Manual of Procedures

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

Version 1.14
May 1, 2021

Please note:
This manual is a working document and will be updated throughout the study as required.

TABLE OF CONTENTS

1. CHAPTER 1: OVERVIEW MANUAL OF PROCEDURES

The Manual of Procedures (MOP) is the detailed blueprint of the study and is designed to serve as the day-to-day instruction manual. It includes instructions as to how the study procedures, including recruitment, screening, testing, and visits, should be performed. The MOP provides the level of detail needed to conduct every aspect of the study in a standard and uniform fashion across sites and over time. In addition, the GRADE study has other specific manuals that serve as supplementary to this manual and include the following:

1. Measurement and Assessment Procedural Manual (MAP)
2. Drug Distribution Center Manual of Operations
3. CBL Biospecimen Collection and Processing Manual
4. Cognitive Assessments Manual
5. Quality of Well-Being Manual of Procedures
6. Electrocardiography Assessment Manual
7. GRADE Forms Manual
8. MIDAS Users Manual
9. Emotional Distress Substudy (EDS) Manual
10. Continuous Glucose Monitoring (CGM) Manual
11. Microbiome Manual of Procedures
12. Beta Cell Ancillary Manual of Procedures

Study forms and templates, including informed consents, are included as appendices to the MOP. In contrast to the study protocol, which is modified infrequently, the MOP will change as improved or new methods are added. To be complete, the MOP should specify both what is permitted as well as what is not. However, it can only represent the best state of our awareness, deliberation, and decision-making to date.

MOP changes do not generally require IRB approval. However, some IRBs, depending on local regulations, may want the MOP submitted for review at the initial and subsequent continuing reviews.

The GRADE Protocol is the public document that describes the background, rationale, design, analytic and statistical considerations and the major organizational features of the study. Although there will inevitably be adjustments to the protocol, these will be kept to a minimum. Changes in the protocol usually require IRB approval.

Therefore, both the protocol and the MOP are considered ‘works in progress’ or ‘living’ documents because even the most experienced collaborative group cannot possibly predict and prepare for every eventuality or cover every contingency that will arise. When an occasion does arise that is not previously covered in the documented procedures, members of the study group may NOT unilaterally resolve or address the situation. Mechanisms are in place to continue to update, clarify, and establish study procedures throughout the course of the trial with input and consensus from the collaborative group.

Manual of Procedures

Chapter 2

TABLE OF CONTENTS

2. CHAPTER 2: STUDY ADMINISTRATION

2.1 Organizational Units

2.1.1 Clinical Sites

Each of the participating clinical sites has agreed to implement the GRADE Protocol and follow the manual of procedures in accordance with all applicable study and institutional and HHS policies and regulations. The clinical sites will do the following: recruit eligible participants; follow participants according to the protocol and the manual of procedures; assume responsibility for the diabetes management of each participant enrolled in GRADE according to protocol; store and dispense diabetes medications; record participant data related to all of the above using the study designed data forms; maintain the security and confidentiality of participant data; review and enter information from the data forms using the web-based data management system; share clinically relevant data with the participant's healthcare provider; and respond to edit queries from the Coordinating Center (CoC). Each clinical site has, at a minimum, a Principal Investigator (PI), Study Coordinator (SC), Recruitment/Retention Coordinator, and additional staff such as research assistants and/or research nurses, to carry out the protocol. Detailed staffing patterns at the sites will be left flexible to best address clinic-specific needs. The PI will be responsible for the overall conduct of the study and implementation of the protocol at his/her site. The SC will be responsible for the day-to-day conduct of the study. The Recruitment Coordinator will be responsible for planning, conducting and tracking recruitment activities. After recruitment has been completed, the staff effort assigned to recruitment activities will be redirected to study implementation and participant retention at the discretion of the PI.

Clinical site staff will be expected to participate in the central study activities such as preparation of presentations and publications, and governance and management of the study through participation in committees, subcommittees and working groups.

The clinical sites will be funded as sub-agreements to the Coordinating Center.

2.1.2 Coordinating Center

The Coordinating Center (CoC) is responsible for all aspects of biostatistical design, analysis, and data processing for GRADE. In collaboration with the Steering Committee, the CoC is responsible for document processing and maintenance of the protocol, Manual of Procedures, and data collection forms. It is responsible for establishing and maintaining the means by which data are transferred from the clinical sites to the CoC, maintaining the security and confidentiality of the study data, and analyzing and interpreting the data for reports, presentations, and publications. The Coordinating Center will maintain and manage compliance activities for the trial to include investigators' duality of interest, institutional review board approvals for the protocol, and documents related to study certification. The CoC also helps monitor protocol performance. It also will establish and coordinate communication among the clinical sites, laboratories and other service cores, and the CoC, and between the Executive Committee and the DSMB, and help to schedule and organize conference calls and meetings. The CoC collaborates with the Research Group members in the preparation of publications, providing design and statistical support. Finally, the CoC provides general logistical and organizational support to the Research Group, its committees, sub-committees and working groups.

The Coordinating Center (The George Washington University Biostatistics Center) is the prime grant recipient; all other study sites will be funded through sub-agreements or subcontracts from the CoC.

These include the clinical sites, the Chairman's Office, the Central Biochemistry Laboratory and the Drug Distribution Center. The functions of these Central Units are described below.

2.1.3 Central Biochemistry Laboratory

The Central Biochemistry Laboratory (CBL) provides laboratory support for GRADE, performing scheduled eligibility measures and outcome measures during the trial and providing reports of assay results. Quality control procedures are established for these centrally performed assessments in collaboration with the Coordinating Center and Outcomes Subcommittee and its Quality Control Working Group (see below), and reports will be furnished periodically to the Research Group. In addition, the laboratory will provide consultation and scientific input to the Steering Committee, and lend expertise to help formulate the manual of procedures, provide specimen and record labeling, and arrange handling and shipping of specimens. Communication systems for data transfer to the Coordinating Center, and in specified instances directly to the clinical sites, will be established and maintained. Reporting safety results in a timely fashion is the responsibility of the CBL. Finally, the CBL is responsible for the purchasing and shipment of supplies necessary to perform designated laboratory tests to the clinical sites.

2.1.4 Drug Distribution Center

The Drug Distribution Center (DDC) will be responsible for procuring, packaging and labeling, and storing study medications and supplies (e.g. pills, insulin and liraglutide pens, pen needles, meters, and test strips), distributing them to the clinical sites in a timely fashion, maintaining central and site study drug inventories, developing and maintaining a web-based study drug assignment system for use by clinical sites, and following appropriate good clinical practice guidelines. The DDC will communicate with the Coordinating Center and with pharmaceutical and other suppliers as necessary to maintain a continuous and reliable supply of study drugs and other supplies to the clinical sites and their participants. The Regulatory and Clinical Compliance (RACC) group at the DDC will also provide safety monitoring by collecting, reviewing, coding, and compiling serious adverse event data supplied by the clinical sites. These data will be used for reporting to regulatory agencies and pharmaceutical sponsors, as required.

2.2 Office of Study Chair

The Study Chair serves as the chief administrative officer of the GRADE study, chairing the Steering and Executive Committees, and serving as an *ex officio* member of other committees and subcommittees, as necessary, and as the liaison to the DSMB and NIDDK. The Chair is responsible for providing leadership to the overall conduct of GRADE.

2.3 NIDDK Project Scientist and Program Official

As a U01 agreement, the NIDDK Project Scientist and Program Official will play important roles in the implementation of the GRADE study as described below.

The Project Scientist provides substantial scientific involvement in the conduct of the GRADE study including:

- Serves on the Executive Committee
- Serves as voting member of the GRADE Steering Committee
- Cooperates, coordinates, and works with GRADE and its clinical sites by overseeing conduct of the research protocol, monitoring recruitment/retention, monitoring of AEs, and ensuring that objectives of the study are achieved
- Participates in study publications

- Attends DSMB meetings

The Program Official provides substantial programmatic involvement in the conduct of the study including:

- Provides budgetary oversight
- Reviews study progress prior to annual study renewal
- Works with the study DSMB in study oversight by serving as liaison to the study Steering Committee

2.4 Funding Mechanism/Study Resources

GRADE will be funded as a cooperative agreement between the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases and the Coordinating Center and the GRADE Co-Principal Investigators (the Study Chairman and PI of the Coordinating Center). The Coordinating Center will be the primary awardee of the grant, and in turn, will execute sub-agreements with the clinical sites, the Chairman's Office, Central Biochemical Laboratory, and subcontracts with other central units, as needed, and the Drug Distribution Center.

2.5 Committees

2.5.1 Executive Committee

The Executive Committee is responsible for the day-to-day management of the study in accordance with the protocol. The Executive Committee, composed of the GRADE Study Chair, Vice-Chairperson(s), PI of the Coordinating Center, the Coordinating Center Project Director, Chair(s) of the Study Coordinator's Sub-Committee, and the NIDDK Project Scientist and Program Official, will meet by phone regularly, with administrative and other support staff in attendance to discuss the progress of the study and provide frequent guidance and supervision. Members of the Steering Committee and chairpersons of the subcommittees working on specific study issues will also join the Executive Committee call, as needed.

2.5.2 Steering Committee

The Steering Committee is the representative body of the GRADE Research Group and will govern the conduct of the study. The Committee, chaired by the Study Chair, consists of the Principal Investigator from each clinical site and of the Coordinating Center, and the NIDDK Project Scientist. In addition, the Chair(s) of the Study Coordinators Sub-committee and PI of the CBL will be members.

The Steering Committee is the policy and decision-making group, and will oversee the administrative aspects of the GRADE Research Group. It provides overall scientific direction for GRADE, taking into consideration recommendations from the subcommittees and working groups. The Steering Committee will approve the details of and changes in study design, all procedure manuals and participant management policies, and assure that sufficient numbers of eligible participants are being screened/randomized into GRADE. The Steering Committee will monitor protocol adherence at the clinical sites including proper data generation, recording, and transmittal. The Steering Committee will meet in person at least once per year. Members unable to attend a meeting may designate an alternate to act on their behalf.

Steering Committee recommendations for changes in the protocol generally require prior consideration by the appropriate subcommittee or working group, and an affirmative vote by two-thirds of the Steering Committee members. One vote is allotted to each Steering Committee member and two votes are allotted to the Co-Chairs of the Study Coordinator Subcommittee.

2.5.3 Subcommittees

Subcommittees include members of the Research Group. Their function is to develop detailed policies and procedures, carry out those procedures as appropriate, and make recommendations to the Steering Committee. The following subcommittees will be formed:

- Recruitment and Retention - assigned to oversee recruitment, define best practices, and help individual sites achieve target recruitment goals. The Coordinating Center will provide timely reports on recruitment for individual clinical sites and study-wide, examining how participants learn about GRADE, which methods of recruitment provide best yield, the barriers to recruitment, and eligibility criteria that exclude most potential participants. After recruitment is concluded, this subcommittee will turn its attention to retention efforts.
- Study Coordinators - address issues of study implementation and participant retention. This subcommittee will include all study coordinators and will provide a forum for training, retraining, certification, and sharing best practices. The Chair(s) of the Study Coordinator subcommittee will be voting members of the Steering Committee and members of the Executive Committee.
- Protocol Oversight - will oversee adherence to the protocol in the clinical sites. Working with reports generated by the Coordinating Center and shared in real time with sites will ensure that the clinical sites are following the protocol and manual in all respects.
    - Intervention Oversight Group (IOG) will provide support for the clinical sites with regard to the study-dictated initiation, titration, and continuation of study medications. Members will be available to address questions regarding implementation of the protocol-dictated therapies.
- Ancillary Studies and Substudies - The Ancillary Studies and Substudies Subcommittee will evaluate proposals for studies that are not part of the GRADE protocol but involve GRADE participants, data, or biological samples. The proposals will generally, but not always, be developed by members of the GRADE Study group. The Ancillary Studies and Substudies Subcommittee will judge proposals based on scientific and clinical merit and importance, keeping in mind the burden on study participants, clinical sites and staff, Coordinating Center and other GRADE resources. Ancillary studies will require independent funding.
- Outcomes - The Outcomes Subcommittee will oversee the measurement of outcomes. It will be responsible for overseeing the methods selected by GRADE, consider and recommend new methods for the study, and oversee the completeness and quality of the data collected. The Outcomes Subcommittee will also adjudicate those outcomes that require it, including cardiovascular events, cancer, lactic acidosis, pancreatitis, death, and severe hypoglycemia. Adjudication will be done in accordance with a procedural document which describes GRADE-defined criteria for outcomes and outlines necessary procedures and documentation required to consistently classify outcomes.
    - Quality Control Working Group will monitor and oversee the quality assurance of the clinics and central units in the study.
    - Severe Hypoglycemia Working Group will adjudicate severe hypoglycemia events reported by sites in real-time.
- Publications and Presentations - The Publications and Presentations Subcommittee (PPS) will coordinate, monitor, review, and assume responsibility for arranging the preparation of all study-wide communications (press releases, interviews, presentations, and publications) relating to the scientific aspects of GRADE.

2.5.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is appointed by and serves as an independent review group for the NIDDK. The DSMB will meet at a frequency stipulated by NIDDK, but no less than annually, and operate in accordance with their charter. The Coordinating Center will supply progress reports to the DSMB focusing on study progress, including recruitment, implementation of the protocol, emerging results, and especially adverse events and safety. The overarching goal of the DSMB is to ensure the scientific validity of the study and safety of GRADE participants. Based on all of the considerations above, the DSMB may recommend to the NIDDK that the protocol be modified or that GRADE be terminated. The DSMB will approve stopping rules and a plan for interim analyses.

2.6 Policies

2.6.1 Publications and Presentations

All publications and presentations of study plans and results require review and approval by a majority of the Publications and Presentations Subcommittee (PPS), and for some types of communications, a majority of the Steering Committee. Refer to Chapter 14 for details regarding the publications and presentations policies.

With respect to publications and presentations from GRADE, the goals of the PPS are to:

1. Ensure accurate, uniform, timely, and high quality reporting of GRADE activities and results;
2. Preserve the scientific integrity of the study;
3. Safeguard the rights and confidentiality of participants;
4. Assure that the timing of publications and presentations serves the right of the public to know the results of the program without jeopardizing its conduct.

The PPS will organize a writing group for each publication or presentation proposed by GRADE investigators. Many, but not all, of the proposed publications will originate in the PPS. Members of the writing group will include members of the GRADE Research Group who are assigned by PPS, including a chair, and investigators and coordinators who may be appointed or may volunteer. The PPS will coordinate the efforts of the writing group, establish priorities for data analysis by the Coordinating Center, and help review and edit the manuscripts produced by the writing groups. A liaison from PPS and from the Coordinating Center will be assigned to each writing group.

There will be several categories of publications and presentations, with different rules for authorship, ranging from publications of the main results of the study (with authorship by the entire research group) to other types of publications with named authors. The authorship rules balance the need to recognize the contributions of all GRADE investigators and staff with the need to recognize individuals for specific contributions to certain types of publications and presentations.

2.6.2 Ancillary Studies

The Ancillary Studies and Substudies Subcommittee will evaluate proposals that are not a part of the GRADE protocol but involve GRADE participants, data or biological samples. Ancillary studies may be performed only in a subset of participants or may include all participants; however, the analyses, studies or, rarely, interventions that are proposed will be extracurricular to the protocol. They must be submitted for review and approval by the Ancillary Studies and Substudies Subcommittee, and subsequently by the Steering Committee. Ancillary studies will have to obtain funding from outside GRADE, including funding to cover any necessary effort by the Coordinating Center. Ancillary studies also need to be approved by the GRADE DSMB. Refer to Chapter 14 for details regarding the ancillary studies policies.

Major factors in approval of ancillary studies will include:

- compatibility of goals with those of GRADE
- scientific-clinical importance
- should not place undue burden on GRADE participants or staff

Ancillary studies will receive a primary, secondary, and statistical review. An outside reviewer may be used if there is insufficient expertise within GRADE in a specific area. Reviews will be returned to the applicant and appeals of decisions of the Ancillary Studies and Substudies Subcommittee may be made to the Steering Committee.

Substudies will be considered by the Ancillary and Substudies Subcommittee and are defined as those studies that fall within the aims and objectives of the protocol. If approved, they will be conducted within GRADE and may require additional funding support. They will undergo a similar review process.

Manual of Procedures

Chapter 3

TABLE OF CONTENTS

3. CHAPTER 3: SITE CERTIFICATION AND REQUIREMENTS

Participating clinical sites must fulfill specific requirements prior to the start of any protocol activity. When a site has met all requirements to start the study, a written notice of "Site Certification" will be issued by the GRADE Coordinating Center. No enrollments or screening visits can be undertaken prior to this "Site Certification" being received. However, once sites have received local IRB approval and all staff members have successfully completed the protocol quiz, they may begin with prescreening activities such as database searches, and other recruitment efforts including prescreening telephone calls. Once authorized to start screening/enrollment, the site will have a continuing responsibility to update the GRADE Coordinating Center of any changes, such as personnel changes. Reminders for annual renewals of documents will be sent to the Principal Investigators and Study Coordinators six weeks in advance of renewal dates.

3.1 Documents to be sent to GRADE Coordinating Center:

See Table 3.1 below for the following items that are collected and maintained at the GRADE Coordinating Center:

Table 3.1 Items to be sent to the GRADE Coordinating Center (CoC) and/or kept on file locally

Documents to be sent to CoC (unless indicated for local filing)	**When to send documents**
Compliance documents	
• Documentation of IRB approval with stamped information • If applicable, stamped informed consents • If separate from informed consent, copy of HIPAA authorization form	• At study initiation • Annually
Documents required for each research staff member	
• Duality of Interest (DOI) Form completed	• At study initiation • Bi-Annually
• Documentation of NIH Education on Protecting Human Subjects training or equivalent training (complete as per local requirements and keep on file locally, do not send to CoC)	• At study initiation
• Documentation of NIH Information Security and Privacy Awareness Training (complete as per local requirements and keep on file locally, do not send to CoC)	• At study initiation • Annually
Documents required for PIs and PIs of Sub-sites	
• Curriculum vitae (signed and dated)	• At study initiation
Contact information	
Clinical Site • Research staff names, mailing addresses, email addresses, office telephone and fax numbers	• At study initiation • Ongoing
Laboratory • Name and location of local laboratory utilized for screening laboratory assays and any other facilities conducting tests, including a copy of the laboratory certificate and reference ranges*	• At study initiation
Pharmacy • On-site pharmacy mailing and contact information where medication will be received*	• At study initiation

*Sites must ensure availability of a centrifuge for blood processing, refrigerators, for medication storage (at site or on-site pharmacy) and short-term storage of blood samples prior to shipment. Proper processing and storage of GRADE lab specimens requires a centrifuge and a -70°C freezer. Clinical centers without access to a -70°C freezer can use a -20°C freezer, however refer to the CBL Biospecimen Collection and Processing Manual for detailed instructions for the initial freeze of processed cryovials prior to storage in a -20°C freezer. Sites are responsible for following local guidelines regarding monitoring of temperature and keeping temperature logs.

3.2 Site Initiation Activities Checklist for Study Coordinators

The Study Coordinator at each clinical site must complete the **Site Initiation Activities Checklist for Study Coordinators** (see Section 16.2.1). This internal checklist covers the basic steps for initiating the GRADE study and will serve as documentation that the following regulatory and compliance documents have been completed and maintained. The following documents should be sent to the Coordinating Center and/or kept on file at the clinical site (refer to Section 3.1 for a schedule of when these documents are required):

3.2.1 IRB Approvals

A copy of IRB approved documents (stamped letter of approval from site IRB, approved informed consent forms, and HIPAA authorization form, if separate from the informed consent form) must be received and on file at the GRADE Coordinating Center. The IRB documents must reflect the appropriate version number and date of the Protocol. To maintain requirements for continuing participation in GRADE, the clinical site must provide their documentation of annual renewal of IRB approval for the study.

3.2.2 Research Staff Requirements

Each GRADE research staff member at the clinical site is required to sign a GRADE Duality of Interest Form and send it to the Coordinating Center. Research staff will be requested to update and provide their Duality of Interest Form twice each year. GRADE research staff will also be required to complete the NIH Education on security awareness and Protecting Human Subjects Training or equivalent training and locally maintain and file documentation.

The clinical site is expected to notify the GRADE Coordinating Center of any changes or additions to research staff as they occur.

3.2.3 Staff Training and Certification Requirements

Training and certification of staff is required for certain measurements, assessments, procedures and data entry. The following table is a guide for the clinical staff training and certification requirements as well as other mandatory documents and steps that must be completed by specific staff members. Table 3.2 provides an overview of the documents, training and certification requirements. Refer to Table 3.3 for an overview of the GRADE training and certification schedule. Detailed instructions on procedures, training and certification can be found in the Measurement and Assessment Procedural Manual (MAP) available on the GRADE study website. Additional training materials are also available on the GRADE study website, including presentations and training videos for certain assessments. Videos posted to the study website may be accessed using the following password: grade.

Table 3.2: Clinical Staff Required Documents, Training and Certifications

	Principal Investigator	Sub-Co Investigator	Study Coordinator	Other Research staff
Required Documents				
Updated CV	**X**	**X**		
Duality of Interest Form	**X**	**X**	**X**	**X**
GRADE Protocol Quiz	**X**	**X**	**X**	**X**
Required Certifications				
MIDAS Data Entry			**X**	**X**
Neurocognitive assessment			**X**	**X**
Peripheral Neuropathy Assessment			**X**	**X**
Quality of Well Being (QWB)			**X**	**X**
Waist-Hip Circumference			**X**	**X**
ECG			**X**	**X**
Microbiome collections			**X**	**X**
Web randomization			**X**	**X**
Required Local Training				
BP, height, weight[@]			**X**	**X**
Oral Glucose Tolerance Test (OGTT)[@]			**X**	**X**
Shipping training[+]			**X**	**X**

At least one person (preferably and typically the Study Coordinator) at the site must be certified in these components to satisfy requirements for Site Certification and initiate protocol enrollment activities. Any staff that perform specific study procedures noted above must be certified.

[@]Documentation of training for BP, height, weight and OGTT performed at local sites (refer to MAP).

[+]Shipping training must be completed as per local regulations prior to shipping samples to the central biochemistry laboratory.

Certification is an important step in ensuring that study procedures are performed consistently across all GRADE sites. Training and certification must be completed initially at the start of the trial (or when a new staff member is added). Procedures will be reviewed at year 3 at a study group meeting. Re-certification will then be done locally with records submitted to the Coordinating Center within 6 months following the refresher at the study meeting. Complete training and certification information is available in the Measurement and Assessment Procedural Manual (MAP) available on the GRADE study website. The following includes a brief description of the components listed in Table 3.2 above:

1. **GRADE Protocol Quiz**: The GRADE Protocol quiz should be completed by relevant staff (refer to Table 3.2) involved in protocol implementation at the clinical site. A successful completion of the quiz is a score of at least 14/17 (>80%).
2. **Web Randomization System**: All study personnel who will be randomizing participants into the study will be required to randomize a "mock" participant by logging into the system and

following the procedures correctly. Information on completing a mock randomization will be provided elsewhere.

3. **MIDAS Data Entry**: All staff members responsible for data entry and all Study Coordinators must complete the data entry certification in MIDAS. The Coordinating Center provides MIDAS training for sites through online WebEx sessions. Instructions for certification are also provided by the Coordinating Center. See the MIDAS manual for further instructions (available on the GRADE study website).
4. **Waist and hip circumference measurement certification**: This certification needs to be completed initially and then mid-way through the study (year 3, unless initial certification was completed within the past year) by all personnel who will perform waist and hip circumference measurements for the study.
5. **Peripheral neuropathy assessment and use of Owen Mumford mono-filament:** The peripheral neuropathy certification will be required by all personnel who will perform the testing. The peripheral neuropathy assessment is conducted at baseline and again at each annual visit. Certification is required at study initiation and again mid-way in year 3 (unless initial certification was completed within the past year).
6. **Blood pressure, height and weight measurement competency:** This consists of documenting local competency and must be completed initially and then mid-way through the study (year 3) by all personnel who perform blood pressure, height and weight measurements for the study (unless initial certification was completed within the past year). The Measurement and Assessment Procedural Manual (MAP) should be reviewed by all staff performing these assessments. There is no formal certification or training for BP, height and weight; rather, sites will be responsible for ensuring training to document competency and maintaining documentation on file at the clinical site.
7. **Neurocognitive assessment**: Certification in the administration of neurocognitive testing will be required by all personnel conducting this procedure. Examiners should continue to administer the neurocognitive assessment at least twice per month thereafter to maintain proficiency. Refer to the Cognitive Assessments Manual available on the GRADE study website for background and detailed information on the certification process. The neurocognitive assessment is conducted at baseline and again in Year 4 and Year 6 of the study.
8. **Oral Glucose Tolerance Test:** Clinical research staff will either attend a study meeting where the OGTT procedures will be reviewed, independently review the OGTT training materials available on the GRADE study website, or be trained locally by another trained staff member prior to conducting an OGTT on a GRADE participant. Although there is no central tracking of the completion of OGTT training, it is expected that sites will track and maintain these informal trainings locally.
9. **Quality of Well Being (QWB):** The QWB assessment will require certification of all personnel who will perform the interview. The assessment will be conducted each study year, and certification should be attained at study initiation and again in Year 3. Please refer to the Quality of Well-Being Manual of Procedures available on the GRADE study website for details.
10. **Electrocardiogram (ECG) Assessment:** Refer to the ECG Manual available on the GRADE study website for background information. ECG assessments will be collected at the Baseline Randomization Visit (alternatively, sites may perform ECG assessment at the Final Run-in Visit), Year 2, Year 4, and Year 6. In addition, certification of study staff must be documented and tracked locally. Staff re-certification may be requested of individual clinics as needed based on ECG quality.

11. **Microbiome Collections:** Training will be provided to clinical site research staff via WebEx. Certification will require review of the procedures as outlined in the Microbiome Manual and successful completion of the microbiome quiz (passing score: ≥80%). Training and certification must be documented and tracked locally.
12. **CGM Certification:** Initial certification will be provided at an in-person training. Training of subsequent staff requires review of the CGM Protocol, CGM Manual of Procedures, completion of the CGM quiz (passing score: ≥80%), and completion of the CGM competency checklist. Training and certification must be documented and tracked locally.

The following table provides a schedule of when training and certification should occur for each of the measurements and assessments:

Table 3.3: Training and Certification Schedule

Measurements and Assessments	Prior to commencing GRADE study	1 Y	2 Y	3 Y	4 Y	5 Y	6 Y
Anthropometric Measurements							
Weight	x			x			
Height	x			x			
Waist and hip circumference	√			√			
Assessments							
Blood Pressure	x			x			
Neuropathy (MNSI/foot exam)	√			√			
OGTT	x			x			
QWB	√			√			
Neurocognitive	√						
ECG	√						
Microbiome Collections	√						
Online Certifications							
Web randomization	√						
MIDAS Data Entry	√						

X= Local training required to document competency and documentation is kept on file locally.
√=Formal certification required and certification documents are kept on file locally.

The **Study Coordinator** at each clinical site must be certified in all required components. The only exception is if the Study Coordinator is serving in an alternate role such as an administrative role and does not perform the measurements or testing. In this situation, the Study Coordinator must delegate a

member of the staff to be certified in all procedures. The Study Coordinator must be certified in MIDAS data entry regardless of their local role. In order to obtain site certification, at least one designated staff member must be certified in all procedures and documentation must be on file at the Coordinating Center. In addition to the Study Coordinator, there are two general categories of staff that must be certified:

1) **Research Staff** – GRADE staff who work directly with the Study Coordinator and are involved with the completion of case report forms and research participant files, participate in the informed consent process, communicate with the GRADE Coordinating Center, conduct participant visits, randomize participants, and/or collect and ship specimens. These staff members will complete the appropriate certification components as delegated by the Principal Investigator.

2) **Other Staff** – PI's, Co-I's, nurses and other staff at the local clinical research unit who will collect specimens, perform study procedures, and/or prepare samples for shipment to the core laboratories. As appropriate per the PI and local site operations, these staff members will complete the appropriate certification components, e.g. GRADE Protocol Quiz, waist/hip circumference certification. Refer to Table 3.2 for a list of clinical staff requirements and certifications.

Any staff member, including **CRC/CTRC staff**, who will be conducting GRADE assessments that require formal individual certification (see Table 3.3) must complete this certification prior to conducting these assessments in study participants. Assessments that require certification include blood pressure, waist and hip circumference, height, weight, MNSI, OGTT, QWB, neurocognitive, and ECG. Training and certification of CRC/CTRC staff should be conducted by GRADE-certified staff and documented in the local regulatory binder (including name of staff member, measures in which they are certified, and name of trainer/certifier). Retraining/recertification of CRC/CTRC staff must be done at least every two years and should be documented in the local regulatory binder. GRADE assessments that do not have specific certification requirements must still be adequately supervised with periodic check-ins by certified GRADE staff to ensure assessments are being completed correctly. Furthermore, GRADE-specific education and medication dispensation must be done by GRADE staff. In the case of more general patient-directed teaching or training (e.g., dietary instruction, recognition and treatment of hypoglycemia), the GRADE staff must ensure that any non-GRADE staff providing such teaching is appropriately prepared (e.g., has requisite education, experience, licensure, or certification) to do so.

Initial certification of the Study Coordinator and any other staff who will be performing the study tasks (as assigned by the PI) and who attend the initial study training meeting will have their training and certification at that time. New study staff at each site will be trained and certified by a site staff member who is already certified (usually the Study Coordinator). The certification documentation for newly certified staff must be transmitted to the Coordinating Center prior to the new staff member carrying out these GRADE activities. Documentation of training and certification must be kept on file locally at each site. Refer to the MAP for detailed training and certification instructions. It is also important to note that the Coordinating Center may also provide additional trainings conducted via WebEx during the lifetime of the study. Study Coordinators are expected to attend required WebEx trainings and include relevant staff when indicated.

3.2.4 Roles of key GRADE staff

Principal Investigator (PI)

The PI at each GRADE clinical site is responsible for the overall conduct of the study at his/her site, including hiring staff and ensuring that the protocol and Manual of Procedures are implemented and followed correctly and faithfully. The PI is required to participate in and oversee recruitment and enrollment and meet with the study team on a regular basis. The PI is responsible for delegating responsibilities to team members as appropriate based on training and scope of practice.

MD or other clinical staff designee (NP/PA/RN)

The study physicians, nurse practitioners (NPs) or Physician Assistants (PAs) at each site, as delegated by the PI, will provide supervision of the diabetes care that is provided according to protocol and oversight of adverse events that may occur during the study, ensuring that they are reported appropriately and, to the extent that they require further care, that the responsible health care team is alerted.
Study care providers will communicate annually with the participants' health care providers (template letters provided centrally) to provide the clinically relevant data (for example, blood pressure and lipid measurements) that are obtained as part of GRADE. In the case of a clinical alert, the site will contact the providers as soon as possible (see section 8.2 for further information regarding clinical alerts).

Finally, a brief physical assessment will be carried out each year by the site staff, limited to measurement of blood pressure and weight and an annual foot inspection. Although other appropriately licensed and trained clinic staff may perform the assessment (for example Registered Nurse, Nurse Practitioner or Physician Assistant), a physician at each site should meet with the participants annually (usually at the participant's annual visit but can be done at another visit as long as it is within one year, plus/minus visit windows, from last contact) to review study results and progress, history of adverse events, and to address any concerns and answer any questions that the participant may have. This meeting may be brief. The intent is to ensure that a study physician has ongoing contact with participants and oversight of the medication protocols. Annual (at a minimum) contact with a study physician should also aid retention and promote good relationships with the PCPs who will be the source of many participants.

Study Coordinator

The Study Coordinator is responsible for the day-to-day operations at his/her site. This includes team meetings, data integrity, staff oversight and training, participant visits, outcome collections, administrative and regulatory aspects of study management such as IRB filings, budget preparation, and being the primary contact for central units. Part of the Study Coordinator's role is to communicate regularly with the PI and keep the PI informed as to study progress.

Recruitment Coordinator

The Recruitment Coordinator is responsible for working with the Study Coordinator and PI to develop the recruitment plan and conduct and track recruitment activities. Other tasks may be assigned depending on local site staffing structure.

Other Staff
Depending on site structure and operations, there may be additional staff such as a Research Registered Nurse (RN), Research Assistant, and administrative staff. Their roles will be defined locally within the parameters of the GRADE protocol and funding.

3.2.5 Components of Staff Certification:

GRADE Protocol Quiz
The Protocol Quiz covers key points of the protocol, such as eligibility criteria and visit procedures, as well as informed consent issues.

Before taking the quiz, the relevant study documents should be reviewed (see Table 3.4). Although staff may refer to these documents while taking the quiz, candidates should be familiar with the concepts covered in them. Allow at least 30-40 minutes to complete the quiz; however, there is no specified time limit.

Table 3.4: GRADE Documents for Review Prior to Protocol Quiz

1. Protocol
2. Manual of Procedures (MOP), Measurement and Assessment Procedural Manual (MAP)
3. Informed Consent Forms (Screening/Run-in (Phase 1) and Clinical Trial (Phase 2))

At study initiation, Study and Recruitment Coordinators will complete the quiz online on the GRADE study website, and scores will be provided online and be available to the Coordinating Center. If there are incorrect items, the protocol management staff at the Coordinating Center can provide references to the missed questions and, if needed, are available to review these items with the individual to ensure that he/she understands the material. In some cases, retesting may be necessary.

All other staff will complete a hardcopy of the quiz which will be maintained on file locally at the site. Study Coordinators will score and review the quiz with their staff members to ensure that he/she understands the material. In some cases, retesting may be necessary.

3.2.6 Notification of Site and Staff Certification

The Coordinating Center tracks all training and certification components for each Study Coordinator at each site, as well as completion of site certification activities required prior to receiving study drug. The Coordinating Center will notify the site when the requirements have been met to initiate the study. All other site research staff trainings and certifications should be tracked, maintained and filed locally at each site. Sites should update the Coordinating Center annually with any changes or additions. A **Staff Certification Tracking Log** is provided on the GRADE study website (also see Section 16.2.2). The Coordinating Center will notify individuals of their successful certification and authorize sites to start protocol screening/enrollment. The **Site Initiation Activities Checklist for Study Coordinators** is available on the GRADE study website and in Section 16.2.1.

Manual of Procedures

Chapter 4

TABLE OF CONTENTS

4. CHAPTER 4: RECRUITMENT AND RETENTION

4.1 Recruitment & Retention Overview

4.1.1 Study Population

The study will recruit and follow people with type 2 diabetes with fewer than ten years since diagnosis at the time of screening and who were 30 years or older (≥ 20 years for American Indians) at the time of diagnosis. The majority of potential participants will be identified on the basis of a prior diagnosis of diabetes detected through reviews of medical histories, self-report, and aided by use of electronic medical records and other databases. The study population will include participants previously treated with metformin for < 10 years and > 6 weeks, but on no other anti-diabetic medications within the past 6 months (see Section 5.3 Screening Inclusion/Exclusion Criteria for more details on previous use of anti-diabetic medications).

4.1.2 Goals

The study recruitment goals are **to recruit and randomize a minimum of 50 participants per year over three and a half years at each site** to meet the planned enrollment target of about 5000 participants.

The study retention goals are to **continue scheduled follow-up of all participants randomized until the close of follow-up in the study**, approximately 7.5 years after the randomization of the first participant, **regardless of the participant's adherence to or ability to tolerate the assigned medication regimen or other observed outcomes.**

4.1.3 Minority Representation

An important objective is to recruit a study population representative of the U.S. population with type 2 diabetes, including representation of racial and ethnic minority groups that are disproportionately affected by type 2 diabetes. Similarly, we will try to recruit a substantial fraction (e.g. >20%) who are 60 years of age and older. It is strongly recommended that clinical sites strive to achieve an adequate distribution by race and age.

4.2 Recruitment Procedures

Recruitment will be a challenge for many GRADE clinics because of the limited number of eligible patients with type 2 diabetes within their catchment areas and competition with other clinical trials. Although potential participants are readily identified by virtue of the presence of diagnosed diabetes, many diabetic patients will be excluded because they do not meet the eligibility criteria. Furthermore, GRADE must compete with the large number of clinical trials that seek patients with type 2 diabetes. The total study duration will be approximately 7.5 years, including approximately 3.5 years of recruitment. The total study recruitment goal is about 5000 participants across all sites (approximately 150 participants per clinical site) during the approximate 3.5-year recruitment period. At each site, a staff member should be given the responsibility for oversight and coordination of recruitment strategies and procedures. This individual is referred to as the 'Recruitment Coordinator' and will assist with administrative and other study procedures as directed by the clinical site PI. In order to reach GRADE recruitment goals, each clinic should develop clinic-specific recruitment plans that include multiple strategies for recruitment. A single strategy is rarely sufficient to reach recruitment goals.

4.2.1 Initiating Prescreening and Screening Activities

Participating clinical sites cannot begin enrolling potential study participants until the protocol has been approved by local IRBs and the site has completed all study certification requirements and received approval to start study implementation by the GRADE Coordinating Center (see Section 3.2 Site Initiation Activities for Study Coordinators for details on the required steps). However, prescreening activities may begin after the site has received local IRB approval and all staff have successfully completed the protocol quiz. The Coordinating Center will inform clinical sites when they have satisfied all certification requirements and are permitted to initiate enrollment. Clinical sites must have approval from the Coordinating Center to begin enrolling, but recruitment plans and strategies and prescreening activities should be formulated well ahead of time so that sites can expediently begin to enroll once they have obtained approval from the Coordinating Center.

4.2.2 Screening

Clinical sites, in compliance with local HIPAA rules, will employ electronic medical records and databases, community-based advertising, social media, mailings, and other means of local recruitment. Based on the high frequency of newly diagnosed patients with diabetes in cardiology clinics and non-endocrine practices (such as internal medicine and primary care), screening and recruitment from these settings is encouraged. The use of electronic medical records and other databases is recommended to make preliminary screening and identification of eligible participants as efficient as possible. Electronic data searches will include criteria such as a diagnosis of diabetes < 10 years, age $\geq$ 30 at time of diagnosis ($\geq$ 20 years of age for American Indians) , and current medication use (treatment with metformin only). Either glucose-based (fasting plasma glucose $\geq$ 126 mg/dl or $\geq$ 200 mg/dl 2 hr after a 75 gm OGTT) or HbA1c-based ($\geq$ 6.5%) can be considered during electronic screening. Since the eligibility criteria are based on HbA1c levels, they are preferred. However, it is important to note that in the GRADE study, the eligibility criteria for screening and randomization includes an HbA1c of ≥ 6.8% and 6.8-8.5%, respectively.

The duration of diagnosed diabetes may be very difficult to ascertain accurately from medical records and patient self-report, especially given the heterogeneous recruitment methods (e.g. advertisements, local clinic populations) that will be used and the diverse sources of potentially eligible participants in GRADE. Moreover, laboratory records may not be readily available. In order to try to ascertain the duration of diabetes from the available records and history, the following information should be sought at each of the following recruitment and screening steps:

- Recruitment and Prescreening from available records
  - As available, determine date that diabetes first appears as a diagnosis in electronic medical records and registry level data.
  - If laboratory data are available, look for first fasting glucose levels $\geq$ 126 mg/dl and/or HbA1c level $\geq$ 6.5% (an HbA1c of 6.5% may be used for confirming a diagnosis of diabetes for recruitment and prescreening purposes; however in GRADE, the screening eligibility criteria includes an HbA1c of ≥ 6.8%).
- Phone screen and initial face-to-face Screen Visit
  - During the phone screen and again at the screen visit, ask the potential participant how long s/he has had diabetes and try to establish the first date that s/he was told (month and year).
  - Establish how long s/he has been treated with metformin and whether patient was treated for diabetes or pre-diabetes.
  - Obtain self-reported medical and medication history.

Even with the best of intentions and methods, it will be difficult to ascertain with complete accuracy the duration of diagnosed diabetes. In the absence of any conclusive data to suggest that diabetes duration will be >10 years at the time of screening, participants' self-reported duration can be taken at face value.

4.2.3 Recruitment Strategies

Timely and effective recruitment is vitally important to the success of the clinical trial. Successful retention of the participants for the entirety of the trial begins during the recruitment phase by enrolling suitable participants. Following is a brief description regarding development of a recruitment plan and strategies for recruiting and retaining GRADE participants.

4.2.3.1 Developing a local site recruitment plan

Given the diverse locations and settings of the clinical sites, local sites will need to be aware of how to adapt recruitment efforts and strategies to their unique circumstances and population. Each site should identify staff involved with recruitment, review their responsibilities, and set regular meeting times to review the outline of the plan designed to meet the recruitment target at their site, such as the number of participants screened per week in order to enroll successfully 150 participants per site.

Topics to be addressed by the recruitment staff at each site include the following:

Clinic contact information

- A designated telephone line, email address or other suitable contact that will remain consistent and be answered regularly is necessary.
- Develop language for flyers, advertisements and other postings for approval by the local IRB so that recruitment activities are not delayed. Sample recruitment materials developed for the study will be available via the GRADE study website.
- Develop letters to PCPs and to participants, and screening logs needed to track mailings, responses, and contact information (refer to Chapter 15; samples are also available on the GRADE study website).

Database queries

- Electronic medical records, data repositories (ICD 9 codes, age and diagnosis, HbA1c values)
- Laboratory databases

System(s) to promote referrals

- Make physicians, nurses, and other health care providers inside and outside your practice aware of GRADE. Give out GRADE eligibility pocket cards with clinical site contact numbers (available on the GRADE study website).
- Present GRADE to your colleagues by placing flyers in their mailboxes, posters, and brochures in common waiting rooms, clinic rooms, and nursing stations, as well as providing educational programs, grand rounds, and in-service meetings. PowerPoint presentations will be available from the GRADE study website.
- Meet with appropriate medical staff (e.g. primary care physicians) to review lists of identified potential participants and flag those who fulfill eligibility criteria and would be good study participants.
- Obtain the appropriate permission/approvals to contact providers and/or potential participants, as per guidelines of the local institutional regulations before initiating recruitment efforts. There is a sample letter to request the support of a physician to enroll the participant (see summary of

letters in Section 15.3 and sample letters on the GRADE study website). Some providers are willing to have a letter sent on their behalf to their potentially eligible patients to inform them about the study (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website).
- Establish a system for addressing referrals. Contact potential participants promptly, and follow-up regularly with their health care provider.

Advertising
- Place articles in practice or hospital newsletters, hang posters and place flyers and brochures in clinics, cafeterias, lobbies, lounges and other areas where colleagues and staff gather as permitted. Also, consider inter-office email and websites.
- Make use of any other source to bring GRADE repeatedly to the attention of the patients and to health care providers at your site so that GRADE automatically comes to mind when they see patients.
- Provide GRADE Eligibility Pocket Cards to all health care providers in clinic (available on the GRADE study website).
- Set up a display table in a high traffic area staffed by a study coordinator or physician offering study information as per local institutional regulations.

External Promotion

External promotion may be another method to recruit study participants. The potential participant's primary care provider should be supportive of his or her participation in the study.
- Plan to provide adequate telephone coverage when using external promotions. You may not have the time to talk in detail to each person who responds to the promotion. At a minimum, however, you should thank them for calling, note their telephone number, and arrange to call them back for a more extensive discussion of GRADE.
- Consider placing flyers/posters, when available, in various community sites or conducting in-service programs or health fairs at the sites. Advertisements in local community newspapers, church bulletins, and targeted mailings of GRADE brochures to residents in the community are other possibilities, but again may not be cost-effective.
- Mass mailings to targeted diabetic and or ethnic groups with high prevalence of diabetes. Historically, the yield from this approach is usually quite low. Therefore, its use should be reserved for special circumstances or for clinics that have had success in recruiting from mass mailings.

Contact with Referring Physicians

Reassure referring providers that their patients will be followed by GRADE investigators for study purposes only and that they will be informed of the patient's status throughout the study (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website). This will promote further referrals and cooperation during the study in notifying or obtaining information regarding events.

Involvement of and oversight by the Principal/Co-Investigator(s) at each site is essential for successful recruitment in clinical trials. Although each clinical site will develop its own strategies, for many sites the most successful techniques involve personal contact with referring clinicians. Possible strategies include:
- Formal presentations (Grand Rounds, in-services, research conferences)
- Informal presentations (house staff rounds, informal clinic in-services)

- Letters from the primary care physician to their patients, brochures describing the study, display of posters in clinics and diagnostic labs, phone calls and /or conversations with physicians soliciting referrals

Print and Electronic Media

Print media, websites and social media, television, and radio may also be effective avenues of communication to potential GRADE participants. The effectiveness of these methods as well as the specific print and electronic media selected may depend on the site-specific media market.

- Consider using public service announcements (PSAs) on radio and television stations in your area or arrange for a television/radio interview or newspaper article using approved GRADE recruitment materials. If you are associated with a university, there may be a Public Relations department to assist you. Paid advertising is usually very expensive and should be considered only as a last resort as it is often not cost-effective.
- Study-wide or local brochures/posters that give basic information about the GRADE design and rationale are available through the Coordinating Center which can be distributed through a variety of means e.g., door-to-door, with existing publications, through worksites, etc.
- Websites and social media may also provide excellent venues for publicizing the study and reaching out to potential participants. Post links to the GRADE public website (www.gradestudy.com) on websites of willing organizations with special interest in diabetes (e.g., local American Diabetes Association website, University Diabetes Centers, local health departments and other health related organizations).
- GRADE also has its own Facebook page as an avenue for participants to learn more about the study. The GRADE public website contains information about the study, FAQ's and an eligibility questionnaire that potential subjects can complete. If the subject qualifies, the site will be notified via email or if at a VA site they will receive a fax.

Recruitment Progress Monitoring

Meet weekly as a team (including the PI/co-PI) to discuss actual progress in meeting your goals. Increase the number of chart reviews each week as needed. Work backwards; specifically, determine approximately how many screens it takes to result in one successful enrollee, how many calls it takes to result in one screen (taking into account no-shows), and how many chart reviews it takes to result in one eligible call. Determine what is working and what is not. Review barriers and problems. Revise the recruitment plan as necessary.

- Maintain a pre-screening log (available on the GRADE study website).
- Stay involved and motivated – keep the momentum going!
- Discuss the topic of targeted mailings during your clinic's recruitment meetings.
- Send potential eligible participants a GRADE brochure and cover letter (see GRADE study website) once you have gained the approval of the patient's primary health care provider, as determined by local policy.
- Follow-up with these patients while the study is fresh on their minds (no longer than a week after the original letter) to discuss GRADE in more detail and to answer any questions that they may have. Design your materials with an opt-out clause (see Summary of Participant and PCP Letters in Section 15.3 and sample recruitment letters on the GRADE study website).

4.3 Retention

Retention will be a challenge in GRADE, as it is in all clinical trials. In GRADE, retention is likely to be an even greater challenge than in many trials because participants will be asked to continue quarterly clinic visits for up to 7.5 years. Every attempt will be made to obtain long-term study measurements and record study outcomes in all randomized participants **up to the close of the study approximately 7.5 years** after the randomization of the first participant, or the death of the participant. Participants who do not adhere to or tolerate the assigned medications may be withdrawn from therapy; however, no participant will be withdrawn from continued follow-up in the study unless the participant formally withdraws consent. Although this may happen rarely, most participants with poor adherence will still agree to be contacted from time to time (to encourage adherence, study visits, re-engage, and potentially to obtain data by phone). The goal is that every surviving randomized participant will complete follow-up in the study to the extent possible up to the study close.

Staff should reference the **GRADE Retention Guide** for recommendations, tips, and tools to assist with participant retention.

4.4 Remote Follow Up

Occasionally, a participant may be unable to attend study visits in person. This may be due to a temporary situation, such as a busy schedule, or it may be that the participant has decided to move away from their original GRADE clinical center. If an in-clinic study visit is not feasible, a remote data and specimen collection should be considered as an alternative. When possible, in-person visits are preferred over remote data collection. Remote collections should only be done after all efforts to conduct in-clinic visits have been exhausted. See Appendix B for information about procedures during the COVID-19 pandemic.

4.4.1 Off-site data collection visits

Under the rare circumstance that a participant is unwilling or unable to travel to the GRADE clinical site for a study visit, the staff may suggest either a home (or other location such as nursing home) visit if feasible. A home visit will be considered feasible only if resources (staff), time, and local site regulations permit such a visit. If a home or other off-site location visit is performed, two staff members should be in attendance, if possible, for safety reasons. Staff members are encouraged to collect only the data and measurements that are practical for the environment and comfortable for the participant (e.g., questionnaires, urine/blood samples, weight, BP, waist/hip, neuropathy exam).

4.4.2 Remote data collection

A phone visit may be done to gather medical history information (**Quarterly** or **Annual Visit forms**) and complete other staff-completed forms. Self-administered questionnaires should not be completed via phone; instead, self-administered questionnaires (except the EDSQ) can be mailed to the participant for completion, if the participant is willing. Include an addressed postage-paid envelope to assist the participant with returning the completed questionnaires to the clinic. Blood pressure, weight, and other similar measurements that are collected outside of the study by clinicians who are not GRADE-certified in these assessments should not be submitted via visit forms as study data. (However, note that external medical data may be used when reporting a targeted or serious adverse event.)

The blood sample for HbA1c testing is the only biospecimen that can be collected off-site if an in-person visit is not held. The capillary blood collection is a method to allow a GRADE participant to self-collect a blood sample to send to the study central laboratory for HbA1c measurement. Remote capillary

collection kits are available to request from the CBL for remote HbA1c specimen collection. Before mailing the kit to the participant, confirm that he/she is willing to complete the collection in their home. Include the partially completed **Capillary Collection Blood Sample Transmittal form** for the participant along with a tailored letter to the participant explaining the procedure. The site will be responsible for contacting the participant to ensure that he/she received the kit and to review the collection instructions to ensure the participant understands the instructions and is willing to complete the procedures. The participant will ship the blood sample and the remaining kit contents to the GRADE Central Biochemical Laboratory (CBL) for processing. The CBL will report the HbA1c results and send a copy of the participant-completed STF to the clinical site staff. The HbA1c results of the capillary collection will be reviewed with the participant in the same manner as in-clinic blood draw results. Note that the capillary collection kit may be used to collect interim confirmation HbA1c samples (i.e. following a trigger >9%) or to collect a scheduled HbA1c sample while a participant is abroad. For participants who are abroad, the CBL will provide specific instructions for shipping based on the country. For more guidance on when this kit can be used, please contact the Coordinating Center. All other specimen collections cannot be completed remotely.

4.4.3 Following Participants who Relocate away from a GRADE Clinical Center

In some cases, participants move somewhere convenient to another clinical center, and in those cases transferring the participant may be a good option (see section 4.5). However, if the participant moves to a place where there are no convenient GRADE clinical centers, a variety of remote follow-up options are available to facilitate continued follow-up for the remainder of the study.

First, the site should determine whether the participant plans to move permanently and whether s/he plans to visit the locale of the original clinical site in the future (and if so, how frequently). If the participant will be returning, for example to visit family members, periodic in-person visits can be completed. Completing Annual visits should be a priority, when possible.

Sites can conduct remote visits around the scheduled visit target date (reference Section 4.4.2). All regularly scheduled study incentives may be given in exchange for continued participation from afar. If the participant is unwilling or unable to complete a remote visit for any of the scheduled time points, a **Missed Visit Form** should be entered for that visit.

4.4.4 Medication Management for Participants who have Relocated

If a participant has relocated but maintains a strong relationship with the GRADE clinical center, staff can continue to provide study medications over periods when the participant cannot attend in-person visits. Medications may be dispensed in person or mailed to the participant; however, medications cannot be mailed to a care provider outside of the study (e.g. local pharmacy) for dispensation on the study's behalf.

If the participant will be away for a short duration of time (e.g. 3-6 months seasonally), the site can dispense additional medication to last until the participant's next in-person visit at the GRADE clinical site.

If the participant has relocated permanently, medications may be mailed to the participant. Annual visits with the participant's local physician can substitute for the required annual PI visit contingent on local institutional guidelines, physician agreement, and continued safety testing. Local serum creatinine/eGFR testing must be completed annually and results shared with the site investigator prescribing the study medications. The GRADE site should inform the local physician about GRADE vitamin B12 testing

requirements and encourage local B12 testing, and must track the results when completed. HbA1c testing should be done via remote capillary collection (for testing by the CBL) every three months to fulfill the dual purposes of data collection and safety monitoring. HbA1c testing is required at least annually for continued mailing of study medications. If pursuing this option, the site PI should engage the participant's local physician to see if s/he is willing to conduct annual creatinine testing while allowing GRADE to continue managing the participant's diabetes medications. Close collaboration between the local physician and site PI is necessary, and the site PI should be comfortable with this arrangement before moving forward.

If, ultimately, the participant is not able to remain on the study medications for whatever reason, s/he should still be approached about remote data collection to the extent that s/he is willing to participate. Maintaining a relationship with each participant is key to preserving our ability to collect end-of-study data points and complete follow-up of participants.

4.5 Transferred Participants

For optimal retention, participants who move to a new location during the study can either be transferred to a GRADE study site located in the area of their new residence or, if the participant prefers and the distance is reasonable, the original site can continue to follow them, budget permitting (see section 4.4.3). The following are guidelines to assist the clinical sites in a smooth and successful transfer.

1. When relocation of a participant is imminent, the original site's coordinator or designated personnel should discuss transfer options vs. remaining with the original site with the participant.

2. The coordinator helps to determine if a GRADE site is located near the participant's new home and then contacts the Coordinating Center to initiate participant transfer.

3. The initiating (sending) GRADE clinical site should work closely with the new (receiving) clinical site to assist in the retention of the participant and ensure a smooth transfer.

4. The Coordinating Center will notify the coordinator at the new site of the transfer. The initiating (sending) site coordinator should contact the participant to inform him/her that the new (receiving) coordinator will be contacting him/her. The new site should then contact the participant to discuss the transfer plan, provide contact information for staff at the new site, and schedule the next appointment.

5. The initiating coordinator must contact the Coordinating Center staff to obtain a copy of the **Participant Transfer Checklist** and the **Participant Transfer Form**. The initiating (sending) coordinator must follow the participant transfer steps as provided by the Coordinating Center.

6. The initiating site is responsible for correcting data queries on forms they completed, and all data queries should be addressed prior to transfer. When the participant moves to the new site, all of the GRADE participant identification information (participant ID and GCode) will remain the same; only the site number will change.

7. The Coordinating Center will then inform the new site's coordinator when data entry can begin for the participant, and will notify the central units. The initiating site should copy all GRADE

data forms and documents in the participant and source documents binder and send these to the new site. Originals should be retained at the initiating site.

8. Both sites should discuss any adjustments to their medication orders with the DDC.

9. Participants will need to sign informed consent forms for the new site. The new site should check with their local IRB concerning regulatory issues.

4.6 Inactive Participants

Clinical sites should make every effort to maintain contact with the participant during the trial. Unless the participant withdraws consent, the clinic staff should try to maintain regular contact with the participant and collect data as specified in the protocol whenever possible. Participants who miss visits should be respectfully encouraged to return to the study over time. The goal of the study is to have complete follow-up of participants.

At this point in the study, the only circumstances under which a participant should be designated as "inactive" are death, withdrawal of consent, pregnancy (temporary), or long-term incarceration (temporary). Participants who are 'temporarily inactive' may later resume active participation in the trial at any time. The designation of "lost-to-follow-up" will apply only to those participants who remain unreachable at the close of the study.

In this context, withdrawal of consent is considered to have occurred when a participant expressly indicates that he/she no longer wishes to participate in any aspect of the study and clearly states withdrawal of consent. If a participant decides to withdraw from all components of the study, the investigator must discontinue interacting with the participant. However, poor attendance history alone is not considered withdrawal of consent and site research team should continue efforts to reengage the participant. We hope that participants who are missing visits or otherwise not complying with the protocol will not withdraw consent.

Participants who become pregnant or incarcerated during the study should be designated as "inactive" as soon as study staff becomes aware of their situation. These participants fall into the category of "protected individuals," therefore no data should be collected for these participants during their period of inactivity. Study staff should wait for the participant to contact them when they are ready to be made active again. Study staff should not initiate the contact.

Study medications **cannot** be supplied to participants who:

- have not been seen by GRADE research staff for >1 year, **or**
- have maintained contact with the site only by telephone for >1 year.

Medications will be provided if the participant later decides to resume attending visits. Exceptions to this policy may be made for participants who are being followed remotely after relocating away from their GRADE clinical site (see Section 4.4.4).

4.6.1 Participants who resume active status

Inactive participants may later resume active participation in GRADE at any time. When a formerly inactive participant returns for a scheduled visit (quarterly, annual, or off-site/remote visits) and the

Change in Status form is entered for the participant, the participant status will update to active. If an inactive participant resumes active status, his/her medication management will need to be reviewed.

4.6.2 Management of medication when participants have been started on non-study diabetes medications

Participants who have had their glycemic management altered by non-study staff as reported when returning from inactive status will be evaluated by the study MD or authorized delegate to consider medication adjustment. The intent is to maintain and return to as much of the original assigned study treatment as possible and to restore the participant's medication regimen to the original pathway, if safely possible. The GRADE staff should take into consideration safety, side effects and tolerability, patient preference, and possible impact on long-term retention. In addition, the participant's relationship with his/her own physician should not be undermined and any suggestions to change from the PCP-prescribed regimen should be discussed with the PCP.

If it is deemed safe and appropriate, the intent would be to resume the original medication assignment as follows:

- If the participant had not reached the primary outcome (A1c $\geq$7% confirmed) at his/her last contact before becoming inactive, resume study medication assigned as per the last visit, being mindful of medications that may require titration due to side effects. For example, if the participant has not taken metformin in a year, he/she may need to start at a lower study metformin dose than he/she was receiving at the last visit.
- If the participant had reached the primary but not secondary outcome as of the last active visit, re-titrate, as needed based on treatment assignment. If the participant had previously reached the secondary outcome (A1c >7.5%, confirmed), re-titrate and add glargine (if in a non-insulin treatment group). Those in the glargine group will require insulin intensification (addition of rapid-acting insulin).
- If the tertiary outcome had been reached, the participant can be started (or restarted) on study metformin and an intensified insulin regimen, without the second assigned medication.
- If the participant has been started by non-study providers on a different drug within the same class of medications under study in GRADE, the study team should consider whether switching back to the GRADE agent is appropriate. For example, if the GRADE drug wasn't tolerated but the new drug is, or if the participant strongly prefers the new drug, that preference should probably be respected, for the sake of retention.
- If a non-GRADE diabetes medication was initiated by non-GRADE health care providers, safety and other factors, such as retention, should be considered. Discussion with the participant and health care provider is appropriate in this setting before potentially stopping the new drug and restarting the GRADE medications (see above).

If a non-study medication has been prescribed by a non-GRADE clinician, it cannot be managed by GRADE staff; however, study staff can still issue study metformin to the participant and follow the protocol with regard to metformin. Care should be taken to ensure that participants are not taking both study and non-study metformin at the same time, and that the PCP is aware that the participant is taking metformin.

Manual of Procedures

Chapter 5

TABLE OF CONTENTS

5. CHAPTER 5: PRE-RANDOMIZATION PROCEDURES/PRESCREEN AND SCREEN

5.1 Screening Procedures - Overview

The GRADE screening process is designed to evaluate eligibility criteria in two phases:

1. **Screening eligibility:** Evaluate the potential participant's eligibility (see section 5.3) to start the run-in period, first assessing the simple criteria through chart review and/or phone screen (prescreen) and continuing to assess criteria based on the interview, measurements, and tests performed at the screen visit (see Chapter 4 for recruitment strategies).
2. **Randomization eligibility:** Evaluate the eligibility criteria (see sections 7.2.2 and 7.2.3) at the end of the run-in period and assess the participant's suitability to be randomized/enrolled in the GRADE study.

5.2 Prescreening Methods, Screening Eligibility and Screening Visit

The screening process is designed to review participant eligibility through a series of stages of increasing participant and staff burden, cost, and invasiveness. Initial eligibility is assessed by obtaining the medical history through chart review and/or phone screen (prescreen). During the Prescreening process, sites may have electronic medical access to diagnoses, specifically the diagnosis of diabetes (often coded as 250.XX), and to laboratory results including glucose and HbA1c levels. The dates of the diagnosis and the lab value may not be contemporaneous; e.g. the date of a clinical diagnosis may follow, or precede, the date of an abnormal HbA1c (>6.5%) by a considerable time. When dates of an abnormal lab test and the recording of a clinical diagnosis conflict, the GRADE study will rely on the clinical diagnosis rather than the date of the lab test to indicate the date of diabetes onset.

During the Prescreening period, clinical sites may internally utilize the Prescreening Worksheet, Prescreening Log, and Phone Screen Script which are all available on the GRADE study website to help recruit and track prescreened subjects. Clinical sites are encouraged to consider initially discussing the details of the randomized treatment arms **at the time that** the potential participants come to the center for a face-to-face recruitment meeting. However, the choice of how phone screens are conducted will be left to the clinical site based on their experience. It is important to note any barriers/issues that arise during the prescreening process and the right balance to the amount of study information provided upfront to participants at the time of initial discussions and information that needs more time to address at an initial visit for potential candidates to consider participation.
Prescreening documentation are not data entered. Sites must follow local IRB guidelines for documentation and record retention of prescreened subjects who are not enrolled in GRADE. Participants who meet eligibility at prescreen then progress to full screening.

At the Screening visit, the Phase 1 Informed Consent (Screening/Run-In informed consent) is obtained, a brief physical assessment is performed, a health history is taken including medication history, and blood is drawn for local determination of eligibility according to estimated GFR (eGFR), ALT, hematocrit, and HbA1c results. During screening, the GRADE staff completes the Screening Visit Worksheet, Participant Contact Information Sheet, **Recruitment Method Form**, and **Screening Visit Form.** All worksheets, logs and forms are available on the GRADE study website. All data collected on study forms will be entered into MIDAS. Refer to Table 5.1 for other documents used during the screening period. Refer to Section 15.2 for a master guide of GRADE forms, questionnaires and supplementary materials organized by visit. If a participant has failed one or more eligibility criteria, screening stops. Complete the relevant sections of the Screening Form and enter the data into MIDAS. If the reason for screen failure is deemed to be permanent, the participant can no longer be considered for GRADE. If the reason for the screen failure is

deemed to be potentially temporary, the participant may be scheduled for a re-screening at a later date (refer to section 5.4.10 for re-screening and re-testing guidelines), as long as he/she continues to meet eligibility criteria. Re-testing (for example hematocrit, ALT, HbA1c) is permitted for eligibility criteria that are not permanent exclusions (refer to section 5.4.10 for re-screening and re-testing guidelines). The eligibility criteria are listed in section 5.3. They include permanent exclusions and temporary exclusions that may permit re-testing/re-screening.

Table 5.1: Documents used in Screening Period

Name	Type	Data entered into MIDAS?
Recruitment Letters	Letter	No
Prescreening Worksheet*	Worksheet	No
Prescreening Participant Log*	Log	No
Phone Script	Script	No
Participant Contact Information Sheet*	Worksheet	No
Appointment Reminder Letters (Screening, Run-In etc.)	Letter	No
Phase 1 Informed Consent*	Consent	No
Screening Visit Worksheet*	Worksheet	No
Recruitment Method Form	Form	**Yes**
Screening Visit Form	Form	**Yes**
Screening Failure or Eligibility Letters	Letter	No

*to be maintained and stored locally at the clinical site

5.3 Screening Inclusion/Exclusion Criteria

The inclusion/exclusion criteria are listed on the screening eligibility checklist, which should be reviewed carefully for each participant before entering run-in. Permanent exclusion criteria are indicated with an asterisk.

The intent of the exclusion regarding interventional studies is two-fold: 1. To ensure that other interventions do not interfere with the GRADE interventions or pose a safety issue (for example, an unexpected interaction between drugs from two different studies); and 2. To make sure that the subject burden from two competing studies does not interfere with the conduct and completion of GRADE.

Observational studies do not pose a problem with regard to interactions and a few interventional studies may not pose a problem. On the other hand, the demands of participating in another study, either observational or interventional, at the same time as GRADE, may interfere with complete adherence to the GRADE protocol. The decision as to whether participation in another study (observational or, very rarely, an interventional study) at the same time as GRADE is exclusionary will be left to the discretion of the Clinic team and its PI; however, investigators should be very cautious regarding the burdens imposed by GRADE and be attentive to additional burdens that may be imposed by participation in other studies.

5.3.1 Screening Inclusion Criteria

1. Men or women diagnosed with type 2 diabetes at age ≥30 years of age, or if American Indian, age ≥20 years at diagnosis
2. Duration of diagnosed diabetes less than 10 years **at time of screening,** determined as accurately as possible based on available records and/or patient self-report at screening

3. Metformin treatment duration of less than 10 years at time of screening
4. HbA1c ≥6.8%
5. Metformin treatment with at least 500 mg metformin/day for a minimum of 6 weeks prior to screening
6. Willingness to administer daily subcutaneous injections, take a second diabetes drug after randomization, potentially initiate insulin and intensify insulin therapy if study metabolic goals are not met, and perform self monitoring of blood glucose
7. Fluent in either English or Spanish
8. For females: participant is not currently pregnant (negative pregnancy test if of childbearing potential which includes pre-menopausal and not surgically sterile women) or currently breastfeeding, and is not planning to become pregnant during the course of the study (See Section 5.4.2.1 for further details on what is considered not of childbearing potential)

5.3.2 Screening Exclusion Criteria

1. *Suspected type 1 diabetes (lean with polyuria, polydipsia, and weight loss with little response to metformin) or "secondary" diabetes due to specific causes (e.g. previously diagnosed monogenic syndromes, pancreatic surgery, pancreatitis)±
2. Currently using or has previously (within past 6 months) treatment with any diabetes drug/glucose-lowering medication other than metformin**
3. History of intolerance or allergy to or other specific contraindication to any of the proposed study medications or sulfa medication******
4. *Current need for any specific glucose-lowering medications solely for other conditions, for example for polycystic ovary syndrome
5. Resides in the same household with another GRADE study participant
6. *Symptomatic hyperglycemia requiring immediate therapy during screening or run-in, in the judgment of the physician
7. A life-threatening event within 30 days prior to screening or currently planned major surgery
8. *Estimated GFR (eGFR) <30 mL/min/1.73 m^2 or history of renal replacement therapy regardless of eGFR
9. Any major cardiovascular event in previous year, including history of myocardial infarction, stroke, or vascular procedure such as coronary artery or peripheral bypass grafting, stent placements (peripheral or coronary) or angioplasty
10. *History of end stage renal disease requiring dialysis or transplantation
11. Any new diagnosis of cancer in the previous 5 years (other than non-melanoma skin cancer), or treatment for any cancer in the previous 5 years (other than for non-melanoma skin cancer). Exceptions may be made, at the discretion of the local Principal Investigator and after review by the subcommittee overseeing protocol implementation, for cancers, such as some thyroid cancers, that have a benign clinical course and are not expected to interfere with conduct of the study.****
12. History of severe liver disease or acute hepatitis or (ALT) >3 times the upper limit of normal. *****
13. *Previous organ transplant
14. *History of pancreatitis (any history of pancreatitis at all)
15. * Personal or ***family history of MEN-2 or family history of medullary thyroid cancer
16. *Treatment with oral or systemic glucocorticoids (other than short-term therapy, for example for poison ivy) or disease likely to require periodic or regular glucocorticoid therapy (Note:

inhaled steroids and/or physiological replacement treatment (e.g. for Addison's Disease) are acceptable)
17. Treatment with atypical antipsychotics known to be associated with a high risk of metabolic dysfunction (refer to Glossary in Appendix A)
18. Current alcoholism or excessive alcohol intake
19. *Hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels*******
20. Hematocrit < 35% for males and < 33% for females
21. *Clinically or medically unstable with expected survival <1 year
22. Unwillingness to permit sites to contact the PCP to communicate information about the study and the participant's clinically relevant data
23. At the time of final run-in, no identified PCP to provide non-study care (Note: in cases where a study MD serves as the participant's PCP, another study provider must assume GRADE management decisions for the participant during the study.)
24. Participation in another interventional clinical trial (includes medication, device, procedure studies)
25. *Previous randomization in this study
26. History of* or planning weight loss surgery, including banding procedures or surgical gastric and/or intestinal bypass (if procedure reversed, may be considered eligible after 1 year).
27. *History of congestive heart failure (NYHA 3 or greater- shortness of breath with minimal exercise or at rest)
28. In the opinion of the principal investigator (PI), any other factor likely to limit compliance with the protocol

***Permanent exclusion criteria**

** Participants who have had limited use of glucose-lowering drugs (other than metformin) of no longer than seven days (for example, during hospitalization) may be screened.

***For this criterion, family is defined as first-degree relatives (a close blood relative which includes the individual's parents, full siblings, or children).

****Participants with cancer who have not required therapy in the 5 years prior to randomization but have serious cancers should not be included in the study. Serious disease may complicate their participation in GRADE and these individuals should be excluded.

*****Participants with history of severe liver disease, active hepatitis A, B, or C, or liver function test (ALT)>3 times the upper limit of normal are excluded from the study. To clarify, history of severe liver disease refers to an ongoing medical problem characterized by hepatic insufficiency which is often but not always accompanied by GI symptoms, edema, ascites, jaundice, encephalopathy, hypogonadism, splenomegaly, esophageal varices, increased risk of hypoglycemia and/or reduced levels of albumin or clotting factors. Such patients are excluded. Those patients with liver function test (ALT) >3 times the upper limit of normal are excluded. Acute hepatitis is a temporary exclusion and when resolved, the participant may be eligible. A remote history of severe liver disease would not necessarily be exclusionary if in the opinion of the investigator the patient is fully recovered (e.g., does not require treatment for liver disease and has normal liver synthetic function, portal blood flow and biliary metabolism). Refer to Section 5.4.11 for guidance on re-testing ALT.

****** A history of an allergic reaction to sulfa drugs is a contraindication on the Amaryl (glimepiride) package insert. Patients are often not clear on what a true drug allergy is so unless a chart review document details about a purported past allergic reaction to a sulfonamide drug, potential participants should be asked during screening what symptoms they experienced when they had the past reaction. If past reactions included hives, rash, angioedema or anaphylaxis, the patient is not eligible for GRADE.

******* If a participant has recently donated blood, sites should delay enrolling for at least three months (but preferably longer) following the donation. Participants may be screened starting two months after the donation with the understanding that the A1c may still be impacted by the donation.
± For more information about specific secondary causes of diabetes, reference Table 1 of the American Diabetes Association's paper entitled, "Diagnosis and classification of diabetes mellitus" (American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014 Jan;37 Suppl 1:S81-90. http://care.diabetesjournals.org/content/37/Supplement_1/S81/T1.large.jpg)

5.4 Screening Visit Procedures

Before the Screening visit, the participant should have received detailed instructions as to location of the appointment and what will be done at the visit (see Summary of Participant and PCP Letters in Section 15.3 and sample appointment reminder letters on the GRADE study website). The study staff should also remind the participant by call or email just prior to the visit of the date and time to arrive at the clinical site and to bring all prescription medications or a list of them to their visit. Screening visits may be scheduled at any time of day (morning or afternoon) that is convenient for the clinic and the participant as they are non-fasting. The participant ID and GCode will be obtained at the Screening visit (see Section 5.4.3).

5.4.1 Informed Consent

Template consent forms are available in Chapter 16 and on the GRADE study website and should be edited to meet local IRB requirements. Copies of IRB approval (including the approved consent form) must be on file with the GRADE Coordinating Center prior to initiation of any screening visit activity.

It is recommended that consent be obtained in two-steps unless the local institution's IRB or clinical site operations require otherwise. The consent forms associated with the GRADE study are the screening/run-in consent (Phase 1 Consent) and GRADE trial consent (Phase 2 Consent). If the clinical site's local IRB insists upon a combined consent, the site may comply with their local IRB policies and submit a combined screening/run-in and clinical trial consent. The information provided in the (currently) two-step informed consent will have to be included in the single-step document.

There was concern that the subject may interpret execution of a single overarching consent to represent a contract to enroll the subject into the long-term study. In fact, however, subjects must complete all screening assessments and a run-in period, during which it may be determined that the subject is not eligible to enroll in the full scale trial. Two separate consents would obviate the possibility for such a misinterpretation of the study's commitments to the patient.

The study coordinator should check in advance with the local IRB to establish the requirements for signing and witnessing consent forms. At some sites, more than one original may be required. At other sites, there may be only a single original with multiple copies made from it. If there is only a single original, local IRB rules must be followed in terms of how and where the original is stored.

Potential participants may learn about GRADE through a variety of recruitment strategies. Screening/run-in informed consent must be obtained at the beginning of the screening visit, including appropriate HIPAA authorization for obtaining medical records. The participant must be provided ample time to review the consent form and ask questions related to the GRADE study. Depending on clinic- and participant-specific factors, clinical sites may provide the informed consent to potential participants

before their screening visit for review prior to their visit. If, after reviewing the consent form and having his/her questions answered, the participant agrees to be screened, the consent form is reviewed, and informed consent obtained. Whether an MD or a local IRB-approved designee can administer the screening/run-in (Phase 1) informed consent will be determined locally; however, the screening/run-in informed consent will include the administration and/or titration of metformin during run-in, and this needs to be considered by local IRBs. A copy (or copies, depending on local IRB requirements) of the signed informed consent is provided to the participant and the original is retained in the participant binder. Depending on the participant's preference, sites may also provide a copy of the GRADE trial consent (Phase 2) for the participant to review.

Once screening/run-in informed consent has been obtained, additional information is collected from the participant. Participant Contact Information Sheets should be completed and updated regularly. They are used to track personal identification information and should be updated during subsequent visits and kept securely on file locally.

5.4.2 Screening Visit Activities and Instructions for Staff

5.4.2.1 Screening Visit Activities

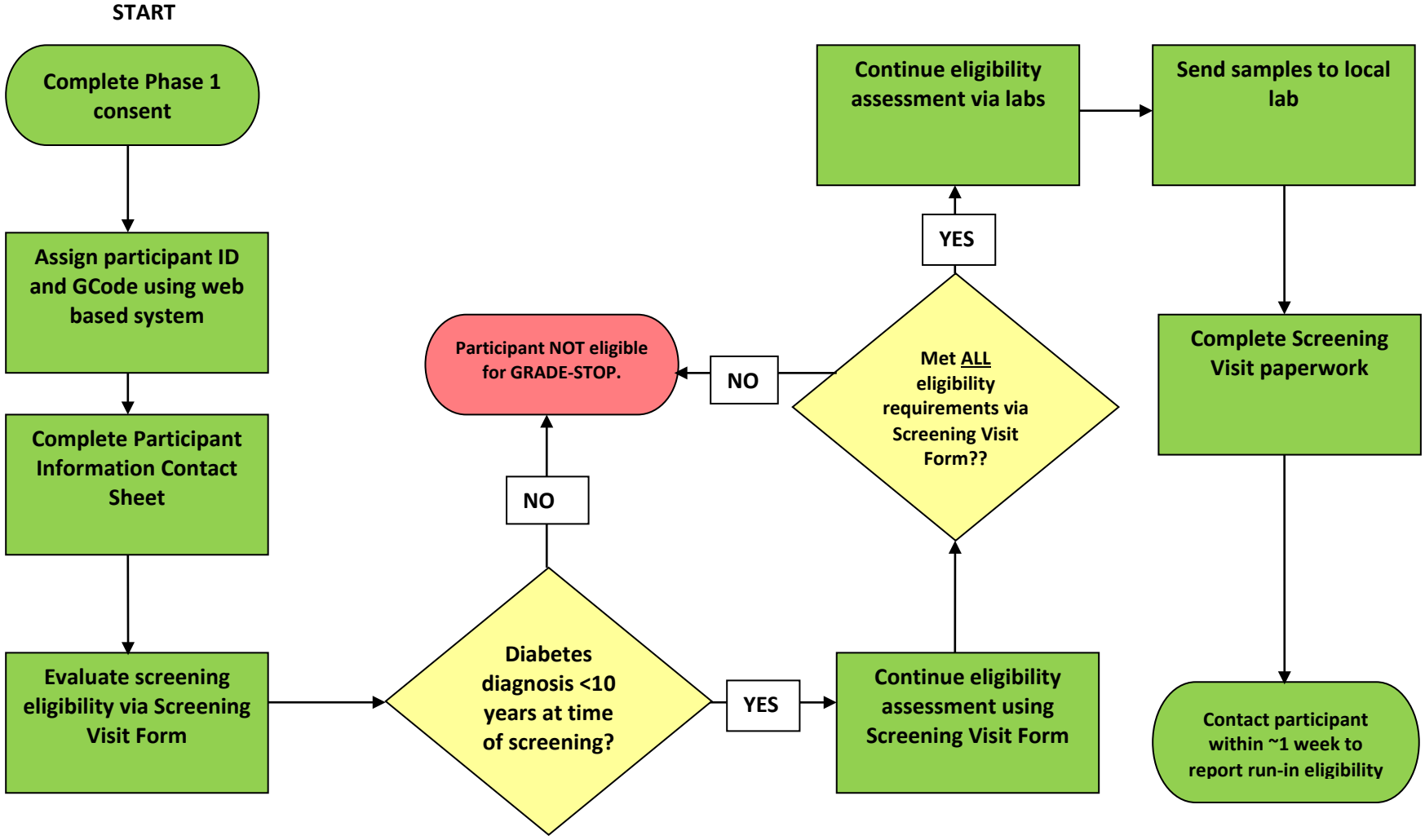
The screening visit includes the following activities:

- All questions about the study are answered
- Participant signs screening/run-in consent (Phase 1 Consent)
- Complete the Participant Contact Information sheet (if participants would prefer to give the information about other contacts and SS number at the next visit that is acceptable, but at a minimum, have them provide their contact information at this visit)
- Evaluate screening eligibility criteria using **Screening Visit Form** and obtain participant ID and GCode (see Section 5.4.3).
- Confirm date of diagnosis (month/year). Must be < 10 years at time of screening
- If NOT eligible at this step ⇒ **STOP.**
- **If eligible at this step, continue** eligibility assessment using the **Screening Visit Form** including:
    - Medical history
    - Medication history including
        - > 6 weeks and no more than 10 years of metformin treatment
- Treatment with any other glucose lowering agents within the past 6 months
- If NOT eligible at this step ⇒ **STOP.**
- **If eligible at this step, continue** to eligibility assessment involving tests and measurements.
    - Physical measurements: (Blood pressure and weight) (see GRADE Measurement and Assessment Procedural Manual, MAP)
    - Blood sample for creatinine/eGFR, ALT, hematocrit, and HbA1c (sent to local lab)*
    - Urine sample for pregnancy as indicated (kits supplied by CBL) on all women with childbearing potential. Participants will not be considered of childbearing potential if: surgically sterile; menopausal (i.e. Age > 45 without a period for >1 year); Age > 55 years; or physically sterile due to other conditions indicated in the participant's medical history. If study staff are uncertain as to whether the participant should have a pregnancy test, we suggest performing it as it is low cost and of limited burden to participants.

** Local lab results obtained ≤ 4 weeks before screening visit are acceptable*

The general process for the screening visit is outlined in Figure 5.1.

Figure 5.1: Screening Visit Flowchart



5.4.2.2 Screening Visit Instructions for Staff

The screening visit will take approximately 60-90 minutes. Below are the screening visit instructions for staff.

1. Complete the screening/run-in informed consent process
2. Provide a copy of informed consent to participant per local regulations
3. Complete the **Screening Visit form***
4. Obtain the physical measurements (blood pressure and weight)
5. Complete screening visit form based on interview and physical assessment
6. If eligible, proceed to collect urine and blood samples

Supplies: Blood collection tubes, urine sample container and HCG (pregnancy test) cartridges if applicable

7. Perform pregnancy test as indicated
8. Send samples to local lab **
9. Inform participant that you will contact him or her within approximately one week to report eligibility to enter run-in and schedule Initial Run-in visit
10. Complete paperwork, data entry, and logs
11. Send lab test results, visit instructions for Initial Run-in visit and make reminder call, once final eligibility is determined

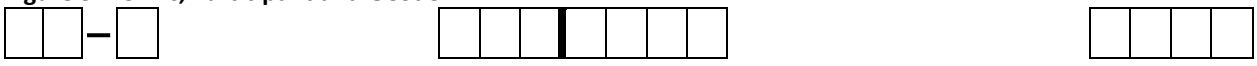
If while completing the **Screening Visit Form the patient is found ineligible, study staff should complete the Screening visit form until a skip pattern is reached. If participant is likely to rescreen in the future, staff may continue to collect data on the **Screening Visit Form**, however data entry for data past the skip pattern is not necessary for the Screening Visit Form. This option is only valid for the **Screening Visit Form**. For all other study forms, staff must enter data as written on the form.*

*** Local lab results obtained ≤ 4 weeks before screening visit are acceptable*

5.4.3 Participant ID

Once the participant has signed the screening/run-in (Phase 1) informed consent, the clinic staff should assign the participant ID using the web based system as directed by the Coordinating Center. A permanent participant ID and GCode are assigned and stay with the participant through screening, run-in and during the entire trial. The participant ID is a 7 digit ID. The first 3 digits identify the clinical site where screening takes place, and the last 4 digits are assigned sequentially prior to randomization within a clinic (see Figure 5.2). The participant ID is entered on all subsequent participant forms. Once the participant ID is assigned to a participant, it must never be used again. Clinical site numbers are assigned and will stay the same for each site throughout the trial.

Figure 5.2 Clinic, Participant and GCode ID



5.4.4 Date of Diagnosis

The date of diabetes diagnosis is used to establish the duration of diabetes, which must be less than 10 years **at the time of screening**. In general, such information will have been obtained during the pre-screening by examining electronic medical records and/or during the telephone interview. During the screening visit, this information should be reviewed and confirmed. An attempt should be made to

verify the date of diagnosis with medical records whenever possible. Date of diagnosis will be recorded as the month and year.

5.4.5 Medication History

Below is a list of targeted exclusionary medications reviewed and recorded on the **Screening Visit Form**:

- *aripiprizole (Abilify)
- *clozapine (Clozaril)
- *lanzapine (Zyprexa, Symbyax)
- *quetiapine (Seroquel)
- *risperidone (Risperdal)
- *prednisone
- *dexamethasone
- *hydrocortisone
- *cortisone

Diabetes medications

- *pioglitazone (Actos)
- *glargine (Lantus)
- *glimepiride (Amaryl)
- *liraglutide (Victoza)
- *sitagliptin (Januvia)

*Exclusionary medications

In addition, metformin history (>6 weeks, <10 years) is reviewed at screening.

Refer to the glossary in Appendix A of Chapter 17 for a complete list of targeted medications for reference purposes. Note: only those marked with asterisks are considered exclusionary.

5.4.6 Medical History

Medical history of the participant is reviewed and recorded on the **Screening Visit Form**.

5.4.7 Anthropometric Measurements

Blood pressure will be measured using standardized methods by trained personnel as described in the GRADE Measurement and Assessment Procedural Manual (MAP). Local equipment in good working order and maintained as per local guidelines is used. Weight will be measured using a local scale. Scales will not be provided by the study and do not need to be uniform across sites but do need to be maintained and calibrated as per local guidelines. (See the GRADE MAP for detailed instructions.)

5.4.8 Urine/Blood Samples

Urine:

Kits are provided by CBL to determine pregnancy in women of reproductive age.

If the result of the pregnancy test is positive ⇒ **STOP**, **ineligible** (temporary).

Blood:

Draw blood samples for local laboratory testing of: HbA1c, serum creatinine/eGFR, hematocrit, and ALT.

5.4.9 Screening Visit Results

The results of the screening visit will be evaluated to determine eligibility for run-in:

- HbA1c: if not $\geq$ 6.8% ⇒ **STOP, ineligible** (temporary)
- Estimated GFR (eGFR) <30 mL/min/1.73 m^2 or history of renal replacement therapy (regardless of eGFR), ⇒ **STOP, ineligible** (permanent)
- Hematocrit: < 35 males, <33 females, ⇒ **STOP**, **ineligible** (temporary)

- ALT: if > 3 times ULN, ⇒ **STOP**, **ineligible** (temporary)

If eligible at this step, the participant continues into the run-in phase. The lab test results and the eligibility decision should be communicated to the potential participant.

5.4.10 Guidelines for Re-testing or re-screening

The overarching goal for screening and run-in is to identify eligible participants who are likely to be able to adhere to the protocol and remain in the study for its full duration. Some eligibility criteria represent permanent exclusions and some are temporary, such as certain lab tests, and may be repeated as discussed in greater detail below. This is referred to in GRADE as "retesting". If too much time passes between the original testing and planned retesting, the entire screening process will need to be repeated. This is referred to in GRADE as "rescreening". The following section explains when re-testing and/or rescreening can be performed. **Please note that re-testing does not allow for extension of visit windows (see Section 15.12).**

5.4.11 Guidelines for Re-testing

Please note that any re-testing of results does not extend visit windows per protocol. Refer to Section 15.12 for The GRADE Help Guide for detailed visit window information. The randomization eligibility criteria require an HbA1c level, measured centrally at final run-in, to be between 6.8% and 8.5%. In addition, the screening eligibility criteria require the following laboratory results, measured locally: HbA1c ≥ 6.8%, eGFR ≥30 mL/min/1.73 m^2, hematocrit ≥ 33% in women and ≥ 35% in men, and liver function testing (ALT) <3 times the upper limit of normal. All of these measures represent potentially temporary exclusions.

The screening *hematocrit and/or ALT* levels can be re-tested once *within* six weeks from the date of the original screening lab draw if there is reason to believe that a repeat test might show that the subject is eligible after an initial result that was exclusionary. If the repeat test(s) shows the participant to be eligible, the entire screening visit need not be repeated. Specifically, the data collected at screening will remain valid. If the repeat level(s) remain ineligible, re-screening (see Guidelines for Re-screening below) may be considered if the exclusionary condition is likely to improve (for example, an anemia that could respond to therapy).

If the randomization eligibility HbA1c, centrally measured at final run-in, does not fall within 6.8-8.5% range, it may be repeated once *within* 6 weeks of the final run-in lab draw (note that re-testing does not allow extension of visit windows – see Section 15.12). If the repeat test falls within the eligible range, the participant does not need to repeat screening or run-in procedures. On the other hand, if the repeat HbA1c test is still in the exclusionary range or if more than 6 weeks have elapsed between the original test and the repeat test, re-screening in its entirety must be performed.

5.4.12 Guidelines for Re-screening

In those circumstances, where the participant does not complete the screen/run-in period or is excluded due to temporary exclusion criteria, re-screening may be performed. In the case of re-screening, all procedures must be repeated. Re-screening cannot be initiated until at least 6 months *after* the prior screening visit.

Only one re-screening is permitted if the exclusionary laboratory test was an out of range ALT or hematocrit. Re-screening is not permitted if the exclusionary laboratory test was an out of range eGFR; this is a permanent exclusion.

If an ineligible HbA1c at screening or final run-in was the reason for rescreening, there is no limit to the number of rescreens that can occur; however, each re-screen must be separated by at least 6 months from the prior ineligible HbA1c.

In addition to the ineligible laboratory values noted above, some examples when re-screening would be appropriate include: positive pregnancy test (the potential participant can be re-screened after delivery and conclusion of breast-feeding) or unexpected medical illness or personal situation rendering participant unable to complete run-in within the required time period. In the setting of a temporary exclusion other than one of the laboratory measurements discussed above, the frequency of re-screening will be left to the discretion of the clinic team and PI. The decision to re-screen should represent a balance between the suitability and likely eligibility of a participant and the effort and resources required to re-screen.

5.4.13 Interrupted Run-in due to non-medical life event

In the case where a participant's run-in period has been interrupted due to reasons other than eligibility, for example when life events (e.g. death or illness in a family member) interfered with the participant's ability to complete their scheduled appointments and complete run-in in the 14 week maximum (refer to Section 15.12), the participant may restart run-in immediately **if** the following criteria are met:

- The participant's eligibility criteria has not changed
- The participant has been on at least 1000 mg per day of metformin for 8 weeks at the time of randomization
- No more than 5 months has passed between the participant's original start of run-in and their randomization
- If more than 14 weeks have elapsed between the local eligibility safety laboratory tests (eGFR, liver function tests, CBC) and the potential randomization date, the laboratory tests must be repeated
- **Received approval from the Coordinating Center prior to re-initiation of run-in**

If all criteria are met and approval has been provided by the Coordinating Center, the participant's prior screening process and information may be counted as valid. Note that potential participants would still need to meet all eligibility criteria at the time of randomization.

Participants meeting the above criteria and approved by the Coordinating Center to resume run-in would continue run-in. An Interim Run-in visit is recommended to review adherence, up-titrate metformin to the maximum tolerated dose and dispense metformin supplies (as needed), to review the clinical trial, and discuss the participant's interest and commitment to the trial. The Eligibility Form should be completed to confirm eligibility based on medical history, safety labs (local) and central labs (CBL). Research staff should confirm that the Baseline Randomization visit will be completed within 45 days of the Final Run-in visit (and within 98 days of local labs). If >6 months have passed since the initial screening date, follow rescreening procedures in the MOP.

To request permission to restart run-in, contact the Coordinating Center Protocol Team liaison and provide the following information:

- Participant ID Number
- Date of Screening visit
- Date and type of last Run-in visit completed
- Reason run-in interrupted
- Plans for resuming run-in
- Date of most recent contact with participant

- Currently daily dose of metformin

The Coordinating Center will review and give authorization to continue run-in.

Manual of Procedures

Chapter 6

TABLE OF CONTENTS

6. CHAPTER 6: PRE-RANDOMIZATION PROCEDURES/RUN-IN PERIOD

The run-in period is designed to adjust and optimize the maximum tolerated metformin dose, further assess eligibility and the ability of potential participants to adhere to study procedures, assess willingness to self-inject medications and test blood sugars, and provide standard diabetes education. All of these tasks need to be completed prior to randomization.

If the participant meets all eligibility criteria following the Screening visit, study staff will contact the participant to schedule the Initial Run-in visit. Alternatively, study staff can schedule the Initial Run-In visit during the Screening visit, anticipating that when the laboratory results return from the local laboratory they are likely to meet the inclusion criteria. The run-in period will consist of an Initial Run-in visit, Interim Run-in visit(s) as indicated, and Final Run-in visit while maintaining contact with the participant throughout the period via phone or email (see Section 6.7.2).

6.1 Maximum Time for Run-In

The maximum time for run-in is 14 weeks from the screening visit. The amount of time spent in run-in will vary depending on the metformin dose at screening. See table 6.1 below for a guide to run-in visits based on metformin dose at screening. The visit scheduler available on the GRADE study website can be used to ensure all pre-randomization visit windows are met – see a screen shot of the visit scheduler in Section 15.11. Also refer to the GRADE Help Guide to Schedule Visits in Section 15.12 and on the GRADE study website for scheduling windows.

Table 6.1 Run-in Schedule

Visit Type	Activities
Screening Visit	Screen/Run-in Consent Confirm eligibility Collect blood (local lab) HbA1c* ALT* Hematocrit* Serum creatinine/eGFR* Urine pregnancy test (if applicable)* Blood pressure Weight
Initial Run-in Visit	Convert to study metformin and adjust dose (if < or >2000 mg daily)[+] Teach titration protocol as needed Demo of injection and finger stick[‡]
Interim contact (phone and/or visit depending on titration schedule)	Ascertain tolerability of metformin and adherence to titration protocol
Final Run-in Visit Length of run-in period will vary depending on metformin dose at screening	Assess adherence[+] Standard diabetes education[$] Collect blood samples (central lab) HbA1c[±] Serum creatinine/eGFR[±] Assess eligibility for optional microbiome collections Consent (Clinical trial[†], optional microbiome collections, & optional audio recordings) Give out stool collection kit & dietary questionnaires (if eligible & consented)
Baseline Randomization Visit. All should occur within approximately 5 to 45 days from blood sample collections at final run-in visit; and between approximately 36 to 98 days from the Screening Visit blood sample collections	Collect fasting blood/urine samples (central lab) DNA[±] Lipids[±] Plasma Glucose[±] Urine albumin/creatinine[±] Blood/urine for storage[±] Oral Glucose Tolerance Test Urine pregnancy test (kit from CBL)* Questionnaires^ Waist/hip circumference^ Blood pressure, height, weight, ECG^ Neuropathy assessment^ Neurocognitive assessment^ Randomization to treatment Dispense study medication

*Performed locally. [±]Performed centrally.

[+]Study goal is 2000 mg per day, minimum 1000 mg per day for at least 8 weeks at final run-in.

[†]Consent for the clinical trial (phase 2) may be obtained at either final run-in or baseline visit (prior to randomization)

[‡] Can be done at any visit during run-in, preferably at visit 1. ^Can be administered at final run-in visit.

[$] May be conducted at Initial Run-In Visit or during Interim Run-In Visits

6.2 Run-in Procedures

An appointment reminder letter with visit instructions will be provided to the participant ahead of the appointment (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website). The run-in period will be used to determine eligibility for randomization and ability to adhere to the study protocol (see Table 6.1). Metformin will be adjusted to 2000 mg daily, as tolerated, with the minimum dose being 1000 mg per day for 8 weeks prior to final run-in in order to be eligible (see metformin titration below). The run-in period will also serve to familiarize the volunteers with the study and the study staff with the potential participants. Finally, all participants will receive diabetes education (4 Steps Booklet) during the run-in period, before randomization.

The first run-in visit must take place within 6 weeks of screening (see Chapter 5), including the local laboratory results (with the 6 week period commencing at the date of screen visit). If the participant does not begin run-in within 6 weeks of being screened, all screening measurements and tests must be repeated and must meet eligibility requirements. It is permitted to combine the Screening Visit and the Initial Run-in Visit if the eligibility labs were performed less than or equal to 4 weeks before the Screening Visit. Although this is not expected to happen often, it is allowable. In this instance, all procedures must be followed for the screening and run-in per the MOP and both visit forms must be completed and entered into MIDAS.

6.3 Interim Run-in Contact

All participants:
Approximately each week during run-in (unless the participant is being seen during that week for an Interim Run-in visit), the study staff will contact the participant by phone or secure email, as permitted by local IRB guidelines and as per participant preference, to assess general compliance with medication regimen, including screening for gastrointestinal (GI) side effects. If GI side effects are reported, study staff will adjust metformin accordingly (decreasing by 500 mg daily). If no side effects are reported, the adjustment schedule will be followed to escalate metformin to maximum tolerated dose. Phone calls should be documented, logged and kept on file locally. Complete the **Interim Run-In Visit Form** and enter into MIDAS if metformin type is changed (e.g. IR, XR) during a phone call or if the dose is adjusted to <1000 mg daily during the phone call (see **Interim Run-In Visit Form** for reference). It is important to reinforce adherence to study metformin and encourage compliance during these calls. Sites must keep local documentation of phone calls as per local site guidelines.

6.4 Medication Management during Run-in

6.4.1 Metformin Adjustment

All participants are required to take a minimum of 1000 mg daily with a goal of 2000 mg daily of metformin in order to be eligible for randomization. At the initial run-in visit, participants will be given study metformin and instructed to stop taking their own metformin. The adjustment schedule for participants during run-in is a recommended schedule that may be modified at the discretion of the investigator and based on medication tolerability by the participant. In general, most participants will receive immediate release metformin (metformin IR). Only those who do not tolerate metformin IR or those who enter the study on controlled released metformin (metformin XR) will receive metformin XR.

Table 6.2 Recommended Metformin Adjustment Schedule for participants at <2000 mg at Screening

	Pre-breakfast	Pre-dinner
Run-in Week 1	500 mg	Add 500 mg
Run-in Week 2	500 mg, add 500 mg	500 mg
Run-in Week 3	1000 mg	500 mg, add 500mg

Step 1: Week 1: If at 500 mg at breakfast, add 500 mg at dinner (500 mg AM, 500 mg PM)
Step 2: Week 2: Add 500 mg at breakfast (1000 mg AM, 500 mg PM)
Step 3: Week 3: Add 500mg at dinner (1000 mg AM, 1000 mg PM)

For participants on less than or more than 2000 mg/day, study metformin IR (500 mg tablets) or metformin XR will be dispensed at the Initial Run-in visit with instructions to adjust to the goal of 2000 mg per day (minimum of 1000 mg per day). For participants treated with less than 2000 mg per day, the dose can be increased by one 500 mg tablet per day starting at the time of the Run-in visit, and weekly thereafter to reach 2000 mg/daily, as noted above. Potential participants who are taking 2000 mg at the beginning of run-in will continue that dose with study supplied metformin (two 500 mg tablets twice per day). Potential participants who take more than 2000 mg will have their dose decreased to two 500 mg tablets twice per day. This can be done as a single step adjustment. If metformin XR was being used prior to the study, the participant should be provided with the study metformin XR with the same dose goals as noted above.

Metformin doses should be taken with meals (usually breakfast and dinner) to a target dose of 2000 mg daily, as tolerated (see Table 6.2). Weekly interim phone calls should assess tolerability and/or side effects. If at least 1000 mg per day is tolerated for 8 weeks at final run visit, the participant is eligible for randomization, assuming other eligibility criteria are met. Two attempts should be made to reach the maximum dose (once with metformin, and once with metformin XR). If eGFR is 30-45 mL/min/1.73 m^2 during run-in, the titration of metformin may be modified based on investigator's clinical judgment. If a minimum of 1000 mg per day is not tolerated, the participant is ineligible.

At the Final Run-in visit, the participant must be on ≥1000 mg of metformin per day for at least 8 weeks. Please note that the target dose is 2000 mg metformin daily.

6.4.2 Adjustment of Metformin in Setting of Gastrointestinal Side Effects

Many participants report modest gastrointestinal symptoms, such as intermittent soft stools or minimal abdominal discomfort, but find that they can tolerate the symptoms. Participants can be informed that these mild gastrointestinal side effects often decrease with time. The local team should judge whether a participant is likely to continue metformin in the setting of gastrointestinal symptoms.

If metformin is causing side effects, confirm that the participant is taking metformin with meals. If participants develop gastrointestinal or other metformin-associated symptoms during the titration to the maximum dose, the total daily dose should be decreased by 500 mg and symptoms reassessed after one week. Continue decreasing the daily dose by 500 mg at weekly intervals until side effects are absent or tolerable. A dose increase, at either meal, should be attempted if no symptoms occur at a lower dose. Two attempts to reach the maximal dose during the run-in are allowed, one with metformin and one with metformin XR. As noted above, as long as the participant tolerates at least 1000 mg of metformin per day and the investigators are relatively confident that the participant will be able to adhere to this dose even if minor gastrointestinal symptoms persist, the participant will be eligible to participate.

6.5 Diabetes Education

All participants will be offered standard diabetes education during the run-in period as well as annual updates. Standardized materials available to study coordinators include information on the pathophysiology of diabetes, prevention of complications, reduction of CVD risk factors, diet/nutrition, exercise goals, and self-care such as foot care and medication adherence. The following materials are available to study coordinators:

Material	Source	Reference Website
Diet		
1. Healthy Eating (English)	AADE7	https://www.diabeteseducator.org/docs/default-source/legacy-docs/_resources/pdf/general/AADE7_healthy_eating.pdf
2. Healthy Eating (Spanish)		https://www.diabeteseducator.org/docs/default-source/legacy-docs/_resources/pdf/general/AADE7_Healthy_Eating_Sp_rev.pdf
3. Portion Sizes (English)	Learning About Diabetes	http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/PortionSizesEN.pdf
4. Portion Sizes (Spanish)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/PortionSizesSP.pdf
5. Eat this, not that (English)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/EatThisNotThatEN.pdf
6. Eat this, not that (Spanish)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/EatThisNotThatSP.pdf
7. Nutrition facts label (English)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/NutritionFactsLabelEN.pdf
8. Nutrition facts label (Spanish)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-healthy_eating/NutritionFactsLabelSP.pdf
9. If you drink alcohol	LookAhead	https://www.lookaheadtrial.org/publicResources/logDocDownload.cfm?docFileName=c9532219-0a9f-4087-a624-603bb9c33704.pdf&docGUID=c9532219-0a9f-4087-a624-603bb9c33704&docVersion=1
10. Food Shopping Tour (English)	TODAY	PDF on GRADE study website
11. Food Shopping Tour (Spanish)		
12. Carbohydrates (English)		
13. What to do if you are feeling sick (English)		
14. What to do if you are feeling sick (Spanish)		
Physical Activity		
15. Being Active (English)	AADE7	https://www.diabeteseducator.org/docs/default-source/legacy-docs/_resources/pdf/general/AADE7_being_active.pdf
16. Being Active (Spanish)		
17. Move those muscles	LookAhead	http://www12.edc.gsph.pitt.edu/DPSCDOCS/Session4MoveThoseMuscles-1.pdf
18. Being active: a way of life		https://www.cdc.gov/diabetes/prevention/pdf/handout_session6.pdf
19. Healthful living: physical activity	NDEI	http://www.ndei.org/uploadedFiles/Common/NDEI/Home/Whats_New/Healthy%20Living%20Handout.pdf
Physiological		
20. Reducing Risks (English)	AADE7	https://www.diabeteseducator.org/docs/default-source/patient-resources/aade7-self-care-behaviors/aade7_reducing_risks.pdf?status=Temp&sfvrsn=0.6869036078392141
21. Reducing Risks (Spanish)		https://www.diabeteseducator.org/docs/default-source/patient-resources/aade7-self-care-behaviors/aade7reducingriskssp.pdf?sfvrsn=4
22. Type 2 and you: Tips to better understand your diabetes pathophysiology	NDEI	http://www.ndei.org/v2/website/Files/T195-04__patienthandout.pdf
23. Type 2 and you: tips to better understand your diabetes and heart disease	NDEI	http://www.ndei.org/v2/website/Files/T195-03__patienthandout.pdf

24. Your Kidneys and the Way They Work (English)	TODAY	PDF on GRADE study website
25. Your Kidneys and the Way They Work (Spanish)		
26. Tips to lower your cholesterol levels (English)		
27. Tips to lower your cholesterol levels (Spanish)		
28. Tips to lower your triglyceride levels (English)		
29. Tips to lower your triglyceride levels (Spanish)		
Goal setting		
30. Setting Goals for Success	AADE	PDF on GRADE study website
31. Setting Good Goals (English)	TODAY	PDF on GRADE study website
Diabetes and Teeth		
32. Diabetes and your teeth (English)	Learning About Diabetes	http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-preventing-problems/Diabetes&YourTeethEN.pdf
33. Diabetes and your teeth (Spanish)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-preventing-problems/Diabetes&YourTeethSP.pdf
Diabetes and Foot care		
34. Be sweet to your feet	NDEP	https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/ndep-health-topics/Documents/be_sweet_to_your_feet_508_2016.pdf
35. Take Care of Your Feet for a Lifetime (English)		https://www.niddk.nih.gov/-/media/4ADA36507AD94759BA05E15986328A6D.ashx
36. Take Care of Your Feet for a Lifetime (Spanish)		
Diabetes and Eye Care		
37. Don't lose sight of Diabetic Eye Disease	NEI	https://nei.nih.gov/sites/default/files/health-pdfs/DEDlayout.pdf
38. Taking Care of Your Eyes When You Have Diabetes (English)	TODAY	PDF on GRADE study website
Diabetes –general information		
39. HbA1c image (English)	TODAY	PDF on GRADE study website
40. Things to do everyday for good diabetes care (English)		
41. Low blood sugar (English)	Learning About Diabetes	http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-blood-sugar/LowBloodSugarEN.pdf
42. Low blood sugar (Spanish)		http://www.learningaboutdiabetes.org/wp-content/uploads/pdfs-blood-sugar/LowBloodSugarSP.pdf
Emotional Health		
43. Diabetes & Your Emotional Health (English)	ADA	PDF on GRADE study website
44. Diabetes & Your Emotional Health (Spanish)	ADA	PDF on GRADE study website

The importance of eating a healthy diet, losing weight if overweight or obese, and being physically active are stressed. All individuals who smoke will be encouraged to stop smoking and provided with self-help materials and/or referral to local programs, as appropriate. The initial education during run-in will

include management of hypoglycemia and the importance of medication adherence. Teaching by staff followed by self-testing with finger stick (alternate site blood glucose testing is acceptable in lieu of finger sticks) and self-injection will be performed during run-in. Sites will have the option of providing education in group or individual sessions and to prioritize the order and frequency of content delivery. Sites have discretion, schedule permitting, as to how much of the education they complete at specific run-in visits. The initial diabetes education must be completed by the Final Run-In visit. Updated diabetes education will be provided during annual visits.

6.6 Initial Run-in Visit

The purpose of the Initial Run-in visit is to titrate study medication (metformin) if the current dose is different than 2000 mg/day, review run-in and randomization procedures and adherence expectations including visits, medication taking, and demonstration with subsequent participant demonstration of self-injection and finger stick (alternate site blood glucose testing is acceptable in lieu of finger sticks) for blood glucose. The visit will take approximately 60 minutes. Standard diabetes education may also be completed at initial run-in.

6.6.1 Initial Run-In Visit Activities

- Confirm eligibility from Screening visit lab results
- Dispense metformin
- Medication teaching regarding metformin (provide handouts to take home)
- Review with and give participant titration schedule
- Discuss willingness to self-inject and self-monitor glucose, and have participant demonstrate both. This task may be completed at any run-in visit prior to randomization but preferably at the Initial Run-in visit.
- Complete and data enter **Initial Run-In Visit Form**
- Discuss interim call schedule and reinforce the importance of medication adherence
- Provide study staff contact information / emergency / overdose information
- Schedule next Run-In visit (either Interim Run-in if participant requires titration, or Final Run-in)
- During or after the visit, provide appointment reminder with instructions (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website) for next Run-in visit and make interim calls per weekly schedule

Labs to be collected:

- None

Forms:

- **Initial Run-In Visit Form**
- **Targeted Adverse Event and Serious AE Form** (if event reported)
- Medical records release form, if needed locally

Supplies:

- Clinical site meter (does not have to be the meter used in GRADE), test strip, lancet, and alcohol pad, for demonstration of self-monitoring of blood glucose (SMBG). The main point of this exercise is to see if the participant can perform a finger-stick (alternate site blood glucose testing is acceptable in lieu of finger sticks), not to teach proficiency of meter use.

- Insulin syringe for demonstration of injection (this injection demonstration does not require having the participant demonstrate competence in drawing up or dialing a dose. It is meant to confirm that the participant will be able to inject themselves with a needle. An insulin syringe with no medication or with sterile saline can be used.)
- Study metformin

See section 15.6 for a flowchart of Initial Run-in visit procedures.

6.7 Interim Run-in visits

Participants who need additional assistance with titrations will have an Interim Run-in visit approximately 4-6 weeks prior to the anticipated randomization date. The purpose of the visit is to assess medication adherence and titrate metformin. The Interim Run-in visit should be completed for subjects who require a change from metformin IR to metformin XR and/or those having difficulty with medication titration or adherence due to GI intolerance (see Section 9.3.4 for metformin side effects).

6.7.1 Face-to-Face Interim Run-in visits

A face-to-face interim visit (vs. phone visit) may be held with any participant. For example, if the participant requires additional time to complete the teaching component, self-management or medication compliance, or additional medication needs to be dispensed, a face-to-face Interim Run-in visit may be scheduled. It is also permitted to schedule more than one Interim Run-in visit if necessary to adjust medication and/or to dispense metformin. Although not required, a face-to-face Interim Run-in visit is recommended for those at a metformin dose of 500-1000 mg at the Screening visit. An **Interim Run-in Visit Form** is completed at all face-to-face Interim Run-in visits. In addition, the **Targeted Adverse Event and Serious AE Form** should be completed as needed.

6.7.2 Weekly Phone Calls

Approximately weekly phone calls should be conducted for all subjects during run-in to assess general overall compliance and medication tolerability and to titrate metformin if needed. If at any time the metformin dose decreases to less than 1000 mg daily or if metformin type is changed (e.g. IR, XR), an **Interim Run-in Visit Form** should be completed and entered into MIDAS.

6.8 Final Run-in visit

The purpose of the Final Run-in visit is to assess adherence and complete the biochemical assessments required to determine eligibility for randomization (see list of inclusion and exclusion criteria for entry in Chapter 7). Final Run-in may occur a minimum of 4 weeks from initial run-in if metformin dose is 2000 mg/day or greater at screening. However, the Baseline Randomization visit must occur after a minimum of 6 weeks from the Screening Visit. If metformin dose is less than 2000 mg/day, it may take longer to reach the Final Run-in visit; for example, if the metformin dose is 1000 to <2000 mg/day at screening, the minimum time from the Initial Run-in visit to the Final Run-in visit is 6 weeks with a minimum time of 8 weeks from screening to baseline randomization, and if the dose is 500 to <1000 mg/day at screening, the minimum time from initial run in to final run-in is 8 weeks and the minimum time to baseline from screening must be > 8 weeks. Please note that all participants must be taking a daily dose of ≥1000 mg metformin for a minimum of 8 weeks at final run-in. See Section 15.12 GRADE Help Guide for Scheduling Visits for detailed information. The visit scheduler available on the GRADE study website can be used to ensure all pre-randomization visit windows are met – see a screen shot of the visit scheduler in Section 15.11. The maximum time for run-in is 14 weeks from screening. The visit will take approximately 90 minutes to 2 hours to complete.

6.8.1 Final Run-in Visit Activities and Instructions for Staff

6.8.1.1 Final Run-in Visit Activities

The following procedures and activities must be completed at the Final Run-in visit:

- Blood is collected for HbA1c and serum creatinine/eGFR (sent to CBL).
- Adherence to medication-taking
    - Questions about the number of pills forgotten in the past 7 days will be asked to assess adherence. Participants can be asked to bring their unused medications with them to all visits to help monitor adherence; however it is not required. In addition, participants must have taken a minimum of 2 metformin 500mg pills per day in the 7 days (or typical week) prior to Final Run-in by self-report. For participants on 1000 mg daily, no more than 3 pills can be missed (80% adherence). The required adherence calculation criteria for those taking 1500 and 2000 is indicated on the **Final Run-in Visit Form**.
- Discuss Clinical Trial (Phase 2) consent and answer all questions
    - It should be mandatory that the subjects review the Clinical Trial (Phase 2) consent no later than Final Run-in to allow a minimum of a few days to digest the trial information before consenting (especially if the subject did not ask for information on the risks of the medications before then).
- If the participant demonstrates acceptable understanding, administer Clinical Trial (Phase 2) consent and have the participant sign the consent. Clinical Trial (Phase 2) consent may also be obtained on the day of randomization before starting any baseline procedures; however it is preferable to allow the subject a few days for review (see bullet above).
- Discuss Microbiome Collections and answer all questions
    - Participants enrolling in GRADE after the implementation of Protocol v1.6 will be invited to participate in the optional microbiome collections.
- Assess eligibility for Microbiome Collections, see Table 6.3 (**Microbiome Eligibility Form**)
    - The Microbiome Eligibility Form should be completed for <u>all</u> participants enrolling in the study after local implementation of Protocol v1.6.
- If the participant is eligible and demonstrates acceptable understanding, administer the Microbiome Collections Consent.
    - Participants must sign the consent for these collections at the Final Run-in visit so that they can perform the first stool sample collection at home in between the Final Run-in and Baseline visits.
    - Give consenting participants a stool collection kit, Microbiome Collection STF, and the two dietary questionnaires to take home with them. **Participants should be instructed to <u>wait</u> to collect their sample until the study coordinator calls to notify them of their eligibility for the main GRADE study.**
    - If time permits, participants may complete the dietary questionnaires at the Final Run-in visit; however, ideally, these questionnaires should be completed as close as possible to the time of stool sample collection.
- Discuss audio recordings and answer all questions.
    - Participants enrolling in GRADE after the implementation of Protocol v1.6 will be invited to participate in the optional audio recordings of study visits.
- If the participant demonstrates acceptable understanding, administer the Audio Recordings Consent. Consent may also be obtained on the day of randomization before starting any baseline procedures.

- Participant questionnaires may be administered during the Final Run-in visit and must be completed before or at the Baseline Randomization visit, depending on visit workload and clinic preference.
- Sites may consider standardizing the timing or developing a tracking system for completion of administration of questionnaires and additional exams and assessments to avoid accidental omission.

See Section 15.7 for a flowchart of Final Run-in visit procedures.

Schedule the randomization visit no less than 5 calendar days from the day that the final run-in labs were collected (to ensure enough time for the CBL to analyze the specimens and return the results) and preferably within 14-30 days, but no more than 45 days, from final run-in lab collection. **If randomization is > 45 days from final run-in, the entire screening process must be repeated.**

6.8.1.2 Establish Adherence During Run-in

Participants will need to take at least 1000 mg of metformin (or metformin XR) for 8 weeks prior to Final Run-in to be eligible. At least 2 pills/per day of metformin will be required for a one week period prior to the Final Run-in. If taking 1000 mg daily, no more than 3 pills can be missed. Potential participants can fail the adherence portion of the run-in by not being able to meet the medication adherence criteria (see medication adherence calculation on the **Final Run-in Visit Form**). During the follow-up phase of the trial, medication adherence will be assessed at all quarterly and annual visit during GRADE. A goal of at least 80% or more should be the target.

6.8.1.3 Informed Consent

The screening and run-in process should allow the clinical site staff to explain fully and discuss the GRADE trial with potential participants. The informed consent process includes the education and familiarization of the potential participant with the study. The review and signing of the informed consent form, approved by the clinical site's IRB, represent the formal culmination of this process.

The informed consent form (see Section 16.1) will be based on the templates (in English and Spanish) prepared by the study and revised according to local institutional requirements. We anticipate that the local IRB review will request some language changes, in addition to the insertion of local institutional sections; however, any style changes that are made should not affect the substance of the document. Sites that encounter any difficulty in this regard should contact and discuss these issues with the Coordinating Center.

All participants should be provided enough time to ask any questions regarding the study and have them answered. The process and meaning of randomization and the potential assignment to an injectable or oral medication should be emphasized. The well-informed volunteer generally makes the best participant with regard to retention, adherence, and overall participation. The informed consent form and specific permissions should be reviewed with the participant each time he/she is re-screened and periodically once enrolled in the study.

6.8.1.4 Final Run-in Visit Instructions for Staff

The Final Run-in visit will take approximately 2 hours to complete. Below are the Final Run-in visit instructions for staff:

- Complete the **Final Run-in Checklist**
- Assess medication adherence (see Section 6.8.1.2)

- Complete the **Microbiome Eligibility Form** (for all participants entering the study after Protocol v1.6 implementation)
- Complete the informed consent process for Clinical Trial (Phase 2), optional Microbiome Collections (if eligible), and optional audio recordings
- Provide copies per local regulations
- Complete the **Final Run-in Visit Form**
- Complete the **Eligibility Assessment for Randomization Form**
- Collect blood sample (for HbA1c and serum creatinine/eGFR)
- Complete the **Final Run-in Specimen Transmittal Form: Fresh Samples**
- For participants who are eligible for the Microbiome Collections, provide the stool collection kit, Microbiome Collection STF, and the two dietary questionnaires (along with postage-paid envelope addressed to site) to take home with them. Participants should be instructed to wait to collect their sample until the study coordinator calls to notify them of their eligibility for the main GRADE study.
- Schedule the Baseline Randomization visit (pending CBL report)
- Inform the participant that you will contact him/her to confirm their eligibility for randomization
- Complete paperwork, data entry and logs
- Send lab results letter, visit instructions for Baseline Randomization visit and make reminder call
- Complete the following physical measurements and/or assessments if performing at Final Run-in, rather than at Baseline Randomization visit:
    - Blood pressure
    - Weight
    - Height
    - Waist and hip circumference
    - Neuropathy assessment and MNSI (must be done on same day)
    - ECG
    - Neurocognitive assessment and complete **Cognitive Assessments Questionnaire**
    - **QWB**
    - **DTSQs**
- Baseline questionnaires may be completed at final run-in or at baseline randomization (see Section 7.2.5 for list of questionnaires.)

Supplies for processing and shipping:

- Final Run-in specimen collection kit (from CBL)
- Stool collection kit (from CBL, for eligible participants)
- Refer to the CBL manual for details on processing and shipping specimens

Barcode Labels:

- Refer to the CBL manual for details on barcode labels

Blood processing and shipping instructions:

- Refer to the CBL manual for details on processing and shipping specimens

Forms:

- Informed consent for GRADE Clinical Trial (Phase 2, Microbiome Collections, & Audio Recording)
- **Final Run-In Checklist** (internal checklist for site)
- **Final Run-In Visit Form**

- **Final Run-in Specimen Transmittal Form-Fresh Samples**
- **Eligibility Assessment for Randomization Form**
- **Microbiome Eligibility Form**
- **Cognitive Assessments Questionnaire** (if administered at Final Run-in rather than at Baseline Randomization visit)
- **Targeted Adverse Event and Serious AE Form** (if event reported)
- **Baseline Questionnaires** (if completed at this visit)
- **ECG Assessment Form** (if completed at this visit)

For participants enrolling in Microbiome Collections, to be completed at home pending eligibility:

- **Microbiome Collection Sample Transmittal Form**
- **Microbiome Collection Dietary Behavior Questionnaire**
- **Microbiome Collection Dietary Screener Questionnaire**

Supplies:

- Final Run-in specimen collection kit (from CBL)
- Microbiome collection kit (from CBL, for consenting participants to take home)
- See the CBL manual for details on required supplies

6.8.1.5 Participant Run-in Failure

If a participant is unable to complete run-in or fails final eligibility criteria, a letter will be provided for them and for their PCP. They may keep their remaining limited supply of study metformin to use until they are able to follow up with their own provider and obtain a prescription. They will be urged to follow up with their provider as quickly as possible. No additional metformin will be provided by the study.

6.8.1.6 After Final Run-in Visit (Microbiome Collections)

All participants entering GRADE after approval of Protocol v1.6 will be given an opportunity to participate in the optional microbiome collections, pending confirmation of eligibility at Final Run-in. The baseline collection will be done at home in between the Final Run-in and Baseline visits.

Eligibility will be assessed first at the Final Run-in visit and again via phone closer to the time of baseline sample collection. The exclusion criteria are described in Table 6.3. The **Microbiome Eligibility Form** should be completed for all participants entering the study after local implementation of Protocol v1.6.

Table 6.3 Microbiome Exclusion Criteria

1. Failure to consent to microbiome permissions.
2. Unwilling or unable to collect a stool sample at home and/or complete the dietary questionnaires.
3. Antibiotic use within the past month.
4. Currently pregnant.*
5. Acute gastrointestinal illness or infection in the past week. **
6. Inflammatory Bowel Disease (IBD), such as Crohn's Disease or Ulcerative Colitis.
7. Currently enrolled in GRADE (i.e. randomized previously).
8. Not fluent in English.

* Exclusion for the main GRADE study

Study site staff should be sure to verify that any gastrointestinal illness was indeed an "illness," as opposed to loose stools.

After the Final Run-in Visit, site staff will call the participant to inform him/her of their eligibility for the main GRADE Study and discuss completion of the microbiome sample and questionnaires. They will confirm no new antibiotics or significant GI illness with the participant and review the logistics of the sample collection. Staff should encourage the participant to set a particular date by which they will complete and mail the sample. Site staff will ask the participant to complete all of the following:

- Stool sample collection and associated STF
- Microbiome Collection Dietary Behavior Questionnaire
- Microbiome Collection Dietary Screener Questionnaire

The participant will complete the stool collection (and accompanying Microbiome Collection Sample Transmittal Form) and mail the sample to the CBL in postage prepaid padded envelope. The participant will also complete the Microbiome Collection Dietary Behavior Questionnaire and the Microbiome Collection Dietary Screener Questionnaire. Ideally, these questionnaires should be completed at the time of stool sample collection. The participant can either mail these to the clinical site in the postage prepaid envelope or bring them back to the clinical site at the Baseline Randomization Visit. If necessary, the questionnaires can be completed on-site at the Baseline Randomization Visit.

Manual of Procedures

Chapter 7

TABLE OF CONTENTS

7. CHAPTER 7: BASELINE AND RANDOMIZATION PROCEDURES

The Baseline and Randomization visit captures baseline clinical and demographic data and records the randomization treatment assignment, dose, and dispensation of the study medications. At the Final Run-in visit, the Baseline Randomization visit should be discussed including tentative dates with participants who are otherwise eligible (pending CBL results). Randomization should occur ideally within 14-30 days (not less than 5 days to allow time for CBL to return lab results) and a maximum 45 days from the last qualifying HbA1c and after completion of the Clinical Trial (Phase 2 consent). **If randomization does not occur within 45 days of final-run in, the screening process must be repeated.** The visit scheduler available on the GRADE study website can be used to ensure all pre-randomization visit windows are met – see a screen shot of the visit scheduler in Section 15.11. Also refer to the GRADE Help Guide to Schedule Visits in Section 15.12 and on the GRADE study website for scheduling windows.

7.1 Randomization Procedure

Randomization of a participant occurs at the Baseline Randomization visit after the site has obtained participant informed consent, reviewed and confirmed eligibility, and received confirmation of eligibility for randomization into the study from the Coordinating Center. The Coordinating Center will assign eligible study participants a study randomization ID number, which is associated with their treatment assignment. Randomization will be conducted via a central web-based system once the participant has arrived for the baseline visit. The participant will remain masked to the forthcoming treatment assignment until the OGTT 30 minute time-point has passed, at which time the treatment assignment will be disclosed to the participant. Thereafter, the treatment assignment will not be masked to clinical personnel or the participant. However, staff in central laboratories or reading centers will be masked to treatment assignment.

7.2 Baseline Randomization Visit Activities and Instructions for Staff

7.2.1 Preparation for the Baseline Randomization visit

- **Confirm the following:**
  - The participant has demonstrated acceptable adherence to metformin (see Section 6.8.1.2)
  - The non-fasting blood samples for HbA1c and creatinine/eGFR were sent to the CBL
  - Dates and times for the Baseline Randomization visit were discussed with the participant and the Baseline Randomization Appointment letter with instructions (see Summary of Participant & PCP Letters in Section 15.3 and sample letter on the GRADE study website) was provided
  - A urine pregnancy test is done locally for women of reproductive age on the day of randomization and must be negative before randomization is performed
- Obtained GRADE Clinical Trial (Phase 2) informed consent. The consent form can be signed at the Final Run-in visit (see Section 6.8) or on the day of randomization; however it **must be signed before randomization** and/or performing any aspects of the Baseline Randomization visit (except for the urine pregnancy test).
- Obtained optional Audio Recording informed consent (for eligible/interested participants)
- Enter the data from the **Eligibility Assessment for Randomization Form** into MIDAS, prior to the actual Baseline Randomization visit. If entries indicate that the participant is not eligible, then at the end of form entry an 'alert' screen appears highlighting the failed criteria. Contact the participant to cancel the Baseline Randomization visit.

- **IMPORTANT**: The actual randomization and medication group assignment cannot occur until the participant has arrived for their appointment on the day of randomization and the Coordinating Center has approved that the participant is eligible for randomization. Coordinating Center approval is obtained via the MIDAS Report: **Eligibility Report for Randomization**. After all Final Run-in Visit forms have been data entered for a particular participant, sites may generate this report for the participant in MIDAS to confirm eligibility for randomization.
- Sites using research pharmacies must pre-arrange for the logistics of medication availability
- Confirm with the participant the visit date, time, location, and directions
- Review the visit instructions, especially the preparation for having the OGTT, from the Baseline Appointment letter (see Summary of Participant & PCP Letters in Section 15.3 and sample letter on the GRADE study website) with the participant when confirming the appointment
- Confirm eligibility for baseline OGTT and baseline lab testing the day before the visit by phone. This is done to avoid the scenario where the participant arrives at the site for the Baseline Randomization visit and the team discovers that the participant does not meet eligibility criteria to conduct the baseline OGTT (e.g. participant has been ill or had major surgery during the previous week or forgot to fast) (see questions on the Baseline Oral Glucose Tolerance Test Form for baseline OGTT and baseline lab eligibility to review during the reminder call)
- Confirm that all relevant GRADE study staff members are aware of and available for the scheduled visit
- Ensure that all necessary arrangements have been made for completion of testing and for post-randomization activities, prior to the Baseline Randomization visit
- Medication teaching materials are available/assembled
- Ensure that medication is available and the research pharmacy has been alerted as needed
- Print out the required forms from the GRADE study website stamped with participant ID, GCode, clinical site assignment, etc.
- Confirm eligibility criteria and have the PI or designee approve based on local site operations
- If the participant is ineligible, contact the participant to cancel the Baseline Randomization visit
- Baseline questionnaires may be completed at the Final Run-in or at the Baseline Randomization Visit (see Section 7.2.5 for a list of questionnaires).

7.2.2 Inclusion Criteria for Entry

The following is a list of inclusion criteria for entry into the GRADE study:

1. Men or women ≥30 years of age at time of diabetes diagnosis; for American Indians, age is ≥20 years at time of diagnosis
2. Duration of diagnosed diabetes <10 years determined as accurately as possible based on available records at screening
3. HbA1c criteria (at final run-in visit, ~2 weeks prior to randomization): 6.8-8.5%
4. Taking a daily dose of ≥1000 mg metformin for a minimum of 8 weeks at final run-in
5. Willingness to administer daily subcutaneous injections, take a second diabetes drug after randomization, potentially initiate insulin and intensify insulin therapy if study metabolic goals are not met, and perform self-monitoring of blood glucose
6. Fluent in either English or Spanish
7. A negative pregnancy test for all females of childbearing potential (i.e. pre-menopausal, and not surgically sterile)
8. Provision of signed and dated informed consent prior to any study procedures

7.2.3 Exclusion Criteria for Entry

The following is a list of exclusion criteria for entry into the GRADE study:

1. *Suspected type 1 diabetes (lean with polyuria, polydipsia, and weight loss with little response to metformin) or "secondary" diabetes due to specific causes (e.g. previously diagnosed monogenic syndromes, pancreatic surgery, pancreatitis)[±]
2. Current or previous (within past 6 months) treatment with any diabetes drug/glucose-lowering medication other than metformin**
3. More than 10 years of treatment with metformin at time of screening
4. History of intolerance or allergy or other contraindications to any of the proposed study medications or sulfa medication******
5. Resides in the same household with another GRADE study participant
6. *Current need for any specific glucose-lowering medications solely for other conditions, for example for polycystic ovary syndrome
7. *Symptomatic hyperglycemia requiring immediate therapy during screening or run-in, in the judgment of the physician
8. A life-threatening event within 30 days prior to screening or currently planned major surgery
9. Any major cardiovascular event in previous year, including history of myocardial infarction, stroke, or vascular procedure such as coronary artery or peripheral bypass grafting, stent placements (peripheral or coronary) or angioplasty
10. Plans for pregnancy during the course of the study for women of child-bearing potential
11. History of* or planning bariatric surgery, including banding procedures or surgical gastric and/or intestinal bypass (if procedure reversed, may be considered eligible after 1 year).
12. *History of congestive heart failure (NYHA 3 or greater- shortness of breath with minimal exercise or at rest)
13. *History of pancreatitis (any history of pancreatitis at all)
14. Any new diagnosis of cancer in the previous 5 years (other than localized non-melanoma skin cancer), or treatment for any cancer in the previous 5 years (other than for non-melanoma skin cancer). Exceptions may be made, at the discretion of the local Principal Investigator and after review by the subcommittee overseeing protocol implementation, for cancers, such as some thyroid cancers, that have a benign clinical course and are not expected to interfere with conduct of the study.****
15. *Personal or ***family history of MEN-2 or family history of medullary thyroid cancer
16. *Estimated GFR (eGFR) <30mL/min/1.73 m^2 or history of renal replacement therapy regardless of eGFR*
17. History of severe liver disease or acute hepatitis or (ALT) >3 times the upper limit of normal *****
18. Current alcoholism or excessive alcohol intake
19. *Previous organ transplant
20. *Treatment with oral or systemic glucocorticoids (other than short-term treatment, for example for poison ivy) or disease likely to require periodic or regular glucocorticoid therapy. Note: inhaled steroids and/or physiological replacement treatment (e.g. for Addison's Disease) are acceptable
21. Treatment with atypical antipsychotics known to be associated with a high risk of metabolic dysfunction (refer to Glossary in Appendix A)
22. *History of Hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels******* or Hematocrit < 35% for males and < 33% for females

23. *Clinically or medically unstable with expected survival <1 year
24. Unwillingness to permit sites to contact the PCP to communicate information about the study and the participant's data
25. At the time of final run-in, no identified PCP to provide non-study care (Note: in cases where a study MD serves as the participant's PCP, another study provider must assume GRADE management decisions for the participant during the study.)
26. Participation in another interventional clinical trial (includes medication, device, procedure studies)
27. *Previous randomization in the GRADE study
28. In the opinion of the principal investigator (PI), any other factor, including language barrier, likely to limit compliance with the protocol

*Permanent Exclusion

** Participants who have had limited use of glucose-lowering drugs (other than metformin) of no longer than seven days (for example, during hospitalization) may be randomized.

***For this criterion, family is defined as first-degree relatives (a close blood relative which includes the individual's parents, full siblings, or children).

****Participants with cancer who have not required therapy in the 5 years prior to randomization but have serious cancers should not be included in the study. Serious disease may complicate their participation in GRADE and these individuals should be excluded.

*****Participants with history of severe liver disease, active hepatitis A, B, or C, or liver function test (ALT)>3 times the upper limit of normal are excluded from the study. To clarify, history of severe liver disease refers to an ongoing medical problem characterized by hepatic insufficiency which is often but not always accompanied by GI symptoms, edema, ascites, jaundice, encephalopathy, hypogonadism, splenomegaly, esophageal varices, increased risk of hypoglycemia, and/or reduced levels of albumin or clotting factors. Such patients are excluded. Those patients with liver function test (ALT) >3 times the upper limit of normal are excluded. Acute hepatitis is a temporary exclusion and when resolved, the participant may be eligible. A remote history of severe liver disease would not necessarily be exclusionary if in the opinion of the investigator, the patient is fully recovered (e.g., does not require treatment for liver disease and has normal liver synthetic function, portal blood flow, and biliary metabolism). Refer to Section 5.4.11 for guidance on re-testing ALT.

****** A history of an allergic reaction to sulfa drugs is a contraindication on the Amaryl (glimepiride) package insert. Patients are often not clear on what a true drug allergy is so unless a chart review document details about a purported past allergic reaction to a sulfonamide drug, potential participants should be asked during screening what symptoms they experienced when they had the past reaction. If past reactions included hives, rash, angioedema or anaphylaxis, the patient is not eligible for GRADE.

******* If a participant has recently donated blood, sites should delay enrolling for at least three months (but preferably longer) following the donation. Participants may be screened starting two months after the donation with the understanding that the A1c may still be impacted by the donation.

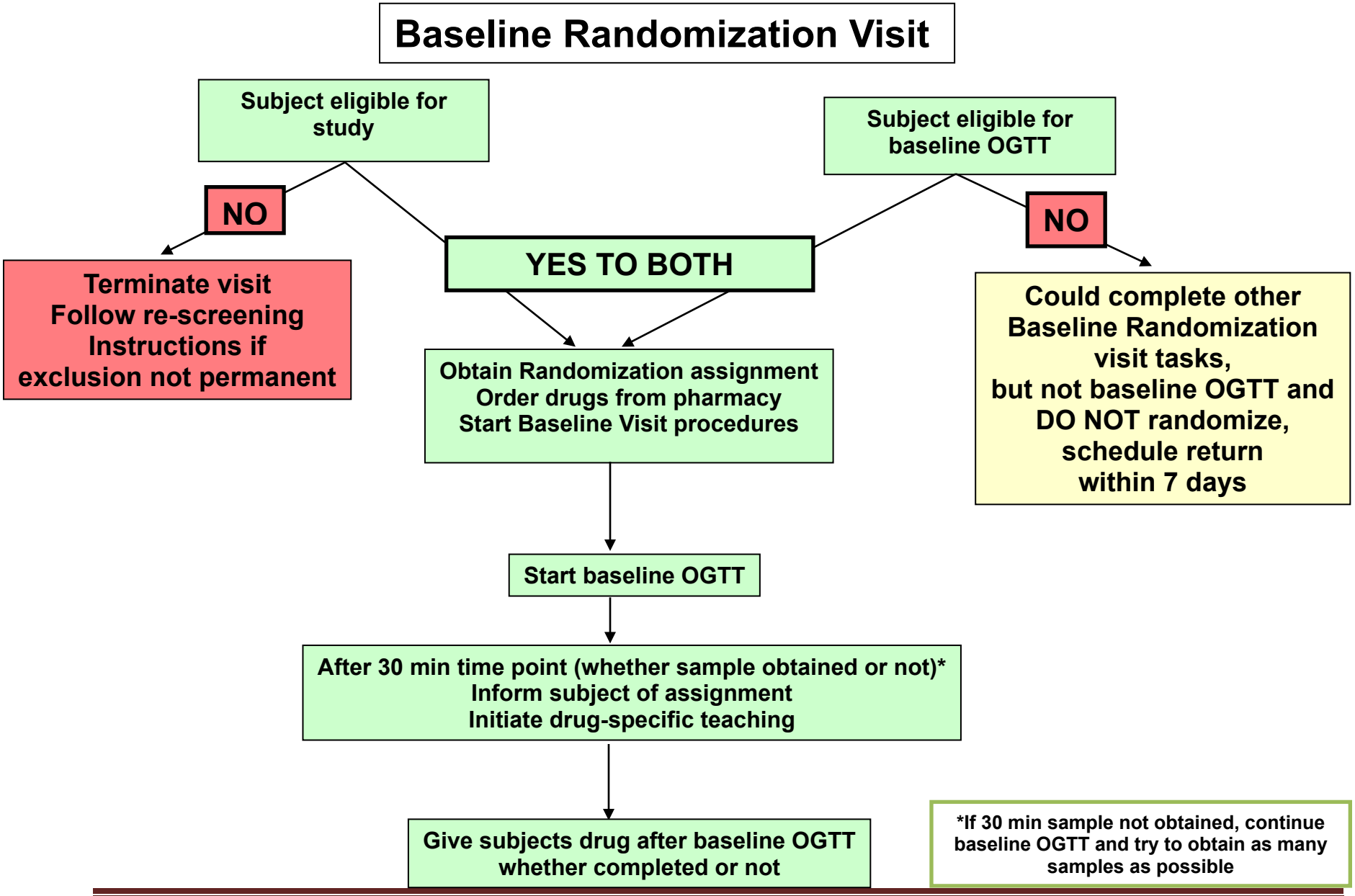
± For more information about specific secondary causes of diabetes, reference Table 1 of the American Diabetes Association's paper entitled, "Diagnosis and classification of diabetes mellitus" (American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014 Jan;37 Suppl 1:S81-90. http://care.diabetesjournals.org/content/37/Supplement_1/S81/T1.large.jpg)

7.2.4 Baseline Randomization Visit Procedures

See Figure 7.1 for a basic flow of the Baseline Randomization visit. The following steps must be completed:

- Confirm the participant has signed the Clinical Trial (Phase 2) informed consent form and optional Audio Recording informed consent form
- Confirm women of childbearing potential have a negative urine pregnancy test
- Assess participant eligibility for baseline OGTT and baseline labs (see Figure 7.1)
    - If the participant is not eligible for the OGTT, DO NOT randomize; schedule a return visit within 7 days (baseline OGTT and randomization must take place on the same day)
- Randomize the participant using the Drug Distribution Center (DDC) website
    - Randomization must occur before baseline tests are performed so that the medication assignment and supply to be dispensed can be prepared
- Begin to collect baseline data after all eligibility requirements have been confirmed and entered into the DDC website, and a random treatment assignment has been issued by the DDC website indicating that the participant is enrolled in the study. The assignment will remain masked to the participant until the visit is well underway. The participant can be informed of his/her assignment after the 30 minute sample time-point of the baseline OGTT has been reached. Please note that even in the case where the sample cannot be obtained (difficult draw, IV line failure), once past the 30 minute time-point, the participant can be informed of his/her specific medication assignment. The remaining 90 minutes of the baseline OGTT can be used to perform medication teaching, as indicated by treatment assignment, and complete questionnaires. The neurocognitive assessment can be performed at the Final Run-in visit or at the Baseline Randomization visit after completion of the baseline OGTT. A snack or meal may be offered to the participant prior to completion of the neurocognitive assessment.

Figure 7.1: Baseline Randomization Visit Flowchart



7.2.5 Baseline Data, Procedures, Questionnaires and Instructions for Staff

Collect and record baseline data (refer to the MAP for detailed instructions for collection of measurements assessments and OGTT).

- For participants who have consented to the optional audio recordings, begin recording at the start of baseline visit activities (after consent has been obtained)
- Perform assessments:
  - Perform baseline OGTT (see Figure 7.1)
  - Can inform the participant of medication assignment after the 30 minute OGTT time-point or at the end of the OGTT (Can use remaining OGTT time for teaching and completing questionnaires. The Neurocognitive assessment can be done **after** the OGTT has been completed.)
  - Peripheral Neuropathy assessment (MNSI) (if not completed at Final Run-in visit)
  - Study drug adherence
  - ECG assessment (if not completed at Final Run-in visit)
- Physical measurements (if not done at the Final Run-in visit):
  - Blood pressure
  - Height
  - Weight
  - Waist and hip circumference
- Collect specimens and send to CBL:
  - Baseline and fasting blood draw/OGTT (IV insertion)
  - Urine for microalbuminuria
  - Blood for DNA and blood and urine for stored samples
- Supplies for processing and shipping:
  - Baseline specimen collection kit (from CBL)
  - Refer to the CBL manual for details on processing and shipping specimens
- Complete baseline visit forms
  - **Baseline Randomization Checklist** (internal checklist for site)
  - **Baseline Randomization Visit Form**
  - **Concomitant Medications Form**
  - **Medication Dispense log**
  - **Baseline Specimen Transmittal Form-Frozen Samples**
  - **Baseline Oral Glucose Tolerance Test Form**
  - **ECG Assessment Form**
  - **Audio Recording Tracking Form** (only for participants who consent to have their visits recorded)
- Complete Questionnaires (if not completed at Final Run-in Visit)
  - **Baseline Participant Information Questionnaire** (self-administered)
  - **Participant Symptoms Questionnaire**
  - **The SF-36 Health Survey (SF-36)**
  - **Quality of Well Being Self- Administered Questionnaire (QWB-SA)**
  - **Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)**
  - **Cognitive Assessments Questionnaire**
  - **Microbiome Collection Dietary Screener Questionnaire** (eligible participants only)
  - **Microbiome Collection Dietary Behavior Questionnaire** (eligible participants only)

- Medication teaching and handouts reviewed (use handouts provided for each medication and FDA circular if applicable)
- Dispense meter and supplies if randomized to Lantus or Glimepiride groups. Enter all supplies being dispensed into the DDC drug dispensing and inventory management system (website).
    - Review other related information associated with treatment assignment
        - For GLP-1 (liraglutide) assigned participants:
            - Pen use and injection techniques
            - Side effect management
        - For insulin (glargine) assigned participants:
            - Pen use and injection techniques
            - Self monitoring of blood glucose and meter use
            - Hypoglycemia recognition and treatment
            - Insulin titration
        - For Sulfonylurea (glimepiride) assigned participants:
            - Timing of medication
            - Self-monitoring of blood glucose and meter use
            - Hypoglycemia recognition and treatment
            - Glimepiride titration
    - Review titration procedures as indicated (see Chapter 9)
- Review of study procedures/expectations (for example, interim phone contact, visit adherence, emergency contact information)
- Complete/update the participant contact information form
- Complete medical records release form if needed
- Dispense assigned medications to the participant with written dose instructions to take home and record dispensed medication in the **Medication Dispense Log**
- **Prepare GRADE study ID card and give to participant**
- Discuss interim phone contact schedule
- Schedule first follow up phone call
- Discuss dates for next 3 month visit and schedule at this visit or by phone

7.3 Treatment Assignments and Medication Initiation

The time between randomization and the start of treatment should be minimal. The second anti-diabetic medication to be combined with metformin will be dispensed at the Baseline Randomization visit and started on the day (at the end of OGTT) of randomization. If randomized to Lantus, give ½ of the dose at the end of the OGTT with instructions to take the full dose starting the next evening, preferably at bedtime. This will allow for instructions on pen use and self-injection to be performed with supervision. (See Chapter 9 for further details on medication management.)

7.3.1 Medication Teaching

Standardized medication teaching materials provided by GRADE will be used as participant handouts to take home. Study medication dosing, action, side effects, and methods of administration will be reviewed thoroughly prior to the conclusion of the Baseline Randomization visit. For medications that involve titration, specific instructions will be reviewed and given to the participants including blood glucose monitoring frequency, and management of hypoglycemia and hyperglycemia. Review frequency of contact with study staff and arrange the first follow-up call at this visit (see specific titration protocols in Chapter 9). For medications delivered by injection, the study staff will teach self-injection, dosing, and

how to measure the medication. The first dose of the injectable medication will be self-administered prior to concluding the visit.

7.3.2 Medication Dispensing

Study medication will be dispensed at this visit per DDC procedures and local regulations. Refer to the DDC manual for detailed instructions. Supplies will be dispensed as needed based on medication assignment. The following list may be used as an approximate guide for the amount of supplies to be dispensed:

Table 7.1: Ancillary Supplies Needed for Baseline Randomization Visit*

Drug	Ancillary supplies
Glimepiride (Amaryl)	• 1 Meter • 2 boxes lancets • 2 boxes of strips • 1 box alcohol pads
Glargine (Lantus)	• 1 Meter • 2 boxes lancets • 2 boxes strips • 2 boxes pen needles • 1 box alcohol pads
Sitagliptin (Januvia)	• None
Liraglutide (Victoza)	• 2 boxes pen needles • 1 box alcohol pads

*Remember to dispense through the DDC site and sign out in GRADE Medication Dispensing/Accountability Log.

7.3.3 Other Post-Randomization Activities

- Introduce study staff and their roles.
- Provide contact information along with the participant handbook.
    - The handbook will hold study documents for the participant's convenience; for example, the 4-Steps booklet, blood sugar log, clinic provided ID card with phone numbers to call for problems or questions, study staff contact, schedule of visits, and a copy of consent form.
- Explain the relationship between the study staff and the PCP, and which questions/issues should be addressed to each.
- Provide an overview of study visits and timeline using the calendar of scheduled visits from the study database.
- Explain drug dosing and titration if applicable (on the provided medication handouts).
- Review adherence expectations (medications, blood glucose monitoring, visit attendance).
- Review reimbursement procedures for parking and other travel expenses.
- Dispense a blood glucose monitor and adequate testing supplies if applicable.
- Check that the participants who will be performing self-monitoring of blood glucose (SMBG) (assigned to glargine or glimepiride) have had adequate teaching and demonstrated competence regarding SMBG.
- Explain the importance of avoiding departures from study procedures (e.g. using non-study diabetes drugs, missing study visits etc.).

- At the end of the Baseline Randomization visit, after all baseline procedures are completed, the next study visit should be discussed and/or scheduled.
- An appointment reminder is sent via mail, email, or phone call (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website).
- Baseline Randomization visit results: A letter will be sent to the participant's PCP (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website) as well as the participant summarizing the baseline results.

7.3.4 Follow-up Phone Call

Within two weeks (preferably within 1 week) after randomization, the study coordinator or research nurse will call the participant to address any concerns, and to follow up with participants who were assigned to agents requiring titration.

Manual of Procedures

Chapter 8

TABLE OF CONTENTS

8. CHAPTER 8: PATIENT CARE AND MEDICAL MANAGEMENT

8.1 Diabetes Care

Study personnel will communicate directly with participants' PCPs so that it is clear that diabetes management, specifically the initiation and adjustment of diabetes medications, will be assumed by the study staff. Participants will be seen quarterly. Diabetes management will follow an established titration protocol depending on treatment assignment as outlined below. For medications that are titrated, titration in GRADE will be based on self-monitoring of blood glucose, aiming for fasting glucose range ideally of 80-130mg/dl, titrating to ≤100 mg/dl without symptomatic hypoglycemia.

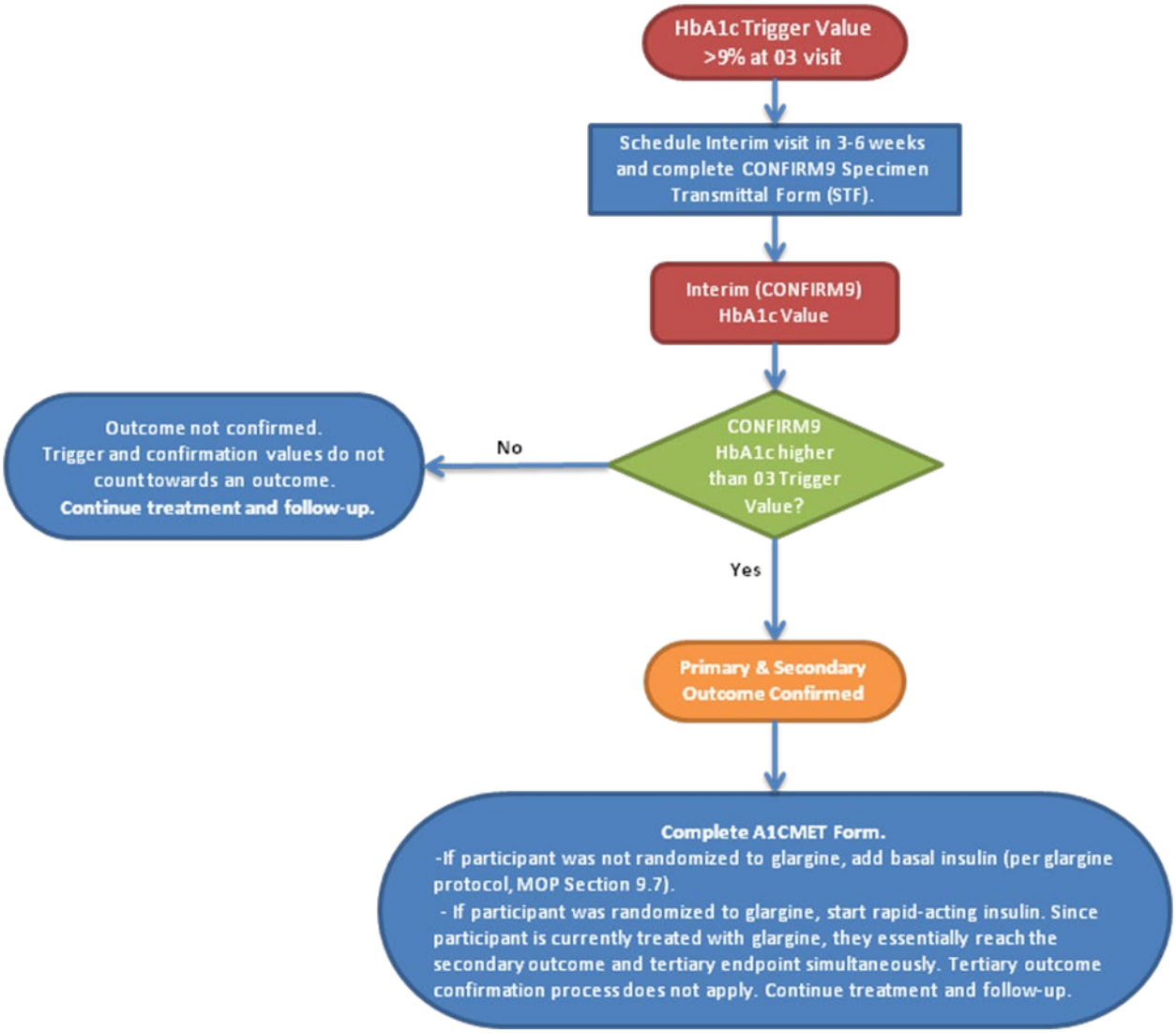
HbA1c monitoring every three months:

- HbA1c will be monitored every three months in the GRADE central laboratory. Lab results are sent electronically from the CBL to the Coordinating Center within approximately 48 hours of sample receipt. Study Coordinators will receive results from the CBL by fax or by an automated email. Hard copy results reports will be auto-faxed to the site coordinator at the clinical center (see CBL manual for details).
- HbA1c values will also be monitored between ≥7.0 and ≤9.0 for the purpose of identifying threshold values and also values of >7.5 or >9.0 for critical alerts. The CBL will provide notifications to the clinical sites when a participant has reached a threshold value for HbA1c so that sites may follow the necessary steps outlined in the **HbA1c Metabolic Outcome Confirmation Worksheet, Interim Checklist for HbA1c Above Goal, and HbA1c Flowchart** to determine whether an outcome has been reached. In addition, PCPs should be notified when therapy is changed (HbA1c values are >7.5 or >9.0 – see sections 8.1.3 and 8.1.4). The study site will send the participant the results of testing. The letter to the participant may reinforce discussion regarding diet, exercise, and protocol-specified medication changes that were discussed at the visit as per the clinical site's discretion. PCPs will be notified if clinical alert thresholds are met ($B_{Psystolic} \geq 160$ or $B_{Pdiastolic} > 100$, or any other clinically significant abnormality is noted); otherwise, letters to PCPs summarizing clinically relevant findings (e.g. BP and study lipid results) will be sent on an annual basis.
- If the HbA1c is ≥7%, participants will receive standardized reinforcement of the importance of medication adherence and lifestyle behaviors, and medication will be adjusted to the maximal dose as tolerated. The study staff will contact the participant by phone and complete the HbA1c Above Goal Checklist.
- If the triggering HbA1c level is greater than 9%, the participant will be called to have a repeat (confirmation) value obtained within 3 to 6 weeks at an interim visit. Interim confirmation A1c tests may be done remotely using the Capillary Collection Kit, if desired. If the triggering HbA1c is ≥7% but ≤9%, the confirmatory HbA1c will be drawn at the next quarterly visit.

8.1.1 HbA1c Triggers at the First Quarterly (03) Visit

Elevated HbA1c values at the first (3-month) Quarterly Visit are treated differently than all subsequent elevated HbA1c values during the study. **If the HbA1c is ≤9% at the first (3-month) Quarterly Visit, the value does not count toward a study metabolic outcome regardless of study medication dose.** If the HbA1c is >9% at the first (3-month) Quarterly Visit and the confirmation value 3 to 6 weeks later is **higher** than the triggering value, then primary and secondary outcomes are confirmed simultaneously. If the confirmation value is equal to or lower than the triggering HbA1c value, neither primary nor secondary outcome is confirmed and the 3-month value does not count toward a study metabolic outcome. The participant will resume the usual schedule of quarterly HbA1c monitoring (see Figure 8.1).

Figure 8.1 Flowchart for HbA1c Trigger Value >9% at 03 Visit



8.1.2 Primary metabolic outcome

The primary outcome is the time to the observation of an **HbA1c ≥7%**, subsequently confirmed in 3 months (or as early as 3 weeks if the trigger value is >9%.)

The primary outcome can only be confirmed after a minimum of 9 months of therapy if the trigger HbA1c is ≥7% but ≤9% (6 months until triggering HbA1c with confirmation 3 months later), or at 4 months if HbA1c is >9% at the 3-month quarterly visit, and the confirmation HbA1c obtained 3 to 6 weeks later is higher than the 3-month triggering value.

If the trigger HbA1c is 7% to 9%, the confirmation value is obtained at the next quarterly visit.

- If the confirmation value (3 months after the trigger) is <7%, then the primary outcome is not confirmed.

- If the confirmation value (3 months after the trigger) is ≥7%, then the primary outcome is confirmed.
- If the trigger value is >7.5% and the confirmation value is also >7.5%, then the primary and secondary outcomes are confirmed simultaneously.
    - If the trigger value is 7% to 7.5% but the confirmation value is >7.5%, then only the primary outcome is confirmed, and the confirmation value counts as the triggering value for secondary outcome.

If the trigger HbA1c is >9%, the confirmation value is obtained between 3 and 6 weeks.

- If the confirmation value (3 to 6 weeks after the trigger) is >9%, then the participant has confirmed primary outcome and secondary outcome simultaneously.
- If the confirmation value (3 to 6 weeks after the trigger) is ≤9%, the outcome is not confirmed, but the triggering value still counts toward a study metabolic outcome, pending confirmation at the next quarterly visit. If the HbA1c at the next quarterly visit is ≥7%, then the primary outcome has been confirmed, and if that value is >7.5%, then the secondary outcome has also been confirmed simultaneously.

Participants should be titrated per protocol, to the maximally tolerated dose. The maximally tolerated dose is defined as the highest dose that the participant is able (and willing) to take without unacceptable side effects. The primary outcome will be counted regardless of adherence to assigned medications at the time of the HbA1c test according to principles of intention-to-treat analysis (see Figure 8.2).

Once primary metabolic outcome has been confirmed, participants are observed on assigned therapy. An HbA1C Metabolic Outcome Confirmation (A1CMET) Form should be completed at the time of primary metabolic outcome confirmation.

8.1.3 Secondary metabolic outcome

The secondary metabolic outcome occurs when **HbA1c is >7.5%** and has been confirmed as described above. The primary and secondary metabolic outcomes may be reached simultaneously if the triggering value and the confirmation are both >7.5%. When secondary metabolic outcome has been confirmed, participants assigned to agents other than insulin will have basal insulin added to continued metformin and randomly assigned study medications. Basal insulin should be initiated within 6 weeks of confirming the secondary outcome. The basal insulin will be adjusted according to the study insulin protocol (see Section 9.7). For participants who were originally assigned to the sulfonylurea glimepiride, the dose of glimepiride may reduced at the time of glargine initiation and even subsequently stopped should the investigator feel that observed hypoglycemia or weight gain may be related to glimepiride.

If, after being started on therapy with basal insulin, the participant's HbA1c reaches or remains >7.5%, confirmed, they will be considered to have reached the **tertiary metabolic outcome** (Section 8.1.4). At that time, insulin therapy will be intensified with the addition of rapid-acting insulin (see Figure 8.2).

Participants who were originally assigned to glargine insulin will initiate intensive insulin therapy with the addition of rapid-acting insulin to metformin and basal insulin at the time that the secondary metabolic outcome occurs. Rapid-acting insulin should be initiated within 6 weeks of confirming secondary outcome (for those assigned to glargine). Since the glargine-assigned group is already treated with glargine, they will essentially reach their secondary and tertiary outcome simultaneously.

A new **HbA1C Metabolic Outcome Confirmation (A1CMET) Form** should be completed once secondary metabolic outcome has been confirmed. If insulin is not initiated within 6 weeks of confirming secondary metabolic outcome, a **Non-Initiation of Insulin Form for Participants Meeting HbA1c Metabolic Outcomes (NONINIT)** should be completed. Once the NONINIT form has been completed, a **Non-Initiation of Insulin Quarterly Follow-Up Form for Participants Meeting HbA1c Metabolic Outcomes (UPNONIN)** should be completed at each study visit if insulin still has not been started.

8.1.4 Tertiary metabolic outcome

Any participant (except for those in the glargine treatment arm) whose HbA1c again reaches >7.5%, confirmed, after having met secondary metabolic outcome and while treated with basal insulin, the assigned study medication, and metformin will be considered to have reached the tertiary metabolic outcome. Upon confirming tertiary metabolic outcome, a new **HbA1c Metabolic Outcome Confirmation (A1CMET) Form** should be completed. These participants will continue their metformin and basal insulin therapy regimen, intensify the insulin regimen with the addition of rapid-acting insulin, according to study protocol, and discontinue the original randomly assigned medication. Rapid-acting insulin should be initiated (and the original randomly assigned medication should be discontinued) within 6 weeks of confirming tertiary outcome. If rapid-acting insulin is not initiated within 6 weeks of confirming tertiary outcome, a **Non-Initiation of Insulin Form for Participants Meeting HbA1c Metabolic Outcomes (NONINIT)** should be completed. Once the NONINIT form has been completed, a **Non-Initiation of Insulin Quarterly Follow-Up Form for Participants Meeting HbA1c Metabolic Outcomes (UPNONIN)** should be completed at each study visit if insulin still has not been started.

Figure 8.2 Metabolic Outcomes and Subsequent Therapy

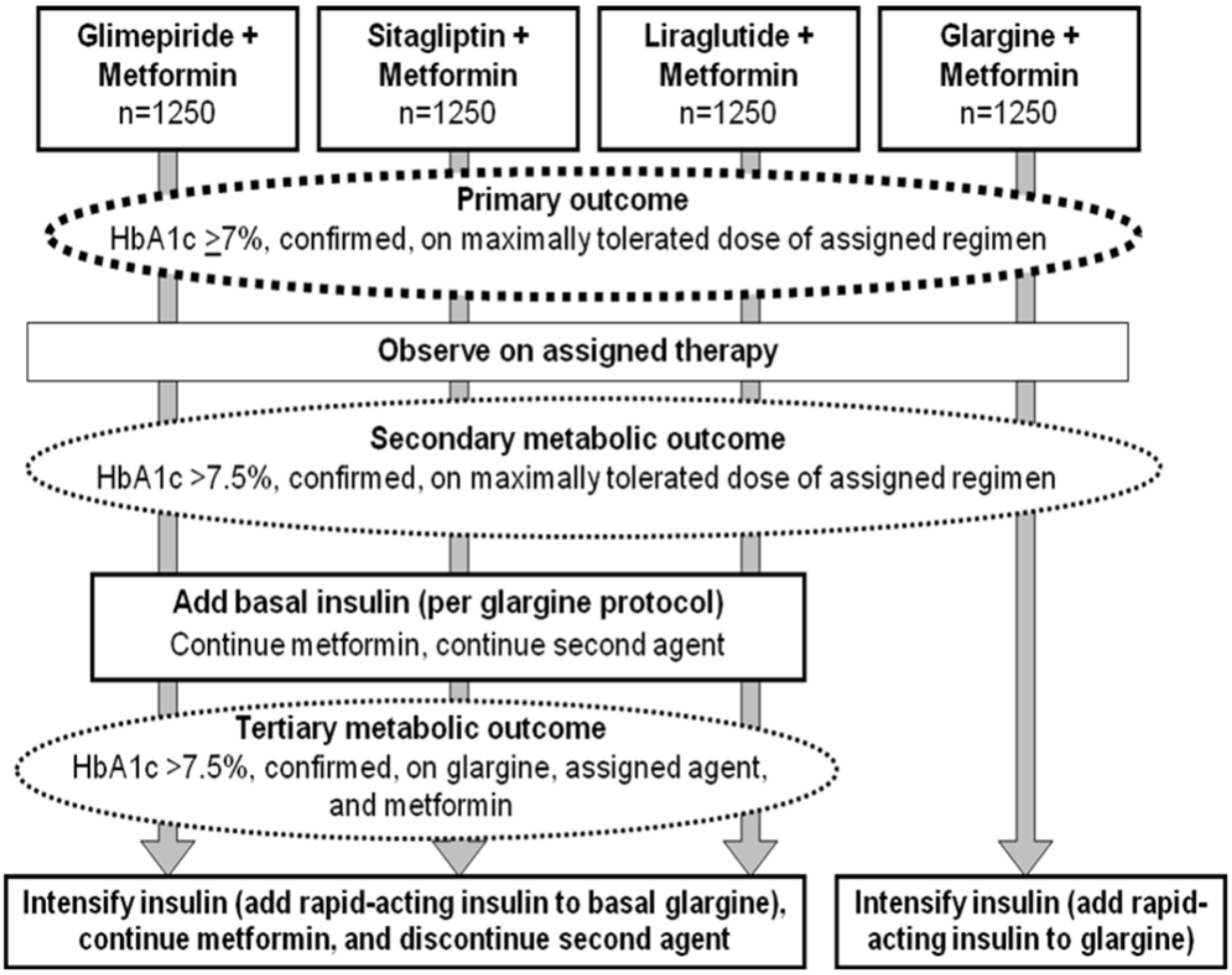


Table 8.1 Summary of A1c Metabolic Outcomes Triggers and Confirmation

Month 3 Trigger (Section 8.1.1)

HbA1c Trigger (%)	3 to 6 weeks Confirmation	Outcome	Action Taken
7-9		Continue treatment & f/u	None
>9	> Than trigger value	Primary & Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
	≤ Than trigger value (or missing value)	Continue treatment & f/u	None

After 3 months:

PRIMARY (Section 8.1.2)

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7-7.5	N/A	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary, plus trigger for Secondary	Observe on assigned therapy
7.6-9	N/A	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
>9	>9		Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
	≤9	<7	Continue treatment & f/u	None
		7-7.5	Primary	Observe on assigned therapy
		>7.5	Primary and Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin

SECONDARY (Section 8.1.3)

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7.6-9	N/A	≤7.5	Continue treatment & f/u	None
		>7.5	Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
>9	>9		Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin
	≤9	≤7.5	Continue treatment & f/u	None
		>7.5	Secondary	Glargine group: Add rapid-acting insulin All others: Add basal insulin

TERTIARY** (MOP 8.1.4) Note: **For all participants except those randomized to glargine

HbA1c Trigger (%)	3-6 weeks Confirmation	Next Quarterly Confirmation	Outcome	Action Taken
7.6-9	N/A	≤7.5	Continue treatment & f/u	None
		>7.5	Tertiary	Add rapid-acting insulin
>9	>9		Tertiary	Add rapid-acting insulin
	≤9	≤7.5	Continue treatment & f/u	None
		>7.5	Tertiary	Add rapid-acting insulin

8.2 Co-morbidities and Clinical Alerts

Results of clinically relevant testing performed as part of GRADE will be forwarded to participants' primary care providers (PCPs) annually. Other than the diabetes interventions that are the focus of this trial, all other treatments, including the management of hypertension and dyslipidemia, will be performed by the participant's own health care provider. With the implementation of protocol version 1.6.1, the study will begin making recommendations to address vitamin B12 deficiencies (initiation of B12 supplements and follow up with their PCP—see below for more information) if B12 levels are found to be <300 pg/mL. On an annual basis, the study sites will send a letter that includes a reference to the American Diabetes Association (ADA) recommendations for care and surveillance, along with a summary of the clinically relevant GRADE results to clinicians providing care to the participants (see Summary of Participant and PCP Letters in Section 15.3 and a sample annual letter to PCPs on the GRADE study website).

In addition, clinical alerts for outcomes that are measured as part of the study will be communicated to primary care providers (PCPs) as they occur (see Summary of Participant and PCP Letters in Section 15.3 and sample alert letters on the GRADE study website). Blood pressure and weight will be measured quarterly. There will be a lower extremity examination at the annual visit to look for foot ulcers including a neuropathy assessment (see Summary of Participant and PCP Letters in Section 15.3 and a sample Abnormal Foot Exam Alert Letter to PCP on the GRADE study website). Foot alerts that require urgent intervention, such as ulcerations and/or potential Charcot foot deformity or fracture, should be reviewed with the site PI and then communicated to the PCP, as deemed appropriate, at the time the abnormal finding is discovered.

Fasting cholesterol levels will be measured at baseline and annually and creatinine/eGFR will be measured annually.

Albuminuria, as an albumin-to-creatinine ratio (ACR), will be measured every six months as an early indicator of the microvascular complication of nephropathy. An elevated ACR, often referred to as microalbuminuria or moderately elevated albuminuria, is conventionally defined in clinical practice as a value 30-300 mg/g creatinine that is confirmed at the next measurement. Only CBL results will be considered in this determination, and values will be considered consecutive regardless of missed visits. The Coordinating Center will notify sites if two consecutive values have been abnormal, confirming a diagnosis of microalbuminuria. Macroalbuminuria, or severely elevated albuminuria, will be considered present if the ACR is >300 mg/g creatinine on a single test; no confirmation result is required. The CBL will alert sites of macroalbuminuria via the CBL results report. The participant's PCP should be notified about microalbuminuria or macroalbuminuria as soon as possible (see Summary of Participant and PCP Letters in Section 15.3 and a sample Annual/Semi-Annual Results Letter to PCP on the GRADE study website). Reference GRADE Memo #50 to Study Group for more information.

For most participants, vitamin B12 levels will be measured twice during study follow-up: At each participant's next semi-annual or annual visit after the implementation of protocol version 1.6.1, and at the Year 4 Annual Visit. If the next visit after B12 monitoring is implemented *is* the participant's Year 4 visit, then they will have just one B12 test (at the Year 4 visit). If B12 is low (<300 pg/mL), the site PI may recommend supplementation with a daily B12 tablet, which the participant can purchase on their own. If B12 is <300 pg/mL, the study will repeat the B12 testing in about 6 months. Reference GRADE Memo #65 to Study Group for more information.

Table 8.2 shows the clinical alert levels that will prompt communication to the participant's own health care providers with a reminder of the recommended levels.

Table 8.2 Clinical Alerts

1. Blood pressure ≥160 systolic and /or ≥100 mmHg diastolic (within 24 hours)
2. ECG alerts per local MD reading (within 24 hours to PCP at Baseline and Years 2, 4 and 6)
3. LDL cholesterol ≥160 mg/dl or triglyceride levels ≥ 500 mg/dl (reported annually)
4. Pregnancy Alert (within 24 hours)
5. Foot abnormality requiring urgent intervention (e.g. ulceration or potential Charcot foot) (within 24 hours)
6. Albumin/creatinine ratio (ACR): • Microalbuminuria (30-300 mg albumin/g creatinine, confirmed) • Macroalbuminuria (>300 mg albumin/g creatinine)
7. Vitamin B12 <300 pg/mL (reported within a week)
8. Other new clinically significant abnormality or concern which, in the opinion of the GRADE clinician, merits clinical follow-up
9. The annual letter to PCPs will include blood pressure, weight, the most recent lab results from the CBL, and a copy of the participant's ECG (if applicable).

Communication with PCPs may be in the form of a printed letter or electronic communication depending on local site preference.

HbA1c values should also be monitored and PCPs should be notified when therapy is changed (HbA1c values are >7.5 or >9.0).

Information on clinical alerts for CGM Substudy participants can be found in Section 5 of the CGM Manual.

8.3 Pregnancy

Participants who are pregnant or breastfeeding, or who plan to become pregnant during the course of the study will be ineligible. Participants who decide to become pregnant after joining the study or who have an unplanned pregnancy during the study will be referred back to their PCP with the recommendation that the subject be referred to a high-risk obstetrical team for medication management and care in anticipation of and during the pregnancy.

8.3.1 Pregnancy during GRADE

If pregnancy is discovered during a study visit, the rest of the visit may be completed, with the exception of the laboratory tests, before referring the participant back to her PCP/OB. Sites may dispense a small supply of study medication sufficient to last the participant until her care can be transitioned to another physician, but study medications should be stopped and replaced with the drug regimen recommended for pregnancy by the participant's PCP and obstetrical team as soon as possible. If the pregnant participant is taking any medications, such as ACE-inhibitors or statins, that are strictly contraindicated during pregnancy owing to teratogenicity, she should be informed that these medications are potentially dangerous to the baby. The GRADE PI should immediately discontinue these medications and notify the PCP/OB that these medications are being discontinued for safety reasons. The importance of the participant seeing her PCP/OB urgently to ensure appropriate obstetrical care should be reinforced. The participant will become "inactive" during pregnancy/lactation, other than to maintain contact and

maximize chances of retention. The **Targeted Adverse Event and Serious AE** and **Change of Status forms** should be completed and site research staff should work out plans to contact the participant on a regular basis during pregnancy.

8.3.2 After pregnancy

Study medications will be restarted in the post-partum period after the completion of lactation. It is important that participants resume follow-up and visit attendance once they are eligible to do so. Another **Change in Status form** should be completed by the site to document the return of the participant to active status.

8.3.2.1 Pregnancy Outcome Form

After the pregnancy has ended, site staff should ask the participant if she is willing to provide information about the outcome of her pregnancy and her baby's health. The participant needs to formally consent to the collection of this data before the **Pregnancy Outcome form** can be completed (refer to **Template Informed Consent: Pregnancy**). The participant will then be asked to complete a Medical Records Release Form for herself and for her baby. It is preferred that the coordinator complete the Pregnancy Outcome form based on the medical records obtained; however, if the participant is not willing to complete a Medical Records Release Form for herself and/or her baby, the Pregnancy Outcome form can be completed via participant interview.

The Pregnancy Outcome form and associated documents are available on request from the Coordinating Center.

8.4 Recommendations regarding Alcohol Intake

Participants will be informed that drinking alcohol in excessive quantities or binge drinking in combination with metformin can increase the risk for lactic acidosis and in combination with sulfonylurea or insulin can increase the risk for hypoglycemia. Participants will be strongly urged to limit alcohol intake to no more than 1 drink per day for women and 2 drinks per day for men (a standard drink is defined as containing 2 ounces of distilled spirits, 12 ounces of beer, or 6 ounces of wine). Participants who do drink alcohol are strongly advised against (1) regular, excessive drinking (for example, average consumption of 3 or more alcoholic beverages daily) or (2) binge drinking (7 or more alcoholic beverages within a 24-hour period). If a participant plans to binge drink (or may be in a situation conducive to unplanned binging), the participant will be advised NOT to take metformin or sulfonylurea on the day of alcohol intake or for 24 hours afterwards, to consider reduction of insulin dose, and to consume food with alcohol.

8.5 Self-monitoring of Blood Glucose

After randomization, participants will be instructed to perform self-monitoring of blood glucose (SMBG) depending on their treatment assignment (glimepiride and glargine groups). Meters and supplies will be provided by GRADE for those randomized to glimepiride and glargine. All participants will be instructed to alert the study coordinator if they have symptoms of hyper- or hypoglycemia or significant change in diet, exercise, or overall health (i.e. when ill). If indicated, the study staff will provide the participant with a glucose meter (if they do not have one from an outside study source) and instruct them on self-monitoring of blood glucose as appropriate. Participants are not required to use the meter supplied by GRADE if they wish to use their own meter. However, GRADE will only supply glucose monitoring strips, supplies and downloading software for the study-issued meter. Specific recommendations for SMBG may be found in sections on each drug in Chapter 9.

Manual of Procedures

Chapter 9

TABLE OF CONTENTS

9. CHAPTER 9: STUDY DRUG MANAGEMENT

9.1 Treatment Initiation - Overview

9.1.1 Metformin

Metformin dosing will be adjusted during run-in (see Chapter 6) to achieve a study goal of 2000 mg per day of study supplied metformin (or metformin XR, as necessary) and a minimum of 1000 mg per day, without intolerable side effects. If adjustment is necessary during the trial, for any reason such as side effects, the strategy will be the same as during run-in with the same dose goals (see Table 6.2).

9.1.2 Randomly assigned study medications

Participants will be randomly assigned to one of the four diabetes study drugs at the randomization/baseline visit, and will initiate this second diabetes drug (added to metformin) on the day of randomization. In general, drugs will be administered at the usual therapeutic dose, aiming to maintain HbA1c at the study goal (<7%), but may be titrated up to the maximal doses usually used in clinical care, as needed to achieve the study goal, unless limited by tolerability. If HbA1c is above goal, the study clinician should telephone the participant between study visits within one week of receiving HbA1c results to optimize medication dosing and adherence and review healthy lifestyle behaviors (**Interim Checklist for HbA1c Above Goal**). If HbA1c falls below 7%, the patient will continue on the same regimen unless intolerable side effects or hypoglycemia occurs. Adjustment of the doses of the medications that require titration (either increases or decreases) will be accomplished through phone calls between scheduled visits. The calls will usually be weekly until the study dictated dose is achieved. It is also permissible to schedule interim visits for the purpose of medication titration or dispensing, and to mail medication as long as the participant has completed a study visit within the last year. Sites will need to check the local procedure for mailing medications to participants and adhere to their institutional policies.

In general, drugs will be administered at the maximal dose specified in the package insert unless limited by tolerability or safety in the judgment of the study MD. In the case of the two drug classes that may cause hypoglycemia (glimepiride and glargine), the maximal dose will not be used if lower doses (e.g. <8 mg glimepiride) achieve the self-monitored glucose goals (range of 80-130 mg/dl titrated to fasting <100 mg/dl) and the HbA1c is <7%. Titration schedules of insulin and glimepiride may be modified by the study treating provider, based on clinical judgment, for safety and tolerability issues that may arise during the trial.

9.1.3 Patients with a history of Cardiovascular disease

The American Diabetes Association has issued new recommendations at the end of 2018 regarding diabetes medications that may be specifically indicated for patients with diabetes and a history of cardiovascular disease (*Diabetes Care*, 2018).

Based on the results of recent cardiovascular outcome studies, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have together recently recommended (Consensus Report & ADA SOC 2019) for patients with type 2 diabetes and HbA1c above target:

1. For patients with established atherosclerotic CVD: SGLT2 inhibitors (SGLT2i) or GLP-1 receptor agonists (GLP-1 RA) with proven cardiovascular benefit as part of glycemic management;

2. For patients with established atherosclerotic CVD in whom heart failure coexists or is of special concern: an SGLT2i with proven cardiovascular benefit;
3. For patients with chronic kidney disease (CKD), with or without CVD, *Consider* the use of an SGLT2i shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 RA shown to reduce CKD progression.

The GRADE Coordinating Center will provide an initial listing of participants with a history of CVD to each clinical site following local IRB approval based on data entered in MIDAS. Clinical sites will complete a CVDHIST form to document any previous history of CVD once for each participant at the first visit following IRB approval. Additionally, a MIDAS report will be available for sites to obtain a live listing of participants with a history of CVD based on newly obtained information from the CVDHIST form. Refer to GRADE Memo #77 "GRADE Response to ADA/EASD 2018 Recommendations" and GRADE Memo #86 "GRADE Response to 2020 Update to ADA/EASD Guidelines" for additional guidance on medication management. For participants with a history of CVD, a letter should be sent to both the participant and PCP with information about the treatment guidelines (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website).

9.2 Treatment Failure, Tolerability, and Discontinuation and Follow-up

9.2.1 Treatment Failure

The *primary outcome* of treatment failure will be met when the participant has a trigger HbA1c ≥7% followed by a confirming HbA1c ≥7% at the next quarterly visit. If the trigger HbA1c is >9%, the confirmation visit should be done within 3 to 6 weeks of the trigger HbA1c. If the trigger and confirmation HbA1c levels are both >7.5%, the participant will have confirmed the primary and secondary outcome. If, after a trigger HbA1c >9%, the confirmation HbA1c is ≤9%, the participant will return to his/her usual quarterly visit schedule for HbA1c monitoring.

NOTE: *The primary outcome can only be confirmed after a minimum of 9 months of therapy (6 months until triggering HbA1c ≥7% but <9% with confirmation 3 months later), or 4 months if the initial HbA1c is >9% at the 3-month quarterly visit and the confirmation HbA1c obtained 3 to 6 weeks later is higher than the 3-month triggering value.*

Once primary outcome has been confirmed, **participants will continue on their assigned interventions**, unless the primary and secondary metabolic outcomes are confirmed at the same time (HbA1c >7.5% at trigger and confirmation testing) (see secondary metabolic outcome below).

The *secondary metabolic outcome* is HbA1c >7.5%, confirmed. After the secondary metabolic outcome is confirmed, the assigned medications in those participants randomized to the three medications other than insulin will be continued and basal insulin (glargine) will be added. The same insulin adjustment protocol as implemented for the participants originally assigned to glargine will be used (see Table 9.1). If the secondary metabolic outcome is confirmed in participants originally assigned to basal insulin, their insulin regimen will be intensified by adding prandial injection(s) of rapid-acting insulin aspart to their basal insulin plus metformin following dosing adjustments as per GRADE insulin start and intensification guidelines.

For participants originally assigned to medications other than insulin, a tertiary outcome will be defined by HbA1c >7.5%, confirmed, after they have been treated with basal insulin plus metformin and their

second assigned medication (3 medications simultaneously). At the time that the tertiary outcome is confirmed, these participants will stop the randomly assigned medication which was started at the baseline visit, continue metformin and glargine, and have their regimen intensified by the addition of rapid-acting insulin aspart.

Table 9.1 Summary of medication adjustments

Randomization arm	Secondary outcome (A1c >7.5%, confirmed)	Tertiary outcome (A1c >7.5%, confirmed, on basal insulin glargine)
Glargine + metformin	add prandial insulin (aspart)	
Glimepiride + metformin	add basal insulin (glargine)	add prandial insulin (aspart), discontinue glimepiride
Sitagliptin + metformin	add basal insulin (glargine)	add prandial insulin (aspart), discontinue sitagliptin
Liraglutide + metformin	add basal insulin (glargine)	add prandial insulin (aspart), discontinue liraglutide

9.2.1.1 Diabetes Management for Participants after Treatment Failure

Some participants may have sustained hyperglycemia despite the treatments prescribed as part of GRADE. Regardless of the reasons for such treatment failures, any participant who has met indications for the addition of glargine or aspart insulin and has nevertheless sustained an HbA1c >8.5% for two consecutive measurements should be considered for additional non-GRADE glucose-lowering medication. Recognizing that initiation and adjustment of the GRADE treatments, including insulin, may take a variable amount of time for specific patients, the GRADE staff will have some latitude in deciding when to start this process.

Ideally, any non-GRADE treatments should be initiated and managed by the participant's own health care providers; however, in certain settings and in the best interests of patient care, the GRADE team may collaborate with the participant's health care provider to develop the treatment plan. With the agreement of the primary care provider or diabetes-care consultant, the study team may continue to provide study metformin, glargine, and/or aspart, while the primary care provider or non-GRADE endocrinologist prescribes additional anti-hyperglycemic medications or other interventions. Coordination of diabetes care is essential and the GRADE team will be required to discuss further care with the participant's PCP. GRADE will continue to follow the participant through study end.

9.2.2 Treatment Tolerability

Inability to tolerate study medications at protocol-specified doses will be recorded using a standard form that documents reasons for lack of tolerability called the **Participant Symptoms Questionnaire**. Participants should be titrated per protocol to the maximally tolerated dose. The maximally tolerated dose is defined as the highest dose that the participant is able (and willing) to take without unacceptable side effects. Participants who are unable to tolerate at least 1000 mg of metformin daily and/or the second agent will continue to be followed for the occurrence of the primary outcome and then beyond (for the occurrence of other pre-specified outcomes of interest), and will be analyzed according to the intention-to-treat analysis regardless of their ability to tolerate the prescribed combination. This includes participants who are unable to tolerate either metformin or the second assigned therapy. Other diabetes medications should not be administered until the primary outcome (HbA1c $\geq$7%) and tertiary metabolic outcome (HbA1c >7.5%) is reached on maximally tolerated dose of the assigned medication.

9.2.2.1 Management of medication when participants have been started on non-study diabetes medications

Participants who have had their glycemic management altered by non-study staff as reported at quarterly visits or when returning from inactive status will be evaluated by the study MD or authorized delegate to consider medication adjustment. The intent is to maintain and return to as much of the original assigned study treatment as possible and to restore the participant's medication regimen to the original pathway, if safely possible. The GRADE staff should take into consideration safety, side effects and tolerability, patient preference, and possible impact on long-term retention. If it is deemed safe and appropriate, the intent would be to resume the original medication assignment as follows:

- If the subject had not reached the primary outcome (HbA1c $\geq$7% confirmed), at his/her last contact before becoming inactive, resume study medication assigned as per the last visit, being mindful of medications that may require titration due to side effects. For example, if the participant has not taken metformin in a year, he/she may need to start out at a lower dose than she was receiving at the last visit.
- If the participant had reached the primary but not secondary outcome as of the last active visit, re-titrate as needed based on treatment assignment. If the subject had previously reached the secondary outcome (HbA1c >7.5, confirmed), re-titrate and add glargine (if in a non-insulin treatment group). Those in the glargine group will require insulin intensification (addition of rapid-acting insulin aspart).
- If the tertiary outcome had been reached, the participant can be started (or restarted) on metformin and an intensified insulin regimen (glargine and aspart) without the second assigned medication.
- If the participant has been started by non-study providers on a different drug within the same class of medications under study in GRADE, the study team should consider whether switching back to the GRADE agent is appropriate. For example, if the GRADE drug was not tolerated but the new drug is, or if the participant strongly prefers the new drug, that preference should probably be respected for the sake of retention. However, GRADE will not provide any diabetes medications other than those stipulated as GRADE medications, i.e. the participant will need to use his/her own diabetes medication supply.
- If a class of diabetes medications not included in GRADE was initiated by non-GRADE health care providers, safety and other factors, such as retention, should be considered. Discussion with the participant and health care provider is appropriate in this setting before potentially stopping the new drug and restarting the GRADE medications (see above).

9.2.3 Discontinuation of Medications

9.2.3.1 Permanent Discontinuation of Study Medications

The clinical site should notify the Coordinating Center who will consult with the Protocol Oversight Subcommittee to determine whether study drug doses should be reduced further than the lowest study recommended dose or discontinued when medications are titrated down to low doses or there is borderline tolerability. If study medications are permanently discontinued, complete a **Study Drug Discontinuation Form**.

9.2.3.2 Temporary Discontinuation of Any Study Medication

Study medications may be discontinued or altered at the time of any hospitalization at the discretion of the treating physician. Study medication may also be stopped for renal failure (see

Section 10.2), pregnancy (see section 8.3), lactation (see Section 8.3), lactic acidosis (see Section 10.3), or diabetic ketoacidosis (see section 10.2.) Study medication may be resumed when clinical circumstances permit.

Metformin will be temporarily discontinued 24 hours before, during, and for 48 hours after the following events:

- Procedure involving the injection of contrast dye;
- Surgery, or other procedure, requiring general anesthesia;
- Any illness that could be associated with hypoxia, circulatory failure, or dehydration.

The two drugs associated with hypoglycemia (glimepiride and glargine insulin) should also be discontinued or dose adjusted in the setting of a concurrent illness during which oral intake may be compromised.

9.2.3.3 Side Effects and Adverse Effects that May Require Discontinuation

Side effects and safety issues related to the use of the specific drugs are discussed in detail in Sections 9.3-9.7. Severe adverse events and adverse events that may require discontinuation are discussed in Chapter 10 (Safety Monitoring and Reporting).

9.2.3.4 Self-Monitoring of Blood Glucose

All participants, regardless of treatment assignment, will be instructed to monitor blood glucose when symptoms of hyperglycemia (polyuria, thirst) or hypoglycemia (palpitations, tremulousness, diaphoresis, confusion) develop. Clinical sites will have glucose meters and appropriate strips available for patients to use if such symptoms develop and require monitoring.

In addition, specific instructions for self-monitoring of blood glucose will be given to participants who are assigned to glimepiride or insulin in order to aid in the titration of their medication regimen and avoid hypoglycemia (see Sections 9.4.6 and 9.7.2.)

9.2.4 Continued Follow-up

It is expected that a fraction of the study cohort will not be able to tolerate the assigned medications, or that for some the assigned medications will prove to be ineffective. Thus, long-term treatment with insulin or an intensive insulin regimen will be required for some. Participants were informed of these potential outcomes when they agreed to participate in the study. However, we cannot tell beforehand which participants will be able to tolerate the study medications and which will not, or which participants will be able to control their glucose levels successfully with the assigned medications and which will not. In order to answer the study questions as to which agent in combination with metformin provides the best long-term control of glucose levels and has the most favorable long-term outcomes, **every participant randomized into the study is equally important.**

Thus, even though some participants may no longer be taking their originally assigned medications, it is just as important for us to know their long-term outcomes as it is for any other participant. That is why it is just as important to the study that they attend outcome assessment visits in the future as it was when they were taking their originally assigned study drugs. **Complete follow-up of the entire randomized cohort throughout the course of the study is our goal.** The importance of this should be conveyed to the participants so that they realize they are still making a very important contribution.

9.3 Metformin

9.3.1 Dosing Schedule

Initiation and initial titration of metformin dose is described in the run-in period procedures (see Section 6.4, Table 6.2). When the participant is taking metformin twice daily, the dose should be taken with food, at breakfast and dinner. If the participant does not have breakfast, it is acceptable to take the dose at lunch rather than breakfast, as long as doses are taken at least 4 hours apart. Participants should withhold metformin if they are ill or eating poorly.

9.3.2 Available Pill Size and Maximal Study Dose

Metformin IR and metformin XR will be available in 500 mg tablets. The maximum dose of metformin (or metformin XR) is 2000 mg daily.

9.3.3 Adjusting Metformin during Trial

All participants are required to take a minimum of 1000 mg daily with a goal of 2000 mg daily (usually 1000 mg pre-breakfast and 1000 pre-dinner) of study-provided metformin (or metformin XR) in order to be eligible for randomization. The dose of metformin will be titrated during run-in as noted in Table 6.2. The recommended schedule may be modified at the discretion of the investigator and based on tolerability by the participant, but as a general rule should be adjusted on a weekly basis. Refer to Section 6.4 for more details.

9.3.3.1 At time that first HbA1c ≥7% occurs

The tolerable metformin dose that was achieved during run-in will be the metformin dose that is continued during the trial with no further titration after randomization. This includes the time at which an HbA1c reaches 7% or above. When the HbA1c reaches ≥7% (prior to confirmation), the study staff should emphasize the importance of medication adherence to both metformin (at the dose achieved by end of run-in) and to the randomly assigned medication. The randomly assigned medication should be titrated to the maximum tolerated dose if not already achieved.

9.3.3.2 Restarting after temporary metformin discontinuation

If metformin is discontinued temporarily owing to surgery or radiologic procedures, it should be restarted in a timely fashion (see Section 9.2.3). In general, the re-starting dose can be the same as the dose before temporary discontinuation.

9.3.3.3 Adjustment if intolerance develops during the trial after run-in

If for any reason, intolerance to metformin IR or metformin XR develops during the trial, use the same titration schedule as for initiation of metformin beginning at the last tolerated dose (select week below with last tolerated dose) and adjust from there. For metformin IR or metformin XR:

- Week 1: Begin at 500 mg at breakfast
- Week 2: Add 500 mg at dinner
- Week 3: 1000 mg AM, 500 mg PM
- Week 4: 1000 mg AM, 1000 mg PM

One titration attempt should be made to increase the dose of metformin IR to reach the maximum dose of 2000 mg daily. If unsuccessful, the participant should be switched to metformin XR and up-titration should be attempted again.

For participants with intolerance to immediate-release metformin who don't tolerate a single titration trial of metformin (see above), a single trial of metformin XR should be attempted. The initial metformin XR dose should be the last dose of metformin IR that was tolerated. The same titration scheme for the metformin XR (see above) may be used.

The goal is to maintain the highest tolerable metformin (or metformin XR) daily dose up to 2000 mg per day.

9.3.4 Side Effects

Side effects and safety issues related to the use of metformin are gastrointestinal (e.g., diarrhea, nausea, metallic taste, abdominal bloating, flatulence, and anorexia), neurologic and hematologic (in association with reduced vitamin B12 levels), resumption of ovulation in women with oligomenorrhea due to polycystic ovarian syndrome, and, very rarely, lactic acidosis. The risk of lactic acidosis with metformin is associated with renal or hepatic dysfunction. For further information on specific adverse events, see Chapter 10: Safety Monitoring and Reporting.

9.3.5 Dose Reduction Guidelines

Metformin should be temporarily discontinued before any of the following:

- Procedure involving the injection of contrast dye;
- Surgery, or other procedure, requiring general anesthesia;
- Any illness that could be associated with hypoxia, circulatory failure, or dehydration.

This information will be provided and reviewed using the written medication information sheet that is given to the participant at the time of drug dispensation.

If GI side effects (see Section 9.3.4) are moderate or difficult to tolerate, metformin will be reduced to the next lowest dose as shown in the example below. If symptoms persist, metformin will be reduced by an additional 500 mg.

If the participant is on 2000 mg and side-effects (e.g. gastrointestinal) develop, decrease weekly by 500 mg until GI side effects disappear or are tolerable. If symptoms persist on a dose of metformin that is only 500 mg BID, reduce dose to 500 mg per day (see Section 6.4). If GI symptoms resolve, metformin will be increased by 500 mg daily each week until reaching the previously tolerated dose. If after re-escalation of the metformin dose, metformin will be permanently decreased to the next lowest dose and recorded in the **Medication Dispense Log**.

Participants who cannot tolerate at least 1000 mg or the recommended 2000 mg of metformin per day should be changed to metformin XR during the study. The same adjustments recommended above for metformin should be used for metformin XR (see Section 9.3.3.3).

9.3.6 Self-Monitoring of Blood Glucose

Participants will be instructed to monitor blood glucose when symptoms of hyperglycemia (polyuria, thirst) or hypoglycemia (palpitations, diaphoresis, and confusion) develop. Clinical sites will have self-monitoring meters and appropriate strips available for participants to use if such symptoms develop and require monitoring.

9.4 Sulfonylurea (Glimepiride)

9.4.1 Initiation of Glimepiride and Dosing Schedule

Glimepiride should be taken with food once per day until the dose is greater than 4mg. Patient education will include self-monitoring of blood glucose (SMBG) and hypoglycemia recognition and management, including the signs and symptoms of hypoglycemia and appropriate treatment of hypoglycemia. SMBG will be performed 1-2 times per day when initiating and titrating glimepiride, and may be reduced to 0-2 times per day when the participant is on a stable dose, at the discretion of the treating provider. Participants should be instructed to skip glimepiride if not eating or to reduce the dose if eating poorly and to perform SMBG during these periods. Participants should also be instructed to reduce the glimepiride dose by half when initiating a sustained exercise program. If there is no hypoglycemia and SMBG reveals random BG >180 mg/dl, the dose should be increased.

The initial dose will depend on the Final Run-in Visit HbA1c:

- HbA1c $\leq$8%: glimepiride 1 mg with first meal of the day
- HbA1c >8%: glimepiride 2 mg with the first meal of the day or before the largest meal

A lower starting dose (<1 mg/day) may be considered, based on investigator judgment, for participants where there is a concern about hypoglycemia.

9.4.2 Available Pill Size and Maximal Study Dose

Glimepiride is available in 2 mg and 4 mg tablets. A limited supply of 1 mg tablets is also available in the event that a participant can only tolerate 0.5 mg at a time. The maximum study dose is 4 mg twice daily. Pills are scored and it is acceptable to split them to achieve the recommended dose. The lowest acceptable starting dose for glimepiride is 1 mg; however, the dose of glimepiride can be down-adjusted and/or titrated during follow-up based on clinical judgment and patient response if absolutely necessary.

9.4.3 Side Effects

Glimepiride causes hypoglycemia and weight gain. Hypoglycemia should prompt re-education. Hypoglycemia that occurs while the participant is following his or her usual diet and exercise routine should prompt reduction of the dose as outlined in Section 9.4.5. For further information on specific adverse events, see Chapter 10: Safety Monitoring and Reporting.

9.4.4 Increasing Glimepiride to Goal Dose

- If the fasting glucose by SMBG is above target (100 mg/dl) in 4 or more tests per week, as communicated to the clinic team during (usually weekly) phone calls for drug adjustment follow-up, the glimepiride dose should be adjusted in weekly increments (see below) until the glucose levels are in the target range, maximal dose (8 mg) is reached, or unacceptable hypoglycemia occurs (any episode of severe hypoglycemia or > 2 episodes of non-severe hypoglycemia in a month).
- If after 3 months, the HbA1c is $\geq$7% without hypoglycemia while the participant is taking less than the maximum dose of 8 mg per day, the dose may be increased again.
- When a dose of 4 mg is reached and higher doses continue to be needed based on the guidelines above, glimepiride doses should be given twice per day with doses increased weekly as below:
    - 4mg in AM + 2 mg in PM with meal
    - 4 mg in AM + 4 mg in PM with meal (maximal dose)

- Though these are general guidelines, there is greater emphasis on attempting to reach the maximal tolerated dose than on the timing and distribution of doses during the day. As an example, if the study physician felt that hypoglycemia would be minimized at 2 mg twice daily instead of 4 mg once daily, that would be acceptable. Sites may use their clinical judgment and preference as to whether to use a 3 mg dose during titration. For example, sites may go from 2 to 4 mg during titration or may titrate in 1 mg increments going from 1 to 2 to 3 and then 4 mg.

9.4.5 Dose Reduction Guidelines

If severe hypoglycemia or repeated (>2 episodes within a one month period) non-severe hypoglycemia occurs *due to administration of medication with decreased food or increased exercise* in glimepiride-treated participants, the participant will be educated regarding holding or reducing the dose in these situations.

If hypoglycemia as defined above occurs *during the participant's usual routine*, the medication will be reduced as follows.

- Reduce dose by half at each administration if hypoglycemia occurs at any time of day.
- If on a twice per day regimen and hypoglycemia is related to low intake at lunch or dinner, the dose before smaller meals may be reduced; the higher dose before the larger meal may be continued.
- If after 3 months, the HbA1c is $\geq$7% or fasting BG exceeds target (80-130 mg/dl), without hypoglycemia, the dose may continue to be adjusted if not at the maximum dose.
- If hypoglycemia recurs, the study dose will again be reduced and will remain at the lower dose.

Upon confirming secondary outcome, the dose of glimepiride may reduced at the time of glargine initiation and even subsequently stopped should the investigator feel that observed hypoglycemia or weight gain may be related to glimepiride.

9.4.6 Self-Monitoring of Blood Glucose

Participants will be instructed to monitor blood glucose when symptoms of hyperglycemia (polyuria, thirst) or hypoglycemia (including palpitations, diaphoresis, tremulousness, confusion or other changes in mental status) develop. In addition, participants should monitor blood glucose one to two times per day (before breakfast and/or dinner) while titrating the medication and 0-2 times per day while on a stable dose.

9.5 DPP-IV Inhibitor (Sitagliptin)

9.5.1 Dosing Schedule

Sitagliptin 100 mg will be taken once per day with or without meals. In some instances, during the follow-up phase of the trial, the dose may be adjusted based on renal function.

9.5.2 Available Pill Size and Maximal Study Dose

The available pill dose for sitagliptin is 25 mg, 50 mg, and 100 mg. The starting dose and maximum study dose is 100mg/day. The only occasion for downward titration will be in the setting of decreased kidney function.

9.5.3 Side Effects

DPP-IV inhibitors are generally well-tolerated. Known adverse effects associated with DPP-IV inhibitors at greater than 5% are upper respiratory infection, urinary tract infection, and headache. Notably,

sitagliptin may be associated with pancreatitis. Other DPP-IV inhibitors have been associated with heart failure in patients who have a prior history of heart disease.

9.5.4 Dose Reduction Guidelines

If any side effects are difficult to tolerate, sitagliptin will be discontinued. It is noted that the prescribing information for sitagliptin suggests dose adjustment based on eGFR. See Table 10.3 for adjustment of sitagliptin due to kidney function.

9.5.5 Self-Monitoring of Blood Glucose

Participants will be instructed to monitor blood glucose when symptoms of hyperglycemia (polyuria, thirst) develop. Clinical sites will have self-monitoring meters and appropriate strips available for participants to use if such symptoms develop and require monitoring.

9.6 GLP-1 Analog (Liraglutide)

9.6.1 Dosing Schedule to Maximal Dose

Participants should be instructed in pen injection technique and should demonstrate ability to self-inject. Liraglutide should be initiated at 0.6 mg once daily for one week. If there is no nausea or abdominal discomfort, it should be increased to 1.2 mg once daily. The participant should be monitored on this dose. If the participant does not have nausea or abdominal pain, the dose will be increased to 1.8 mg within the first month. It should be noted, however, that the overarching goal of these titration guidelines is to get participants to maximal doses that are safe and tolerated according to usual clinical practice and as guided by labeling. The medication doses achieved and any side effects are among the outcomes measured by the study. Therefore, some flexibility in the suggested titration schedule will be allowed.

9.6.2 Available Dose Size and Maximal Study Dose

The liraglutide multi-dose pen syringe is available in doses of 0.6, 1.2, and 1.8 mg/day. The maximal study dose is 1.8 mg/day. The study recommended dose of liraglutide is 0.6, 1.2, or 1.8 mg/day; however, the dose can be titrated during follow-up using doses in between these targets based on clinical judgment and patient response if absolutely necessary.

9.6.3 Side Effects

Side effects related to the use of liraglutide are discussed further in Chapter 10: Safety Monitoring and Reporting. The most common side-effects associated with liraglutide are gastrointestinal and include nausea, vomiting, diarrhea, constipation, decreased appetite, headache, upper respiratory infection, and acute gallbladder disease. An increased risk of pancreatitis has also been reported. Pancreatitis is an exclusion criterion and an absolute contraindication to continuing liraglutide. In addition, increased levels of calcitonin, which are associated with a rare form of thyroid cancer, have been reported. Medullary thyroid cancer is an exclusion criterion in GRADE.

9.6.4 Dose Reduction Guidelines

If GI side effects occur and are moderate or difficult to tolerate, liraglutide will be administered at a different time of day, at least 1 hour prior to a meal. If this does not improve tolerability, the dose will be reduced to the next lowest increment (liraglutide 0.6 or 1.2 mg). If GI symptoms improve and the participant is willing, the medication will be re-escalated. The lowest dose allowed by the study is 0.6 mg per day; however, the dose can be titrated during follow-up using doses in between target doses based on clinical judgment and patient response if absolutely necessary.

9.6.5 Self-Monitoring of Blood Glucose

Participants will be instructed to monitor blood glucose when symptoms of hyperglycemia (polyuria, thirst) develop. Clinical sites will have self-monitoring meters and appropriate strips available for participants to use if such symptoms develop and require monitoring.

9.7 Insulin in GRADE

Basal insulin (glargine) will be used as one of the four assignments at randomization and when secondary and tertiary metabolic outcomes are reached. Prandial insulin (aspart) will be used at secondary outcome (glargine arm) and tertiary outcome (glimepiride, sitagliptin and liraglutide arms). Sites will follow dosing adjustments as per GRADE insulin start and intensification guidelines. **The conditions under which glargine and aspart should be initiated are described in Table 9.1.**

Participants will have an in-person visit to learn insulin administration and/or insulin intensification and review home blood glucose monitoring techniques. Education for participants initiating insulin should include injection techniques with a pen, self-monitoring of blood glucose (SMBG), and hypoglycemia teaching regarding the signs and symptoms of hypoglycemia and appropriate treatment of hypoglycemia. Appropriate times to contact the healthcare team will be reinforced. Glargine will be initiated and titrated under the supervision of the study physician or appropriate delegate using the guidelines below. The first dose of insulin should be taken by the participant at the initiation visit if possible, for example, taking ½ of the glargine dose with instructions to take the full dose starting the next evening, preferably at bedtime, or for intensification taking the first dose of aspart with a meal if possible at the visit. If it is not possible to take the aspart at the visit (due to timing or logistics), the participant may take their first dose at home if adequate teaching has been provided.

9.7.1 Available Dose Size and Maximal Study Dose

Glargine multi-dose insulin pens will be provided. They hold 300 units per cartridge. There is no study maximal dose for insulin; the maximal dose is only limited by hypoglycemia.

Basal insulin will be initiated under one of two circumstances during the GRADE study:

- Randomization to the metformin plus glargine arm.
- Attainment of secondary metabolic outcome of HbA1c >7.5%, confirmed, on maximally tolerated dose of assigned regimen (metformin plus second non-glargine agent).
  (Confirmation HbA1c is obtained 3 to 6 weeks if HbA1c >9%, or at 3 months if HbA1c is between 7.5 and 9%).

In both circumstances, insulin will be initiated with glargine according to the basal glargine titration protocol. After attainment of the tertiary metabolic outcome (or the secondary outcome in the glargine arm), prandial insulin (aspart) will be added according to the prandial insulin titration protocol (see Table 9.4).

9.7.1.1 Initiation of glargine

Glargine will be initiated and titrated under the supervision of the study physician or appropriate delegate using the guidelines below.

1) The recommended starting dose of glargine in the evening (from pre-dinner to bedtime or in shift workers between before the last meal of the day and bedtime) is:
   a) 10 units subcutaneously if A1c $\leq$8%

b) 20 units subcutaneously if A1c > 8%

The dose can be down-adjusted and/or titrated during follow-up based on clinical judgment and patient response if absolutely necessary. Dose may be taken in the morning depending on clinical judgment and participant preference.

2) Test blood glucose in the morning (fasting). Participants may also monitor at other times of the day routinely. They should be asked to monitor blood glucose when symptoms of hyperglycemia or hypoglycemia develop.

3) Basal insulin titration schedule

Increase the glargine dose to the increments listed in Table 9.3 until morning blood glucose level is lower than 100 mg/dl without hypoglycemia.

Table 9.3: Glargine dose titration based on self-monitored blood glucose

If fasting morning blood glucose is *:	Then increase glargine dose that night by:	Aiming for fasting blood glucose target of:
≥180 mg/dl	2 units	<100 mg/dl without hypoglycemia
100-179 mg/dl	1 unit	

*With usual diet and activity or PI discretion

If the morning (am) fasting reading is:

- Less than 80 mg/dl, reduce daily glargine dose by 2-5 units depending on insulin dose and clinical judgment.
- At the target level between 80 mg/dl and 100 mg/dl for several days in a row with no readings below 80 mg/dl, do not make any further adjustments to your glargine dose.
- If you think the blood sugar is high because of a change from a usual routine, such as an unusually large meal, do not change the glargine dose based on the morning blood sugar that day.
- If you think the blood sugar is low because of a change from a usual routine, such as extra physical activity, continue the usual glargine dose on inactive days and reduce the dose on active days.

Clinical judgment and safety should be considered when adjusting insulin for each participant. The titration schedule is to be used as a general guide but can be modified based on provider discretion.

1. If hyperglycemia persists at 1 month despite following the titration schedule,
    a. Review adherence and injection technique with the participant
    b. Titrate further with guidance of study provider
2. If participants are not performing requested monitoring, insulin may be initiated and titrated based on HbA1c level at the discretion of the investigator. However, every effort should be made to promote self-monitoring of blood glucose.
3. If the patient develops daytime or nocturnal hypoglycemia, evaluate the reason for the hypoglycemia and review the hypoglycemia section below

4. If there is clinical suspicion that the participant is having nocturnal hypoglycemia, consider monitoring blood glucose mid-sleep to rule out hypoglycemia

Insulin titration should be tracked via phone calls or other contact (email/fax) and dose titration should be documented including glucose monitoring, titration scheme, and reasons for non-adherence to the prescribed scheme as well as actions taken in the case of non-adherence.

When a stable glargine dose without hypoglycemia is achieved, continue to monitor fasting and bedtime blood glucose levels at least two times per week to ensure stability.

4) Recurrent hyperglycemia:

If fasting blood glucose rises above 100 mg/dl for the majority of measurements and more than 3 times per week, after achieving a stable insulin (glargine) dose or after reducing the dose for previous hyperglycemia, the insulin (glargine) dose may be titrated again according to the above protocol under the supervision of the site study provider.

9.7.2 Side Effects, Hypoglycemia, and Adjustment of Insulin for Changes in Exercise and Diet

Side effects related to the use of insulin are discussed in Chapter 10 on Safety Monitoring and Reporting. Known side effects of insulin include hypoglycemia, weight gain, and hypokalemia. Weight will be monitored as part of the trial.

9.7.2.1 Hypoglycemia

During the initial titration, participants should be instructed to reduce their insulin dose by 2-5 units depending on the dose and clinical judgment for any unexplained blood glucose level less than 70 mg/dl; i.e., documented glucose <70 mg/dl in the absence of skipped, delayed, or reduced food intake or increased physical activity. Later in the study, occasional glucose levels of 55-70 mg/dl with mild symptoms may be tolerated, i.e. episodes occurring less than weekly. Any unexplained glucose <55 mg/dl should result in a 2-5 units decrease depending on the insulin dose and clinical judgment. Episodes of severe hypoglycemia should be tracked using the **Targeted Adverse Event and Serious AE (SAE) Form.**

The participant should be instructed to call the study team for the following:

1. Any episode of severe hypoglycemia (hypoglycemia requiring assistance from a third party) or any episode of hypoglycemia about which the participant or his or her family is concerned
2. Recurrent hypoglycemia, defined as two or more glucose levels <70 mg/dl despite appropriate titration of insulin
3. Planned change in diet or carbohydrate restriction, or change in diet related to change in appetite, associated with hypoglycemia
4. Planned increase in physical activity, whether as part of a new lifestyle plan or as a result of new domestic or work duties

Clinical judgment should be used in these circumstances, with reduction in insulin dose generally of at least 10 units or 20% (whichever is greater) followed by re-titration as needed. In the case of severe hypoglycemia or recurrent hypoglycemia, more frequent glucose monitoring should be prescribed, particularly before meals, at bedtime, and mid-sleep. If asymptomatic hypoglycemia

(hypoglycemia unawareness) is present (glucose <55 mg/dl without accompanying symptoms), study investigators should adjust insulin regimen as clinically appropriate. Consideration should be given to relaxing the glycemic target to 100-150 mg/dl for a period of weeks to months or longer until symptoms of hypoglycemia return, reducing the glargine dose by 10%, and/or other measures as appropriate.

9.7.2.2 Additional considerations in adjusting glargine dose

Exercise: Participants who are at goal or close to target range should be instructed to reduce the insulin dose by 25% when starting a new exercise program.
Fasting: Participants who anticipate a procedure where they will be NPO or fasting should reduce the dose by 50%.

Current doses and need for dose reductions after a stable dose of glargine has been achieved, and the reason(s) for the dose reduction, should be reported at the time of dose change and/or at quarterly visits if not reported previously.

9.7.3 Intensification of Insulin Therapy

9.7.3.1 Initiation of prandial insulin

Intensification of insulin therapy with rapid-acting insulin (aspart) coverage at meal(s) will occur at the time of attainment of tertiary metabolic outcome of HbA1c >7.5%, confirmed at 1 or 3 months, while on maximally tolerated doses of the assigned regimen (metformin, second non-glargine agent, and glargine). When rapid-acting insulin (aspart) is added, the non-insulin assigned agent (glimepiride, sitagliptin, or liraglutide) is discontinued; metformin and glargine are continued. For participants randomized to glargine, intensification of insulin therapy with rapid-acting insulin (aspart) coverage at meal(s) will occur at the time of attainment of secondary metabolic outcome of HbA1c >7.5%, confirmed at 1 or 3 months, while on maximally tolerated doses of metformin and glargine (Table 9.1).

Rapid-acting insulin (aspart) should be initiated and titrated under the supervision of the study provider. Providers should use the guidelines below for aspart initiation and then adjust according to patient-specific factors. Calls or other contact (email, fax) by study staff will be made to review blood glucose levels regularly during this time.

1. At the time of rapid-acting insulin (aspart) initiation, monitor blood glucose before meals and at bedtime.
2. Start aspart 0.1 unit/kg (up to a maximum of 10 units as an initial dose) at the largest meal of the day. The dose may be adjusted based on pre-meal and bedtime blood glucose and/or as outlined below.
3. After 3 months, if HbA1c and self-monitoring of blood glucose suggest that additional prandial insulin is required, rapid-acting insulin (aspart) should be added at a second meal, then at a third meal, using the achieved insulin doses, self-monitored blood glucose, meal size, and participant activity to guide dosing recommendations. If the patient does not perform recommended self-monitoring of blood glucose, prandial insulin may be cautiously initiated based on elevated HbA1c levels after ascertaining that the patient has no signs or symptoms of hypoglycemia by history.

9.7.3.2 Adjustment of prandial insulin (aspart) according to target blood glucose levels

The ADA and GRADE blood glucose targets for most people with diabetes are 80-130 mg/dl fasting and pre-meal without hypoglycemia.

To accomplish this, titration goals should be wider to prevent hypoglycemia.

Fasting and pre-prandial: <100 mg/dl without hypoglycemia

Bedtime/mid-sleep: <140 mg/dl without hypoglycemia

Table 9.4 lists the prandial insulin (aspart) adjustment algorithm based on patterns of mealtime blood glucose values.

Table 9.4: Prandial insulin (aspart) adjustment algorithm

Mealtime dose, units	Pattern of mealtime blood glucose values <80 mg/dl	Pattern of mealtime blood glucose values >110 mg/dl
≤10	Decrease by 1 unit	Increase by 1 unit
11-19	Decrease by 2 units	Increase by 2 units
≥20	Decrease by 3 units	Increase by 3 units

Manual of Procedures

Chapter 10

TABLE OF CONTENTS

10. CHAPTER 10: SAFETY MONITORING AND REPORTING

Each GRADE participant is given an identification card that clearly states procedures to reach the GRADE clinic in case of medical emergency. The card will include the participant's name, diagnosis of diabetes, and treatment assignment (e.g. metformin plus insulin therapy). It will also state clearly that the GRADE clinical site is the primary contact for diabetes treatment and will provide an emergency contact number for clinical staff.

Medications may be discontinued for reasons outlined in each section. The Intervention Oversight Group will assign an Intervention Monitor to aid clinical sites and ensure that the intervention protocol detailed in Chapter 9 is followed. The clinical sites should discuss the decision to discontinue any study medications permanently with the Intervention Monitor. If medication needs to be discontinued for safety reasons, the clinical site should act expeditiously and not wait to discuss the discontinuation with the Monitor.

10.1 Adverse Events and Serious Adverse Event Definitions and Assessment

10.1.1 Definitions

Adverse Event (AE)

An adverse event (AE) is any unfavorable, unintended and/or unexpected change in the structure, function or chemistry of the body experienced by a study participant during the study regardless of the relationship of this change to administration of the study intervention or participation in the study.

All AEs are divided into those that are serious (SAEs) and those that are non-serious (AEs). For non-serious AEs, only the subset that might be associated with study interventions will be documented for this study using the SAE Form. These events will be referred to as *targeted AEs.* Information about targeted and serious AEs will be collected via the **Targeted Adverse Event and Serious AE Form** (SAE Form), which will be reported on-line and in real time within 24 to 48 hours of becoming aware of the event (see section 10.5).

Other non-serious AEs that do not fall into the category of targeted AE will be documented on the annual and quarterly visit forms in the interval history section (see Section 10.1.2). These will be referred to as *other AEs*. Symptoms will also be collected on the Participant Symptoms Questionnaire. These *other AEs* are reported only at scheduled study visits unless they meet the criteria for being a Serious Adverse Event (SAE).

Serious Adverse Event (SAE)

The distinction between an SAE and an AE is a regulatory definition established by the FDA. The determination of being an SAE is not always related to clinical severity of the event. An AE will be considered serious (SAE) when it satisfies any one or more of the following criteria, which incorporate the FDA definitions and GRADE-specific SAEs of interest:

a. The event results in an inpatient hospitalization (any hospital admission 24 hours or more);
b. The event results in the prolongation of a hospital stay;
c. The event results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
d. The event results in death;

e. The event results in a congenital anomaly/birth defect;
f. The event results from an overdose (either accidental or experimental) of the study medication;
g. The event is life-threatening;
h. Treatment is required to prevent a serious event

Although the FDA definition of SAE does not include specific medical conditions, for purposes of the GRADE study, the conditions below will be considered SAEs even if they do not meet other criteria for an SAE (a-h above):

i. Acute metabolic decompensation (e.g. DKA or HHS)
j. Lactic acidosis
k. Pancreatitis
l. Medullary thyroid carcinoma
m. Severe hypoglycemia (i.e. another person was required to help treat the episode, usually because the participant was confused or otherwise impaired and could not treat him/herself)

Inpatient Hospitalization or Prolongation of Hospitalization:
Hospitalization itself, including for surgical and diagnostic procedures, is neither an AE nor an SAE; it is the underlying condition that constitutes the adverse event. For example, if a participant is hospitalized (post-randomization) for gallbladder surgery due to gallstones, neither the hospitalization nor the cholecystectomy is the AE - the cholelithiasis (gallstone) is the AE. Additionally, it would be an SAE because it resulted in an inpatient hospitalization.

Any condition that results in hospitalization for at least 24 hours must be recorded as an SAE, including hospitalization due to elective surgery. For example, if a participant is hospitalized for an elective hernia repair after randomization, and the hernia was present prior to randomization, the event must be recorded as an SAE. A prolonged stay, for example a 12-hour emergency unit or short-stay unit, that does not include at least a 24-hour hospital admission does not qualify as an SAE unless the condition that prompted the hospital visit meets any of the other criteria for being an SAE. For example, a severe asthma attack might be life-threatening even if it did not result in a 24-hour hospitalization. Hospitalizations for elective long-term treatment programs (>24 hours), such as for PTSD, alcoholism, or depression, would qualify as an SAE under this definition.

Persistent or Significant Incapacity or Substantial Disruption of the Ability to Conduct Normal Life Functions:
Any condition that results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions will require the completion of an SAE form. These are defined as conditions causing persistent or significant disruption of one's ability to carry out normal life functions.

Death:
Death, regardless of its cause, is considered an SAE and must be reported on an SAE Form. A new SAE form must be completed to report the death, or, if the death occurred as part of a previously reported adverse event, the original SAE Form must be updated. A copy of the death certificate should be obtained. Death should not be listed as the classification term for the adverse event. In the case of death, the event that caused death should be used to code the SAE.

Congenital Abnormality/Birth Defect:
Any study pregnancy with a congenital abnormality during the study requires prompt notification by the completion of an SAE form.

Life-Threatening Event:
The life-threatening event category is meant to provide a safety net for those AEs that should be promptly reported, but that fail to meet the other criteria for "serious." In reality, it is very rare for an AE to be life-threatening, yet fail to result in hospitalization. To be considered life-threatening, the AE must place the participant at immediate risk of death from the adverse event as it occurred. A life-threatening AE may be completely unrelated to study participation. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered immediately life-threatening even though drug-induced hepatitis can be fatal. This category does not include a hypoglycemic reaction that had it occurred in a more serious form or had there been no intervention might have caused death. In contrast, thrombocytopenia to a platelet count of 5000 associated with a massive GI hemorrhage treated with multiple blood transfusions would certainly be considered life-threatening. No AE or SAE is automatically life-threatening.

Overdose:
An overdose is defined as having taken or been given an excess of any medication that results in adverse clinical signs or symptoms. Hypoglycemic reactions due to the administration of too much insulin or glimepiride should be considered to be due to overdose only when the participant intentionally or accidentally took a much higher dose than was prescribed (at least double the prescribed dose without a clinical reason for doing so).

Treatment to Prevent a Serious Adverse Event:
In accordance with the FDA guidelines that were effective on April 6, 1998, the category "Treatment to Prevent a Serious Event" was added to the definition of a Serious Adverse Event. This category captures important medical events that may not result in death, be life-threatening, or require hospitalization. If a medical event is thought to jeopardize the participant and may require medical or surgical intervention to prevent a serious adverse event (SAE), that event should be captured as an SAE.

DKA:
Although the FDA definition of SAE does not explicitly include DKA, treatment for DKA, even in an emergency unit setting and without hospitalization, is considered treatment to prevent a serious event, and therefore DKA should always be reported as an SAE. In the GRADE study, diabetic ketoacidosis (DKA) is defined as:

1) documented acidosis (HCO_3^- <15 and/or pH <7.3), **and**
2) urine ketones moderate or large and/or serum ketones $\geq$4.0 mMol.

Targeted AEs:
The following targeted AEs should be documented using the SAE Form within 24 to 48 hours of becoming aware of the event.

i. Myocardial infarction
ii. Revascularization (coronary, peripheral, or cerebral)
iii. Stroke
iv. Congestive heart failure
v. Pancreatic cancer
vi. Other cancer
vii. Pregnancy

Only certain revascularization procedures are considered to be targeted AEs. Interventional cardiology procedures, such as coronary artery stent placement or percutaneous coronary angioplasty, as well as other vascular interventions, such as lower extremity stent, lower extremity angioplasty, carotid endarterectomy, carotid stent, renal artery stent, renal artery angioplasty, and aortic aneurysm repair should be reported as targeted AEs via the SAE Form. Revascularization procedures done purely for diagnostic purposes (e.g. diagnostic stent) are not considered targeted AEs.

If the event meets any of the above criteria for an SAE (a-h), this should be indicated on the SAE Form.

10.1.2 Assessment of Other AEs

It is essential that AEs be ascertained in a non-biased manner using standard questions that are identical and identically administered to participants in all treatment arms. Therefore, AEs will be ascertained during regular study follow-up visits (every 3 months) and reported on the **Quarterly** or **Annual Visit Form**. In addition, AEs may also be ascertained via the **Participant Symptoms Questionnaire** that will generally be completed by the participant and reviewed by the study staff. Participants will be instructed to inform study staff as soon as possible if adverse events occur that warrant temporary or permanent discontinuation of study medication. If study medications are discontinued for >28 days, the site must also complete a **Study Drug Discontinuation Form**.

The following list of events that occur at >5% frequency for the study drugs or are of special concern for GRADE has been selected for targeted capture at visits and will be recorded on the **Participant Symptoms Questionnaire** at quarterly visits. The **Participant Symptoms Questionnaire** will address any symptoms that have occurred during the previous 30 days. Participants will be asked the frequency (Never, Occasionally, Weekly, Daily) that they have had the following during the prior 30 days (usually since the last visit):

- Stomach pains or bloating
- Nausea
- Diarrhea
- Vomiting

Any episodes of the following during the previous 30 days will also be reported at regular quarterly follow-up visits:

- Symptoms consistent with congestive heart failure, such as shortness of breath when lying down (orthopnea) or increased shortness of breath with exertion (NYHA II or greater)
- New infection requiring medical attention
- Episode(s) of hypoglycemia (low blood sugar) symptoms (e.g. otherwise unexplained sweating, heart racing, and/or confusion) that got better with glucose or food, and/or blood sugar level by finger-stick (alternate site blood glucose testing is acceptable in lieu of finger sticks) <70mg/dl
- Episodes of severe hypoglycemia (requiring assistance) —this is also an SAE (see Section 10.1.1)
    - Loss of consciousness or seizure

10.1.3 Critical and Abnormal Laboratory Values

Table 10.1 lists the critical laboratory values for GRADE.

Table 10.1 Critical Laboratory Values

Description	Critical Values
Pregnancy*	Positive
BP	≥ 160 systolic and/or ≥ 100 mmHg diastolic

*Pregnancy tests are conducted locally, therefore alerts will not be provided by the CBL. Sites should monitor pregnancy test results locally.

Critical alerts should be reported to the PCP within 24 hours.

Table 10.2 lists the abnormal laboratory values for GRADE.

Table 10.2 Abnormal Laboratory Values

Description	Abnormal Values
LDL cholesterol	≥ 160 mg/dL
Triglycerides	≥ 500 mg/dL
Albumin-to-creatinine ratio (ACR): Microalbuminuria Macroalbuminuria	 30-300 mg/g creatinine, confirmed >300 mg/g creatinine
Serum creatinine	≥1.5 mg/dL (males) ≥1.4 mg/dL (females)
eGFR	<30 mL/min/1.73m^2 30-45 mL/min/1.73m^2
Vitamin B12	<300 pg/mL

Abnormal values should be reported to the PCP within 1 week.

HbA1c values will be monitored between ≥7.0 and ≤9.0 for the purpose of identifying threshold values and also values of >7.5 or >9.0 for critical alerts. The CBL will provide notifications to clinical sites when a participant has reached a threshold value for HbA1c so that sites may follow the necessary steps outlined in the **HbA1c Metabolic Outcome Confirmation Worksheet, Interim Checklist for HbA1c Above Goal,** and **HbA1c Flowchart** to determine whether an outcome has been reached (see Section 8.1). In addition, PCPs should be notified when therapy is changed (HbA1c values are >7.5 or >9.0).

10.1.4 Electrocardiogram (ECG) Alerts

ECGs are collected at Baseline and Years 2, 4, and 6. Refer to the ECG Manual for GRADE-defined alerts to be specified on the ECG Form and reported for the study. Immediately following collection, the ECGs must be locally read by an MD for clinical abnormalities. The participant's PCP should be sent a tracing and followed up per standard care. Participants should be provided with a letter (see Summary of Participant and PCP Letters in Section 15.3 and sample letters on the GRADE study website) to indicate whether their ECG results are 1) within normal limits, 2) have some abnormality, or 3) have a major abnormality that requires immediate attention.

The ECG manual defines GRADE alerts as the following:

a) Heart rate below 40 or over 120 beats/minutes
b) Atrial fibrillation (See ECG manual: **Figure 11**) or atrial flutter (See ECG manual: **Figure 12**) not known by the participant
c) Ventricular tachycardia (See ECG manual: **Figure 13**)
d) Acute myocardial infarction (See ECG manual: **Figure 14**)
e) Ventricular preexcitation/Wolff-Parkinson-White (WPW) ECG pattern (See ECG manual: **Figure 15**)
f) Complete atrioventricular block (See ECG manual: **Figure 16**)
g) Any statement which includes a reference to **acute** injury or ischemia

There are other significant ECG abnormalities that warrant treatment, but because they do not require prompt action or immediate notification to the participant, they are not included in the "alert" ECG list. Also, since local reading of the study ECGs for alerts is not part of the ECG reading center procedure, this list of ECG abnormalities may be modified by adding or deleting more ECG abnormalities to match the overall safety measures implemented by the GRADE study. Always refer to the ECG manual for detailed information on ECG alerts.

10.2 Adverse Events that May Require Medication Adjustment or Change in Therapy

10.2.1 Kidney Function Monitoring

Acute or chronic renal insufficiency increases the risk of lactic acidosis associated with metformin and may affect the doses that can be used safely for several other drugs.

If the creatinine is ≥1.5 mg/dl in men or ≥ 1.4 mg/dl in women, selected study medications (including liraglutide, and glimepiride) will either be discontinued or dose-adjusted based on Table 10.3. For metformin and sitagliptin, the dose reduction guidelines are based on eGFR values.

If the subsequent repeat creatinine is below the thresholds in Table 10.3, study medication will be resumed at the previous dose. If the subsequent repeat creatinine is again above the thresholds in Table 10.3, study medication will be adjusted or discontinued permanently as indicated in Table 10.3.

Table 10.3 below reviews the drug stopping rules and dose adjustment required based on creatinine. Permanent discontinuation or temporary discontinuation of study medication based on renal function for greater than 28 days should be reported to the Coordinating Center using the **Study Drug Discontinuation Form**.

Table 10.3 When to Discontinue or Adjust Study Medication Dose Based on Renal Function

Drug	eGFR 30-45 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2
Metformin	Continue with caution. Clinician to review the safety of continuing metformin based on a number of considerations (e.g. frailty, co-morbidities, risk for unexpected worsening of renal function.) Interim levels of creatinine/eGFR can be assessed more frequently than indicated at the GRADE CBL if indicated. Reduction of metformin dose can be considered based on investigator discretion.	Discontinue permanently
Sitagliptin	Reduce to 50 mg	Reduce to 25 mg

Drug	Creatinine ≥ 1.5 mg/dl in men or ≥ 1.4 mg/dl in women
Liraglutide	Use with caution. Discontinue or reduce dose with nausea or vomiting. May rechallenge when symptoms resolve.
Glimepiride	Reduce dose based on SMBG
Glargine	Reduce dose based on SMBG

10.2.2 Heart Failure

If there is clinical evidence of heart failure other than peripheral edema, specifically NYHA II (defined as: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea).

10.2.3 Excessive Weight Gain

If a ≥10% increase in weight occurs since the most recent scheduled study visit, the study staff should meet with the participant to reinforce dietary recommendations. Each episode of a 10% or greater increase in weight since the most recent scheduled study visit is considered to be an adverse event.

10.2.4 Gastrointestinal Symptoms

Gastrointestinal symptoms can occur with metformin, liraglutide, and, possibly, sitagliptin (see Sections 9.3-9.7). Data regarding gastrointestinal symptoms will be collected from all participants at quarterly visits with the **Participant Symptoms Questionnaire**. Metformin and GLP-1 analogs will be increased slowly to minimize side effects. If GI side-effects develop and are mild, the participant will be encouraged to remain on the study medication.

If GI symptoms are severe enough to interfere with adherence, specific instructions regarding adjustment or discontinuation of the medications is included in the drug-specific sections (see Sections 9.3-9.7).

10.2.5 Hypoglycemia

Severe Hypoglycemia:

- Severe hypoglycemia for the purpose of the GRADE study is defined as documented or clinically suspected hypoglycemia that requires assistance from a third party to resolve the event, needs to be treated with glucagon or intravenous glucose, results in injury to the participant or others (e.g. motor vehicle accident in which the participant was the driver), or includes loss of consciousness or seizure (major hypoglycemia). This definition requires that the participant ***needed*** assistance (for example because of confusion), not that the participant simply received assistance. Requiring assistance means that the participant would not have been able to take care of the problem him or herself because of the low blood sugar and not for some other reason. The site clinical staff must consider and make this distinction. After an occurrence of severe hypoglycemia, the second study drug may require adjustment, as described in the algorithm in each medication section (see Sections 9.3-9.7).
- If reduction of study medication is felt to be indicated by the local study staff, the participant will be instructed to decrease medications as outlined in each medication section (see Sections 9.3-9.7).
- In every case of severe hypoglycemia, the participant should be re-educated on all aspects of hypoglycemia recognition and management from the standard diabetes education materials.
- In the GRADE study, any severe hypoglycemia in a study participant will be considered to be a targeted adverse event and should be reported on the SAE Form (see Section 10.5). If more than 2 episodes of severe hypoglycemia occur in glargine or glimepiride-treated participants, despite adjustments made according to the algorithm, the clinic staff must discuss other modifications that should be considered with the Intervention Monitor.
- Participants who experience severe hypoglycemia during the study, and remain at risk for another episode, will be provided with a glucagon kit for use in an emergency. A **Glucagon Kit Request (GLUCAGON) Form** should be completed each time a glucagon kit is requested for a participant. *If a participant is no longer considered to be at risk, for example, has been taken off hypoglycemia causing medication(s), the participant does not need to be given glucagon. The assessment of risk is per the PI or clinician.*
- For participants who need to be provided with a glucagon kit, under the supervision of the PI, the GRADE staff will have the participant attend a glucagon kit training session during an interim or regularly scheduled clinic visit. It is strongly advised that the participant bring a caregiver or family member to the training as this is not a medication the participant can self-administer. The GRADE staff will provide training along with an approved GRADE participant information sheet to review the following:
    - When to use this medication
    - Contraindications
    - Storage and Use
    - How to prepare the injection
    - Side effects

10.2.5.1 Non-Severe Hypoglycemia

In the GRADE study, non-severe hypoglycemia will be defined as symptomatic or asymptomatic hypoglycemia with **documented** blood glucose <70 mg/dl, but not meeting the criteria for severe hypoglycemia. Probable symptomatic hypoglycemia (i.e. relieved by food but without confirmation with blood glucose testing) will be reported; however, symptoms consistent with

mild hypoglycemia that are not relieved by food and without documentation, should not be reported since participants may experience these symptoms with normal glucose levels.

If the GRADE study physician feels that repeated non-severe hypoglycemia is uncontrollable despite adjustments based on the protocol (see Section 9.4 and 9.7), he/she should notify the the Intervention Monitor for discussion and advice.

10.2.6 Management of Acute Metabolic Decompensation

Since the GRADE staff has assumed responsibility for glycemic management, we must also be prepared to help manage acute metabolic decompensation in collaboration with the participant's own care providers and emergency room and inpatient clinical staff, as appropriate.

The overarching goals of managing acute metabolic decompensation are:

1. To ensure participant safety and high quality care during the event;
2. To maintain protocol-driven interventions as much as possible, assuming that it is safe to do so;
3. If protocol-driven interventions are interrupted, to resume them as soon as it is safe and feasible;
4. To communicate and coordinate with non-study care providers.

10.2.6.1 Definition

Acute metabolic decompensation is defined as hyperglycemia (BG >250 mg/dL) accompanied by clinically significant symptoms (e.g., vomiting, dehydration, lethargy) and/or signs of the same on clinical examination or laboratory tests consistent with hyperosmolar hyperglycemic syndrome (HHS) or diabetic ketoacidosis (DKA). Of note, polyuria, polydipsia, and nocturia by themselves and without other clinically significant symptoms, as described above, and in the absence of HHS or DKA do not meet the study definition of acute metabolic decompensation. The use of the HbA1c to indicate metabolic outcomes that require protocol-driven interventions will in general protect participants from chronic hyperglycemia.

Acute metabolic decompensation could be due to an identifiable precipitant such as intercurrent illness, glucocorticoid treatment, or other unusual circumstance, or to stopping study medications. The cause may not be identifiable, and the metabolic decompensation may prove to be a consequence of diabetes progression and may not resolve even after precipitants have been addressed. Decompensation and any identified precipitants should be noted as outlined below.

10.2.6.2 Evaluation

Acute metabolic decompensation should be evaluated and treated immediately at an appropriate health care facility such as an emergency room. Whether the participant should be evaluated in the GRADE center or in a clinical setting, such as an emergency room, should be determined on a case-by-case basis and in consultation with the participant's usual health care provider. Acute metabolic decompensation, as defined above, is considered a targeted adverse event and, even if it does not qualify as a serious adverse event (e.g. did not require hospitalization), will be reported on the **Targeted Adverse Event and Serious Adverse Event Form**.

The participant should be evaluated to determine if an identifiable and treatable cause for glycemic deterioration is present (e.g. a urinary tract infection or other systemic infection) and whether insulin

therapy is required. The evaluation (e.g. chemistry laboratory tests, urine cultures or chest x-rays) for acute metabolic decompensation will be paid for by the participant's usual health care coverage.

All study measurements and assessments should continue to be collected according to the participant's usual GRADE schedule of study visits.

10.2.6.3 Medical management and use of insulin to treat acute metabolic decompensation

Clinical judgment by the treating clinicians will dictate what therapies, including but not limited to hydration, treatment of underlying precipitants, and insulin, should be employed. The expectation is that inpatient or emergency room providers will manage the glycemic regimen if a participant is cared for in those settings, ideally with input from GRADE PIs, if possible. Any costs associated with the clinical management of acute metabolic decompensation will be borne by the participant's usual health care coverage. After discharge, we expect that the GRADE PI and team, rather than the primary care provider, will resume management of the glycemic regimen.

Assuming that the participant has not reached the secondary or tertiary metabolic outcome that requires the initiation or intensification of insulin therapy by protocol, insulin therapy ideally should only be started if the participant meets the study definition of acute metabolic decompensation. Short-term insulin use or initiation of insulin for reasons other than the development of primary or secondary outcomes should be recorded on the **Targeted Adverse Event and Serious Adverse Event Form.** Attempts to wean insulin should be made as soon as safely possible after the participant has been appropriately treated and triggering events have been treated or have resolved. Coordinating the weaning of insulin as soon as safely possible will be facilitated through communication between the GRADE study clinicians and the medical staff treating the participant for his/her acute metabolic decompensation

10.2.6.4 Management of study medications, including metformin

Depending on the clinical circumstances, study medications may need to be stopped or adjusted for safety reasons (see Sections 9.2-9.7, 10.2-10.4 for a description of when to stop GRADE medications, including metformin and/or the assigned medicines). If metformin or the randomly assigned medications can be safely continued during the acute metabolic decompensation, and it is practical to do so, they should be continued. However, it is likely, for a variety of reasons, that the study medications may be discontinued. If study medications were stopped during an episode of acute, transient metabolic decompensation, they should be restarted as soon as safely possible (see Section 10.2.6.6 for resumption of metformin). The reinstitution of metformin and the assigned study medication should be done based on the principles in the MOP with the input from the clinician staff members. Changes in eGFR, BMI, diet, activity, and symptoms may require dose adjustment or re-titration. With short interruption of therapy, previously well tolerated study medications can be restarted at the dose taken by the participant prior to the interruption.

Communication between the GRADE clinical staff and the care providers treating the acute metabolic decompensation will be essential in determining which study treatments, including metformin and the randomly assigned therapy, should be continued and which should be held or adjusted during a period of metabolic decompensation. Careful collaboration will also help re-initiate the study medications according to protocol and the weaning and stopping of non-study insulin per the Investigator's discretion, if safe to do so, after the resolution of the metabolic decompensation.

10.2.6.5 Reporting changes in study medication during acute metabolic decompensation

Any changes in study medication(s) during an acute metabolic event should be included on the Targeted Adverse Event and Serious Adverse Event Form. If the discontinuation of metformin or randomly assigned medication is expected to be permanent or >28 days, the **Study Drug Discontinuation form** must be completed.

10.2.6.6 Resumption of metformin and/or study drug after recovery from metabolic decompensation

In the case of HHS, DKA, or metabolic decompensation with acute kidney injury, metformin should be discontinued during the episode. Metformin may be resumed after recovery from metabolic decompensation if renal function remains normal, unless there is concern that metformin-associated lactic acidosis was in whole or in part a cause or a consequence of the intercurrent metabolic state that might recur. Risk of metformin-associated lactic acidosis is thought to be exceptionally rare. Changes in eGFR, BMI, diet, activity, or symptoms may require dose adjustment or re-titration. With short interruption of therapy, previously well tolerated study medications can be restarted at the dose taken by the participant prior to the interruption.

10.2.7 Effect of Metabolic Decompensation on Study Outcomes

The occurrence of an acute metabolic decompensation episode should not take the place of or qualify as a study metabolic outcome (defined by HbA1c ≥7%). The participant's usual outcome study schedule should be continued as closely as possible after the resolution of the acute metabolic decompensation. Study metabolic outcomes will continue to be defined based on HbA1c levels, with required confirmation (see Section 8.1).

10.3 Diagnosis and Management of Lactic Acidosis

Lactic acidosis is a very rare but potentially fatal complication of metformin therapy. The recommendations for management below should be communicated to the medical team caring for the patient.

10.3.1 Description

Lactic acidosis is a rare, but serious, metabolic complication due to metformin accumulation. Based on reported experience, the incidence of metformin-associated lactic acidosis (MALA) varies from 1/25,000 to 1/150,000 patient-years with an overall rate (as assessed by the FDA) of about 1/33,000 patient-years. With increasing attention to monitoring and discontinuation of metformin when appropriate, the incidence appears to be much lower than this. Based on the incidence and guidelines for metformin use, we do not anticipate any episodes of MALA in the course of the GRADE trial. However, MALA will be treated as a potentially serious complication and will be considered and reported as a Serious Adverse Event (SAE). Lactic acidosis may also occur in association with a number of other pathophysiologic conditions including diabetes mellitus and renal insufficiency, and whenever there is significant tissue hypoperfusion and/or hypoxia.

Lactic acidosis is characterized by:

1. elevated blood lactate levels, typically >5 mmol/L (normal level is <1.5 mmol/L);
2. metabolic acidosis with decreased blood pH;
3. electrolyte abnormalities with an increased anion gap (>12, regardless of lab normal range, adjusted for albumin)

   Albumin-corrected anion gap = **Anion gap**, mEq/L + [2.5 × (4 – **albumin**, g/dL)]

The onset of lactic acidosis is often subtle with only nonspecific symptoms including malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may also be hypothermia, hypotension, and bradyarrhythmias if the acidosis is severe. The participant, his or her primary care provider, and the GRADE study clinicians must be aware of the possible significance of these symptoms; the participant will be instructed to call immediately if these symptoms occur.

10.3.2 Study Medication Adjustment in Setting of Lactic Acidosis

Lactic acidosis is a medical emergency that requires immediate treatment in a hospital setting. Study metformin should be discontinued immediately and general supportive measures should be promptly instituted.

If lactic acidosis is suspected, study metformin should be withheld until the situation is clarified. Evaluation and treatment, usually in an emergency room, should be sought immediately. Serum electrolytes, blood glucose, hepatic function (ALT, AST, alkaline phosphatase, bilirubin), and urinary ketones should be measured. If the electrolytes are normal without evidence of metabolic acidosis, study drug can be continued at the discretion of the study physician when clinically appropriate. If acidosis (serum HCO_3 <15 mEq/L and the anion gap is >15) that cannot be explained by ketones is present, lactic acidosis should be considered and further evaluation should be undertaken immediately. Blood pH and a serum lactate level should be measured. Blood should also be obtained for measurement of serum ketones (β-OH butyrate).

If lactic acidosis is confirmed, study metformin will be permanently discontinued.

10.3.3 Reporting of Lactic Acidosis

Lactic acidosis should be reported as a Serious Adverse Event (**SAE Form)** that should be promptly reported to the local IRB and the Coordinating Center. The Coordinating Center will notify the study chair, the chair of the Intervention Oversight Group (IOG), the appropriate representative at NIH, and the chairperson of the DSMB. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. The outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking at the time of the initial presentation with symptoms of lactic acidosis
7. If the event was fatal, report the presumed cause of death

The following laboratory results should be reported as available from the medical record:

1. Blood lactate levels (specify if arterial or venous)
2. Arterial blood gas (pH, pO_2, pCO_2, total CO_2, O_2 saturation)
3. Plasma glucose level
4. Serum ketones (β-OH butyrate)
5. Electrolytes (Na, Cl, K, CO_2, Ca, anion gap)
6. Renal function (serum BUN & creatinine)
7. Hepatic function (ALT/SGOT, AST/SGPT, alkaline phosphatase, bilirubin)

Copies of the medical records, hospital discharge summary and autopsy report (if the event was fatal) will be required for adjudication.

10.4 Diagnosis and Management of Pancreatitis

Pancreatitis associated with liraglutide therapy is very rare, but can be fatal. The recommendations for management below should be conveyed to the medical team caring for the patient.

10.4.1 Description of Pancreatitis

Pancreatitis is characterized by severe mid-epigastric pain radiating to the back in association with anorexia with elevations of amylase and lipase. The specific incidence with liraglutide is not known, but case reports indicate a non-statistically significant 4:1 excess of cases in liraglutide-treated participants in randomized trials.

10.4.2 Management and Study Medication Adjustment in Setting of Pancreatitis

Patients presenting with signs and symptoms of pancreatitis should be admitted to the hospital for evaluation and treatment. Evaluation should include history of other common precipitants, such as alcohol, and should rule out treatable causes of pancreatitis, such as uncontrolled diabetes with hypertriglyceridemia or gallstones. Treatment includes rehydration with IV fluids, pain control, and antibiotics and other treatments as indicated. All participants with suspected pancreatitis should have liraglutide and sitagliptin withheld along with any other potentially causative agents. Gastrointestinal and surgical specialists should be consulted as needed.

If pancreatitis is confirmed, liraglutide and sitagliptin will be permanently discontinued.

10.4.3 Reporting of Pancreatitis

Pancreatitis should be reported as a Serious Adverse Event (**SAE Form**) that should be promptly reported to the local IRB and the Coordinating Center. The Coordinating Center will notify the study chair, the chair of the Intervention Oversight Group (IOG), the appropriate representative at NIH, and the chairperson of the DSMB. The following information should be provided to the Coordinating Center as soon as feasible:

1. Summary of the illness
2. Summary of any treatment given
3. Outcome of the event
4. Summary of other associated acute medical disorders, their treatment and outcome
5. Summary of the participant's past medical history
6. Report of all concomitant medications the participant was taking and alcohol consumption at the time of the initial presentation with symptoms of pancreatitis
7. If the event was fatal, report the presumed cause of death

The following laboratory results should be reported, as available:

1. CBC with differential
2. Amylase and lipase
3. Electrolytes (Na, Cl, K, CO_2, Ca, anion gap)
4. Renal function (serum BUN & creatinine)
5. Hepatic function (ALT/SGOT, AST/SGPT, alkaline phosphatase, bilirubin)
6. Results of imaging (abdominal CT scan, right upper quadrant ultrasound, ERCP, etc.
7. Potential metabolic contributors: serum calcium and triglycerides

Copies of the medical records, hospital discharge summary and autopsy report (if the event was fatal) should be provided for review.

10.5 Serious Adverse Events (SAEs)

The safety oversight for the study will ultimately be in the hands of the DSMB. The Coordinating Center will provide the DSMB with timely reports of serious and non-serious adverse events according to treatment assignment. The Intervention Oversight Group (IOG) will examine adverse events only insofar as they affect the implementation of the protocol. Specifically, the IOG will ensure that the medication adjustments are carried out according to the protocol, especially focusing on the protocol and manual-driven adjustment of medications including when adverse events occur (see chapter 9).

10.5.1 Reporting and Documentation of Adverse Events

At each scheduled clinic visit, participants will be questioned about targeted symptoms related to study medications since the last visit using the Participant Symptoms Questionnaire.

Serious Adverse Events will be documented on the SAE Form and entered into MIDAS. Some SAEs will require additional documentation such as medical records. Study coordinators may want to have all participants sign a medical record release depending on local permissions. A template release is available on the GRADE study website.

10.5.2 Reporting of Serious Adverse Events (SAEs)

Participants should be reminded at quarterly visits to contact the clinic with any serious adverse events, including hospitalization, that may occur between quarterly visits. Study participants should contact the clinic with any Serious Adverse Event (SAE) meeting the criteria above as soon as possible after its occurrence. All SAEs should be reported by the clinical sites to the Coordinating Center as soon as possible after they occur and should also be reported to the local IRB and any other institutional monitoring committee, as per local requirements.

- SAEs must be entered into the **Targeted Adverse Event and Serious AE (SAE) Form** as soon as possible (and preferably within 24 hours of clinic notification) even if data are incomplete. The initial report that was entered should be edited and completed once all information is available.
- If there is uncertainty about whether an event represents an SAE or if a clinical site has any questions about reporting an SAE, they should contact the Coordinating Center.
- The completeness of the SAE report will be reviewed. The Regulatory and Clinical Compliance (RACC) group at the DDC will provide safety monitoring by collecting, reviewing, coding, and compiling serious adverse event data supplied by the clinical sites. The RACC will communicate with the clinical site to ensure complete, appropriate reporting (see Section 10.6.2 below).

10.5.3 Documentation of SAEs

Complete the **Targeted Adverse Event and Serious AE (SAE) Form** to capture any event of a serious nature and enter the MIDAS data entry system. If a participant calls the clinic to report an SAE, complete the **SAE Form** as soon as possible, preferably on the same day.

- The SAE report should be dated according to when the participant notified the clinic that the SAE has occurred (which should be identical to the date that the SAE Form is completed). The

report from the participant may have been by phone or at an interim or scheduled visit. The date will always be the same as or after the date the SAE occurred.

- An SAE report is necessary for any hospitalization of 24 hours or more (admitted to hospital, excluding "23-hour" and overnight observation admissions). In the case of hospitalization, the SAE pertaining to the hospitalization generally begins with the date of admission and ends with the date of discharge, regardless of whether the event actually resolved prior to that time, i.e. the SAE dates must reflect the dates of the hospitalization. Significant changes (i.e., changes in classification term, addition of a resolution date, or change in relationship to the intervention, e.g. from "probable" to "definite") require a new SAE Form. SAE Forms should be entered into the MIDAS data entry system as soon as possible (preferably within 24 hours of notification) even if the data are incomplete. Follow-up information should be entered later when additional information is available.
- Hospital discharge summaries and face sheets should be obtained for each hospitalization. If the discharge summary does not sufficiently describe the AE or hospital events, the entire chart should be requested. Clinics should refer to the discharge summary for verification of the adverse event as reported by the participant and update the SAE Form.

Even if the entire SAE report cannot be completed, the SAE Form must be filled out as completely as possible and entered into MIDAS within 24 hours of the clinic being notified of the SAE. If any data are missing at the time that the form is initially completed, or if any additional information becomes available, the initial form and MIDAS should be updated to reflect these changes.

The date of onset of an SAE is the date that the condition causing the event to be considered serious began. For hospitalizations, in general, this would be the date that the person was admitted to the hospital. There are some instances where an event might be considered serious prior to admission to the hospital.

The SAE would be considered resolved when the event is no longer considered to be "serious". In the case of hospitalization, although an individual's condition may not be considered life-threatening, the fact that he/she still requires hospitalization makes the event serious. Thus, the SAE would not be considered resolved until the date that the participant is discharged from the hospital.

10.5.4 Documentation of SAEs after Last Study Visit

Participants who are still taking the study medication at the time of the last study visit (LSV) must be instructed to call the study if they have any serious adverse events within 14 days after stopping the study medication. This instruction should be documented in the study progress notes at the last study visit.

For any participant who discontinues the study intervention prior to the end of study, SAEs will be collected for the entire duration of follow-up even if the participant is no longer continuing assigned medication(s) or has reached study outcomes.

Any SAE that is continuing and unresolved at the time of the last study visit (unresolved SAEs refers to those SAEs in which information required on the SAE form is missing) and continues after the protocol-specified 14 day follow-up period, should be followed until study end and noted as ongoing. Resolution of an SAE refers to obtaining all necessary information pertaining to the SAE so that the diagnosis is complete; therefore an SAE may be "continuing" and still be resolved for study purposes with no

requirement for obtaining additional information.

10.6 Study Group Monitoring of Adverse Events and Reporting of SAEs

All SAEs will be reported to the Coordinating Center as noted above. The Coordinating Center will forward all SAE reports to the DSMB as stated in their charter, with a copy sent to the Study Chair and NIDDK. The aggregate SAEs and targeted AEs will be reviewed periodically (at regularly scheduled meetings and potentially at other times as circumstances dictate) by the DSMB for patient safety. The entire DSMB will periodically review all SAEs and targeted AEs at its regularly scheduled meetings for patient safety. The DSMB function and review procedures are described in a separate document.

The Intervention Oversight Group (IOG) is a part of the Protocol Oversight Subcommittee. IOG members (Intervention Monitors) will review SAEs and targeted AEs on a rotating basis prior to each Protocol Oversight Subcommittee call and study group meeting in order to ensure that the protocol and MOP are being followed. SAEs and targeted AEs are also reviewed by the full Protocol Oversight Subcommittee and discussed as needed during calls and meetings. Specifically, the Intervention Monitors will be responsible for supervising the implementation of the interventions and, in particular, the appropriate dose adjustment instructions in response to AEs and SAEs as delineated in Chapter 9. The clinics will be encouraged to check with the Intervention Monitors when study drugs are being adjusted in response to AEs or SAEs.

10.6.1 Meetings of the Protocol Oversight Subcommittee (POS) and Intervention Oversight Group (IOG)

The Protocol Oversight Subcommittee meets in person at the time of each study group meeting, and by conference calls monthly or as often as necessary to review AEs and SAEs during the treatment phase of the study (see Chapter 11 for additional information about the role of the Protocol Oversight Subcommittee). The POS considers whether changes in the protocol or Manual of Procedures (monitoring, consent process, etc.) are indicated based on the occurrence, frequency, or severity of AEs and SAEs. Thresholds for considering further review or action are as indicated. The subcommittee also evaluates whether there is any clustering of AEs by clinical site, or whether the frequency has crossed the designated threshold at any clinical site(s). As deemed necessary, a member of the Intervention Oversight Group (IOG) will communicate with the local site PI to obtain additional information about SAEs and observed local trends in reporting of targeted non-serious AEs.

The IOG chair reports its deliberations at the regularly scheduled POS calls, at regularly scheduled study group meetings, or at any time that he/she considers it necessary based on safety concerns. Neither the Outcomes Subcommittee, POS, nor the Steering Committee have access to information about AEs or SAEs by study group assignment. If unmasking of group assignment is deemed necessary or appropriate, the study chair may ask NIDDK to refer the issue to the DSMB.

10.6.2 Regulatory and Clinical Compliance Group

A Regulatory and Clinical Compliance (RACC) group will work out of the DDC. This group will review SAEs in a timely fashion, determine if they qualify as SAEs, and request documentation for eventual adjudication. The RACC group will review all reported SAEs to determine the completeness and accuracy of the reporting and will communicate with the clinical sites for clarification and to encourage follow-up and completion of documentation. The goal of the RACC group is to ensure that SAEs are reported as thoroughly and accurately as possible.

10.6.3 Protocol Deviations

All trials experience departures or deviations from established study procedures. Non-adherence to study procedures is known by several terms—departure, deviation, or violation of procedures. The terms seem to indicate a continuum from least to most severe, but in fact, there is no standard definition or distinction among them in the trial lexicon. Non-adherence is rarely undertaken with deliberate mischief or malice, and most commonly occurs inadvertently or under the best intentions as members of the study group do their best to adhere to the principles of the study while operating within a very complex patient care environment. Also, sometimes study procedures are not clear or do not cover every possible scenario, so there is room for interpretation. Non-adherence is considered most serious when it relates to safety and confidentiality of study participants, the rights of study participants, or the integrity and quality of any aspect of the study.

A **major protocol deviation** is defined as any action taken that directly affects the safety of the individual or potentially affects the outcome of the study. Protocol deviations include: enrollment of ineligible participants, medication errors, or other deviations related to the protocol. Sites should report such events to their local IRB per institutional guidelines.

Operational deviations are deviations from study procedures detailed in the Manual of Operations (MOP/MAP) that may affect the validity or interpretation of the study data. Examples include: study assessment or sample collection missed due to staff error, staff performing assessments who are not certified, etc. Sites should report such events to their local IRB per institutional guidelines.

The range of impact or response depends on the nature of the non-adherence and may involve:

- Creating a new procedure or clarifying an existing procedure
- Amending or modifying the protocol
- Re-consenting study participants
- Reporting to the DSMB and/or IRB

To avoid and prevent procedures non-adherence, the study group takes the following actions:

- Ensure familiarity with and knowledge of study procedures through ongoing training and regular communications throughout the study group by e-mails, calls, meetings, and posted journals of deliberations and decisions.
- Establish a process for submitting queries about procedures and receiving clarification or specification. This is accomplished through the Protocol Oversight Subcommittee (POS).

Manual of Procedures

Chapter 11

TABLE OF CONTENTS

11. CHAPTER 11: STUDY OVERSIGHT - PROTOCOL OVERSIGHT SUBCOMMITTEE (POS)

Most trials conducted by a collaborative group form a procedures oversight committee—also known as a Protocol Oversight Subcommittee, which leads to the acronym POS. In GRADE, the POS is a sub-committee of the Steering Committee.

The POS is charged with:

- monitoring study progress and status, including
    - data collection and clarification
    - intervention administration and delivery
- addressing performance issues
- reviewing and modifying or clarifying existing procedures
- developing new procedures and guidelines
- monitoring adherence to procedures and reviewing, evaluating, and responding to non-adherence.

The roles of the other sub-committees, including Recruitment and Retention, Study Coordinators, Outcomes, Ancillary Studies and Substudies, and Publications and Presentations are described separately.

11.1 Operations

POS membership is broadly representative of the study group, including principal investigators, study coordinators, staff from the Coordinating Center, and other staff with a thorough understanding of the various study procedures. During the course of the study, the POS holds regularly scheduled conference calls and convenes at study group meetings to review reports and conduct business. The POS may investigate and propose resolution of any problems with study conduct and procedures.

The main routes by which issues in need of attention are brought to the POS are:

1. The POS may itself detect or identify an issue based on review of the study status and tracking reports supplied by the Coordinating Center.
2. A member of the POS may bring an issue that has been raised in a committee or at a site represented by that member.
3. Clinical Site staff may raise issues that require attention.
4. The Coordinating Center may bring issues of concern to the POS.
5. The Executive Committee may ask the POS to address specific issues.

The POS then deliberates, engages in additional information gathering as needed, and works closely with relevant study group members, teams, and sub-committees or the Steering Committee to first develop an action plan in response and then to track implementation and progress to resolution. The action plan may include contact via conference call or site visit.

11.2 Protocol Deviation Alert

We anticipate that site personnel will encounter problems implementing study procedures as presented in the protocol, manuals of procedures, forms instructions, training materials, and any other official study documents. Deviations or departures from established procedures will occur. We need to pay

attention to these incidents throughout the course of the study in order to completely understand the implementation and conduct of the study, and to take corrective action or response as needed, including modification of procedures.

The **Protocol and Operational Deviation (PROTDEV) Form** is used by sites to report the occurrence of procedure deviations or departures, including the most serious protocol violations. The form is completed by the principal investigator and/or study coordinator with the involvement of other site staff members as relevant. Guidance will be provided throughout the study about situations requiring a PROTDEV form. The form should be downloaded from the GRADE study website and the Coordinating Center should be contacted for guidance. Contact the Coordinating Center for questions about when to complete this form, but in general "if in doubt, fill it out."

The POS reviews all deviations that are reported, may request additional information from the site, and provides or confirms a resolution. As appropriate, resolution may involve additional study group deliberation and/or modifications or clarifications.

Manual of Procedures

Chapter 12

TABLE OF CONTENTS

12. CHAPTER 12: STUDY SUPPLY PROCEDURES

12.1 Mailing Medications to Participants

Participants should generally obtain their medications when they are at the study site for study visits. This ensures that participants receive the proper medication in a timely fashion and that the quality of the medications can be assured. GRADE does not routinely mail medications to participants. However, there are some circumstances in which mailing medications to participants may be necessary. We recognize that because participants are receiving their medications from us, they can't go to the local pharmacy for refills and that the study must be able to provide some service to the participant to make up for this restriction.

The amount shipped should be no more than the amount needed to last until the next regularly scheduled visit within the visit window to ensure safety and adherence. **If the participant has not been seen in more than 1 year, sites are not permitted to dispense and/or ship medications**. Additionally, telephone contact alone for >1 year is **not** sufficient to dispense and/or ship medications. Exceptions to this policy may be made for participants who have relocated away from the study site and are maintaining a relationship with the study remotely (see Sections 4.4.3-4.4.4). Sites must record a safe and reliable mailing address. This should be an address where medications will not be at risk for loss, diversion, or deterioration. Inability to identify a safe mailing address should lead sites to refuse to mail medications. Sites must follow any local institutional polices that apply regarding mailing of medications.

Manual of Procedures

Chapter 13

TABLE OF CONTENTS

13. CHAPTER 13: VISIT SCHEDULES AND PROCEDURES

As stated previously (Section 4.3 and 9.2.4), the goal is for every surviving patient to complete the full schedule of visits regardless of their ability to continue to follow the initially randomized therapeutic regimen or other outcomes that have been observed. Participants who become inactive may resume the schedule of visits at any time. It is especially important that every attempt be made for all surviving participants to complete the final closeout visit.

13.1 Overview

Study clinic visits after Baseline are characterized as Quarterly, Semi-annual, Annual (which are all fasting), or Interim. Each type of visit is described in detail below. Each site is given flexibility in the order in which the visit components are completed to accommodate local clinical site scheduling needs and participant preference. However, it is recommended that sites aim to complete all tests on the same day if possible. See the MAP for detailed instructions on procedures.

13.2 Visit Schedule

Regularly scheduled visits are as follows:

Quarterly

Year 1 - Months 3, 6, 9
Year 2 - Months 15, 18, 21
Year 3 - Months 27, 30, 33
Year 4 - Months 39, 42, 45
Year 5 - Months 51, 54, 57
Year 6 - Months 63, 66, 69
Year 7 - Months 75, 78, 81
Year 8 - Month 87

Annual (Fasting)

Year 1 - Month 12
Year 2 - Month 24
Year 3 - Month 36
Year 4 - Month 48
Year 5 - Month 60
Year 6 - Month 72
Year 7 - Month 84

Refer to Section 15.1 for a summary of GRADE assessments by scheduled visit.

Additional visits are scheduled as follows:

Interim

Interim visits are defined as extra (other than quarterly, annual and confirmation) visits that may be conducted to address safety issues, drug titration for tolerability, medication initiation or adjustment for the sequential treatment group, or for other unexpected events (e.g. need to replace drug supply or other supplies before next scheduled visit). Although some of these tasks could be carried out by phone and not require a clinic visit, others will require an in-person visit.

When participants add glargine insulin therapy or have their regimen intensified with short-acting insulin, they will be seen for an interim visit for teaching.

Interim visits are also scheduled for confirmation of HbA1c values. Visits are performed at the next quarterly visit if HbA1c is ≥7% and ≤9%, i.e. no extra confirmation visit is required. However, if A1c is >9%, an extra confirmation visit should be scheduled within 3 to 6 weeks of the date of the original test.

The **Interim Visit Form** should be completed for each in-person interim visit occurring after randomization to document drug titration, treatment intensification, safety issues discussion, etc. The Interim Visit Form is not needed for interim outcome confirmation visits, interim repeat laboratory visits (e.g. creatinine), visits held in response to adverse events or protocol deviations, or if the participant just stops in to pick up medications or supplies.

Last Study Visit

Participants will have one designated "Last Study Visit" based on their date of randomization. A routine study visit and regular data collection will be completed at this visit, and it will be the last visit at which regular data collection occurs. After the Last Study Visit, no further data will be collected, aside from collection of medical records from SAEs that have already been reported. (See section 10.5.4. for documentation of SAEs after the Last Study Visit). Participants will be provided with a final, 30-day allocation of study medications at the last study visit. The supply may be slightly more depending on the medication (bottles will not be divided). The limitation comes from the availability of the study drug supply. The participant will also be instructed to see their PCP for transfer of care and new prescriptions if they have not already done so. See Section 13.7 for additional information about study closeout.

Table 13.1: Schedule of Measurements and Assessments (Table 2 from GRADE Protocol)

Measurements and Assessments	Screen	Final run-in	Base-line	1 Y	2 Y	3 Y	4 Y	5 Y	6 Y	7 Y
HbA1c¶	L	C		Q/C	Q/C	Q/C	Q/C	Q/C	Q/C	Q/C
Oral Glucose Tolerance Test (OGTT)±			C	C		C		C		
DNA			C							
Fasting lipids			C	C	C	C	C	C	C	C
Liver function tests (ALT)	L									
Serum creatinine/eGFR (safety labs)	L	C		C	C	C	C	C	C	C
Albumin:creatinine (urine)			C	C/S	C/S	C/S	C/S	C/S	C/S	C/S
Blood and urine samples for storage#			C	C	C	C	C	C	C	C
Stool samples for storage# & dietary questionnaires in subset of participants			C/S§							
Urine pregnancy@	L		L							
Hematocrit	L									
Vitamin B12				C¥			C			
History (events-medications)	L		L	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q
Physical Assessment (BP, Weight)	L		L*	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q
Height			L*				L			
Waist and hip circumference			L*		L		L		L	
Peripheral neuropathy			L*	L	L	L	L	L	L	L
ECG (read centrally)			L*		L		L		L	
Study drug adherence		L	L	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q	L/Q
Cognitive Battery			L*				L		L	
QOL-SF-36, QWB, Treatment Satisfaction+			L*	L	L	L	L	L	L	L

C=Performed centrally, L=Performed locally, Q=quarterly, S= semi-annually

¶Quarterly. Needs confirmation at next (3 month) visit if ≥7% (in 3-6 weeks if >9%)

#Biological samples saved as aliquots for substudies/ancillary studies.

§Stool samples and microbiome related data will be collected on a subset of participants at baseline and 6 months, with additional samples funding permitting.

±OGTT will include insulin, C-peptide and glucose measures at fasting, 2 hours and other selected times; however insulin is not measured in insulin-treated subjects.

@As indicated

+DTSQ performed at baseline, 6 months and 1 year.

*May be completed at the Final Run-in visit

¥Will be tested at intervals during the study depending on the participant's randomization date.

Visit Schedule Windows

The quarterly and annual visit windows are as follows:

Quarterly - visits can occur as early as 6 weeks before or as late as 6 weeks after the target date. Quarterly visit target dates are based on the date of randomization and occur every 3 months (beginning with 3 months after the baseline randomization visit) for the duration of study follow-up. If the visit doesn't occur within 6 weeks after the target date, the visit will be considered "missed" and the next visit will be considered to be the next scheduled quarterly (or annual) visit.

Annual - visits should preferably occur within 6 weeks of the target date. Annual visit target dates are based on the date of randomization and occur on a yearly basis (beginning with 1 year after the baseline randomization visit) for the duration of study follow-up. However, since data collected at the annual visit are critical to obtain, the allowable window for an annual visit will be +/- 6 months. Under unusual circumstances, for example when in the clinic staff's opinion the participant cannot reliably be expected to return for the next annual visit, the data collection for an annual visit may occur at any time.

13.3 Quarterly Visits

The Quarterly visit is primarily a visit for diabetes management, HbA1c monitoring, and selected data collection. Quarterly visits may be scheduled in the morning or afternoon. This section also includes semi-annual visits which are similar to quarterly visits with additional assessments and sample collection per the Schedule of Measurements and Assessments (see Table 13.1).

13.3.1 Quarterly Visit Procedures and Forms

At this visit, information is obtained regarding glycemic control, intercurrent events, changes in other medications, potential adverse events associated with the study medications, blood pressure and weight measurement, along with laboratory measures to monitor glycemic control. For a detailed description of each procedure, see the MAP. For a detailed description of sample collection, see the CBL Biospecimen Collection and Processing manual.

- For participants who have consented to the optional audio recordings, obtain oral consent and begin recording at the start of quarterly visit activities
- Interim history included on **Quarterly Visit Form**
    - Intercurrent events
    - Diabetes management update
    - Non-study medication update
- Study medication review
    - Adherence
    - Dose review
- Physical assessment
    - Blood pressure
    - Weight
- Laboratory tests
    - Non-fasting blood sample for HbA1c (sent to CBL)
    - Urine sample for microalbumin: creatinine (done only at 6 monthly intervals)

  - Urine pregnancy test (Locally; Annual visit only, or as indicated)
- Meter download, calibration, and battery check as needed
- Forms
  - **Quarterly Visit Form**
  - **Quarterly & Semi-Annual Specimen Transmittal Form**
  - **Concomitant Medications Form**
  - **Microbiome Collection Sample Transmittal Form** (only to be given at the 3 month Quarterly Visit to participants who completed the baseline stool collection and questionnaires)
  - **Microbiome 6-Month Collection Form** (to be completed over the phone prior to the 6-month stool collection for participants who completed the baseline stool collection and questionnaires)
  - **Audio Recording Tracking Form** (only for participants who consent to have their visits recorded)
  - **Non-Initiation of Insulin Quarterly Follow-Up Form for Participants Meeting HbA1c Metabolic Outcomes (Secondary and Tertiary)** (complete at every visit after a Non-Initiation of Insulin Form for Participants Meeting HbA1c Metabolic Outcomes (NONINIT) has been completed and the participant has not yet started glargine or Novolog)
- Questionnaires
  - **Participant Symptoms Questionnaire**
  - **Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)** (at 6 month Semi-annual Visit)
  - **Microbiome Collection Dietary Screener Questionnaire** (only to be given at the 3 month Quarterly Visit to participants who completed the baseline stool collection and questionnaires)
  - **Microbiome Collection Dietary Behavior Questionnaire** (only to be given at the 3 month Quarterly Visit to participants who completed the baseline stool collection and questionnaires)
- Supplies and updates
  - Quarterly specimen collection kit (CBL) (or Semi-Annual specimen collection kit for semi-annual visits)
  - Stool collection kit (to be given only to eligible participants at the 3 month Quarterly Visit)
  - Distribute medication
  - Appointment and reminders for next visit
  - Review contact information, emergency phone numbers and addresses
  - Meter supplies if applicable
  - Reimbursement for travel

13.3.2 Suggested Quarterly Visit Flow

There is no mandated approach to completing quarterly visits. The following represents an approach to this visit that uses time efficiently and may serve as a template for planning visits.

1. Collect meter and returned medication
2. Start meter download
3. Perform history and physical measurements, complete **Quarterly Visit Form**

4. Review medication adherence
5. Collect required lab samples
   - HbA1c
   - Pregnancy test for females if indicated
   - Urine for albumin: creatinine at 6 month interval
   - B12 sample if needed B12 (twice during study follow-up: at the next semi-annual or annual visit after this testing is implemented, and at the Year 4 Annual visit. Note: Participants whose first B12 test is at the Year 4 Annual Visit will only have one regularly scheduled B12 test.)
6. Confirm contact information
7. Provide participant with:
   - Supplies
   - Next appointment and reminders about bringing meter, study medications, and all other medications to next visit

See Section 15.9 for a flowchart of quarterly visit procedures.

13.3.3 6-month Microbiome Collection

For participants enrolled in the optional Microbiome Collections, a second stool sample will be collected along with the associated dietary questionnaires around the 6-month time point. Reference the Microbiome Manual (Section 3.3) for more information on the activities to be performed starting at the 3-month Quarterly Visit.

13.4 Annual Visits

The Annual visit consists of all those procedures and exams associated with the quarterly visit plus: (1) a blood draw for serum creatinine/eGFR annually; (2) a fasting blood draw to measure lipids, glucose, and insulin levels; (3) Oral Glucose Tolerance Test (if scheduled); (4) urine sample to assess microalbuminuria; (5) blood and urine samples for storage; (6) peripheral neuropathy; (7) neurocognitive assessment at years 4 and 6; (8) ECG at years 2, 4, and 6; (9) height at year 4; (10) waist and hip circumference at years 2, 4, and 6;(9) selected questionnaires; and (10) an update of standard diabetes education. All annual visits are fasting visits. Visit windows are described above (Section 13.2).

13.4.1 Tests and Procedures

The following tests and procedures must be accomplished during each **Annual** visit, unless noted otherwise, **in addition to the quarterly visit tests and procedures** (see 13.3.1). For a description of each procedure, see the MAP. For a detailed description of sample collection, see the CBL Biospecimen Collection and Processing manual.

- For participants who have consented to the optional audio recordings, obtain oral consent and begin recording at the start of annual visit activities
- Quarterly visit tasks plus
- *Laboratory samples*
  - HbA1c
  - Urine for albumin: creatinine

  - Fasting lipids
  - Serum creatinine/eGFR
  - Vitamin B12 (twice during study follow-up: at the next semi-annual or annual visit after this testing is implemented, and at the Year 4 Annual visit. Note: Participants whose first B12 test is at the Year 4 Annual Visit will only have one regularly scheduled B12 test.)
  - Insulin and glucose
  - Urine and blood for storage
- Physician contact (For the purposes of clinical coverage, an MD or MD-equivalent (e.g. NP, PA) needs to see the participants once per year)
- Oral glucose tolerance test (if scheduled—see MAP for detailed instructions)
- Waist and hip measurements (Years 2, 4, and 6 only)
- Height measurement (Year 4 only)
- Peripheral neuropathy assessment (MNSI)
- Neurocognitive assessment (Years 4 and 6 only)
- ECG assessment (Years 2, 4, and 6 only)
- Forms
  - **Annual Visit Form**
  - **Annual Specimen Transmittal Form: Refrigerated and Frozen Samples**
  - **Audio Recording Tracking Form** (only for participants who consent to have their visits recorded)
  - **Direct Nonmedical Costs Evaluation Form** (at the annual visit after implementation only)
- Questionnaires
  - **The SF-36 Health Survey**
  - **Quality of Well Being Self- Administered Questionnaire (QWB-SA)/**
  - **EQ-5D-5L and Visual Analolg Scale Questionnaire** (at the annual visit after implementation only)
  - **Both DTSQs and DTSQc** (Year 1 Annual visit only) in that order
- Supplies for processing and shipping:
  - Annual specimen collection kit (from CBL)
  - Refer to the CBL manual for details on processing and shipping specimens
- Provide standard diabetes education update

13.4.2 Suggested Annual Visit Schedule and Flow

Completion of annual visit testing (see Section 13.4.1) should ideally be accomplished in a single day. However, scheduling of testing may be customized to meet the needs of GRADE staff and participant preference with the overarching goal to complete all testing.

It is important to note that reliable interpretation of the fasting lab samples requires that adequate fasting (a minimum of 8 hours) be ensured prior to initiation of the test. Careful instructions and confirmation of the required fast are critical. If the participant is taking insulin, the last (usual) dose of insulin should be given the night before (8 hours prior to) the fasting tests or OGTT. If insulin is usually administered in the morning, it should be withheld until the fasting tests and OGTT (if scheduled) have been completed. Diabetes medications should be held until the fasting tests or OGTT have been completed; other medications the participant is taking can be taken as usual. Participants are permitted to drink water before and during the OGTT as desired for their comfort.

In general, participants will need to arrive at the site before 9 AM to perform the fasting tests and begin the OGTT before 10:30 AM. If the OGTT is performed after 10:30 AM due to unforeseen circumstances such as difficulty with IV insertion or parking issues, the site will be required to notify their protocol liaison and complete a procedural deviation (noting the reason for the deviation). If the participant is unable to schedule the OGTT for a 10:30 AM start time at the visit, the OGTT should be rescheduled. Special circumstances, such as alternate shift work may warrant a late start as long as it is consistent at each of the participant's OGTT visits. In cases where travel requirements prohibit this scheduling, participants may need to stay close by the clinical site overnight. Either CRCs or local hotels may be used in these unusual circumstances, keeping cost considerations in mind. Staff should make an appointment reminder call and confirm eligibility for OGTT, if applicable, before the visit. Refer to the MAP for detailed eligibility and instructions on performing the OGTT.

1. Withhold morning diabetes medication.
2. Collect urine pregnancy sample as indicated for women of childbearing potential. Review sexual activity, birth control, and menstrual history.
3. Collect medical history and obtain weight, and anthropometrics.
4. Begin meter download as applicable.
5. Review medication adherence.
6. Draw fasting blood work between 6:00 and 10:30 AM.
7. Collect urine sample for measurement of microalbumin. Preferably, this sample should be collected prior to administering the glucose drink (if participant is scheduled for an OGTT); however, non-fasting samples are acceptable.
8. Offer a meal to participant and provide if desired following completion of fasting tests or OGTT.
9. After the 30 minute sample has been collected (if applicable), administer questionnaires and education.
10. If the neurocognitive assessment is performed at the Annual Visit (Years 4 and 6), administer it after the OGTT has been completed (if applicable). A snack or meal may be offered to the participant prior to administration of the neurocognitive assessment.
11. Complete the **Annual Visit Form**.
12. Update contact information.
13. Provide participant with supplies.
14. Provide participant with next appointment and reminders about bringing log, meter, study medications, and all other medications to the next visit.

See Section 15.10 for a flowchart of annual visit procedures.

13.5 Interim Confirmation Visit

HbA1c outcome triggers are usually confirmed at the next quarterly visit, unless the trigger HbA1c result is >9%, in which case an interim visit is scheduled for 3 to 6 weeks after the triggering HbA1c result. At this interim confirmation visit, HbA1c is tested and evaluated for confirmation of the outcome.

13.5.1 Preparation for and Scheduling of Confirmation Visit

Timeliness is of the essence and it is recommended that the clinic staff contact the participant as soon as they receive notification from the central lab of the HbA1c value. The following steps should be followed:

- Contact participant (usually by phone)
- Discuss the reason for call: HbA1c >9%

- Discuss adherence to medications and encourage full adherence to assigned medications and lifestyle changes
- Schedule interim visit if medication titration requires an interim visit
- Schedule confirmation visit for 3-6 weeks from time of original HbA1c test (window 3-6 weeks)

13.5.2 Confirmation Visit Tasks

The interim confirmation visit is a non-fasting visit during which HbA1c is obtained for confirmation of primary, secondary, or tertiary metabolic outcomes.

13.6 Remote Contact Log

The Study Remote Contact Log (CONTACT) is used to document communications with randomized participants between regularly scheduled visits. Voice or video calls, electronic communications (e.g., e-mails, text messages, or portal messages), or mail communications with GRADE participants for diabetes management, counseling, or education may require substantial amounts of health care provider time and could generate substantial hidden costs. The frequency and duration of these remote communications may differ across the four GRADE treatment groups. To collect information on these types of communications, the Contact Log will be completed study-wide once per year, beginning in 2017.

13.6.1 Implementation

The Contact Log will be completed once per study year. All GRADE sites will complete the Contact Log during the same designated time period (+/- 2 weeks of a target week). The GRADE Coordinating Center will inform all sites of the target week for data collection each year. All GRADE staff members who have remote contact with randomized GRADE participants for diabetes management, counseling, or education each will complete the log individually. **All GRADE staff members within one clinical site must complete their individual logs during the same calendar week.** All voice or video calls, mail, or electronic communications related to the following topics should be documented using the log:

- Diet and physical activity
- Study medication adherence
- Study medication titration
- Review of glucose logs or laboratory results
- Adverse events

Note that remote communications for visit reminders, visit scheduling, remote study visits, etc. will NOT be captured on the log.

13.7 Study Closeout and End of Study Data Collection

Follow-up visits for all GRADE participants will conclude in the closeout phase. The study closeout plans for GRADE take into account our obligation to care for our participants and ensure a lapse-free transition of diabetes management back to their own healthcare providers, as well as the need to report the study results uniformly, accurately, and in a timely fashion to our participants and the scientific community. The coordination of these two major goals will be key to the successful closeout of GRADE.

Specifically, GRADE clinical sites will meet closeout objectives with the following activities:

1) Provide each participant with a report of their individual lab data and medication history at their final GRADE visit, as well as a short summary explaining any clinically relevant results;
2) Assist in the transition of a participant's diabetes management provided through the study to care from their own health care providers;
3) Complete data clean-up and SAE reporting as quickly as possible after final study visits to ensure timely data analysis;
4) After completion of analyses, inform participants of the overall study results and distribute recommendations to participant providers.

For visit prioritization during Closeout, the most important visits are the Last Study Visit and the Final Annual Visit:

The Last Study Visit: The designated visit wherein a participant is officially closed-out of the study. These "Last Study Visits" take place at regularly scheduled visits (quarterly, annual, or semi-annual) during the study closeout phase. The specific "closing out" activities expected at the Last Study Visit can be found in the Transition of Care Acknowledgment Checklist. Refer to Table 13.1 for other documents used during the closeout period. (Note that Last Study Visits may occur earlier if required by participant circumstances. This should be discussed with the GRADE Coordinating Center.)

The Final Annual Visit: The participant's annual visit that falls during the last year of the study.

More specifically, of all the final year visit activities, sites should focus on:

- The Final Annual Visit and its assessments (regardless of whether this is designated to fall as the "Last Study Visit" or not)
- Ensuring the participant is successfully closed-out of the study—most importantly, that they understand GRADE will no longer be providing their care and that they will need to work with an outside PCP for diabetes management

13.7.1 Closeout Phase Visit Procedures

Activities to prepare the participant for the culmination of GRADE and facilitate their transition of care will take place at the final visit and in the 3 visits leading up to it. Clinic staff should refer to the comprehensive listing of closeout activities and schedule for implementation below. The **Closeout Activities Tracker for One Participant** provides a checklist of these items at the participant level.

The PI does not need to be present for every participant's Last Study Visit; however, they should plan to speak with each participant to review their progress in GRADE and during at least one of the last few visits. The site should design a transition plan for each participant, which the PI can address in person, and can be reinforced by other study team members at any final visits the PI cannot attend.

- Ongoing activities
    - Distribute **Closeout "Heads-Up" Letter to Participant** (in-person or by mail) and review any concerns with participant
    - Update **GRADE Resource Packets** with local information; review with participant as needed
    - Refer to **Coordinator Talking Points** for guidance on answering participant questions

    - Discuss participant's PCP status (ensure PCP identified)
- 6-9 months before Last Study Visit
    - Encourage participant to schedule PCP appointment within 30 days after their Last Study Visit
    - Work with participant to identify any treatment goals (**Transition Readiness Worksheet**)
    - Give **GRADE Resource Packet** to participant (mail for phone visits/missed visits)
- 3 months before Last Study Visit
    - **During Visit**
        - Revisit **Transition Readiness Worksheet** and **GRADE Resource Packet** as needed
        - Confirm that participant has made PCP appointment—record date if known
    - **After Visit**
        - Send **PCP Heads-Up letter** (upload in EMR, mail, or fax)
        - Prepare **PCP Transition Letter** (update template with participant information and clinical summary/any salient clinical concerns)
        - If PCP appointment will occur before the Last Study Visit, send **PCP Transition Letter** and **Individualized Participant History Report** to PCP
        - Print and prepare **Certificate of Participation**

Table 13.2: Documents used in Closeout Period*

Name	Type	Data entered into MIDAS?
Transition of Care Acknowledgement Checklist	Checklist	No
Closeout Visit Activities Checklist for One Participant	Checklist	No
"Heads-Up" Letter to Participant	Letter	No
GRADE Resource Packet	Participant Handout	No
Coordinator Talking Points	Coordinator Reference	No
End-of-Study Transition Readiness Worksheet	Worksheet	No
PCP "Heads-Up" Letter	Letter	No
PCP Transition Letter	Letter	No
Individualized Participant History Report	Report	No
End of Study Worksheet	Worksheet	No
End of Study (EOS) Form	Form	**Yes**
Certificate of Participation	Participant Handout	No

*Materials are available on the GRADE study website

13.7.2 Scheduling the Final Annual Visit and Last Study Visit

During the final year of visit activities, sites should prioritize the Last Study Visit and Final Annual Visit when scheduling decisions must be made and it is not possible to conduct all of a participant's study visits in person or remotely during the final year.

Participants will have one designated "Last Study Visit" based on their date of randomization. A routine study visit and regular data collection will be completed at this visit, and it will be the last visit at which regular data collection occurs. There will be no additional assessments conducted as part of the Last Study Visit. If a participant's Last Study Visit falls on their Year 1, 3, or 5 annual visit, then the OGTT should be conducted as expected.

An in-person visit is always preferred to a phone visit. If the Final Annual Visit and/or the Last Study Visit must be conducted remotely, sites are instructed to follow existing guidance on collection of missed assessments. However, missed assessments should not be collected after the conclusion of study data collection. A Protocol and Operational Deviation (PROTDEV) Form should be completed if any assessments are completed after the last date of study data collection. Sites are encouraged to conduct visit components that can be completed remotely as close to the date that the main visit form was completed as possible. All activities associated with closing a participant out can be completed remotely. As such, conducting the Final Annual Visit and its assessments in person should be prioritized over conducting the Last Study Visit in person.

13.7.3 Last Study Visit Procedures

The following tasks should be carried out at the Last Study Visit:

- **During Visit**
  - Complete the **End of Study (EOS) Form** to document the date of Last Study Visit
  - Finalize PCP Transition Letter; fill-in **Individualized Participant History Report** with current medications
  - Give participant copies of **PCP Transition Letter** and **Individualized Participant History Report** – instruct participant to bring these to their PCP visit
  - Give participant final allocation (30 days) of study medications and supplies; review medication expiration dates with participant
  - Give participant **Certificate of Participation** (ensure it is signed by coordinator and PI) and GRADE blanket (end of study gift)
  - Instruct participant to contact site with changes in address or contact information—let participant know how to reach the site with any contact information changes
  - Inform participant of plans to share overall study results
  - Review **Transition of Care Acknowledgement Checklist** with participant and sign
- **After Visit**
  - Mail **PCP Transition Letter** and **Individualized Participant History Report** to PCP
    - Upload materials as a note in the EMR, if possible
    - Fax materials to PCP day before participant's scheduled appointment date, if known

13.7.4 HbA1c Outcomes and Safety Concerns at the Last Study Visit

If an HbA1c Outcome is triggered at the Last Study Visit, the site should not attempt to confirm the outcome (this would include an HbA1c >9) as the follow-up per protocol is now completed.

If lab results from the Last Study Visit pose safety concerns, then in general, sites should proceed with informing the participant and their PCP as the site would normally do following any study visit. For example, a participant's medication may need to be adjusted to lower doses or stopped. Refer the participant to their PCP for new medications.

13.7.5 Participants Lost-to-Follow-Up

The site should pursue efforts to make contact with each participant to schedule and complete a Last Study Visit except for in cases of participant death, incarceration, pregnancy, or if the participant has withdrawn consent.

If the site is unable to establish contact with a participant to schedule a Last Study Visit within the participant's expected Last Study Visit window, the site team should attempt to confirm the participant's vital status until the end of the study using IRB-permitted means. If allowed by the site's IRB, the site team should also attempt to confirm vital status for pregnant and incarcerated participants and participants that have withdrawn consent. The **End of Study Worksheet** can be used to document outreach efforts for lost-to-follow-up participants. The designation of "lost-to-follow-up" will apply to those participants who remain unreachable at the close of the study database.

The database will remain open for end-of-trial follow-up data until the final database lock. Therefore, sites should continue their attempts to locate missing participants or obtain information about their vital status until the Coordinating Center advises them to stop.

13.8 Guidelines for Shipment of Fresh and Frozen Specimens

Timeliness in shipment of both fresh (HbA1c) and frozen laboratory specimens to the CBL is very important, especially if the sample is collected for confirmation. Proper processing and storage of GRADE lab specimens requires a centrifuge and a -70°C freezer. Clinical centers without access to a -70°C freezer can use a -20°C freezer; however refer to the CBL Biospecimen Collection and Processing Manual for detailed instructions for the initial freeze of processed cryovials prior to storage in a -20°C freezer. It is preferred that lab specimens from all other visits are shipped to the CBL on the day of collection. However, if sites are unable to ship the day of collection, samples must be shipped within 10 days of collection. Do not ship a participant's refrigerated samples separate from the frozen samples. Refer to the CBL manual for specific guidelines for specimen processing, storage and shipping.

13.9 Lab Results

Within two weeks of visits when laboratory data are obtained, study staff will contact the participant to provide feedback about clinically relevant laboratory results. Any lab values flagged 'ALERT' must be communicated to the participant and the PCP as soon as possible, preferably within 24 hours. The CBL sends all lab results, including critical alerts, directly to the PI and coordinator at the clinical site.

13.10 Data Collection for Missed Visits and Missed Outcomes

A regularly scheduled visit that does not take place before the next visit window opens is considered a missed visit. If a participant misses a visit, the data are considered missing and a **Missed Visit (MISSVIS) Form** should be entered into the data management system. Repeated missed visits are an indication of a potential retention issue which requires intervention by the Study Coordinator.

13.10.1 Communication strategies for participants at risk of repeatedly missing visits

If a participant is at risk of repeatedly missing study visits, consider the following strategies:

1. Call the participant to maintain contact. A flexible, non-confrontational individualized approach should be taken to working with participants who are not regularly attending study visits.
2. Write and send a certified letter to the participant to explore options for continuing levels of participation in the study.

3. Use the alternative contacts provided by the participant to facilitate contact with the participant.
4. Check the EMR and with the participant's permission, contact the PCP to ascertain reasons for non-response from the participant.

Note that any and all efforts to communicate with a participant should be locally documented.

13.11 Prioritizing Data Collection and Collection of Missed Assessments

If a participant has a limited amount of time to attend a study visit, key aspects of the study visit should be prioritized. Refer to the *Assessments by Study Visit for Prioritization* in Section 15.13 and on the GRADE study website for details. It is recommended that you contact the Coordinating Center to discuss each case to ensure as much data is collected as possible.

Some assessments can be collected on a date other than the visit date if they are missed for any reason such as the participant had limited time for the visit, a certified staff member was not available to complete the assessments, and site error. Refer to the *Guidelines for Collecting Missed Assessments* in Section 15.14 and on the GRADE study website for details.

Manual of Procedures

Chapter 14

TABLE OF CONTENTS

14. CHAPTER 14: STUDY POLICIES

This chapter provides the GRADE study policies regarding Duality of Interest disclosures, Presentations and Publications, and Ancillary Studies and Substudies.

14.1 Duality of Interest (DOI) Disclosure

The duality of interest disclosure policy is provided to assist members of the Study Group with disclosure of relationships (financial and other) with commercial entities to manage potential or perceived conflicts of interest relating to the GRADE study. The purpose of this guidance is to manage potential bias or the appearance of bias related to commercial entities (such as pharmaceutical, biotechnology, and medical device manufacturers) whose products or services may be used, tested and/or affected by the results of the GRADE study.

The DOI policy and its application further these objectives. A copy of the duality of interest disclosure policy is available on the GRADE study website.

14.2 Presentations and Publications

The goals of the Publications and Presentations Subcommittee (PPS) are to:

1. Ensure that all publications and presentations from GRADE are of the highest scientific quality;
2. Preserve the scientific integrity of GRADE in publications and presentations;
3. Protect the rights and privacy of the subject participants in publications and presentations;
4. Promote the selective generation of as many high quality publications and presentations as possible with the resources available and establish priorities for the allocation of resources to do so;
5. Ensure that authorship of all publications and presentations is equitable and that proper attribution to GRADE is provided.

The PPS policy and its application further these objectives. A copy of the Presentations and Publications policy is available on the GRADE study website.

14.3 Ancillary Studies and Substudies

Ancillary studies and substudies that complement the objectives and thereby enhance the value of the study are encouraged. Such studies should augment and promote the continued interest of both participants and investigators. To protect the integrity of the GRADE study, a proposal to conduct an ancillary study must be reviewed and approved by the Ancillary Studies and Substudies Subcommittee, the GRADE Steering Committee, and the Data and Safety Monitoring Board before its initiation. A major review criterion is the impact on the GRADE protocol. No clinical center will be required to participate in an ancillary study.

The Ancillary Studies and Substudies policies further these objectives. A copy of the Ancillary Studies and Substudies policy is available on the GRADE study website.

14.4 Copyright Policies

In accordance with the license agreements, questionnaires in the GRADE study are for GRADE purposes only and permission to obtain the questionnaire is for GRADE, not for other purposes outside the GRADE study. To use the DTSQ (both status and change versions, English and Spanish), QWB, SF36, and EQ5D for the GRADE study, we are required to provide the copyright information with the questionnaires. Please see the copyright language below. It is important that we comply with the policies and that copyrighted forms for use in the GRADE study are used solely for the purposes, and in the manner, in which it was agreed upon by the licenser and licensee.

Figure 14.1: DTQS Copyright Information

DTSQs © Prof Clare Bradley 9/93 Spanish for the USA 4.9.03A (from std. UK English rev. 7/94)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

Figure 14.2: QWB Copyright Information

© Copyright 1996, All Rights Reserved. Modification, duplication, or further distribution in any form strictly prohibited without written permission, Robert M. Kaplan, Theodore G. Ganiats, and William J. Sieber. Questions 9a and 9b are publicly available through copyright held by THE RAND CORP.

Figure 14.3: SF36 Copyright Information

GRADE SF-36 – Jan 03, 2013
Copyright © 1992 Medical Outcomes Trust.
All right reserved.
(SF-36 Standard U.S. Version 1.0)

Figure 14.4: EQ5D Copyright Information

USA(English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

Manual of Procedures

Chapter 15

TABLE OF CONTENTS

15. CHAPTER 15: VISIT COMPLETION FLOW CHARTS AND TOOLS

The tables and flow charts provided in this chapter can be used as a quick reference to the steps and forms that need to be completed for each type of visit.

15.1 Summary of GRADE Assessments by Visit

	Screening Visit 1	Run-In Visit 2 and 3		Baseline/Randomization Visit 4	Quarterly Visits	Annual Visits
Informed consent	X		X[2]	X[2]		
Medical history review	X			X	X	X
Current medications review	X	X		X	X	X
Randomization				X		
Height				X[3]		X (Year 4)
Weight	X			X[3]	X	X
Waist and Hip Measurement				X[3]		X (Years 2, 4 & 6)
Blood pressure	X			X[3]	X	X
Foot Exam				X[3]		X
ECG				X[3]		X (Years 2, 4 & 6)
Blood Draw	X		X	X	X	X
Urine Sample				X	X*	X*
Stool Sample				X[5]	X[5]	
Diabetes Education		X[1]				X
Oral Glucose Tolerance Test (OGTT)				X		X (Years 1, 3 & 5)
Questionnaires				X[3]	X[4]	X[4]
Neurocognitive Assessment				X[3]		X (Years 4 & 6)
Return Study Medication			X	X	X	X
Pregnancy Test (if applicable, done as needed)	X					
Adverse Event Review		X	X	X	X	X
Distribute Medication		X		X	X	X

*Every 6 months after Baseline Randomization visit

[1] May be completed at Initial Run-in (Visit 2) or Final Run-in (Visit 3)

[2] Phase 2 and optional Audio Recording consent may be completed at Final Run-in (Visit 3) or Baseline and Randomization (Visit 4). Optional Microbiome Consent must be obtained at the Final Run-in visit.

[3] May be completed at Final Run-in (Visit 3) or Baseline and Randomization (Visit 4).

[4] DTSQs completed at 6 month Quarterly Visit and DTSQs and DTSQc performed at 12-month Annual Visit

[5] Eligible participants who consent to the microbiome collections collect stool sample & complete two dietary questionnaires at home in between the Final Run-in and Baseline visits and again in between the 3- and 6-month quarterly visits.

15.2 GRADE Forms, Questionnaires and Supplementary Materials: Master Guide by Visit

Visit/Event	Visit Number	Required Forms for Data Entry (Abbreviated Name)	Questionnaires Required for Data Entry (Abbreviated Name)	Ancillary Worksheets, Source Docs, other
Prescreening				▪ Prescreening Worksheet ▪ Prescreening Log ▪ Phone Screen Script
Screening	S1, S2, etc.	▪ Screening Visit Form (SCREEN) ▪ Recruitment Method Form (RECRUIT)		▪ Screening Visit Worksheet ▪ Phase 1 Informed Consent Form ▪ Participant Contact Information Sheet ▪ Staff Contact Sheet ▪ Screening Appointment Reminder Letter ▪ Screening Eligibility Letter ▪ Screening Failure Letter ▪ Screening Visit Progress Note/Source Doc ▪ Pre-Randomization Letter to PCP
Initial Run-In	R1, R2	▪ Initial Run-In Visit Form (RUNIN1)		▪ Initial Run-in Visit Appointment Notification Letter ▪ Metformin Medication Handout ▪ NDEP 4-Steps Booklet ▪ Initial Run-In Progress Note/Source Doc ▪ Other education materials: BD's "Using Insulin Pens and Pen Needles", BD's "Site Selection", BD's "Hypoglycemia and Diabetes", Accu-Chek Meter Instructions, Family Doctor Smoking Cessation, NCI's "Clearing the Air"
Interim Run-In	I1, I2, etc.	▪ Interim Run-In Visit Form (INTRUN)		▪ Interim Run-In Progress Note
Final Run-In	F1, F2, etc.	▪ Final Run-In Visit Form (FINALRUN) ▪ Eligibility Assessment for Randomization (ELIG) ▪ Final Run-In Specimen Transmittal Form: Fresh Samples (FRISTF) ▪ Phase 2 Initial Consent & Permissions Form (PH2CNST)* ▪ Electrocardiogram Form (ECG)* ▪ EDS Specimen Transmittal Form: Refrigerated or Frozen Samples (EDSSTF)* § ▪ Microbiome Eligibility Form (MBIOELIG)	▪ Baseline Participant Information Questionnaire (BASEINFO)* ▪ Participant Symptoms Questionnaire (SYMPTOM)* ▪ Health Survey Questionnaire (SF-36)* ▪ Quality of Well Being Self-Administered (QWB-SA)* ▪ Michigan Neuropathy Screening Instrument (MNSI)* ▪ Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)* ▪ Cognitive Assessments Questionnaire (NEURO)* ▪ EDS Questionnaires Packet (EDSQ)* §	▪ Final Run-In Visit Checklist ▪ Final Run-In Visit Appointment Notification Letter ▪ Informed Consent for GRADE Clinical Trial (Phase 2) ▪ Final Run-In Visit Progress Note/Source Doc ▪ Run-In Failure Participant Letter ▪ Microbiome Informed Consent† ▪ Microbiome Collection Instructions† ▪ Audio Recording Informed Consent ‡

Baseline Randomization	00	▪ Baseline Randomization Visit Form (BASELINE) ▪ Baseline Oral Glucose Tolerance Test Form (BASEOGTT) ▪ Concomitant Medications Form (CONMED) ▪ Baseline Specimen Transmittal Form: Frozen Samples (BASESTF) ▪ Phase 2 Initial Consent & Permissions Form (PH2CNST)* ▪ Electrocardiogram Form (ECG)* ▪ EDS Specimen Transmittal Form: Refrigerated or Frozen Samples(EDSSTF)* § ▪ Microbiome Collection Sample Transmittal Form (MBIOSTF) † ▪ Audio Recording Tracking Form (AUDIO) ‡	▪ Baseline Participant Information Questionnaire (BASEINFO)* ▪ Participant Symptoms Questionnaire (SYMPTOM)* ▪ Health Survey Questionnaire (SF-36)* ▪ Quality of Well Being Self-Administered (QWB-SA)* ▪ Michigan Neuropathy Screening Instrument (MNSI)* ▪ Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)* ▪ Cognitive Assessments Questionnaire (NEURO)* ▪ EDS Questionnaires Packet (EDSQ)* § ▪ Microbiome Collection Dietary Behavior Questionnaire (MBIODIET) † ▪ Microbiome Collection Dietary Screener Questionnaire (MBIODSQ) †	▪ Baseline/Randomization Appointment Notification Letter ▪ Baseline Randomization Visit Checklist ▪ Medication Information Handouts ▪ Medication Adjustment Schedules ▪ Patient ID Card ▪ Participant Blood Sugar Log or Log Book ▪ Baseline Visit Progress Note/Source Doc
Quarterly	03, 09, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81	▪ Quarterly Visit Form (QUART) ▪ Concomitant Medications Form (CONMED) ▪ Quarterly & Semi-Annual Specimen Transmittal Form (QTSMISTF) ▪ Audio Recording Tracking Form (AUDIO) ‡	▪ Participant Symptoms Questionnaire (SYMPTOM)	▪ Quarterly & Annual Visit Reminder Letter ▪ Quarterly Visit Checklist ▪ Medication Dispensation Log ▪ Lab Results During Trial to Participant Letter
Semi-Annual	06, 18, 30, 42, 54, 66, 78	▪ Quarterly Visit Form (QUART) ▪ Concomitant Medications Form (CONMED) ▪ Quarterly & Semi-Annual Specimen Transmittal Form (QTSMISTF) ▪ EDS Specimen Transmittal Form: Refrigerated or Frozen Samples (EDSSTF)§ ▪ Microbiome 6-Month Collection Form (MBIO6MO)† ▪ Microbiome Collection Sample Transmittal Form (MBIOSTF) † ▪ Audio Recording Tracking Form (AUDIO) ‡ ▪ Vitamin B12 Specimen Transmittal Form: Frozen Samples (B12STF)¥	▪ Participant Symptoms Questionnaire (SYMPTOM) ▪ Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) (6 month visit only) ▪ EDS Questionnaires Packet (EDSQ)§ ▪ Microbiome Collection Dietary Behavior Questionnaire (MBIODIET)† ▪ Microbiome Collection Dietary Screener Questionnaire (MBIODSQ)†	▪ Quarterly & Annual Visit Reminder Letter ▪ Semi-Annual Visit Checklist ▪ Semi-Annual Visit Progress Note/Source Doc ▪ Medication Dispensation Log ▪ Lab Results During Trial to Participant Letter ▪ Microbiome Collection Instructions† ▪ Audio Recording Permission Oral Script ‡

Annual	12, 24, 36, 48, 60, 72, 84	▪ Annual Visit Form (ANNUAL) ▪ Concomitant Medications Form (CONMED) ▪ Annual Oral Glucose Tolerance Test Form (ANNOGTT) (Years 1, 3, and 5 only) ▪ Annual Specimen Transmittal Form: Fresh and Frozen Samples (ANNSTF) ▪ Electrocardiogram Form (ECG) (Years 2, 4 and 6 only) ▪ EDS Specimen Transmittal Form: Refrigerated or Frozen Samples (EDSSTF)§ ▪ Audio Recording Tracking Form (AUDIO) ‡ ▪ Vitamin B12 Specimen Transmittal Form: Frozen Samples (B12STF)¥ ▪ CGM Substudy Annual Visit Form (CGMANN)** ▪ CGM Substudy Sensor Shipment Form (CGMSHIP)** ▪ CGM Substudy Specimen Transmittal Form (CGMSTF)** ▪ Direct Nonmedical Costs Evaluation Form (COSTS) £	▪ Participant Symptoms Questionnaire (SYMPTOM) ▪ Health Survey Questionnaire (SF-36) ▪ Quality of Well Being Self-Administered (QWB-SA) ▪ Michigan Neuropathy Screening Instrument (MNSI) ▪ Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs), then Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc) (Year 1 only) ▪ Cognitive Assessments Questionnaire (NEURO) (Years 4 and 6 only) ▪ EDS Questionnaires Packet (EDSQ)§ ▪ CGM Hypoglycemia Daily Diary (CGMDIA)** ▪ EQ-5D-5L and Visual Analog Scale Questionnaire (EQ5D) £	▪ Quarterly & Annual Visit Reminder Letter ▪ Annual Visit Checklist ▪ Annual Visit Progress Note/Source Doc ▪ Medication Dispensation Log ▪ Lab Results During Trial to Participant Letter
As-Needed Forms				
HbA1c Outcome Confirmation Materials		▪ HbA1c Metabolic Outcome Confirmation Form (A1CMET) ▪ HbA1c Confirmation (>9%) Specimen Transmittal Form: Fresh Sample (CONFIRM9) ▪ Non-Initiation of Insulin Form for Participants Meeting HbA1c Metabolic Outcomes (Secondary and Tertiary) (NONINIT) ▪ Non-Initiation of Insulin Quarterly Follow-up Form for Participants Meeting HbA1c Metabolic Outcomes (Secondary and Tertiary) (UPNONIN)		▪ HbA1c Metabolic Outcome Confirmation Worksheet ▪ HbA1c Outcomes Quick Reference Guide ▪ Interim Checklist for HbA1c Above Goal ▪ Summary of A1C Metabolic Outcomes Triggers and Confirmation ▪ Outcome Confirmation Flowcharts ▪ Request Form to Add Novolog

Consent Update	▪ Consent Update & Permissions Change Form (UPDTCNST)	▪ Participant Contact Information Sheet ▪ Medical Record Release Form
SAE	▪ Targeted Adverse Event and Serious AE Form (SAE) ▪ Targeted Adverse Event and Serious AE Follow-up Form (SAEFOLUP)	
Protocol Deviation	▪ Protocol and Operational Deviation Form (PROTDEV)	
Missed Visit	▪ Missed Visit Form (MISSVIS)	
Redraw	▪ Redraw Specimen Transmittal Form: Fresh and Frozen Samples (REDRAW)	
Cost Economic	▪ Interim Visit Form (INTERIM) ▪ Study Remote Contact Log (CONTACT)	
CGM Substudy Visit	▪ CGM Substudy Eligibility Form (CGMELIG)** ▪ CGM Substudy Specimen Transmittal Form (CGMSTF)**	
Other	▪ Participant Transfer Form (TRANSFER) ▪ Study Drug Discontinuation Form (DRUGDC) ▪ Capillary Collection Blood Sample Transmittal Form (CAPLSTF) ▪ Change in Status Form (STATUS) ▪ Pregnancy Outcome Form (PREGOUT) ▪ CGM Participant Consent Log (CGMLOG) ▪ Glucagon Kit Request Form (GLUCAGON) ▪ End of Study Form (EOS)	▪ Unscheduled Visit Progress Note/Source Doc ▪ Informed Consent: Pregnancy ▪ Medical Records Release Forms (participant, baby)

* Either final run-in or baseline visit
§ Only for participants consented to Emotional Distress Substudy (EDS)
**For participants consented to CGM Sub-study only
† Only for participants consenting to Microbiome Collection (Baseline and 06 semi-annual visit only)
‡ Only for participants consenting to audio recordings
¥ Completed twice during the study at the next Semi-annual or Annual visit after implementation and at the Year 4 Annual Visit
£ Completed at the annual visit after implementation

15.3 Summary of Participant and PCP Letters

Study Visit/Results	Letter	When to send	Recipient
Recruitment	PCP recruitment letter	When recruiting the participant	PCP
	Recruitment Letter to Participants	When recruiting the participant	Participant
Screening Visit and Screening Results	Screening Appt Reminder Letter	Prior to the appointment	Participant
	Screening Eligibility Letter	Post appointment if found eligible for run-in	Participant
	Screening Failure Letter	Post appointment if participant fails screening	Participant
Initial Run-in Visit	Initial Run-in Visit Appointment Notification Letter	Prior to the appointment	Participant
Final Run-in Visit	Final Run-in Visit Appointment Notification Letter	Prior to the appointment	Participant
Run-in Failure	Template Letter to PCP For Potential Participants who do not Qualify for GRADE during Run-In	Post appointment if participant fails final run-in	PCP
	Run-in Failure Participant Letter	Post appointment if participant fails final run-in	Participant
Pre-Randomization	Template Pre-Randomization Letter to PCP	Prior to the appointment	PCP
Baseline Randomization Visit	Appointment Letter to Participant with Instructions	Prior to the appointment	Participant
Baseline Results	Template Baseline Results Letter to PCP, with ECG and lab work attached	Post appointment participant	PCP
Outcomes: primary metabolic outcome	Template Outcome Letters to PCP	Upon reaching primary outcome	PCP
Outcomes: secondary metabolic outcome	Template Outcome Letters to PCP	Upon reaching secondary outcome	PCP
Outcomes: tertiary metabolic outcome	Template Outcome Letters to PCP	Upon reaching tertiary outcome	PCP
Regular Results: BP	Template Laboratory Results Letter During Trial for Participant	**Annually** to provide the clinically relevant data	Participant

Weight HbA1c Fasting lipids Albumin/Creatinine ratio – measured semiannually Serum Creatinine/eGFR)- measured annually ECG (electrocardiogram) – performed at baseline and at years 2, 4 and 6 and interpreted locally Vitamin B12			
Regular Results: BP Weight Most recent lab results ECG (electrocardiogram) – performed at years 2, 4 and 6 and interpreted locally (baseline ECG should be sent after the baseline visit along with the tracing)	Annual Results Letter to PCP	**Annually** to provide the clinically relevant data	PCP
ECG results	Local Read ECG Lab Results Letter During Trial to PT	Post appointment where an ECG was collected	Participant
Quarterly and Annual Visits	Quarterly & Annual Visit Reminder	Prior to the appointment	Participant
Vitamin B12 Results	GRADE B12 PCP Letter Template	At least once during study follow-up (after each B12 test)	PCP
Critical Laboratory Values: HbA1c: HbA1c values should also be monitored and PCPs should be notified when therapy is changed (HbA1c >7.5% or >9.0%).		Notify the participant's PCP and participant within **24 hours**	Participant and PCP
Critical Laboratory Values: BP Alert: BP ≥ 160 systolic and/or ≥ 100 mmHg diastolic	BP Alert Letter to PCP	Notify the participant's PCP and participant within **24 hours**	Participant and PCP
Critical Laboratory Values: Pregnancy Alert: positive pregnancy test	Template Pregnancy Alert Letter to PCP	Upon positive pregnancy test within **24 hours**	Participant and PCP
Foot Exam Alert	Template Abnormal Foot Exam Alert Letter to PCP	Notify the participant's PCP within **24 hours** of discovering an urgent abnormality	Participant and PCP

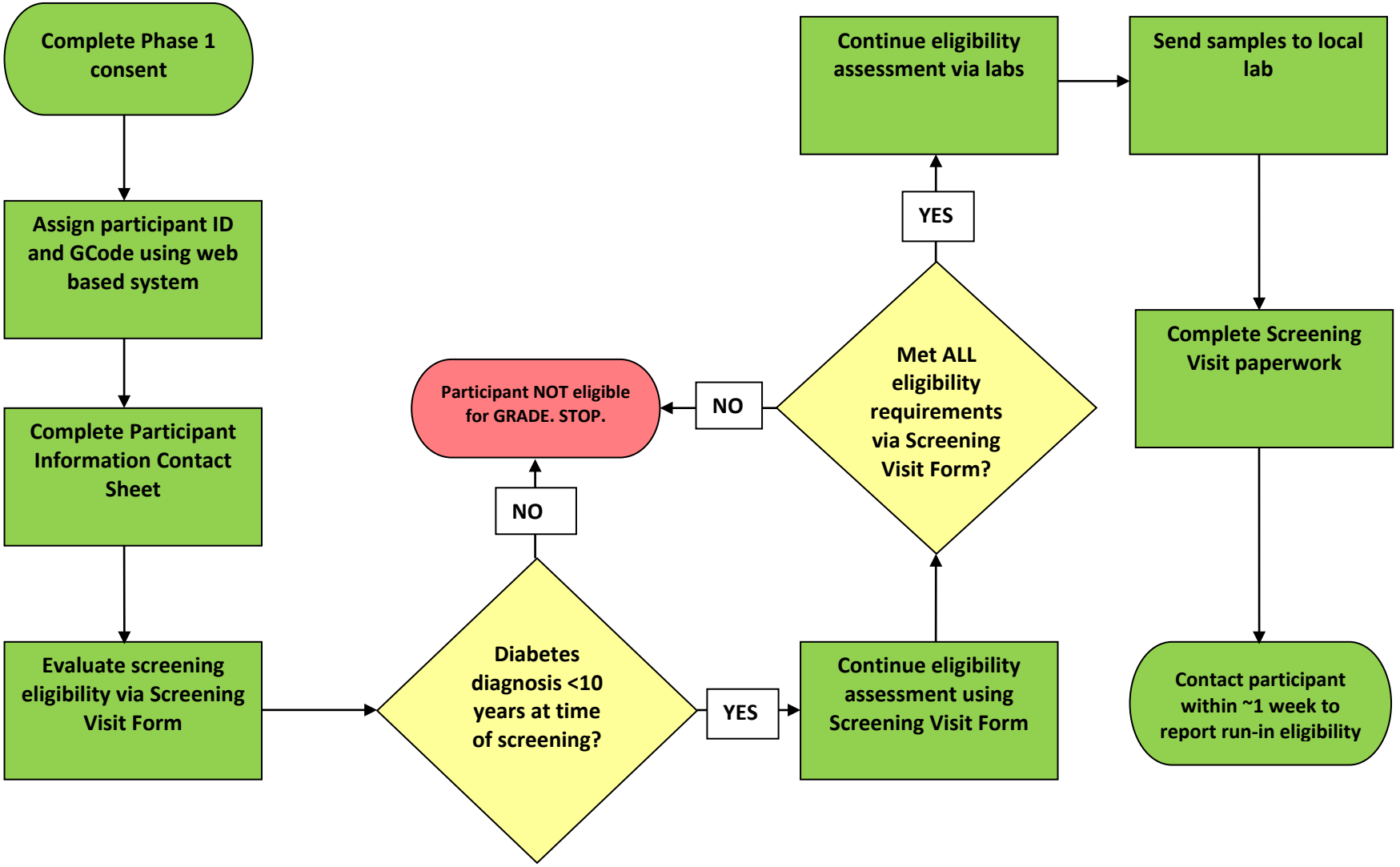
CVD, CKD, or HF History PCP Letter (according to randomized medication)	PCP letter for GRADE participants with prior CVD, HF, or CKD	Notify the participant's PCP of treatment guidelines if the participant has a history of cardiovascular disease, chronic kidney disease, or heart failure	PCP
CVD, CKD, or HF History Participant Letter	Letter to participants with CVD, CKD, or HF	Notify the participant of treatment guidelines if the participant has a history of cardiovascular disease, chronic kidney disease, or heart failure	Participant

15.4 Summary of GRADE Study Drug Titration Algorithms

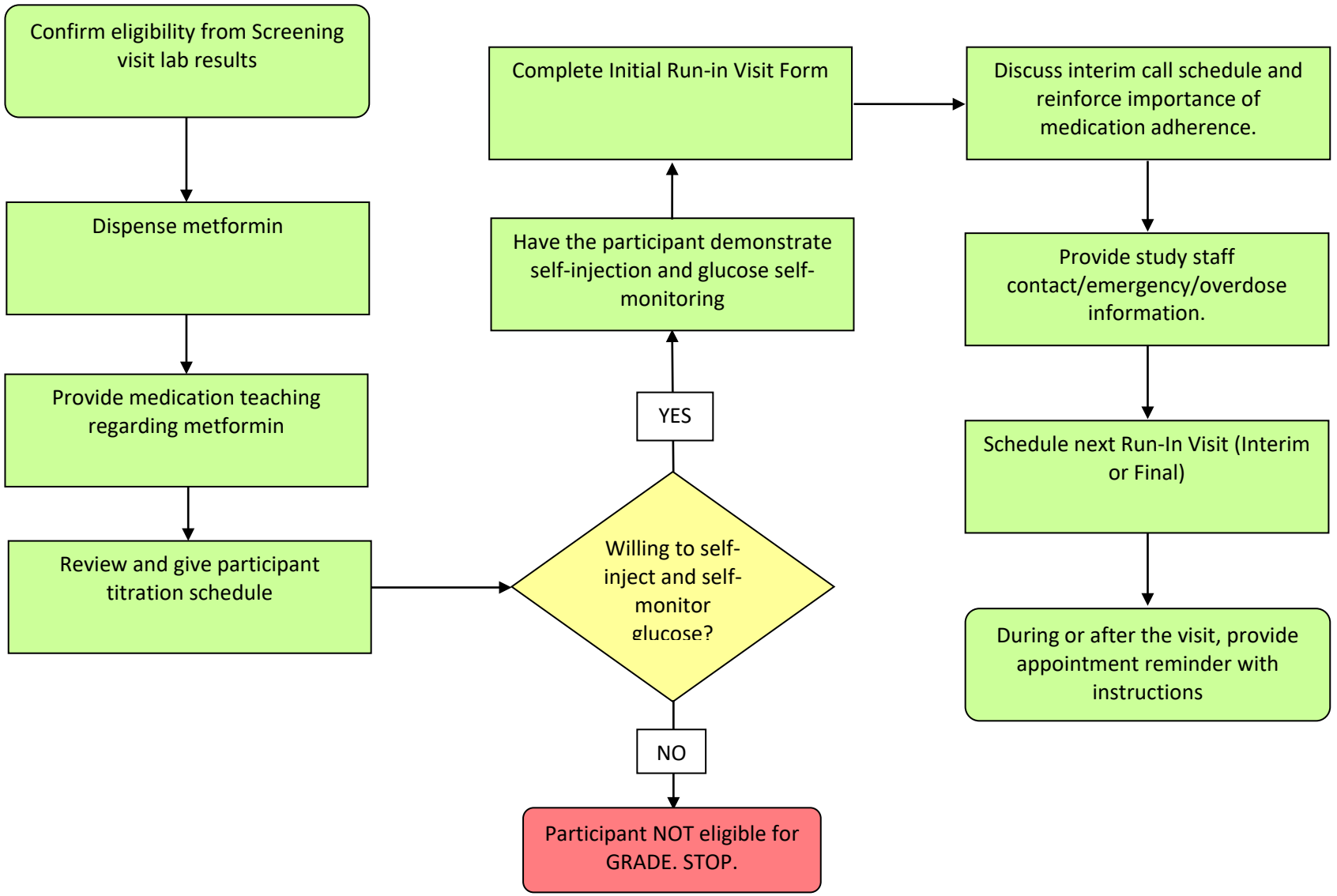
Drug	Maximum Target Dose	Initial Dose	Titration Frequency	Dose	Dosing Schedule	MOP
Metformin (Glucophage, (Glucophage XR)	2000 mg/day	If at <2,000 mg: at run-in	Weekly	a) If on 500 mg daily b) If on 1,000mg daily	Run-in Week 1 a) Give 500 mg breakfast and 500 mg at dinner b) Give 1000 mg at breakfast and 500 mg at dinner	6.4 Consult MOP if unable to tolerate 2,000 mg daily, also see Section 9.3 for both IR and XR formulations
				a) If on 1,000 mg daily b) If on 1,500mg daily	Run-in Week 2 a) Add 500 mg to breakfast, (1000 mg breakfast) continue 500mg at dinner b) Continue 1000mg at breakfast and add 500 mg to dinner (1,000mg dinner)	
				a) If on 1,500mg daily b) If on 2,000 mg daily	Run-in Week 3 a) Continue 1000mg at breakfast and add 500mg at dinner (1,000mg dinner) b) Continue 1,000 mg breakfast and 1,000mg at dinner	
Glimepiride (Amaryl)	8 mg/day	If Final Run-in Visit HbA1c ≤8%: 1 mg with first meal of the day	Weekly	**Weekly Titration Schedule** **If glucose > 100 mg/dl in 4 or more tests per week**, continue to titrate weekly until SMBG results <100 mg/dl in 4 tests per week. If hypoglycemia, consult MOP section 9.4.5		9.4.1 , 9.4.4, 9.4.5
		If the Final Run-in Visit HbA1c >8%: 2 mg with the first meal of the day or before the largest meal		**Weekly Titration for doses above 4 mg** 4 mg in AM + 2 mg PM with meal 4 mg in AM + 4 mg in PM with meal (maximal dose) Continue to titrate weekly until SMBG results <100 in 4 tests per week If hypoglycemia, consult MOP section 9.4.5		
				Note: If after 3 months, the HbA1c is ≥7% without hypoglycemia and the fasting glucose by SMBG is above target (100 mg/dl) in 4 or more tests per week, glimepiride should continue to be adjusted in weekly increments until 8 mg or the maximally tolerated dose is reached		
Sitagliptin (Januvia)	100 mg/day*	100mg/day *	N/A	100 mg/day*	starting dose and maximum study dose is 100mg/day*	9.5.2
Glargine (Lantus SoloStar)	No study maximal dose for insulin; maximal dose is only limited by hypoglycemia, aiming for fasting <100 mg/dl without hypoglycemia	a) 10 units subcutaneously if Final Run-in HbA1c ≤8% b) 20 units if Final Run-in HbA1c > 8%	Daily	Initial Dose: give ½ of the dose once OGTT has been completed with instructions to take full dose the next evening at bed	Start glargine dose in evening (from pre-dinner to bedtime or in shift workers between or before the last meal of the day and bedtime)	9.7.1.1, 9.7.2
				Increase by 2 units each day	If fasting morning blood glucose is >180 mg/dl	
				Increase by 1 unit each day	If fasting morning blood glucose is 100-179 mg/dl	
				Reduce daily glargine (Lantus) dose by 2-5 units	If fasting morning blood glucose is < 70 mg/dl, consult Section 9.7.2 of the MOP.	
Liraglutide (Victoza)	1.8 mg/day	0.6 mg /daily	Weekly		initiated at 0.6 mg once daily for one week	9.6.1
				1.2 mg /daily	If no nausea or abdominal discomfort, increase to 1.2 mg daily	
				1.8 mg/daily	If no nausea or abdominal discomfort, increase to 1.8 mg daily in the first month	

* See Table 10.3 for adjustment of sitagliptin due to kidney function.

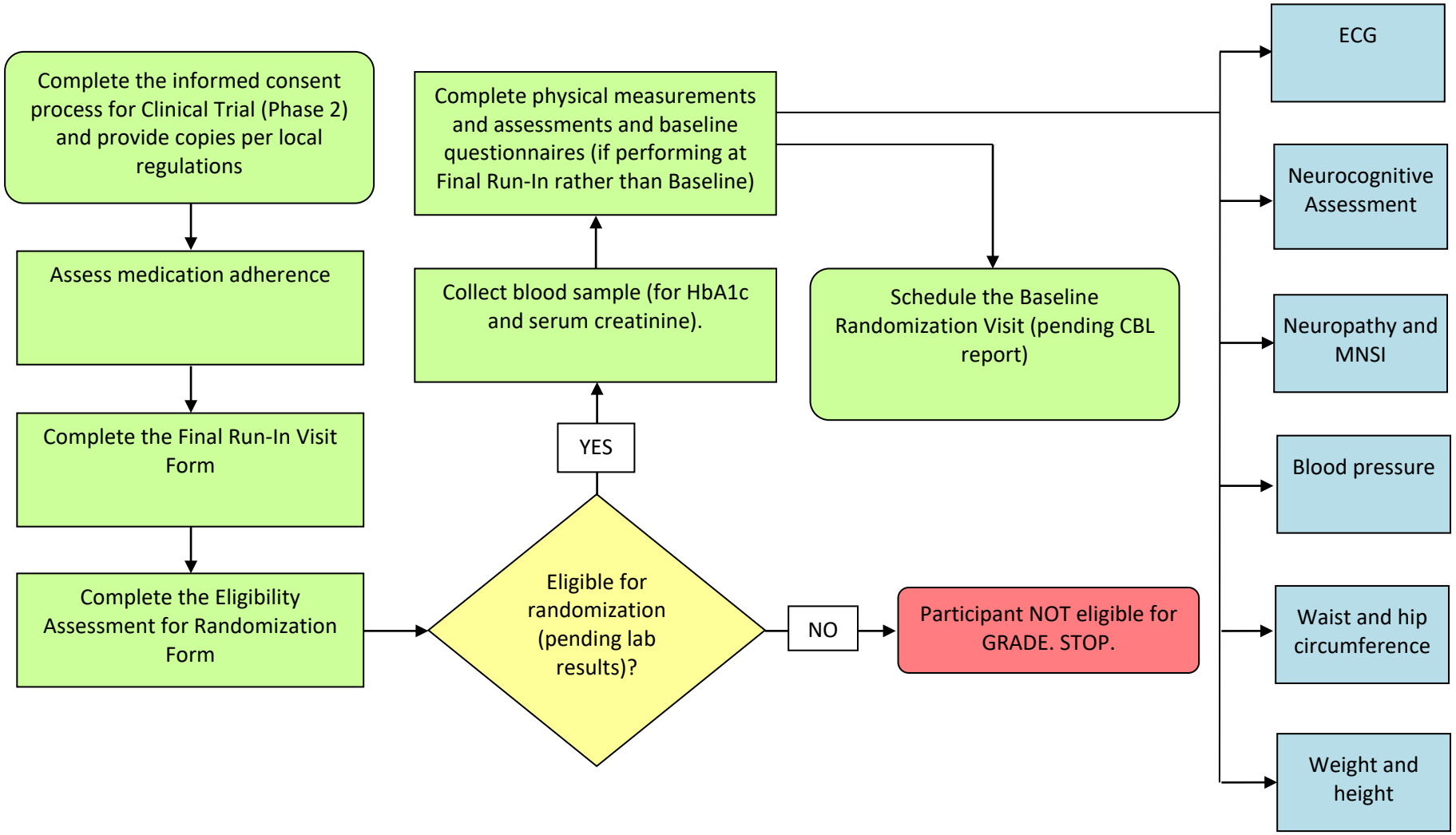
15.5 Screening Visit



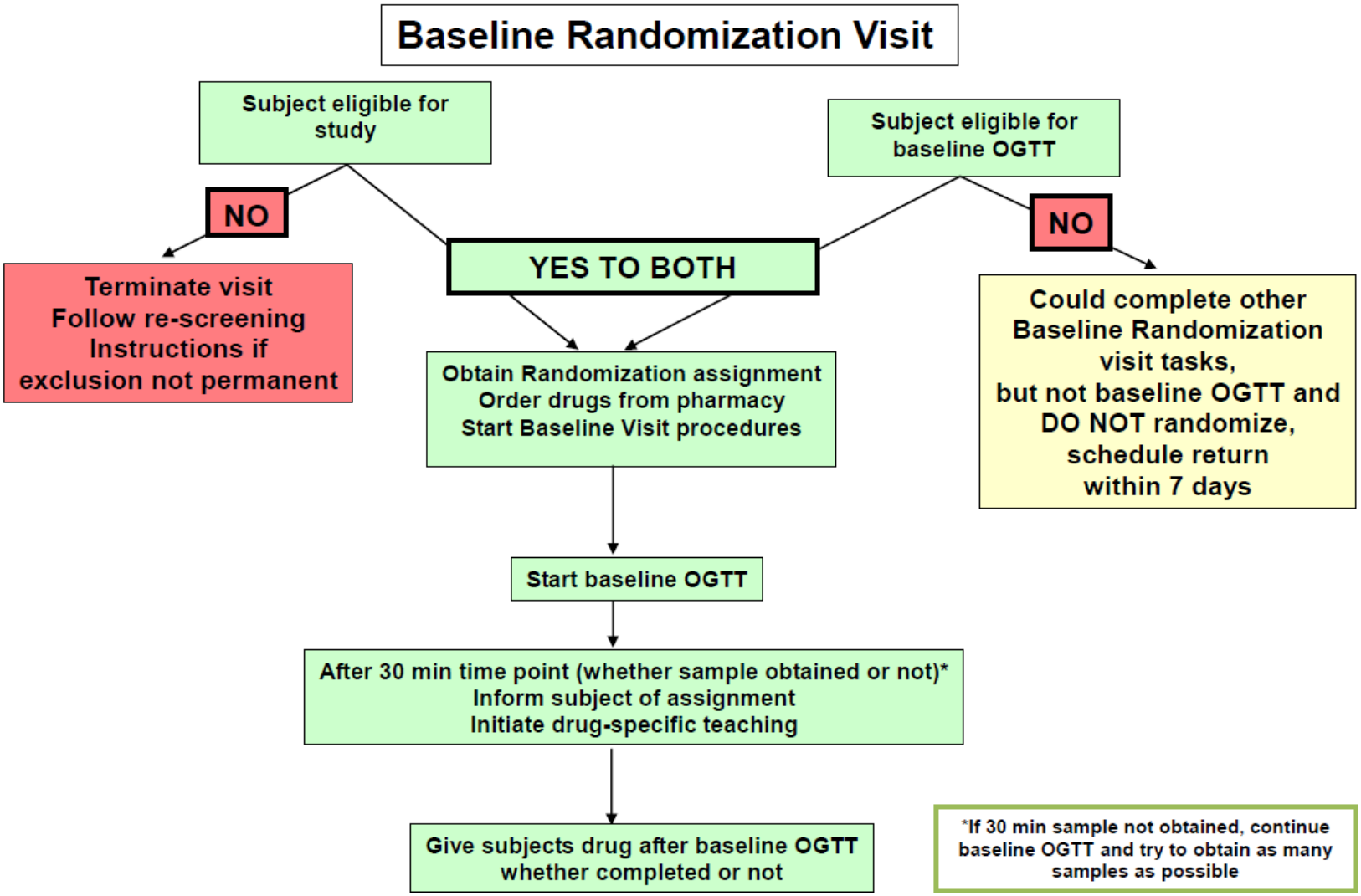
15.6 Initial Run-in Visit



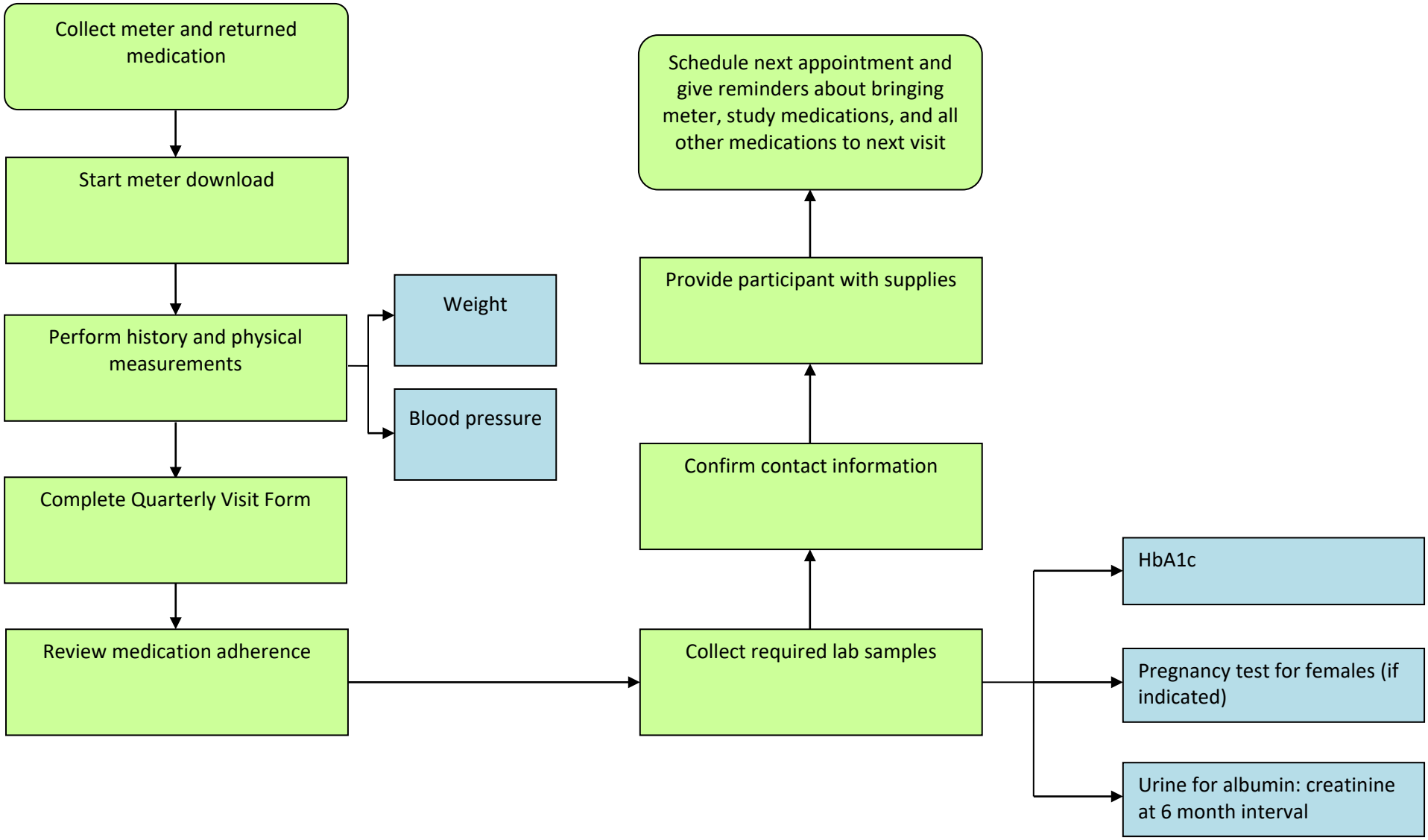
15.7 Final Run-in Visit



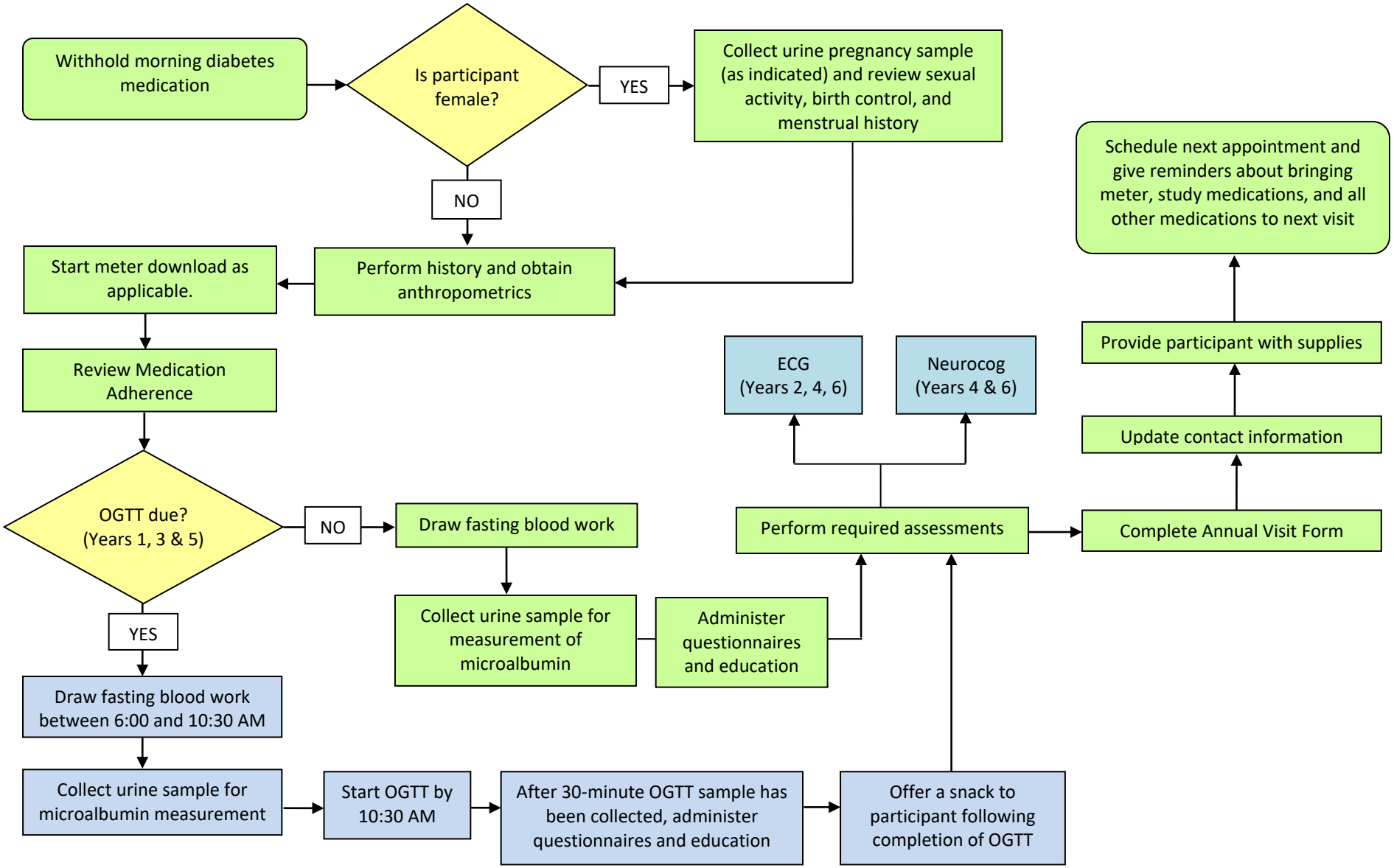
15.8 Baseline Randomization Visit



15.9 Quarterly Visit



15.10 Annual Visit



15.11 Visit Scheduler

Below is a screen shot of the visit scheduler. This visit scheduler is available on the GRADE study website under “Tools.” Refer to Section 15.12 to ensure all pre-randomization visit windows are met.

GRADE The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE Study)

Instructions: Use the table below that corresponds to the metformin dose of the participant at Screening to keep track of patient visit dates prior to Randomization. Fill in the Participant ID number and the date of the Screening Visit. Then, schedule the subsequent visits (Initial Run-In, Interim Run-In, Final Run-In, Baseline Randomization) based on the visit minimum/maximum window information provided in the comments below the table.

ON METFORMIN 2,000mg/day mg or > at Screening*

			Initial Run-In Visit Minimum Window'	Initial Run-In Visit Maximum Window	Interim Run-in Visit Weekly Calls (see MOP 6.8)	Interim Run-in Visit Weekly Calls (see MOP 6.8)	Interim Run-in Visit Weekly Calls (see MOP 6.8)	Final Run-in Visit Minimum Window	Baseline/ Randomize <u>Minimum</u> Window	Baseline/ Randomize <u>Maximum</u> Window
			#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	From FINAL RUN-IN, minimum: 5 days	From FINAL RUN-IN maximum: 45 days
	Patient ID	Screening Visit	Initial Run-in Visit		Interim Run-In	Interim Run-In	Interim Run-In	Final Run-In	Baseline Randomization Visit	
SITE ENTER INFO THIS ROW	000-00001	ENTER DATE	ENTER DATE							

ON METFORMIN 1000 to < 2000 mg at Screening

			Initial Run-In Visit Minimum Window'	Initial Run-In Visit Maximum Window	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Final Run-in Visit Minimum Window	Baseline/ Randomize <u>Minimum</u> Window	Baseline/ Randomize <u>Maximum</u> Window
			#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	From FINAL RUN-IN, minimum: 5 days	From FINAL RUN-IN maximum: 45 days
	Patient ID	Screening Visit	Initial Run-in Visit		Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Final Run-In	Baseline Randomization Visit	
SITE ENTER INFO THIS ROW	000-00002	ENTER DATE	ENTER DATE										

ON METFORMIN 500 to < 1000 mg at Screening

			Initial Run-In Visit Minimum Window'	Initial Run-In Visit Maximum Window	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Interim Run-in Visit Weekly Calls or Visits depending on titration during and metformin tolerance (see MOP 6.8)	Final Run-in Visit Minimum Window	Baseline/ Randomize <u>Minimum</u> Window	Baseline/ Randomize <u>Maximum</u> Window
			#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	From FINAL RUN-IN, minimum: 5 days From	From FINAL RUN-IN maximum: 45 days
	Patient ID	Screening Visit	Initial Run-in Visit		Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Interim Run-In	Final Run-In	Baseline Randomization Visit	
SITE ENTER INFO THIS ROW	000-00003	ENTER DATE	ENTER DATE												

* See MOP for Participants on metformin dose >2000 mg at Scr

' If using prior local lab measurements (obtained within 4 weeks of the screening visit date) as the eligibility lab values for the Screening Visit, the Initial Run-In Visit can occur the same day as the Screening Visit.

Make sure that <u>all participants</u> have been exposed to at least 1000 mg/day of metformin for 8 weeks at final run-in. For example, if participant went from 500-1000 mg daily right at the same time as screening, use the time table in column 3 instead of column 2 to ensure adequate medication exposure at time of final run-in A1c.

scheduled at 26-28 days (no earlier).

15.12 GRADE Help Guide to Schedule Visits

The GRADE Help Guide may be used to assist in scheduling participants from Screening Visit to a Baseline Randomization Visit.

Study Visit	Visit Windows Participant at 2000 mg or >[#] metformin at Screening	Visit Windows Participant at 1000 to < 2000 mg metformin at Screening	Visit Windows Participant at 500 to <1000 mg metformin at Screening	Comment
Initial Run-in	From SCREENING, *minimum:* 1 day* *maximum:* 6 weeks **(42 days)**	From SCREENING, *minimum:* 1 day* *maximum:* 6 weeks **(42 days)**	From SCREENING, *minimum:* 1 day* *maximum:* 6 weeks **(42 days)**	Visit may occur on the same day as Screening Visit if local screening labs* confirm eligibility.
Interim Run-in	Weekly calls (see MOP 6.7.2)	Weekly calls or visits (see MOP 6.7.1)	Weekly calls or visits (see MOP 6.7.1)	Subject may have multiple interim visits (see MOP)
Final Run-in	From INITIAL RUN-IN, *minimum:* 4 weeks **(28 days)**	From INITIAL RUN-IN, *minimum:* 6 weeks **(42 days)**	From INITIAL RUN-IN, *minimum:* 8 weeks **(56 days)**	**All participants must be taking a daily dose of ≥1000 mg metformin for a minimum of 8 weeks at final run-in**
Baseline Randomization	From SCREENING, *minimum:* 6 weeks **(42 days)** *maximum:* 14 weeks **(98 days)** & From FINAL RUN-IN, *minimum:* 5 days *maximum:* 45 days	From SCREENING, *minimum:* 8 weeks **(56 days)** *maximum:* 14 weeks **(98 days)** & From FINAL RUN-IN, *minimum:* 5 days *maximum:* 45 days	From SCREENING, *minimum:* > 8 weeks **(>56 days)** *maximum:* 14 weeks **(98 days)** & From FINAL RUN-IN, *minimum:* 5 days *maximum:* 45 days	

[#] See MOP for Participants on metformin dose >2000 mg at Screening Visit

* If using prior local lab measurements (obtained within 4 weeks of the screening visit date) as the eligibility lab values for the Screening Visit

MAKE SURE THAT ALL PARTICIPANTS have been exposed to at least 1000 mg/day of metformin for 8 weeks at final run-in. For example, if participant went from 500-1000 mg daily right at the same time as screening, use the time table in column 3 instead of column 2 to ensure adequate medication exposure at time of final run-in A1c.

Minimum visit windows defined in weeks can be scheduled up to 2 days earlier if needed for the participant's convenience. For example, the 4-week minimum window for the Final Run-in visit can be scheduled at 26-28 days (no earlier).

15.13 Assessments by Study Visit for Prioritization

Below is a screen shot of the assessments by study visit for prioritization. This document outlines the assessments at Annual, Semiannual, and Quarterly visits, as well as their priority for completion, and their ability to be collected at a phone visit.

Assessments by Study Visit for Prioritization**

Quarterly/Semi-Annual Visit

LAB SPECIMENS	Priority for Completion	Phone Visits
HbA1c	1	✓
Safety labs: B12 as applicable – *only at semi-annual visits*	1	
Additional EDS sample (as applicable, at months 06, 18, 30 only)	2	
Urine pregnancy (if indicated – local lab)	1	
Urine sample for microalbumin:creatinine – *only at semi-annual visits*	2	
STUDY VISIT FORMS		
Quarterly Visit Form	1	✓
Medical History (Section A)	1	✓
Serious Adverse Events (Section B)	1	✓
Weight	1	
Metformin and Randomized Study Drug Adherence (Sections D and E)	1	✓
Study Medication Dose and Dispensation (Section F)	1	✓
Blood pressure	2	
Medical Care Utilization Outside the GRADE Study (Section G)	2	✓
CONMED Form	1	✓
PARTICIPANT QUESTIONNAIRES+		
Symptoms Form	1	✓
DTSQ (Non-EDS pts: month 06 only; EDS pts: months 06, 18, 30 only)	2	✓
EDSQ (as applicable, at months 06, 18, 30 only)	2	
OTHER ACTIVITIES		
Order and dispense metformin, randomized drug, and drug supplies*	1*	✓
Discuss insulin initiation with participants who met outcome but have not yet started glargine and/or Novolog	1	✓
Complete NONINIT or UPNONIN form, as appropriate	1	✓
Audio Recording (as applicable)¥	2¥	

** This table can be used as a guide to determine which assessments take priority at each type of visit. Every case is highly individualized. Please contact your GRADE protocol management representative to discuss.
+ If participant-completed questionnaires can be collected for phone visits, they must be sent to the participant to fill out and should not be collected over the phone
* For participants who complete visits remotely, see MOP Section 4.4.1.1 for guidance on continued medication dispensing
¥ Only if participant has consented to specific component (initiated with Protocol v1.6)

Annual Visit

LAB SPECIMENS	Priority for completion	Phone Visits
HbA1c	1	✓
Safety labs: serum creatinine and B12 as applicable	1	
Plasma/serum storage samples	2	
Urine pregnancy (if indicated – local lab)	1	
Urine for storage and albumin:creatinine	2	
Fasting lipids	2	
OGTT (0, 15, 30, 60, 90, 120-minute time points) *Note: 0 and 120 are the priority time points if venous access difficulty*	3	
STUDY VISIT FORMS		
Annual Visit Form	1	✓
Pregnancy (Section B)	1	✓
Weight	1	
Medical History (Section E)	1	✓
Serious Adverse Events (Section G)	1	✓
Metformin and Randomized Study Drug Adherence (Sections H and I)	1	✓
Study Medication Dose and Dispensation (Section J)	1	✓
Medical Care Utilization Outside the GRADE Study (Section M)	1	✓
Diabetes Education (Section O)	1	✓
Blood pressure	2	
Height (Year 4 only)	2	
Neuropathy foot exam (Section D) *Note: Visual inspection of feet should always be done for safety purposes and should be a priority even if full foot exam and MNSI not completed*	2	
Alcohol and Smoking History (Section F)	2	✓
Self-Monitoring of Blood Glucose (SMBG) (Section K)	2	✓
Number of Concomitant Prescription Medications Outside the GRADE Study (Section L)	2	✓
Eligibility Assessment for Oral Glucose Tolerance Test (OGTT) and other Annual Labs (Section A)	3	
Waist and hip circumference (Years 2, 4, 6 only)	3	
Indirect Costs (Section N)	3	✓
CONMED Form	1	✓
PARTICIPANT QUESTIONNAIRES AND ASSESSMENTS+		
Symptoms Form	1	✓
DTSQ (Non-EDS pts: Year 1 only; EDS pts: Years 1, 2, 3 only)	2	✓
MNSI questionnaire	2	
QWB	2	✓
SF-36	2	✓
EDSQ (as applicable, at Years 1, 2, and 3 only)	2	
ECG (Years 2, 4, 6 only)	2	
Neurocognitive questionnaire (Years 4 and 6 only)	3	
COSTS form and EQ-5D-5L questionnaire (once per pt at annual visit after implementation)	3	✓
OTHER ACTIVITIES		
Order and dispense metformin, randomized drug, and drug supplies*	1*	✓
Discuss insulin initiation with participants who met outcome but have not yet started glargine and/or Novolog	1	✓
Complete NONINIT or UPNONIN form, as appropriate	1	✓
Deliver standard diabetes education	3	✓
Audio recording (as applicable)¥	3¥	

+ If participant-completed questionnaires can be collected for phone visits, they must be sent to the participant to fill out and should not be collected over the phone
* For participants who complete visits remotely, see MOP Section 4.4.1.1 for guidance on continued medication dispensing
¥ Only if participant has consented to specific component (initiated with Protocol v1.6)

15.14 Guidelines for Collecting Missed Assessments

Below is a screen shot of the guidelines for collecting missed assessments. This document outlines what assessments can be collected at a date other than the date of the visit, how far from the visit the assessment can be collected, how the assessment can be collected, and information about documentation.

Guidelines for Collecting Missed Assessments – Quarterly and Semi Annual Visits

Important Note: All missed Quarterly and Semi Annual assessments must be collected within the visit window unless otherwise indicated with an *.

- If the visit window has passed, the only assessments that can still be completed are marked with an * below.
- If the visit was partially completed, please see recollection guidelines below:

	Collection allowed?	How far from the visit can the assessment be collected?	Means of Collection	Possible visits	Form(s) Needed	Lab kit	Documentation Notes
Labs							
HbA1c	Yes	Within 4 weeks	Capillary kit mailed or sent home with pt	N/A	CAPLSTF	Capillary kit with 4xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
B12*	Yes	Refer to B12 Report in MIDAS for next available collection	In person	Semi-Annual	B12STF	Semi-annual kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
				Annual	B12STF	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
Urine for albumin:creatinine*	Yes	Within 3 months	In person	Quarterly	REDRAW	Semi-annual kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
Serum creatinine for EDS	Yes	Within 2 weeks	In person	Interim	EDSSTF	EDS kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected

	Collection allowed?	How far from the visit can the assessment be collected?	Means of Collection	Possible visits	Documentation Notes
Visit Forms					
QUART Form	No				
CONMED Form	No				
Participants Questionnaires & Assessments					
Symptoms Form	Yes	Within 4 weeks	Complete at home and return by mail	N/A	Enter SYMPTOM form under the original quarterly/ semi annual visit **
DTSQ	Yes	Within 4 weeks	Complete at home and return by mail	N/A	Enter DTSQ form under the original quarterly/ semi annual visit **
EDSQ	Yes	Within 2 weeks	In person	Interim	Enter EDSQ form under the original quarterly/ semi annual visit **
Clinical assessments					
Weight and blood pressure	No				

** Requires unlocking of restriction on the 'Date of Visit' question. Enter the form and then contact the Coordinating Center for removal of the restriction.

Guidelines for Collecting Missed Assessments – Annual Visits

Important Note: All missed Annual assessments must be collected within the annual visit window unless otherwise indicated with an *.

- If the Annual visit is missed, the only assessments that can still be completed are marked with an * below. **The deadline to collect these assessments is the next annual target date** (Excluding B12. Refer to B12 Report in MIDAS for information on when to recollect B12 samples)
- If the Annual visit was partially completed, please see recollection guidelines below:

	Collection allowed?	How far from the visit can the assessment be collected?	Means of Collection	Possible visits	Form(s) Needed	Lab kit	Documentation Notes
Priority Labs							
HbA1c	Yes	Within 4 weeks	Capillary kit mailed or sent home with pt	N/A	CAPLSTF	Capillary kit with 4xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
Serum creatinine	Yes	Within 3 months	In person	Quarterly	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
B12*	Yes	Refer to B12 Report in MIDAS for next available collection	In person	Semi-Annual	B12STF	Semi-annual kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
				Annual	B12STF	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
Other Labs							
Urine for storage and albumin:creatinine	Yes	Within 3 months	In person	Quarterly, Semi-Annual	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
Fasting lipids and Plasma/serum storage	Yes	Within 3 months	In person	Quarterly, Semi-Annual	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
OGTT	Yes	Within 3 months	In person	Quarterly, Semi-Annual	REDRAW, ANNOGTT	Annual kit with 7xxxxxxxx lab id	Enter REDRAW form under the visit at which the sample should have been collected. Update the original ANNOGTT form with updated eligibility**

	Collection allowed?	How far from the visit can the assessment be collected?	Means of Collection	Possible visits	Documentation Notes
Visit Forms					
ANNUAL Form	No				
CONMED Form	No				
Participants Questionnaires & Assessments					
Symptoms Form	Yes	Within 4 weeks	Complete at home and return by mail	N/A	Enter SYMPTOM form under the original annual visit **
DTSQ	Yes	Within 4 weeks	Complete at home and return by mail	N/A	Enter DTSQ form under the original annual visit **
MNSI /Neuropathy	Yes	Within 3 months	In person	Quarterly, Semi-Annual	Enter MNSI under the original annual visit ** and update ANNUAL form with the neuropathy information. Include a variable comment on the first question for each foot indicating the date collected and why it was missed
QWB	Yes	Within 3 months	Complete at home or in person	Quarterly, Semi-Annual	Enter QWB form under the original annual visit **
SF-36	Yes	Within 3 months	Complete at home or in person	Quarterly, Semi-Annual	Enter SF-36 form under the original annual visit **
EDSQ /EDSSTF	Yes	Within 2 weeks	In person	Interim	Enter EDSQ/EDSSTF form under the original annual visit **
Neurocognitive questionnaire*	Yes	Within 6 months	In person	Quarterly, Semi-Annual, Annual	Enter NEURO form under the original annual visit **
Clinical assessments					
Weight and blood pressure	No				
ECG *	Yes	No later than the next annual visit	In person	Quarterly, Semi-Annual, Annual	Enter ECG form under the visit at which the ECG was actually conducted. Add a comment on the Visit Number question to explain why the ECG was missed and confirm which visit the ECG should be associated with
Height*	Yes	No later than the next annual visit	In person	Quarterly, Semi-Annual, Annual	Document on the ANNUAL form with a comment on the Height question indicating the date collected and why it was missed
Waist and hip circumference*	Yes	Within 6 months	In person	Quarterly, Semi-Annual, Annual	Document on the ANNUAL form with comments on *each* of the waist and hip measurements indicating the date collected and why it was missed

** Requires unlocking of restriction on the 'Date of Visit' question. Enter the form and then contact the Coordinating Center for removal of the restriction.

Manual of Procedures

Chapter 16

TABLE OF CONTENTS

16. CHAPTER 16: GRADE SAMPLE TEMPLATES

These sample templates and associated documents are available on the GRADE study website. Note that following implementation of the Emotional Distress Substudy (EDS), two versions of the template Phase 1 and 2 Informed Consent Forms (ICFs) are available. One version contains additional language describing the Emotional Distress Substudy (EDS), an embedded substudy being implemented at select GRADE clinical sites. Sites participating in the EDS should use the EDS version of the ICFs for all participants enrolled after the point of local approval of Protocol v1.5. Additionally, two new consent forms were developed for the optional microbiome collections and audio recording of study visits once these aspects were implemented. A template informed consent for pregnancy was also developed. **The EDS versions of the Phase 1 and 2 ICFs, Microbiome ICF, Audio Recording ICF, and Template Informed Consent: Pregnancy are not included here, but are available on the GRADE study website.**

16.1 Template Informed Consents

16.1.1 Phase 1 Template Informed Consent Version 1.6.1 (no EDS)

Template Informed Consent- Phase 1
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)
PRINCIPAL INVESTIGATOR:
SITE PRINCIPAL INVESTIGATOR:
DESCRIPTION OF SUBJECT POPULATION: Adults with type 2 diabetes
(Consent for Screening and Trial Run-in)

About this consent form
Please read this form carefully. It tells you important information about a research study called the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study or GRADE Study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "participants." This term will be used throughout this consent form.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

The consent form you are being asked to sign today is for the screening and run-in period (**Phase 1**) of the GRADE study. **By signing this form, you are giving your permission for Phase 1 – Screening and Run-In. Phase 1 will determine whether you are eligible for the GRADE clinical trial (Phase 2). Once you have completed the screening and run-in period you will be given a separate consent form to review and sign. It will explain the details of the clinical trial (Phase 2).** This consent form gives a description of the clinical trial (Phase 2) to help you decide whether or not to participate in the screening and run in period (Phase 1). You may also ask to review the full Phase 2 consent document now if you would like.

Why is this research study being done?
The GRADE study is a research study for people with type 2 diabetes. This research study will compare the effectiveness of four different medications that are used to treat type 2 diabetes. Each of the 4 medications will be used together with metformin. Metformin is the medication used most often to treat type 2 diabetes. Each medication combination used in the GRADE study has been approved by the U.S. Food and Drug Administration (FDA) and is commonly used to treat type 2 diabetes in adults. However, no study has ever compared these combinations "head-to-head". Therefore, which combination treatment is best for adults with type 2 diabetes is not known. The GRADE study will compare how well the different medication combinations control blood sugar levels. We will also look at other benefits or side effects of

each medication combination. Information from the GRADE study will help to determine the best treatment for type 2 diabetes.

Who can be in this research study?
To be in the GRADE study, you need to have type 2 diabetes for less than 10 years. You must have been at least 30 years of age when you were diagnosed (if you are an American Indian, you must have been at least 20 years old at the time of diagnosis). You also must be taking metformin to treat your type 2 diabetes. You cannot currently be taking any diabetes medications other than metformin. If you take less than 2000 mg of metformin per day, that dose will be increased during the first few weeks of the study (called the "run-in" period). You must be able to take at least 1000 mg of metformin per day (goal being 1000 mg twice per day) to be in the GRADE study.

To be in the GRADE study, you must be willing to take a second randomly assigned study medication by self-injection or pill every day along with your metformin. You must be willing to test your blood sugar by finger stick (or from an alternate site, such as your arm) up to 2 times daily at home. If needed to keep your blood sugar levels within the recommended range, you must be willing to take more than one type of insulin and more than one injection per day, and take up to 3 medications daily.

Once you successfully complete the screening and run-in period you will be randomized to one of the four study diabetes medications. Being randomized means that the medication will be assigned by chance, like the flip of a coin. **You will not have a choice about the second diabetes medication that will be assigned to you**. Some of the medications are taken by injection and some as pills. You will stay on that randomly assigned medication, in addition to your metformin, for the duration of the GRADE study assuming that you tolerate the assigned medication. If your diabetes control worsens we may ask you to add one or more types of insulin given by injection, as is usually done in clinical practice when a combination of two different drugs is not enough to keep blood sugar levels in the recommended ranges.

You must have a regular health care provider (primary care provider) by the end of the run-in period in order to be in the study. If you do not have a primary care provider, the GRADE study may be able to help you identify one. While you are in the GRADE clinical trial, the study team will help you with your diabetes treatment plan and will provide all study medication free-of-charge. You and your primary health care provider will still be responsible for other parts of your health care, including general preventive measures such as monitoring blood pressure, blood cholesterol, foot exams, eye exams, and immunizations. The GRADE Study will send results of your GRADE blood tests that are part of "usual care" reports to your primary care provider. If the study medications fail to lower your glucose levels to an acceptable range, we will reach out to your own care provider to discuss adding non-study medications. Any additional medications prescribed by your care provider would be billed to your insurance and would not be provided by the study.

We expect to enroll about 5000 people with type 2 diabetes at GRADE study sites throughout the United States. We will enroll about 150 participants ***(OR INSERT LOCAL INSTITUTION TARGET NUMBER IF GREATER THAN 150)*** at ***(INSERT LOCAL INSTITUTION)***. The GRADE study is sponsored by the National Institutes of Health (NIH), meaning that they are providing funding and other support to carry out the study. Medications used in the GRADE study are being donated by the following companies: Bristol-Myers Squibb, Merck, Novo Nordisk, and Sanofi. Roche Diagnostics will donate blood sugar monitors and test strips. BD Medical is providing insulin starter kits and the needles to be used for insulin injections. None of the companies has had any part in designing or carrying out the study and they will not be involved in evaluating the study results. The Centers for Disease Control and Prevention (CDC) is providing financial support for the economic analysis. The National Diabetes Education Program (NDEP) is donating copies of the booklet, *4 Steps to Control Your Diabetes for Life*, to the study.

How long will I take part in this research study?
The screening and run-in period (Phase 1) will take about 6-12 weeks to complete. During screening and run-in, we will ask you to make 2 or 3 study visits to (***INSERT SITE NAME***). Each visit will take about 60-120 minutes. We will be in contact with you between visits to review how you are doing taking metformin.

Your participation in the GRADE clinical study (Phase 2) will be for 4 years up to 7.5 years depending on when you enroll. The study is planned to end in 2021. Phase 2 visits will be every 3 months. Most of these visits will take about an hour. Once each year you'll have a longer visit (3-4 hours) that will require that you fast (nothing to eat for at least 8 hours before the visit). The visit will start between 8 and 9:30 AM. We may occasionally ask you to come in for an extra visit from time to time to re-check a blood test result or to adjust your medications. Extra visits will generally take an hour or less.

What will happen in this research study?
Phase 1: Screening and Run-in

Screening Visit
The first visit (screening visit) will be done to find out whether you initially qualify for the study. It will take about 60 to 90 minutes. Your medical history will be reviewed and we will measure your blood pressure and weight. About 3 tubes of blood (about 3 teaspoons total) will be collected. We will test your blood for red blood cell count, liver function, kidney function, and hemoglobin A1c, a test that tells us about your average diabetes control. If you are a woman of childbearing age, we will do a urine pregnancy test.

It will take a few days to get the results of your tests. We will check the results to make sure that you qualify for the study and that any of the 4 study medications would be safe for you. If you are eligible, we will ask you to come for another appointment to start the run-in part of the study. If you do not qualify for the study, we will tell you why. In some cases, such as a temporary condition or blood test that made you ineligible, we can schedule a repeat screening visit and/or blood test.

Run-in Visits

The purpose of Run-In Visits is:

- To be sure you can tolerate taking the study medication metformin, which you will be required to take twice per day.
- To make sure that you are able to come to your appointments, give yourself an injection and test your blood sugar as requested.
- To make sure that you understand what you will be expected to do over the next 4 to 7.5 years of the study.

The first run-in visit will take place within one to two weeks of your screening visit. It will take about 60 to 90 minutes. We will give you the study-supplied metformin and, if necessary, begin to adjust the dose. We will teach you how to test your own blood sugar by pricking your finger (also called "doing a finger stick") or testing from an alternate site, such as your arm, and ask you to demonstrate it. We will also show you how to give yourself a practice injection without medicine (there are two medicines in the study that are given by injection), and we will ask you to give yourself a practice injection before you leave the visit so that you can be confident that you will be able to give yourself an injection during the study.

You must be able to take at least 1000 mg of metformin per day and the goal is to have you taking 1000 mg twice daily. If you are already taking the recommended study dose of 1000 mg twice per day, no changes will be made and you will continue on that dose. If you take more than that, we will reduce the dose to 1000 mg twice per day. If you take less than that, we will increase your dose weekly until you are taking 1000 mg twice per day. If, by increasing the dose you start having side effects (the most common problems are stomach upset and diarrhea), we will decrease the dose and try again. If you still have side-effects, we will change you to a longer-acting/slower release type of metformin, which may reduce the side effects. If you need to have your metformin dose adjusted, we may ask you to come for an additional run-in visit about 4 to 6 weeks after the screening visit.

During run-in, you will meet with the GRADE staff for diabetes education. The GRADE staff will review the basics of diabetes self-management, exercise goals, and healthy eating. Your final run-in visit will be about 6 to 12 weeks after your screening visit. This visit will take about 2 hours to complete. We will ask you to bring back any unused study medication (metformin). We will check to see that you have been able to take the recommended amount of metformin and collect some blood samples (about 1 teaspoon) for kidney function and diabetes control.

You will be asked to sign the clinical trial (Phase 2) consent form either at the final run-in visit or at your next visit, which would be the start of the clinical trial. That visit will be scheduled for a week or two after the final run-in visit, when we will have received the results of your blood tests to make sure that you are still eligible to participate in the study. We will let you know the results and if you are not eligible for the clinical trial we will tell you why. If you are not eligible, we will provide a small amount of metformin so you won't run out as you go back to your own health care provider.

Phase 2: GRADE Clinical Trial

We will give you a consent form for Phase 2 if you are eligible for the clinical trial after the screening and run-in phase. However, you may ask to review the consent form at any time. We describe the clinical trial in general terms below so that you will know what would be expected of you should you enroll in the clinical trial.

Once you have enrolled into the GRADE clinical trial, your participation will be for 4 up to 7.5 years depending on when you enroll. You will continue to take metformin and you will start a second diabetes medication. **As a reminder, the second diabetes medication is assigned by chance. Neither you nor any member of the GRADE study team will be able to decide which medication is assigned.** There are four possible medications. Two are taken by mouth (pills) and two are given by injection (one injection per day). You will have a visit with the study staff every three months. At each visit, the study staff will perform a blood test (hemoglobin A1c) that measures your average blood sugar control to see if it is in the desired range. If your hemoglobin A1c is not "at target" with the combination of metformin and the assigned study medication, we will ask you to add insulin. If one type of insulin does not keep your hemoglobin A1c in an acceptable range, we may ask you to add a second type of insulin.

Clinical Trial: Treatment and Follow-up

Your first visit in Phase 2 of the GRADE clinical trial is called the baseline randomization visit. This visit will take about 5 hours to complete. We will ask you to be "fasting" (no food for 8 hours; you may drink water). Please take your usual morning medications (except for your diabetes medications) with a small amount of water. We will ask you not to take your metformin on the morning of your visit but would like you to bring your metformin with you to take when the visit is over.

At this first visit, you will be assigned to your second study medication, to be taken in combination with the metformin. The medications that will be used in Phase 2 of the GRADE study are glimepiride, sitagliptin, liraglutide, and glargine. All of these medications are taken daily, all are commonly used to treat type 2 diabetes, and all are approved by the FDA for use with metformin. Glargine and liraglutide are taken by injection once per day. Glimepiride and sitagliptin are taken by mouth as a pill once or twice daily. If you are assigned to take glargine or glimepiride we will give you a blood glucose meter, testing supplies, and instructions on testing your blood sugar by finger stick at home since both of these medications will be adjusted based on your home blood sugar test results. The other two medications, liraglutide and sitagliptin are not adjusted based on blood sugar results. The study staff will review your assigned medication with you in detail during this visit. This will include a review of how to take the medication, when to take the medication, how to store the medication, and common side effects and risks of the medication. If you are assigned to glargine or liraglutide we will teach you how to give an injection and have you demonstrate how it is done before the end of the appointment.

Blood and urine samples, questionnaires, measurement of your blood pressure, electrocardiogram (ECG), height, weight, waist and hips, and a foot exam will be done at the baseline visit. We will test your memory with standard testing.

If time permits, some of your testing, measurements or other questionnaires can be completed at your final run-in visit (blood pressure, height, weight, waist and hips, foot exam, ECG, the memory test, and/or questionnaires about your quality of life, diabetes symptoms and care). Your waist and hips will be measured with a tape measure and we will test your memory with standard testing. You will have an ECG, a heart tracing, to measure the electrical activity of your heart. The ECG will be repeated at some annual visits during the study.

The memory testing will require about 20-30 minutes to complete. At your baseline randomization visit you will also have an Oral Glucose Tolerance Test (or OGTT). The OGTT measures your glucose and insulin response to carbohydrate and takes about 2 hours to complete. You will be given a flavored drink with glucose (sugar), and we will take blood samples periodically during the test. The OGTT will be performed at baseline and at some annual visits (years 1, 3 and 5).

At the conclusion of the baseline randomization visit we will give you a 3 month supply of study medication and will schedule you for a follow-up visit in 3 months. The study team will be available by phone to talk with you in between visits. You will continue to have visits every 3 months for the duration of the GRADE clinical trial. Most visits will take 60 to 90 minutes. One visit per year (scheduled around the time of your anniversary of your baseline randomization visit) may take up to about 3-4 hours to complete (depending on whether or not an OGTT is scheduled).

What are the risks and possible discomforts from being in this research study?
There is a small risk of infection at the site of the needle stick for blood drawing. This occurs in less than 1 in 1,000 people. The risk is minimized by standard blood collection practices, such as cleaning the skin before the needle stick, and wearing gloves/washing hands. In some cases, a person may faint or become sick to the stomach at the sight of a needle or when blood is drawn. In about 1 in 4 people, there may be minimal discomfort or bruising at the site of the needlestick. The GRADE staff who perform these procedures have special training and experience in drawing blood. This should help keep these risks at the lowest possible level.

If the blood tests done in GRADE show abnormal results, this may be stressful to you. However, studies have shown that the sooner health problems are found and treated, the better the outcome. In addition, many of the problems identified by the GRADE staff might be easily treated. For example, we may find an abnormal amount of fat (cholesterol, lipids) in your blood. We know this problem can be treated by changing your diet and/or prescribing cholesterol-lowering medications.

The total amount of blood obtained annually during the GRADE study is somewhat more than the amount of blood that would be obtained during usual clinical care, but is not unsafe for

adults and will not cause low blood counts (anemia). Also, the results of the blood tests during GRADE may take the place of some of the tests that your own care provider would otherwise perform.

There is a slight amount of pain associated with checking blood sugar levels using finger sticks. There is also a very low risk of infection at the site of the finger stick. The GRADE staff will help you find the best ways to check your blood sugar levels and how to minimize discomfort and avoid infection.

There may be a small amount of pain associated with injection of medications into the fatty tissue in your abdomen or thigh (the most common sites for injections). The GRADE staff will help you find the best place to inject to keep the pain as little as possible.

Some people may get slightly nauseated or get an upset stomach from the glucose (sugar) drink given during the OGTT. These symptoms are rare and disappear within 15 to 30 minutes.

Metformin

The FDA has approved the use of metformin for treating diabetes in adults. It is the most common diabetes medication used worldwide, and all potential participants will be treated with metformin before entering screening. There are, however, risks associated with metformin that you should know.

The most common side effects of metformin include nausea, headaches, diarrhea, vomiting, bloating, excessive gas, loss of appetite, and an unpleasant taste in the mouth. These are more common when the medication is first started and lessen or disappear over time. About 10 out of 100 people using metformin may experience these symptoms to some degree. However, these side effects are rarely severe enough to result in needing to stop the medication. Other side effects include lower-than-normal levels of vitamin B12 in the blood, which can rarely lead to anemia (low blood count). Hypoglycemia (low blood sugar) rarely occurs when metformin is taken by itself, but it can occur when metformin is combined with some other diabetes medications.

In very rare instances (fewer than 3 in 100,000), a condition called lactic acidosis has been reported in patients taking metformin. When lactic acidosis occurs it is usually in persons who have other severe medical problems, such as kidney disease, liver disease, or severe circulatory problems. We will check blood tests and ask about symptoms to make sure it is safe for you to continue to take this medication. In addition, you must notify the GRADE study team if you experience any severe disease that results in hospitalization since, for safety, we will want to stop metformin during the illness. If ignored or untreated, lactic acidosis can lead to serious health problems that can progress to coma or death.

You should talk to the study team before you undergo any surgery, X-ray procedures, or CT scans that use any type of injection (such as a dye that makes X-rays easier to see) as you will need to stop your metformin during the time of the procedure. Alcohol should not be used in

excess while taking metformin. Inform your study doctor if you now have (or develop during the course of the trial) kidney or liver disease, heart failure, or severe infections.

Other Study Medications

The FDA has approved the use of all the medications used in the GRADE study for treating diabetes in adults. However, there are risks associated with each medication that you should know. For example, allergic reactions may occur. Any medication may be associated with an allergic reaction. Although the medications studied in GRADE are only rarely associated with an allergic reaction, one may still occur. If you develop any symptoms of an allergic reaction (itching, rash, hives, difficulty breathing) while you are taking the study medication you should contact the study staff.

According to most treatment guidelines, younger people, for example less than 65 years of age, should aim for HbA1c less than 7% in order to decrease their risk of developing diabetes complications. Higher levels of HbA1c, such as 7.5% or higher, may be appropriate for older people with longer duration diabetes who have other diseases, such as heart disease. A recent large study showed that patients treated to achieve near-normal blood sugar levels (an average HbA1c level of 6.4%) had a higher risk of death, including death from heart attacks and strokes. The risk of having one of these events was higher in patients with a prior history of heart disease and with diabetes for longer than 10 years. Several other studies with persons who were more similar to those who will be recruited in GRADE have not shown any increased risk for heart attacks, stroke, or deaths when their HbA1c levels were reduced to an average of 6.4%.

In order to reduce possible increased risk, GRADE will include lower risk persons who have had diabetes for less than 10 years. In addition, GRADE is excluding persons who are very ill or who have had a heart attack, stroke or a surgical procedure to prevent or treat such diseases in the previous year. It is unknown whether the GRADE protocol will increase the risk for heart attacks and strokes in some persons whose HbA1c level is decreased to less than 6.8%.

The effects of some diabetes medications on how an unborn baby grows and develops are not known. None of the medications in the study are known to be associated with specific birth defects. In fact, three of the medications are commonly used during pregnancy. However, because we do not know for certain the effects of some of the diabetes medications used in the study on a baby before it is born, it is important that you do not become pregnant while you are taking study medications. We will do a urine pregnancy test at the screening and randomization visit if you are a woman of childbearing age. We may also ask you to provide a urine sample for pregnancy testing at other times during the study. If you suspect that you are pregnant or are concerned you may have become pregnant while taking the study medications, you should advise the GRADE study team immediately. If you become pregnant you will be advised to stop taking the study's medications and switch to medications specifically prescribed by your own health care

provider during the pregnancy. We will recommend that your primary care provider find a doctor for you who specializes in taking care of pregnant women who have diabetes.

Each of the study medications has some known side effects. These are carefully described in the Phase 2 (Clinical Trial) consent form. Two of the study drugs have a side effect of weight gain. We will counsel you to minimize that risk and monitor you for that possibility.

Any time that a diabetes medication is started, stopped, or changed, there is a risk that you may have high blood sugar levels (hyperglycemia) or low blood sugar levels (hypoglycemia). The symptoms of high blood sugar levels include drowsiness, thirst, excessive urination, and loss of appetite. If you start to go to the bathroom more often than usual, you may need to check your blood sugar levels more often, and also check your urine for ketones.

The symptoms of low blood sugar levels include sweating, fatigue, nervousness, shakiness, rapid heartbeat, nausea, and confusion or personality changes. If a person drinks or eats sugar-containing food right away, the symptoms will often stop. In the most severe cases, low blood sugar can cause unconsciousness and seizures. If you have any of these symptoms, you will need to check blood sugar levels to be sure the symptoms are caused by low blood sugar. As part of the GRADE diabetes education, we will teach you about the signs and symptoms of high and low blood sugar levels and what to do about them.

We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may not be effective to control their blood sugar levels. If this happens, long-term treatment with insulin or a more intensive insulin regimen (more than 1 injection of insulin daily) may be required. However, we cannot tell beforehand which participants will be able to tolerate the study medications and which will not; or which participants will be able to successfully control their blood sugar levels with the assigned medications and which will not. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels and has the most favorable long-term outcomes, every participant randomized into the study is equally important. Even if you are no longer taking your originally assigned medications, it is just as important for us to know your long-term outcomes as it is for any other participant. That is why it is important for you to attend all study visits even if you aren't taking some or all of your study-assigned medications, or if you are taking other diabetes medications prescribed by your care provider.

What are the possible benefits from being in this research study?

If you decide to take part in this study, there is no guarantee that your health will improve. We will follow your diabetes closely. You will receive additional education about diabetes and how to take care of it. The GRADE study team will help you manage your diabetes free-of-charge. You will have blood tests and procedures to monitor your health at no charge and the results will be shared with you and, with your permission, with your primary care provider who may use them to help with your medical care. In addition, you will receive the following at no charge:

- Glucose testing equipment as needed at no cost to you
- Diabetes medication at no cost
- Diabetes care from a team of diabetes experts at no cost

What other treatments or procedures are available for my condition?
You do not have to take part in this study to be treated for type 2 diabetes. Other treatments or procedures that are available to treat diabetes include receiving care for your diabetes from your primary care provider or other health care providers rather than the GRADE study. You are not obliged to take part in the GRADE study to receive treatment for diabetes.

Can I still get medical care within (*INSERT INSTITUTION NAME*) if I don't take part in this research study, or if I stop taking part?
Yes. Your decision will not change the medical care you get within (***INSERT INSTITUTION NAME***) now or in the future. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to join the study. If you decide to join now, you may change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?
If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed. It is possible that we will have to ask you to stop your participation before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?
You will not be paid for your participation during the screening and run-in phase (the "tryout"). We will pay for local travel costs and provide parking vouchers and meal replacements if we ask you to fast for an appointment.

There is no cost to you for being in this study. There will be no charge for procedures or medications required by the study.

What happens if I am injured as a result of taking part in this research study?
Taking part in this research study may hurt you (this was explained in the section called "Risks and Discomforts"). If you need to get medical care right away, you should go to the nearest emergency care center. Be sure to explain that you are participating in a research study. If you do not need emergency care, you should contact your primary care provider. The GRADE investigators may also take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. You will be responsible for any costs not covered by your health insurance. GRADE and the clinical site you go to will not pay for your care. Likewise,

GRADE and your clinical site will not pay you for pain, worry, lost income, or non-medical costs that might occur from being in this research study.

If I have questions or concerns about this research study, whom can I call?
You will receive a copy of this consent form. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, primary care provider, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may ask your questions to _____ at phone _____.

You can contact the local Institutional Review Board at _____ for further information about your rights as a research subject.

Confidentiality
Your consent to be in this study includes consent for the GRADE researchers to review your health records as may be needed for the purposes of this study. Your consent also gives GRADE researchers permission to collect study information (data) related to this study and to use it for research purposes. Your consent also includes permission for the sponsor of this study (NIH) to review your study records.

Information from your medical records and information obtained about you during the GRADE study will be sent to the GRADE central coordinating center at The George Washington University for statistical analysis. No personal information that directly identifies you will be included with this data. Personal information is information such as your name that directly identifies you. Instead, you will be assigned a unique study code. The key to the code, linking it to you, will be kept in a locked file here at *(**INSERT NAME OF STUDY SITE**)*. Only *(**INSERT NAME OF PI AND HIS/HER STUDY STAFF AT STUDY SITE**)* will have access to the key to the code. Research records will be stored securely. After the study is completed, the study data may be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever this information is used.

Your study data and information from your medical records may be reviewed for safety monitoring purposes by pharmacists and nurses at the GRADE Drug Distribution Center or by the GRADE safety monitor. Your study data may be shared with companies that are donating the study medications for purposes of reporting safety information to the Food and Drug Administration (FDA). As described above, no personal information that directly identifies you will be included with any data or medical information reviewed by the Drug Distribution Center, the GRADE safety monitor, drug companies, or the FDA.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, GRADE researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give

information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether at the federal, state, or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others, if you wish.

There are some rare exceptions to the protection offered by the Certificate of Confidentiality. GRADE researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

GRADE researchers will consider your records private. Rarely, representatives of the U.S. Department of Health and Human Services (DHHS) or GRADE may review or request a copy of your study records. If this happens, these requests will be honored. Also employees of the *(**INSTITUTION'S NAME**)* _____or its agents could be allowed to see your study records to make sure that the study is being done properly.

A description of this clinical trial will be available on www.ClinicalTrials.gov. as required by the U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this site at any time.
The results of this study may be published for scientific purposes. These results could include laboratory tests. By signing this form, you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

Informed Consent

Study Doctor or Person Obtaining Consent	Date/Time

Signature of Subject:
I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date/Time

16.1.2 Phase 2 Template Informed Consent Version 1.7 (no EDS)

Template Informed Consent - Phase 2
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)
PRINCIPAL INVESTIGATOR:
SITE PRINCIPAL INVESTIGATOR:
DESCRIPTION OF PARTICIPANT POPULATION: Adults with type 2 diabetes
(Consent for GRADE Clinical Trial)

About this consent form

Please read this form carefully. It tells you important information about a research study called Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study or GRADE. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "participants." This term will be used throughout this consent form.
If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

The GRADE Study is a 7-year clinical trial designed to compare the effects of combining each of 4 different medications that are currently used to treat type 2 diabetes with a drug called metformin in individuals who have had type 2 diabetes for less than 10 years.

The medication combinations are all commonly used, but studies comparing each of these drugs in combination with metformin over a number of years have not been done. The GRADE study has been designed to compare how well each of these 4 drugs work (in combination with metformin) in controlling type 2 diabetes and in addition to examine any other benefits and potential side effects of the medications. All medications and the medication combinations used in the GRADE study have been approved by the U.S. Food and Drug Administration (FDA).

The GRADE trial is a multicenter study and we expect to enroll a total of about 5000 people with type 2 diabetes within the United States. We expect to enroll about 150 participants ***(OR IF >150 INSERT LOCAL INSTITUTION TARGET NUMBER)*** at (***INSERT LOCAL INSTITUTION NAME***).

You have already completed Phase 1 of the GRADE study, called the screening and run-in phase. During Phase 1, you were found to be eligible for the GRADE study.

This consent form focuses on **Phase 2** of the GRADE clinical trial, the long-term treatment and follow-up study. It describes in detail what will happen during the clinical trial.

By signing this consent, you are giving your permission to be entered into Phase 2 of the GRADE clinical trial. You will be asked to participate in the study up to its planned end in 2021. The GRADE study is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which is a branch of the National Institutes of Health (NIH). NIDDK is providing funding and other support to carry out the study. The National Heart, Lung, and Blood Institute (NHLBI) is providing funding for the electrocardiogram (ECG) tests to measure

the electrical activity of the heart. Medications used in the GRADE study are being donated by the following companies: Bristol-Myers Squibb, Merck, Novo Nordisk, and Sanofi. Roche Diagnostics will donate blood sugar monitors and strips. BD Medical is providing insulin starter kits and the needles to be used for insulin injections. None of the companies has had any part in designing or carrying out the study. The Centers for Disease Control and Prevention (CDC) is providing financial support for the economic analysis. The National Diabetes Education Program (NDEP) is donating copies of the booklet, *4 Steps to Control Your Diabetes for Life,* to the study.

How long will I take part in this research study?

If you enroll in the GRADE clinical trial, you will be asked to come for visits every three months until the end of study follow-up that is projected to be reached in 2021. So, depending on when you enroll, you will have as few as about 16 visits or as many as about 28 visits to your GRADE clinical center during the entire study. Most visits will take about an hour but once per year you will have an "annual" visit that will take about 3-4 hours. We may occasionally ask you to come in for an extra visit to re-check a blood test result or to adjust your medications. These extra visits should take an hour or less.

What will happen in this research study?

GRADE Clinical Trial

You will continue to take metformin. When your eligibility to participate has been established you will attend a baseline (or randomization) visit at which time you will start to take a second diabetes medication that will be assigned at random or by chance, like a flip of a coin. **Neither you, nor your study team will select the second medication that will be assigned to you**. The second medication will be one of four possible medications which will be described later on in this document.

You will be asked to come to the study clinic for a visit every 3 months until 2021. The GRADE staff will be available by phone to talk with you in between visits. Most of these every 3-month visits ("quarterly visits") will take about an hour. Once per year, on about the anniversary of your baseline visit, you will have a longer "annual visit" that will take about 3-4 hours. At each quarterly and annual visit, one of the blood tests will be a hemoglobin A1c test (called a HbA1c which measures your average level of blood sugar over the past 3 months). If your HbA1c is higher than 9%, which means that your blood sugar levels are very high, you will be asked to come to the GRADE clinic for a repeat test 3 to 6 weeks after the initial test. There may be additional or interim visits scheduled if we think that you would benefit from additional monitoring.

If you enroll in this study, the study medical team will treat your diabetes according to the GRADE protocol, and provide all study medications at no cost to you. You and your primary health care provider are still responsible for other parts of your care, including general preventive measures such as treating high blood pressure and elevated cholesterol levels, if you have those conditions, and giving vaccinations and providing foot care and eye care. The results of some of the tests done by the GRADE study will be shared with your regular health care provider (for example, blood pressure and cholesterol levels), which should help them provide you with care.

Baseline Randomization visit

Your first visit in Phase 2 of the GRADE clinical trial is called the baseline randomization visit. Prior to the visit we will check the results of your blood tests done at your last run-in visit to make sure that you are eligible for the GRADE clinical trial. We will also assess how many metformin pills you have taken during run-in. You will need to bring all unused study medication with you to the visit. If you are a woman of childbearing age, we will

ask you for a urine sample to test for pregnancy before the randomization process starts. If you are pregnant or planning a pregnancy during the course of the study, you cannot be in the study.

The baseline randomization visit will take about 5 hours to complete. We will ask you to be "fasting" (no food for 8 hours; you may drink water) on the day of your visit. Please take your usual morning medications (except for your diabetes medications) with a small amount of water. Do not take your diabetes medications on the morning of the visit. We will provide visit instructions and will remind you about your appointment either by phone, email, or mail.

We will collect blood and urine samples. The blood samples (about 13 teaspoons) will be collected to measure lipids (blood fats including cholesterol), sugar, insulin (the hormone in your body that controls glucose levels), and C-peptide (a protein that is produced by your body and tells us how much insulin your body is making). Blood and urine samples will be collected for long-term storage and future analyses. The urine sample will be used to measure albumin (a type of protein) and creatinine (a waste product) to see how well your kidneys are working.

During this visit, we will perform an oral glucose tolerance test (OGTT). The OGTT measures your blood glucose levels in response to a sweet drink and measures your body's ability to make insulin. It requires frequent blood sampling (5 times) over a period of 2 hours. You must be fasting for at least 8 hours before this test, which will be started before 10:30 AM.

We will ask you to drink a flavored sweet drink and we will check blood tests before and afterwards to see your body's response. At the start of the test we will place an IV (intravenous catheter) in a vein in your arm or hand. An IV is a small plastic catheter inserted into a vein that will stay in your vein during the 2-hour test so that we can draw several blood samples without doing a needle stick each time. When the test is done we will remove the IV from your vein.

You will have a brief physical exam at your baseline randomization visit. Your evaluation will include blood pressure, electrocardiogram (ECG), height, weight, waist and hip measurement, and a foot exam, unless any of those measurements were completed during your final run-in visit. During the foot exam we will test your reflexes and do other simple measurements to assess nerve function in your feet. These include using a soft filament on your foot to see whether or not you can feel it and test light touch sensation. The filament is a soft flexible piece of nylon, like a bit of fishing line. It does not hurt, and does not puncture the skin. We will also use a tuning fork to test if you can feel vibration on your big toe. This feels like a slight buzzing sensation and is not painful. We will ask you some questions about your past medical history. We will measure your waist and hips with a tape measure. You should wear loose-fitting comfortable clothing. You will have an ECG, a heart tracing, to measure the electrical activity of your heart.

We will ask you to complete about 6 brief questionnaires. Two of these questionnaires ask about your quality of life and one asks about symptoms you may be having. Another will give us information about costs of caring for diabetes. If not completed at your final run-in visit, we will test your memory with standard testing. The memory testing will require about 20-30 minutes to complete.

Medication assignment

You will be assigned a second diabetes medication at the baseline randomization visit. As stated earlier, **neither you, nor your study team will be able to select the second medication that will be assigned to you.** The second medication (one of 4 second medications used in this study) will be assigned by chance, like a flip

of a coin. It is therefore important that you have considered and are willing to accept an assignment to any one of the four medications. That includes being willing to take one of the two diabetes medications that are given by injection. In this case, you must be willing to give yourself medication by injection daily in order to take part in the study.

As long as your blood sugar levels remain under acceptable control, you will take the assigned medication along with your metformin for the duration of the study. If your blood sugar control worsens, once per day insulin therapy will be started for the three groups that weren't assigned initially to insulin. Insulin therapy will be further increased, with more than once per day injections, if once per day insulin doesn't adequately control your diabetes. We will provide you with the study medication at no charge, and provide instructions for taking it. Each of the 4 possible medications that will be added to your metformin at the baseline randomization visit are commonly used to treat diabetes. They are glimepiride, sitagliptin, liraglutide, and glargine. Glargine and liraglutide are taken by injection once per day. Glimepiride and sitagliptin are taken by mouth as a pill once or twice daily. If you are assigned to take glargine or glimepiride, we will give you a blood glucose meter, testing supplies and instructions on testing your blood sugar by fingerstick (or sticking another site like your arm) at home. The doses of these two medications will be adjusted based on your home blood sugar test results. The other two medications, liraglutide and sitagliptin are not adjusted based on blood sugar results.

We will teach you how to take the medication, when to take the medication, how to store the medication, and common side effects and risks of the medication. If you are assigned to glargine or liraglutide we will teach you how to give an injection and have you demonstrate how it is done before the end of the appointment. If it is later determined that you need to add insulin to your treatment regimen in order to maintain acceptable control, we will also teach you how to give yourself an injection.

Quarterly Visits

You will be asked to come to the GRADE clinical center for routine visits every 3 months. There will be 4 visits a year. Each year there are 3 quarterly visits and one annual visit from the date that you entered the study. The scheduled quarterly visits are listed below.

Year 1 at 3, 6, and 9 months after your randomization visit
Year 2 at 15, 18 and 21 months after your randomization visit
Year 3 at 27, 30 and 33 months after your randomization visit
Year 4 at 39, 42 and 45 months after your randomization visit
Year 5 at 51, 54 and 57 months after your randomization visit
Year 6 at 63, 66 and 69 months after your randomization visit
Year 7 at 75, 78 and 81 months after your randomization visit

If you were enrolled in the first year of the study, 2013, you may be asked to complete two more quarterly visits at 84 and 87 months (after your randomization visit) until the study ends in 2021.

At each quarterly visit the GRADE staff will talk with you about the medication you are taking, review your blood sugar levels if needed, give you a new supply of study medication, review any side effects or problems that you are having from the medication, measure your weight and blood pressure, review any other medications you are taking, and ask you some questions about your medical history. You will have a blood sample taken to check your average glucose control over the past 3 months (HbA1c test). This is about ½ teaspoon of blood. Twice per year, we will ask you for a urine sample to check your kidney function. Twice

during the study we will do a blood test for a vitamin B12 level. This may require about ½ teaspoon of blood if done at a semi-annual visit. If done at an annual visit no additional blood is needed. If you are using a glucose meter we will review the fingerstick readings that are recorded in your meter or log book. The quarterly visits will take about one hour to 90 minutes.

It is important that you bring your unused medication with you to each study visit.

Annual visits
You will have a scheduled annual visit each year that you are in the GRADE study. We will ask you to be fasting (no food or drinks except for water for 8 hours) before the visit. Please take your usual morning medications (except for your diabetes medications) with a small amount of water. Do not take your diabetes medications on the morning of the visit if you are having an OGTT. We will ask you to arrive at the appointment by 9:30 AM or earlier. The annual visits that include an OGTT will take about 4 hours each. Annual visits without an OGTT will be about 3 hours each. Your study team will inform you prior to the visit if you will be receiving an OGTT. The schedule of annual visits is listed below.

Annual fasting visits
- Year 1 at 12 months after randomization
- Year 2 at 24 months after randomization
- Year 3 at 36 months after randomization
- Year 4 at 48 months after randomization
- Year 5 at 60 months after randomization
- Year 6 at 72 months after randomization
- Year 7 at 84 months after randomization

Because special tests are conducted at these annual visits, you should fast for 8 hours before the visit.

At each annual visit the GRADE staff will talk with you about medication taking, review your blood sugar levels if needed, give you a new supply of study medication and collect any study medication you have returned, review any side effects or problems that you are having from the medication, examine your feet, measure your weight, blood pressure, waist and hips, review any other medications you are taking, and ask you some questions about your medical history. We will ask you to complete the same brief questionnaires that were completed during the randomization visit and were described above.

You will have blood samples collected which include a test to check your average glucose control over the past 3 months (HbA1c), and a test to check your kidney function (creatinine) at each annual visit. Lipids (fats in your blood such as cholesterol) will be tested at some of the annual visits. Your blood level of vitamin B12 will be measured at your next semi-annual or annual visit, whichever comes first, after this is started in about April, 2017, and again at your year 4 annual visit. Your vitamin B12 results will be provided to you and your primary care physician (PCP). We will tell you if the result is in the normal or abnormal range. We are measuring vitamin B12 levels because long-time use of metformin may cause vitamin B12 levels to be low. Low vitamin B12 levels can usually be easily treated with a daily vitamin pill. The GRADE study will not provide

the vitamin as part of the study but will provide you with information about B12 supplements and where to purchase them or will provide a prescription for you if you prefer. If your vitamin B12 level is considered to be very low, we will repeat the test in about 6 months to check that the vitamin pill is working.

In addition, we will perform the same oral glucose tolerance test (OGTT) that was performed at the baseline randomization visit at some annual visits (years 1, 3 and 5). If an OGTT is performed, an IV catheter will be placed to limit the number of "sticks" necessary to obtain the blood samples. We will also ask you for a urine sample to check your kidney function every year. If you are using a glucose meter we will review the fingerstick readings. In addition, 4 tubes of blood will be collected for long-term storage and future analyses. In total, all of the blood tests performed at the annual visit will add up to a maximum of 200 cc (or 13 tablespoons) of blood. Rarely, a tube of blood may be damaged or lost during preparation or shipment. If this happens, we may ask you for an extra tube of blood at a later visit.

The electrocardiogram (ECG) will be done at baseline and at some annual visits to measure the electrical activity of your heart.

Long-term Follow-up

GRADE is a long-term study to look at the effectiveness of the 4 drugs (plus metformin) used in the study. This study is planned to end in 2021. Each participant's long-term follow-up information is important to the study. We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may prove to be ineffective. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels, and has the most favorable long-term outcomes, every participant randomized into the study is equally important. It is important for study participants to attend all quarterly and annual study visits until the end of the study even if they are not taking some or all of their study-assigned medications, or if you are taking other diabetes medications prescribed by your care provider.

We realize there may be circumstances that prevent you from attending all of your study visits at the clinic. If that happens, the study staff may arrange for a phone call or a visit to your home to perform some of the study visit at your convenience. In addition, you may be asked to collect a small blood sample in your home from your finger. If you are willing to collect the sample, we would mail a collection kit to you and review the details of the procedure with you to make sure you understand how to collect the sample, and to allow you to ask questions. The sample will be mailed to the GRADE laboratory by you and the GRADE study will cover the postage. We hope that when you are able you will return to the clinic to resume your usual study visits. GRADE study staff will ask your permission to get copies of your medical records if you are hospitalized during the study. Review of the records will be used to determine the cause of the hospitalization.

Monitoring Your Blood Sugar and Changes to Your Diabetes Medications

The effectiveness of each diabetes treatment will be measured by HbA1c. HbA1c is a blood test which measures your average level of blood sugar over the previous 3 months. After your first 6 months in the study, an HbA1c level that is above 7.5% for two consecutive visits will require that additional medication be added. However, if your HbA1c level is >9% during the first 6 months you are in the study, we may add another medication sooner.

If you were randomly assigned to the glargine insulin (a long-acting insulin) treatment group and your HbA1c result goes above 7.5% for two consecutive tests despite dose adjustments, we will add an injection of rapid-acting insulin in addition to your long-acting glargine insulin and your metformin. If you are randomly

assigned to the other medication groups (glimepiride, sitagliptin or liraglutide) and your HbA1c goes above 7.5% for two consecutive tests, you will continue the metformin and your second randomly assigned diabetes medication, and we will ask you to start taking once per day glargine insulin. If your HbA1c stays above 7.5% on these 3 medications we will ask you to add a second type of insulin, which is rapid-acting. When you add the rapid-acting insulin we will ask you to stop the 2nd diabetes medication that was assigned at randomization. You will continue to take metformin and 2 types of insulin.

At each study visit the study staff will monitor your lab test results, talk with you about any side effects you are having and will adjust medication doses as needed. If the side effects are frequent or severe we will decrease or discontinue the study medication. If at any time during the study, your HbA1c level goes above 9%, we will ask you to come back for a repeat measurement within 3 to 6 weeks instead of the usual 3 months between visits.

If the study medications fail to lower your glucose levels to an acceptable range, we will reach out to your own care provider to discuss adding non-study medications. Any additional medications prescribed by your care provider would be billed to you or your insurance and would not be provided by the study.

What are the risks and possible discomforts from being in this research study?

There is a minor risk of infection at the site of the needle stick for blood drawing or intravenous (IV) insertion. This occurs in less than 1 in 1,000 people. The risk is minimized by following standard clinical practices such as cleaning the skin before the needle stick, and washing hands prior to blood collection. In some cases a person may faint or become sick to the stomach at the sight of a needle or when blood is drawn. In about 1 in 4 people, there may be some discomfort or bruising at the site of the needlestick. The GRADE staff who conduct these procedures have special training and experience in drawing blood and placing IVs. This should help keep these risks at the lowest possible level.

If the blood tests done in GRADE show abnormal results, this may be stressful to you. However, studies have shown that the sooner health problems are found and treated, the better the outcome. In addition, many of the problems identified by the GRADE staff might be easily treated. For example, we may find an abnormal level of fats (such as cholesterol) in your blood that, once identified, can be treated by changing your diet and/or having your own physician prescribe cholesterol-lowering medications.

There is a slight amount of pain associated with checking blood sugar levels using fingersticks. There is also a very low risk of infection at the site of the fingerstick. The GRADE staff will help you find the best ways and places to check your blood sugar.

There is a very slight amount of pain associated with the injections of the study medications (long-acting and rapid-acting insulins and liraglutide) into the fatty tissue in your abdomen, arms or legs. The GRADE staff will help you find the best place to inject to keep the discomfort as minimal as possible. Do not share the pen devices which are used to administer the injected medications or the pen needles with others as it could cause transmission of infection like hepatitis or HIV.

Some people may get slightly nauseated or get an upset stomach from the glucose (sugar) drink given during the OGTT. These symptoms are rare and disappear within 15 to 30 minutes.
The FDA has approved the use of all the medications used in the GRADE study for treating diabetes in adults. However, there are risks associated with each medication that you should know. For example, allergic reactions may occur. Any medication may be associated with an allergic reaction. Although the

medications studied in GRADE are only rarely associated with an allergic reaction (itching, rash, hives, or difficulty breathing for example), it may still occur. If you develop any symptoms of an allergic reaction while you are taking the study medication, you should stop the medication and contact the study staff as soon as possible.

According to most treatment guidelines, younger people, for example less than 65 years of age, should aim for HbA1c less than 7% in order to decrease their risk of developing diabetes complications. Higher levels of HbA1c, such as 7.5% or higher, may be appropriate for older people with longer duration diabetes who have other diseases, such as heart disease. A recent large study showed that patients treated to achieve near-normal blood sugar levels (an average HbA1c level of 6.4%) had a higher risk of death, including death from heart attacks and strokes. The risk of having one of these events was higher in patients with a prior history of heart disease and with diabetes for longer than 10 years. Several other studies with persons who were more similar to those who will be recruited in GRADE have not shown any increased risk for heart attacks, stroke, or deaths when their HbA1c levels were reduced to an average of 6.4%.

In order to reduce possible increased risk, GRADE will include lower risk persons who have had diabetes for less than 10 years. In addition, GRADE is excluding persons who are very ill or who have had in the previous year a heart attack, stroke or a surgical procedure to prevent or treat such diseases. It is unknown whether the GRADE protocol will increase the risk for heart attacks and strokes in some persons whose HbA1c level is decreased to less than 6.8%.

The effects of some diabetes medications on how an unborn baby grows and develops are not known. None of the medications in the study are known to be associated with specific birth defects. In fact, three of the medications are commonly used in diabetic patients during pregnancy. However, because we do not know for certain the effects of some of the diabetes medications used in the study on a baby before it is born, it is important that you not become pregnant while you are taking study medications. We will do a urine pregnancy test at the screening and randomization visit if you are a woman of childbearing age. We may also ask you to provide a urine sample for pregnancy testing at other times during the study. If you suspect that you are pregnant or are concerned you may have become pregnant while taking the study medications, you should advise the GRADE study team immediately. If you become pregnant you will be advised to stop taking the study's medications and switch to medications specifically prescribed by your own health care provider during the pregnancy. We will recommend that your primary care provider find a doctor for you who specializes in taking care of pregnant women who have diabetes.

Any time that a diabetes medication is started, stopped, or changed, there is a risk that you may have high blood sugar levels (hyperglycemia) or low blood sugar levels (hypoglycemia).
The symptoms of high blood sugar levels include thirst and increased frequency of urination, including the need to urinate more often than usual during sleeping hours. If you start to go to the bathroom more often than usual, you may need to check your blood sugar levels more often.

The early symptoms of low blood sugar levels include sweating, fatigue, nervousness, shakiness, and rapid heartbeat. If a person drinks or eats sugar-containing food right away, the symptoms of low blood sugar will stop, usually within 10 minutes. Most cases of low blood sugar, if treated rapidly and appropriately, cause only minimal symptoms and no harm. However, if low blood sugar episodes are not detected and treated quickly, they can become more severe, causing confusion. In the most severe cases, low blood sugar can cause unconsciousness and seizures. If you have any of the early warning symptoms, you will need to check blood sugar levels to be sure the symptoms are caused by low blood sugar. If you cannot

check your fingerstick blood sugar for some reason, you should treat yourself with a sugary snack as if your blood sugar is low. As part of the GRADE diabetes education, we will teach you about the signs and symptoms of high and low blood sugar levels, how to prevent them and what to do about them.

We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may prove to be ineffective. If this happens, long-term treatment with insulin or a more intensive insulin regimen (more than 1 injection of insulin daily) may be required. However, we cannot tell beforehand which participants will be able to tolerate the study medications and which will not; or which participants will be able to successfully control their blood sugar levels with the assigned medications and which will not. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels and has the most favorable long-term outcomes, every participant randomized into the study is equally important. Even if you are no longer taking your originally assigned medications, it is just as important for us to know your long-term outcomes as it is for any other participant. That is why it is important for every study participant to attend all study visits even if you are not taking some or all of the study-assigned medications.

The actions, side effects, and risks of metformin, as well as of each of the 4 secondary medications and the fast acting insulin used in this study are described below.

GRADE Trial Medications, Risks and Side Effects

Hypoglycemia:

Medications used to treat high blood sugar in persons with diabetes can sometimes cause blood sugar to become too low (hypoglycemia). Hypgolycemia can result from diabetes medications or from a change in your diet, activity level, or exercise routine. Symptoms of hypoglycemia can range from mild to severe. Mild to moderate symptoms of hypoglycemia include increased hunger, anxiety, shaking, or feeling dizzy or light-headed. More severe symptoms can include confusion or loss of consciousness and may require emergency treatment or hospitalization. Severe episodes of hypoglycemia may cause brain damage, coma or death. Your study team will teach you how to recognize and treat hypoglycemia.

Metformin

If you have advanced to the clinical trial phase informed consent, you are taking metformin and tolerating at least 1000 mg per day. Metformin is used to help control blood sugar in patients with type 2 diabetes. This medication decreases the amount of glucose absorbed from your diet and made by your liver. It also makes the body more sensitive to insulin.

The most common side effects of metformin include nausea, headaches, diarrhea, vomiting, bloating, excessive gas, loss of appetite, and an unpleasant taste in the mouth. These are more common when the medication is first started and lessen or disappear over time. About 10 out of 100 people using metformin may experience these symptoms to some degree. However, these side effects are rarely severe enough to result in needing to stop the medication. Other side effects include lower-than-normal levels of vitamin B12 in the blood, which may rarely lead to anemia (low blood count). Numbness and tingling in the extremities can also be caused by low levels of vitamin B12. Low vitamin B12 levels can generally be treated with a vitamin B12 supplement tablet. Hypoglycemia (low blood sugar) rarely occurs when metformin is taken by itself, but it can occur when metformin is combined with some other diabetes medications.

In very rare instances (fewer than 3 in 100,000), a condition called lactic acidosis has been reported in patients taking metformin. When lactic acidosis occurs it is usually in persons who have other severe medical problems, such as kidney disease, liver disease, or severe circulatory problems. We will check blood tests and ask about symptoms to make sure it is safe for you to take this medication. In addition, you must notify the GRADE study team if you experience any severe disease that results in hospitalization since, for safety, we will want to stop metformin during the illness. If ignored or untreated, lactic acidosis can lead to serious health problems that can progress to coma or death.

You should talk to the study team before you undergo any surgery, X-ray procedures, or CT scans that use any type of injection (such as a dye that makes X-rays easier to see) as you will need to stop your metformin during the time of the procedure. Alcohol should not be used in excess while taking metformin. Inform your study doctor if you now have (or develop during the course of the trial) kidney or liver disease, heart failure, or severe infections.

Glimepiride (Amaryl)

Glimepiride is in a class of type 2 diabetes medications called sulfonylureas. This class of drugs stimulates your pancreas to produce more insulin and makes your body more sensitive to insulin. Insulin is the hormone naturally made by your pancreas which helps you to absorb glucose (sugar) into your muscles and tissues. Without enough insulin the glucose remains in your bloodstream causing your blood sugar levels to rise.

Glimepiride may cause low blood sugar (hypoglycemia) or weight gain. Other common side effects include upset stomach, nausea, dizziness, itching, and sensitivity to light. Rare complications include blood cell abnormalities including low platelet count with easy bruising and allergic reactions causing itching, rash, swelling, wheezing or shortness of breath. If you have low blood sugars when following your usual diet and activity plan, we will adjust your dose of this medication to be sure it is safe for you. You will need to check your fingerstick blood sugar levels in order to help your team adjust your doses. We will provide supplies and education for testing your blood sugar by fingerstick at home and teach you how to recognize and treat low blood sugar levels. Tell your study doctor if you now have (or develop during the trial) an inherited condition called G6PD disease, heart, liver or kidney disease or a disorder of the thyroid, adrenal or pituitary glands.

Sitagliptin (Januvia)

Sitagliptin is in a class of type 2 diabetes medications called dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 is an enzyme in your body that breaks down certain hormones in your body known as incretins. Sitagliptin inhibits DPP-4 and slows the breakdown of incretin hormones in the body. When the body's blood sugar rises in response to a meal, Sitagliptin helps to increase the body's production of insulin and decreases the amount of glucose (sugar) produced by the liver.

Sitagliptin is generally well-tolerated. Because incretin hormones are more active in response to higher blood sugar levels (and are less active in response to low blood sugar), the risk of dangerously low blood sugar (hypoglycemia) is low with sitagliptin. Sitagliptin has been associated with more frequent infections such as bladder infections (urinary tract infection), cold-like symptoms (upper respiratory infection), headache, diarrhea, inflammation and muscle or joint pains. It has also been associated, although very rarely, with pancreatitis (an inflammation of the pancreas), and rarely with painful skin blisters or sores. Symptoms of pancreatitis include severe abdominal pain, nausea, and vomiting. Tell your study doctor immediately if you experience any of these symptoms. If you have ever had pancreatitis, you are not eligible for the GRADE study. Similar drugs that work like Sitagliptin have been associated with heart failure in patients who have a prior history of heart disease. If you have shortness of breath, difficulty doing your usual daily activities, or

unexplained weight gain, tell your study doctor about these symptoms.

Liraglutide (Victoza)

Liraglutide is a form of natural hormone called Glucagon-like peptide (GLP-1). It is one drug in a class of type 2 diabetes medications called incretins. When the body's blood sugar rises in response to a meal, GLP-1 works by helping your pancreas to increase production of insulin. It also slows down the emptying of the stomach and decreases the amount of glucose (sugar) produced by the liver. Liraglutide is given by injection once daily. We will teach you how to give the injections and provide the supplies necessary. Liraglutide (Victoza®) is now approved by the FDA to reduce the risk of major adverse cardiovascular (CV) events which include CV death, non-fatal heart attack, or non-fatal stroke in adults with type 2 diabetes mellitus and known cardiovascular disease.

Common side effects of liraglutide include nausea, vomiting, diarrhea, decreased appetite and stomach discomfort, which may affect from 15 to 40% of people. Liraglutide may cause low blood sugar (hypoglycemia). These side effects are often temporary and disappear or decrease with continued treatment. In addition, by starting with a smaller dose and increasing it, the risk for these side effects can be reduced. An increased risk of pancreatitis has also been reported. If you develop nausea, vomiting or have abdominal pain that last for more than a few hours, you will be advised to hold the liraglutide and call the study team. A recent clinical trial reported an increased risk of gallbladder inflammation (cholecystitis) and/or gallstones in the gallbladder (cholelithiasis) in those taking liraglutide when compared to those who were assigned to a placebo. Contact your study doctor if you develop sudden abdominal, shoulder or upper back pain, fever, chills or yellowing of the skin. High levels of calcitonin, a substance in your blood that is associated with a rare form of thyroid cancer, have been reported. You are not eligible for the GRADE study if you have had pancreatitis or medullary thyroid cancer.

Glargine (Lantus) Insulin

Glargine is a long-acting insulin that is administered by injection once per day. Insulin is a hormone in your body that helps you absorb sugar and other nutrients into your muscles and other body tissues and cells. It also decreases the amount of glucose produced by the liver.

We will teach you how to give the injections and provide the supplies necessary. We will provide supplies and education for testing your blood sugar by fingerstick at home and teach you how to adjust your dose based on the blood sugar results. If you are assigned to glargine, the dose of glargine will be adjusted based on your self-tested blood sugar levels and the hemoglobin A1c blood tests performed every 3 months so that you can achieve the study targets with minimal hypoglycemia.

Side effects of glargine include low blood sugar (hypoglycemia) and weight gain. Other side effects may include itching, redness, or swelling at the injection site, allergic reaction and low potassium. Tell your study team if any of these symptoms are severe or persistent.

Aspart (Novolog) Insulin

Some participants in the study who do not achieve the goal blood sugar control with their assigned study medications may take aspart insulin in addition to glargine. Aspart is a rapid-acting insulin that is given by injection to help control blood sugar levels when other medications don't achieve the study goals. Although aspart may be given up to 3 times daily, most participants who need the rapid-acting insulin added will only take 1 injection per day. The dose of aspart will be adjusted based on the results of self-monitoring of fingerstick blood sugar testing. We will provide supplies and education for testing your blood sugar by

fingerstick at home and teach you how to recognize and treat low blood sugar levels.

Side effects of aspart insulin include low blood sugar. Other side effects may include weight gain, or itching, redness or swelling at the injection site. Tell your study team if any of these symptoms are severe or persistent.

What are the possible benefits from being in this research study?

If you decide to take part in this study, there is no guarantee that your health will improve. We will follow your diabetes closely. You will receive education about diabetes and how to take care of it. The GRADE clinic team will help you manage your diabetes at no cost to you. You will receive tests and procedures to monitor your health at no charge and the results will be shared with you and, with your permission, with your primary care provider who may use them to help with your medical care. In addition, you will receive the following at no charge:

- Glucose testing equipment as needed at no cost to you
- Diabetes medication at no cost
- Care from a team of diabetes experts at no cost

Use of Stored Samples during and after Study End

With your permission, we would also like to store blood and urine samples for possible use during GRADE or after GRADE is over. Your samples will be stored indefinitely. Your blood and urine samples could be used to help health researchers learn more about what causes diabetes and how to treat it better. They could also help them learn more about diabetes, its complications (such as eye, nerve, and kidney damage), and other conditions for which people with diabetes may be at increased risk.

Your blood and urine samples will be stored at the GRADE central laboratory during the study and some of the extra "storage" samples at a place that is maintained for research purposes by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (sample repository). The samples stored at the sample repository will not have your name or any other identifying information that could directly link them with you. However, even with this confidentiality measure, there is no absolute guarantee that your identity will be protected.

As long as GRADE continues, it is possible for you to change your mind about having your blood and urine samples stored for future use. When GRADE is over, your remaining samples will be stored under the control and protection of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Researchers will not be able to use your samples without the permission of the NIDDK. You should understand that you can still be in this study without permitting the storage of your samples for further testing after GRADE is over.

Genetic Testing

We will ask your permission to allow us to study your DNA to understand how genes may affect the immune system, diabetes, complications associated with diabetes, or the response to the study medications. We will not provide the results of your testing to you or anyone else. Although we will try very hard to keep any information about your testing private, there is a very small possibility that someone else could learn about your testing. Some people worry that genetic information could be used to discriminate against them. To prevent misuse, the researchers will take special precautions to protect your information. The data will be collected and stored with a code number only. We have obtained a Certificate of Confidentiality from the

National Institutes of Health to protect the information we obtain about you. In addition, a law was passed in 2008 by the Federal Government that prohibits many forms of discrimination based on genetic information.

With your permission, DNA samples, which will be used to study the genetic (inherited) basis of diabetes, its complications, and response to therapy, will also be stored in the sample repository.

What other treatments or procedures are available for my condition?
You do not have to take part in this study to be treated for type 2 diabetes. Other treatments or procedures that are available to treat diabetes include receiving care for your diabetes from your primary care provider or other health care provider rather than the GRADE study. You are not obliged to take part in the GRADE study to receive treatment for diabetes.

Can I still get medical care within (*INSERT NAME OF INSTITUTION*) if I don't take part in this research study, or if I stop taking part?
Yes. Your decision will not change the medical care you get within (***INSERT NAME OF INSTITUTION***) now or in the future. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to join now, you may change your mind and stop participating later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?
Your choice to be in this study is completely voluntary. At any time you may choose to stop taking your study medications or to stop attending your study visits. If you wish to do so, you should tell us. We will make sure that you stop the study medications safely and will provide you with instructions about follow-up care.

What if I have difficulty with my study medication?
Your study doctor may choose to discontinue your study treatment at any time if it is felt that continuing treatment may hurt you. If this happens, we will tell you why. We will also help arrange other care for you, if needed. You will be told of any new findings that affect your being in this study.

Will I be paid to take part in this research study?
You will be provided an honorarium of $100 per year during your participation in the GRADE study. The honorarium will be provided after the annual visit each year. We will also pay for local travel costs and provide parking vouchers and meal replacements if we ask you to fast for an appointment. By signing this consent you understand and agree that, if this research study results in the development of any product that can be sold, you will not receive a share of any money that is made.

What will I have to pay for if I take part in this research study?
There is no cost to you for being in this study. There will be no charge for procedures or medications required by the study.

What happens if I am injured as a result of taking part in this research study?
Taking part in this research study may hurt you (this was explained in the section called "Risks and Discomforts"). If you need to get medical care right away, you should go to the nearest emergency care

center. Be sure to explain that you are participating in a research study. If you do not need emergency care, you should contact your primary care provider. The GRADE investigators may also take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. You will be responsible for any costs not covered by your health insurance. GRADE and the clinical site you go to will not pay for your care. Likewise, GRADE and your clinical site will not pay you for pain, worry, lost income, or non-medical costs that might occur from being in this research study.

If I have questions or concerns about this research study, whom can I call?
You will receive a copy of this consent form. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, primary care provider, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may ask your questions to _____ at phone_____.

You can contact the local Institutional Review Board at _____ for further information about your rights as a research subject.

Confidentiality
Your consent to be in this study includes consent for the GRADE researchers and representatives of the sponsoring agency (NIDDK/NIH) to review your health records as may be needed for the purposes of this study. Your consent also gives GRADE researchers permission to collect study information (data) related to this study and to use it for research purposes. Information from your medical records will be sent to the GRADE central coordinating center at The George Washington University for statistical analysis. No personal information that directly identifies you will be included with this data. Personal information is information such as your name that directly identifies you. Instead you will be assigned a unique study code. The key to the code, linking it to you, will be kept in a locked file here at *(**INSERT NAME OF STUDY SITE**)*. Only *(**INSERT NAME OF PI AND HIS/HER STUDY STAFF AT STUDY SITE**)* will have access to the key to the code. Research records will be stored securely. After the study is completed, your study data, without any personal identifying information, will be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever these data are used.

Your study data and information from your medical records may be reviewed for safety monitoring purposes by pharmacists and nurses at the GRADE Drug Distribution Center or by the GRADE safety monitor. Your study data may be shared with companies that are donating the study medications for purposes of reporting safety information to the Food and Drug Administration (FDA). As described above, no personal information that directly identifies you will be included with any data or medical information reviewed by the Drug Distribution Center, the GRADE safety monitor, drug companies, or the FDA.

In the event that the study team loses contact with you during the trial, they will contact your primary care doctor and/or consult your medical record to collect information about your medical condition.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, GRADE researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether

at the federal, state, or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others, if you wish.

There are some rare exceptions to the protection offered by the Certificate of Confidentiality. GRADE researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

GRADE researchers including representatives of NIH will consider your records private. Rarely, representatives of the U.S. Department of Health and Human Services (DHHS) or GRADE may review or request a copy of your study records. If this happens, these requests will be honored. Also employees of the ***(INSTITUTION'S NAME)*** _____or its agents could be allowed to see your study records to make sure that the study is being done properly.

A description of this clinical trial will be available on www.ClinicalTrials.gov. as required by the U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this site at any time.

The results of this study may be published for scientific purposes. These results could include laboratory tests. By signing this form you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

AUTHORIZATION INFORMATION:

Use of DNA samples:
Please indicate whether you are willing to provide a DNA sample to help us understand how genes may affect diabetes or related diseases. You can still be in the GRADE study even if you decide not to provide a DNA sample.

☐ Yes, I am willing to provide a DNA sample for use during this study ____ Initials
☐ No, I do not give permission to obtain or use a DNA sample during GRADE ____ Initials

Stored Samples:
Please indicate whether you are willing to allow blood and urine samples to be stored after GRADE is over, including DNA samples. These samples could be used to help researchers learn more about diabetes and its treatment. These samples could also be used to help them learn more about diabetes, its complications (such as eye, nerve, and kidney problems), and other conditions for which people with diabetes are at higher risk. You can still be in the GRADE study even if you decide not to have blood or urine samples stored once the GRADE study is over.

I give permission to have my blood and urine samples and/or DNA stored: (check one below)

☐ Yes, store my blood and urine samples including DNA _____ Initials
☐ Yes, store my blood and urine samples but not DNA _____ Initials
☐ Yes store my DNA, but not my blood or urine samples _____ Initials
☐ No, I do not give permission to have my blood, urine samples or DNA stored _____ Initials

Permission for Use of Social Security Number for Future Contact:
In the event that we have lost contact with you and cannot reach any of the individuals you have listed as contacts if we are having difficulty reaching you, we would like to have your permission to use your social

security number to assist in locating you. We would ask public services that assist in locating individuals for your address and contact information or ask state and/or federal agencies to check their survival reports. We will only use these services as a last resort if we are unable to locate you. You can still be in this study if you decide not to give us permission to use your social security number to help us contact you.

Please indicate whether you are willing to provide your social security number to help us locate you.
☐ Yes, I am willing to provide my social security number for use to locate me for the study. ____ Initials
☐ No, I do not give permission to use my social security number to locate me during the study ____ Initials

Informed Consent

Study Doctor or Person Obtaining Consent Date/Time

Signature of Subject:
I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject Date/Time

16.2 GRADE Sample Templates

16.2.1 Site Initiation Activities Checklist for Study Coordinators

GRADE

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

Site Initiation Activities Checklist for Study Coordinators to be completed for Site Certification

This is an internal checklist for use by Study Coordinators (SC) at clinical sites that covers the basic steps for initiating the GRADE study. This checklist will serve as documentation that the necessary regulatory and compliance documents have been completed and maintained. Email this checklist to the Coordinating Center and keep on file.

Item	Completed		Date		Initials
A. IRB Approvals					
1. Prepare IRB submission and submit to local IRB	☐	☐			
2. Receive approval from local IRB with appropriate GRADE Protocol version number and date reflected on documents	☐	☐			
3. Scan and send to CoC: a. Copy of IRB Submission and Approval Tracking Log b. Letter of IRB approval c. Informed consent form (ICF) with stamped IRB approval (include HIPAA authorization form if separate from ICF)	☐ ☐ ☐	☐ ☐ ☐			
B. Drug Distribution Center (DDC)					
1. Complete DDC Site Personnel & Address Form, on website 2. SC to review DDC manual & website user guide and practice on training site, then sign up for and obtain authorization for Drug Inventory Management System and Web Randomization	☐ ☐				
C. Central Biochemistry Laboratory (CBL)					
1. If urine pregnancy testing is performed by study staff, site is covered under institutional CLIA certificate or site has obtained a CLIA waiver. 2. Complete CBL Contact Information Form (email CoC for form)	☐				
D. Research Staff Requirements					
1. SC and Investigator sign and send to CoC or obtain: a. Duality Of Interest Form for all staff b. GRADE website username and password to access website	☐ ☐				
2. SC and Investigator complete NIH Education on (and file at clinical site): a. Protecting Human Subjects Training (e.g. CITI or equivalent training) b. Security Awareness Training (e.g. FISMA)	☐ ☐				
E. Recruitment and Site Management Plan					
1. Submit detailed Site Recruitment Plan to CoC 2. Submit detailed Site Management Plan to CoC 3. Submit Delegation of Responsibilities Log to CoC	☐ ☐ ☐				
F. Research Clinic Staff Requirements					
1. SC to review the following GRADE Documents: a. Protocol b. Manual of Procedures (MOP) c. Measurement and Assessment Procedural Manual (MAP) d. Drug Distribution Center Manual of Operations e. Biospecimen Collection and Processing Manual f. Neurocognitive Assessments Manual g. Quality of Well-Being Manual of Procedures h. ECG Manual of Procedures	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐				
2. SC to complete the Protocol Quiz (online or hardcopy)	☐				
3. SC certified for data entry in MIDAS	☐				
4. SC to complete ***Initial Staff Certification Checklist*** (for detailed instructions refer to the MAP)	☐				

These requirements are necessary for continuing participation in the study (If site includes Co-SCs or Co-PIs these requirements apply):

- Sites must provide copies of their renewal of IRB and informed consent approval annually.
- Research staff must update their Duality Of Interest Form annually.
- Sites must notify the CoC of any changes or additions to research staff as they occur.

Signature of Study Coordinator _____ **Date:** _____

16.2.2 Staff Certification Tracking Log

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

Staff Certification Tracking Log

This is an internal log for use by the Study Coordinator to track clinical research staff certification. This log will serve as documentation that the necessary certifications by clinical research staff at clinical sites have been completed. Study Coordinators should fill out the information in the header of the log and complete the rest of the log by inputting information regarding certified staff members. Study Coordinators should upload this log to the GRADE study website at study start up and are expected to continually update this log and provide it annually to the Coordinating Center. This log should also be maintained on file at the clinical site.

Name of Primary clinic certifier (Study Coordinator or designee)	Primary certifier phone no.	Primary certifier email	Position	Date *Initial Staff Certification Checklist* completed
				☐☐ month ☐☐ day ☐☐☐☐ year

If applicable:

Name of Secondary clinic certifier	Secondary certifier phone no.	Secondary certifier email	Position	Date *Initial Staff Certification Checklist* completed
				☐☐ month ☐☐ day ☐☐☐☐ year

Name of certified staff member	Staff phone no.	Staff email	Position	Date *Initial Staff Certification Checklist* completed
				☐☐ month ☐☐ day ☐☐☐☐ year
				☐☐ month ☐☐ day ☐☐☐☐ year
				☐☐ month ☐☐ day ☐☐☐☐ year
				☐☐ month ☐☐ day ☐☐☐☐ year
				☐☐ month ☐☐ day ☐☐☐☐ year

Reminder: Study Coordinators should send completed log to GRADE Coordinating Center at study start up and annually to inform the Coordinating Center of changes or additions.

17. APPENDIX A: GLOSSARY

THIS GLOSSARY IS PROVIDED AS A REFERENCE FOR THE CONVENIENCE OF THE GRADE STAFF. IT ALSO PROVIDES A LIST OF EXCLUSIONARY MEDICATIONS FOR REFERENCE DURING THE PRESCREENING AND SCREENING PERIOD. EXCLUSIONARY MEDICATIONS ARE MARKED WITH AN ASTERISK. MEDICATIONS SHOULD NOT BE CHANGED IN ORDER TO MAKE A PATIENT ELIGIBLE FOR PARTICIPATION; HOWEVER, IF A PATIENT'S MEDICATIONS CHANGE IN THE FUTURE, HE/SHE SHOULD CONTACT THE STUDY REGARDING HIS/HER ELIGIBILITY AT THAT TIME.

Alpha adrenergic blockers/vasodilators:
Doxazosin (Cardura)
Hydralazine
Minoxidil

Angiotensin Receptor Blockers (ARBs):
Azilsartan (Edarbi)
Irbesartan (Avapro)
Losartan, olmesartan (Benicar)
Telmisartan (Micardis)
Valsartan (Diovan)

Antihypertensive agents (if combination agents used, should be listed separately)
ACE-inhibitors:
Benazepril (Lotensin)
Captopril
Enalapril
Fosinopril
Lisinopril
Moexepril (Univasc)
Perindopril (Aceon)
Quinapril (Accupril)
Ramipril (Altace)
Trandalopril (Mavik)

Beta-adrenergic blockers:
Atenolol
Carvedilol
Labetolol
Metoprolol
Nadolol
Pindalol
Propranolol
Sotalol
Timolol

Calcium channel blockers:
Amlodipine (Norvasc)
Diltiazem (Cardizem, Tiazac)

Felodipine
Nicardipine
Nifedipine (Procardia, Adalat)
Nisoldipine (Sular)
Verapamil (Calan, Verelan)

Diabetes medications (if combination agents used, should be listed separately)
Note: all diabetes medications except for metformin are exclusionary within 6 months of screening.

***Alpha-glucosidase inhibitors**
Acarbose (Precose)
Miglitol (Glyset)

Biguanides
Metformin IR (Glucophage and others)
Metformin XR

***Dopamine agonists**
*Bromocriptine (Cycloset)

***DPP-4 inhibitors**
* Sitagliptin (Januvia)
* Saxagliptin (Onglyza)
* Linagliptin (Tradjenta)
* Alogliptin (Nesina)

***GLP-agonists**
* Exenatide (Byetta, Bydureon)
* Liraglutide (Victoza)

***Insulins**
* Glargine (Lantus)
* Detemir (Levemir)
* Lispro (Humalog)
* Aspart (Novolog)
* Glulisine (Apidra)
* NPH (Novolin, Lilly NPH)

***Sulfonylureas**
* Glipizide (Glucotrol and others)
* Glyburide (Micronase and others)
* Glimepiride (Amaryl and others)

***Thiazolidinediones**
* Pioglitazone (Actos and others)
* Rosiglitazone (Avandia)

***Bile acid binding resins**
*Colesevelam (Welchol)

Diuretics:
Hydrochlorthiazide
Dyazide
Dyrenium

Furosemide (Lasix)
Spironolactone (Aldactone)

Atypical antipsychotics potentially associated with hyperglycemia:
*Aripiprizole (Abilify)
*Clozapine (Clozaril)
*Olanzapine (Zyprexa, Symbyax)
*Quetiapine (Seroquel)
*Risperidone (Risperdal)

Common glucocorticoids (steroids for oral and injection use):
*Cortisol
*Cortisone
*Dexamethasone (Decadron)
*Methylprednisolone
*Methylprednisone
*Prednisone
*Hydrocortisone

Congestive heart failure (NYHA 3 or more):
Class III (Moderate) Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe) Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Diabetes definition for GRADE (from medical records or history): fasting plasma glucose level $\geq$ 126 mg/dl, 2 hr level after an oral glucose tolerance test $\geq$ 200 mg/dl, HbA1c $\geq$ 6.5% or diagnosis in medical records or by self-report.

MEN-2: Multiple endocrine neoplasia- 2. Rare inherited (familial disease) which includes tumors of the parathyroid, thyroid and adrenal glands.

Pancreatitis: a (usually very painful) inflammation of the pancreas that can be acute or chronic and is associated with an elevation of pancreatic enzymes (lipase and/or amylase).

Polycystic Ovary Syndrome: A syndrome in girls and women which is associated with ovarian cysts, obesity, hirsutism (increased facial hair), acne, irregular periods, and infertility

*Exclusionary Medications

18. APPENDIX B: PROCEDURES DURING THE COVID-19 PANDEMIC

This appendix outlines procedures for conduct of visits, providing diabetes care and medications, and collection of data during the COVID-19 pandemic. Sites should follow their local institution's guidelines for conduct of research.

18.1 Priorities during COVID-19

Since GRADE is responsible for each participant's diabetes care, supplying medications to participants is of utmost importance. Sites should utilize capillary collection kits so that HbA1c can be safely collected and monitored (see section 4.4.2 for additional information about capillary collection kits). Any data that can be collected over the phone or via mail should be completed whenever possible. See section 18.3 for more information about data collection during COVID-19.

As sites resume normal operations, participant safety is of high importance. Sites should only resume in-person activities when they are fully ready to do so.

18.1.1 Contacting Participants

A template letter is available to send to participants regarding site closure and contact information. In addition, a template phone script is available to inform participants about the change in operations. Site staff should modify these materials to match their current institutional guidance.

18.1.2 Supplying Medications

Sites must adhere to their local institution's restrictions and regulations when supplying medications to participants. Room-temperature medications should be mailed to participants. Cold-chain medications (including insulin and liraglutide) can be shipped using a cold pack or insulated box if allowed by their local institution. If shipping cold-chain medications is not allowed, other means must be used to supply participants with medication, such as meeting the participant at their car outside the site to bring them their medication, or using a courier service.

Study medications can be supplied to participants as long as the most recent eGFR result is from within the past 12 months. Outside (non-study) eGFR results can be used if available to determine whether it is safe to prescribe study medications. If study medication is dispensed when the most recent available eGFR result is more than 12 months ago, a Protocol and Operational Deviation (PROTDEV) form should be completed.

18.1.3 Prioritization of Study Assessments and Remote Data Collection

Refer to the *Prioritization of Assessments* in Figure 18.1 below and on the GRADE study website for information about assessments/data to prioritize and what can be collected for phone visits.

Figure 18.1: Prioritization of Assessments During the COVID-19 Pandemic

Assessments by Study Visit for Prioritization**

Quarterly/Semi-Annual Visit

LAB SPECIMENS	Priority for Completion	Phone Visits
HbA1c	1	✓
Safety labs: B12 as applicable – *only at semi-annual visits*	1	
Additional EDS sample (as applicable, at months 06, 18, 30 only)	2	
Urine pregnancy (if indicated – local lab)	1	
Urine sample for microalbumin:creatinine – *only at semi-annual visits*	2	
STUDY VISIT FORMS		
Quarterly Visit Form	1	✓
Medical History (Section A)	1	✓
Serious Adverse Events (Section B)	1	✓
Weight	1	
Metformin and Randomized Study Drug Adherence (Sections D and E)	1	✓
Study Medication Dose and Dispensation (Section F)	1	✓
Blood pressure	2	
Medical Care Utilization Outside the GRADE Study (Section G)	2	✓
CONMED Form	1	✓
PARTICIPANT QUESTIONNAIRES+		
Symptoms Form	1	✓
DTSQ (Non-EDS pts: month 06 only; EDS pts: months 06, 18, 30 only)	2	✓
EDSQ (as applicable, at months 06, 18, 30 only)	2	
OTHER ACTIVITIES		
Order and dispense metformin, randomized drug, and drug supplies*	1*	✓
Discuss insulin initiation with participants who met outcome but have not yet started glargine and/or Novolog	1	✓
Complete NONINIT or UPNONIN form, as appropriate	1	✓
Audio Recording (as applicable)¥	2¥	

** This table can be used as a guide to determine which assessments take priority at each type of visit. Every case is highly individualized. Please contact your GRADE protocol management representative to discuss.
+ If participant-completed questionnaires can be collected for phone visits, they must be sent to the participant to fill out and should not be collected over the phone
* For participants who complete visits remotely, see MOP Section 4.4.1.1 for guidance on continued medication dispensing
¥ Only if participant has consented to specific component (initiated with Protocol v1.6)

Annual Visit

LAB SPECIMENS	Priority for completion	Phone Visits
HbA1c	1	✓
Safety labs: serum creatinine and B12 as applicable	1	
Plasma/serum storage samples	2	
Urine pregnancy (if indicated – local lab)	1	
Urine for storage and albumin:creatinine	2	
Fasting lipids	2	
OGTT (0, 15, 30, 60, 90, 120-minute time points) *Note: 0 and 120 are the priority time points if venous access difficulty*	3	
STUDY VISIT FORMS		
Annual Visit Form	1	✓
Pregnancy (Section B)	1	✓
Weight	1	
Medical History (Section E)	1	✓
Serious Adverse Events (Section G)	1	✓
Metformin and Randomized Study Drug Adherence (Sections H and I)	1	✓
Study Medication Dose and Dispensation (Section J)	1	✓
Medical Care Utilization Outside the GRADE Study (Section M)	1	✓
Diabetes Education (Section O)	1	✓
Blood pressure	2	
Height (Year 4 only)	2	
Neuropathy foot exam (Section D) *Note: Visual inspection of feet should always be done for safety purposes and should be a priority even if full foot exam and MNSI not completed*	2	
Alcohol and Smoking History (Section F)	2	✓
Self-Monitoring of Blood Glucose (SMBG) (Section K)	2	✓
Number of Concomitant Prescription Medications Outside the GRADE Study (Section L)	2	✓
Eligibility Assessment for Oral Glucose Tolerance Test (OGTT) and other Annual Labs (Section A)	3	
Waist and hip circumference (Years 2, 4, 6 only)	3	
Indirect Costs (Section N)	3	✓
CONMED Form	1	✓
PARTICIPANT QUESTIONNAIRES AND ASSESSMENTS+		
Symptoms Form	1	✓
DTSQ (Non-EDS pts: Year 1 only; EDS pts: Years 1, 2, 3 only)	2	✓
MNSI questionnaire	2	
QWB	2	✓
SF-36	2	✓
EDSQ (as applicable, at Years 1, 2, and 3 only)	1	✓
ECG (Years 2, 4, 6 only)	2	
Neurocognitive questionnaire (Years 4 and 6 only)	3	
OTHER ACTIVITIES		
Order and dispense metformin, randomized drug, and drug supplies*	1*	✓
Discuss insulin initiation with participants who met outcome but have not yet started glargine and/or Novolog	1	✓
Complete NONINIT or UPNONIN form, as appropriate	1	✓
Deliver standard diabetes education	3	✓
Audio recording (as applicable)¥	3¥	

+ If participant-completed questionnaires can be collected for phone visits, they must be sent to the participant to fill out and should not be collected over the phone
* For participants who complete visits remotely, see MOP Section 4.4.1.1 for guidance on continued medication dispensing
¥ Only if participant has consented to specific component (initiated with Protocol v1.6)

18.2 Visit Scheduling during COVID-19

18.2.1 Follow-up Visit Scheduling

Quarterly, semi-annual, and annual visits should be scheduled during the visit window as best as possible. It is recommended that annual visits be scheduled as usual and not be delayed in an effort to minimize missed visits and keep participants on schedule.

18.2.2 Training Sessions During COVID-19

Training sessions for starting insulin can be conducted virtually (ex: Zoom, Skype, or other video platform) if allowed by the site's local regulations. Participants who are assigned to liraglutide or glargine (participants who are accustomed to doing injections) may be walked through insulin use over the phone if local regulations permit.

Similarly, glucagon kit training sessions can be conducted virtually if allowed by the site's local regulations. Another option that some sites may allow would be to conduct training at the participant's home through a window.

18.3 Data Collection during COVID-19

18.3.1 Staff-completed Forms

Fillable PDF versions have been created for all staff-completed forms in case staff need to conduct phone visits from home and are unable to print forms as usual. Staff should ask the questions and complete the fillable PDF while on the phone with the participant. Upon returning to the clinical site, the completed fillable PDF files should be printed and added to the participant's binder.

18.3.2 Participant-completed questionnaires

As with staff-completed forms, fillable PDF versions have been created for all participant-completed questionnaires to provide another method for participants to complete questionnaires. Fillable PDFs can be emailed to participants for completion and emailed back to the Study Coordinator or other staff member at the clinical site if allowable per local institutional guidelines.

Typically, all participant-completed questionnaires can be completed remotely except the EDSQ. However, during COVID-19, remote completion of the EDSQ is allowed so that it is still possible to collect the data while sites are closed to in-person visits or have severe time constraints for how long participants are allowed to be at the site.

18.3.3 Sample collection

The only sample that can be collected remotely (such as at the participant's home) is HbA1c via the participant capillary self-collection kit provided by the GRADE central laboratory. Sites should ensure they have an ample supply of capillary collection kits so that a kit can be mailed to each participant completing a phone visit. If there is a limited supply of capillary collection kits, kits should be prioritized for participants whose HbA1c values are needed for safety concerns. Refer to Study Memo #83 Prioritizing Capillary Collection Kits on the GRADE study website for more information.

Other samples, including urine and other blood samples, should be collected once the site's operations allow in-person collection of samples. Deadlines to collect samples have been extended in response to COVID-19. Refer to the *Guidelines for Collecting Missed Assessments* in Figure 18.2 below and on the

GRADE study website for details. A Protocol and Operational Deviation (PROTDEV) Form should be completed for any samples that are collected after the deadline.

Figure 18.2: Guidelines for Collecting Missed Assessments During the COVID-19 Pandemic

Guidelines for Collecting Missed Assessments – Quarterly and Semi Annual Visits

Visit Forms	Collection details
QUART Form	The date the quarterly visit form was done is the date of the visit event
CONMED Form	The CONMED form must be collected the day of the visit

	How far from the visit can the assessment be collected?	Means of Collection	Collect at visit:	Form(s) Needed	Lab kit	Documentation Notes
Labs						
HbA1c	6 weeks/before the beginning of the next visit window (whichever comes first)	Capillary kit	N/A	CAPLSTF	Capillary kit with 4xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
B12**	No deadline; collect when possible	In person	Annual	B12STF	Annual kit with 7xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
			Semi-Annual	B12STF	Semi-annual kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample was **actually** collected
Urine for albumin:creatinine**	Next quarterly visit	In person	Interim, Quarterly	REDRAW	Semi-annual kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected
Serum creatinine for hsCRP**	Next quarterly visit	In person	Interim, Quarterly	EDSSTF	EDS kit with 5xxxxxxxx lab id	Enter form under the visit at which the sample should have been collected

	How far from the visit can the assessment be collected?	Means of Collection	Collect at visit:	Documentation Notes
Participant Assessments				
Weight & BP	Before the beginning of the next visit window	In person	Interim	Enter the SPLITVIS form with the original annual visit number and indicate which assessments were completed
SYMPTOM*	Within 4 weeks	Complete at home	N/A	Enter SYMPTOM form under the original quarterly/ semi annual visit
DTSQ **	Next quarterly visit	Complete at home or in person	Quarterly	Enter DTSQ form under the original semi annual visit
EDSQ **	Next quarterly visit	Complete at home or in person	Quarterly	Enter EDSQ form under the original semi annual visit

*Must be completed within the visit window

**Must be completed by the participant's last study visit

Guidelines for Collecting Missed Assessments – Annual Visits

Note: If the annual visit was conducted outside of the 12 week window and the next quarterly visit was missed, contact your CoC liaison

Visit Forms	Collection details
ANNUAL Form	The date the annual visit form was done is the date of the visit event
CONMED Form	The CONMED form must be collected the day of the visit

	How far from the visit can the assessment be collected?	Means of Collection	Visits where collection is possible	Form(s) Needed	Lab kit	Documentation Notes
Labs						
HbA1c	6 weeks/before the beginning of the next visit window (whichever comes first)	Capillary kit	N/A	CAPLSTF	Capillary kit with 4xxxxxxxx lab id	Enter form under the original annual visit
Serum creatinine**	Next quarterly visit	In person	Interim, Quarterly	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the original annual visit
B12 or hs-CRP for EDS**	No deadline; collect when possible	In person	Interim, Quarterly***	B12STF or EDSSTF	Annual kit with 7xxxxxxxx lab id	Enter form under the original annual visit
			Semi-Annual	B12STF or EDSSTF	Semi-annual kit with 5xxxxxxxx lab id	**B12:** Enter form under the visit at which the sample was **actually** collected; **EDS:** Enter form under the original annual visit
			Annual	B12STF or EDSSTF	Annual kit with 7xxxxxxxx lab id	**B12:** Enter form under the visit at which the sample was **actually** collected; **EDS:** Enter form under the original annual visit
Urine for storage and albumin:creatinine**	Next quarterly visit	In person	Interim, Quarterly	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the original annual visit
Fasting lipids and Plasma/serum storage**	Next quarterly visit	In person	Interim, Quarterly	REDRAW	Annual kit with 7xxxxxxxx lab id	Enter form under the original annual visit
OGTT**	Next quarterly visit	In person	Interim, Quarterly	REDRAW, ANNOGTT	Annual kit with 7xxxxxxxx lab id	Enter REDRAW form under the original annual visit. Update the original ANNOGTT form with updated eligibility and date of visit

	How far from the visit can the assessment be collected?	Means of Collection	Visits where collection is possible	Documentation Notes
Participant Assessments				
Weight & BP*	Before the beginning of the next visit window	In person	Interim	Enter the SPLITVIS form with the original annual visit number and indicate which assessments were completed
SYMPTOM*	Within 4 weeks	Complete at home	N/A	Enter SYMPTOM form under the original annual visit
DTSQ **	No deadline; collect when possible	Complete at home or in person	Interim, Quarterly, Semi-Annual, Annual	Enter DTSQ form under the original annual visit
EDSQ**	No deadline; collect when possible	Complete at home or In person	Interim, Quarterly, Semi-Annual, Annual	Enter EDSQ form under the original annual visit
MNSI /Neuropathy**	Next quarterly visit	In person	Interim, Quarterly	Enter MNSI under the original annual visit and enter the SPLITVIS form with the original annual visit number and indicate which assessments were completed
QWB**	Next quarterly visit	Complete at home or in person	Interim, Quarterly	Enter QWB form under the original annual visit
SF-36**	Next quarterly visit	Complete at home or in person	Interim, Quarterly	Enter SF-36 form under the original annual visit
Neurocog**	Within 6 months	In person	Interim, Quarterly, Semi-Annual, Annual	Enter NEURO form under the original annual visit
ECG **	No later than next annual visit	In person	Interim, Quarterly, Semi-Annual, Annual	Enter ECG form under the visit at which the ECG was **actually** conducted. Add a comment on the Visit Number question to explain why the ECG was missed and confirm which visit the ECG should be associated with
Height**	No deadline; collect when possible	In person	Interim, Quarterly, Semi-Annual, Annual	Enter the SPLITVIS form with the original annual visit number and indicate which assessments were completed
Waist and hip circumference**	Within 6 months	In person	Interim, Quarterly, Semi-Annual, Annual	Enter the SPLITVIS form with the original annual visit number and indicate which assessments were completed

* Must be completed within the visit window

** If assessment is missing from the Final Annual visit, deadline is extended to the end of the last visit window. Must be completed no later than the participant's last study visit window.

*** B12 or hsCRP can be tested at a quarterly or interim visit only if the serum cryovials from the annual visit are being collected at that time

At-home pregnancy test kits can be provided to participants of childbearing potential for safety.

18.3.4 Collection of In-Person Assessments

Some assessments, including blood pressure, weight, height, waist/hip circumference, ECG, neurocognitive assessment, and neuropathy assessment can only be collected in person and should be collected as close to the date of the phone visit as possible given local institutional COVID-19 policies. If any in-person assessments are collected on a different date than the date the QUART/ANNUAL form is completed, the Collection of Physical Assessments from Split Visits and Recollections (SPLITVIS) Form should be used rather than updating the QUART/ANNUAL form at a later date. Deadlines to collect missed assessments have been extended in response to COVID-19. Refer to the *Guidelines for Collecting Missed Assessments* in Figure 18.2 for details. A Protocol and Operational Deviation (PROTDEV) Form should be completed for any assessments that are collected after the deadline.

18.3.5 Collection of Missing Samples and Assessments Upon Reopening

Clinical centers should only resume in-person visits when their local institution allows them to resume clinical research unit operations. Sites should inform the Coordinating Center when such visits will be allowed. If prioritization is needed due to having to recollect samples/assessments from phone visits in addition to conducting visits that are scheduled, sites should prioritize catching up with safety measurements and annual visits that are near the end of the study window when first reopening. Refer to GRADE Memo #85 "Return to Usual Activity" on the GRADE study website for additional information.

18.4 COVID Resources

A number of resources pertaining to policies and procedures during COVID-19 are available on the COVID page of the GRADE study website. See table 18.1 below for a summary of COVID-19 resources. See also the FAQs on the COVID page for guidance on particular issues.

Table 18.1 Summary of COVID-19 Resources

Category	Material	Purpose
Study Memos	Memo #80 Participant Visits and COVID-19	Memo detailing that diabetes care must continue
	Memo #81 Response to COVID-19	Recommendations on how to continue critical assessments and data collection in a remote setting while maintaining data integrity
	Memo #83 Prioritizing Capillary Collection Kits	Detailed priority list for capillary collection kits due to limited supply
	Memo #85 Return to Usual Activity	Priorities for sites as normal operations and in-person visits resume
Contacting Participants	COVID Phone Script	Inform participants about the change in study operations
	Letter to Participants	Inform participants about site closure and contact information
Visits and Data Recollection	Assessments by Study Visit for Prioritization*	Ranks the priority for all data collected at quarterly/semi-annual and annual visits, and indicates what can be completed for phone visits
	Guidelines for Collecting Missed Assessments*	Provides timeframe where labs and assessments can be collected if they are missed during a visit

*Material was updated as a result of the COVID-19 pandemic