CHAPTER 21

Safety Management

(Revised 02/21/2012)

Summary of Changes:

21.4. Hypoglycemia Management

Added definition of serious hypoglycemia.

CHAPTER 21

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CHAPTER 21

SAFETY MANAGEMENT

21.1. SAFETY MANAGEMENT OVERVIEW

Safety management in Look AHEAD is intended to achieve six objectives: 1) to minimize the occurrence of adverse effects, especially those related to interventions; 2) to effectively manage adverse events as they relate to the study; 3) to identify when Look AHEAD interventions should be suspended because of concerns for participant safety; 4) to determine when interventions may be resumed after having been suspended; 5) to monitor whether participants have medical care and assist them in identifying care if necessary; and 6) to provide information to the participant and the Primary Care Provider (PCP) related to management of type 2 diabetes, hypertension, dyslipidemia and other cardiovascular disease risk factors.

Each Look AHEAD investigator will have primary responsibility for the safety of participants as it relates to the study protocol. The Data Safety Monitoring Board will have responsibility for monitoring study data for evidence of adverse effects attributable to participation in Look AHEAD.

21.2. SAFETY CONSIDERATIONS WITH RESPECT TO STUDY PROTOCOL

As described in Chapter 11, the Look AHEAD trial will not directly provide medical care to participants in either the Intervention or Diabetes Support and Education arms. Instead, participants will receive medical care from a PCP. Medical therapy to achieve contemporary standards of control of hyperglycemia, lipids, and blood pressure will, accordingly, be the responsibility of a participant and his or her PCP. These will not be considered safety issues except when

alert levels are reached. These alert levels are defined in this chapter of the MOP.

During screening, each participant should have a history and physical examination performed by Look AHEAD medical staff or medical staff performing the graded exercise test. The details of the examination should be recorded in the local clinic chart.

21.3. DIABETES

Hemoglobin A1c values will be measured at baseline and annually and reported to each participant and his or her PCP. The target for this assay is the American Diabetes Association recommended goal of < 7.0% which will be included in these reports, together with prior values for HbA1c obtained during Look AHEAD. The report will list a goal of < 7%, borderline values of 7 – 8 % and high values of > 8%.

21.4. HYPOGLYCEMIA MANAGEMENT

Exercise and reduced caloric consumption are effective for reducing hyperglycemia in type 2 DM. However, in individuals treated with insulin, sulfonylureas, repaglinide or nateglinide, exercise and reduced caloric consumption can provoke symptomatic hypoglycemia. For all participants (Diabetes Support and Education and Lifestyle Intervention), regardless of diabetic medication regimen, an education program will be provided and will include information regarding symptoms and signs of hypoglycemia, instruction in the use of home blood glucose monitoring to detect hypoglycemia, and instruction on treating hypoglycemia.

In Look AHEAD, the main priority with respect to weight loss will be to avoid serious hypoglycemia. Thus, additional safety measures will be directed at those

participants who are randomized to the Lifestyle Intervention arm and who are receiving insulin, sulfonylureas, repaglinide or nateglinide. These additional safety measures are planned to coincide with the initiation of the intervention program and will concentrate on the early weight loss intervention. It is anticipated that this will be the interval of greatest identifiable risk for hypoglycemia.

Serious hypoglycemia is defined as any episode of loss of consciousness or level of confusion that prevented self-treatment or requires hospitalization or emergency care.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolved on their own or within 15 minutes of such self-treatment.

For participants randomized to the Diabetes Support and Education arm, it is difficult to anticipate when, or under what circumstances, weight loss efforts will be undertaken. Thus, it is not practical to implement the same type of risk management plan for both arms of Look AHEAD. The participants in the Diabetes Support and Education arm will receive, as part of the diabetes education program, information on hypoglycemia. They will be instructed to seek the advice of their PCP for specific recommendations for adjusting medication. However, if a participant in the Diabetes Support and Education arm contacts Look AHEAD staff with questions about hypoglycemia, or to report hypoglycemia, the medical staff will provide advice and assistance.

During periods of weight loss, participants in the Lifestyle Intervention arm who are taking insulin, sulfonylureas, repaglinide or nateglinide may need reductions in diabetes medication(s) to reduce their risk of hypoglycemia. Medication

reduction for participants will be conducted by Look AHEAD medical staff and communicated to both the participant and the intervention staff. At the time participants are enrolled, a colored sticker should be placed on the participant's chart to identify those participants who will need to be considered for reduction of medication. However, it is clearly not desired that these reductions in diabetes medication(s) lead to long-term deterioration in glycemic control. Once a period of heightened risk for hypoglycemia has passed, it may be necessary for Look AHEAD medical staff to return doses of diabetes medication(s) to baseline levels. The Look AHEAD medical staff should notify the participant's PCP that changes in diabetic medications may be made to prevent hypoglycemia. The protocol for reduction is described below. Hypoglycemia Risk Reduction: Plan A should continue to be used for newly randomized participants entering the first 6 months of the Intervention Arm of Look AHEAD. Hypoglycemia Risk Reduction: Plan B is a modification of this prior algorithm.

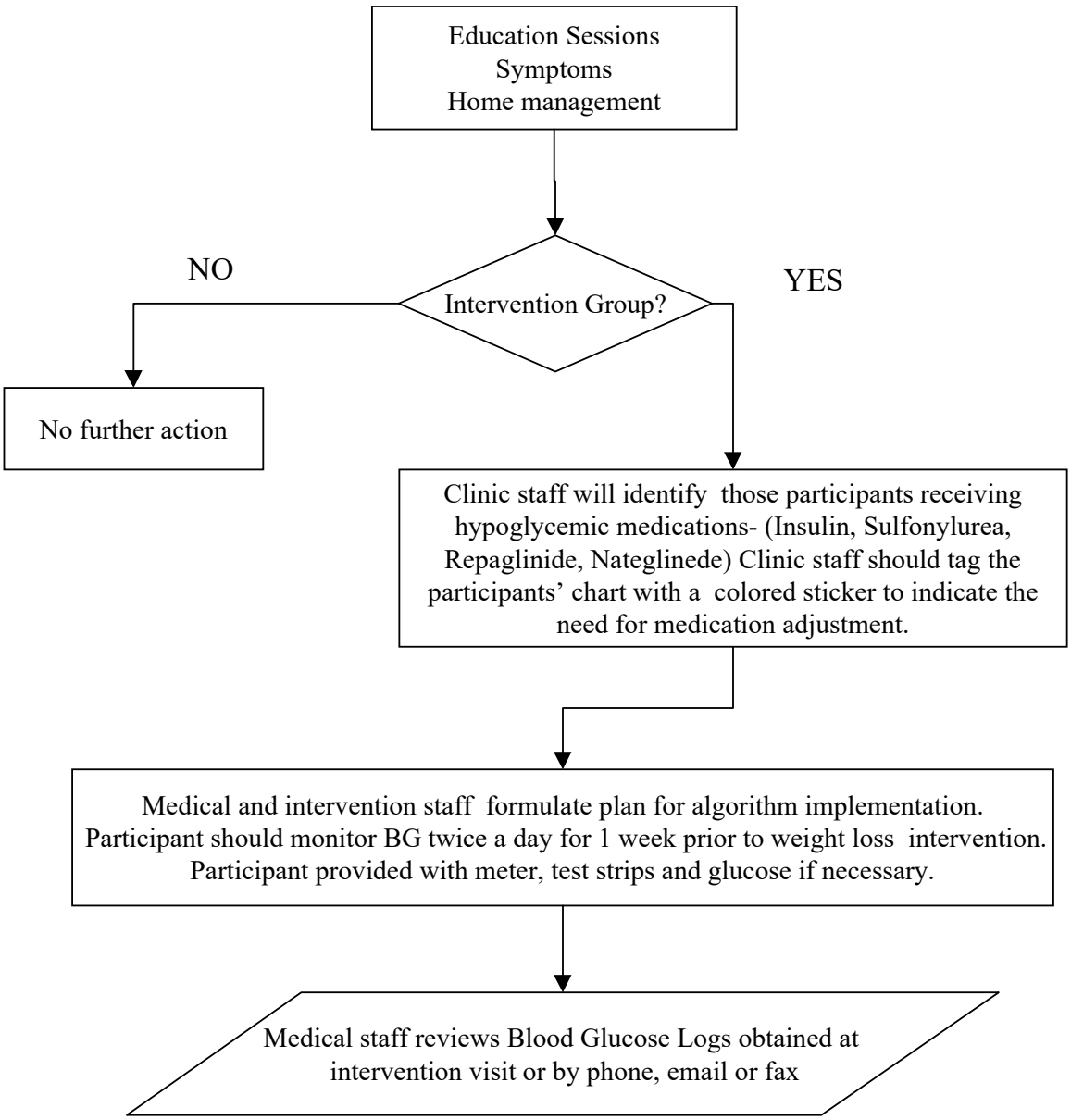
Hypoglycemia Risk Reduction: Plan A

Figure 1 (hypoglycemia management algorithm) describes the protocol for managing hypoglycemic medications in participants in the Lifestyle Intervention arm during periods when active weight loss might put the participant at risk of hypoglycemia. Prior to initiation of this algorithm, Look AHEAD medical staff and intervention staff will meet to formulate a plan for coordinating implementation of the hypoglycemia management algorithm with the Lifestyle Intervention. This plan will include delineation of responsibilities for: (1) informing participants when blood glucose monitoring should be performed; (2) obtaining participants' blood glucose records for review; and (3) communicating medication adjustments to the participant.

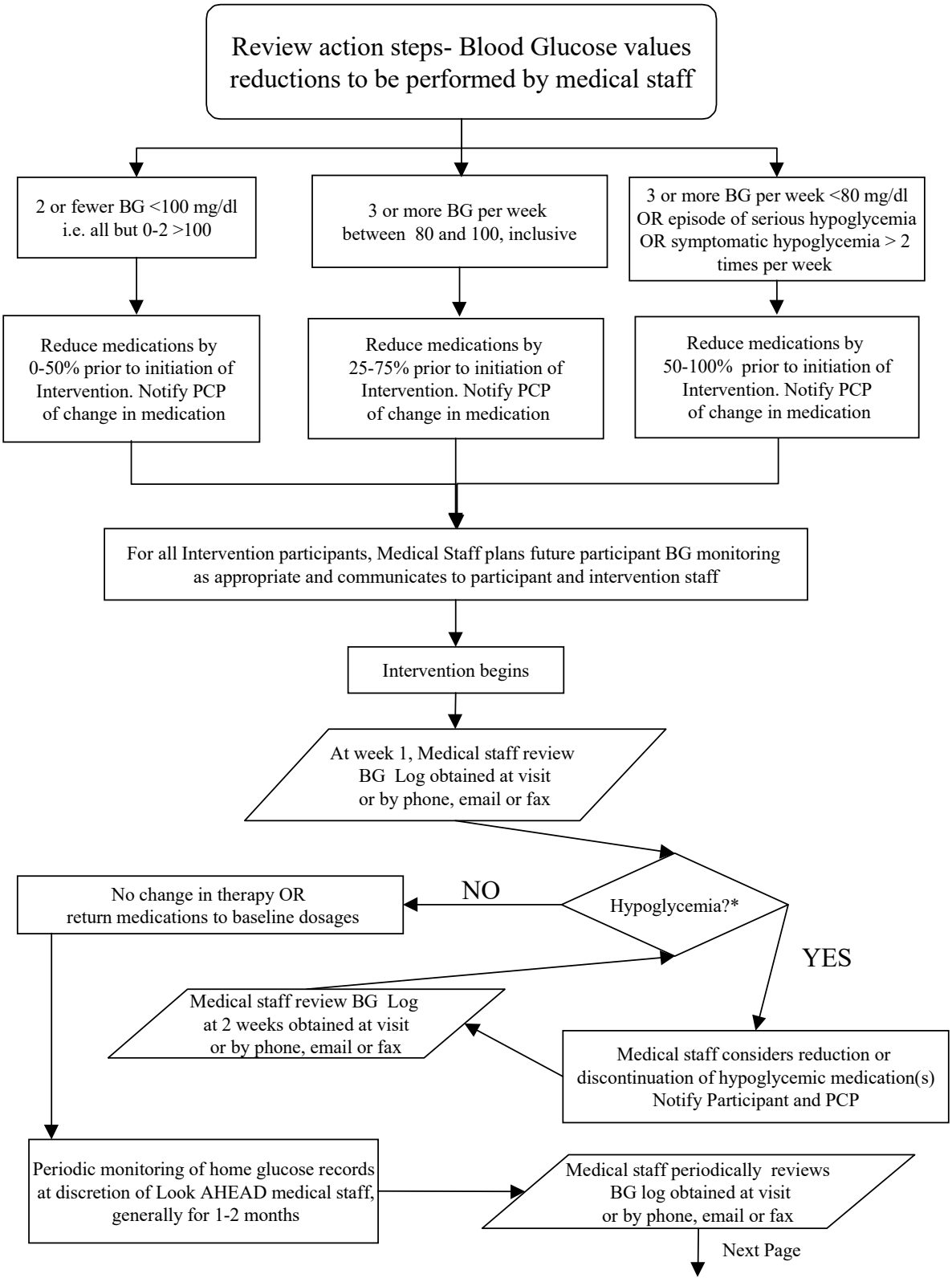
Implementation of the hypoglycemia management algorithm will be documented by medical staff on the Look AHEAD Medication Reduction form.

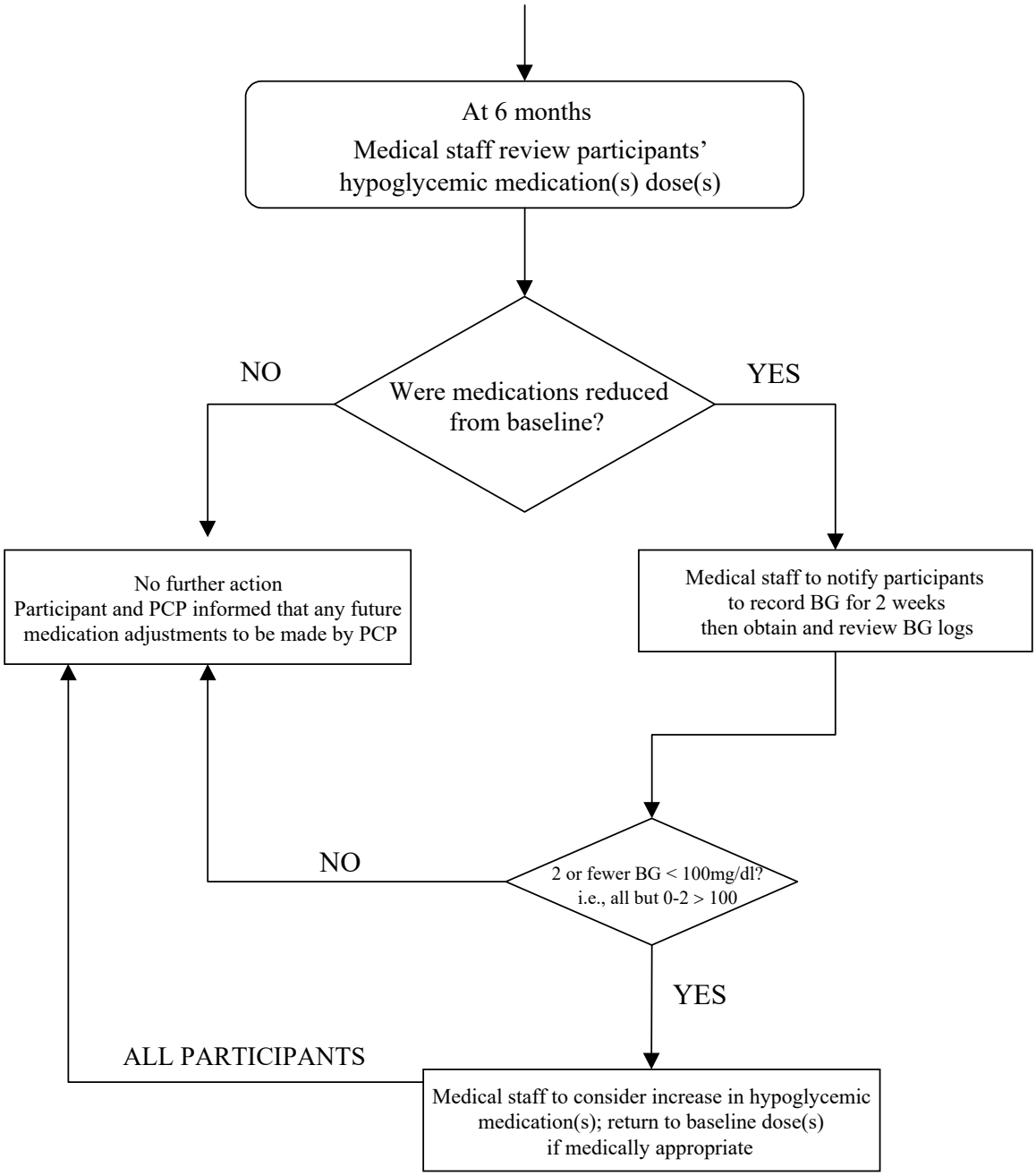
If, at any time, a participant in the Lifestyle Intervention arm is to receive a new weight loss intervention (e.g., formula diet, weight loss medication), the interventionist should contact the medical staff to review the current diabetes pharmacological management of this participant. Any recommendations to reduce diabetes medication(s) should be communicated to the participant and the intervention staff. As the new intervention is initiated, on-going communication between the interventionists and the medical staff is strongly encouraged.

Figure 1. Hypoglycemia Management Algorithm



Go to Action Steps
Next Page


Review action steps- Blood Glucose values reductions to be performed by medical staff
2 or fewer BG <100 mg/dl i.e. all but 0-2 >100
3 or more BG per week between 80 and 100, inclusive
3 or more BG per week <80 mg/dl OR episode of serious hypoglycemia OR symptomatic hypoglycemia > 2 times per week
Reduce medications by 0-50% prior to initiation of Intervention. Notify PCP of change in medication
Reduce medications by 25-75% prior to initiation of Intervention. Notify PCP of change in medication
Reduce medications by 50-100% prior to initiation of Intervention. Notify PCP of change in medication
For all Intervention participants, Medical Staff plans future participant BG monitoring as appropriate and communicates to participant and intervention staff
Intervention begins
At week 1, Medical staff review BG Log obtained at visit or by phone, email or fax
Hypoglycemia?*
NO
No change in therapy OR return medications to baseline dosages
YES
Medical staff review BG Log at 2 weeks obtained at visit or by phone, email or fax
Medical staff considers reduction or discontinuation of hypoglycemic medication(s) Notify Participant and PCP
Periodic monitoring of home glucose records at discretion of Look AHEAD medical staff, generally for 1-2 months
Medical staff periodically reviews BG log obtained at visit or by phone, email or fax
Next Page


At 6 months
Medical staff review participants' hypoglycemic medication(s) dose(s)
Were medications reduced from baseline?
NO
YES
No further action
Participant and PCP informed that any future medication adjustments to be made by PCP
Medical staff to notify participants to record BG for 2 weeks then obtain and review BG logs
2 or fewer BG < 100mg/dl? i.e., all but 0-2 > 100
NO
YES
ALL PARTICIPANTS
Medical staff to consider increase in hypoglycemic medication(s); return to baseline dose(s) if medically appropriate

BG = blood glucose

PCP = primary care provider

Serious hypoglycemia = hypoglycemia with loss of consciousness or a level of confusion that prevented self-treatment.

*Hypoglycemic Decision Point = One episode of serious hypoglycemia, symptomatic hypoglycemia > 2 times per week, OR BG frequently < 100 mg/dL.

Prior to initiating the calorie restriction component of the Lifestyle Intervention program, participants treated with insulin, sulfonylureas, repaglinide or nateglinide will be asked to start monitoring blood glucose at least twice daily. Participants should be encouraged to monitor before breakfast, before meals and at bedtime. After at least one week of blood glucose data have been collected, the blood glucose data should be used to pre-emptively reduce hypoglycemic medication according to the following scheme:

If three or more blood glucose values per week are less than 80 mg/dL, or if the participant is experiencing symptomatic hypoglycemia more than two times per week or if the participant has experienced an episode of serious hypoglycemia during the monitoring period (defined as hypoglycemia with loss of consciousness or a level of confusion that prevented self-treatment), the Look AHEAD medical staff (MD, PA, RN, NP, LPN) guided by the hypoglycemia management algorithm, and under the direction of the Look AHEAD MD, should reduce hypoglycemic medication by 50% to 100%.

If the above criteria are not met but if three or more blood glucose values per week are between 80 and 100 mg/dL, hypoglycemic medication should be reduced by 25% to 75%.

If neither of the above criteria is met and if two or fewer blood glucose values per week are less than 100 mg/dL; i.e., if most blood glucose values are ≥ 100 mg/dL, it is recommended that clinical judgment be used and doses of hypoglycemic medication be reduced by 0% to 50%.

Any recommended reductions in insulin, sulfonylureas, repaglinide or nateglinide should be made before the weight loss intervention is initiated. This applies to the initial weight loss intervention and any weight loss intervention that is initiated later in Look AHEAD. As a new intervention is initiated, on-going communication between interventionists and medical staff is strongly encouraged.

This scheme is intended as a general guide. A Look AHEAD physician or nurse should use clinical judgment to modify these recommendations for specific circumstances of any participant.

21.4.1. Follow-up Procedures to Monitor Hypoglycemia Risk and Management

After the weight loss intervention has been started (generally week 3 of the intervention), participants on insulin, sulfonylureas, repaglinide or nateglinide will be asked to provide one or more weeks of blood glucose records for review. These records should be brought to a group intervention session. Participants will also be asked to promptly report episodes of serious hypoglycemia, blood glucose values <100 mg/dL three or more times per week, or symptomatic hypoglycemia >2 times per week to the intervention staff. This process of reviewing records should continue until the blood glucose records satisfy the following criteria:

(1) no episode of serious hypoglycemia,

(2) symptomatic hypoglycemia no more often than two times per week, and

(3) blood glucose values infrequently less than 100 mg/dL.

If the risk of hypoglycemia has not been adequately reduced, doses of hypoglycemic medication(s) should be reduced again or discontinued if appropriate.

The length of monitoring by Look AHEAD personnel will vary depending upon the circumstances of a specific participant, but in general will not exceed several months. The participant's PCP should be informed of any changes in diabetes medication made by Look AHEAD staff during the management of hypoglycemia.

In the event of serious hypoglycemia, clinic staff should remember to document these episodes on the Serious Adverse Event form.

21.4.2. Returning Medications to Baseline Levels

At six months, participants who had their doses of hypoglycemic medication(s) reduced by Look AHEAD medical staff will be asked to record blood glucose values for two weeks and provide a record of those values. If there are two or fewer blood glucose values per week <100 mg/dL, increasing the hypoglycemic medication(s) should be considered. Subsequently, hypoglycemia monitoring by Look AHEAD medical staff will stop and the participant will be informed that future medication adjustments should be made by his or her PCP. The PCP should be informed by letter of any changes from baseline in hypoglycemic medication(s).

The medical staff should plan to systematically review, at six months, the glycemic control of all participants for whom hypoglycemic medication(s) were reduced to prevent hypoglycemia. As a safeguard, the interventionists should contact the medical staff as the six-month mark approaches to make sure the review takes place.

This process may be repeated for each successive weight loss intervention. The need for pre-emptive medication reduction should be based on the potential for the intervention to cause hypoglycemia.

Look AHEAD participants at risk of hypoglycemia who do not have blood glucose monitoring equipment will be provided with a blood glucose meter and sufficient test strips to monitor blood glucose for at least two months. Clinics may provide glucose tablets if necessary.

21.4.3. Hypoglycemia Risk Reduction: Plan B

Introduction:

An algorithm for reducing the risk of hypoglycemia during the initial weight loss and physical activity phase of the first 6 months of the Intervention Arm has already been developed. Plan B, the algorithm described in this section, is intended to be used during other periods that re-emphasize calorie restriction at times after the initial six months.

Indications for Use:

Hypoglycemia Risk Reduction: Plan B is to be used when the Intervention Arm plans scheduled "special" periods of reducing calories. One particular instance is the plan to systematically re-introduce meal replacements toward the end of the first year of Intervention. Other instances may be more individualized, such as those that entail use of the Intervention Tool Box. If uncertain as to whether one of the options of the Tool Box should trigger use of this Hypoglycemia Risk Reduction algorithm, please consult with the Principal Investigator or appropriate Look AHEAD medical staff. The Hypoglycemia Risk Reduction: Plan B is not intended to be continuously used throughout the Intervention. This would be a breach of the protocol and would be an over-application of medical monitoring by the Look AHEAD medical staff. Instead, the use of this algorithm is intended to be for relatively short-term periods and to be restricted to those instances when

the Look AHEAD Intervention introduces new aspects of treatment that reduce caloric intake and therefore raise short-term concerns about an increased risk for inducing hypoglycemia.

Identifying Participants at Risk: As with the Hypoglycemia Risk Reduction algorithm used during the first 6 months of Intervention, the modified algorithm should only be applied to certain participants. With calorie restriction, the risk for hypoglycemia is only present in those taking certain medications. These medications are listed below:

Insulin (any form of insulin)

Sulfonylureas (e.g. glyburide, glipizide)

Meglitinides (e.g. repaglinide, nateglinide)

If a participant is not taking one of the above medications, the Hypoglycemia Risk Reduction: Plan B does not need to be used, unless there are other unusual circumstances for a participant specifically identified by the medical staff of Look AHEAD.

Assessing Current Risk of Hypoglycemia: If prior conditions are met, then the individual risk of hypoglycemia needs to be appraised. In addition to the type of medication being used, risk for hypoglycemia is related to current levels of glucose control and also, to any past experience of the participant that indicates vulnerability for hypoglycemia during periods of reduced calorie intake; in particular, the experience during the first six months of Look AHEAD should be considered. In general, an individual for whom a majority of blood glucose values are near the target range for control of type 2 DM is at greater risk of hypoglycemia with a reduction of calorie intake than is someone in whom most blood glucose values exceed desired target values. One exception to this general rule is a patient with diabetes mellitus in whom blood glucose values fluctuate broadly from marked hyperglycemia to periodic episodes of

hypoglycemia, though this pattern is quite uncommon in type 2 DM and is most often observed in type 1 DM.

Risk Stratification Based on Current Levels of Glucose Control

Current Glucose Control	**Risk**	**Action**
BG<80 mg/dl, an episode Of serious hypoglycemia in the Past month or symptomatic Hypoglycemia >2 times per Week	**High**	**Reduce Medication by 50-100%**
Two or more BG values 81-100 mg/dL	**Moderate**	**Reduce Medication by 0 to 50%**
BG consistently above 100 mg/dl	**Low**	**No Change**

The best measure of current glucose control is to review recent values for home monitoring of blood glucose, especially values obtained fasting and pre-meal. If a participant has 2 or more values obtained weekly for a several week period prior to starting the new phase of intervention, then the Look AHEAD staff should use this information to make their judgment of risk. If these values are not available, then request that 2 or more blood glucose values per week be obtained for at least 2 weeks. Clearly, with more information, a clearer the assessment can be made. Pragmatically, however, it may be difficult to obtain frequent monitoring values and the minimum should be at least 2 values weekly over a 2 week period.

If a participant is taking a medication described above, but will not or can not provide any home monitoring values, then alternatives are to a) defer the intervention until home blood glucose values can be obtained; b) obtain the

cooperation of the PCP; or 3) arrange unscheduled medical visits to measure blood glucose at least twice a week over a two week period. Any of these options is far from ideal.

Follow-up:

In Plan A, a formal follow-up plan was used. This approach can certainly be used again but in most instances this may be more than is actually needed. A minimum should be to re-instruct the participant in signs and symptoms of hypoglycemia and instruct him / her to contact Look AHEAD (ideally, the medical staff) if more than 2 mild episodes occur weekly or if a single serious episode occurs, or if he / she needs to eat extra amounts to prevent episodes of hypoglycemia. If one of these circumstances arises, then medications should be further reduced or discontinued. The medical staff of Look AHEAD should then re-contact the participant after one week to ascertain whether further reduction in medications is necessary. A follow-up contact should occur after any dose reduction.

Re-adjusting medications at the completion of this phase of Intervention:

As it is the policy of Look AHEAD to not take long-term responsibility for adjustment of diabetes medications, staff should make it clear to the participant when this period of altering doses of medication has come to an end. At the end of this period, if the intervention has achieved new amounts of weight loss and activity, the participant may need less medication that at the start. In an opposite manner, medications might need at this time to be re-adjusted to higher doses. At the end of the intervention, Look AHEAD staff should review current blood glucose values from those subjects who had a reduction in medication and should recommend an increase in medication back to or toward the pre-intervention dose, when appropriate. The volunteer should be instructed to seek the opinion of his / her PCP as to any subsequent changes in the dose of

medication. A post-intervention letter can be sent to the PCP providing information on the changes made, the nature of the recent intervention, and asking the PCP to assume management of any further medication changes.

This scheme is intended as a general guide. Look AHEAD medical staff should use its clinical judgment to modify these recommendations for any specific circumstances of a participant.

21.5. PLASMA LIPIDS

Fasting plasma lipids will be measured at baseline and annually. These values will be reported to each participant and his or her PCP along with recommended guidelines. The goals are as follows:

LDL cholesterol: < 100 mg/dL

Triglycerides: < 200 mg/dL

HDL cholesterol for men: > 45 mg/dL

HDL cholesterol for women: > 55 mg/dL

It will be the responsibility of the PCP to take action to achieve these goals.

An alert value has been set for fasting plasma triglycerides of ≥ 1000 mg/dL since values above this level are associated with an increased risk of pancreatitis. If triglyceride values exceed these levels, Look AHEAD medical staff will contact the participant and his or her PCP within one week and encourage intervention.

21.6. BLOOD PRESSURE

21.6.1. Hypertension

Blood pressure will be measured at baseline and annually and reported to each participant and his or her PCP along with the recommended JNC VI goal of 130/80 mmHg. It will be the responsibility of the PCP to take action to achieve this goal.

The alert values for hypertension are taken from JNC VI. If blood pressure is greater than 170 mmHg systolic or 100 mmHg diastolic at any study visit, the participant will be advised of the problem and the PCP will be called within one week. The participant will be asked to see his or her PCP for evaluation. The participant will be instructed to suspend Look AHEAD interventions involving exercise until blood pressure is controlled. Before exercise is restarted, the participant should return to the Look AHEAD clinic for a blood pressure check. Optimally, this should occur within six weeks.

21.6.2. Hypotension

In participants receiving pharmacological agents to reduce blood pressure, weight loss and exercise interventions can increase the risk of hypotension. During Look AHEAD, if a participant reports symptoms attributable to hypotension, such as lightheadedness upon standing, blood pressure should be checked. If appropriate, the participant should be referred to their PCP for this blood pressure check. If not appropriate, the blood pressure should be measured by the Look AHEAD clinic staff. Consideration should be given to other indications for which the participant might be taking these medications such as migraine headaches, angina, congestive heart failure or other medical conditions. If feasible, blood pressure medication changes should be made by the PCP or by Look AHEAD staff after consultation with the PCP. A decision should also be made as to who will be responsible for monitoring blood pressure after a medication reduction. If done in the Look AHEAD clinic, participants should have blood pressure checked by clinic staff at one and three weeks. If

blood pressure medications are adjusted by the Look AHEAD clinic staff, they should fill out a Look AHEAD Medication Modification form.

21.7. SAFETY CONSIDERATION FOR INTERVENTIONS

21.7.1. Safety Considerations for Initiating Exercise

Since all Look AHEAD participants will have passed a maximal exercise test prior to randomization, all participants will be eligible to begin an exercise program immediately after randomization. Look AHEAD staff, including lifestyle interventionists, should be familiar with the warning signs of heart attack and stroke. It is recommended that Look AHEAD staff who supervise exercise activity be trained in basic life support procedures. If a participant reports to the study staff, either at a regularly scheduled visit or otherwise, symptoms consistent with cardiac disease, stroke or transient ischemic attack (TIA), or develops such symptoms during Look AHEAD activities, these symptoms should be evaluated either by Look AHEAD medical staff, by the participant's PCP, or by sending the participant to the emergency room. The decision as to who should evaluate these symptoms should be based on the location of the participant at the time of the report and the nature of the complaint. If the Look AHEAD physician or other medical staff concludes that the symptoms, exam findings or electrocardiogram may be due to cardiac disease or cerebrovascular disease, exercise will be suspended and the participant will be referred to his or her PCP for a more complete evaluation. The exercise intervention should not be resumed until the safety criteria described below have been addressed.

21.7.2. Safety Recommendations for Resumption of Exercise after a CVD Event

Look AHEAD recognizes the guidelines of the American College of Sports Medicine (ACSM), the American Heart Association (AHA), and the American

Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) when considering resumption of exercise for a participant following a CVD event. These guidelines provide criteria for risk stratification and recommendations for medical supervision during exercise training. Nevertheless, no set of guidelines for risk stratification, exercise testing, and exercise training cover all potential participant circumstances. These guidelines, for the most part, are based on the results of exercise testing and structural and functional assessment of the cardiovascular system. However, they do not consider co-morbidities such as diabetes, hypertension, obesity, and hypercholesterolemia that further adversely affect risk during exercise.

It is recommended that all participants join a cardiac rehabilitation program after an event. After a period of recovery, usually two to three months for uncomplicated myocardial infarction, two to three months for coronary artery bypass surgery, and one to two months for PTCA, participants should be evaluated by the PCP, cardiologist or Look AHEAD medical staff for resumption of the intervention. It is recommended that the evaluation include an exercise stress test to assess the participant's ability to resume a moderate intensity exercise program without medical supervision. In most cases, the PCP or cardiologist caring for the participant will be responsible for conducting this treadmill test.

Unsupervised exercise interventions may also be stopped by the Look AHEAD medical staff for reasons of increased angina, dyspnea, fatigue or other symptoms for which medical evaluation is deemed appropriate. If a CVD event has not occurred, unsupervised exercise can be resumed without the need for a repeat treadmill test. One example might be an increased frequency of angina but without evidence of MI. <u>After participants have completed a medical evaluation by their PCP, Look AHEAD medical staff should obtain written approval from the PCP for the participant to resume unsupervised exercise.</u>

Look AHEAD staff should not resume unsupervised physical activity without the permission of the cardiologist or PCP. A letter should be sent to the cardiologist and or PCP with Guidelines for Resuming Physical Activity after a Cardio-Vascular Disease Event (Appendix A and B, found at the end of this chapter). The letter provides the following check boxes for the physician:

Resume prior unsupervised physical activity program

Discontinue unsupervised physical activity program

Modify physical activity program in the following manner.

Since after an event, participants might be at increased risk for another event, the Look AHEAD medical staff should consider one or more of the following options to safely re-introduce exercise. First, participants should be re-instructed on self-monitoring (pulse and RPE) and to promptly re-contact their PCP and halt exercise if symptoms recur on resuming exercise. Second, Look AHEAD staff may decide to have a participant resume exercise under supervised conditions, such as one or two sessions at the Look AHEAD site. Third, depending on the individual circumstances, participants may be instructed to resume exercise on a more restricted basis and to gradually increase duration or intensity of exercise. Fourth, Look AHEAD medical staff may decide to contact the participant several weeks after exercise is resumed in order to monitor whether there has been recurrence of prior symptoms.

21.7.3. Additional Safety Considerations for Exercise

Foot Care

Because diabetes mellitus increases the risk for foot ulceration, use of proper footwear during exercise is essential for all participants. The use of silica gel or

air midsoles is to be encouraged, as is the use of polyester or cotton-polyester blend socks to keep the feet dry and prevent blisters. Participants should also be taught to inspect their feet for blisters and other damage daily. For participants with severe peripheral neuropathy, insensitivity to monofilament testing, or the presence of a foot ulcer, non-weight-bearing exercise will be recommended, such as swimming and bicycling. For participants with severe neuropathy, walking for more than 30 minutes should be avoided.

Hypoglycemia

Exercise can provoke hypoglycemia in individuals with type 2 diabetes although this risk is limited to those receiving insulin, sulfonylurea, repaglinide or nateglinide. All participants in Look AHEAD will receive education on the risk of hypoglycemia. Participants will be encouraged, though not required, to perform self-monitoring of blood glucose before and following exercise sessions to determine the effect of exercise on blood glucose. Participants will be encouraged to review this information with their PCP or with the Look AHEAD medical staff. Participants will be instructed to carry a small amount of carbohydrate (e.g., glucose tablets or hard candy) in the event they experience a hypoglycemic reaction while exercising.

21.8. INTERVENTIONS

21.8.1. Lifestyle Modification

Since lifestyle modification includes caloric restriction and regular exercise, procedures for monitoring for hypoglycemia and adjusting hypoglycemic medications and procedures for exercise should be initiated along with the intervention. See Section 21.4, Hypoglycemia Management.

21.8.2. Orlistat

If a participant is started on orlistat, the PCP will be notified. Orlistat (Xenical) is an inhibitor of pancreatic lipase that interferes with the digestion of dietary fat. At recommended doses, about 30% of ingested fat is lost in the stool. Orlistat is indicated for people with diabetes and BMI > 27 kg/m^2 at the time of drug initiation. Orlistat is contraindicated in people with chronic malabsorption problems, cholestasis (e.g., active gallbladder disease) or a history of hypersensitivity (e.g., allergic reaction) to orlistat. If appropriate, clinic staff may suggest that pre-menopausal women contact their PCP for birth control advice when taking orlistat.

The manufacturer's recommended dose of orlistat is one 120 mg capsule three times daily with each meal containing fat. Orlistat should be taken during or up to one hour after meals. To reduce side effects, orlistat should be used with a reduced fat diet providing only about 30% of calories as fat. Adverse effects are primarily gastrointestinal and include oily stools, oily spotting, and flatus with discharge, fecal urgency and increased defecation.

Because orlistat may interfere with the absorption of fat-soluble vitamins, participants treated with orlistat should take a multivitamin that contains fat-soluble vitamins (vitamins A, D, E and beta-carotene) provided by the study. The multivitamin should be taken two hours before or after orlistat. Orlistat should not be given to participants receiving cyclosporine. If orlistat is given to participants receiving warfarin (coumadin), a coagulation parameter such as INR should be monitored.

When orlistat is initiated, procedures for monitoring for hypoglycemia and adjusting hypoglycemic medications should be initiated. Pre-emptive reduction

of hypoglycemic medication(s) should not usually be necessary. If a participant is concerned about side effects caused by orlistat, he or she should be encouraged to contact Look AHEAD medical staff to discuss the side effects. The participant will, of course, have the option to discontinue orlistat.

21.8.3. Pregnancy or Nursing

If a participant in the Lifestyle Intervention arm becomes pregnant, the weight loss intervention should be suspended until after delivery or after the weaning if the participant is nursing. Clinic or intervention staff should notify the coordinating center in writing of any pregnancy.

Orlistat should not be used by pregnant or nursing women. If a participant becomes pregnant while taking orlistat, the medication will be stopped until she is six months post-partum or after nursing has stopped.

21.8.4. Interventions Which May Be Added Later

If additional weight loss interventions are added to the protocol at later time points, specific safety monitoring procedures are found under Section 21.4.3 Plan B.

21.9. Look AHEAD ALERTS

There are several types of alerts in Look AHEAD. The table below describes a summary of alerts and the appropriate action.

ALERT	ACTION
Blood Pressure SBP > 170mm/Hg or DBP > 100mm/Hg	Clinic staff will inform the participant and call PCP within one week
Triglycerides	Clinic staff will inform the participant and

TG ≥ 1000 mg/dl	call PCP within one week
Estimated Glomerular Filtration Rate (GFR) GFR < 60mL/min/1.73m2	Clinic staff will note alert in chart and send central lab report, positive GFR letter, and NIDDK brochure to participant within one week. The PCP letter and central lab report should be sent to the participants PCP within one week. It is at the discretion of the Look AHEAD MD to determine if the GFR score is significantly high to warrant an SAE form being filled out. A GFR score <60 will not constitute an SAE but the participant and PCP should be notified.
Serum Creatinine > 2	Note alert in chart and send central lab report to participant and PCP
HbA1c > 12	Note alert in chart and send central lab report to participant and PCP
Any laboratory values which Look AHEAD MD defines as significantly high	Note alert in chart and send central lab report to PCP
Bone mineral density on DEXA decreases by > 10% for spine or hip at Month 12 Cumulative BMD decreases > 12% from Baseline to Month 48 for spine or hip	Repeat scan according to Excessive Bone Loss Procedures, Chapter 17. If excessive bone loss is confirmed by DEXA Reading Center, follow procedures in Section 17.3.1. of the MOP for informing participant and PCP
MOODS Questionnaire, if question 9, item 2 or 3 is checked	Immediate evaluation by medical staff and appropriate intervention initiated. See Section 21.11. No PCP letter is sent.
MOODS Questionnaire, total score ≥ 24	Qualified staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation. No intervention. No PCP letter.
ECG – Printout report Atrial fibrillation – if new finding since previous ECG Atrial flutter Ventricular tachycardia Acute myocardial infarction Complete atrioventricular block Bradycardia with heart rate < 40	In the case of any of these alert statements, the tracing should be reviewed by a clinic physician who will decide if any further action is needed. It is not advisable to alarm the participant by revealing these unconfirmed interpretative statements. However, it is helpful to casually inquire if the person has recently had chest pain or discomfort. A negative answer does not mean that the alert can be ignored because heart attacks can be asymptomatic (silent). These "asymptomatic alerts" are less urgent than alerts associated with recent chest pain/discomfort or fainting attacks.

	See Chapter 21, Section 21.11. for further procedures.

21.9.1 Glomerular Filtration Rate (GFR) Alert

In the past, most physicians judged how well the kidneys were working by the blood creatinine level. Kidney experts now recommend that physicians consider the creatinine level along with age, gender and race and calculate a estimated GFR rate. A GFR of 60 or more is good, but a GFR of 59 or less might indicate chronic kidney disease. Please refer to the following table and instructions when reporting GFR scores to the Look AHEAD participants.

Individuals with a GFR score falling in stage 1-2 should be sent the normal GFR letter. Individuals with a GFR score < 59 which is Stage three, four and five of chronic kidney disease should be sent the positive GFR letter within one week. For these individuals, clinic staff will also send the GFR physician letter to the PCP. These documents will be posted on the Look AHEAD website in the Program Coordinators section and the Safety Section under Documents.

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm

21.10. CLINICALLY SIGNIFICANT EVENTS

All clinically significant events should be documented using the Serious Adverse Event form and reported to the Coordinating Center and the local IRB. See Chapter 22 for these procedures.

21.10.1. Myocardial Infarction

If a participant gives a history of new myocardial infarction, develops significant new Q waves on electrocardiogram, new LBBB on electrocardiogram, findings consistent with a silent MI, or other significant abnormalities, Look AHEAD interventions involving exercise will be suspended until evaluation for resumption of exercise is completed. See safety recommendations for resumption of exercise after a CVD event (Section 21.7.2).

21.10.2. Angina Pectoris

If a participant develops new symptoms consistent with angina (e.g., pressure, fullness or squeezing pain in the chest related to exercise and relieved by rest; pain in the shoulders, neck or arms related to exercise and relieved by rest; shortness of breath inappropriate for level of exercise), the participant should be immediately referred to his/her PCP. If such a referral is not possible, then a Look AHEAD physician should make an immediate referral. If a physician concludes that the symptoms, exam findings or electrocardiogram suggest angina pectoris, Look AHEAD interventions involving exercise will be suspended and the participant will be referred to his or her PCP for further evaluation. Interventions involving exercise will not be resumed until the PCP has evaluated the participant and approved resumption of exercise.

21.10.3. Congestive Heart Failure

If a participant develops new symptoms consistent with congestive heart failure (e.g., increased dyspnea on exertion, nocturnal dyspnea, ankle edema), Look AHEAD interventions involving exercise will be suspended and the participant will be referred to her or his PCP for further evaluation. Interventions involving exercise will not be resumed until the PCP has evaluated the participant and approved resumption of exercise.

21.10.4. Re-vascularization Procedures

If a participant undergoes a revascularization procedure (e.g., coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or stent placement, carotid endarterectomy, peripheral vascular surgery), Look AHEAD interventions involving exercise will be suspended until the PCP has approved resumption of exercise.

21.10.5. Atrial Fibrillation or Other Arrhythmia

If a participant is found by examination to have irregular heart rate, and/or electrocardiogram reveals new atrial fibrillation, or if heart rate is < 110 beats/minute and the participant is asymptomatic, the participant should be instructed to see his or her PCP as soon as possible for further evaluation and treatment. If the heart rate is > 110 beats per minute or if the participant has dyspnea, chest pain light headedness or other symptoms that the Look AHEAD physician considers secondary to arrhythmia, the participant should be sent to an emergency room for further evaluation. Other significant arrhythmias will be referred to the PCP or emergency room as appropriate for evaluation. Look AHEAD interventions involving exercise will be suspended until the PCP has provided written approval for the resumption of exercise.

21.10.6. Electrocardiogram Abnormalities

Development of significant new electrocardiogram abnormalities such as new Q waves, ST segment depression, T wave inversion, or left bundle branch block will require that Look AHEAD interventions involving exercise be stopped and that the participant be referred to his or her PCP for further evaluation. See section 21.7.2. for resumption of exercise.

If the ECG shows, nonspecific ST-T abnormalities, bundle branch block, ventricular preexcitation or Wolff-Parkinson-White (WPW) ECG pattern, atrial fibrillation (if present on previous ECG; if new finding, see below), cardiac pacemaker, junctional rhythm, or low voltage QRS, the technician may say, "the ECG does not show any MAJOR abnormality, but it will be reviewed by a physician later."

However, certain ECG findings printed on the clinic ECGs need to be reviewed by the clinic physician before the participant leaves the clinic. Technicians need to look for and clinic study physicians need to review and report on "alert" ECGs at baseline or follow-up; i.e., when the printout of a clinic recorded ECG on the MAC 1200 electrocardiograph indicates one of the following conditions (see Figures 1A-H following the Appendices).

a) Atrial fibrillation – if new finding since previous ECG

b) Atrial flutter

c) Ventricular tachycardia

d) Acute myocardial infarction

e) Complete atrioventricular block

f) Bradycardia with heart rate < 40.

In the case of any of these alert statements, the tracing should be reviewed by a clinic physician who will decide if any further action is needed. It is not advisable

to alarm the participant by revealing these unconfirmed interpretative statements. However, it is helpful to casually inquire if the person has recently had chest pain or discomfort. A negative answer does not mean that the alert can be ignored because heart attacks can be asymptomatic (silent). These “asymptomatic alerts” are less urgent than alerts associated with recent chest pain/discomfort or fainting attacks.

See Safety Management (Section 21.10) for responses to specific arrythmias and ECG abnormalities. Most of the alert conditions will result in referral to the PCP or the emergency room, as appropriate, for further evaluation.

21.10.6.1 Silent MI

Silent myocardial infarction (MI) in LOOK AHEAD is defined as *serial* ECG evidence of new MI in study-scheduled ECG records in the absence of a prior MI.

At **Baseline** - With a single record, evidence of an old MI is less certain, so these will be classified as a Possible MI (There are no “definite” ECG MIs at baseline).

At **Follow up** – The report of Silent MIs from annual scheduled ECGs will only apply to incident Q-wave MI. This is an underestimate of silent MI, because (i) all MIs do not have Q-waves and (ii) Q-waves often disappear with time following an MI – and the scheduled ECGs in LOOK AHEAD are only recorded every 2 years. However, the category is very specific and carries an independent risk of future mortality, equal to that occasioned following a hospitalized, confirmed clinical MI. For the MI to be silent it requires that there is no history or record of a clinical MI prior to the evidence on a follow-up ECG. Many of these serial changes are subtle and understandably may not be found by the study physician at the time of the annual visit.

The ECG Reading Center will review and compare all follow-up ECGs with the most recent scheduled ECG on a monthly basis. If the reference ECG or follow-up ECG is hardcopy only, they will use visual coding comparison, otherwise, all comparisons are electronic. To ensure timely participant notification, it is important to transmit ECGs twice weekly as indicated in the ECG MOP Chapter.

When a Silent MI is coded by the reading center, the Coordinating Center will notify the site by phone and written notification. The PC should check to see if there was a Serious Adverse Event reported prior or at the time of the follow-up ECG. A SAE form should be data entered if a SAE was not reported.
It is important to contact the participant by phone and send a letter enclosing copies of the most recent ECG and the last study ECG recorded. The ECG tracings and the letter should also be mailed to the participant's PCP. A model letter is attached below as Appendix F and may also be found on the Look AHEAD website.

21.10.7. Stroke

If a participant experiences a stroke (focal neurologic deficit lasting more then 24 hours or brain infarct by CT or MRI scan), any Look AHEAD interventions involving exercise will be suspended until the PCP has approved resumption of exercise.

Exercise interventions may be modified to take into account the participant's neurologic deficit.

21.10.8. Transient Ischemic Attack (TIA)

If a participant reports new symptoms consistent with TIA (focal neurologic deficit lasting less than 24 hours), the participant should be instructed to see her or his PCP immediately or advised to go to an emergency room as appropriate. Look AHEAD interventions involving exercise will be suspended until the PCP has approved resumption of exercise.

21.10.9. Claudication

If participant reports new symptoms consistent with claudication (e.g., calf pain with exercise that is relieved by rest), or a low ankle-brachial-index, the participant will be asked to see his or her PCP for evaluation. Look AHEAD

exercise interventions do not need to be stopped but may need to be modified to take into account the symptoms.

21.10.10. Retinopathy

All participants should have an annual eye examination by an ophthalmologist. If a participant develops proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy, certain types of exercise should be discouraged. Look AHEAD clinic staff should be notified and should review the exercise intervention. In such individuals, exercises that cause straining, jarring, or Valsalva-like maneuvers (forced expiratory effort against a closed airway) should be avoided. Examples of exercises and activities to be avoided are jogging, high-impact aerobics, racket sports, weight lifting and strenuous trumpet playing. These activities may cause vitreous hemorrhage or traction retinal detachment in participants with advanced retinopathy.

21.10.11. Neuropathy

If a participant develops peripheral neuropathy (e.g., the inability to detect sensation using a 5.07 or 10 g monofilament), then the participant should be discouraged from doing certain types of exercise such as jogging, step exercises, treadmill exercises and prolonged walking (over 30 minutes). Look AHEAD clinic staff will educate the participant regarding appropriate exercise activity.

21.10.12. Foot Ulcers

If a participant develops foot ulceration, any exercise program that involves walking or other weight bearing activity will be suspended until the foot ulcer is healed.

21.10.13. Limb Amputation

If a participant undergoes limb amputation, Look AHEAD exercise interventions may need to be modified to take into account the disability.

21.10.14. Depression

Participants with a total depression score ≥ 24 on the MOODS Questionnaire should be informed of the possibility that they are depressed and referred to their PCP for further evaluation and treatment. If a participant responds to question 9 about suicide intent on the MOODS Questionnaire (Q #9) with answer 2 or 3, he or she should be evaluated immediately by Look AHEAD medical staff and appropriate intervention initiated (e.g., staff accompany subject to the emergency room, immediate psychiatric consultation). After the depression has been evaluated and treated, a determination about the safety of continued participation in Look AHEAD should be made. The PCP and any mental health professional involved in the participant's care should help with this determination.

21.10.15. Cancer

If a participant should develop cancer and spontaneous or unintentional weight loss as a result, Look AHEAD weight loss interventions may need to be stopped. This will be done if either the participant's PCP or a Look AHEAD physician decides that further weight loss is medically undesirable for that participant.

21.10.16. Excessive Weight Loss

If BMI decreases to < 20.0 kg/m^2 as a result of Look AHEAD interventions, such interventions must be stopped. However, weight maintenance interventions may be continued unless BMI decreases to < 19.0 kg/m^2, at which point these interventions must also be stopped.

21.10.17. Other Events

The occurrence of any medical event that, in the judgment of the participant's PCP or a Look AHEAD clinician, makes application of a Look AHEAD intervention unsafe for that participant will require that the intervention in question be discontinued for that participant.

In the case of any clinical significant event such as MI, stroke, or those alerts described above, and the participant is in the Lifestyle Intervention group, unblinded staff should complete the Intervention Modification form.

21.10.18. Loss of PCP

Participants who, for whatever reason, lose their PCP will be asked to find and establish care with a new PCP. Look AHEAD staff may assist the participant in identifying an appropriate PCP. In some instances it may be necessary for a Look AHEAD physician to provide short-term care (e.g., renew prescriptions) until care has been established with the new PCP. However, such care by a Look AHEAD physician should only be short-term.

21.11.1. Instructions for Medication Modification Form

The Look Ahead Medication Modification form should be used any time the Look AHEAD staff are adjusting medications for hypoglycemia medication management or for an emergency reduction in hypertension medication or if the

clinic staff initiate a medication change with the participants PCP. Perhaps the most frequently asked question is what do I do if the PCP changes the medication without letting me know? In that circumstance you would not fill out a medication form. However, if the clinic staff reviewed the blood glucose values and called the PCP to report the values and the PCP made a change based on the recommendation from clinic staff then a medication reduction form would be filled out.

Question 1: asks for the category of event, which will most often be hypoglycemia medication management during the intensive phase of the Lifestyle Intervention. In a rare case the clinic staff might need to adjust Hypertensive medication to prevent hypotension in the event that the participant could not get in to see his/her PCP in a timely manner. Check the appropriate box.

Question 2: Please list the current diabetes and/or blood pressure medication and dose that you are reducing.

Question 3: Action taken. This asks that you enter the reduction or increase in medication and what the new level is. In addition, you may check if no medication change was necessary, if patient education was given or if the PCP was notified for some reason. Please check all that apply.

Question 4; this question asks about monitoring of blood glucose. Please check the appropriate box. The intent of this question is to affirm that the participant has the ability to monitor during the intensive phase of the intervention.

Question 5: Has the participant experienced symptomatic hypoglycemia more than 2 times per week? Check the appropriate box. If yes, enter how many times the participant has had symptomatic hypoglycemia.

Question 6: Has the participant had any episodes of serious hypoglycemia (defined as hypoglycemia with loss of consciousness or a level of confusion that prevented self treatment. Check the appropriate box and if yes, explain what

happened. The Look AHEAD Safety Committee is reviewing and tracking all serious hypoglycemia, a yes on question 6 should alert clinic staff that a Serious Adverse Event form should be filled out.

The form provides a comment section as well as signature space and date for the clinic staff making the modification.

21.12.1. Intervention Modification Form

The intervention Modification Form is to be completed when the Lifestyle Intervention needs to be stopped or modified for a participant because of an event. Examples include but are not limited to the following: cardiovascular events, blood pressure alerts where it would be unsafe for the individual to exercise, physical injury and other events such as cancer, foot ulcers etc. The Medication Modification form should not be filled out if the intervention is only being modified for a short time, i.e. because of the flu, a sore muscle etc. If the intervention is being modified for several weeks or months, then the form would be filled out, for example if a participant had an MI, the exercise intervention might be stopped for several months.

Question 1: This question asks you to choose one category that best describes the event. Choose the appropriate box and if other, list what the problem was.

Question 2: List the action taken, you may choose more than one answer if needed.

Question 3: Provides space for additional comments.

Clinic staff should sign and date the form and enter the form in the data base system.

Look AHEAD staff should be encouraged to keep some sort of record to track when a participant may need to resume or restart the intervention.

Appendix A

Date: _____

Dear Dr. _____,

Your patient _____ (DOB _____) is a participant in the Look AHEAD research study, a multi-center NIH-funded clinical trial examining the effects of weight loss and physical activity on cardiovascular disease in type 2 diabetes mellitus. The exercise advocated for participants in Look AHEAD is approximately 30 minutes or more of daily, moderate intensity, unsupervised physical activity, with the most common form being brisk walking. We understand that _____ experienced a _____ on _____. He or she may have been asked to suspend exercise following the event. We would now like to evaluate whether it is appropriate for your patient to resume the Look AHEAD exercise intervention and we need your assistance and medical opinion in this regard.

At the bottom of this letter are several questions seeking your opinion of whether it is appropriate for _____ to resume physical activity as previously recommended by the Look AHEAD research study. We have also attached a summary of contemporary recommendations regarding the resumption of a physical activity program following various types of cardiovascular events. We hope this information might be useful for you.

We greatly appreciate your timely response, as we will not advise _____ regarding resumption of Look AHEAD exercise interventions until we hear from you. If you have any questions or concerns, please do not hesitate to contact us.

Sincerely,

Yes_____ No_____ Resume prior unsupervised physical activity program
Yes _____ No_____ Discontinue unsupervised physical activity program
Yes _____ No _____ Modify physical activity program in the following manner:
_____
_____

Signature of M.D. _____ Date: _____

Printed name of M.D. _____ Phone #: ( )_____

Please fax this form to Look AHEAD study nurse at ( ) _____- _____.

Appendix B

Guidelines for Resuming Physical Activity after a Cardio-Vascular Disease Event

Myocardial Infarction: In general, policies regarding resumption of exercise after an MI have incorporated a risk stratification nomogram based on the post-MI course and findings (taking into account CHF, arrhythmias, ischemia, etc). Most recommendations concur that patients should complete "Phase 2" cardiac rehabilitation programs (CRP), which would entail cardiovascular monitoring during physical activity. After "passing" Phase 2 CRP, Phase 3 – or unsupervised activity - can be performed and is encouraged. If a patient cannot safely pass Phase 2 CRP, then unsupervised physical activity is not prescribed. An ideal situation is that the participant complete a cardiac rehabilitation program and be cleared for unsupervised exercise prior to resuming the Look AHEAD intervention and that the Look AHEAD physical activity not initially exceed the levels performed in the cardiac rehabilitation program.

Coronary Artery By-pass Graft Surgery: Contemporary standard of care includes the resumption of activities of daily living within one week of surgery (in the absence of operative or post-operative complications.) During the following several weeks increasing activity (low impact) is prudent but a formal exercise program is usually not recommended until one month post-operatively, provided there have not been complications. Many cardiologists will arrange for a treadmill test at this juncture, but this is not a universal recommendation. Generally, physical exercise is resumed at approximately 50% of prior levels and gradually increased in duration and intensity during the next month as tolerated. The safest manner in which to resume an exercise program is through participation in, and completion of a Phase 2 CRP.

Percutaneous Coronary Intervention: A contemporary standard of care for patients who have undergone a PCI is that physical activity can be resumed once

the puncture site in the groin has healed and it is apparent that there have not been complications related to the procedure. Most cardiologists instruct their patients to resume physical activity within a few days after an uncomplicated PCI procedure, initially at a lesser intensity for several days, but then at usual intensity and duration after 7-10 days.

Stroke: Resumption of usual physical activity or modified physical activity will depend upon the extent of residual impairment. The advice and recommendations of the primary care physician or appropriate specialist physician (e.g. neurologist and/or physical medicine and rehabilitation) should form the basis for any specific restrictions to physical activity and for medical clearance to resume a program of physical activity.

Further specific information can be obtained by reviewing the American Heart Association position statement on exercise in secondary prevention of heart disease which can be found at http://circ.ahajournals.org/cgi/content/full/96/1/355

Appendix C
Normal GFR Participant Letter

Dear Mrs. Smith:

I am pleased to send you the results from your latest set of Look AHEAD blood tests. As usual, we have also sent a copy to your physician.

This report shows a new result called “GFR”— short for glomerular filtration rate. The GFR is a new way to check on your kidneys.

When Look AHEAD started, most doctors judged how well your kidneys were working by the blood creatinine level test alone. Less than 1.0 was great, 1.0 to 1.5 was good, 1.5-2.0 was not as good, and more than 2.0 was bad. We have reported your blood level of creatinine to you since you enrolled in the Look AHEAD and we continue to do so.

In the past few years, kidney experts began to suggest that doctors look at the creatinine level along with age, sex, and race. The idea was that the same level of blood creatinine could mean something much different in a bigger, more muscular, younger man than in a smaller, less muscular, older woman. They recommend that doctors calculate “GFR” using all that information.

Because of those suggestions, the Look AHEAD Team has added “GFR” to our reports. A GFR of 60 or more is good, but a GFR of 59 or less might be a sign of chronic kidney disease.

If your GFR is 59 or less, please talk with your doctor about it the next time you see him/her. If your doctor confirms that you have chronic kidney disease, he/she might advise you to change your diet or treatment to better protect your kidneys.

Please call your local Look AHEAD team if you have any questions.

Sincerely,

The Look AHEAD Safety Committee

Appendix D
Positive GFR Letter

Dear Mrs. Smith:

I am pleased to send you the results from your latest set of Look AHEAD blood tests. As usual, we have also sent a copy to your physician.

This report shows a new result called “GFR”— short for glomerular filtration rate. The GFR is a new way to check on your kidneys.

When Look AHEAD started, most doctors judged how well your kidneys were working by the blood creatinine level test alone. Less than 1.0 was great, 1.0 to 1.5 was good, 1.5-2.0 was not as good, and more than 2.0 was bad. We have reported your blood level of creatinine to you since you enrolled in the Look AHEAD and we continue to do so.

In the past few years, kidney experts began to suggest that doctors look at the creatinine level along with age, sex, and race. The idea was that the same level of blood creatinine could mean something much different in a bigger, more muscular, younger man than in a smaller, less muscular, older woman. They recommend that doctors calculate “GFR” using all that information.

Because of those suggestions, the Look AHEAD Team has added “GFR” to our reports. A GFR of 60 or more is good, but a GFR of 59 or less might be a sign of chronic kidney disease.

If your GFR is 59 or less, please talk with your doctor about it the next time you see him/her. If your doctor confirms that you have chronic kidney disease, he/she might advise you to change your diet or treatment to better protect your kidneys.

Please call your local Look AHEAD team if you have any questions.

Sincerely,

The Look AHEAD Safety Committee

Appendix E
Positive GFR Physician Letter

RE: Ms. Mary Jones, DOB 01/01/40

Dear Dr Smith:

We had the pleasure of seeing Ms. Jones in our Look AHEAD Study clinic on March 15, 2007. The results of the blood tests we took that day are attached. I'm writing to let you know that we believe that she may have chronic kidney disease.

On that date, her serum creatinine was 1.4 mg/dL. Following guidelines recently developed by the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation. The Look AHEAD Central Lab uses the IDMS-traceable MDRD Study Equation to estimate glomerular filtration rate (GFR) with the following formula:

$GFR = 175 \times (SCr^{-1.154}) \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

Based on this formula, we estimated GFR to be 52 mL/min/1.73m^2. According to KDOQI guidelines this represents stage 3 chronic kidney disease. (For more information about KDOQI and to find a web-based GFR calculation, please visit their website at http://www.kidney.org/professionals/KDOQI/.)

We let Ms. Jones know about the abnormal test and referred her to you for follow up. We told her that, if you confirm the presence of chronic kidney disease, you might ask her to make changes in her medicines or diet to improve blood pressure or glycemic control.

In Look AHEAD, we will be tracking estimated GFR along with SCr and microalbuminuria for the remainder of the study and we promise to keep you posted. Many thanks—and please don't hesitate to call if I can provide further assistance.

Sincerely,

PI

Appendix F
Silent MI Letter

Appendix _____

Dear Participant

The heart tracing (also called an electrocardiogram, ECG, or EKG) performed as part of Look AHEAD was determined to have an abnormality by the ECG Reading Center in Winston-Salem, NC. Because the reading center uses different criteria than the machine in the clinics that take the ECG, this may not have been found at the time of the test in the clinic. The abnormality found indicates that you may have had a heart attack in the past. This may have been a "silent" one, in that you had no symptoms. You and your doctor may already be aware of this finding. We are enclosing copies of the most recent ECG and the last study ECG recorded prior to this one with this letter. We are also sending a copy of this letter to your primary care doctor along with copies of the ECGs.

Subsequent to this ECG, you had stress tests prior to randomization and again at Year 1 which determined it was safe for to you to proceed with the study; therefore this finding does not affect your continued participation in Look AHEAD. Look AHEAD does not recommend any specific therapy or testing because of this abnormality. Rather, we urge you to discuss this finding further with your primary care doctor, who may or may not recommend changes in your medical regimen and/or additional tests, depending on your particular health circumstances.

Sincerely,