Manual of Procedures (MOP)
Section 17. Participant Retention

Table of Contents

17.1 OVERVIEW 3
17.1.1 Monitoring of Retention 3
17.2 FACTORS IN STUDY DESIGN AND DEFINITIONS 3
17.2.1 Non-retention ("off study") vs. non-adherent ("off study medication") 3
17.2.1.1 "Off Study" vs. "Inactive" 3
17.2.1.2 "Off study medication" 4
17.3 RETENTION STRATEGIES AND TOOLS 4
17.3.1 Recruitment Process 4
17.3.2 Informed Consent Process 4
17.3.3 Relationships of Participants with Study Staff 5
17.3.3.1 Participant Information Brochure 5
17.3.3.2 D2d Folders 5
17.3.3.3 D2d Business / Appointment Cards 6
17.3.3.4 Clinical Provider Information Handout 6
17.3.1.5 Letters to Primary Care Physicians 6
17.3.1.6 Newsletter to Participants 7
17.3.1.7 Follow up letters to participants 7
17.3.1.8 Birthday and Holiday Cards 7
17.3.1.9 Occasional brief notes by PI to participants 7
17.3.1.10 Mementos 7
17.3.1.11 Website 8
17.3.2 Support and Education Program 8
17.3.3 Research Environment 8
17.3.4 Reminders 8
17.3.5 Contact Information 8
17.3.5.1 Difficult to Contact Participants 9
17.4 SITE TRANSFER AND PARTICIPANT SHARING 10
17.4.1 Definitions 10
17.4.2 Procedure 10
17.4.2.1 Joint Management (Shared) Procedure 10
17.4.2.2 Transferred Participant Procedure: 11
17.5 RETENTION STRATEGY FOR "INACTIVE" PARTICIPANTS 11
17.5.1 Maximize data collection 11
17.5.2 Gauging participant willingness 12
17.5.3 Modified study pill distribution 12

17.5.4 Alternate participation scenarios 12
17.5.4.1 Commitment to at least one visit per year, agrees to non-visit contact 12
17.5.4.2 No definitive commitment to a specific schedule, agrees to non-visit contact 13
17.5.5 EDC data entry 14
17.5.6 Participant stipends 14
17.6 APPENDICES 15
Appendix 1 Participant Information Pamphlet 15
Appendix 2 Clinical Provider Information Pamphlet 15
Appendix 3 Letter to Provider Enrolled Participant 15
Appendix 4 Letter to Randomized Participant 15
Appendix 5a Follow-up Letter to Provider (enrolled participants not diagnosed with diabetes) 15
Appendix 5b Follow-up Letter to Provider (enrolled participants diagnosed with diabetes) 15
Appendix 6 Sample Follow-up and Reminder Letters to Participant 15
Appendix 7 Newsletter to Participants (see http://www.d2dstudy.org/newsletters) 15

17.1 OVERVIEW

Participant retention and adherence to study procedures are key components of study quality as they minimize the occurrence of missing data and enhance the validity of study results. Therefore, *a key determinant of the success of the D2d study is the ability of the sites to maximize retention of participants until study completion and avoid missing data*. Many potential problems with retention and adherence can be prevented or minimized in the following components: (1) during the study design phase, and (2) during active recruitment by selecting a study population that is likely to have high adherence. Once participants are enrolled, the focus shifts to the third component: (3) enhancing and monitoring adherence and retention.

Two major components of low retention that can be addressed by planning ahead are the following: (1) participant withdrawal from the study (going "off study") and (2) loss to follow up.

17.1.1 Monitoring of Retention

The Coordinating Center and the Recruitment and Retention subcommittee (RRS) will monitor retention rates at each site and provide reports to the Executive Committee and Steering Committee. Comparisons will be made within site (e.g. last 3 months vs. previous 3 months) as well as across all sites. When reductions in retention are noted, the subcommittee will make recommendations to the sites for improving retention.

17.2 FACTORS IN STUDY DESIGN AND DEFINITIONS

To maximize adherence and retention, several key elements have been taken into consideration during the study design, as described in the protocol and below (e.g., the study has kept the intervention and follow-up procedures uncomplicated, exclusion criteria designed to exclude those with a higher probability of non-adherence, the informed consent process emphasizes the importance of adherence, and support and educational sessions are provided).

17.2.1 Non-retention ("off study") vs. non-adherent ("off study medication")

⇒ The D2d study emphasizes the distinction between *non-retention*, which is defined as going "off study," and *non-adherence*, which is defined as going "off study medication" or not following up with study procedures and visits.

17.2.1.1 "Off Study" vs. "Inactive"

Participants can go "off study" due to withdrawal of consent, which is defined as *no longer wishing to participate in all aspects of the trial.* Withdrawal of consent needs to be obtained verbally or in written form and clearly documented. Proper use of the term "withdrawal of consent" will be monitored during the study by the CC. Site investigators may withdraw participants if their continued participation in the D2d is not in the best interests of the study.

⇒ *Unless participants go permanently "off study," they will be asked to return for all scheduled follow-up evaluations to collect outcome and safety data.*

If a participant does not return for study visits or cannot be contacted, attempts to contact the participant will continue every 3 months until the participant is contacted and resumes active participation or actively withdraws consent.

⇒ Participants who have missed 2 consecutive visits but have not gone formally "off study," will be termed *"inactive"* to reflect the possibility that they may resume adherence with study medication and may return for outcome measurements. Inactive participants will be further classified as "in contact with site" or "no contact with site."

⇒ It is important to note that participants will *not be considered "lost to follow-up" until the end of the study.* Therefore, it is expected that few participants will go "off study" during the study.

17.2.1.2 "Off study medication"

Participants, for safety reasons, personal choice or any other reason, may need to go "off study medication;" however, they will *continue with all outcomes assessment, including assessment for diabetes, as planned.*

✓ Going "off study medication" is **not the same** as going "off study." It is important that study staff do not confuse these two definitions.

17.3 RETENTION STRATEGIES AND TOOLS

Prior to the start of enrollment, each site will build on its experience to develop strategies to maximize participant retention and adherence. Examples of several strategies are provided below.

17.3.1 Recruitment Process

At recruitment, study staff should elicit and understand participants' motivation for participation in research. Identify any red flags (e.g., high "no show" rate for clinic visits; monetary motivation for participation).

17.3.2 Informed Consent Process

An informed participant is much more likely to stay in the study and be adherent with procedures; therefore, it is critically important that participants have a clear understanding of what to expect during their participation in the study. Lack of clarity regarding study expectations is a common, and potentially the most important, reason for withdrawal from participation or for being non-adherent with study procedures and visits. *Therefore, the informed consent process is a key retention strategy.* The informed consent form should provide all of the necessary information as clearly as possible while avoiding any confusing or unnecessary jargon. The research staff members performing the consent process must know the study well and must convey study expectations to participants (e.g. 4-year long study), including educating participants on the importance of following all study procedures and completing all assessments, even if they discontinue study pills or have initiated other interventions (e.g. diabetes pharmacotherapy).

Good communication with the participant's primary care physician to inform him/her about his/her patient's progress is very important and a key factor in promoting adherence.

✓ A letter to the primary care physician should be sent *twice a year after each visit* where diabetes is being evaluated (see section below).

Below are several tools that can be used to educate participants and physicians about the study.

17.3.3 Relationships of Participants with Study Staff

All research staff, not just the D2d research team, can influence retention. Everyone the participant interacts with should be pleasant and kind to make the participant's experience more enjoyable and increase retention.

Continuity of care is a high priority for participants. Therefore, each participant should be assigned a primary person (research coordinator, research nurse, or research assistant) she can go to with questions or to report a problem. During the first visit, the participant should be provided with this person's contact information, written on the Participant Information brochure and also provided on the business/appointment card, and told how best to reach the contact person to discuss any urgent or non-urgent issues.

⇒ Study staff should build relationship with participants early in the study. Developing a good rapport with the participant is valuable and will encourage the participant to share concerns or problems that may impact continued participation. Regular contact with the primary person at study visits and phone calls is essential in developing rapport. Additional ideas for developing rapport include:

- Understanding and planning study visits around participants' life events have an impact on adherence.
- Sending a birthday card or holiday card (see section above).
- Making note of significant events a participant reports and asking about it at the next visit (e.g. a vacation, birth of a grandchild, new job).
- Involvement of the Principal Investigator and other team members (e.g. nurses) at visits whenever possible in critically important. This is also of practical value to provide continuity in the event of any staff turnover.

17.3.3.1 Participant Information Brochure

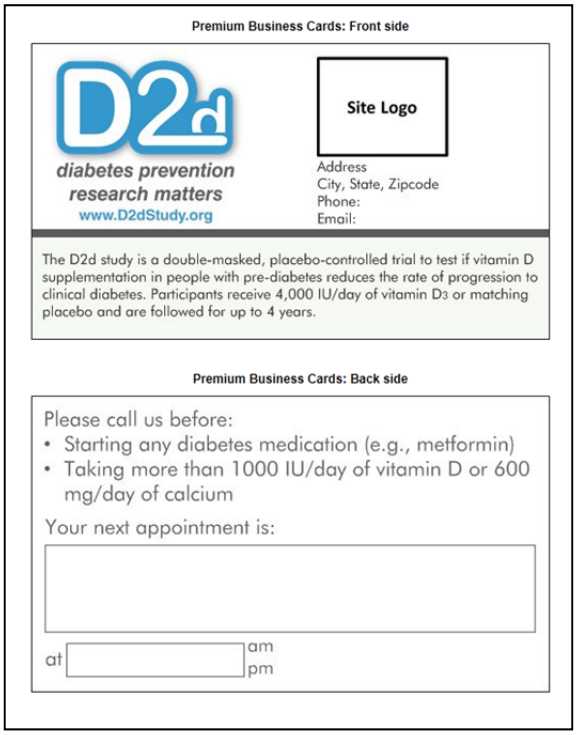
At the baseline visit and every visit thereafter, site staff should give the participant the Participant Information brochure (see Appendix). The site can customize the brochure by entering the clinic contact information. The participant's next appointment will be written on the back of the brochure during each visit. Alternatively, the site may use appointment cards (see later).

17.3.3.2 D2d Folders

Each site is supplied with D2d folders to give to participants at randomization. The folder can be used to hold the participant's copy of the signed informed consent form, the participant' study schedule, D2d business/appointment card and any other study related documents.

17.3.3.3 D2d Business / Appointment Cards

Participants will be provided with a site-specific D2d business/appointment card, at the end of each visit. The appointment cards include the site contact information, participant reminders, and a space to write in the next scheduled appointment. The CC orders the appointment cards for each site (see below for a template). The site provides the CC with the site logo and specific contact information to be included on the front side of the card.



17.3.3.4 Clinical Provider Information Handout

The Clinical Provider Information pamphlet (see Appendix) may be included with the letter sent to a participant's primary care provider when a person is randomized into the study. The pamphlet provides the clinician with details on the study and, together with additional communication tools, is intended to establish a partnership with the clinician.

17.3.1.5 Letters to Primary Care Physicians

Primary care providers (PCP) can assist in promoting continued participation of enrolled participants. Therefore, educating the PCP and other clinical providers about the study at the time of the participant's enrollment, and *engaging the PCP during the study (after each 6 month visit)* by providing regular updates on the study and his/her patient's status, is a study requirement. The following template letters have been developed (see Appendix) for use after enrollment and during the study.

- Template letter to Provider for enrolled participants
- Template follow-up letter to Provider (for enrolled participants not diagnosed with diabetes)

- Template follow-up letter to Provider (for enrolled participants diagnosed with diabetes)

17.3.1.6 Newsletter to Participants

About three times a year, the CC will develop a D2d participant newsletter, for sites to send to participants by mail or e-mail. The newsletter will have updates on the study, a section on healthy nutrition and exercise, and will also include specific tips to promote adherence to study procedures. The CC highly encourages sites to contribute material to the Newsletter. Please send ideas for content to the CC at d2d@tuftsmedicalcenter.org.

17.3.1.7 Follow up letters to participants

Several examples of follow-up letters to participants (e.g. reminders, missed visits, etc.) are shown in the Appendix.

17.3.1.8 Birthday and Holiday Cards

Most people appreciate a personalized note or card. Sites are supplied with D2d birthday and holiday cards to send to randomized participants. The sites are encouraged to write a personal note and sign each card before sending.

17.3.1.9 Occasional brief notes by PI to participants

It is important that the PI maintains contact with the participants during the study. If the PI cannot see participants once a year, it is recommended that the PI send a hand-written card to participant on his/her letterhead following critical visits (e.g. M06, M12 visits). Below is an example of text.

"Dear XX,

I am sorry I missed you at the month 6 visit of the D2d study. I was happy to hear from [name of coordinator] that you are doing very well and I hope you had a nice vacation at the Cape. I am very pleased to let you know that we have completed recruitment ahead of schedule and I thank you for all the referrals. Enjoy the rest of the summer and I look forward to seeing you at the next visit.

Name of PI"

17.3.1.10 Mementos

Participation mementos are provided to sites to give to participants to promote retention, by serving as reminders of the study and as "thank-you" for participating. Mementos are selected to promote the study and a healthy lifestyle. Mementos may include study pill boxes, lunch bags, water bottles, and magnets. All mementos will have the study logo and website to act as a reminder to particpants.

✓ Please see the portal for an up-to-date list of mementos (provided by the CC) and when these should be given to participants.

17.3.1.11 Website

The D2d public website, www.D2dstudy.org will present general study information to the public, including progress updates. The study also will maintain Facebook and Twitter accounts.

17.3.2 Support and Education Program

The D2d Support and Education Program (SEP) will invite participants to attend group meetings, held twice a year at each site, to discuss specific topics in nutrition, exercise and diabetes (e.g., healthy eating strategies for the holidays). These meetings allow the opportunity to meet other participants and serve as a way to enhance retention (see MOP section 12). To improve attendance at these meetings, sites may want to provide reasonable incentives, e.g., snacks and/or small study-related gifts (e.g., coffee mug).

17.3.3 Research Environment

The environment where participants will be seen should be welcoming and comfortable. Participants should be seen on time and wait time should be minimized, especially if they are fasting. Participants should be thanked when they come for scheduled visits and efforts must be made to ensure that participants are respected and stay fully informed throughout the visit. For example, the sites should have extra large blood pressure cuffs, vital signs should not be conducted in front of others, and participants should be informed of what will happen next and of approximate wait times. Sites can provide reading materials and/or access to television or the Internet so that participants can stay occupied during their OGTT visits.

17.3.4 Reminders

Sites will use various types of reminders for upcoming clinic visits and study procedures, including mail or e-mail reminders for adherence with study pills (see Appendix). The use of pillboxes (provided by the study) will be encouraged.

17.3.5 Contact Information

At the screening visit, detailed contact information will be obtained, which should include current address, contact information, and best time and place to contact participants (e.g., home, work, cell phone numbers, e-mail address), as well as contact information for people who know the participants and might be able to contact them. At the baseline and all other visits, participants should be asked to update their contact information. The participant contact information sheet (located with the sample source documents) may be used to keep track of the information.

If a participant's contact information no longer seems valid, a note should be made, but the information should not be discarded, as the contact information may become valid again at a later time (for instance if a participant moved out of a home and back in, or used a prepaid cell phone and needed to refill the balance).

17.3.5.1 Difficult to Contact Participants

Each site is likely to have participants that are difficult to contact. In some instances, the reasons may be clear (e.g., participant does not have a phone, works during business hours). In other instances, the reason may not be clear but it *should not be assumed* that the participant does not want to be contacted. For example,

- If a participant has an outstanding bill at the hospital, she may be wary of answering any call that comes from the hospital. Participants may also be wary of answering calls that come from numbers labeled as private on caller ID. If you suspect this may be the case, consider calling from a different number or contacting the participant via e-mail or certified mail.
- If the participant works odd hours, please leave a message encouraging him to return your call or e-mail you to let you know when it would be a good time to speak.
- Consider calling participants in the evening and weekends.

If the contact information on record does not seem to be valid and staff has unsuccessfully tried directory assistance, consider using web-based tools to look for the participant, as follows:

- www.anywho.com. Research staff can enter a phone number and the website will search for an address. Research staff can also enter a name and state and the website will search for people by that name.
- www.intellius.com. Research staff can enter a name and get contact information. Research staff can also enter a phone number and get an address that is associated with the phone number. This may be of use if a person moved in the same city and kept their landline phone number. The new address can be used to send a letter.
- www.peoplefinder.com.

If you suspect a person has passed away and you cannot contact one of the their contacts, you can use the internet to search the participant's local newspaper's obituaries or you can try to find information in the social security death index by going to http://search.ancestry.com/oldsearch/obit. There is a 14-day free trial.

17.4 SITE TRANSFER AND PARTICIPANT SHARING

In order to retain participants who spend time away from their primary residence (e.g. to a winter or summer home) or permanently move to a different location, a person's participation can be transferred to a different site if the participant permanently moves or can be shared between two sites if the participant moves temporarily or splits time between two homes.

17.4.1 Definitions

Primary site: The D2d site where a participant was randomized.
Secondary site: The D2d site where a participant will be followed for some visits or for the remaining of the study.
Shared participant: A participant who is followed (i.e. comes in for visits) at two different sites, either for convenience or a temporary move.
Transferred participant: A participant who completely transferred participation to a secondary site.

17.4.2 Procedure

If a participant notifies the site that she is moving permanently, temporarily or will be splitting time between two locations the primary site should explore the possibility of the participant being followed at a secondary site. Site staff should thank the participant for her willingness to continue participating in the study at a different location and ask the following preliminary questions:

- Where is the participant moving to (city, state)?
- Is this a permanent move, one-time temporary move or recurrent move (e.g., primary residence is in Maine, but winters are spent in Florida)?
- If a temporary move or recurrent move
    - How long will the participant be away?
    - When will she go and when will she return?
- Will participant have access to transportation?
- When is participant leaving?

Site staff should review the location of the D2d sites with the participant and determine if there are any sites that are within a reasonable travel distance to the participant's home. If so, inform the participant that you will begin the process of transferring or sharing the participant with the secondary site and that you will be in touch regarding the logistics.

17.4.2.1 Joint Management (Shared) Procedure

A participant can be managed jointly (shared) between two sites, if he divides time in two homes or makes a temporary move (i.e. a long-term job assignment). As soon as it is determined that the participant is willing to attend study visits at a secondary site, the primary site should contact the Coordinating Center to set up a call to discuss the logistics with the two sites.
The following will be discussed

- Sharing of source documents

- Consenting participant at the second site. The consent form provides the participant with the study staff and IRB contact information as well as the stipend structure at the secondary site. Site participant stipends vary in amount, frequency and form.
- Plan for obtaining release of medical records to allow for the sharing of information between the two sites.
- Plan for scheduling follow-up appointments.
- Reporting of results to participant and participant's providers.
- Sending visit follow-up letters.
- Site visit payments from the Coordinating Center. The site conducting the visit and entering the data into EDC will receive the payment for the visit.

Communication between the coordinators at the two sites is essential for a successful joint management of the participant. After the conference call, and confirmation that the participant has signed the release of medical information, the participant's EDC folder will be shared with the second site. The primary site must send to the CC a memo confirming that the participant has provided a release of medical information granting the primary site permission to share the participant's information with the secondary site. The CC will then provide the site staff at the secondary site with access to all of the participant's e-CRFs so that they can enter and edit data. Note the secondary site staff will only have access to the shared participant's EDC folder, not other participants from the primary site.

17.4.2.2 Transferred Participant Procedure:

The procedure for transferring a participant from the primary site to the secondary site is as above except that primary site access to the transferred participant's EDC folder will be discontinued after data from all visits and encounters that occurred at the primary site has been entered, queries resolved and is considered ready for locking.

17.5 RETENTION STRATEGY FOR "INACTIVE" PARTICIPANTS

This section defines alternate participation scenarios when a participant would otherwise withdraw consent completely and go "off study."

17.5.1 Maximize data collection

To maximize statistical power for data analyses, sites must make **every effort** to follow all participants for the entire duration of the study and collect as much data as possible, according to the study timeline and procedures.

Participants have the right to withdraw consent at any time and for any reason. However, there may be cases where a participant might be willing to continue in the study in a modified capacity if they are made aware of this possibility.

A participant may express a desire to discontinue participation for a variety of reasons (e.g. not wanting to travel to the clinic for visits due to distance and/or lack of time, experiencing an adverse event, moving to another state or starting a new job). In such instances, the participant may believe that since she cannot adhere to ALL visits and procedures, she no other choice but to quit altogether.

From the study's perspective, however, any follow-up that can take place and any data that can be collected is preferable to none at all, consistent with the intent-to-treat principle.

The alternate participation scenarios described below are a ***last resort*** and must not be given to the participant as an option under normal circumstances, and they must not be offered simply for the sake of convenience.

17.5.2 Gauging participant willingness

When a participant first states their desire to discontinue the study, it is important for study personnel to assess the reason for wanting to end participation and express understanding and flexibility. The participant needs to know that their concerns and feelings are being heard and taken seriously. Depending on these underlying reasons, it may be possible for them to continue in the study without modification, and this should always be the first course of action (for example, the site may offer to see the participant on Saturday mornings). If this is not successful, understanding their reasons will be key to negotiating and developing an alternate participation plan.

17.5.3 Modified study pill distribution

If a participant is not willing or able to come in for all regularly scheduled visits, she may remain on study pills if she agrees to return for safety labs collected at the scheduled annual visits (e.g. M12, M24, M36).

If a participant is unable to come for a semi-annual visit (e.g., month 18, month 30) and had a normal safety assessment done at the last annual visit, the semi-annual visit may be conducted over the phone and, provided there are no safety concerns, a 6-month supply of study pills may be shipped to the participant with a return shipper addressed to the clinic for the participant to return the previous bottle of study pills. The participant needs to return for the next annual visit, before any more study pills are dispensed.

⇒ Pills cannot be shipped to a participant who skips the M06 visit. She needs to return for the M12 visit before receiving more pills.

17.5.4 Alternate participation scenarios

In determining an optimal alternate participation plan, study personnel should start with proposing the most visits and data collection possible, and gradually reduce these, only as necessary, based on the participant's response.

17.5.4.1 Commitment to at least one visit per year, agrees to non-visit contact

Scenario: A participant is unable or unwilling to adhere to the complete study schedule but is willing to come in for the annual visits. These annual visits should coincide as close as possible with their original schedule.

- Optimally, the participant agrees to the full annual-type visit each year (OGTT and safety labs).

- If the participant agrees to the yearly visits, but is NOT willing to have the OGTT done, then a visit with fasting testing may be performed (A1c, FPG, and safety labs).

✓ Pills may be shipped to a participant who does not return for a semi-annual visit but, had safety measures completed at the prior annual visit and plans to return for the next annual visit (see section 17.5.3).

Note: These occurrences are expected to be rare.

A non-visit (phone or email) follow up should be conducted in lieu of regularly scheduled study visits and contacts (M06, M18, M21, etc.). These non-visit encounters should coincide with the participant's regularly scheduled contacts (M06, M09, M12 etc.) based on participant's willingness. If the participant is not amenable to frequent contact, it is up to the discretion of the site to determine a sustainable and tolerable schedule. A source document template is available (MOP section 13) that provides all the questions to be asked during the encounter.

If a diagnosis of diabetes made outside of the study is reported during a non-visit contact, all information needed for the adjudication process should be obtained (per MOP section 18.5)

Assessment of the diabetes outcome will follow standard procedures to the extent possible (see MOP section 18).

17.5.4.2 No definitive commitment to a specific schedule, agrees to non-visit contact

Scenario: A participant does not return for a scheduled visit and is unable or unwilling to commit to future visits, but agrees to non-visit contact.

- Because safety labs cannot be assessed with certainty, study pills must be discontinued.
- The participant is encouraged to come in for any visit he is able to complete. Data collected at such visits should follow annual (e.g., OGTT, safety labs) or semi-annual (e.g. A1c, FPG) type visits.

✓ Pills cannot be shipped to participants who do not commit to future visits. Pills may be re-started if the participant's situation changes and he is willing to return for at least yearly visits (for safety labs).

A non-visit (phone or email) follow up should be conducted in lieu of regularly scheduled study visits and contacts (M06, M12, etc.). These non-visit encounters should coincide with the participant's regularly scheduled contacts (M06, M09, M12 etc.) based on participant's willingness. If the participant is not amenable to frequent contact, it is up to the discretion of the site to determine a sustainable and tolerable schedule. A source document template is available (MOP section 13) that provides all the questions to be asked during the encounter.

If a diagnosis of diabetes made outside of the study is reported during a non-visit contact, all information needed for the adjudication process should be obtained (per MOP section 18.5)

17.5.5 EDC data entry

Visits that coincide with the original schedule should be entered in the appropriate visit folder in EDC.

Data obtained via phone/email contact in lieu of an in-person visit, will be entered by selecting the visit type as a “non-visit encounter” on the Visit Date e-CRF. This will generate a non-visit e-CRF.

If the participant has committed to at least one study visit per year and wants to remain on study pills, then the Study Pill Distribution form should also be completed. This applies only after the M12 visit (see 17.5.3).

17.5.6 Participant stipends

In general, since the study does not reimburse participants for non-visits (phone or email), participants who do not come in for visits do not receive stipends. However, this is a site-specific issue.

17.5 APPENDICES

Appendix 1 Participant Information Pamphlet

Appendix 2 Clinical Provider Information Pamphlet

Appendix 3 Letter to Provider Enrolled Participant

Appendix 4 Letter to Randomized Participant

Appendix 5a Follow-up Letter to Provider (enrolled participants not diagnosed with diabetes)

Appendix 5b Follow-up Letter to Provider (enrolled participants diagnosed with diabetes)

Appendix 6 Sample Follow-up and Reminder Letters to Participant

Appendix 7 Newsletter to Participants (see http://www.d2dstudy.org/newsletters)