Emotional Distress Substudy Manual

Version 1.3

May 1, 2021

TABLE OF CONTENTS

INTRODUCTION

The Emotional Distress Substudy will use measures such as a self-administered questionnaire and a small blood sample tested for high-sensitivity C-Reactive Protein (hs-CRP, a protein produced by the liver to measure levels of inflammation in the body) to assess emotional distress among the four treatment assignment groups in GRADE. The data from this substudy will be used to examine the roles of depressive symptoms and diabetes distress, factors that share significant overlap but require distinct approaches to screening and treatment. Consideration of these emotional distress factors will inform practice decisions regarding screening and treatment for emotional distress as part of diabetes care.

2. PURPOSE

The purpose of the Emotional Distress Substudy (EDS) is to evaluate whether elevations in emotional distress at baseline predict shorter time to A1c failure, with mediation by medication non-adherence and/or neuroendocrine dysregulation (i.e. hs-CRP) and whether emotional distress will be greater among participants initially assigned to insulin treatment over follow-up.

3. ELIGIBLE PARTICIPANTS

Participants not yet randomized in GRADE and who have provided informed consent for the EDS (GRADE Protocol Version 1.5 or higher) are eligible to participate and should be administered the assessment and blood sample. We will enroll about 2,250 participants until the end of randomization at a subset of participating GRADE clinical sites for baseline and semi-annual assessments up to 3-4 years of follow-up. The planned study duration is for 3-4 years. All sites will obtain IRB approval for the EDS Substudy prior to enrolling any participants.

4. TRAINING AND CERTIFICATION

Training and certification of Study Coordinators consists of two parts. The first part of training includes a review of the relevant documents, going through the questionnaire battery and scoring the Patient Health Questionnaire (PHQ-8). The second part of training includes attending an in-person meeting or WebEx with the EDS Investigators (or review of slides if unable to attend) to discuss participant follow-up upon completion of the EDS questionnaire and scoring.

4.1 Training

In order to complete training, Coordinators must complete the following:

1. Review the EDS Manual.
2. Review the CBL Manual, Appendix K.
3. Review the study questionnaire, related forms and schedule of assessments (refer to Tables 5.1 and 6.1).
4. Complete a sample questionnaire.
5. Score the PHQ-8.

4.2 Certification

In order to complete certification, Coordinators must complete the following:

1. Attend an in-person meeting or WebEx (or review slides) with Investigators to discuss participant follow-up upon completion of the EDS questionnaire and scoring.
2. Complete and pass the EDS protocol quiz. A score of 80% or higher is required.

5. REQUIRED MATERIALS

5.1 EDS Forms Packet

The EDS Forms Packet is included as an option to print as part of the regular study visit forms packet for applicable visits (Baseline Randomization, Semi-Annual and Annual visits). The EDS questionnaire in the forms packet is available in both English and Spanish.

The EDS forms are available for download from the GRADE study website and are located under Study Documents → Form Packets by Study Visits (CRFs) in the applicable packets. Clinical sites are responsible for printing the EDS forms for eligible participants (refer to Section 3) at applicable visits mentioned above, throughout the study.

Table 5.1: Required EDS forms

EDS Form (Abbreviated Name)	Study Visit	Required for Data Entry
EDS Specimen Transmittal Form (EDSSTF)	Baseline**, Semi-Annual, Annual	Yes
EDS Questionnaire (EDSQ)	Baseline**, Semi-Annual, Annual	Yes
DTSQs±	18, 24, 30, 36 month visits	Yes

** EDS Assessment may be completed in entirety at Final Run-in visit

± All GRADE participants also complete the DTSQs at baseline, month 6, and 12 (regardless of EDS participation)

5.1.1 EDS Specimen Transmittal Form

The EDS Specimen Transmittal Form: Refrigerated or Frozen Samples (EDSSTF) must be completed for eligible participants at Baseline Randomization (or Final Run-in) and participating subjects at Semi-Annual and Annual Visits. The EDSSTF will be included as an option to print as part of regular study visit forms packet for the applicable visits (Baseline Randomization (or Final Run-in), Semi-Annual and Annual visits).

5.1.2 EDS Questionnaire

The battery consists of 6 self-administered questionnaires/sections in a single packet (refer to Table 5.2 for breakdown) with 59 questions in total, available in both English and Spanish. The entire battery will take approximately 25 minutes to complete. The battery is divided into 2 sections for completion, Part 1 and Part 2 (see Table 5.2 for breakdown) to allow for flexibility

in the visit flow (see Section 6.3 for suggested visit flow); however, **the EDS assessment must be completed in its entirety at a single visit**. Part 2 of the battery includes scoring of the Patient Health Questionnaire and follow-up discussion with the participant. The EDS questionnaire administration should follow the same protocol adopted for other GRADE participant self-report measures. For remote visits, the EDS questionnaire may be mailed for self-completion or the questionnaire can be completed in person at a later date. As necessary, the questionnaire can be completed via telephone.

Table 5.2: List of questionnaires in EDS Battery

Part	Section	Title	Questions
1	A.	Your Diabetes Self-Care	5
	B.	Your Diabetes Medications	4
	C.	Your Views About the Diabetes Medicines Prescribed for You (Beliefs About Medicines Questionnaire - BMQ)	10
	D.	Your Personal Views of How You Now See Your Diabetes (Beliefs About Medicines Questionnaire - BMQ)	6
	E.	How Well Are You Managing Your Diabetes (Perceived Diabetes Self-Management Scale - PDSMS)	8
			Total Part 1: 33
2	F.	Diabetes Distress Scale (DDS)	17
	G.	Patient Health Questionnaire (PHQ-8) – To be scored by Coordinator	9
			Total Part 2: 26
			Total Part 1+ Part 2= 59

5.2 Specimen Collection Kits

One-half teaspoon of blood will be collected at the Baseline (or Final Run-in), Semi-Annual and Annual study visits and tested for hs-CRP. For the Baseline and Annual Visits, no separate blood collections or collection kits will be required, as the CRP analysis will be performed on the blood sample already collected at these visits. If the baseline collection is collected at Final Run-in, use the appropriate tube and an EXTRA label from the baseline visit kit and send to the CBL.
Only at the Semi-Annual visits (e.g. 6, 18, 30 months, etc.) will a separate blood sample be collected. GRADE clinical staff will collect the serum with the current Baseline and Annual collection kits as specified in the main protocol and ship it to the Central Biochemistry Laboratory (CBL) as per usual GRADE study procedures for hs-CRP testing. At the Semi-Annual visits, an additional ½ teaspoon of blood will be collected into a 2.5 mL SST tube using a separate collection kit called the EDS Semi-Annual Collection kit and shipped to the CBL for processing. See Table 5.3 for a breakdown of specimen collection kits required for EDS specimen collection. Refer to the CBL Manual, Appendix K for detailed instructions.

Table 5.3: EDS Specimen Collection by Visit

EDS visit	Separate collection required in addition to regular GRADE visit collection?	Collection kit(s) used	STFs completed at visit
Baseline If Final Run-in	NO YES	Baseline Final Run-in Tube and EXTRA label from Baseline kit	BASESTF, EDSSTF FRISTF, EDSSTF
Semi-annual	YES	Semi-Annual EDS Semi-Annual	QTSMISTF EDSSTF
Annual	NO	Annual	ANNSTF EDSSTF

6. PROCEDURES

6.1 IRB Approval, Participant Informed Consent and Compensation

All participating sites will obtain IRB approval for the EDS Protocol and the corresponding GRADE Study consent form prior to initiating the substudy. Consent to participate in this substudy is included in the informed consent forms (Version 1.5 or higher) for Phase 2 of the GRADE study; therefore, there is no separate consent process required for the EDS. Participants will receive an annual compensation of $25 for participating in the EDS. While it is up to the site to determine the timing of distributing the compensation to the participant, it is recommended that sites provide the compensation for the substudy at the Semi-Annual visit since compensation for the main study is commonly provided at the Annual visit.

6.2 Schedule of Assessments

Participants will complete the EDS self-administered questionnaire at the Baseline Randomization visit, Semi-Annual and Annual visits. Blood samples will also be obtained at Baseline Randomization, Semi-Annual and Annual visits to assess high-sensitivity C-reactive protein (hs-CRP) levels.

Table 6.1: Schedule of Assessments for Participants Enrolled in the EDS

	Baseline*	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
hs-CRP	X	X	X	X	X	X	X
EDS questionnaire	X	X	X	X	X	X	X
DTSQs±	XX±	XX±	XX±	X	X	X	X

*EDS Assessment may be completed in its entirety at Final Run-in visit

± All GRADE participants also complete the DTSQs at baseline, month 6, and month 12 (regardless of EDS participation)

6.3 Suggested Visit Flow

To allow for flexibility in administration of the EDS assessment for the baseline collection, it is permissible to conduct the assessment in its entirety (sample included) at the Final Run-in visit **or** at the Baseline Randomization visit; however, the assessment may NOT be split across visits.

For the semi-annual and annual collection, the EDS battery must be completed at a single time point or in two parts (Part 1 and Part 2) during that study visit.

6.3.1 Baseline Randomization Visit

The EDS assessment (including the sample) may be completed at either Final Run-in or Baseline Randomization, but cannot be split up across two visits.

Once it is decided that a participant will be administered the EDS assessment and sample collection at either the Final Run-in visit or the Baseline Randomization visit, it is possible for sites to administer the EDS battery in a single setting or in two parts at the selected single visit.

If the site chooses to conduct the EDS assessment at the Final Run-in visit:
It is possible to administer the questionnaire at the same time as other questionnaires are given, in two parts, or where it fits during that visit, per local clinical site flow.

If the site chooses to conduct the EDS assessment at the Baseline Randomization visit:
It is recommended that the battery be administered at either a single time point before the OGTT, or in two parts during the OGTT. If sites choose to administer the questionnaire during the OGTT, administration should begin only *after* the 15 minute time-point has passed. It is recommended to complete Part 1 of the battery *after* the 15 minute time-point and Part 2 *after* the 30 minute time-point of the OGTT, but before informing participants of their randomization assignment.

6.3.2 Semi-Annual Visit

The EDS battery may be folded into the Semi-Annual visit wherever possible. It is recommended to complete the battery after the blood draw at a single time point. However, sites may choose whether or not to administer both Part 1 and Part 2 of the EDS battery in a single sitting or separately throughout the visit.

6.3.3 Annual Visit

The EDS battery may be conducted at a single time point or in two parts during the Annual visit during the OGTT, similar to the manner in which it is done at the Baseline visit (see Section 6.3.1).

6.4 Administration of the EDS Battery of Questionnaires

a. Remind participants that answering the questions is voluntary and their answers will not be shared with anyone other than the research study staff. Participants have the right to stop answering these questions at any time. **The questionnaire is considered complete when the participant is done answering what he or she is willing to answer.** We are

interested in their opinion and partial data will be used for purposes of substudy analysis. Make sure that adequate time is allowed to complete the questionnaire. For remote visits, administration may include mailing of the questionnaire for self-completion or recollection of the questionnaire in person at a later date. As necessary, the questionnaire can be completed via telephone.

b. Inform participants that the questionnaire should take about 25 minutes to complete (or approximately 15 and 10 minutes, if completed as Part 1 and Part 2, respectively).

c. Instruct participants that if they do not know the answer to a question, they should answer it as best they can.

d. Study Coordinators may answer questions about the administration of the assessment, but may not guide the participant in their answers or influence their responses in any way. If asked about a specific question, Study Coordinators should respond with: "I can't answer that for you, but please choose the best answer." If completing by telephone, repeating the response scale with each item will facilitate accurate reporting. Be careful not to react to responses (neither with encouragement, nor judgment) so as not to influence reporting.

e. If the EDS battery is accidently missed at a scheduled time point during follow-up (e.g. 6 month visit), it can be made-up outside of the study visit. Ideally, this would be completed within 14 days of the study visit. The participant may complete this battery via telephone or mail for a phone visit, or in person at a later date. Note: If the EDS battery was missed but the hsCRP sample was collected at the scheduled visit, the sample does not need to be collected again at the time of make-up EDS battery completion.

6.5 Specimen Collection

There are no additional collections for EDS participants at the Baseline Randomization or Annual visits. Samples are tested for hs-CRP from the regularly collected samples at those visits. However, if the EDS assessment and sample collection are completed at the Final Run-in visit, an additional small amount of blood (1/2 teaspoon) is collected. Likewise, a small amount of blood (1/2 teaspoon) is collected at the Semi-Annual visit for EDS participants. An EDSSTF must be completed for EDS participants at the Baseline Randomization (or Final Run-in), Semi-Annual and Annual visits. Refer to Section 5.2 above and the CBL manual, Appendix K for detailed instructions. If the collection of the hsCRP sample and accompanying EDSSTF are accidently missed at a scheduled time point during follow-up (e.g. 6 month visit), it can be made-up within 14 days of the visit; however, when delayed due to the pandemic, specimens will be accepted if collected before the next EDS study visit window. Note: If the hsCRP sample collection was missed but the EDS battery was completed at the scheduled visit, the EDS battery does not need to be completed again at the time of the make-up hsCRP sample collection.

7. PROCESSING COMPLETED QUESTIONNAIRES

7.1 Review of Completed Questionnaires

Once the participant has completed the questionnaire, the Coordinator or designated research staff should review the questionnaire for completion and if a question was unanswered, confirm with the participant that it was meant to be unanswered. Do not insist if the participant chooses not to respond to questions. This quality control review can be modified as needed for remote administration. For mailed surveys that are reviewed after receipt, a follow-up phone call can be made to attempt to obtain a response if missing data is apparent that might suggest unintentionally missed items. This judgment is left to the Coordinator or designated research staff member's discretion.

7.2 Scoring of Patient Health Questionnaire (PHQ-8)

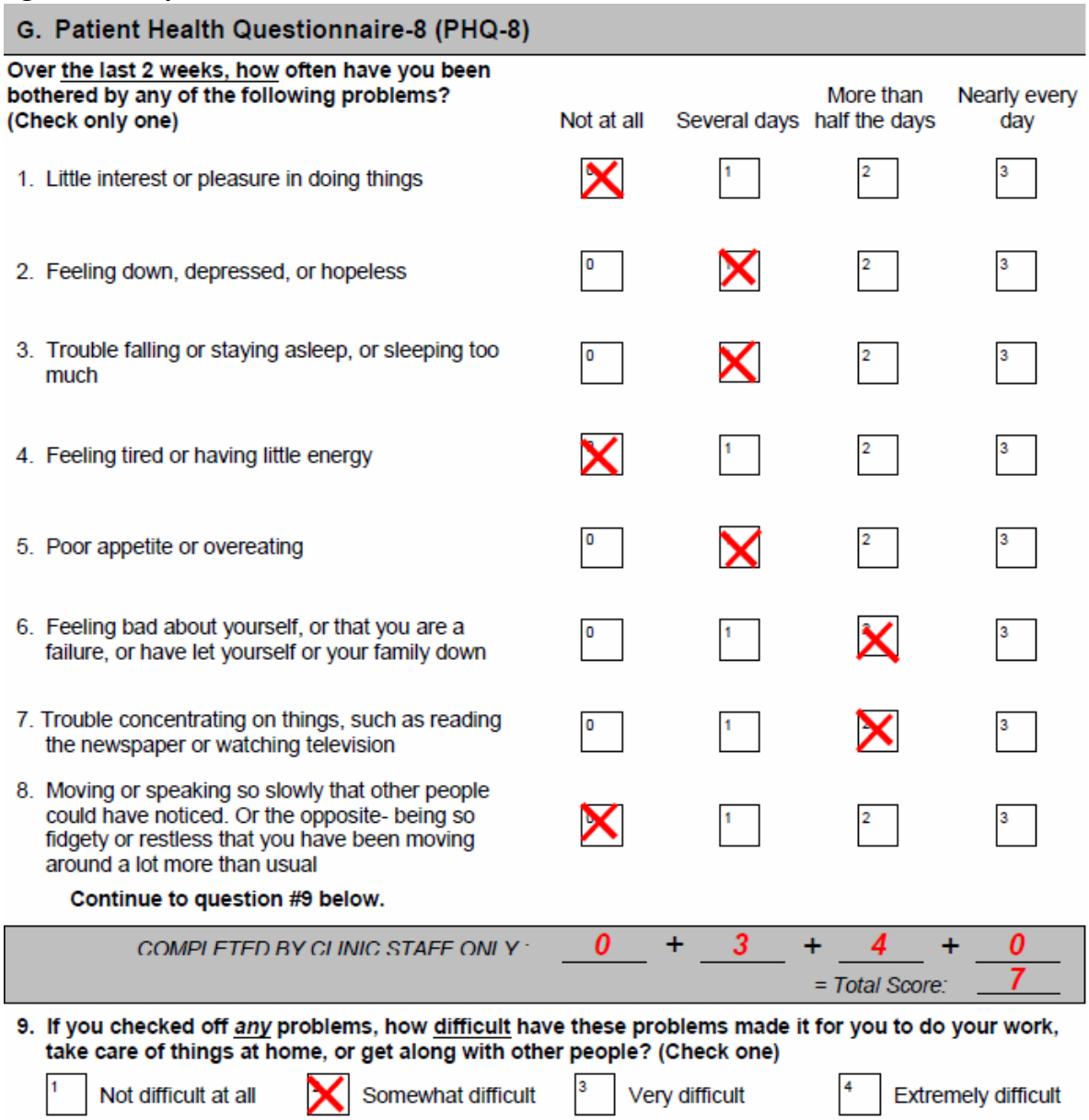
After the participant has completed the EDS questionnaire, the Coordinator must score Section G of the questionnaire, titled Patient Health Questionnaire (PHQ-8), which will be used to evaluate participants for depressive symptoms. The PHQ-8 consists of 9 questions, however, only the first 8 questions are scored. Each response has a numeric value associated with it between 0-3 points. See Table 8.1 for a list of the values for each of the four response types. When the participant has completed the 9 questions, add up the response values for the first 8 questions per Table 7.1. The total will be the participant's score. See Figure 1 below for a sample of a scored PHQ-8.

Table 7.1: Response values for scoring PHQ-8

PHQ-8 Response	Response Value
Not at all	0
Several Days	1
More than half the days	2
Nearly every day	3

If a participant misses a response to an item on the PHQ-8, ask the participant to review the missed question. Do not insist if the participant chooses not to respond to questions. This quality control review can be modified as needed for remote administration. For mailed surveys that are reviewed after receipt, a follow-up phone call can be made to attempt to obtain a response if missing data is apparent that might suggest unintentionally missed items. This judgment is left to the Coordinator or designated research staff member's discretion.

Figure 1: Sample of Scored PHQ-8



G. Patient Health Questionnaire-8 (PHQ-8)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Check only one)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	X 0	1	2	3
2. Feeling down, depressed, or hopeless	0	X 1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	X 1	2	3
4. Feeling tired or having little energy	X 0	1	2	3
5. Poor appetite or overeating	0	X 1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	X 2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	X 2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite- being so fidgety or restless that you have been moving around a lot more than usual	X 0	1	2	3

Continue to question #9 below.

COMPLETED BY CLINIC STAFF ONLY: 0 + 3 + 4 + 0 = *Total Score:* 7

9. If you checked off *any* problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? (Check one)

1 Not difficult at all | X 2 Somewhat difficult | 3 Very difficult | 4 Extremely difficult

7.3 Interpretation of the PHQ-8 Score

Scores of 1-4 should be interpreted to indicate no depressive symptom severity, 5-9 indicate mild severity, 10-14 moderate, 15-19 moderately severe and 20-27 severe.

7.4 Follow-up after Scoring Patient Health Questionnaire

After scoring the PHQ-8, trained and certified local site staff will discuss screening results with at-risk participants, emphasizing the need for further evaluation by the primary care doctor due to the likelihood of false-positive results. Staff is not required to provide feedback for all negative screens; however, staff should provide feedback in the event that participants who screen negative ask about their results. Coordinators must be trained and certified in

procedures (refer to Section 4) and Investigators will provide additional guidance for yearly re-certification (refer to Section 4.3), and when necessary.

At the baseline randomization visit (or Final run-in if EDS assessment conducted), all EDS and non-EDS participants will be provided with an informational booklet, *Diabetes and Your Emotional Health,* developed by the American Diabetes Association (ADA), regardless of their score or participation in the substudy. This informational booklet is available in both English and Spanish.

At follow-up visits, EDS participants who score ≥10 (positive screens) will receive a letter for follow-up with their PCP (see Section 11) in addition to the ADA informational booklet, *Diabetes and Your Emotional Health*. During remote visits, these same procedures can be completed when scoring is complete (i.e., at the end of the call or when a mailed survey is received and scored). Follow-up can occur by telephone and the ADA booklet can be mailed (via regular mail or e-mail) to interested participants (note: Table 7.2 indicates that all positive screens will have received at least one ADA booklet at a prior visit). Refer to Table 7.2 for guidelines on distribution of the ADA booklet, *Diabetes and Your Emotional Health.*

Table 7.2: Distribution guidelines for ADA booklet, *Diabetes and Your Emotional Health*

Study Visit	**Participants to receive booklet**
Baseline	All participants regardless of score and EDS participation
Semi-Annual	Positive screens, interested participants only, or participants who may benefit in the judgment of the clinical site staff
Annual	Positive screens, interested participants only, or participants who may benefit in the judgment of the clinical site staff

Note: If a participant is routinely a positive screen, the clinical site staff should distribute the booklet on an as needed basis.

Research studies of similar patient demographics show that 10-15% of participants may score high enough on the PHQ-8 to be considered at risk for depression.

The PHQ-8 does not ask about suicidal ideation and has been completed by telephone in numerous prior studies. In fact, its development was specifically intended to provide a tool for the assessment of depression that would not assess suicidal risk when follow-up cannot be provided. Staff will be able to seek input from the Site PI in any case of perceived high risk. They can also obtain consultation from the EDS PI, as needed.

7.4.1 Detailed Instructions for Follow-up and Sample Script

1. PHQ-8 is scored after completion (or receipt by mail, if applicable).

2. A total score of ≥10 is considered a positive screen and steps 3-7 below should be taken. If the total score is ≤9, no further action is required.

   If negative screen, stop here and reference Table 7.2 for guidelines on distribution of the ADA booklet, *Diabetes and Your Emotional Health.*
   If positive screen, continue to step 3.

3. Inform the participant that their responses to one of the questionnaires suggest he/she may be experiencing significant depression but emphasize that only his/her doctor or a mental health professional can say for sure. Further evaluation will be necessary and they should contact their doctor to arrange that.

4. Provide the participants with the educational booklet, *Diabetes and Your Emotional Health*, developed by the American Diabetes Association and encourage them to look through it to prepare for their discussion with their doctor and to learn more about depression and treatment options. Emphasize that this is a common problem in diabetes. The booklet also discusses emotional stress that is even more common than the kind of depression that requires treatment by a doctor or mental health care provider as well as tips for dealing with stress. Encourage the participant to read it over when they have the time and bring any questions to their doctor.

   Note: Refer to Table 7.2 for guidelines on distribution of the ADA booklet, *Diabetes and Your Emotional Health.*

5. Explain that you will send a letter to the participant's PCP (see Appendix C) to encourage the PCP for further evaluation and that you will provide them with a copy.

6. Complete letter and provide a copy to the participant.

7. Ask if the participant has any questions and thank them for their participation. In concluding, normalize the problem (e.g., "A lot of participants I talk to tell me they have problems like this") and inform them about the availability of effective treatments. Emphasize that talking to their PCP is the first step and highlight the toll-free phone number in the booklet that may be used in case of suicidal thoughts, hopelessness, or feeling 'like you can't go on.'

8. Send the letter to the participant's PCP.

8. FUNDING AND CAPITATION REIMBURSEMENT

Participating clinical sites will be funded on a capitated reimbursement basis. There will be separate site agreements for sites participating in the EDS. Sites will be paid based on participants enrolled in the EDS and completed visit forms (e.g. questionnaires, EDSSTF, and related forms). Funding will be provided for the study startup to cover the costs of training and IRB submission. Reimbursement will be provided based on EDS forms submitted. Funding will be provided by the Coordinating Center on a regular basis and is planned as quarterly payments.

APPENDIX A: EMOTIONAL DISTRESS SUBSTUDY QUESTIONNAIRE

The EDS questionnaire (Version 1.0) is 10 pages long, including the instruction page. A sample is provided below.

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

Instructions to the Participant

To better understand the management of diabetes from the patient's perspective, the following questions will ask you about your experience with taking care of your diabetes, taking your medications, and your views about your diabetes medicines and overall diabetes self-care.

You will also be asked about any emotional distress that you may or may not have experienced recently. We know that taking care of your diabetes can be challenging and we want to make sure that we learn about some of the stressful parts of living with diabetes. These statements may or may not apply to you, but they're based on issues we've learned about from other patients like you.

Do your best to answer each question as accurately as you can. Remember there are no right or wrong answers; we just want your opinion. Your responses will not be shared with anyone else without your permission.

Thank you for your time in completing this survey!

EDS Questionnaire Packet - EDS Form

COMPLETED BY CLINIC STAFF ONLY

Date of visit: mm dd yyyy

Visit Number:

PART 1

INSTRUCTIONS:

- **Please complete this questionnaire to the best of your ability.**
- **Please read and answer each question below.**
- **Mark an 'X' in the appropriate box for each question.**

A. Your Diabetes Self-Care

Over the past 30 days, how difficult has it been to do each of the following exactly as the doctor who takes care of your diabetes suggested? (Check only one)

1. Take your diabetes medications (pills and/or insulin) exactly as prescribed

- [1] SO DIFFICULT - I couldn't do it at all
- [2] VERY DIFFICULT - I hardly ever took them as prescribed
- [3] DIFFICULT - I took them some of the time
- [4] NOT VERY DIFFICULT - I took them most of the time
- [5] NOT DIFFICULT AT ALL - I did it exactly right

2. Exercise regularly

- [1] SO DIFFICULT - I couldn't do it at all
- [2] VERY DIFFICULT - I hardly ever exercised regularly
- [3] DIFFICULT - I exercised some of the time
- [4] NOT VERY DIFFICULT - I exercised most of the time
- [5] NOT DIFFICULT AT ALL - I did it exactly right

A. Your Diabetes Self-Care (continued)

Over the past 30 days, how difficult has it been to do each of the following exactly as the doctor who takes care of your diabetes suggested? (Check only one)

3. Follow your recommended eating plan

- [1] SO DIFFICULT - I couldn't do it at all
- [2] VERY DIFFICULT - I hardly ever follow my recommended eating plan
- [3] DIFFICULT - I followed it some of the time
- [4] NOT VERY DIFFICULT - I followed it most of the time
- [5] NOT DIFFICULT AT ALL - I did it exactly right

4. Check your blood sugar as frequently as your doctor recommends

- [1] SO DIFFICULT - I couldn't do it at all
- [2] VERY DIFFICULT - I hardly ever checked my blood sugar
- [3] DIFFICULT - I checked my blood sugar some of the time
- [4] NOT VERY DIFFICULT - I checked my blood sugar most of the time
- [5] NOT DIFFICULT AT ALL - I did it exactly right

5. Check your feet for wounds or sores

- [1] SO DIFFICULT - I couldn't do it at all
- [2] VERY DIFFICULT - I hardly ever checked my feet for wounds
- [3] DIFFICULT - I checked my feet some of the time
- [4] NOT VERY DIFFICULT - I checked my feet most of the time
- [5] NOT DIFFICULT AT ALL - I did it exactly right

Site | Participant ID | GCode

INSTRUCTIONS:

- **Taking medications the way they are prescribed can often be difficult. Sometimes patients report taking less medication than was prescribed.**
- **We'd like to hear about your experience. The following questions ask about your DIABETES MEDICATIONS.**
- **This includes all of the medications that you've been prescribed as part of the GRADE Study, including injections.**
- **Please read and mark an 'X' in the appropriate box for each question, or answer as instructed. If you are not sure how to answer a question, please give the best answer you can.**

B. Your Diabetes Medications

1. In **the last 30 days**, on how many **days** did you miss at least one dose of any of your diabetes medications?

   Write in the number of days: _____ (0-30)

2. **In the last 30 days**, how good of a job did you do at taking your **diabetes medications** in the way you were supposed to? **(Check only one)**

Very Poor	Poor	Fair	Good	Very Good	Excellent
1	2	3	4	5	6

3. **In the last 30 days**, how often did you take your **diabetes medications** in the way you were supposed to? **(Check only one)**

Never	Rarely	Sometimes	Usually	Almost Always	Always
1	2	3	4	5	6

4. **In the last 30 days**, what percent of the time did you take all your **diabetes medications** in the way you were supposed to? **(Check only one)**

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
1	2	3	4	5	6	7	8	9	10	11

Site | Participant ID | GCode

INSTRUCTIONS:

- **We would like to ask you about your personal views about medicines prescribed for you.**
- **These are statements that other people have made about their medicines.**
- **Please show how much you agree or disagree with them by marking 'X' in the appropriate box for each statement.**
- **There are no right or wrong answers. We are interested in your personal views.**

C. Your Views About the Diabetes Medicines Prescribed for You

Mark an 'X' in the appropriate box for each question (Check only one)	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
1. My health, at present, depends on my diabetes medicines.	1	2	3	4	5
2. Having to take diabetes medicines worries me.	1	2	3	4	5
3. My life would be impossible without my diabetes medicines.	1	2	3	4	5
4. I sometimes worry about long-term effects of my diabetes medicines.	1	2	3	4	5
5. Without my diabetes medicines, I would be very ill.	1	2	3	4	5
6. My diabetes medicines are a mystery to me.	1	2	3	4	5
7. My health in the future will depend on my diabetes medicines.	1	2	3	4	5
8. My diabetes medicines disrupt my life.	1	2	3	4	5
9. I sometimes worry about becoming too dependent on my diabetes medicines.	1	2	3	4	5
10. My diabetes medicines protect me from becoming worse.	1	2	3	4	5
11. My diabetes medicines give me unpleasant side effects.	1	2	3	4	5

Site | Participant ID | GCode

D. Your Personal Views of How You Now See Your Diabetes

Mark an 'X' in the appropriate box for each question (Check only one)	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
1. There is a lot which I can do to control my diabetes.	1	2	3	4	5
2. What I do can determine whether my diabetes gets better or worse.	1	2	3	4	5
3. The course of my diabetes depends on me.	1	2	3	4	5
4. Nothing I do will affect my diabetes.	1	2	3	4	5
5. I have the power to influence my diabetes.	1	2	3	4	5
6. My actions will have no effect on the outcome of my diabetes.	1	2	3	4	5

Site | Participant ID | GCode

INSTRUCTIONS:

- **This section is to help us to understand how well you feel you (yourself) manage your diabetes.**
- **Each item is a belief statement with which you may agree or disagree.**
- **Consider each statement separately. Choose your responses thoughtfully and make them as true *FOR YOU* as you can.**
- **Read and respond to each statement to show how much you agree or disagree with it by marking an 'X' in the appropriate box. The responses range from 1, *Strongly Disagree* to 5, *Strongly Agree*.**
- **Please respond to every statement.**

E. How Well Are You Managing Your Diabetes?

Mark an 'X' in the appropriate box for each question (Check only one)	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
1. It is difficult for me to find effective solutions to problems that occur with managing my diabetes.	1	2	3	4	5
2. I find efforts to change things I don't like about my diabetes are ineffective.	1	2	3	4	5
3. I handle myself well with respect to my diabetes.	1	2	3	4	5
4. I am able to manage things related to my diabetes as well as most other people.	1	2	3	4	5
5. I succeed in the projects I undertake to manage my diabetes.	1	2	3	4	5
6. Typically, my plans for managing my diabetes don't work out well.	1	2	3	4	5
7. No matter how hard I try, managing my diabetes doesn't turn out the way I would like.	1	2	3	4	5
8. I'm generally able to accomplish my goals with respect to managing my diabetes.	1	2	3	4	5

Site | Participant ID | GCode

PART 2

INSTRUCTIONS:

- **Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties.**
- **Below are 17 potential problem areas that people with diabetes may experience.**
- **Consider the degree to which each of the 17 items may have distressed or bothered you DURING THE PAST MONTH and mark an 'X' in the appropriate box for each statement.**

We are asking you to answer the level that each item may be bothering you in your life, NOT whether the item is just true for you.

If you feel that a particular item is not a bother or a problem for you, you would put an 'X' in the box marked "Not a Problem". If it is very bothersome to you, you might mark an 'X' in the box marked "A Very Serious Problem".

F. Diabetes Distress Scale

Mark an 'X' in the appropriate box for each question (Check only one)	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
1. Feeling that my diabetes is taking up too much of my mental and physical energy every day.	1	2	3	4	5	6
2. Feeling that my doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
3. Feeling angry, scared, and/o depressed when I think about living with diabetes.	1	2	3	4	5	6
4. Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	1	2	3	4	5	6
5. Feeling that I am not testing my blood sugars frequently enough.	1	2	3	4	5	6
6. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6

Site | Participant ID | GCode

Mark an 'X' in the appropriate box for each question (Check only one)	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
7. Feeling that friends or family are not supportive enough of self care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat "wrong" foods).	1	2	3	4	5	6
8. Feeling that diabetes controls my life.	1	2	3	4	5	6
9. Feeling that my doctor doesn't take my concerns seriously enough.	1	2	3	4	5	6
10. Not feeling confident in my day-to-day ability to manage diabetes. Feeling that diabetes controls my life	1	2	3	4	5	6
11. Feeling that I will end up with serious long term complications, no matter what I do.	1	2	3	4	5	6
12. Feeling that I am not sticking closely enough to a good meal plan.	1	2	3	4	5	6
13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.	1	2	3	4	5	6
14. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
15. Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	1	2	3	4	5	6
16. Not feeling motivated to keep up my diabetes management.	1	2	3	4	5	6
17. Feeling that friends or family don't give me the emotional support I need.	1	2	3	4	5	6

Site | Participant ID | GCode

INSTRUCTIONS:

- **Please complete the following questions to the best of your ability.**
- **Mark an 'X' in the appropriate box for your answer to each statement.**

G. Patient Health Questionnaire-8 (PHQ-8)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Check only one)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite- being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

If not bothered by any problems for all 8 questions above, Stop here.

9. If you checked off *any* problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? (Check one)

1 Not difficult at all | 2 Somewhat difficult | 3 Very difficult | 4 Extremely difficult

COMPLETED BY CLINIC STAFF ONLY FOR QUESTIONS 1-8: _____ + _____ + _____ + _____

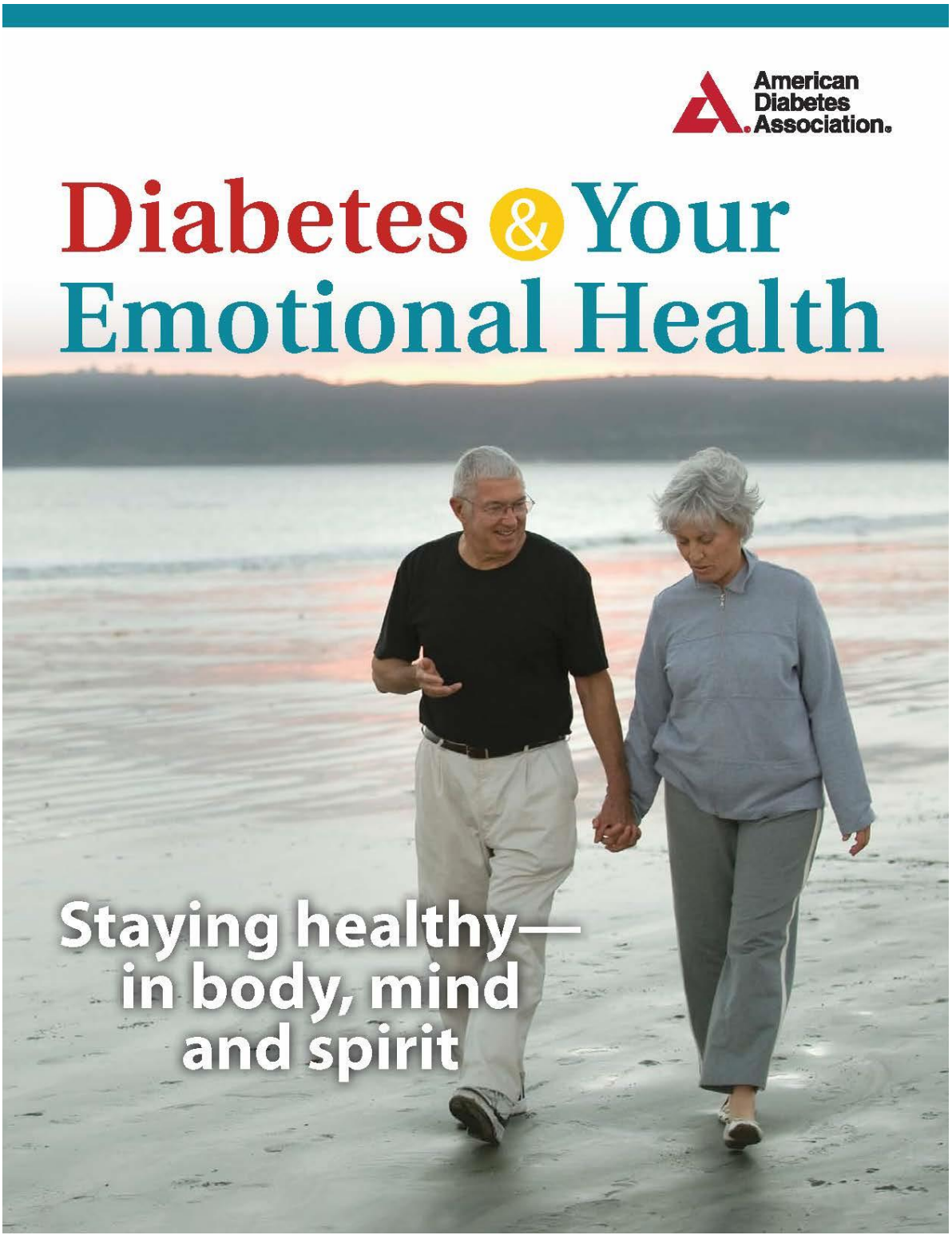
= Total Score: _____

COMPLETED BY CLINIC STAFF ONLY

Reviewer Initials:	Date form completed (mm/dd/yyyy):	Form entered in MIDAS?

APPENDIX B: PARTICIPANT EDUCATIONAL MATERIALS

Sites will be provided with the American Diabetes Association handout, *Diabetes and Your Emotional Health*. A sample is provided below.



Healthy living means taking care of your body, mind, and spirit.

Learning that you have diabetes can be hard, and living with diabetes is not simple. Managing diabetes can lead to many different emotions and stresses. Some days, you may handle it better than other days. With diabetes education and support, you can learn how to balance your life and diabetes care.

Everyone has their own story about being diagnosed with diabetes. Some people adjust to having diabetes easily while others find it harder. Many people feel some loss, guilt, fear, and anger after they are diagnosed. These are common feelings. Learning how to take care of diabetes often relieves them, and they usually get better over time.

Some people are unable to accept that they have diabetes. You may have a sense of disbelief. You may say "I just have a touch of diabetes" and don't see the need to change your lifestyle or take your medicine. These are red flags that you may need help coping with diabetes.

The sooner you talk about your feelings, the better. Once you start to take care of your diabetes you will see how much better you feel in body, mind, and spirit.

Diabetes & Depression

We all feel stressed, anxious, or sad at times. But emotions can have an effect on your diabetes, and we know that people with diabetes are at greater risk for depression than people without diabetes. If you have symptoms of depression, you may want to talk with a therapist. Ask your diabetes team if they know a therapist who would be a good match for you.

Remember, you can live a full and happy life with diabetes.

Signs of Depression

- Feeling sad, blue or depressed for more than two weeks.
- Unable to find happiness in things you usually enjoy.
- Becoming easily frustrated.
- Being less patient with others.
- Eating too much or too little.
- Unable to sleep or sleeping too much.
- Low energy.
- Poor attention span.
- Not wanting to be around people.
- Little interest in sex.
- Thoughts about death or hurting yourself.

Sometimes, depression can be so severe that people think about hurting themselves. Get help now if you:

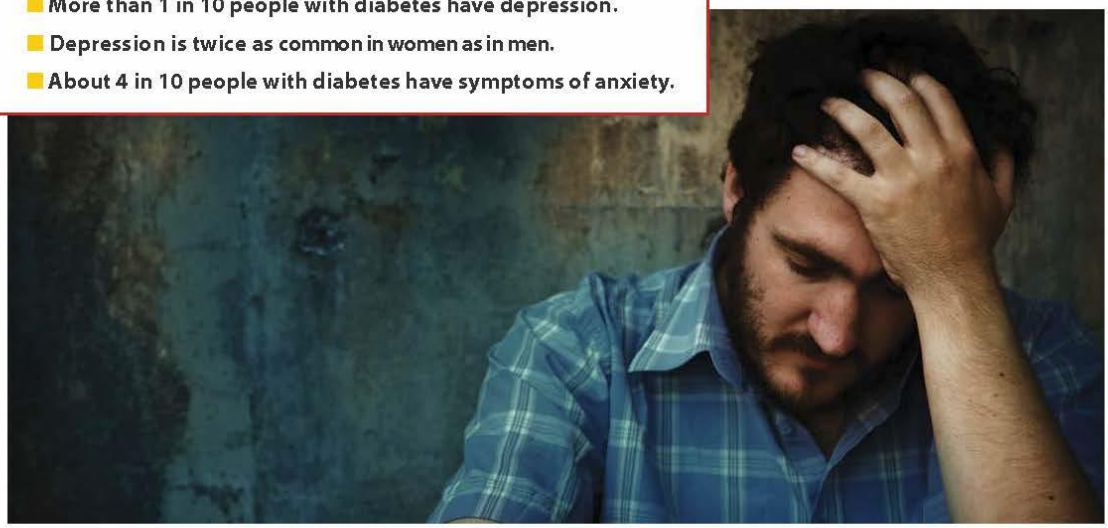
- **Feel that life is not worth living or have no sense of purpose in life**
- **Act reckless with your diabetes management**
- **Don't care about your health or safety and engage in reckless or risky activities**
- **Are thinking about or threatening to hurt or kill yourself**

Call the National Suicide Prevention Lifeline at 1-800-273-TALK (1-800-273-8255).

This free and confidential service is available to anyone.

HOW COMMON ARE DEPRESSION AND ANXIETY?

- **More than 1 in 10 people with diabetes have depression.**
- **Depression is twice as common in women as in men.**
- **About 4 in 10 people with diabetes have symptoms of anxiety.**



Diabetes & Stress

Everyone has stress in their lives. Whether it's being stuck in a traffic jam, worrying about paying the bills, starting a new job, or caring for a sick parent, stress affects everyone. For people with diabetes, stress management isn't just about finding ways to relax, it's also about managing blood glucose levels.

Your body makes stress hormones when under stress. These hormones can make your blood glucose go up, making diabetes harder to manage.

Stress can also affect your blood glucose numbers in other ways: it can make it harder to focus on your diabetes care. You may eat too much or not enough, avoid exercise, or forget to take your medicines.

Sometimes, no matter how hard you try, your blood glucose levels don't stay in your target range. You're not alone. In addition to stress, there are so many things that can affect your blood glucose each day — and not all of them are within your control. You may have variations in insulin absorption or changes in the amounts of food or levels of physical activity from day to day.

Other Effects of High and Low Blood Glucose

While stress can affect your blood glucose levels, the opposite is true too. High or low blood glucose levels can affect your emotions.

When blood glucose is high, you may feel cranky, tired and not have enough energy to get things done. Having high blood glucose may also cause you to worry more about your diabetes and increase your stress level.

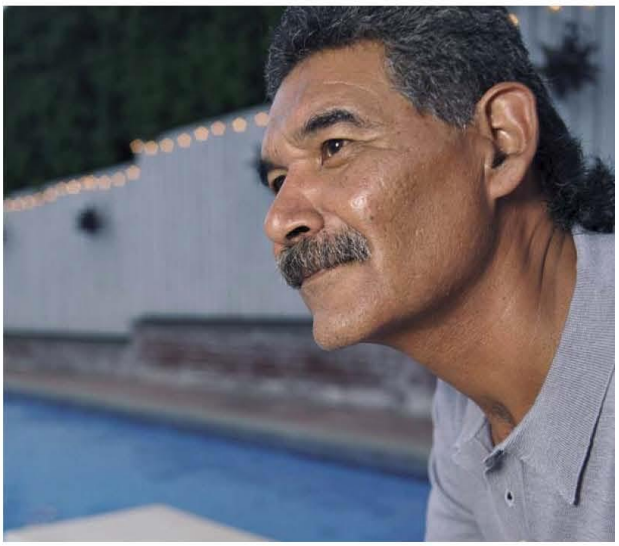
If your blood glucose is too low, you may feel nervous, start to argue, or not be able to think clearly. If your blood glucose is low you may need help getting something to eat.

If your blood glucose is out of your target range most of the time, too high or too low, talk with your diabetes team about a change to your diabetes care plan.

Checking Blood Glucose

It's important to check your blood glucose regularly so you can see how your diabetes care plan is working.

There are many different types of blood glucose meters out there so be sure to talk to your diabetes care team to learn how to use your meter properly. Also talk to your provider about when and how often you should check your blood glucose.



Q&A

Question: *How can I relax when I have so much stress in my life?*

Mary F., age 47, type 2 diabetes

Answer: Ignoring stress or pretending it does not exist does not help. Using alcohol, cigarettes or other substances to cope with stress can harm your health and make it harder to manage diabetes. Instead, make time to spend with friends. You could go on a walk together. Physical activity, a good laugh or talking with good friends can relieve stress and help you feel much better!

Here are some ways you can manage stress:

- Talk to someone you trust about your stress.
- Allow time to pray or meditate.
- Find ways to laugh and spend time with people you enjoy.
- Be physically active.
- Get help instead of trying to do everything yourself.
- Set limits on what you will do for others.
- Schedule only those things you can really complete each day.
- Work on one thing at a time.
- Take up a hobby or activity you enjoy.
- Join a support group or online chat.
- Try ways to relax such as deep breathing, yoga, or dancing.
- Think of what you have done to help yourself. Do not put yourself down about the things you have not been able to do yet.

Diabetes & Emotional Well-Being

Having diabetes, like many other things in your life, is a source of stress. Learning how to manage your diabetes is key to your emotional well-being. Here are a few steps to help you feel good and live well with diabetes.

STEP 1 Identify your stress

Often, we're stressed about things that we don't notice. These stressors seem part of everyday life, but they can make your diabetes harder to control. To see if there's a connection between your blood glucose levels and stress, try this simple test.

Before you check your glucose levels, ask yourself, "How stressed am I?" Use the scale below to illustrate your stress level.

Stress-Free		Mildly Stressed		Moderately Stressed		Very Stressed		Stressed Out	
1	2	3	4	5	6	7	8	9	10

1. Write it down.

Keep track of your blood glucose and stress levels in different situations.

Think about what is making you stressed.
For example:

- Are you thinking about family problems or money issues?
- Did you do anything differently today?
- Did you eat new foods?
- Did you change your exercise routine?
- Did you miss taking your medicine (if so, why)?
- Did you do anything today to reduce stress?
- Did you have a great time with your kids, friends, or family?
- Did you attend a program for weight loss, exercise, or nutrition?
- Did you attend a diabetes support group meeting?

2. Try this for 2 weeks.

When you look at the results, do you see a pattern?
When is your blood glucose in your target range?
When is it high?

3. Share with your health care provider.

It will provide important information about how stress may be affecting your blood glucose levels. Your provider may also be able to help you find ways to manage stress so you can better manage your diabetes.

Date	Glucose Level	Stress Level	Am I Stressed?
2/19	102	2	Took long walk w/friend
2/20	167	7	Kids were out of control
2/21	198	8	Argued with husband!

STEP 2 Build your support system

Whether it's your partner, brother, aunt or friend, having someone to talk to and feeling supported in your diabetes management can reduce your stress level. This network of family and friends is your support system. The people in your support system want you to succeed in managing your diabetes. They want to help.

If you don't have a support system, build one. You might include:

- **Your family, friends, partner, and/or siblings.**
- **Your diabetes educator.** He or she may also know about local support groups or organizations that you could join for no or low cost.
- **Members of Internet groups** such as the American Diabetes Association online communities (go to **diabetes.org** and click on Message Boards).
- **Your religious leader at your place of worship.**

Once you build your support system, don't be afraid to use them. Get them involved!

- **Take them along** — Invite members of your support system to your diabetes appointments or education classes so they can learn about diabetes with you. Attending these sessions can help them understand how diabetes affects you.
- **Get physical** — Ask members of your support system to exercise with you. Just going for a 30-minute walk most days of the week can make a big difference in your diabetes control. This will also be a great opportunity to relax and catch up with friends.
- **Ask for help** — Sometimes just having a little help can make all the difference in managing your stress. For example, ask family members to try healthier snack options with you. Snacking on carrots instead of chips is healthier for everyone in your home and you don't have to do it alone.

STEP 3 Work with your health care provider

Let your health care provider or diabetes care team know if you are depressed, stressed, or worried about your diabetes care. They can help reduce your stress by:

- Helping you improve your blood glucose control. You can work together to figure out how you can make healthier food choices, fit more physical activity into your day or adjust your medicines to work better.
- Connecting you to other health care professionals who can help you.
- Giving you information about support groups and other resources.

Make the most of your appointment

Write down questions you want to ask your health care provider. Bring them with you. Your questions might include:

1. What can I do to get better control of my diabetes?
2. What can I do if I can't afford my medicine?
3. What symptoms need immediate medical attention?
4. How can I get help to improve my diet, exercise, and weight?
5. My stress level is pretty high and I think it's affecting my blood glucose. What can I do?
6. My day is so busy, sometimes I forget to take my medicine. What should I do when I remember?
7. How do my other medical conditions (list them) affect my diabetes?

YOUR DIABETES CARE TEAM

You may work with many different kinds of health care providers as part of your diabetes care team. Some of these professionals are described below.

Primary care provider
This professional gives you routine medical care, including physical exams, lab tests, and prescriptions for medicines. This person may be a doctor, nurse practitioner, or physician assistant.

Diabetes educator
A diabetes educator can help you manage your diabetes by teaching you self-management skills. This professional can also help you figure out how best to include your diabetes management plan in your lifestyle. To work with a diabetes educator in a diabetes education program recognized by the American Diabetes Association, visit diabetes.org/findaprogram to find a program or call 1-800-DIABETES (342-2383) for a list of recognized programs in your community.

Mental health professional
This professional may be a psychiatrist, psychologist, social worker, or counselor. He or she can help you manage stress, anxiety or depression and help you deal with the day-to-day challenges of living with diabetes.

Registered dietitian
A registered dietitian can help you with meal-planning and making healthy food choices. Working with this professional will help you to get the nutrition you need, control your diabetes, and control your weight.

STEP 4 Every day is a new day

Living with diabetes is not always easy. You'll have good days and bad days. When you have a bad day, don't let it get you down. Treat each day like a new day and do the best you can.

There's a lot that goes into managing diabetes. While you work to make healthy food choices, be more physically active, take your medicines, and check your blood glucose, don't forget to take time for yourself as well. Take time to reflect on the positive things you're doing, reward yourself when you have a good day and go easy on yourself when you have a bad day.

Remember, managing stress and emotional well-being plays a big part in managing diabetes.

APPENDIX C: LETTER TO PCP

EDS Follow-up Letter to PCP

Site Investigator
Address
Contact Information (Tel)
(Email) (FAX)

PCP
Address
Contact Information (Tel)
(Email) (FAX)

Date: mm/dd/yyyy

Re: Patient Name

Patient date of birth: mm/dd/yyyy

Dear Primary Care Provider,

Your patient FIRST LAST has been screened or is participating in the clinical research study, ***Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)***, a National Institute of Health (NIH)-sponsored clinical trial.

This letter is being sent to alert you that your patient screened positive for depression with a self-report questionnaire as part of a study assessment. Because the results of this screening indicate the possible presence of clinically significant depression, we recommend further evaluation to confirm this possibility and to rule out false-positive findings. Although this screening result indicates increased risk of depression, research in diabetes indicates that over 50% of positive screens for depression will be false-positives. Thus, further evaluation is essential.

We have notified your patient that the results of this screen may warrant medical attention, and have advised him or her to contact you. In addition, we have provided your patient with an informational brochure about depression, a copy of this letter and have encouraged them to bring this letter to their next visit with you for further evaluation and, if indicated, to discuss treatment options with you.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Site Investigator, MD