Manual of Procedures (MOP)
Section 21. Non-diabetes Outcome Assessment

Table of Contents

21.1 OVERVIEW OF NON-DIABETES OUTCOMES

As the largest modern trial enrolling participants with prediabetes, the D2d study can achieve the following additional aims: (1) evaluate the effect of vitamin D supplementation on incident cancer (CA) and cardiovascular disease (CVD); (2) define the CA and CVD risk in people with prediabetes.

- ✓ Existing D2d study procedures and processes will be harnessed to obtain the data needed to adjudicate cancer and cardiovascular disease outcomes in the most efficient manner.
- ✓ There is no additional burden to participants and no safety concerns. Minimal additional burden for sites is expected.

21.2 CANCER OUTCOME AND RISK ASSESSMENT

Cancer outcomes will be assessed at scheduled study encounters (4 times/year) by asking a few specific questions related to cancer screening and any diagnoses of cancer (see source documents in MOP section 13).

The following are cancer / pre-cancer related outcomes that the D2d study is interested in:

- Cancer diagnosis of any type
- Colonoscopy (preventive or symptom related)
- Breast biopsy
- Prostate biopsy
- Skin cancer

Cancer risk: D2d is interested in the following factors that may impact a participant's risk of certain cancers:

- Family history of cancer in first degree relatives
- Cancer screening rates: mammography and colonoscopy/sigmoidoscopy

21.2.1 Cancer Outcome Assessment Implementation

The D2d Cancer Source Data Collection Form – Initial (see MOP section 13) will be used first to collect data since randomization. At subsequent visits, the D2d Cancer Source Data Collection Form – Subsequent (see MOP section 13) will be used to collect data since the last encounter (phone or visit).

- Each time a participant responds positively to a question or reports a diagnosis of cancer, site staff will collect supporting medical record documentation related to the event (e.g., physician notes, pathology reports, laboratory results). The **Cancer Record Submission Checklist/Coversheet (Appendix 2)** will be utilized to ensure essential records are collected.

- As a secondary method for identifying potential cancer-related events, the CC will examine all reported AEs. For any that *may* harbor cancer, the CC will either query the sites for additional information or ask the site to also enter the event on the Non-Diabetes Outcome Cancer e-CRF (see section 21.2.2) and collect the records.

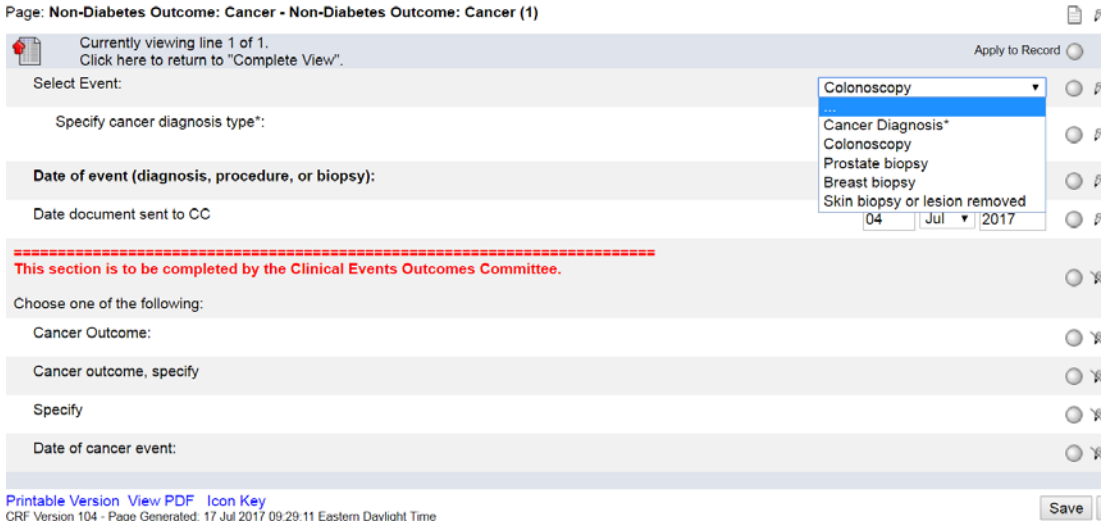
- Site staff will de-identify the records and send to the CC with Appendix 2 as a cover page.

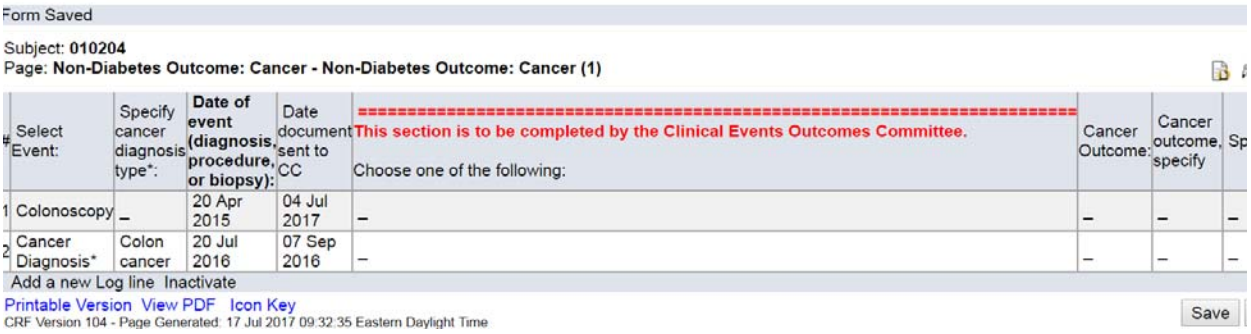
Upon receipt of the records, the CC will organize into an event file, communicate with the site regarding incomplete files, and, once complete, will forward the file to the Cancer Clinical Events Committee (CA-CEC) for adjudication. The CA-CEC will review the information and the event adjudication will be entered into the EDC by the CC.

21.2.2 Cancer Outcome Assessment e-CRF completion

- When a participant responds positively to a cancer question or reports a diagnosis of cancer, the site will initiate the Non-Diabetes Outcome Cancer e-CRF.

  This e-CRF is added utilizing the "Add event" drop down on the participant's EDC homepage. After the form is added, it will appear in the listing of forms on the left side of the screen. The log form is similar to the adverse event form in EDC. Multiple cancer events will be captured in the same log form by adding a row (as in the AE log form). Please see examples below.





→ **NOTE**: When a participant reports the diagnosis of cancer, the event will also need to be reported as an adverse event, following established procedures.

→ Diagnostic or screening procedures are not entered as adverse events, (e.g. having a mammogram or colonoscopy are not adverse events).

→ Any events that are considered a *cancer-related* event (as identified by the CC), but do not fit in any other category in the "select event" dropdown menu, should be entered as "Cancer Diagnosis" (this includes *possible* cancer diagnoses).

21.2.3 Cancer Risk Assessment Implementation

At the next scheduled visit, the site Investigator, Research Coordinator or designee will inform the participant that the D2d study is interested in learning about the risk of cancer among D2d participants and the study is collecting information on family history and cancer screening rates. The participant will be provided with the Cancer Screening/Family History Questionnaire (see appendix 4) and asked to complete it. If the participant needs assistance completing the form, the site staff can assist the participant. This form is completed once during the study.

21.2.4 Cancer Risk Assessment e-CRF completion

After a participant completes the Cancer Screening/Family History Questionnaire, the site staff will initiate the Cancer Screening/Family History e-CRF, by adding it from the "Add event" drop down on the participant's EDC homepage. After the form is added, it will appear in the listing of forms on the left side of the screen.

21.3 CARDIOVASCULAR OUTCOME ASSESSMENT

CVD outcomes include only events that require hospitalization and are classified as Serious Adverse Events (SAE); therefore the general questions currently asked for the collection of SAEs will be utilized. These will be adjudicated by the CVD Clinical Events Committee (CVD-CEC).

21.3.1 Implementation

- Sites will continue to report CVD SAEs via the EDC system, collect supporting documentation related to the event (e.g., medical records, laboratory results), de-identify the data and submit to the CC, as routinely done with all SAE, for review by the Safety and Outcomes Subcommittee.

- In addition, the site will utilize the **CVD Record Collection Checklist (Appendix 3)** to ensure that essential records are collected for adjudication by the CVD-CEC reviewer. The checklist is included in the SAE packet sent to the Coordinating Center.

→ If the CC reviews an SAE and considers it appropriate for CVD-CEC adjudication and the checklist (Appendix 3) was not used to collect essential records, the CC will ask the site to complete the checklist and submit any additional medical records.

→ Upon receipt of the records, the CC will organize the records into an event file, communicate with the site regarding incomplete files, and, once complete, will forward the file to the CVD-CEC for adjudication. The CVD-CEC will review the information and the event adjudication will be entered into the EDC by the CVD-CEC.

21.3.2 CVD Outcome Assessment e-CRF completion

- No additional forms need to be completed EDC.

21.4 APPENDICES

Appendix 1a D2d Cancer Source Data Collection Form – Initial ***(see Source documents, MOP 13)***

Appendix 1b D2d Cancer Source Data Collection Form – Subsequent ***(see Source documents, MOP 13)***

Appendix 2 Cancer Record Submission Checklist/Coversheet

Appendix 3 CVD Record Submission Checklist/Coversheet

Appendix 4 Cancer Screening/Family History Questionnaire ***(see Source documents, MOP 13)***