers may also be fitted or returned to

study team members to assess physical activity. If patients do not turn up for the visit, the clinical research coordinator will call the patient to administer the questionnaire and the food diary and obtain a self report height and weight. The clinical research coordinator will attempt up to 3 times to contact the patient. It will be considered a loss of follow up for that visit if patient returns for visit after the window period of 12-23 weeks.

Visit 4: (week 24-36)

Metabolic blood tests (HbA1C, fasting lipid panel, oral glucose tolerance test, fasting insulin level and liver function test) were collected after a minimum 8 hour fasting period together with bloods for AAA, BCAA and long chain acylcarnitines approximately before visit 5 appointment to aid discussion with the doctor during WMC appointment. Vitamin D level, calcium, magnesium,phosphate and alkaline phosphatase may be performed to assess the bone health of the adolescents. Blood tests are optional for patients. Accelerometers may also be fitted or returned to study team members to assess physical activity.

Visit 5: (week 24-36)

The follow up will be timed together with the WMC appointment to measure the patient's weight and height, body fat composition, waist circumference and blood pressure as well as administration of the questionnaire. Accelerometers may also be fitted or returned to study team members to assess physical activity. If patients do not turn up for the visit, the clinical research coordinator will call the patient to administer the questionnaire and the food diary and obtain a self report height and weight. The clinical research coordinator will attempt up to 3 times to contact the patient. It will be considered a loss of follow up if patient returns for visit after the window period of 24-36 weeks.

Anthropometric measurement and blood pressure will be measured by trained staff at each clinic visit. The height and weight were measured to the nearest 0.1 cm via a stadiometer (Seca, Model 220; Germany) and 0.1kg via a medical weighing scale (Tanita HD-316, Tanita Corp.;Tokyo, Japan) respectively without shoes and in light clothing. Blood pressure was measured via an electronic sphygmomanometer (Dinamap model 8101, Critikon Inc.; Florida, USA). Waist circumference is measured at the narrowest point between the lower costal (rib) border and the iliac crest using a nonextensible steel tape.
Blood tests are optional for patients. Following an overnight 12-hour fast, a blood sample will be drawn for measurement of fasting plasma glucose (FPG), fasting plasma insulin and lipid panel comprising triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), in addition to HbA1c. The participants will then under-go an oral glucose tolerance test by consuming a 75g glucose drink over no more than 5 minutes. Another blood sample is drawn 120 minutes later for measurement of 2-hour plasma glucose (2hrPG).A small amount of blood sample (0.5 ml) will be taken during collection of the fasting samples for metabolomics profiling, 2ml for vitamin D level, calcium, magnesium,phosphate and alkaline phosphatase will be performed to assess the bone health of the adolescents as well as for point of care testing of HbA1C and lipid panel. Testing for vitamin D level, calcium, magnesium,phosphate and alkaline phosphatase can be done at visit 1 or visit 4.

A targeted mass spectrometry approach using stable isotope dilution will be used for quantification of the metabolites as described. In brief, fasting plasma samples obtained from study participants will be spiked with known amounts of stable-isotope labeled internal standards before precipitation with HPLC grate methanol to remove proteins in the samples. The protein-free supernatant will then be evaporated to dryness under nitrogen flow and reconstituted with 100 ul of 0.1% formic acid for LC-MS/MS analysis. Metabolites to be analysed include BCAA (isoleucine, leucine, valine), AAA (phenylalanine and tyrosine) and acylcarnitines (C0, C2, C3, C4, C5, C8, C12, C14, C16, C18) All 15 metabolites concentrations will be reported in μmol/L

Questionnaires will be administered to adolescents to assess quality of life, disordered eating and physical activity

assessment as part of a routine comprehensive assessment at visit 0, 3 and 5.Pediatric Quality of Life Inventory (PedsQL; UK version 4) will be administered as a comprehensive and multi-dimensional construct that includes physical, emotional, and social functioning to assess quality of life in the adolescents. (32). Psychological dimensions of eating behaviors were determined using a validated self-reporting Eating Pattern Inventory for Children (EPI-C) at visit 0,3 and 5.The 20-item questionnaire assessed four dimensions ((dietary restraint, external eating, parental pressure to eat, and emotional eating). Responses to each item were listed on a 4-point Likert scale (1 = not at all, 2 = sometimes, 3 = mostly, 4 = always). Higher scores in the respective dimensions are indicative of greater external eating, emotional eating, dietary restraint or parental pressure to eat.

Questionnaires will also be administered to one parent to obtain baseline demographics and parental report of Pediatric Quality of Life. A month 3 evaluation questionnaire for Kurbo program will be administered at visit 3.

Three day food diary of actual intake of foods and beverages at the time of consumption will be administered. Food will be estimated using household measures (e.g. cups, tablespoons) and food pictures. This method was chosen as it is a direct observation of what is eaten on the current diet and not based on respondents' memory. The duration of 3-day was chosen because this study is only assessing the trends of energy intake, amino acid intake, fruits and vegetables consumed at the initial, intermediate and final stages over 6 month period.

In this study, training on the portion size estimation using visual tools (e.g. household measures, food models) will be conducted to the caregivers and participants by the investigator on the recruitment day. Participants will need to complete a 3-day food records at baseline, visit 3 and 5. The assigned investigator will remind the patients/caregiver to complete the food record one week before the given deadline by telephone

Physical activity will be assessed using the wGT3X+Actigraph accelerometer. Participants were fitted with an Actigraph, which was worn for 7 days. The monitor was placed centrally on the hip and were set to record acceleration and movement frequency at 5-s epochs, the shortest epoch allowing for seven consecutive days of continuous measurement. The volunteers were asked to wear the monitors during waking hours and to remove them while bathing, showering, and swimming. The Actigraph data were processed using the Actilife 6 software. All days consisting of over 500 min of valid data were included in the analysis. Published thresholds (39) were used to estimate the time spent in different activity intensities. Sedentary activity was classed as <100 counts per minute (cpm) and light intensity activity as between 100 and 1,951 cpm. A threshold of 1,952 cpm was used to estimate time spent in moderate-to-vigorous PA (MVPA). Accelerometer will be provided at suitable timing for the participant to wear for 1 week, preferably during baseline, before or after visit 3, before or after visit 5. If there were any technical glitch, patient can choose to re-wear the accelerometer.

Visit 0: Recruitment, three day food diary, questionnaire and measurement and use of accelerometer

Visit 1(preferably before visit 2): Taking of fasting bloods

Week 1-12: 12 weekly sessions of Kurbo online coaching

Phone call 1 (Week 4): Nurse clinician call to follow up on Kurbo Program progress

Visit 2 (preferably between Weeks 4-11): Doctor's visit for weight management clinic and Measurements

Visit 3 (week 12-23): Measurements, three day food diary, questionnaires and Doctor's visit for weight management clinic and use of accelerometer

Visit 4 (week 24-36): Taking of fasting bloods and use of accelerometer

Visit 5 (week 24-36): Measurements, three day food diary, questionnaires, Doctor's visit for weight management clinic and return of accelerometer

Clinical Research Coordinator may provide timely reminder for patient's visits.

Subjects who miss any visits/ anthropometric measurements/ food diary/ questionnaires/ blood-taking/ recording of physical activity with accelerometer will be excluded from data analysis for that assessment and as long as patient returns for 2 out of 5 visits, it will not be considered as protocol deviation.

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

6.2. Collecting, Recording and Reporting of Serious Adverse Events to CIRB

Reporting of adverse events involves the Principal Investigator submitting to CIRB the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

<table>
<tr><th>Severity:</th><th>Nature:</th><th>Reporting Requirement:</th><th>Form to use:</th></tr>
<tr><td>Local SAE -resulting in death#</td><td>Unexpected/ Expected</td><td>Report within 24 hours*.</td><td>LSAE Report Form</td></tr>
<tr><td>Local SAE – life-threatening</td><td>Unexpected/ Expected</td><td rowspan="3">Report as soon as possible but not later than 7 calendar days*.</td><td rowspan="3">LSAE Report Form</td></tr>
<tr><td>Local SAE – not life-threatening</td><td>Unexpected</td></tr>
<tr><td>Local SAE – not life-threatening**</td><td>Expected</td></tr>
<tr><td>Non-local*** SAE – fatal or life threatening</td><td>Unexpected</td><td>Report within 30 calendar days. Submit through Other Reportable Event Form.</td><td>Available format (e.g. CIOMS)</td></tr>
</table>

Only related SAE (definitely / probably / possibly) need to be reported to CIRB. Unrelated SAE do not need to be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by the procedures involved in the research.

6.3. Safety Monitoring Plan

As this is an unblinded study with no substantial risk, the Principal investigators, together with the Co-Investigators and research coordinators, who are responsible for the day-to-day management of the trial, will ensure that the research methodology is adhered to and that appropriate action is taken to ensure to safeguard participants and the quality of the trial itself. They will also meet at least quarterly throughout the course of the trial. Data entered by the clinical research coordinator will be counter checked by the investigators to ensure that the data correlates with the case report forms.

6.4. Complaint Handling

Complaints will be handled as per the Hospital's policy on handling patients' complaints.

7. DATA ANALYSIS

7.1. Data Quality Assurance

The clinical research coordinator will ensure that the data entry forms are completed. The data entry forms will be counter checked by the investigators to ensure that the data obtained is accurate and reliable.

7.2. Data Entry and Storage

Data will be entered electronically into Microsoft Excel spreadsheet, which is password protected, with only the Principal Investigators and Co-Investigators having access to the data.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

There is no sample size calculation for this pilot study. The Weight Management Clinic receives new referral to WMC of 20 new patients per month with approximately 20% of the new referrals being adolescents (10). Using a conservative estimate of 50% uptake rate, we will be able to get 2 patients per month over 20 months to get 45 adolescents enrolled into Kurbo program.

8.2. Statistical and Analytical Plans

Data will be analysed using SAS version 9.3 for Windows (SAS, Inc., Cary, NC USA). BMI will be calculated as kg/m2 and BMI-z score calculated using the L, M, S parameters published by the CDC. (34) Baseline demographic, anthropometric measurements, parental BMI, quality of life measurement, disordered eating and physical activity were compared between those in low risk WMC versus those in high risk WMC using the Wilcoxon rank-sum test and the two-sample-t-test for non-normal and normal continuous variables, respectively, and the Fisher's exact test for categorical variables. Changes in cardiometabolic risk factors between first visit and at month 12 will be compared using the paired-sample t-test. Generalized linear mixed model will be carried out on the BMI z-score over multiple visits over 12 month follow up period. The mean value of BMI z-score is considered as a function of time from the baseline. The variance components is used as the covariance structure in generalized linear mixed model. It models a different variance component for each random intercept to allow each child to have his/her own overall level of BMI z-score after taking into account baseline covariate. A time-group interaction will be included to test whether the rate of change of BMI z-score is different between adolescents in low risk and high risk WMC.

There is no reason to assume that this project will lead to an excess of adverse events as the waitlist intervention consists of advice from the nurse and offer of referral to a Kurbo program, neither of which seem likely to create harm. Nonetheless, there are several safety net in place for the waitlist intervention. Firstly, as part of standard Kurbo procedures, any excessive weight loss or weight gain will prompt the Kurbo coaches to inform parents to seek help from their GP and the WMC nurse coordinator will be informed if any concerns arise. Secondly, the WMC nurse coordinator will have administrative rights to Kurbo program and will be able to monitor patient's weight data and communication with Kurbo coaches and will highlight any concerns that arise as a result of intervention. There will also be a feedback form (A month 3 evaluation) administered by the clinical research coordinator on the participants' attitudes to the waitlist intervention and to identify any adverse events at the first WMC visit. As this is a pilot study, there will be no interim analyses.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted in accordance with the current protocol and the Principal Investigator and clinical research coordinator are SG-GCP registered. As this is an unblinded study with no substantial risk, the Principal investigators, together with the Co-Investigators and research coordinators, who are responsible for the day-to-day management of the trial, will ensure that the research methodology is adhered to and that appropriate action is taken to ensure to safeguard participants and the quality of the trial itself. They will also meet at least quarterly throughout the course of the trial. Data entered by the clinical research coordinator will be counter checked by the investigators to ensure that the data correlates with the case report forms.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

Physicians, nurses, clinic assistants and wards assistants in the outpatient clinics and the inpatient wards will be informed about the study. When the patient is referred to the weight management clinic, the clinical research coordinator will be informed about the referral. A trial screening form will be completed by the clinical research coordinators to identify potential participants; the research team will ask to keep a copy of this if a person is eligible for the study but declines participation. This is to compare the characteristics of people who participate to those who do not.

Consent process will take place in an outpatient clinic setting after a physician referred the patient to the weight management clinic. The physician or clinic assistant will inform the study team members about potential research participants. Consent process will take place in an outpatient clinic consultation room which is quiet and free of interruptions.

The research coordinator or nurse coordinator will provide the Participant Information Sheet and Consent Form to the participant and parent for reference. If participant and parent are agreeable to the research study then the research coordinator/nurse coordinator will obtain written informed consent to participate in the trial. Participants are also free to consider and contact the research coordinator if they require time to consider their participation. A letter of invitation will be sent to invite eligible participants to participate in the study before the appointment if study team members are unable to recruit the patient at the point of referral. Participants can contact the research coordinator or the nurse clinician if they have any queries regarding the study. The nurse clinician or other co-investigators, who are not directly involved in the care of the participant, will be conducting the consent process to reduce the possibility of coercion or undue influence. Participants are also free to withdraw from the study anytime as documented in the consent form which is provided in the Participant Information Sheet and Consent Form provided to participants. Participants' assent will be obtained together and documented using the full consent form, together with the documented consent form of the parent or legal guardian.

11.2. Confidentiality of Data and Patient Records

Hardcopy of the data will be stored in a cupboard with lock and key access in an access controlled room. Soft copy of the data will be stored in a password protected file. Only study team members and the research coordinators will have access to the research data. Research data will be stored in a password protected file with only team members and research coordinators having access to the password. The records will be accessible for inspection and copying by authorized authorities and will be stored for 7 years after the study is completed.

12. PUBLICATIONS

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The funding source's contribution will be acknowledged but will have no contribution in publication decisions.

13. RETENTION OF STUDY DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility under key and lock. The records will be accessible for inspection and copying by authorized authorities and will be stored for 6 years after the study is completed.

14. FUNDING and INSURANCE

Grant agency is Paediatrics Academic Clinical Programme under the grant name: Tan Cheng Lim Research and Education Fund Grant Award. The grant has been approved with the budget allocation of $50,000 over 1.6 years from 01 April 2017 to 30 November 2018.

The participants will be reimbursed SGD50 to compensate the travelling expenses for each visit they attend in the window period.

List of Attachments

Appendix 1 ***References***

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