Title: The Healthy Eating and Lifestyle Programme (HELP) study protocol: an efficacy randomised controlled trial of the HELP intervention compared with enhanced standard care of obese adolescent in the community

Authors:

Deborah Christie (Deborah.Christie@uclh.nhs.uk)
Lee Hudson (Lee.Hudson@uclh.nhs.uk)
Anne Mathiot (a.mathiot@ich.ucl.ac.uk)
Tim J Cole (tim.cole@ich.ucl.ac.uk)
Saffron Karlsen (s.karlsen@ucl.ac.uk)
Anthony Kessel (anthony.kessel@hpa.org.uk)
Sanjay Kinra (Sanjay.Kinra@lshtm.ac.uk)
Steve Morris (steve.morris@ucl.ac.uk)
Irwin Nazareth (i.nazareth@ucl.ac.uk)
Ulla Sovio (Ulla.Sovio@lshtm.ac.uk)
Ian Wong (ian.wong@pharmacy.ac.uk)
Russell M Viner (r.viner@ich.ucl.ac.uk)

Author's response to reviews:

HELP TRIAL: The Healthy Eating and Lifestyle Programme (HELP) study protocol: an efficacy randomised controlled trial of the HELP intervention compared with enhanced standard care of obese adolescent in the community

Thank you for asking us to respond to the Reviewer's comment. We note that during the funding application, this Trial went through three layers of review at the UK National Institute of Health Research as well as review by the National Research Ethics System. We welcome comment on methodology however as the trial is currently underway, and given the extensive previous review undertaken, our ability to make changes is highly constrained.

Response to Reviewer 1

Point 1. The randomization section is inadequate (indeed, it appears to end with asentence that is incomplete). The authors must specify the exact logistic stepstaken to ensure full allocation concealment. I would also recommend stratifyingon baseline BMI.

We have expanded the randomization section in our revised protocol.

This section now reads:

"Randomisation will be undertaken independently of the investigators by the Health Services Research Unit (HSRU) University of Aberdeen. Randomisation to the HELP Trial is performed using a secure website. A minimisation protocol will
be used for randomisation[20]. Allocation to treatment will ensure balance in respect of one key prognostic variable (sex). The program design has been successfully used by HSRU in several trials and incorporates the use of a library of stored procedures to calculate the appropriate treatment based on subgroup totals stored in SQL Server 2005 data tables. Allocation will be 1:1 to Intervention:Control.

The program will generate a 5-digit Study ID. The first 2 digits identify the recruiting centre (Centre IDs will be allocated when they join the study) and the last 3 identify the individual patient recruited. This Study ID number can then be used subsequently to maintain patient anonymity. At the time of randomisation the HSRU user will select values for the minimising variable Gender, then click on the 'Randomise' button. The study number and the allocated treatment will be displayed and this data then conveyed to the Trial Manager.”

Reviewer point 2. There are a very large number of secondary outcomes: I counted 28. There are several problems.

1. How will all this information be interpreted? For example, what if social on the PedsQL is positive but the IWQOL negative? I felt that the secondary outcomes were thrown together because they seemed sort of sensible at first blush, not because it had been rationally assessed why they would add pertinent information.

Response: In error, some data being collected in sub-studies of the main trial were included as secondary outcomes. These (stress, exercise tolerance, CRP, HbA1c) have been removed. Liver function is a safety variable and not a trial outcome, so has been removed.

However, the other secondary outcomes are all highly pertinent to obesity interventions and for assessing the pathway of change as a result of the intervention.

We are assessing lifestyle (diet, exercise), psychological function, quality of life and metabolic function. Diet and exercise, psychological function and quality of life are all potentially on the pathway of change, and thus are being assessed for this purpose. It is standard for obesity trials to assess BMI, waist circumference, fat mass and metabolic function as outcomes.

2. When will the measures be taken. This wasn't always clear. I suggest a table with columns as time points and rows as outcomes with X’s marking assessment times.

Response: The timing of assessments is outlined in Table 2 in the original manuscript.

3. Will the secondary outcomes be analyzed by ANCOVA approaches (i.e. With baseline as covariate)? This isn't clear.
Response: The study is not powered for secondary outcome. Thus analyses done will be largely exploratory. A similar approach will be used to that applied to the primary outcome.

Reviewer point 3. I can't agree with the CACE analysis. Compliance is the whole deal here! In the case of a drug therapy, you might say "let's do a CACE to get at the biological effect of the drug, adjusting out for non-compliance." This doesn't makesense for a weight loss programme of counselling and advice.

We believe that the CACE analysis is entirely appropriate. There is a body of literature referring to the application of CACE to RCTs of psychological interventions (e.g. Dunn and White).

Reviewer point 4. The sample size calculation is totally wrong! In brief, because the main analysis is ANCOVA (which is entirely correct), the sample size calculation has to take into account the correlation between baseline and follow-up measures (see Frison and Pocock Stat Med 1992). My guess is that the correlation between baseline and follow-up BMI will be very large, drastically reducing sample size requirements. On the other hand, the authors are looking for a very large effect size. My guess is that, with a correlation between baseline and follow-up BMI of 0.85, the investigators would have 80% power to detect a d of 0.3

Response: The Frison-Pocock paper is useful for a general discussion of ANCOVA, but it assumes that the correlation between baseline and outcome will be in the range 0.5 to 0.7, which is far below our correlation. In recent data from two childhood obesity intervention trials, the baseline to outcome correlation for BMI was 0.98 and 0.94. Thus both are extremely close to 1 and very different to the scenario described by Frison-Pocock.

When the correlation is close to 1 then our approach is a simple and valid one. It also avoids the issue of having to guess what the baseline-outcome correlation is, or what the SDs of baseline and outcome are.

The reviewer's comment about our sample size, based upon an estimate of baseline-outcome correlation that is too low, is therefore incorrect.