Look AHEAD Protocol Issue and Revision Dates

10th Revision – November 7, 2012
9th Revision – September 5, 2011
8th Revision – October 30, 2009
7th Revision- April 29, 2009
6th Revision – August 20, 2007
5th Revision – November 4, 2005
Amendment to 4th Revision – September 1, 2005
4th Revision – July 28, 2005
3rd Revision – May 16, 2003
2nd Revision – October 28, 2002
1st Revision – May 10, 2001 (Re: Memo to Steering Committee and Program Coordinators)
1st Issue – April 16, 2001

Summary of PROTOCOL Amendments
10th Revision – November 7, 2012

Look AHEAD Protocol
Changes between Ninth and Tenth Revisions
September 5, 2011 to November 7, 2012 Version

Page 2, New Section in Executive Summary: 1.8 Transition from a Randomized Trial to an Observational Study

Page 17, New Section: 3.3.5 Phase IV, Defining a new phase of the study

Page 28, description of the new Phase IV

Page 29, a brief description of the intervention shared by ILI and DSE in Phase IV

Page 37, change to the collection of serious adverse events during Phase IV

Page 39, an indication that the trial was stopped for futility.

Page 57, Formatting corrections.

Page 81, Added new appendix: APPENDIX D.2b MODEL CONSENT, GENERAL PHASE IV

Summary of PROTOCOL Amendments
9th Revision – September 5, 2011

Sections Amended

Table of Contents. Sections shaded in the TOC indicate amendments or additions occurred.

3.3.5 Coordinating Center Follow-up of UCLA Participants (Amended) to address close-out procedure.

8. 2 Schedule of Data Collection Visits. (Amended) to include self-administered outcomes forms.

Table 8.2 Measures and Frequency. (Amended) to remove text regarding blood samples collection points and number in cohort.

8.2.1 Home Visits. (Amended) to include "Out-Of-Clinic Visit" text.

8.6 Questionnaires and Frequency Table. (Added) Technology Use (new form).
(Amended) Paffenbarger Measure to clarify number of cohort included at different collection points.

10.9 Data and Safety Monitoring Board. (Amended) the ordinance and description for the DSMB.

11. Study Timeline. (Amended) trial activities and calendar times.

12.1 Clinical Sites. (Amended) listing for Seattle. Should read: VA Puget Sound Health Care System and University of Washington. (Amended) listing for Phoenix. Should read: Southwestern American Indian Center Arizona.

Model Consents.
Appendix D.11 (Added) Consent for GWAS (Sharing of Genetics results with NIH data bank.

Summary of Protocol Changes 8th Revision – October 30, 2009

3.2 Clinical Trial Objectives

3.2.1.1 Rationale for Change in Definition or Primary Endpoint

Amended description of process by adding the following text. The members of the Endpoints Working Group were masked to data on differences between intervention groups throughout the course of determining the revised endpoints. The Data and Safety Monitoring Board was not involved in choosing the revised endpoints, although they did approve the process by which the Endpoints Working Group developed the revised endpoints.

8.2 Measures and Frequency

Additions to table. eGFR and NOTE that urine samples will be collected at one additional visit during the out years, frozen and stored at central lab.

Added 8.2.1 Home Visits

8.2.1 Home Visits

Home visits may be completed for participants who are "lost-to-follow-up" to collect data and to provide an opportunity to encourage them to attend clinic for outcome measurements. A home visit may be done at the participant's (residence (e.g., home, institution, or health care facility). Home visits are expected to be rare and may not be used regularly to take place of cinic visits.

8.6.1 Physical Measures

Amended Accelerometry pargraph

Accelerometry At Baseline, Year 1, and Year 4, 2,400 participants will wear accelerometers for one-week periods to monitor physical activity. These participants will also complete the Paffenbarger questionnaire for the same one-week period[112] and repeat the questionnaire at Year 8 and Year 12 or close-out. Centers participating in this substudy will be selected based on criteria proposed by the Core Measures Committee relating to experience, overall costs, and inclusion of a range of populations.

Amended Albuminuria paragraph

Albuminuria Albumin and creatinine will be measured in a spot urine sample at Baseline and annually through Year 4 by the Look AHEAD Central Laboratory and every other year thereafter ~~dependent upon funding~~. The incidence and progression of microalbuminuria or greater levels of excretion will be assessed using an albumin to creatinine ratio. Serum creatinine will also be measured at these times and GFR will be estimated, In addition to the analyses above, urine will be collected at one additional visit during the out years. These samples will be frozen and then stored at the Look AHEAD Central Lab for future research.

Amended Health behaviors paragraph

Health behaviors Participants will report on their weight control practices, eating habits, and use of tobacco and alcohol and frequency of self-monitoring blood glucose at each biannual assessment through Year 4 and then Year 8 and Year 12 or close-out. Beginning with Year 8 and then annually, participants will report their weekly average use of aspirin, multi-vitamins, calcium and vitamin D and report the number of falls they experienced in the past year. Physical activity will be monitored in a subset of approximately 2400 ~~1200~~ participants through the use of the Paffenbarger Questionnaire at Baseline, Year 1, and Year 4. This subset of participants will also wear an accelerometer for this period (see above). Dietary intake will be assessed in the first 157 participants enrolled in each clinic at Baseline, Year 1, and Year 4. Note: The Paffenbarger Questionnaire will also be administered to the entire study cohort at Year 8 and Year 12 or close-out.

8.6 Questionnaires and Frequency Table

Amended Table to correct Extended Follow-up Column for Sociodemographics to occur at Yr8, Yr12 or close-out.

Added Appendix D.9. Model Consent – Storage of Urine Samples in NIDDK Central Repository

Added Appendix D.10 Model Consent – Use and Storage of Urine Samples

Summary of Protocol Changes (other than editorial corrections): 7th Revision – April 29, 2009

1.5 Outcomes. **Amended**. Follow-up period and primary outcome has been changed as described in 3.2.1.1 Rationale for Change in Definition of Primary Endpoint.

3. Overview of Trial Design. Amended. Participants will be followed annually through 2014, resulting in a maximum of 13.5 years of participant follow-up.

3.2.1 Primary Trial Hypothesis. Added. iv. Hospitalization for angina….over a planned follow-up period of up to 13.5 years.

3.2.1.1 Rationale for Change in Definition of Primary Endpoint. Added. Endpoint Working Group rationale and recommendation to expand the primary endpoint to include hospitalized angina and to extend the duration of the trial by two years.

3.2.2 Secondary Trial Hypothesis. **Amended.** Now includes, as composite 1, the original primary outcome consisting of - cardiovascular death (including fatal myocardial infarction or stroke), non-fatal myocardial infarction, or non-fatal stroke.

3.3.4 Phase III Amended. This phase of the trial will be variable in length, ranging up to 13.5 years.

Table 3.4.1 Power Detection. Amended. Results from revised projections of power are now summarized in this section and detailed in Appendix H. These revisions incorporate the longer planned follow-up and now assume an event rate of 2% per year for the comparison group. Appendix H provides information on how the monitoring plan has changed with the longer follow-up.

4.4.1 Institutional Regulatory Requirements Added.

6.1.2 Providing Patient Education and Medical Information to Participants. Added. Data related to estimated GFR will also be sent to participant's health care provider.

8.1 Overview of Data Collection Schedule. Amended. Phase III amended to include extended follow-up through 2014, resulting in a maximum of 13.5 years. Analyses of inflammatory markers collected and stored at baseline, Yr1 and Yr4 will be determined at closeout. Height was added at Yr8 and Yr12 or closeout. DEXA will be collected at four sites at Year 8. All sites will collect urine; albumin and creatinine will be analyzed biannually.

8.2. Schedule of Data Collection Visits. Amended. Close-out in 2014.

Table 8.2 Measures and Frequency. Amended. Measurement Schedule Table amended to reflect revised collection points.

8.4 Primary Outcome Measure. Added. Hospitalization for angina.

8.5 Secondary Outcome Measures. Added. Hospitalization for angina.

8.6.1 Physical Measures. (See below).

Albuminuria. Added. GFR will be estimated.

Body Composition. Added. DEXA performed at Year 8.

Electrocardiograms. Added. ECGs will be obtained at Baseline and biannually until closeout.

Stored samples and DNA. Amended. DNA samples will be collected at Baseline (and subsequent years, if baseline samples are inadequate).

Table 8.6 Questionnaire and Frequency. Amended. The Dietary Questionnaire will not be obtained beyond Year 4.

8.6.2 Self-Reported Measures. Amended. ***Health behaviors*** will be reported at each annual assessment through Year 4, Year 8 and Year 12 or closeout. The Paffenbarger Questionnaire/Exercise Habits will be administered on all study participants at Year 8 and Year 12 or close-out.

8.8 Data Management. Added. An explanation of privacy disclosure protection covered in the Confidentiality Certificate from the Department of Health and Human Services.

9. Data Analysis. Added. Reference to Appendix H which provides additional details of the major statistical approaches and analyses that will be performed during Look AHEAD.

9.1 Primary and Secondary Hypotheses. Amended - The composite outcomes now defines three secondary hypotheses. The formal subgroups to be assessed are listed in the analysis plan (Appendix H).

9.2 General Statistical Approach. Added. The formal subgroups to be assessed are listed in the analysis plan (Appendix H).

Appendix A. Added - GFR – Glomerular filtration rate.

Appendix C
C.1.4 Primary Outcome Measure. Added. Hospitalization for angina.

C.2. Secondary Outcome Measures. Added. Three secondary outcome measures make up the clusters of events based on the components of the primary outcome measure.

Appendix D. Model Consents. **Added.** Titled each of the consent components
D.1 General,
D.2 General, Phase III,
D.3 Accelerometry,
D.4 Orilistat,
D.5 DNA,
D.6 DNA-NIDDK Repository
D.7 Supplemental General Consent for Use of Stored Blood by Non-Look AHEAD Researchers, and
D.8 Storage of Blood Specimens in NIDDK Repository.

Appendix E. Duality of Interest Policy. Amended. Instructions and reporting form for submitting DOI are accessible via the study web site beginning 2008.

Appendix G. Ancillary Studies Protocol. Amended. Corrected study website address.

Appendix H. Statistical Analysis Plans. **Added new document.**

Summary of Protocol Changes: 6th Revision – August 20, 2007

Sections revised:

3.3.5 Coordinating Center Follow Up of 49 Participants

The Coordinating Center will follow the remaining 49 participant who were a part of the Look AHEAD research study and who did not transfer to the new site when the study moved from UCLA to USC, and will have permanent access to all records. The CoC proposes to track and follow the 49 participants for vital status either with an annual call or by using the internet and Social Security Death Index or similar death search engines until the study ends.

Summary of Protocol Changes: 5th Revision–November 4, 2005

Sections revised:

3.3.4 Phase III (page 15)
Participants in the Lifestyle Intervention will be offered monthly on-site individual contact with a counselor. Open groups will be offered one time per month. Sites will offer one refresher group and one national campaign per year.

5.4.1 Contact Mode and Frequency (page 25)

Phase III (Months 49+) From Month 49 on, participants will be offered monthly on-site individual contact with a counselor. Open groups will be offered one time per month. Sites will offer one refresher group and one national campaign per year.

Table 5.4.1 Look AHEAD Lifestyle Intervention Arm (page 26)

Phase III Months 49 and beyond	Monthly on-site individual contact with a counselor. Open groups offered one time per month. One refresher group and one national campaign offered per year.

Summary of Protocol Amendment to 4th Revision - July 28, 2005

One minor edit was made to the Protocol and resulted in an amendment. Table 8.2 "Measures and Frequency" was amended to indicate that serum and plasma storage will be collected every other year. No change was made to the 4th Revision "Summary of Changes", as it states this measure frequency correctly.

Two minor edits were made to the Phase III Model Consent which are to specify in the Follow-up Procedures Section that the blood draw is "fasting" and in the Other Medical Tests Section, last sentence, eliminate the reference to the accelerometer. For most sites these minor changes may not require any resubmittal of the revised documents to IRB's, however, for the sake of correctness the entire documents will be redistributed to PCs and reposted to the website.

Summary of Protocol Changes: 4th Revision – July 28, 2005

3.3.4 Phase III – Amended frequency of contacts for Lifestyle Participants. Monthly individual session will continue, refresher groups will be offered twice a year and national campaigns will be offered once a year. Monthly contact via phone or e-mail will not be mandatory. Participants assigned to Diabetes Support and Education will be seen once yearly throughout this phase, with the added options of continuing to attend one annual session throughout Phase III and repeat the 3 educational sessions for as long as these are being conducted for participants still in Phase II.

4.4 Informed Consent – Revised and referred to as "Phase III, Beyond Year 4 to End of Trial" and used for the purposes of reconsenting of participants. To the extent to which adjustments to specific study interventions, measurement collection points and data collection forms have been amended and will apply to participants currently enrolled into the study, these changes will be addressed in the content of their appropriate sections of the protocol. Sites' IRB's may require that participants be reconsented at the beginning of the out years phase of the study.

5.3. Deleted reference to "groups".

5.3.1. Corrected text AND deleted the reference to sessions being offered annually to specifically state, "beginning with year 5".

5.3.2. Replaced the reference to "Medical Care" with "Diabetes Support and Education Committee."

5.3.3. Deleted reference to "groups".

5.4.1. Lifestyle Intervention - Contact Mode and Frequency – AND
5.4 Table - Amended contact frequency from two to one on-site individual contact per month. Amended modes of communication in which site may have contact with participant throughout Phase III.

8.1 Overview of Data Collection Schedule for follow-up visits past Year 4. Added note that the Year 8 designation may be changed; it is meant to indicate a single time point in Phase III. Other footnotes included: Urine measure every other year and DEXA measurement at year 8 are dependent upon funding and fitness test at end of study has been omitted. Added text that interviews will be collected at reduced frequency during this phase.

8.2 Measures and Frequency Table – Amended table to add note that serum and plasma storage would occur every other year. Urine measure every other year and DEXA measurement at Year 8 on sub study cohort is dependent upon funding. Removed cardiovascular fitness test on substudy cohort at end of study. Added height measure at Year 4.

8.6 - Other Outcomes – Amended measure point year(s) on following measures: (1) accelerometry, (2) albuminuria, (3) body composition, (4) cardiorespiratory fitness, (5) stored samples and DNA, (6) weight, height, and waist circumference, (7) health behaviors, (8) EuroQol feeling thermometer, (9) health utilities index, (10) quality of life and (11) sociodemographics. Added NOTE (where applicable), that the Year 8 designation may be changed; it is meant to indicate a single time point in Phase III.

8.6 Questionnaires and Frequency Table – Specific frequencies for extended follow-up has been determined and added to table.

12. Amended participating sites to replace UCLA with University of Southern California, Los Angeles, California. Added clinic codes for clarification.

Summary of Protocol Changes: 3rd Revision - May 16, 2003

Deleted text is stricken through
Newly added text is underlined

Termination of 3- and 9-month Contacts

Protocol Section 8.2 Schedule of Data Collection Visits
Follow-up data will be collected through regularly scheduled examinations and telephone interviews as outlined in Table 8.2. Clinic visits will occur annually (Months 12, 24, 36, etc. post-randomization until close-out in 2012). At Months 3 and 9, questionnaires will be mailed to all participants <u>randomized prior to January 1, 2003</u>. Structured telephone interviews will also occur at Month 6 and midway between each annual visit (i.e. at Months 18, 20, 42, etc. until close-out in 2012). These clinic visits and telephone interviews will obtain interim medical history with a special emphasis on cardiovascular disease events, other illnesses, operations, hospital admissions, and alterations in prescriptions. Some will assess aspects of quality of life and health utilities. Each scheduled visit will include a discussion of adherence issues.

Self-Reported Measures

Protocol Section 8.6.2
....
Quality adjusted life years (QALYS) Two common approaches are routinely used to calculate QALYs. One reflects participants' preferences for their health, while the second reflects society's preferences. Both are included in Look AHEAD:

1. <u>EuroQol Feeling Thermometer</u> This is a visual analog scale that assesses participant-based preferences for their current health status.[116,117] It will be measured at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months thereafter through Year 4 <u>on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date.</u>

2. <u>Health Utilities Index</u> This series of questions has been indexed to population norms for health states and allows the estimation of comparable population-based preference weights for quality adjusted life years (QALYs).[118-120] It will be measured at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months through Year 4 <u>on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date.</u>

Total QALYs are then calculated as the sum of the product of the number of years of life and the preference weights in each of those years, for both the study participant's and society's perspectives.

Quality of life The Short Form 36 (SF-36) version will be used to measure general health related quality of life.[126] It can be used to calculate domain scores plus two summary scores: physical summary (four domains, 21 items), and mental health summary (four domains, 14 items). The SF-36 will be collected at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months through Year 4 on participants randomized prior to January 1, 2003; it will be collected at these times except Month 3 and Month 9 for participants randomized on or after this date.

Table 8.6 Questionnaires and Frequency

Measure	**Baseline**	***Months***								**Extended Follow-up**
		6	12	18	24	30	36	42	48	
Costs										
Outpatient visit uestionnaire	x	x	x	x	x	x	X	x	x	
Participant resource use	x		x		x		X		x	
Events										
CVD events and health outcomes		x	x	x	x	x	x	x	x	x
Health Behaviors										
Eating patterns	x		x		x		X		x	
Dietary assessment (N=157 per clinic)+ (THIS CORRECTS A MISTAKE)	x		x						x	close-out in parallel with randomization
Paffenbarger (N=1,200)+	x		x						x	close-out in parallel with randomization
Tobacco and alcohol use	x		x		x		X		x	
Weight control practices	x		x		x		X		x	
Health Outcomes										
Knee osteoarthritis	x		x						x	
Reproductive history	x		x		x		x		x	
Urinary incontinence	x		x		x		x		x	
Symptoms checklist	x		x		x		x		x	
Prescription medication use	x		x		x		x		x	
Psychosocial Measures										
Beck Depression Inventory	x		x		x		x		x	
Eating disorders	x		x		x		x		x	
Quality Adjusted Life Years										
EuroQuol Feeling Thermometer	x	**	x	x	x	x	x	x	x	
Health Utilities Index	x	**	x	x	x	x	x	x	x	
Quality of Life										
Health quality of life (SF-36)	x	**	x	x	x	x	x	x	x	
Sociodemographics	x		x		x		x		x	
Weight, Personal Medical, and Family Medical History	x									

+ Indicates sub study questionnaire

** Indicates administration at Month 3, Month 6, and Month 9 on participants randomized prior to January 1, 2003 and at Month 6 only for participants randomized after this date

Formal Definition of Subgroup Analyses

Protocol Section 9.2 General Statistical Approach
The objectives in Look AHEAD require a broad range of analytical techniques. In reporting Look AHEAD results, we will clearly distinguish between the primary hypothesis and secondary objectives and will discuss results from these different outcome measures appropriately. In this context, we are comfortable with performing significance tests of secondary objectives at 0.05 levels of significance.

Many objectives for Look AHEAD involve comparisons of distributions of times to events. Incidence distributions will be compared using survival analyses. The general approach to these data will follow that for the testing the primary study hypothesis, as described above. Other important questions concern the impact of intervention assignment on clinical measures, laboratory measures, symptoms and events, health-related quality of life, adherence measures, and cost will be assessed. Many of these measures will be collected longitudinally. Both relational and distributional descriptions will be made. Patterns of continuous variables across time, by intervention arm and for various subgroups will be explored by repeated measures methods.[127-129] Patterns of categorical variables across time will be addressed via generalized estimation equations.[130-132] Predictors of outcome and compliance will be identified. Participant adherence data (e.g. self-reported physical activity and attendance at intervention sessions) will be modeled across time and contrasted among interventions. In secondary analyses, adherence data will be used as a predictor variable in modeling intervention efficacy ~~and the relative efficacy of intervention arms will be assessed separately in subgroups defined by factors such as diabetes severity, gender, and ethnicity. The significance of the treatment by time interaction terms will be tested~~.

Look AHEAD will assess, for subgroups of participants, the relative effect of intervention assignment on the incidence of primary and secondary endpoints. Point estimates for the relative hazard of endpoints will be developed for each subgroup and formal tests for the equivalence of these estimates will be conducted. Factors defining the subgroups were selected based on the expectation that they may be important for determining whether weight loss interventions are prescribed for individuals, influencing either the relative success of the intervention in producing and sustaining weight loss or the relationship between weight loss and cardiovascular disease. The formal subgroups to be assessed are listed in the analysis plan.

Correction of Mistakes

Protocol Section 3.3.2 Phase I
The first year after randomization will be Phase I of the study. Participants randomized to the Lifestyle Intervention will be seen four times per month (three group sessions and one individualized session) for six months and then twice per month for six months, with an opportunity for more frequent follow-up. The goal will be to induce a 7-10% weight

loss and to increase exercise to 175 minutes per week. Participants assigned to Diabetes Support and Education will be offered three educational/support sessions. Post-randomization assessments for events will occur at ~~Month 3~~, Month 6~~, and Month 9~~ by phone and at Month 12 during a clinic visit. Most baseline measures will be repeated at Year 1 (see Table 8.2).

Protocol Section 4.10
~~Honarium~~ replaced with Honorarium

Protocol Section 8.6.2 Self-Reported Measures
...
Health behaviors Participants will report on their weight control practices, eating habits, and use of tobacco and alcohol and frequency of self-monitoring blood glucose at each annual assessment. Physical activity will be monitored in 1200 participants through the use of the Paffenbarger Questionnaire at Baseline, Year 1, and Year 4. These same participants will also wear an accelerometer for this period (see above). Dietary intake will be assessed in ~~all~~ the first 157 participants enrolled in each clinic at Baseline, Year 1, Year 4 and close-out.

Summary of Protocol Changes: 2nd Revision – October 28, 2002

Section 1.2 Objective
The primary objective of Look AHEAD is to examine, in overweight volunteers with type 2 diabetes the long-term effects of an intensive lifestyle intervention program designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity. This program is compared to a control condition involving a program of diabetes support and education

Section 1.4 Study Interventions
Eligible volunteers are randomly assigned to an intensive lifestyle intervention or to diabetes support and education. Treatment assignments are unmasked. The lifestyle intervention is implemented with individual supervision and group sessions and is aimed at achieving and maintaining at least a 7% decrease in weight from baseline and 175 minutes per week in physical activity. It is implemented during a four-year period with the most intensive application during the first year, less frequent attention during the next three years, and a minimum of twice yearly contacts during an extended follow-up period. To help participants achieve and maintain weight loss, a variety of diet strategies (e.g. prepared meals and liquid formula), exercise strategies, and optional weight loss medications are utilized based on a preset algorithm and participant progress. Participants assigned to diabetes support and education are offered three sessions each year in diabetes management and social support. Study personnel advise volunteers' health care providers regarding the currently recommended metabolic and blood pressure goals and the therapies necessary to achieve those goals.

Section 3. OVERVIEW OF TRIAL DESIGN
...
Participants will be stratified according to center, and randomly assigned to either Lifestyle Intervention or a control intervention, Diabetes Support and Education. ... The Diabetes Support and Education group will receive sessions of nutrition and physical activity education and social support.

<u>Section 3.1.2 Selection of Interventions</u>
Since Look AHEAD is an efficacy study designed to evaluate the health outcome of lifestyle intervention, a decision was made to compare a control condition of diabetes support and education with a maximal weight loss program (rather than comparing several different approaches to weight loss).

<u>Section 3.2.1 Primary Trial Hypothesis</u>
The primary hypothesis is that the incidence rate of the first post-randomization occurrence of a composite outcome, including

i. cardiovascular death (including fatal myocardial infarction and stroke),
ii. non-fatal myocardial infarction, or
iii. non-fatal stroke

over a planned follow-up period of up to 11.5 years will be reduced among participants assigned to the Lifestyle Intervention compared to those assigned to the control group (Diabetes Support and Education).

Section 3.2.2 Secondary Trial Hypothesis

The secondary trial hypothesis is that the incidence rate of a broad composite secondary outcome consisting of first post-randomization occurrence of

i) death (all cause),
ii) myocardial infarction,
iii) stroke,
iv) coronary artery bypass grafting and/or percutaneous coronary angioplasty,
v) hospitalization for congestive heart failure,
vi) carotid endarterectomy, or
vii) peripheral vascular disease (bypass procedure or angioplasty)

over a planned follow-up period of up to 11.5 years will be reduced among participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.

Section 3.2.3 Other Objectives

...

Costs and cost effectiveness Look AHEAD will estimate cost, cost effectiveness, health state preferences (or "utilities"), and cost-utility ratios associated with its interventions. It will determine the net cost of the Lifestyle Intervention relative to Diabetes Support and Education.

...

General health Look AHEAD will contrast Lifestyle Intervention with Diabetes Support and Education with respect to a number of health conditions that may also influence the overall prescription of weight loss: incident obesity-related cancer, gall bladder disease, fractures, bone mineral density, self report of knee osteoarthritis symptoms and disability, sleep apnea, and urinary incontinence.

Section 3.3.2 Phase I

... The goal will be to induce a 7-10% weight loss and to increase exercise to 175 minutes per week. Participants assigned to Diabetes Support and Education will be offered three educational/support sessions

Section 3.3.3 Phase II

... The goal of Phase II is to maintain a weight loss of 7-10% and an activity level of greater than 175 minutes per week. Participants assigned to Diabetes Support and Education will be offered three educational/ support group sessions each year throughout this phase

Section 3.3.4 Phase III

.... Participants assigned to Diabetes Support and Education will be seen once yearly throughout this phase, with the added options of continuing to attend an annual social

support group throughout Phase III and attending educational sessions for as long as these are being conducted for participants still in Phase II.

Section 3.4 Sample Size Justification

... The rate of primary outcomes among participants assigned to Diabetes Support and Education is expected to be approximately 3.125% per year (see Appendix B for discussion of event rate projection).

Table 3.4 Power to detect a relative 18% decrease in the annual rate of primary outcomes for varying annual event rates among participants assigned to Diabetes Support and Education

Annual Event Rate: Diabetes Support and Education	Maximum Length of Follow-up (Years)					
	9.5	10.0	10.5	11.0	11.5	12.0
2.750 %	0.83	0.84	0.86	0.87	0.89	0.90
3.000 %	0.85	0.87	0.88	0.90	0.91	0.92
3.125 %	0.87	0.88	0.90	0.91	0.92	0.93
3.250 %	0.88	0.89	0.91	0.92	0.93	0.93
3.500 %	0.90	0.91	0.92	0.93	0.94	0.95

Section 4.1 Eligibility Criteria

...

Glycemic control Look AHEAD will enroll individuals whose HbA1c is less than 11 [(1)] or equal to 11%. Individuals whose HbA1c exceeds this level may require more urgent care and will be told to seek treatment. Such individuals may be re-screened after three months to re-assess HbA1c eligibility.

...

Willingness to participate Participants must be willing to be randomized to either Diabetes Support and Education or the Lifestyle Intervention and to follow the protocol to which they have been assigned.

Section 4.7 Randomization Visit

Eligible participants will be randomized to one of the two arms of the study, Diabetes Support and Education or Lifestyle Intervention, according to a randomization scheme that will be controlled by the coordinating center. Randomization will be stratified by clinical center.

Section <u>4.8.1 Retention Promotion Efforts</u>

Retention will be promoted by:

...

2) incorporating a variety of methods to promote contact with all participants and provide social support for all participants, including those in Diabetes Support and Education;

Section 4.10 Participant Honarium
... The honorarium is given for attendance at annual assessments, regardless of level of participation in intervention activities.

Section 5.1 Interventions
Eligible participants are randomized to the two arms of the study: a control group referred to as "Diabetes Support and Education" or to Lifestyle Intervention.

Section 5.3 Diabetes Support and Education
The control group for Look AHEAD is known as Diabetes Support and Education

Section 5.3.1 Contact Mode and Frequency
Participants assigned to Diabetes Support and Education are invited to attend three group educational / social support sessions each year for 4.0 to 6.5 years after randomization.

Section 5.3.2 Content of Educational Sessions
The educational sessions offered for Diabetes Support and Education include one session each year on diet/nutrition and one session related to exercise.

Section 5.3.3 Content of Support Sessions
Support groups are offered annually to participants assigned to Diabetes Support and Education.

Section 5.4.1 Contact Mode and Frequency
Participants assigned to the Lifestyle Intervention will receive education in diabetes management that will parallel sessions provided those assigned to Diabetes Support and Education.

Section 6.1.1 Goals of Medical Care
It is the position of Look AHEAD that all participants, regardless of randomization to Lifestyle Intervention or Diabetes Support and Education, should receive comprehensive management of type 2 diabetes mellitus and of other cardiovascular risk factors, notably, hypertension and plasma lipids.

Section 6.2.1 Hypoglycemia Related to Exercise and Lifestyle Interventions
...
Participants will be educated about symptoms of hypoglycemia, instructed to self-monitor glucose levels, and urged to contact the clinic if they have symptoms or blood glucose values suggestive of hypoglycemia. Look AHEAD clinic staff may reduce medications according to a standard algorithm based on glucose levels and symptoms. Changes in diabetic regimens will be communicated to the participant's primary care physician. Overall management of diabetes medications will remain under the control of the participant's primary care physician.

Section 7.1 Feasibility Evaluation

...

1. To demonstrate success of the intervention at achieving a difference between study arms at one year, there must be at least a 5 percentage points difference in the average percentage point change in weight from Baseline to Year 1 between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.

...

3. ... At Year 2, for the first 25% of participants there must be at least a 5% difference in the average percent change in weight or fitness from Baseline between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.

Section 8.2 Schedule of Data Collection Visits

Follow-up data will be collected through regularly scheduled examinations and telephone interviews as outlined in Table 8.2. Clinic visits will occur annually (Months 12, 24, 36, etc. post-randomization until close-out in 2012). At Months 3 and 9, questionnaires will be mailed to all participants. Structured telephone interviews will also occur at Month 6 and midway between each annual visit (i.e. at Months 18, 20, 42, etc. until close-out in 2012).

Section 8.3 Masking of Data Collection

.... Data collection staff will not be involved in conducting the Lifestyle Intervention or the Diabetes Support and Education sessions.

Section 9.1 Primary and Secondary Hypotheses

....

Alternative methods will be used to describe the distribution of time-to-primary outcome for persons randomized to receive the Lifestyle Intervention and those assigned to receive Diabetes Support and Education

Section 9.3 Economic Evaluation

...

These will be confirmed if the net health benefits of those in the active intervention arm (calculated using a current and acceptable ceiling ratio at end of study) are greater than those in the Diabetes Support and Education arm ($p < 0.05$).

...

Multiple regression analyses will be used to test whether participants assigned to the Lifestyle Intervention have higher summary scores on the SF-36 (Version 2) and significantly higher physical function, energy/fatigue, role-emotional, and pain domain scores than will participants assigned to Diabetes Support and Education.

REFERENCES

38. Wing RR, Jeffery RW. Effect of modest weight loss on changes in cardiovascular risk factors: are there differences between men and women or between weight loss and maintenance? Int J Obesity 1995;19:67-73.

Appendix B.1 Summary

.... Table 3.4 shows the sensitivity of this estimate to changes in the overall event rate and length of follow-up for the primary outcome in the Diabetes Support and Education group.

Appendix D: REPLACED WITH NEW MODEL CONSENT FORMS

Appendix F:

Procedure for Proposing an Ancillary Study in Conjunction with Look AHEAD

.... This form is also available on the Look AHEAD website: www.LOOKAHEAD.phs.wfubmc.edu/. The form may be submitted online or by mail or FAX.

....

Where will the data analyses be conducted? What is the estimated burden to the Coordinating Center?

Summary of Protocol Changes: 1st Revision – May 10, 2001

To: Look AHEAD Steering Committee
Look AHEAD Program Coordinators Committee

From: Look AHEAD Coordinating Center

Date: May 10, 2001

Attached is a revision of the protocol document, which was first approved by the Steering Committee and the Protocol Review Committee in February, 2001. Since then, a number of minor changes in the document have taken place. These include the Items 1-2 (below) discussed during the May 4 Steering Committee, revisions to the informed consent documents (new documents have been added to cover the accelerometry and orlistat), and a few minor word changes and corrections.

1. The name of the control condition has been changed from "Diabetes Education and Support" to "Diabetes Support and Education."

2. Two sentences in Section 6.2.1 have been deleted. "To reduce the risk of hypoglycemia, participants on medications that may increase the risk of hypoglycemia will be called within two weeks, or as needed, after starting their intervention to inquire about hypoglycemic symptoms and any self-monitored blood glucose values. This will be done for both groups."

We are labeling this document as the "1st Revision". Our plan is for all subsequent versions to be sequentially numbered (as well as dated) and for any new revisions to be indicated with editing symbols (including striking out any deleted text).