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1. Background/Rationale:

This electronic data capture system (EDC) has been designed and developed to support the research goals of VICC clinical trial protocol HEM1538; please see the protocol for more information on study objectives.

For more details on variable definitions, also refer to the data dictionary.

2. Overview

HEM1538db was developed and is hosted by the Center for Quantitative Sciences (CQS) at Vanderbilt University. CQS coordinates and integrates the work of quantitative scientists across the disciplines of biostatistics, bioinformatics, biomathematics, computational biology, biomedical engineering, and other related fields, with the end goal of building bridges and streamlining quantitative collaboration for improved biomedical research. One of many services offered by CQS is the Data Coordinating Service (DCS). The DCS team works with investigators to:

- Define technical requirements and expectations for data management, including database design and routine data reporting.
- Develop appropriate data dictionary and data entry manual to ensure comprehensive documentation of data elements in support of data collection goals.
- Develop custom data collection, management, and storage solutions, appropriate to the needs of each project.
- Maintain ongoing communication and service to provide training on data entry, ensure IRB compliance, address any issues or bugs and ensure data quality control.
- Provide routine and custom data reports and summary statistics as data accrues.

Please direct any general questions or concerns to:
Dr. Lynne Berry, *Deputy Director (*lynne.d.berry@vanderbilt.edu*) or*
Ms. Lena Hussain, *Associate IT Project Manager* (lena.k.hussain@vanderbilt.edu)

For more technical inquiries relating to the database, please contact:
Mr. David Biagi, *Health Info System Project Manager II (*david.biagi@vanderbilt.edu*)*

3. Disclaimer

The examples utilized in this user manual are fictitious. Real patient data are not shown.

At times, testing within the live production EDC may be necessary. All test cases will be identified with site ID 99 (e.g., HEM1538-99-001). Test cases will be deleted as soon as possible following testing. If, however, you should see a case with site ID 99, please be aware that this is a test case.

4. Instructions: General

To ensure accurate data entries, the Center for Quantitative Sciences recommends that each user follow the instructions provided in this manual, step by step, for the first several patient entries or until familiar with how to complete accurate entries.

Ideally, we would instruct users to enter data in real time; however, because that is not always feasible, we ask that users enter data in the order that it happened.

For example, when you attach treatment period visits to a patient record, the EDC will automatically attach these sequentially, per study calendar (i.e., C1D1 will be created first, then C1D8, etc.). It is possible to create, say, C1D8, leave all forms for that visit blank, skip ahead to create C1D15, and enter data for

C1D15 prior to data entry for C1D8. Again, however, we encourage data entry in the same order in which study events occurred, whenever possible.

5. Web Interface

5.1 Accessing the web interface

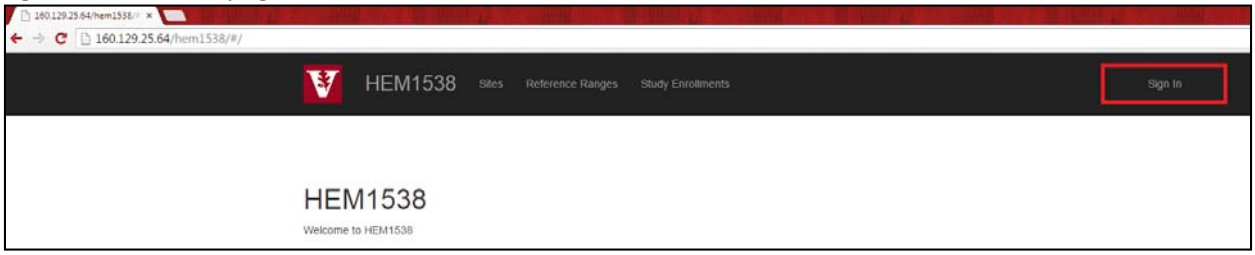
The HEM1538db web interface is available at: https://cqsclinical.mc.vanderbilt.edu/hem1538
This application is optimized for use with the latest edition of either Google Chrome or Mozilla Firefox. Please note that we do NOT support Internet Explorer, due to lack of modern features in IE. Please use Chrome or Firefox to access the EDC.

To access the web interface, you must have a valid user account. To set up an account:

1. Send an email to Lena Hussain (lena.k.hussain@vanderbilt.edu) with the ***full name, email address (non-Vanderbilt users) or VUNetID (Vanderbilt users)***, the ***user role*** and ***site affiliation of the person who needs an account***. This email must come from an authorized study contact in the trial coordinating center at Vanderbilt.
2. The CQS will set up an account linked to the email address or VUNetID and performance site indicated.
    a. If you are a Vanderbilt user, you may proceed directly to login with your VUNetID and e-password
    b. If you are a non-Vanderbilt user, you will receive an email with a link and instructions to confirm account setup and select a password. Upon confirmation, the account becomes active, and you may login to the web interface. Please activate accounts promptly.

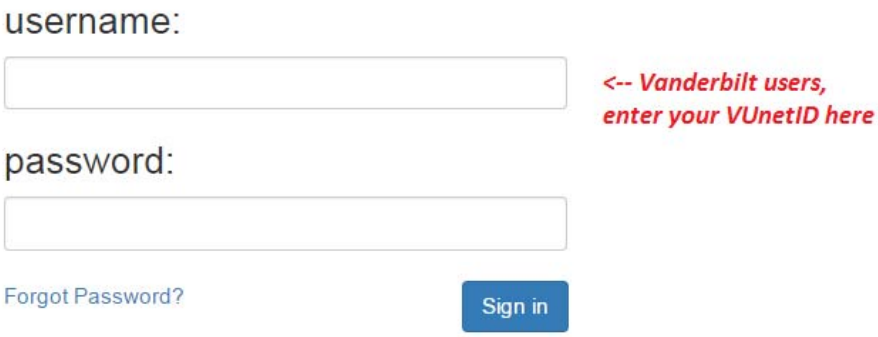
To log into HEM1538db:

1. Navigate to: https://cqsclinical.mc.vanderbilt.edu/hem1538 and click on the 'Sign in' icon at the top right corner of the page.



2. A) For non-Vanderbilt users:
Sign in with your email and the password you have selected.

B) For Vanderbilt users:
Sign in with your VUnetID and password



5.2 Navigating the web interface

5.2.1 Tabs

After logging into HEM1538db, users will see a navigation panel consisting of a maximum of three sections of the EDC. Permission to enter and/or access data in these sections will vary depending on your user role. If you do not see a section of the EDC you believe you need, you may have the incorrect user role, and should speak to your PI or the trial coordinating center. The following are all of the EDC sections:

- HEM1538. In this section, users will find a welcome note, news or updates about HEM1538db, and reference material such as the user manual, data dictionary, and tutorial.
- Reference ranges. This section captures upper and lower bounds of normal findings for each lab assay at each lab where testing is performed.
- Study enrollments. This section comprises the majority of the EDC, and is your entry point to all patient records. Please note this page tends to load slowly, as the system works in the background to filter the patient set to those accessible to you based on your permissions. Please allow this page a few seconds to load.

5.2.2. Patient view pages

A ***patient view page*** is created for each patient enrolled on the trial and entered in the database (refer to section 5.5 for an example). From the patient view page, data entries can be made into all forms for that patient. The view page consists of three tabs (log forms, visit forms, and deviations). The patient case report forms (e-CRFs) are divided among the tabs as follows:

Patient view page: log-forms tab

- Adverse events forms
- Medical history form
- Concomitant medication form
- Comments form

Patient view page: visit-forms tab

- All study-calendar and unscheduled visits with the subset of procedure and assessment forms relevant to each visit. Visit forms are described in greater detail in section 5.7.

Patient view page: deviations tab

- Deviations form

Patient log-forms tab and visit-forms tab: These tabs on the patient view page will be important starting points for the majority of data-entry work. We will refer to these views throughout this user manual. Please see screenshots in sections 5.6 and 5.7.3. To toggle back and forth among the log-form, visit-form, and deviations tabs, simply click on the tab of interest on the patient view page.

5.3 General tips

- Treatment period visits. Because each patient may complete a different number of treatment-period visits, depending on his/her disease and treatment course, the HEM1538db is set up for dynamic addition of treatment-period visits to a patient record. With each new treatment period visit completed by a patient, you will have the opportunity to create this visit in the EDC patient record by indicating that a new treatment period visit has occurred (detailed instructions in section 5.7). The EDC will add treatment-period visits in order, per study calendar, i.e.: C1D1, C1D8, C1D15, C1D22, C2D1, C2D8, C2D15, C2D22, C3D1, C3D15, C4D1, C4D15, C5D1, C6D1, C7D1, C8D1, etc.

- Form attachment to visits. For entry of data associated with a study calendar or unscheduled study visit, you will be asked to provide data relevant only to the procedures or assessments performed at that visit. Therefore, on the visit-forms tab of the patient view page, you will see each study visit associated with a different set of forms. If a form appears for a particular visit, that form must be completed for that visit—even if the associated protocol-specified procedures or assessments were not performed. Within the form, you will have an opportunity to indicate any procedures or assessments that were not performed, along with the reason for the omission. **Any omission that constitutes a protocol deviation also should be reported in the deviations form**.

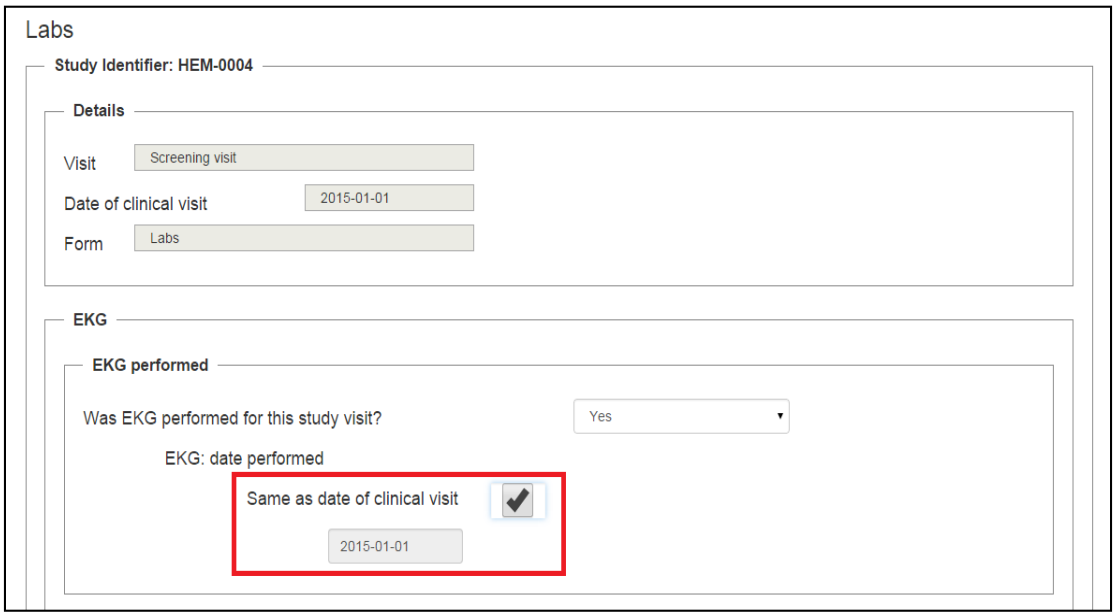
- Variable display within forms. Similar to differing attachment of forms to differing visits, display of form sections, subsections, as well as individual fields is dependent on visit type as well as other criteria. For example, in some forms, differing variables will display depending on the patient diagnosis (MF vs. PCV vs. MDS/MPN). As with form attachment to visits: **if a variable appears on a particular form for a particular patient for a particular visit, that variable must be completed**. You will be unable to finalize forms with incomplete data. If you are uncertain how to complete a variable for a particular patient, please contact the trial coordinating center or the CQS for guidance.

- Draft and complete status. Most forms in the EDC have the option of being saved as a draft ('incomplete' status), or saved as complete. Use the draft mode when you are called away in the middle of data entry, and wish to save your work thus far, but have not yet completed the form. Alternatively, use draft mode if you are still waiting on data to complete the form (for example, some labs have come back, but other labs are still pending). Use complete mode when all of the findings for a particular form are available, and you have completed the form in its entirety. When you save in complete mode, validations on the form will run when you click the submit button; these validations will alert you if you have left any fields blank, or have entered any data that violates a logic check or a protocol-specification check. You may then review your work, correct, the error, and resubmit. If you do not know how to correct the error or realize you are missing required data, change the status of the form to draft, and submit in draft mode; validations will not run, so you will be able to submit incomplete data. **Note that forms may NOT be verified by the data monitor or signed off on by the PI until they are saved in complete mode**; therefore, for accurate and timely data management, it is important to return to draft-status forms as promptly as possible to complete data entry.

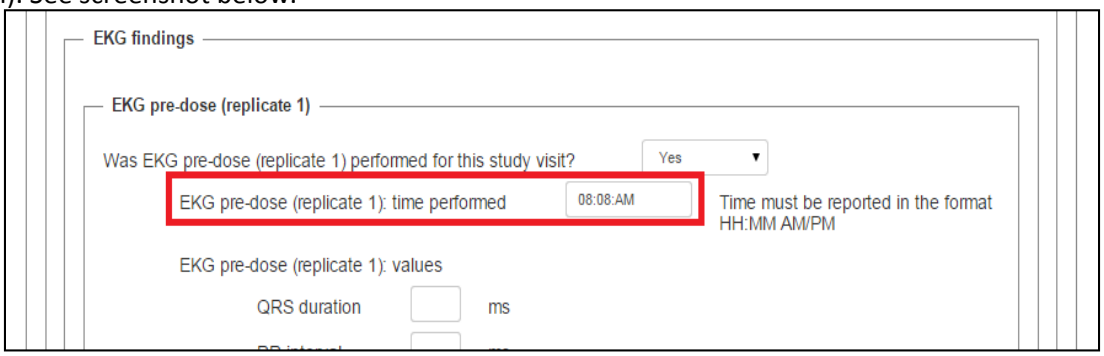
- Recording dates. Please use the format YYYY-MM-DD for entry of dates. For dates associated with medical history and concomitant medications, incomplete and unknown dates are permitted. Please use the following to record incomplete or unknown dates:
    - For unknown day, enter YYYY-MM-99.
    - For unknown day and month, enter YYY-99-99.
    - If all three components are unknown, enter 9999-99-99.

  Note that trial-specific visit, procedure, and assessment dates may not be unknown, and must be entered in their entirety.

- Recording dates: same as date of clinical visit. Per protocol, study-calendar procedures and assessments may occur within a permitted window around the date of the associated clinical visit. Therefore, you will be asked to record the actual date of any procedure or assessment. When procedures are performed on the same date as the clinical visit, you may simplify your data entry by selecting the 'Same as date of clinical visit' checkbox when asked to record the date of the procedure. When the checkbox is ticked, the clinical visit date will auto-populate into the field for procedure date. An example is shown below. **Important**: when procedures are performed on a different date than the clinical visit date, you will need to enter the actual date directly into the date field, using the YYYY-MM-DD format.



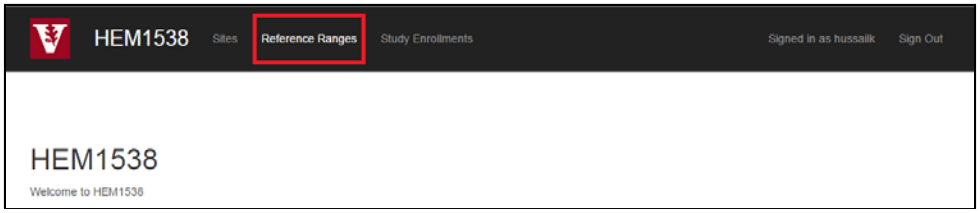
- Recording times. Please use the format **HH:MM AM/PM**. You must enter a space between the minutes and the AM/PM. Also, if the hour or minute is a single digit, be sure to enter a leading zero. For example, to record the time of eight o'clock in the morning, please use 08:00 AM (rather than 8:00 AM). See screenshot below.



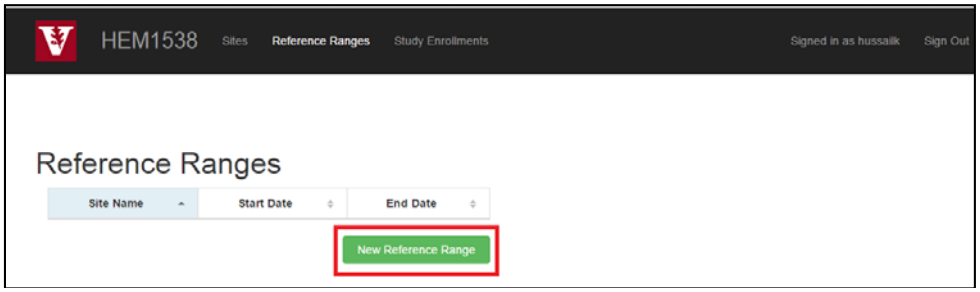
5.4 New entries: reference ranges

The reference range form captures the upper and lower bounds of normal findings for each lab assay at each lab where testing is performed. To enter the reference ranges for your lab:

a) From the navigation panel, click on 'Reference Ranges'.



b) Click on ‘New Reference Range’.

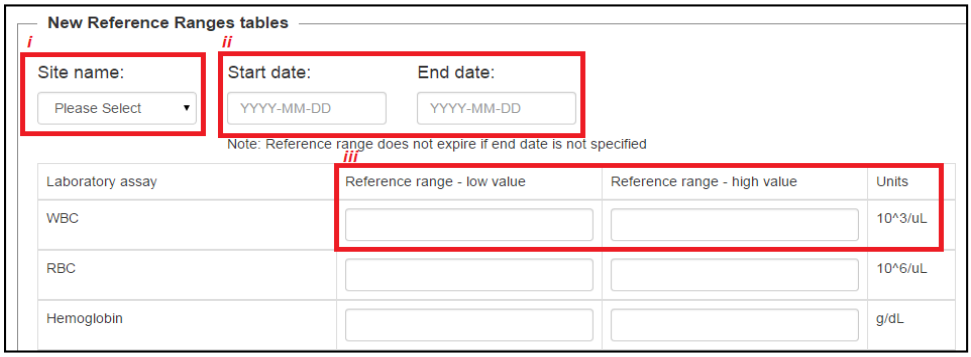


c) Fill out the form:

a) From the ‘Site name’ dropdown menu, select the name of the institution for which you wish to enter lab value reference ranges.

b) Enter the start and end dates during which these reference ranges are valid.

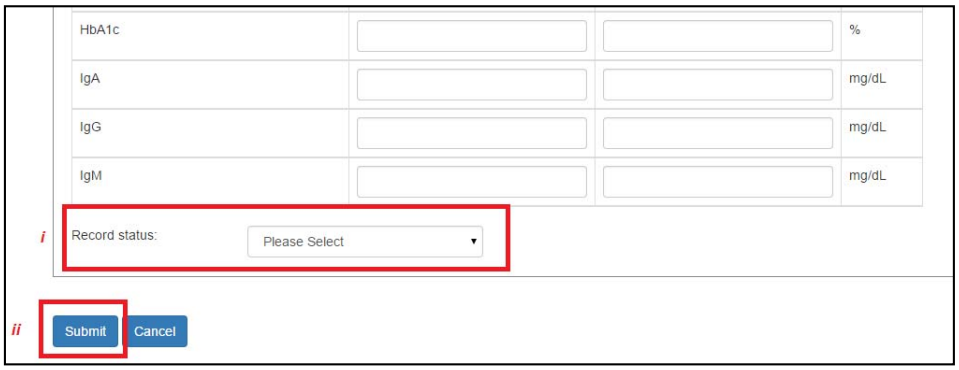
c) Enter the low and high bounds of normal for each laboratory assay.



d) Mark the record status and submit:

a) Mark the record status as ‘draft’ or ‘complete’ (see general tips in section 5.3)

b) Click ‘Submit’.



TIPS:

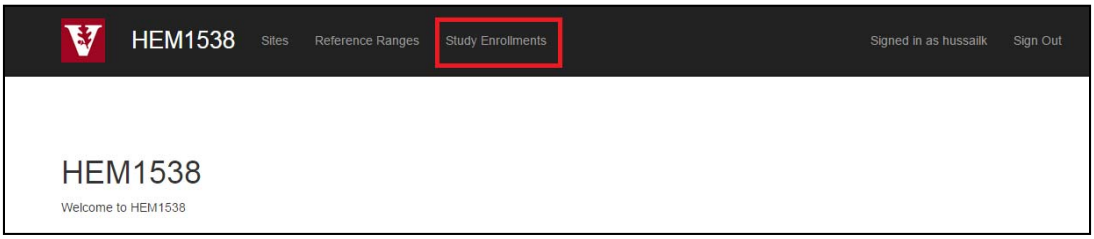
- **PLEASE NOTE**: You must click the ‘Submit’ button before navigating away from the page. Although data points appear in the table, they are NOT saved in the database until the ‘Submit’ button is clicked.
- For correct entry of date values, please see general tips in section 5.3.
- Upon initial entry of a reference-range record, the end date for the reference range may be left blank. This indicates that the reference ranges should be considered valid for the duration of the study. If there is later a change to this lab’s reference ranges, the record may be edited to add the end date, and the revised ranges may be added in a new record.

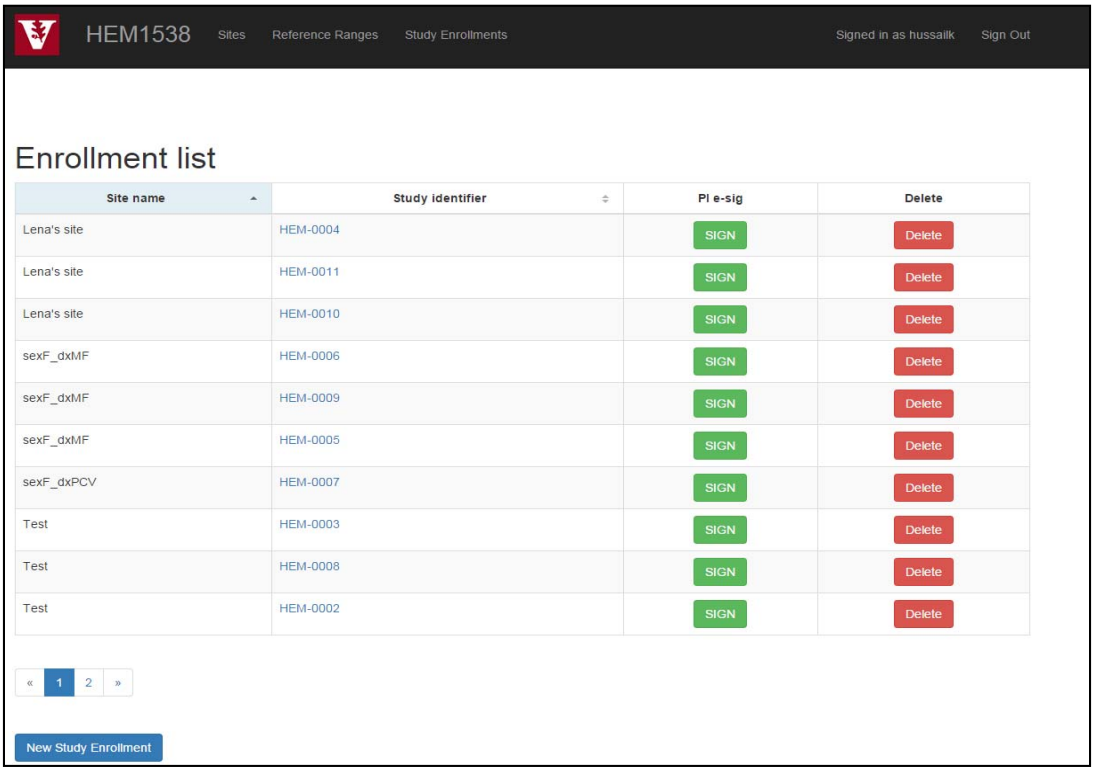
- Entries into this form do not need to be in order. For sample, you may enter the range for INR first, then skip back to WBC, etc.

5.5 New entries: Study enrollment

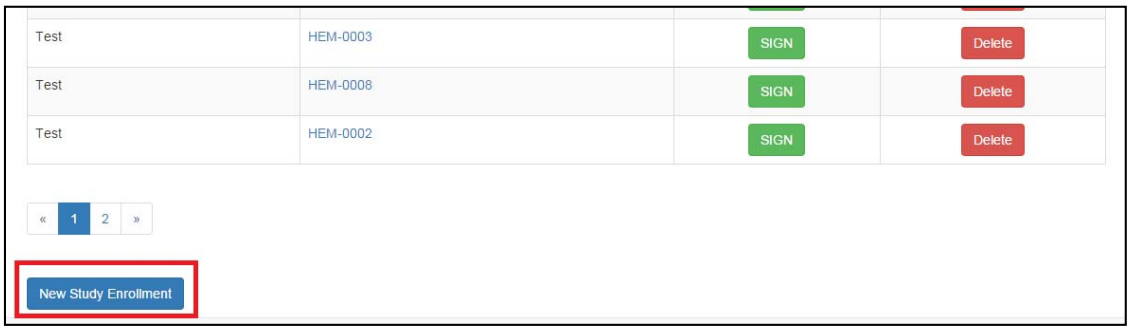
To enroll a patient in the EDC:

a) From the navigation panel, click on the 'Study Enrollments' tab. Here, users will see a listing of the study identifiers for all patients in the database enrolled at their site or according to their permissions.

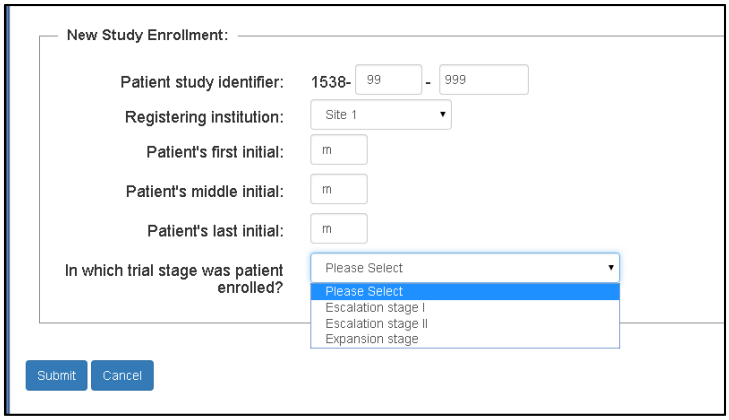




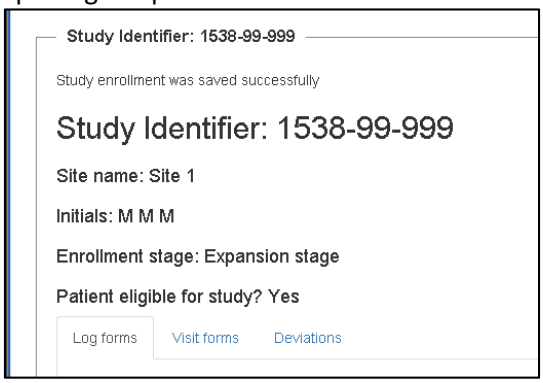
b) Click on 'New Study Enrollment' at the bottom left corner of the page.



c) Enter all requested data into the appropriate fields. Once data entry is complete, click on 'Submit' to save the entry.



d) Upon submission of the study enrollment form, you will be redirected to the ***patient view page*** for the patient you have just enrolled. You will see the following on the patient view page:
   a) A message indicating successful creating of the new patient record.
   b) The study identifier you have assigned to the patient, in the format 1538-XX-YYY, where XX is the two-digit site ID and YYY is the three-digit patient ID. Please note: the study identifiers as shown in the screenshots in this manual do not necessarily conform to this pattern, as these are general identifiers for demonstration purposes only. In the live database, identifier will all conform to 1538-XX-YYY.
   c) The study enrollment information that you have just entered, along with a default eligibility status. (Patients entered into the database are considered eligible for the study until the patient record is edited to indicate otherwise, in the event that later information reveals an eligibility failure.)
   d) Three tabs for completing the patient's other forms

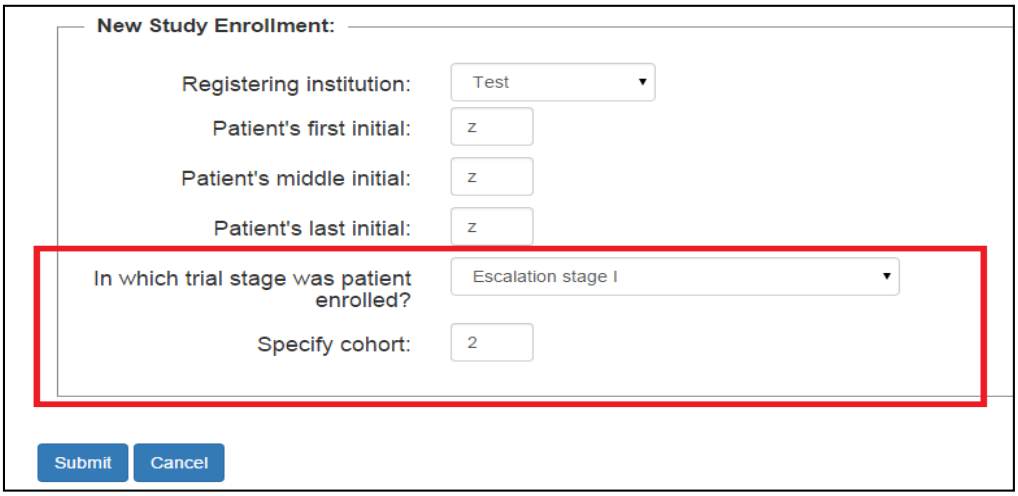


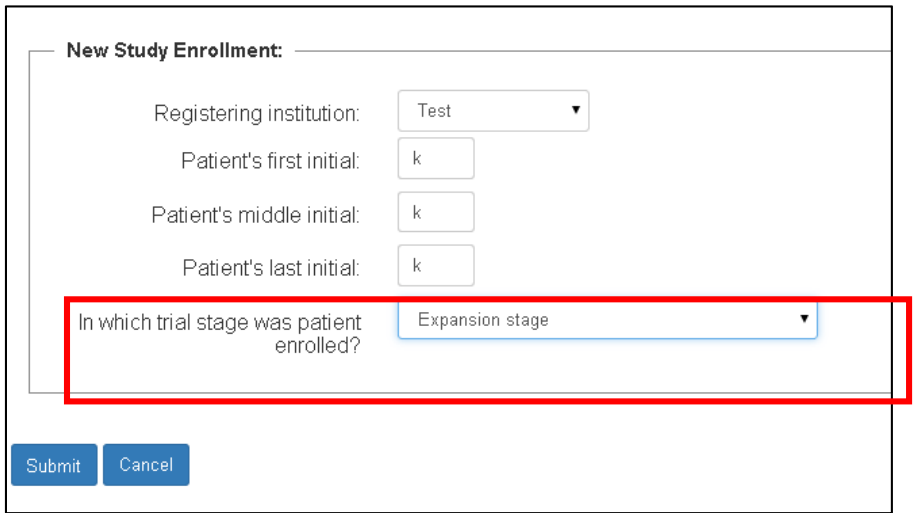
TIPS:

- As shown above, each patient's assigned study identifier will display at the top of the study identifier box in the ***patient view page***. This identifier will be the identifier of record for all study-related communications. The trial coordinating center maintains concordance between the study identifier and true identifiers (i.e., name and medical record number). In addition, trial performance sites are encouraged to maintain a local concordance log to facilitate and ensure accurate data entry.
- From the enrollment list page, you can enroll a new patient, as described above. This page also allows you to navigate to the record for any patient already entered into the database (and visible to you according to your user permissions), by clicking on the study identifier for that patient. To more easily find a patient of interest, the enrollment list may be sorted by study identifier (click on the up/down

arrows in the study identifier column header) or by site (click on the up/down arrows in the site column header).

- After enrollment of a new patient, the very next data entry that must occur for that patient is creation of the screening visit, and completion of the baseline covariates form. **Other data entry will be blocked until the baseline covariates form is complete**, due to key data contained in the baseline covariates form, which is needed to provide information for the display logic and other logic-checks incorporated into other forms.
- If there is an error in enrolling a patient into the database, the enrolment may be deleted, or the patient information may be edited. Note, however, that patients may be deleted ONL Y prior to submission of any associated forms. Therefore, if an error is made and a patient needs to be deleted, please do so promptly to avoid confusion.
- As noted in the general tips, conditional display is incorporated throughout HEM1538db. To minimize data entry error and save time, form sections, subsections, and variables are displayed only when those data are required per study calendar or other criteria. For example, the HEM1538 trial includes both an escalation stage (in which patients are enrolled in dose-escalation cohorts) and an expansion stage (in which all patients are enrolled at the doses established during the escalation stage). Therefore, in the study enrollment form, for patients enrolled in escalation stage I or II, a cohort must be specified; however, for patients enrolled in the expansion stage, the 'Specify cohort' field does not display. Please see screenshots below.





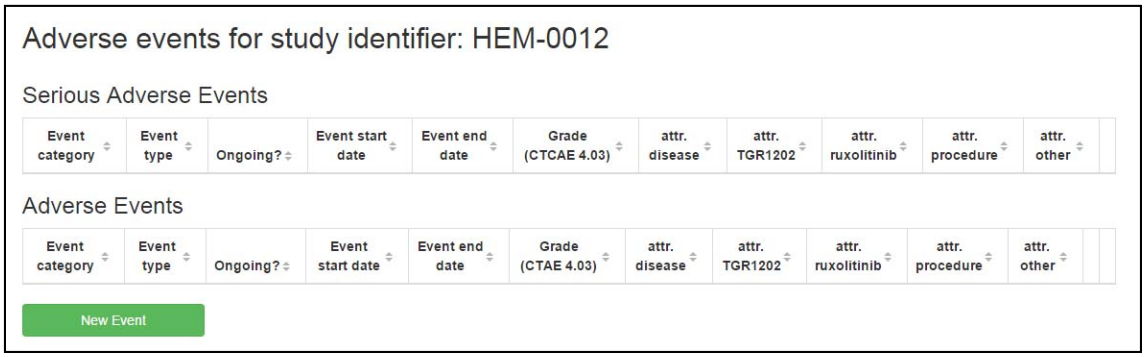
5. 6 New entries: Log forms

Next we will cover data entry into the log forms. Note, however, that in real-time usage of the HEM1538db, data entry for newly enrolled patients must start with creation of the screening visit and completion of the baseline covariates forms, as described in the tips above.

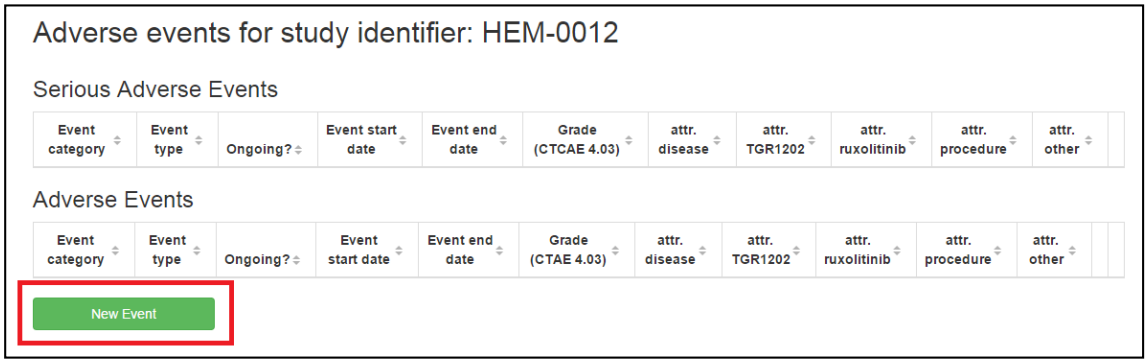
5.6.1 New adverse event

To enter a new adverse event for a patient:

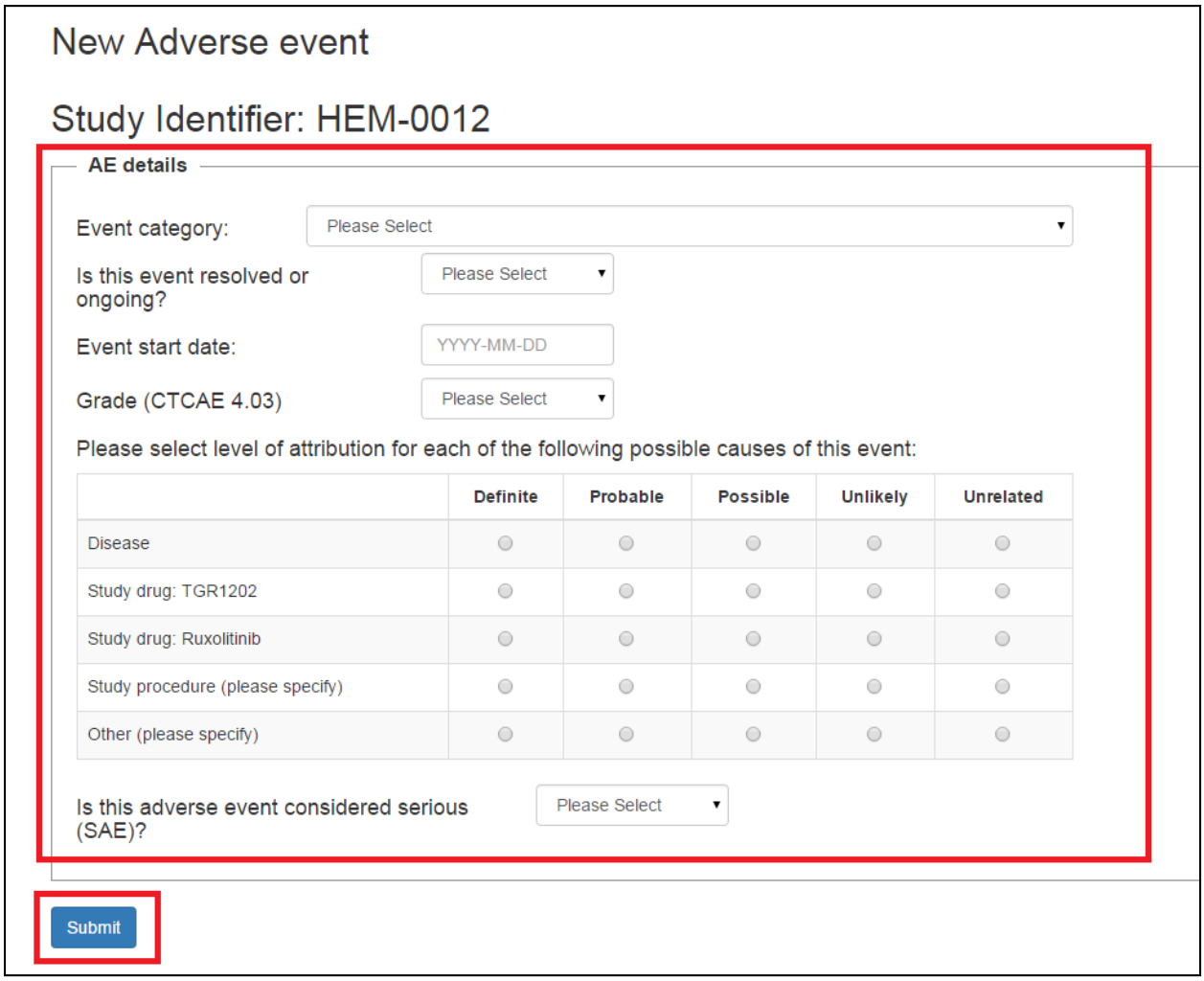
a) From the *log forms* tab of the *patient view page*, click on 'Access log' and the AE log page will load.



b) From the log, click on 'New Event'.



c) Complete the form and click 'Submit' to save the entry. You will be redirected to the adverse event log for this patient, where you can enter additional adverse event data as applicable.

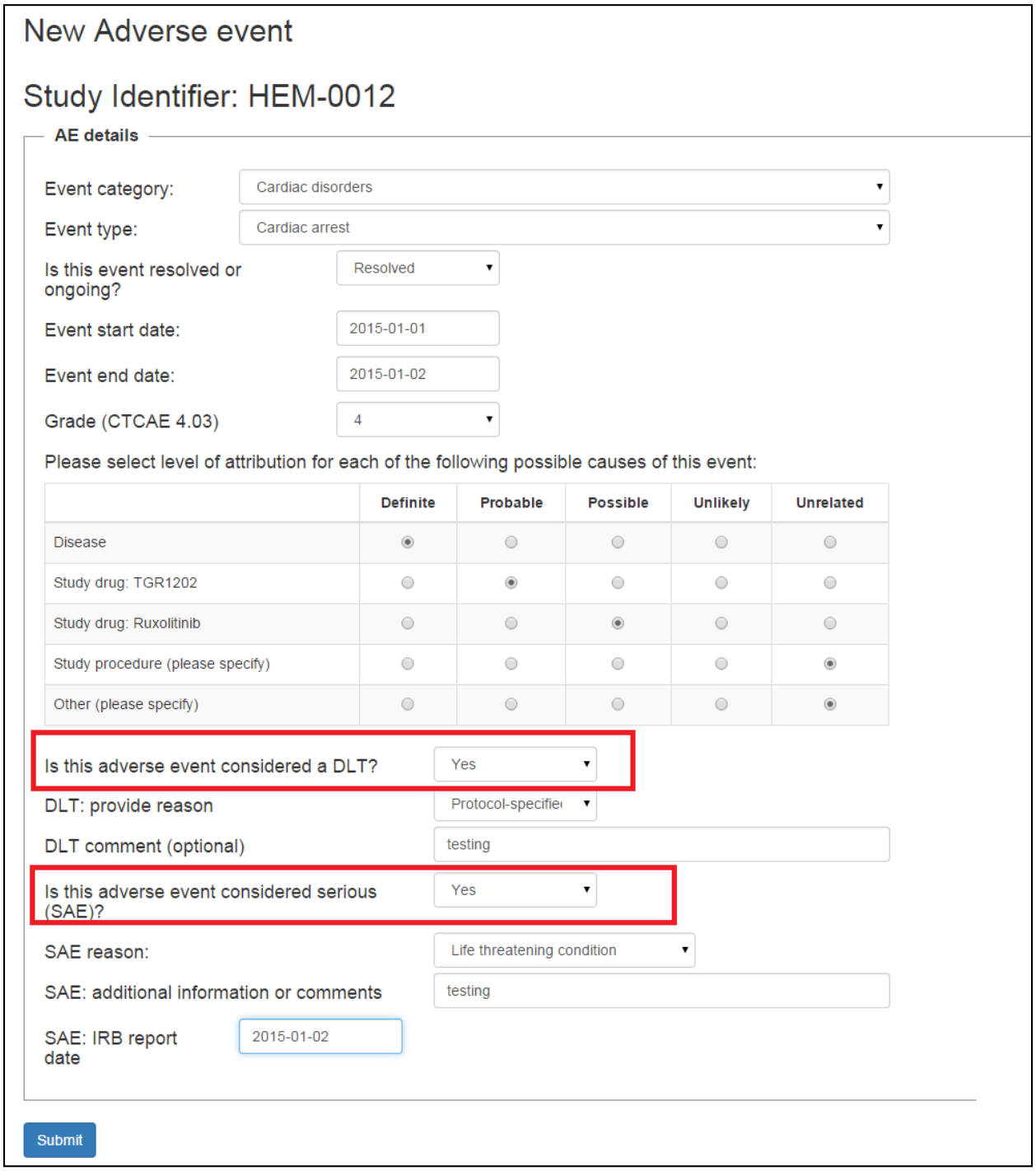


TIPS:

- Remember that the baseline covariates form in the screening visit must be completed before entering any k records for a patient
- Note that adverse events of grade less than 3 are not reportable for this study, with the exception of events of special interest, which include anemia, neutropenia, thrombocytopenia, and infections. For these events of special interest, all applicable event grades will be available for selection in the grade dropdown menu; for other events, grade selection is restricted to 3, 4, and/or 5 (as applicable per event type).
- Dose-limiting toxicities (DLT) will be captured for this trial during treatment cycle 1 only. You will be asked whether an adverse event should be considered a DLT only if the event start date falls within cycle 1, and only if the event attribution to TGR-1202 and/or ruxolitinib is greater than 'unrelated'. When the DLT question displays, please refer to the study protocol for DLT criteria or ask your PI if you are uncertain whether a particular event should be considered a DLT. If you do indicate that an event should be considered a DLT, follow-up questions will appear on the AE form (please see screenshot below); please complete these questions. In addition, when you submit the AE form with

a DLT indicated, an email from the EDC to the trial coordinating center is generated; the trial coordinating center will follow-up with you as needed for additional information.

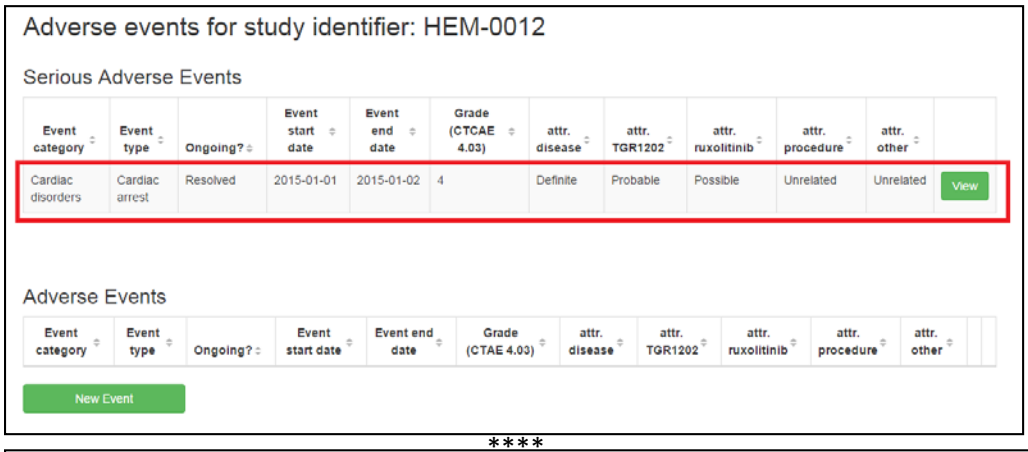
- If an adverse event is considered a serious adverse event (SAE), be certain to select 'Yes' in response to the question, 'Is this adverse event considered serious?' Follow-up questions will display on the form (please see screenshot below); please complete these variables. Please refer to the HEM1538 protocol for criteria for classifying an AE as serious, and for other important information regarding obligations related to the reporting and follow-up on SAEs.



5.6.1.2 New entry: SAE follow-up

a) SAE follow-up in HEM1538 is structured as a review and potential revision of any and all data points from the initial SAE report, to allow for updates on key information that may not have been available when the SAE was first reported. To update information on an SAE by entering a follow-up, first navigate to the SAE of interest. From the *log forms* tab of the *patient view page* for the affected patient, click on 'Access log' in the adverse events sections, and the AE log page will load.

b) Click on the 'View' button for the SAE of interest. The SAE tracking page will load with the most recent follow-up toggled open. (Note: Initial entry of the SAE is considered as entry (0), with subsequent follow-ups numbered sequentially from (1).)



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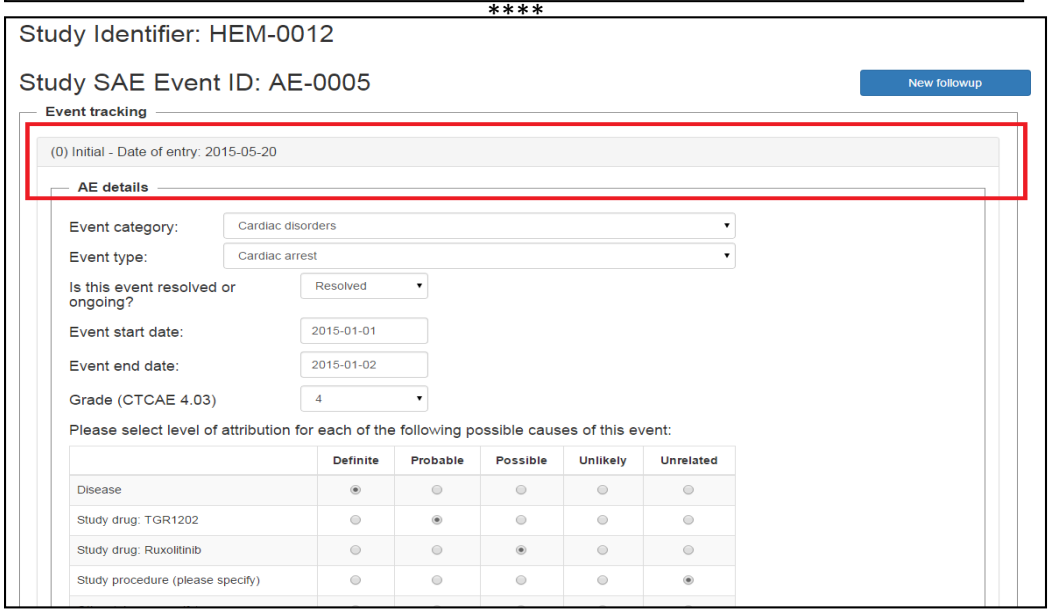
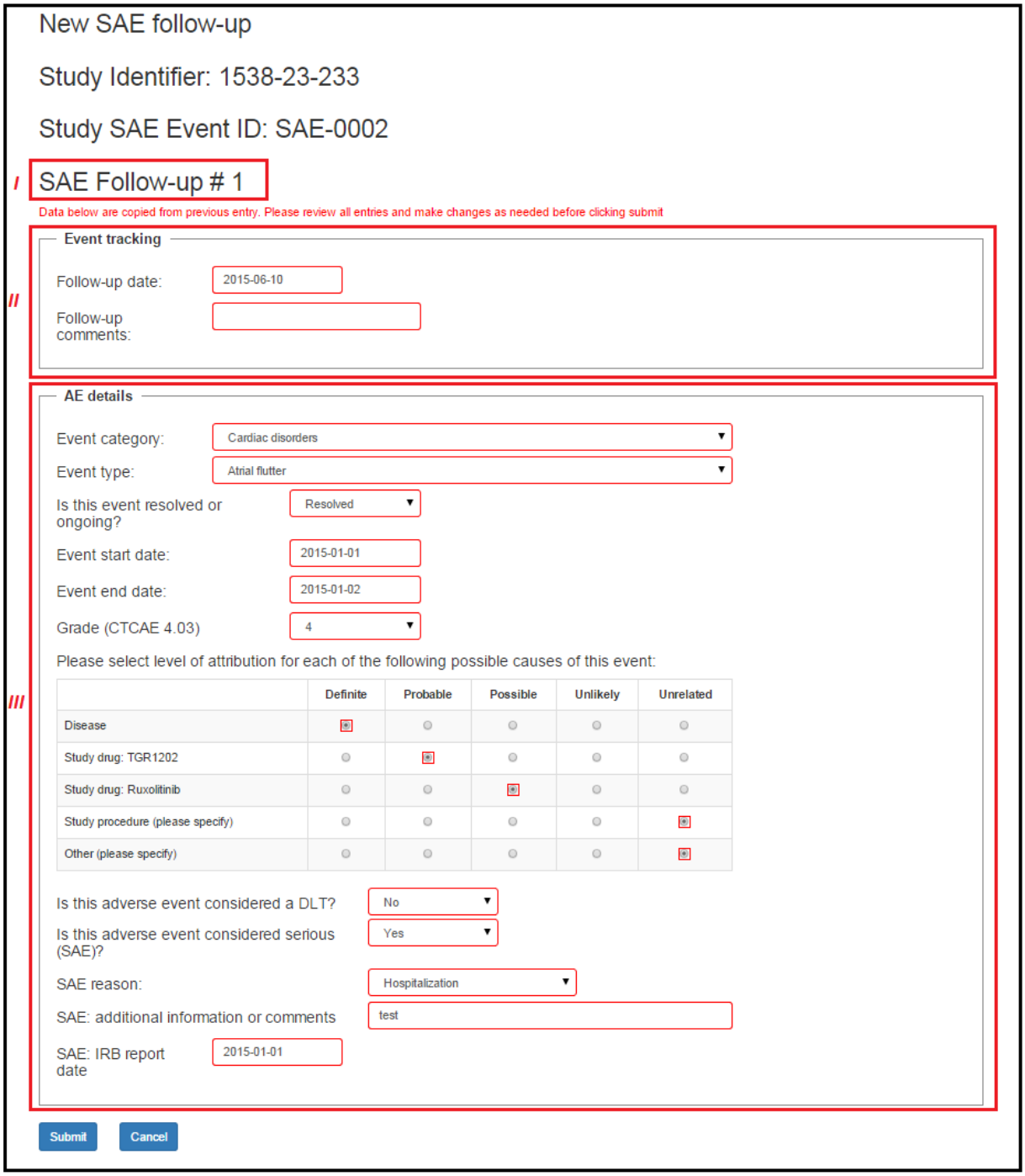


c) Click the 'New followup' button to enter your follow-up data. On the follow-up form:

i. The system will assign an SAE follow-up number.

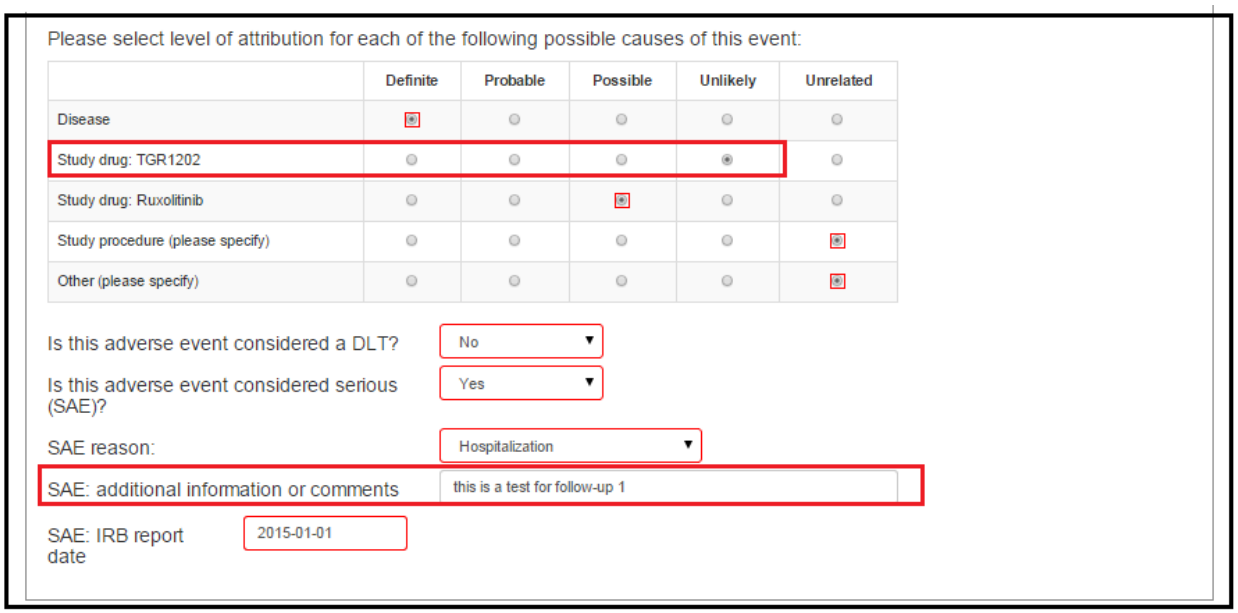
ii. In the event-tracking section, the follow-up date will auto-populate as today's date, with the expectation that SAE data will be entered in real time. If not, change the date of follow-up to the actual follow-up date. Then enter any comments in the 'follow-up comments' field.

iii. In the AE details section of the form, you will see the data as last entered. For example, if you are entering follow-up (1), the data from initial entry of the SAE will be displayed. If you are entering follow-up (2), the data from follow-up (1) will be displayed, and so on. All fields in this section will be demarcated in red.

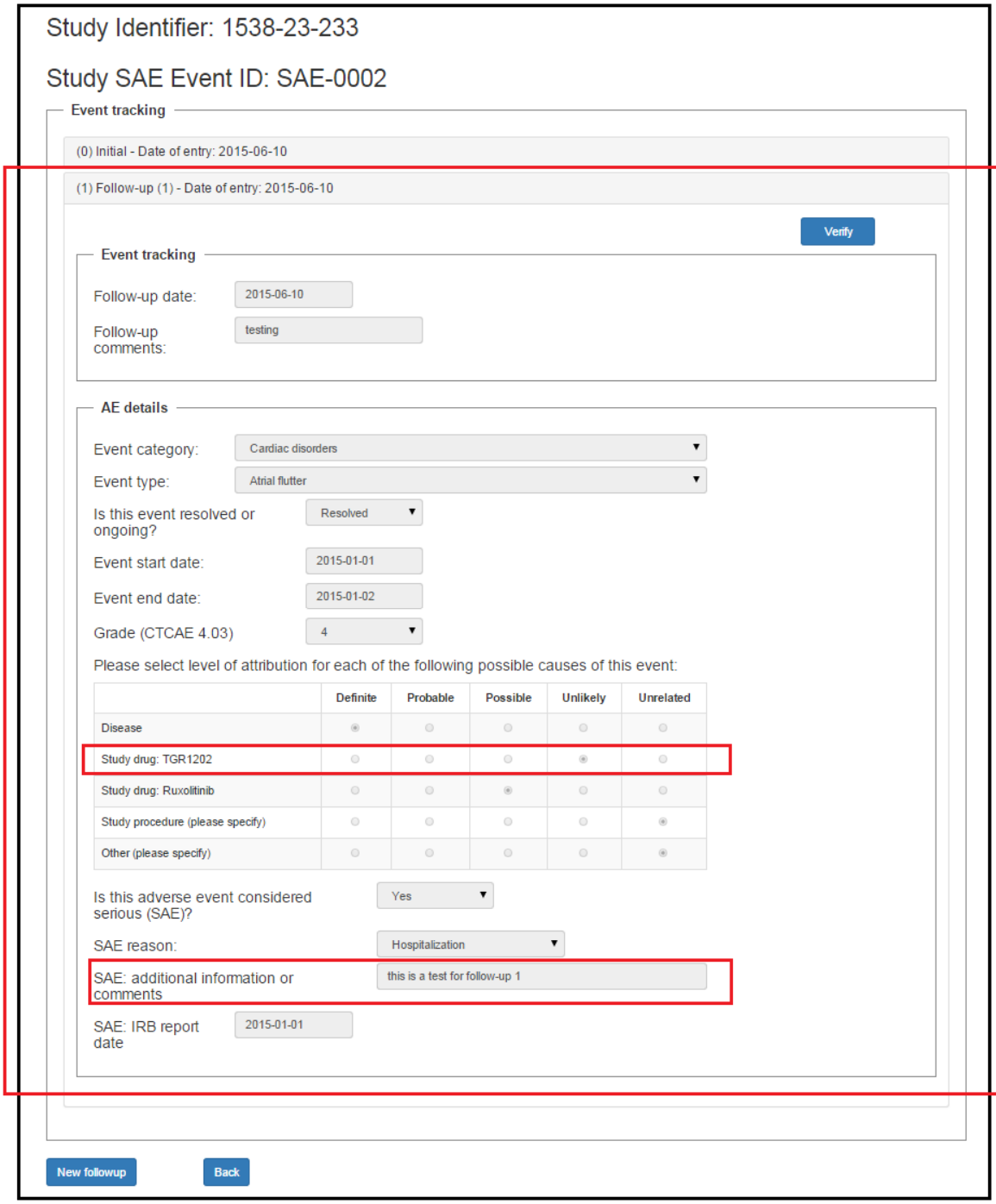


d) Make changes to any fields for which you have new or changed data from the previous record for this SAE. For example, in the screenshot below, we have changed:
    i. The attribution level for the TGR-1202 study drug
    ii. The additional information or comments on the SAE

As shown in the screenshot, fields with changes to the data lose their red demarcation, and appear in black type as in a typical form. **Before submitting, take a moment to review those fields left in red and those now in black type-face, to ensure that all fields requiring change have been changed accordingly**.

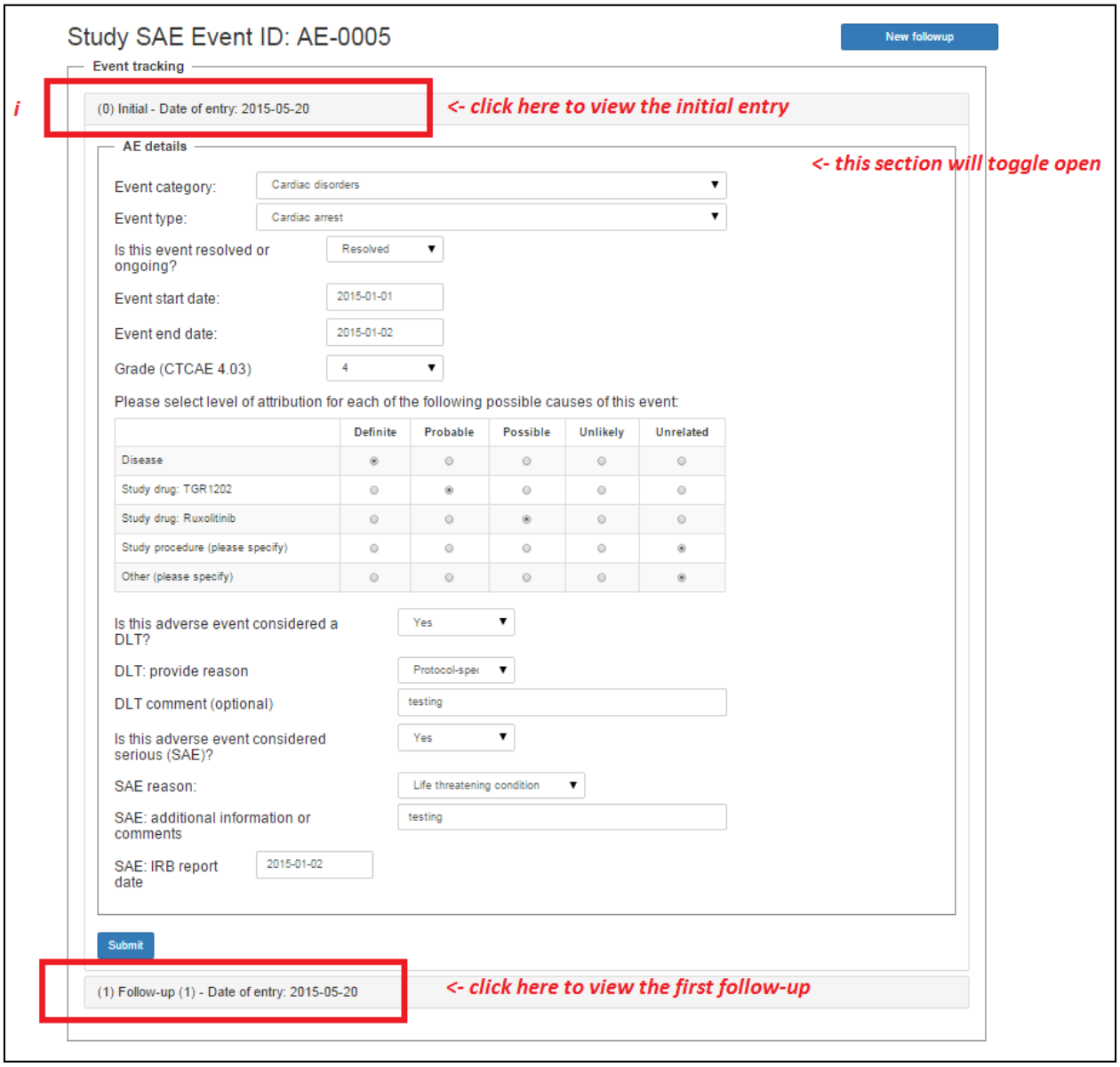


e) Click ‘Submit’. You will be redirected to the SAE page, with the most recent follow-up toggled open, as shown below.



TIPS:

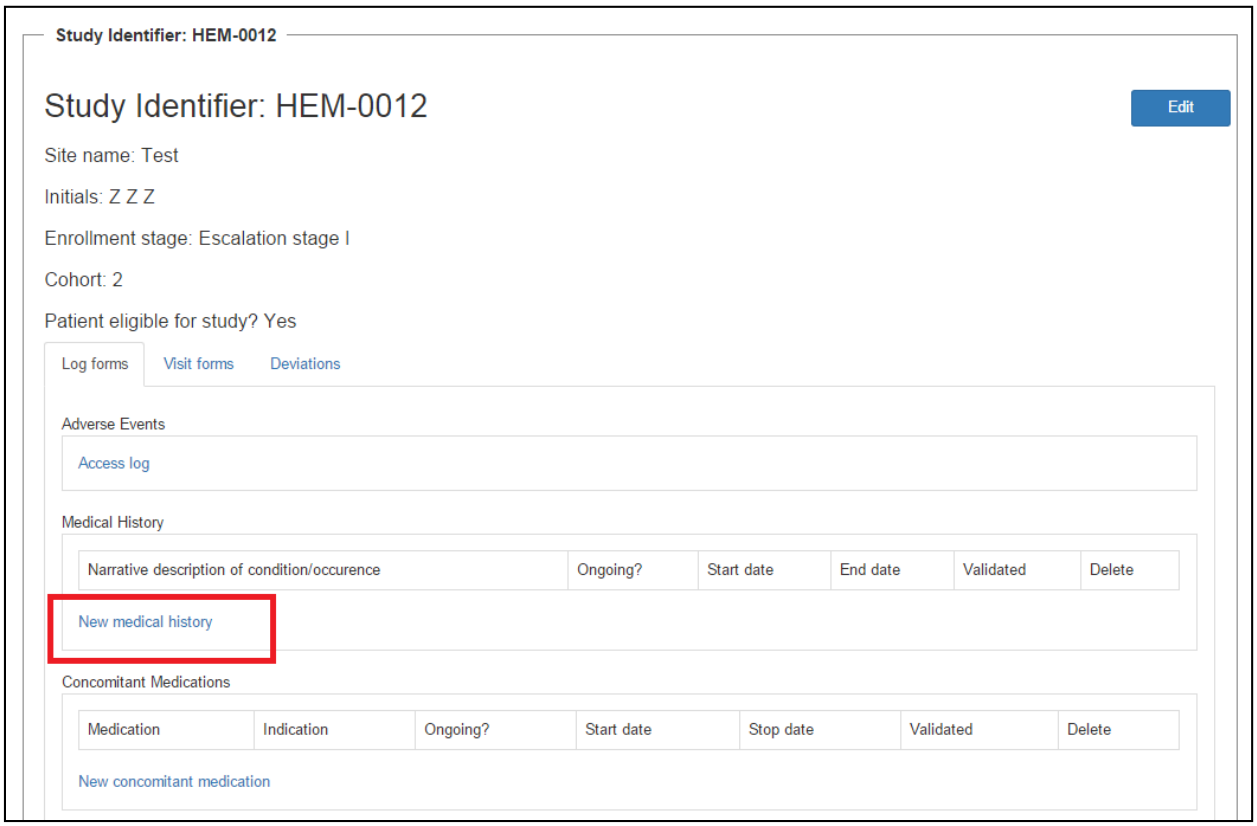
- Initial and subsequent follow-up SAE entries may be toggled open and closed by clicking on the toggle bar for the record of interest. For example, as shown in the screenshot below, click on the toggle bar for the initial entry to see the data as entered initially; click on the toggle bar for follow-up (1) to review the data as submitted at this follow-up.



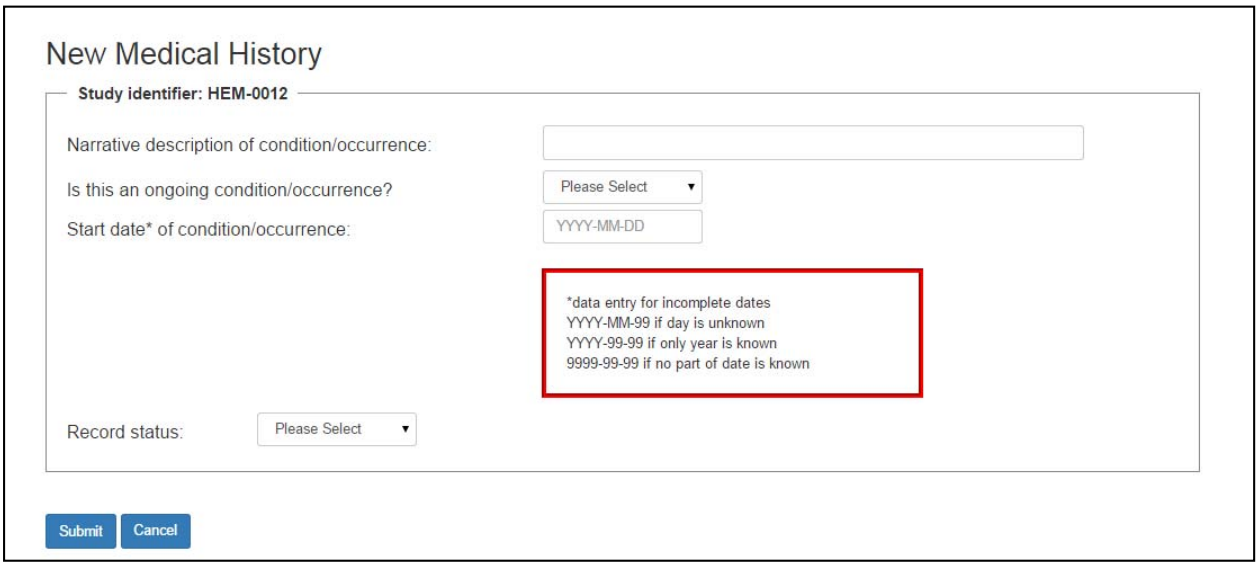
5.6.2 New medical history

To enter medical history information for a patient, navigate to the *patient view page* and follow these steps:

a) From the *log forms* tab on the *patient view page*, click on 'New medical history'.



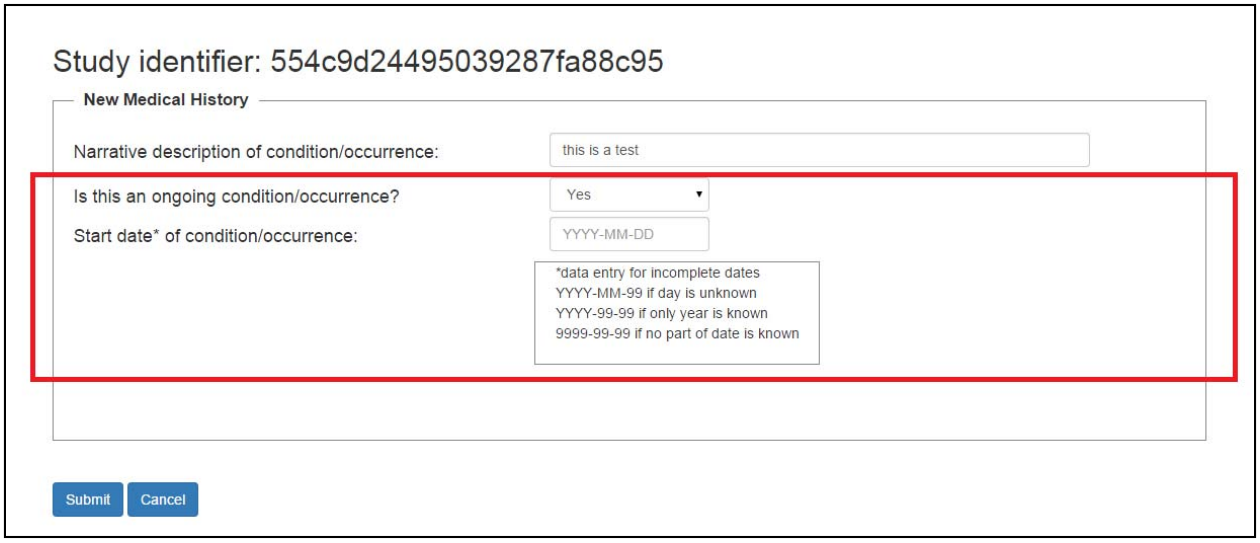
b) Complete the form and click on the 'Submit' button.



c) After submitting the form, you will be redirected to the *patient view page*. A table will display the data you have submitted.

TIPS:

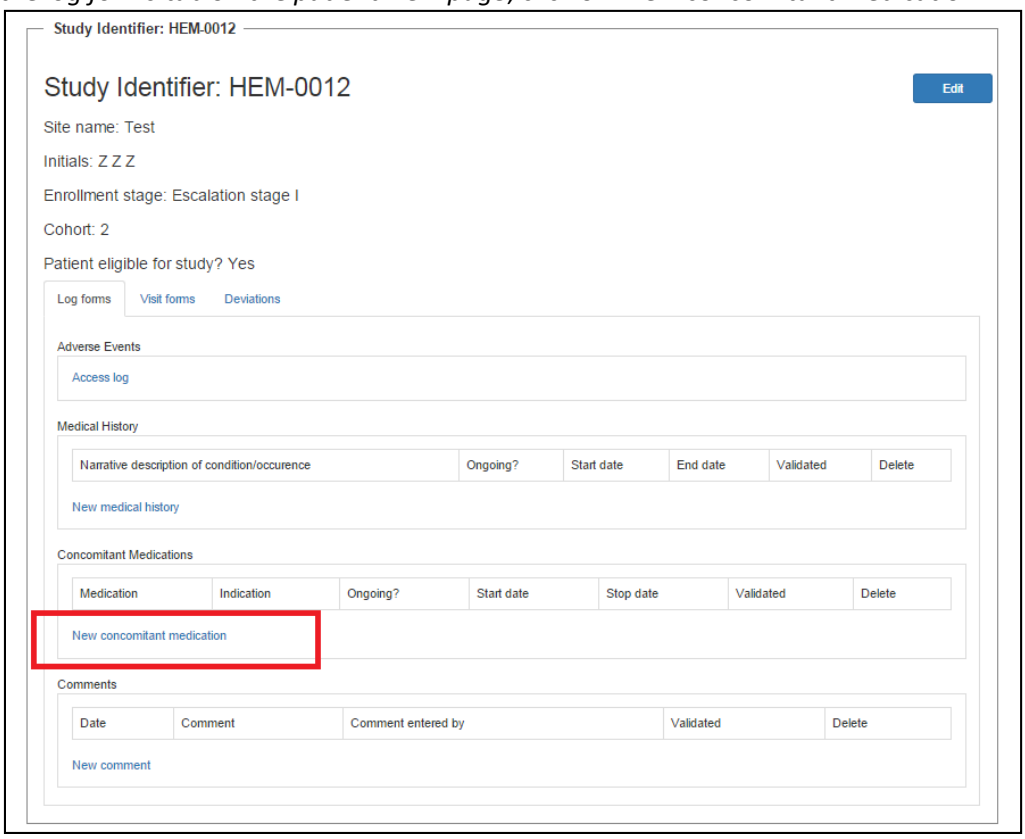
- Remember that the baseline covariates form in the screening visit must be completed before entering any medical history records for a patient.
- Remember that incomplete or unknown dates may be entered as follows:
  - For unknown day, enter YYYY-MM-99
  - For unknown day and month, enter YYY-99-99
  - If all three components are unknown, enter 9999-99-99
- If a medical condition is ongoing, you will be asked for the start date only for the condition (see screenshot below). If the condition or occurrence later resolves, you may edit the record to indicate that the condition is no longer ongoing, and then enter an end date for the condition.



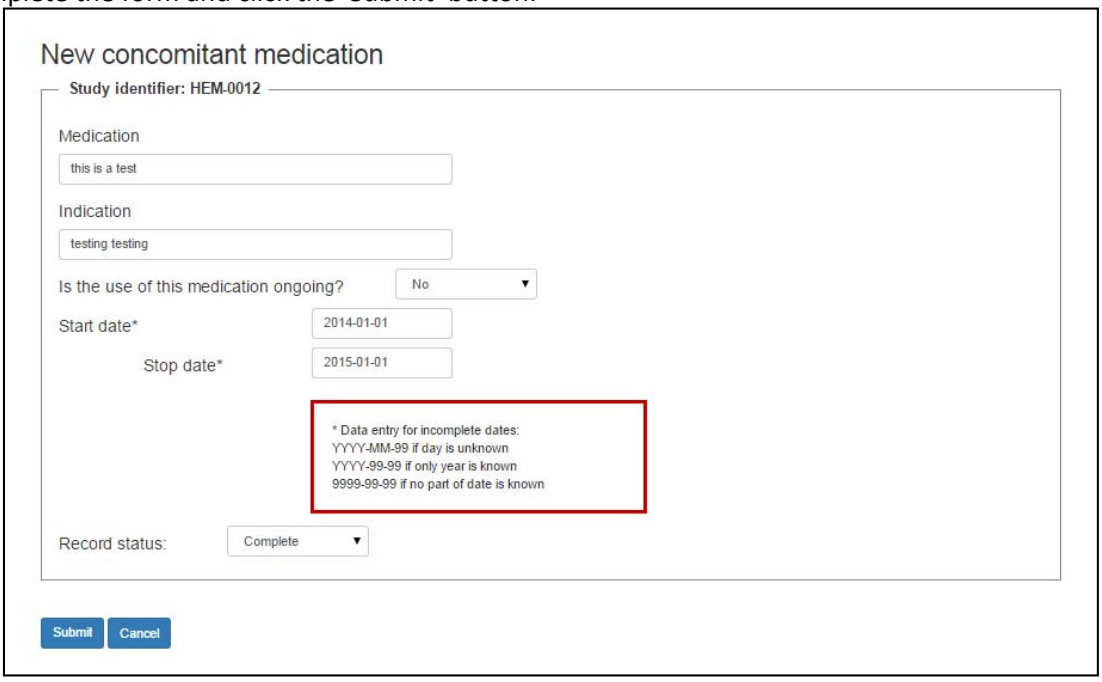
5.6.3 New concomitant medication

To enter concomitant medication information for a patient, follow these steps:

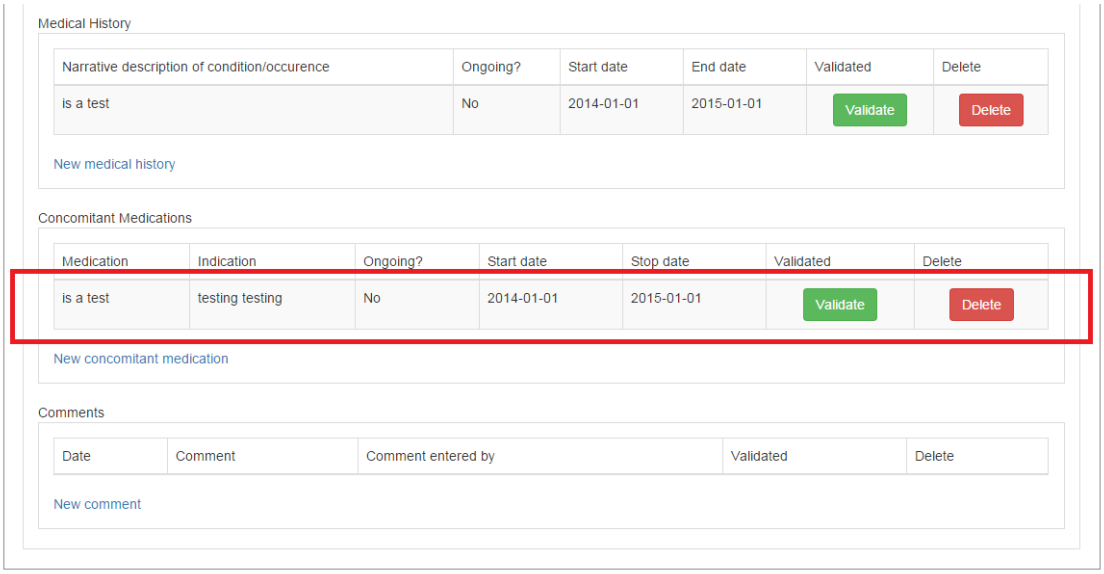
a) From the *log forms* tab on the *patient view page*, click on 'New concomitant medication'.



b) Complete the form and click the 'Submit' button.



c) After submitting the form, you will be redirected to the *patient view page*. A table will display the data you have submitted.



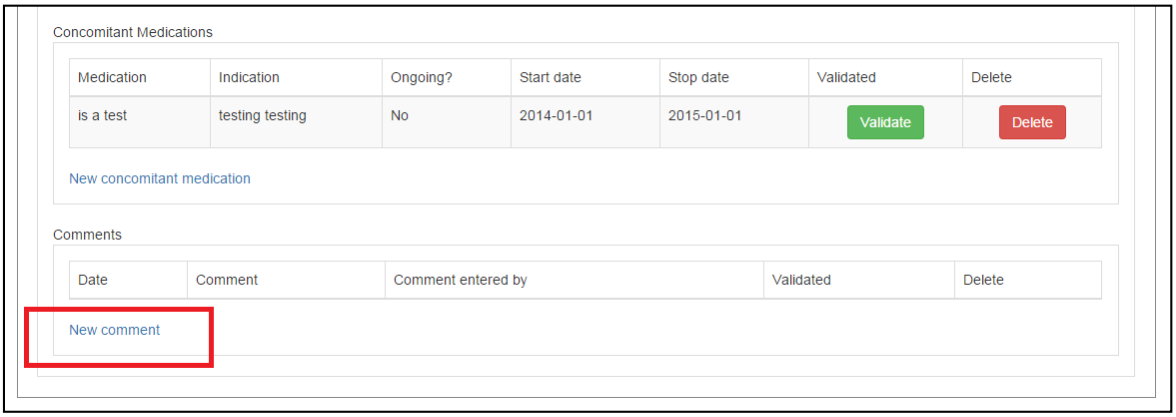
TIPS:

- Remember that the baseline covariates form in the screening visit must be completed before entering any concomitant medication records for a patient.
- Please be certain to refer to the HEM1538 protocol for information about prohibited or warned concomitant medications. **If a patient uses a concomitant medication that may constitute a protocol deviation, be sure to enter this information in the deviation form as well as the concomitant med form**.

5.6.4 New comment

To enter comments, follow these steps:

a) From the *log forms* tab on the *patient view page*, click on 'New comment'



b) Complete the form and click on the 'Submit' button. Note that the EDC automatically captures and records the login credentials of the user entering the comment, to facilitate any follow-up queries related to the comment.

c) After submitting the form, you will be redirected to the *patient view page*. A table will display the data you have submitted.

5.7 New entries: visits and visit forms

Visit types for HEM1538db include all study-calendar visits (screening, treatment period, end-of-treatment, end-of-study), as well as unscheduled visits and dose adjustment by phone. Visit forms include a total of 13 different eCRFS. For each visit, however, you will have only a subset of these forms to complete, because forms attached to each visit are restricted according to the procedures and evaluations specified for that visit (per protocol). To demonstrate data entry for all 13 forms, this manual will cover three visit types as examples:

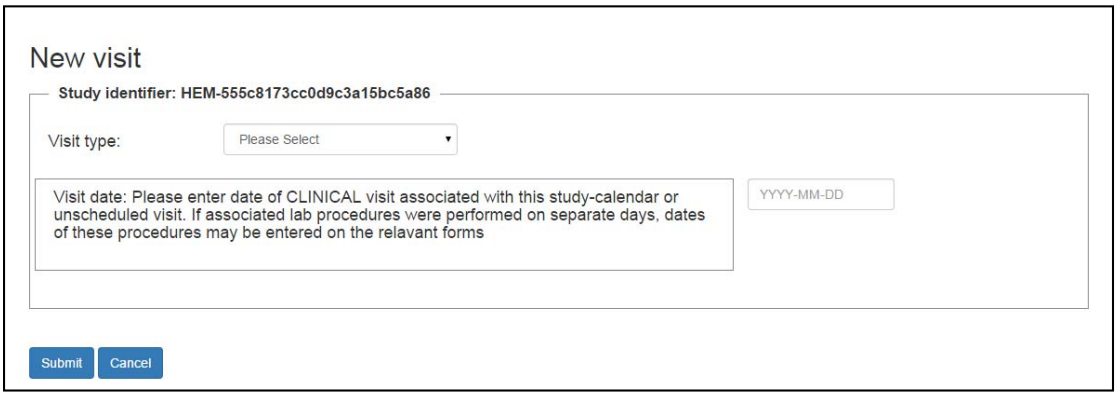
1. How to add a screening visit and all associated forms (9 forms in total);
2. How to add a treatment period visit (using C1D1 as an example);
3. How to add a treatment period with end-of-treatment visit (using C1D8+EoT) and all associated forms (4 forms in total).

5.7.1 New visit: screening visit

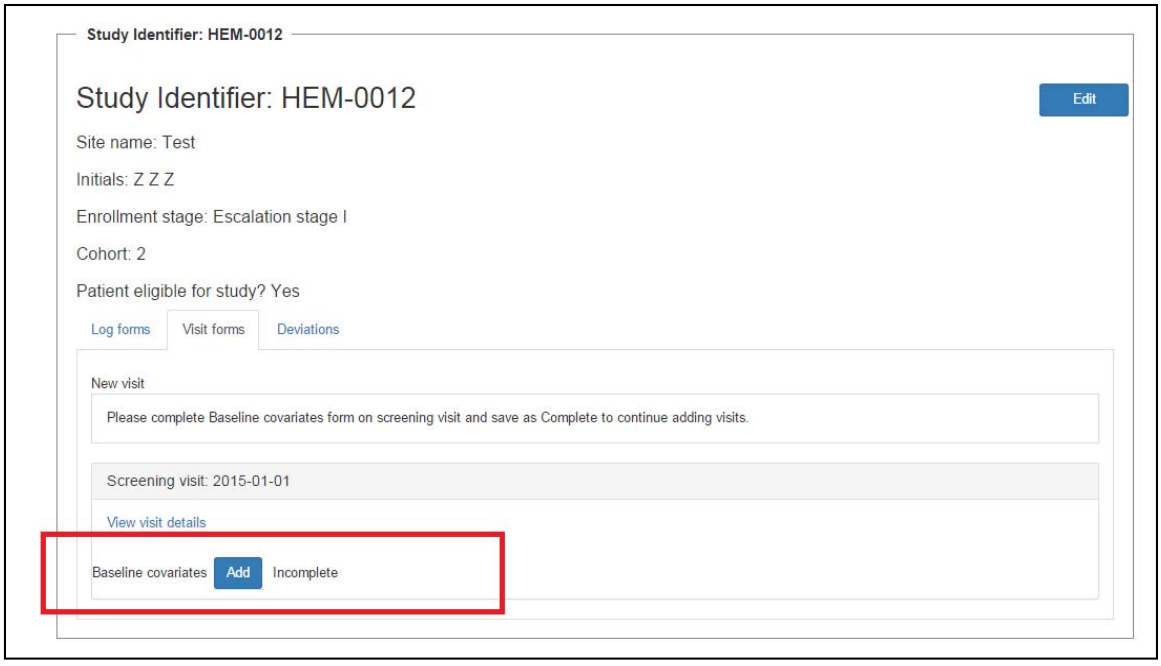
a) Navigate to the *visit-forms tab* for the patient of interest.

b) Click on ‘Add new visit’.

c) From the ‘Visit type’ dropdown menu, select ‘screening’. Enter the visit date. Then click the submit button.

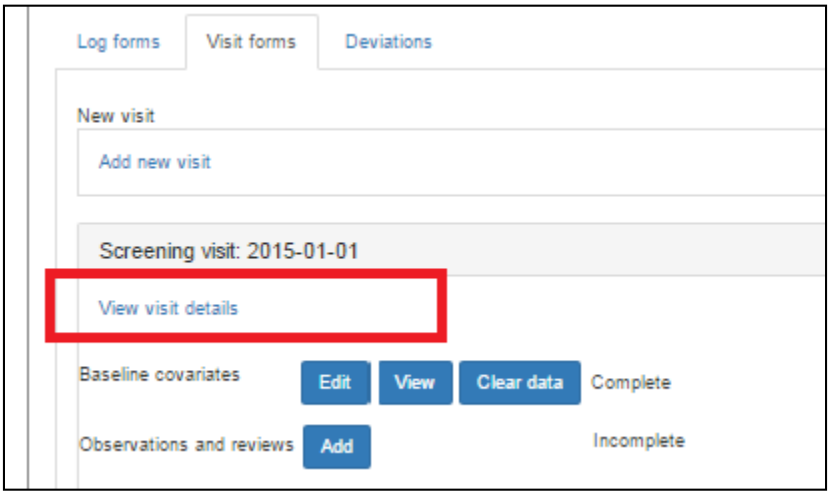


d) You will be redirected to the visit-forms tab, with the screening visit toggled open. The only form available to you at this point will be the ‘Baseline covariates’ form, as shown in the screenshot below. This form must be completed before you can proceed with any other data entry for this patient.



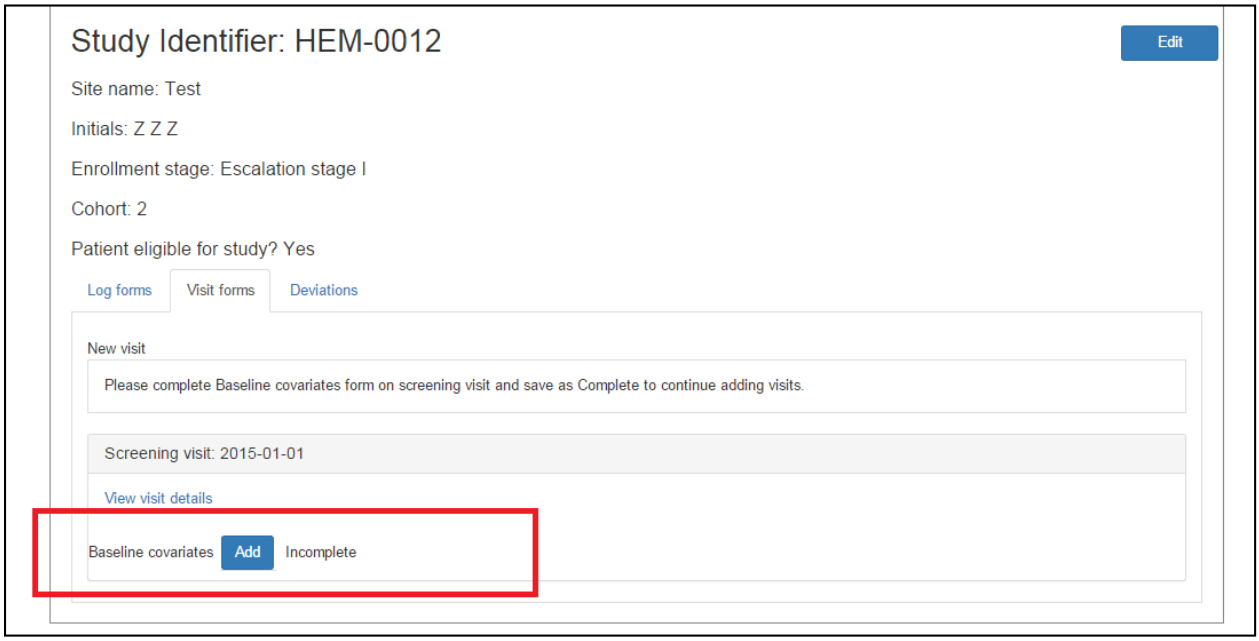
TIPS:

- To view details about a visit (visit date, as well as additional data points for some visit types), click on 'View visit details' from the visit-forms tab.

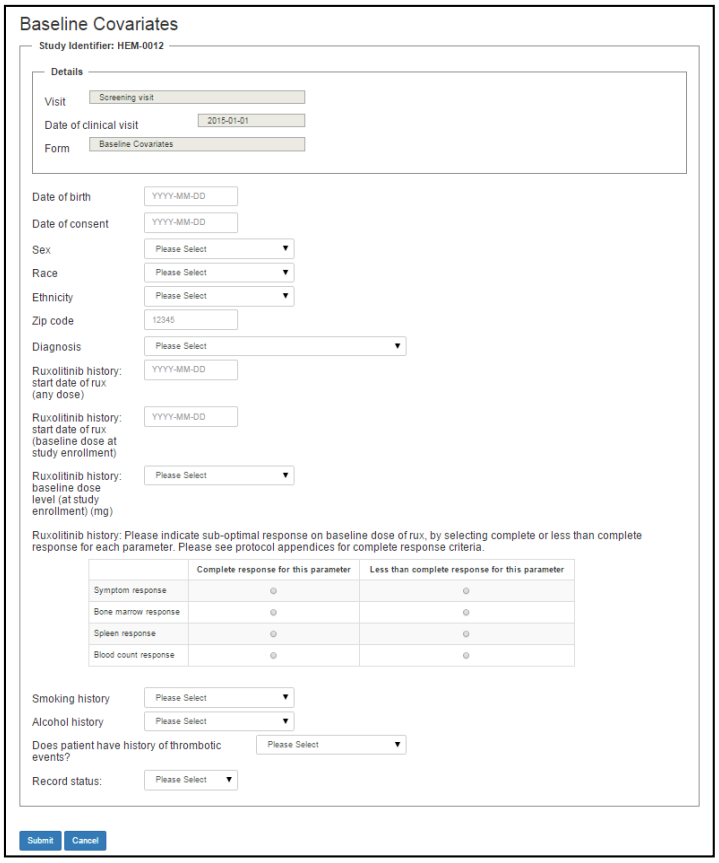


5.7.1.1 Screening visit forms: Baseline covariates

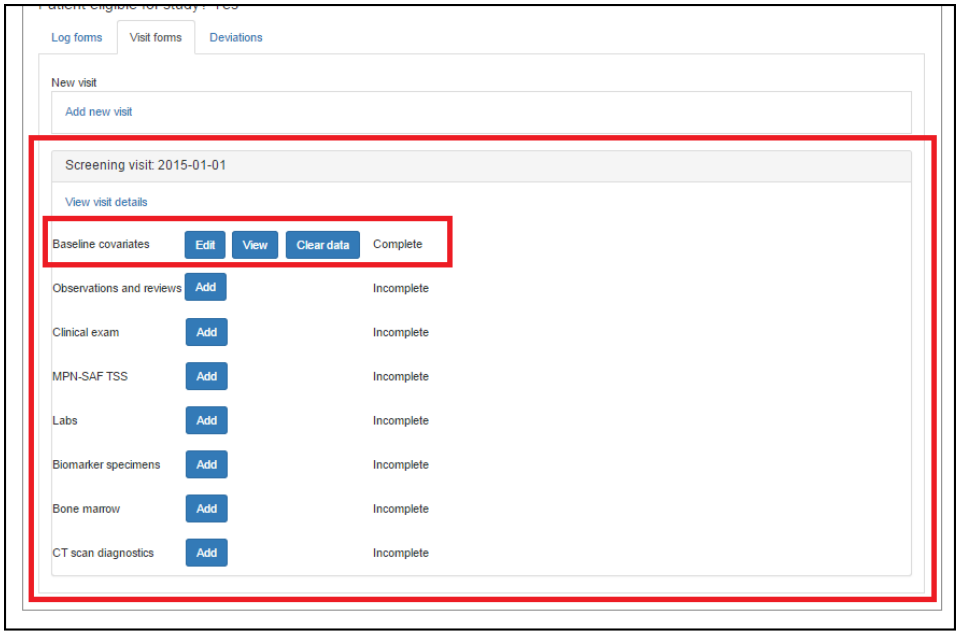
a) Navigate to the *visit forms* tab. Toggle open the screening visit section as needed. Click on the ADD button for the baseline covariates form.



b) Complete the form in its entirety and click ‘Submit’.



c) After submitting the form, you will be redirected to the *visit-form tab* for the patient. If you marked the baseline covariates record status as ‘complete’ to submit the form, the remainder of the forms associated with a screening visit will now be available to you, and the baseline covariates form will be marked as ‘complete’, as shown in the screenshot below.

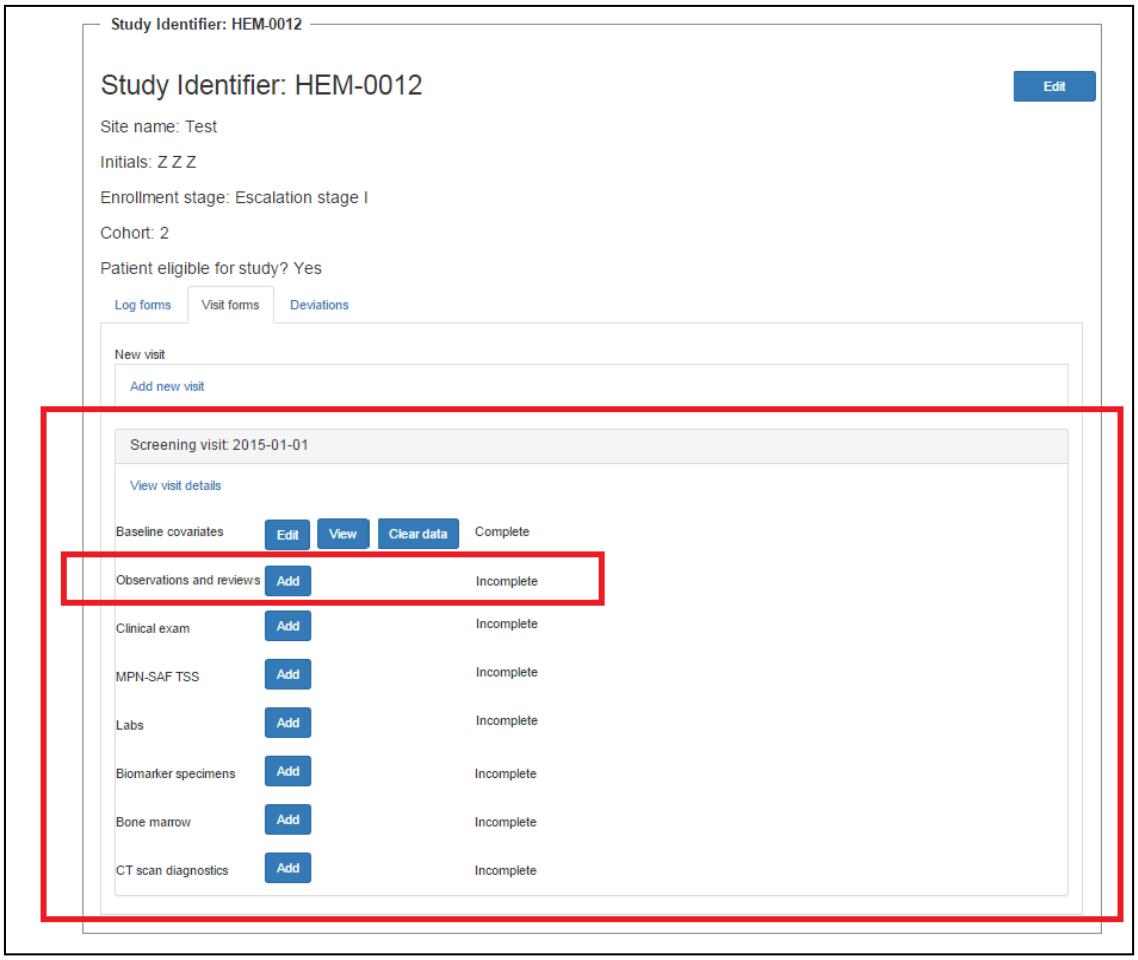


TIPS:

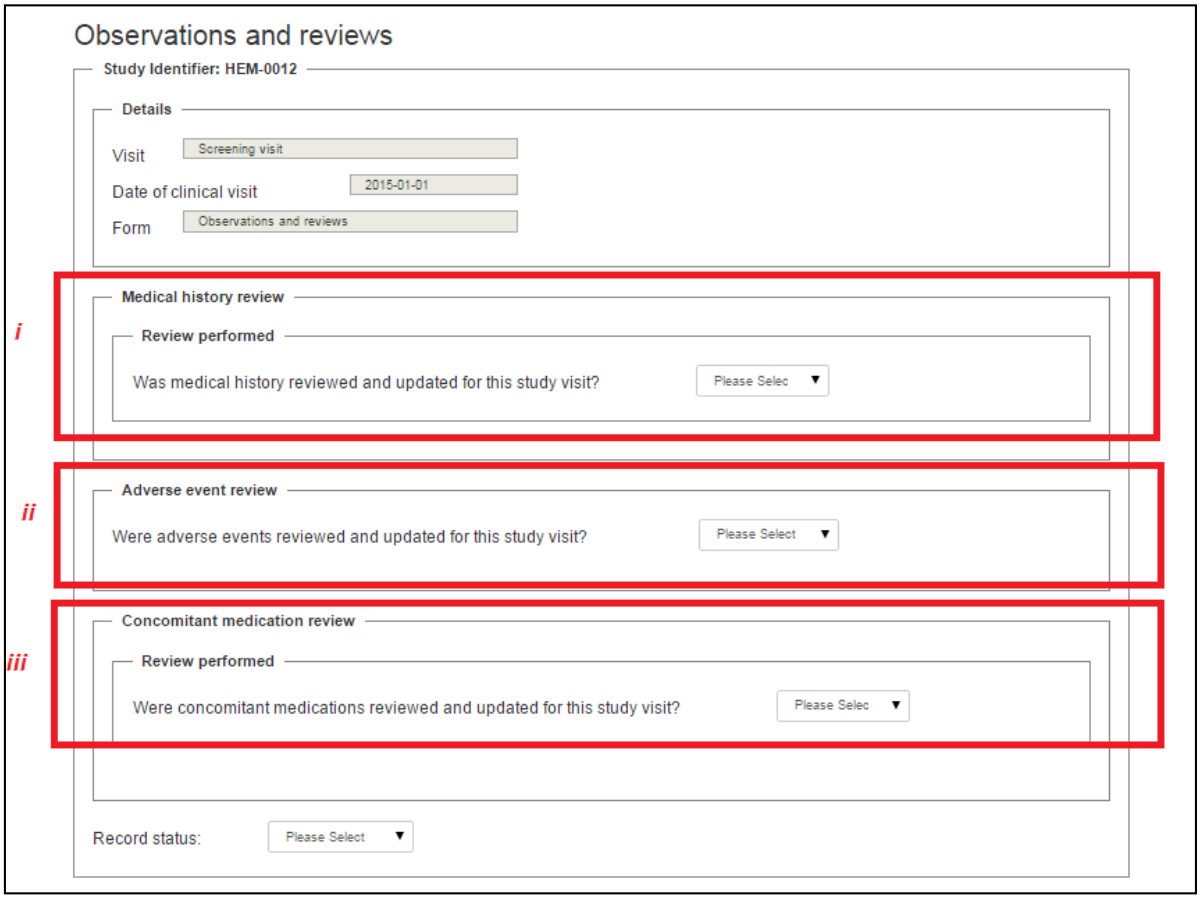
- Remember, the baseline covariates form must be completed before any other data entry for the patient will be permitted. If you submit the baseline covariates in 'draft' status, this does not fulfill the requirement to complete the form, and the remaining forms for the screening visit will remain hidden. You also will be unable to create additional visits until you complete the baseline covariates form.
- Completion of the baseline covariates form is a prerequisite for entry of other data in part because patient diagnosis information is captured on this form, and diagnosis affects which variables display on certain of the forms. In particular, on the 'observations and reviews' form and the 'disease assessment' form, different variables display in certain sections and at certain visits, depending on patient diagnosis. For this reason, if an edit is made to the diagnosis information in the baseline covariates form, any previously completed 'observations and reviews' or 'disease assessment' forms will be cleared, and will need to be re-entered. Please pay careful attention to selection of correct diagnosis information for each patient to avoid this situation.
- After adding and submitting a form, the buttons available to you to manipulate that form will be updated. Depending on your permissions, you will now have available to you buttons to edit, view, or clear data from the form. To the right of the buttons is an indicator of the form status: 'incomplete' for forms without any data entry or saved in draft ('incomplete') status, and 'complete' for forms saved as such.

5.7.1.2 Screening visit forms: Observations and reviews

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the observations and reviews form.



b) Complete the form in its entirety (three sections): medical history review, adverse event review, and concomitant medication review. Medical history and concomitant meds review are further divided into two subsections each: review performed and findings. Other forms are similarly subdivided. After completing all variables in all sections, click the submit button to save your entries.

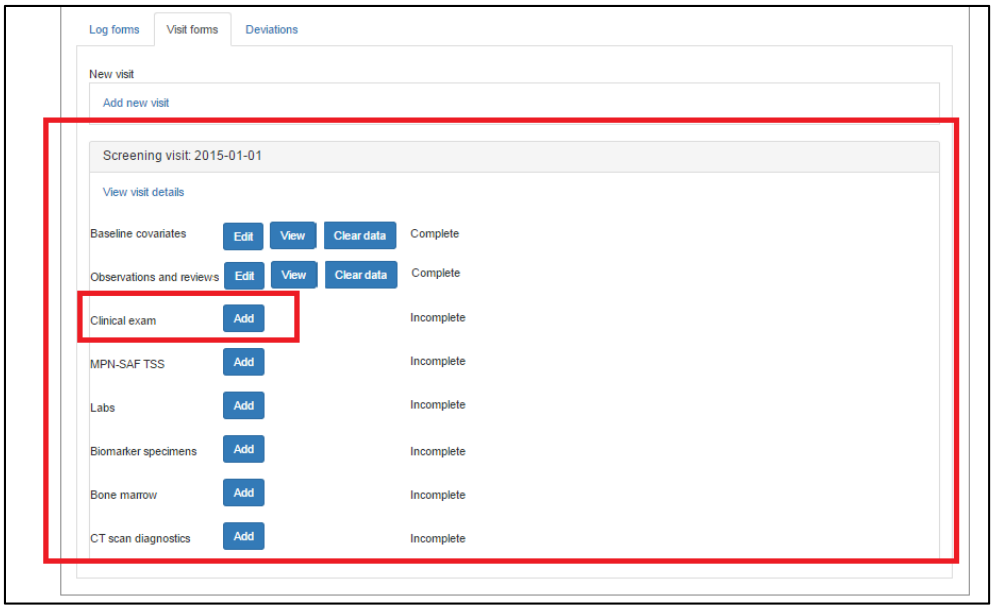


TIPS:

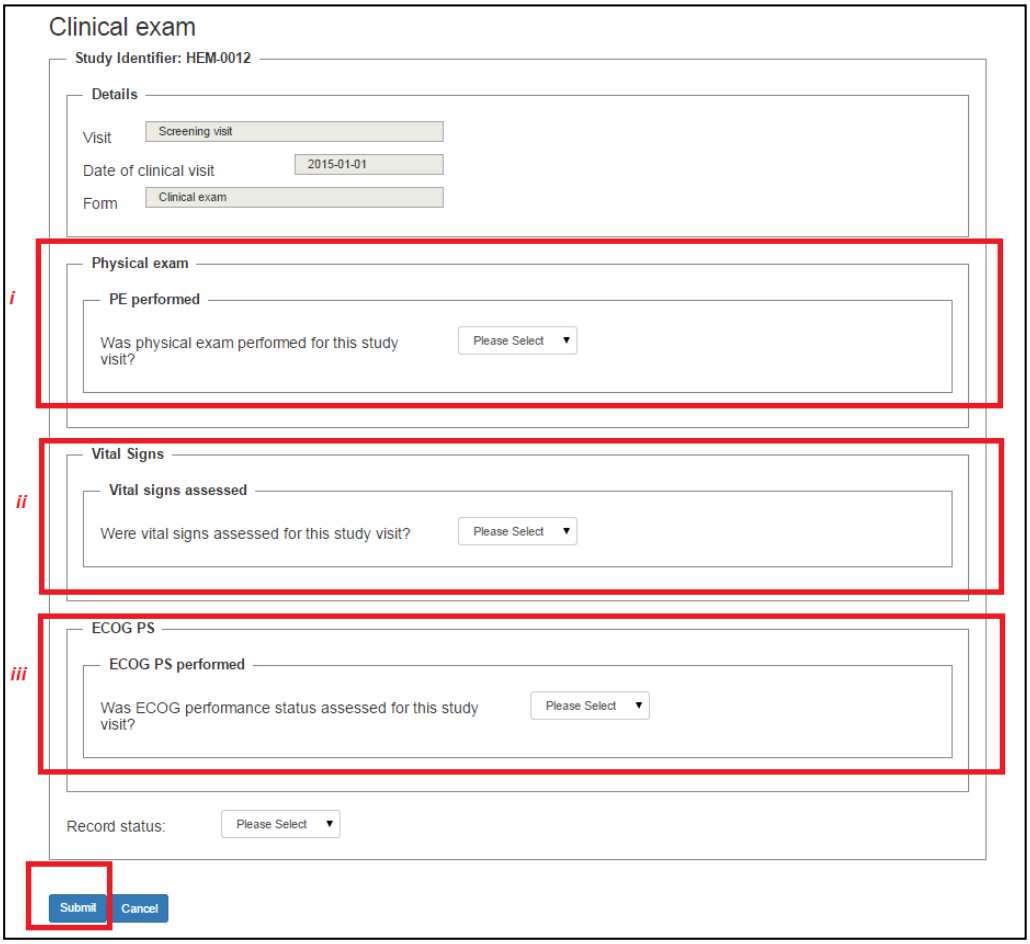
- The observations & reviews form has two functions: (1) to document that reviews (medical history, AE, and medications review) were performed per study calendar, and (2) to collect certain key information from those reviews in structured format. Capturing these key data in structured format will help with later disease assessment work. For example, at certain visits, for patients with diagnoses of MF or MDS/MPN, the medical history findings section will include specific questions related to transfusion history, to auto-calculate transfusion-dependency status for disease assessment. **IMPORTANT NOTE: as appropriate per protocol, any clinically significant findings that may be noted on the observations and reviews form also should be captured in the relevant log form (i.e., medical history, concom meds, or AE)**.
- Reminder: display of form sections, subsections, as well as individual fields is dependent on study calendar as well as other criteria. You will be presented with all required fields for data entry for the visit and patient under consideration, and each of those fields must be completed.

5.7.1.3 Screening visit forms: Clinical exam

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the clinical exam form.

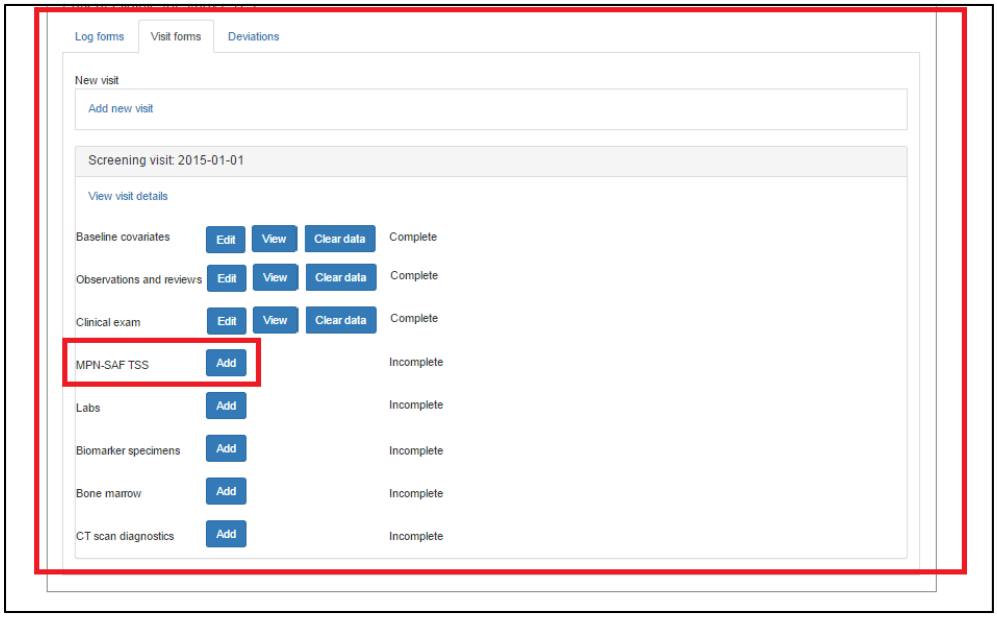


b) Complete the form in its entirety and click 'Submit'. Note that, as with other forms, section, subsection, and variable display will depend on study calendar and other criteria. At screening, you will see all three section of the clinical exam form: physical exam, vital signs, and ECOG PS.

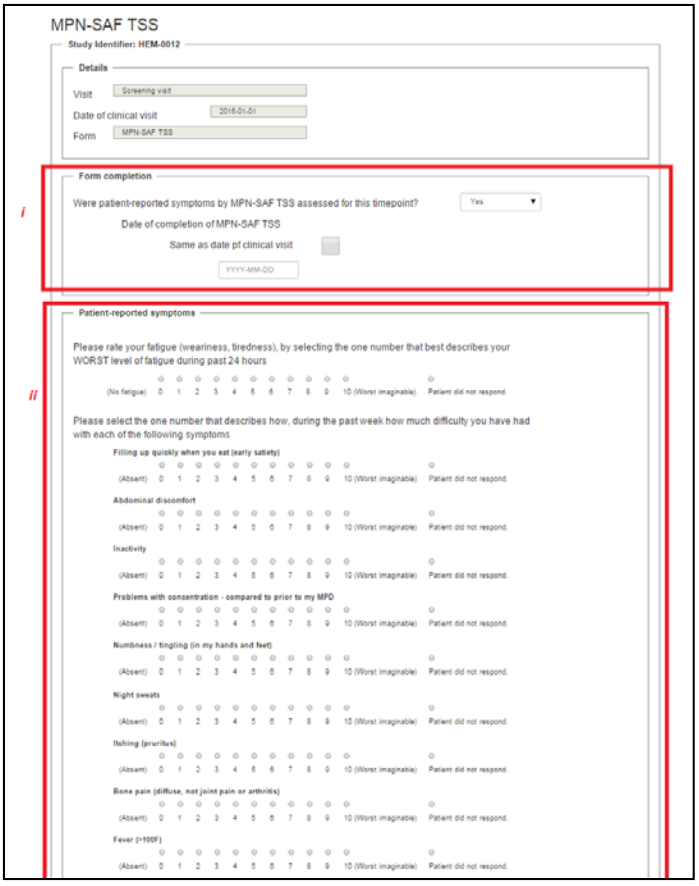


5.7.1.4 Screening visit forms: MPN-SAF TSS

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the MPN-SAF TSS form.

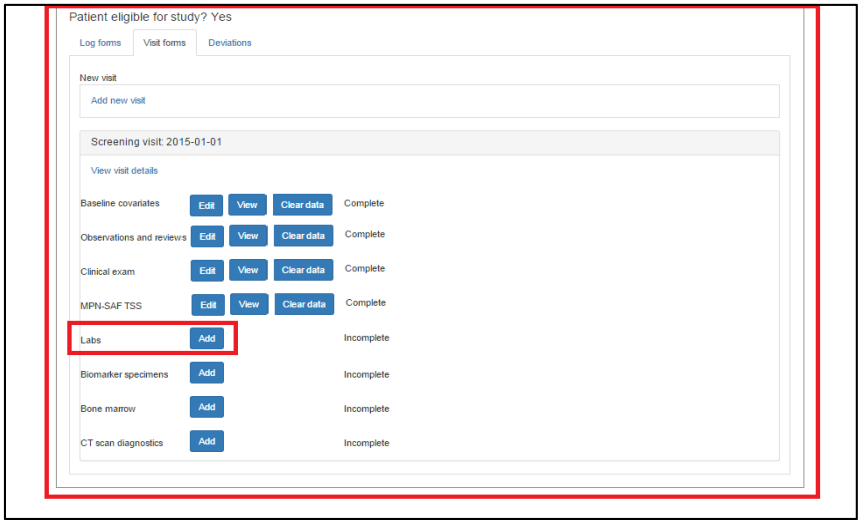


b) Complete the form in its entirety (two sections) and click 'Submit'. Note that, for date of completion of the MPN-SAF TSS form, you may utilize the 'Same as date of clinical visit date' checkbox, as appropriate; see general tips in section 5.3 for details.

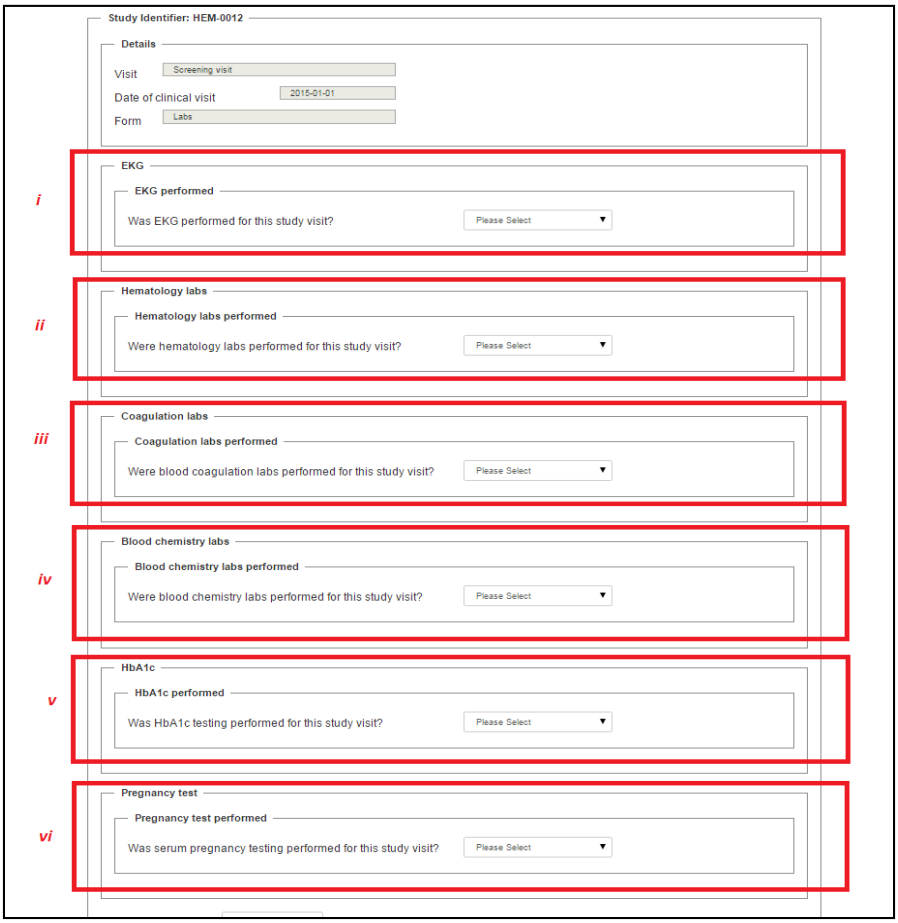


5.7.1.5 Screening visit forms: labs

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the labs form.

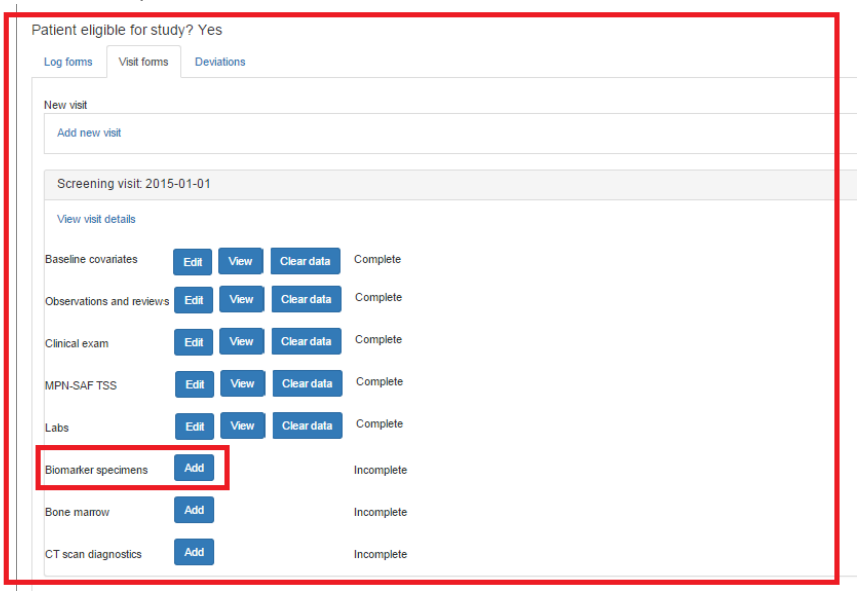


b) Complete the form in its entirety (six sections) and click 'Submit'. Note that several sections of the lab form will display only at the screening visit. At most treatment period visits, only hematology and blood chemistry labs are performed, and these are the only two sections that will display. At some visits (in addition to screening), you also will need to complete the EKG and coagulation labs. The pregnancy test section will display only for female patients, and only at screening. Please also note use of the 'Same as date of clinical visit' checkbox for lab dates; see general tips in section 5.3 for details.

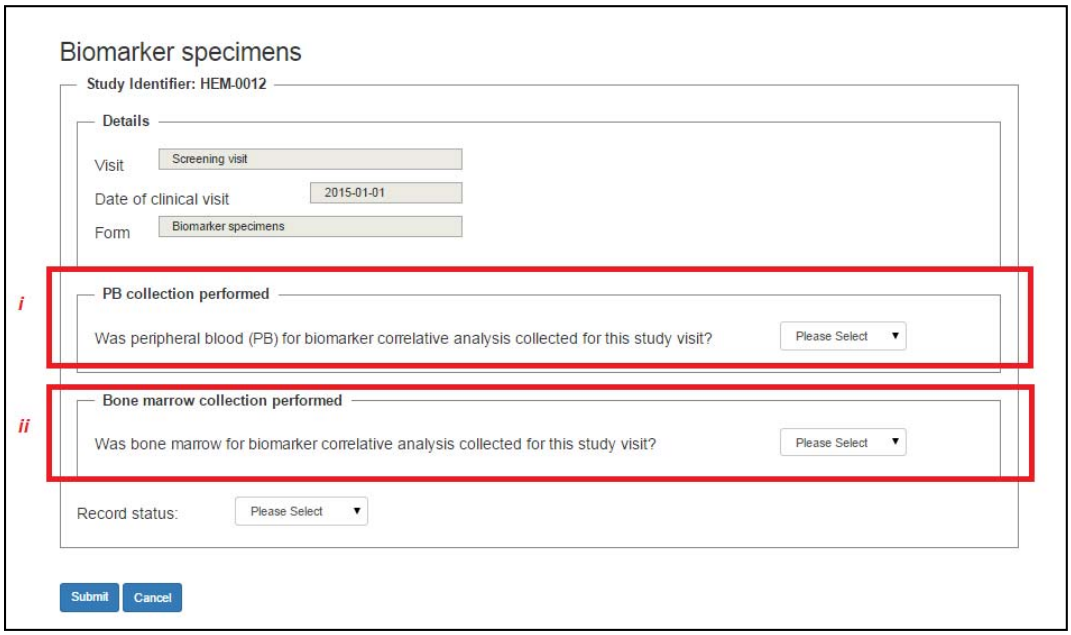


5.7.1.6 Screening visit forms: Biomarker specimens

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the biomarker specimens form.



b) Complete the form in its entirety (two sections) and click 'Submit'.

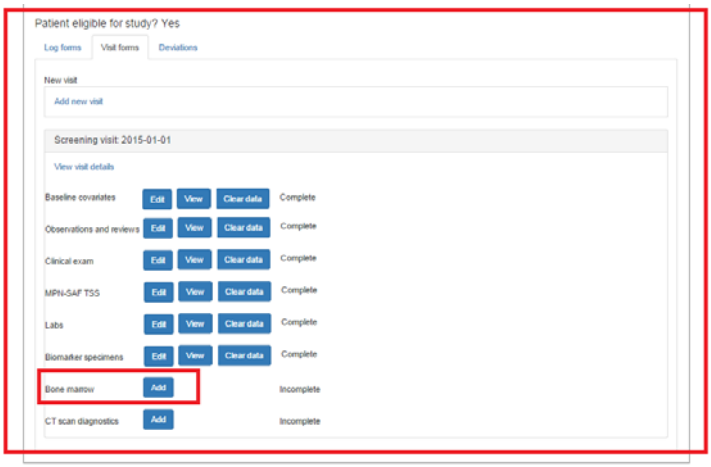


Tips:

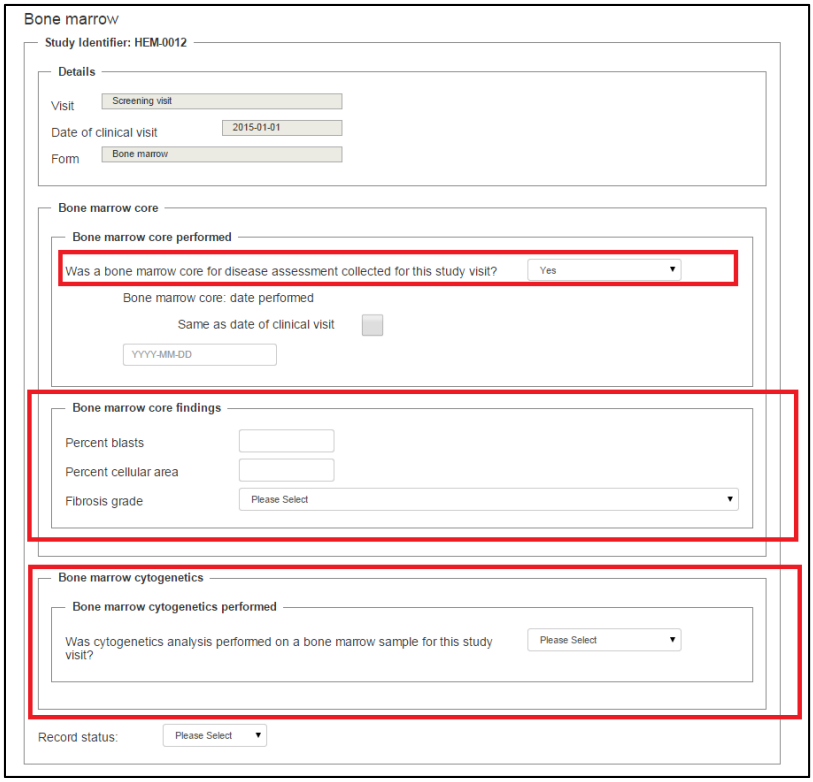
- At screening, archival FFPE tissue is a permitted specimen type for biomarker correlative analysis. If this is the tissue type submitted for biomarker analysis, for date of collection of specimen, be sure to enter the original date of collection of the tissue, and not the date of requisition of the archival FFPE.

5.7.1.7 Screening visit forms: Bone marrow

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the bone marrow form.



b) Complete the form in its entirety (one section with up to three subsections) and click 'Submit'.



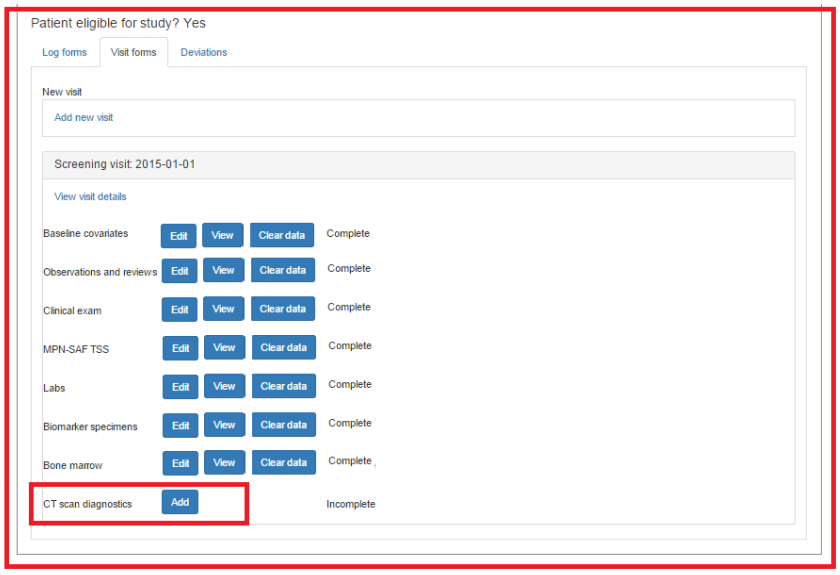
TIP:

- **VERY IMPORTANT**. At screening, bone marrow core must be performed for disease assessment. If you indicate that bone marrow core was not collected for this visit, you will receive a warning message that the patient is ineligible. If the data entry was in error, correct your data entry to indicate that bone marrow core was performed, and continue with the rest of the form. If bone marrow core was not, in fact, performed at screening, please follow instructions (1) (below) if lack of baseline bone marrow core already has been entered in the EDC as a protocol deviation, and instructions (2) (below) if this deviation has not yet been entered in the EDC.
    - **(1) Deviation already reported in EDC**. After the warning message appears on the bone marrow form, submit the form without further data entry, and do not submit any further forms for this patient.
    - **(2) Deviation not yet reported in EDC**. After the warning message appears, cancel out of the bone marrow form. Enter the associated protocol deviation in the EDC, consulting the trial coordinating center as needed. Then return to the bone marrow form, indicate the coring was not performed, and submit the form. It is very important to proceed in this order (i.e., enter the deviation FIRST), because you will be locked out of the patient record as soon as you submit the bone marrow form with the indication that bone marrow core was not performed at screening.

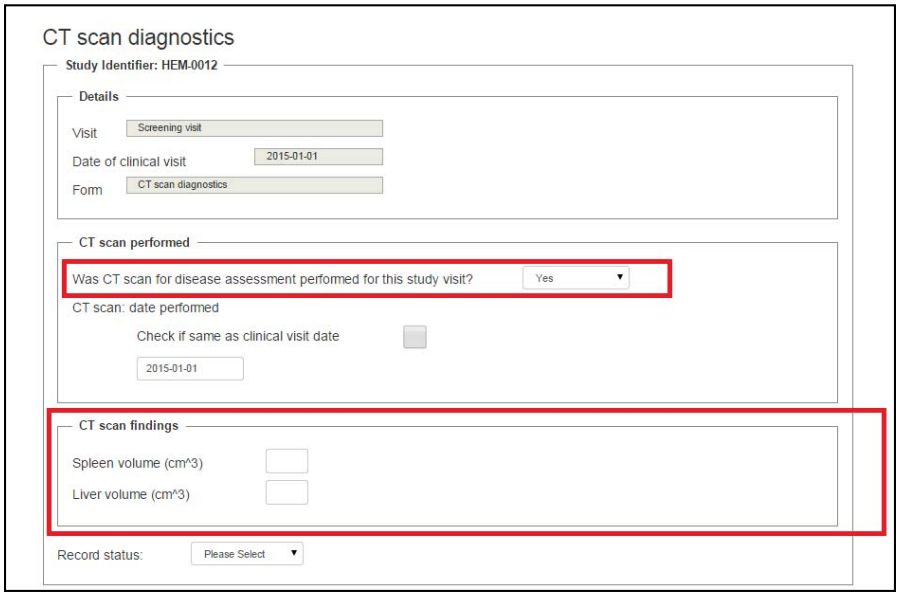
Note that the trial coordinating center will receive an email about the eligibility issue, and will follow-up with you as needed for additional information.

5.7.1.8 Screening visit forms: CT scan diagnostics

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the CT scan diagnostics form.



b) Complete the form in its entirety (one section with up to two subsections) and click 'Submit'. As with other forms, please note use of the 'Same as date of clinical visit' checkbox for procedure dates; see general tips in section 5.3 for details.



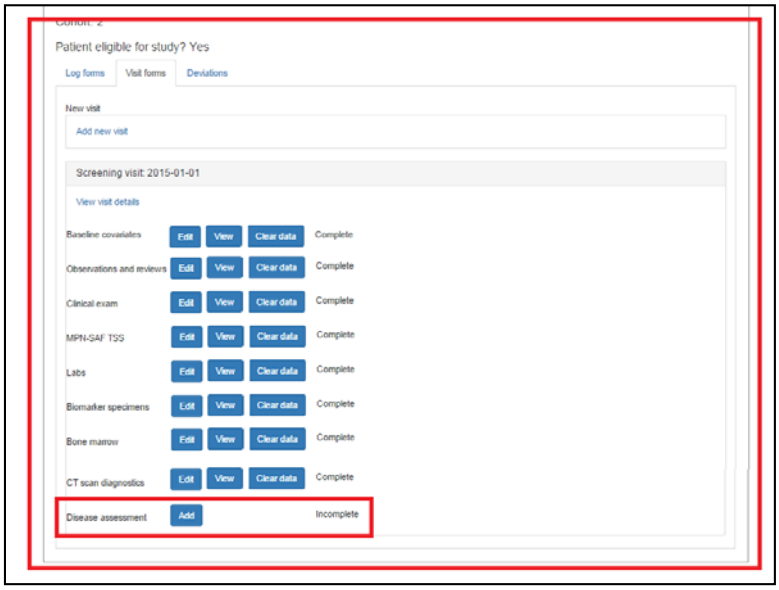
TIP:

- **<u>VERY IMPORTANT</u>**. Similar to bone marrow core, at screening, CT scan must be performed for disease assessment. Please review the tip in section 5.7.1.7 regarding how to report that bone marrow core was not performed at screening, and proceed in similar fashion for reporting CT scan not performed at screening.

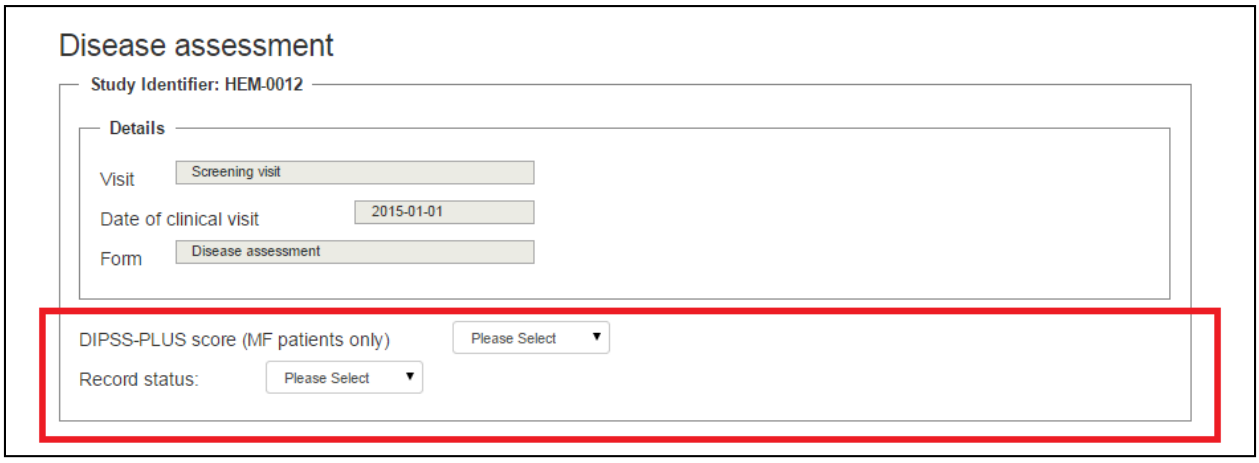
5.7.1.9 Screening visit forms: Disease assessment

Note: the disease assessment form will only be displayed at screening for patients with diagnosis of MF.

a) Navigate to the *visit forms* tab. Toggle open the 'Screening visit' section as needed. Click on the ADD button for the disease assessment form.



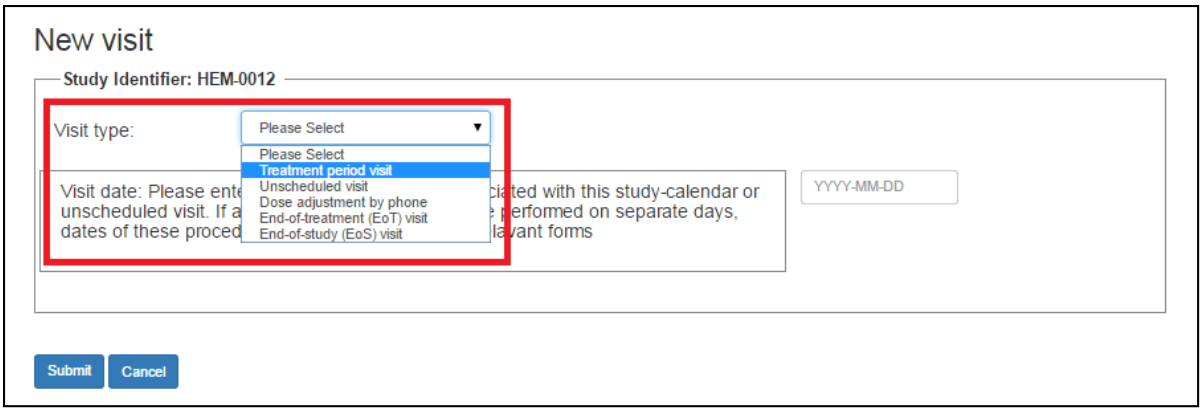
b) Complete the form in its entirety and click 'Submit'. Note: At screening, the disease assessment form will capture only DIPSS-PLUS score, for patients with MF only. At later disease assessment time-points (C3D1, C5D1, etc.), the disease assessment form will capture overall response to treatment (i.e., complete response, partial response, etc.) for all patients. For patients achieving clinical benefit, additional data on categories of clinical benefit is captured as well.



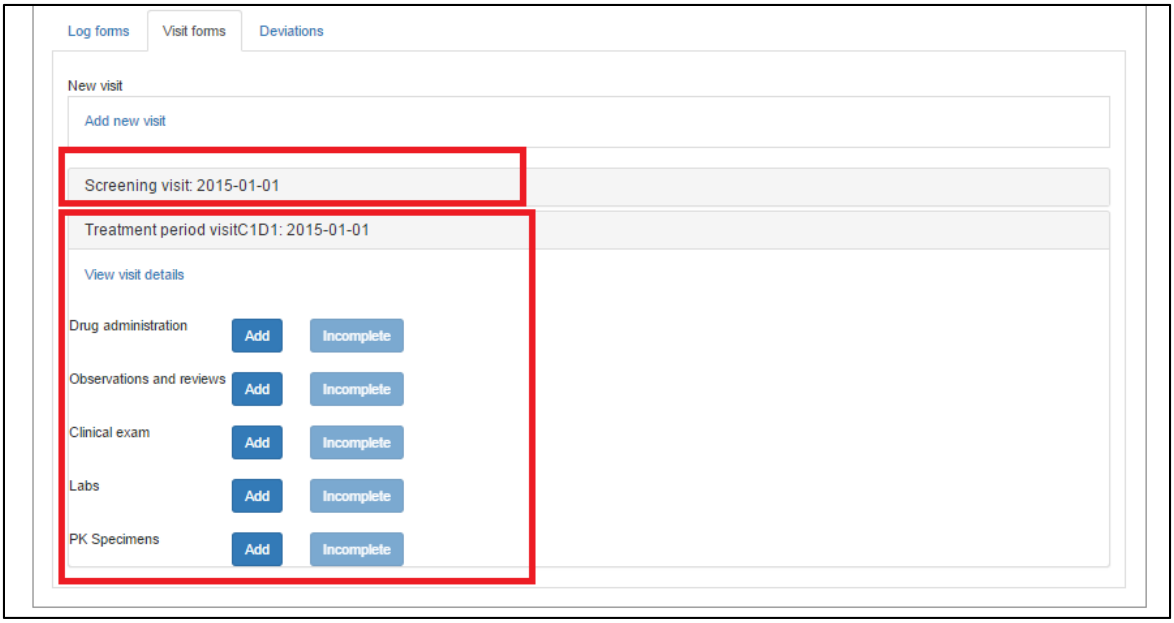
5.7.2 New visit: Treatment period visit (C1D1)

a) Navigate to the *Visit forms tab* and click on 'Add new visit'.

b) From the 'visit type' dropdown menu, select 'Treatment period visit'. Enter the date of the visit, then click the submit button.



c) You will be redirected to the visit-forms tab of the patient view page, with the newly added visit toggled open, and the appropriate forms for the C1D1 visit available to you.

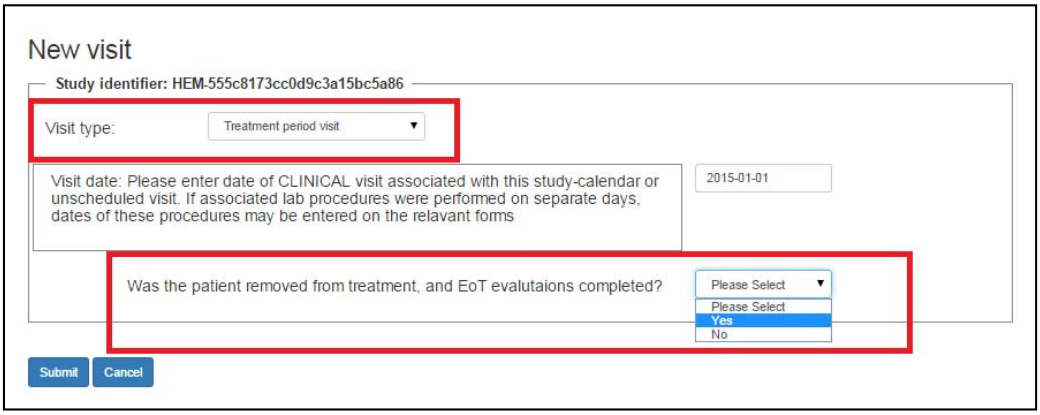


5.7.3 New visit: Treatment period with end-of-treatment visit (C1D8+EoT)

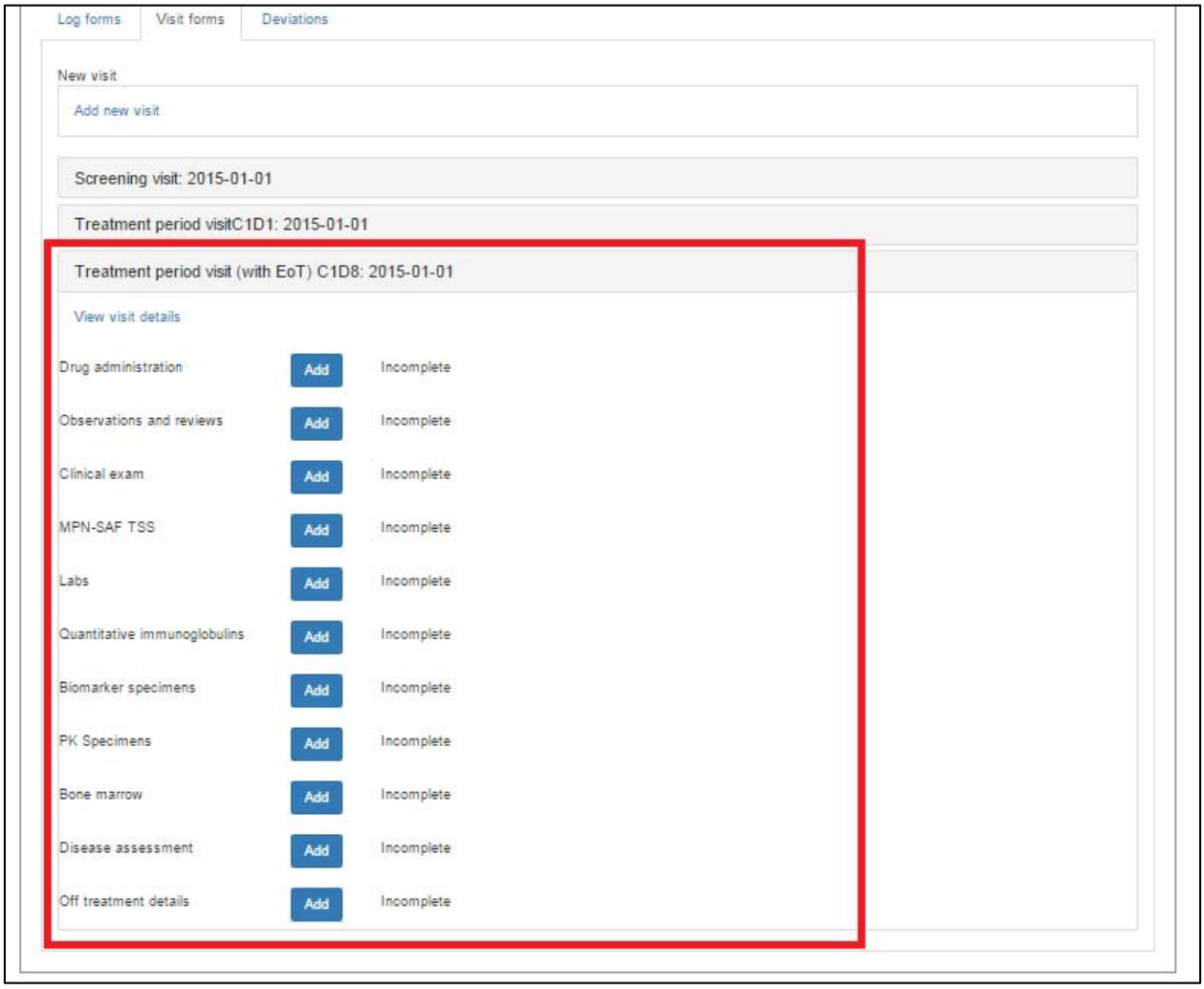
This visit type should be created when a treatment-period visit also serves as an end-of-treatment (EoT) visit, with all EoT evaluations completed. For example, the patient may arrive at clinic for the scheduled treatment-period visit, and the decision is made to remove the patient from treatment. The EoT evaluations are scheduled and completed at this visit or within the permissible window per protocol. This visit should be entered as treatment period with EoT, as shown in the following example.

a) Navigate to the *Visit forms tab* and click on 'Add new visit'.

b) From the 'Visit type' dropdown menu, select 'Treatment period visit'. Enter the date of the visit, and then select 'Yes' in response to the question: 'Was the patient removed from treatment, and EoT evaluations completed?' Then click the submit button.



c) You will be redirected to the visit-forms tab of the patient view page. The new visit will appear, with the appropriate forms attached.

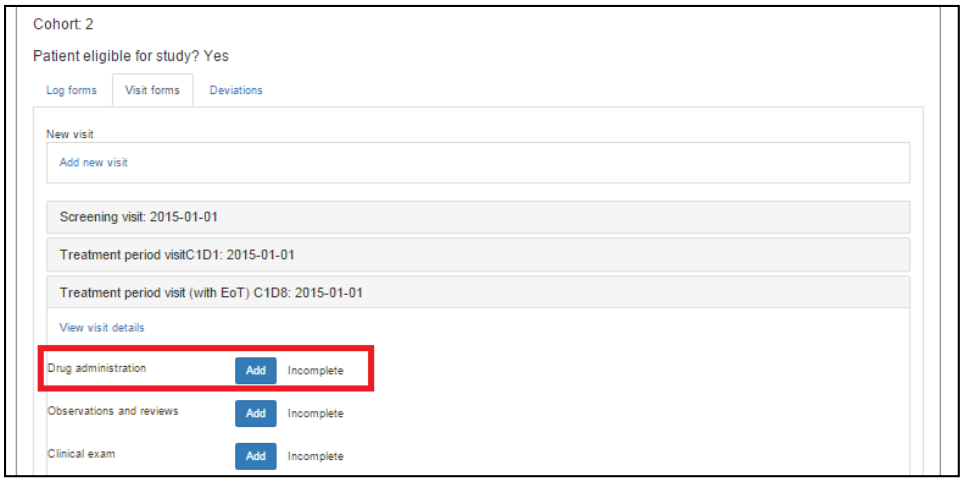


TIPS:

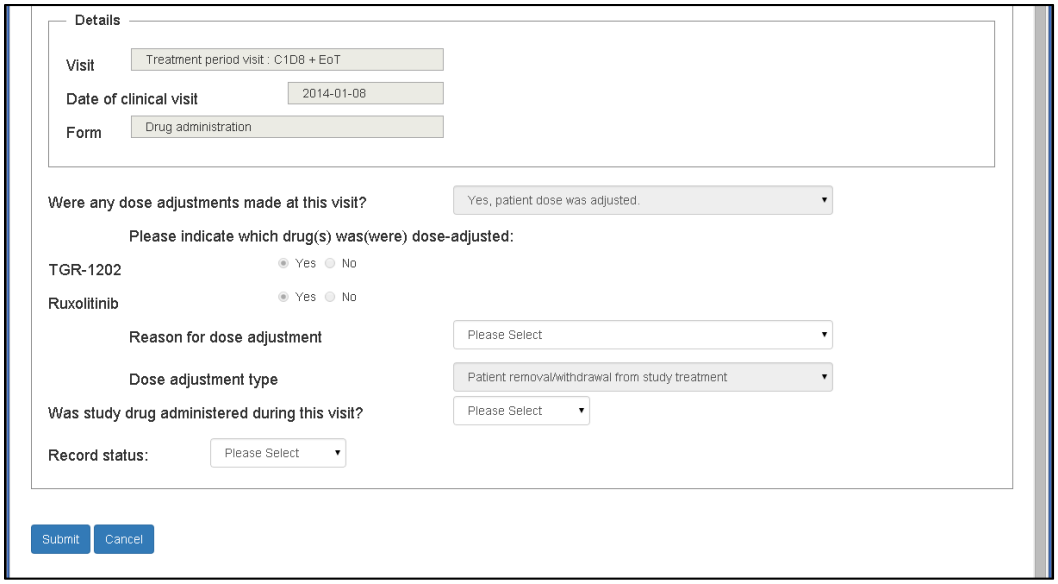
- For a typical treatment period visit, be sure to select 'No' in response to the question, 'Was the patient removed from treatment, and EoT evaluations completed?'
- After a treatment-period +EoT visit is added to a patient record, no additional treatment period visits may be added for that patient.

5.7.3.1 C1D8+EoT visit forms: Drug administration

a) Navigate to the *visit forms* tab. Toggle open the 'C1D8+EoT visit' section as needed. Click on the ADD button for the drug administration form.



b) Complete the form in its entirety and click 'Submit'. Note that, with a '+EoT' visit, many of the fields on the drug administration form are fixed to required values. For example, because we know that the patient was removed from treatment at this visit, a dose adjustment type of patient removal/withdrawal from treatment is pre-specified. The only field requiring selection in this scenario is the reason for the dose adjustment. Note that, in a typical treatment-period visit, the fields on this form will not be fixed to required values as in this example, and the user will perform usual data entry.

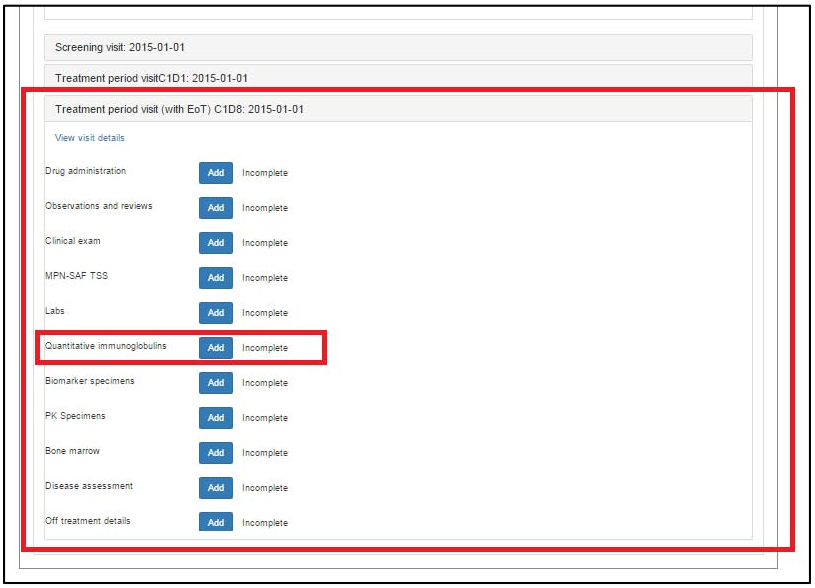


TIPS:

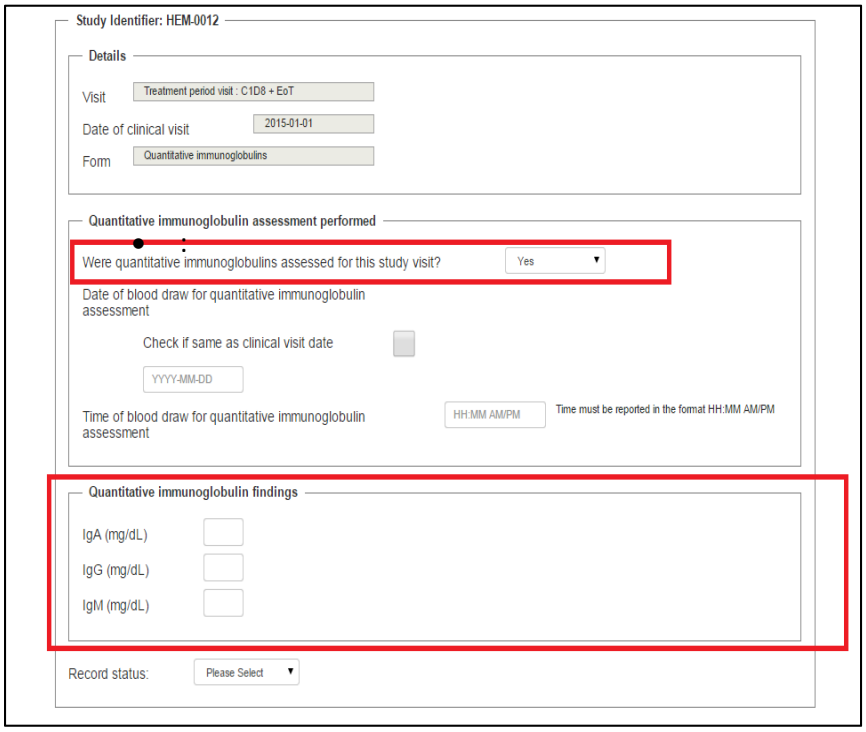
- The drug administration form includes fields for the actual dosages of TGR1202 and ruxolitinib ordered/dispensed at each treatment-period visit. These fields are included to confirm the patient's dose was dispensed correctly at each visit. If the patient has had a dose adjustment, be sure to select the actual dose ordered/dispensed at the visit, and not the originally assigned dose. If the dose adjustment is a dose delay, please select '0' dosage for the drug(s) delayed.

5.7.3.2 C1D8+EoT visit forms: Quantitative immunoglobulins

a) Navigate to the *visit forms* tab. Toggle open the 'C1D8+EoT visit' section as needed. Click on the ADD button for the quantitative Ig form.

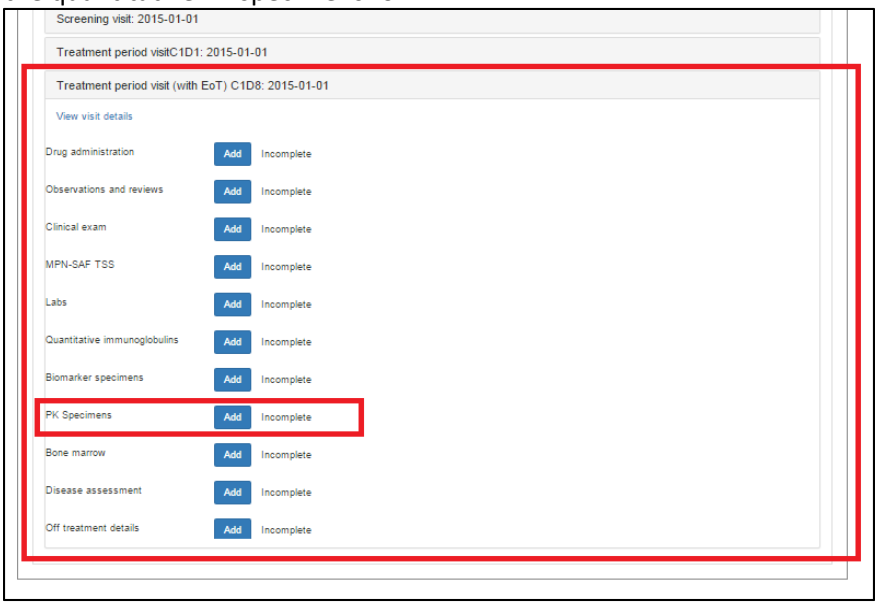


b) Complete the form in its entirety (up to two sections) and click 'Submit'.

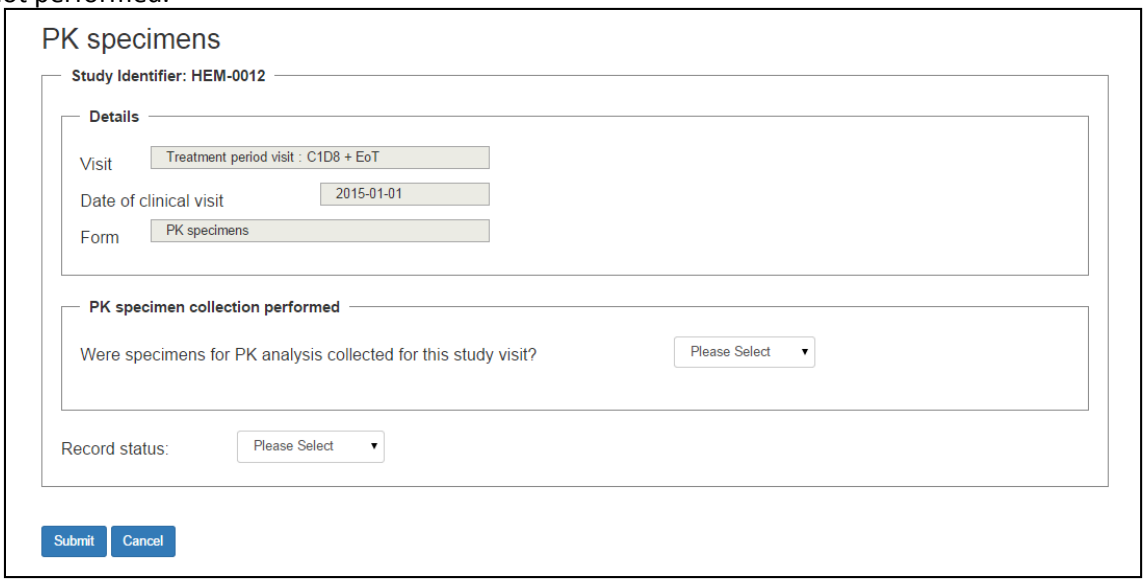


5.7.3.3 C1D8+EoT visit forms: PK specimens

a) Navigate to the *visit forms* tab. Toggle open the 'C1D8+EoT visit' section as needed. Click on the ADD button for the quantitative PK specimens form.

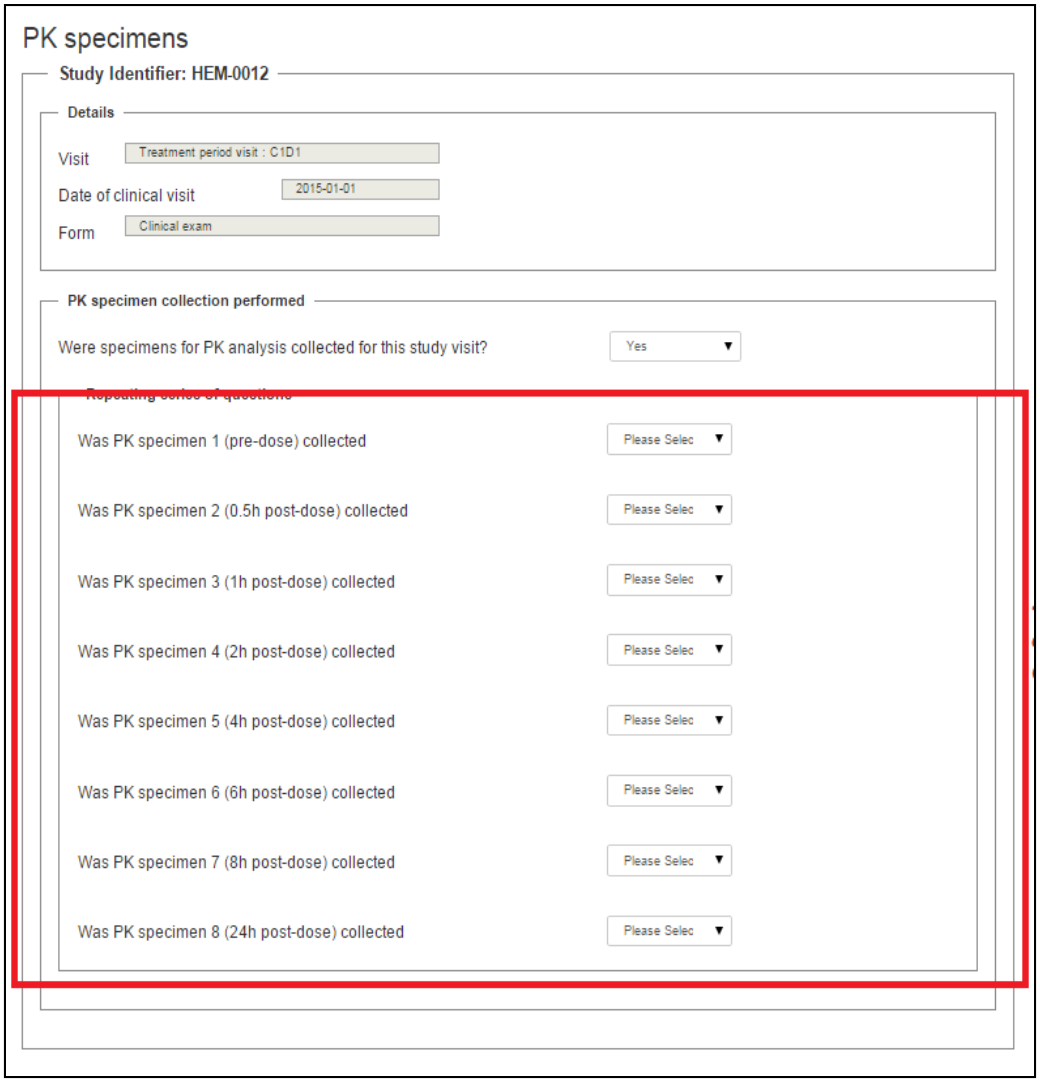


b) Complete the form in its entirety and click 'Submit'. Note that, at C1D1, a full time course of PK specimens are collected, for full PK analysis (see screenshot on next page). At subsequent PK time-points, only a single pre-dose specimen is collected, to evaluate accumulated blood levels. In addition, note that the PK specimen form is attached to '+EoT' visits that occur at scheduled PK specimen collection visits (such as C1D8+EoT, the example here), due to the fact that removal from treatment at that visit should not preclude evaluation of accumulated blood levels to date. If PK specimens are not collected at a '+EoT' visit, however, simply indicate on the PK form that this specimen collection was not performed.



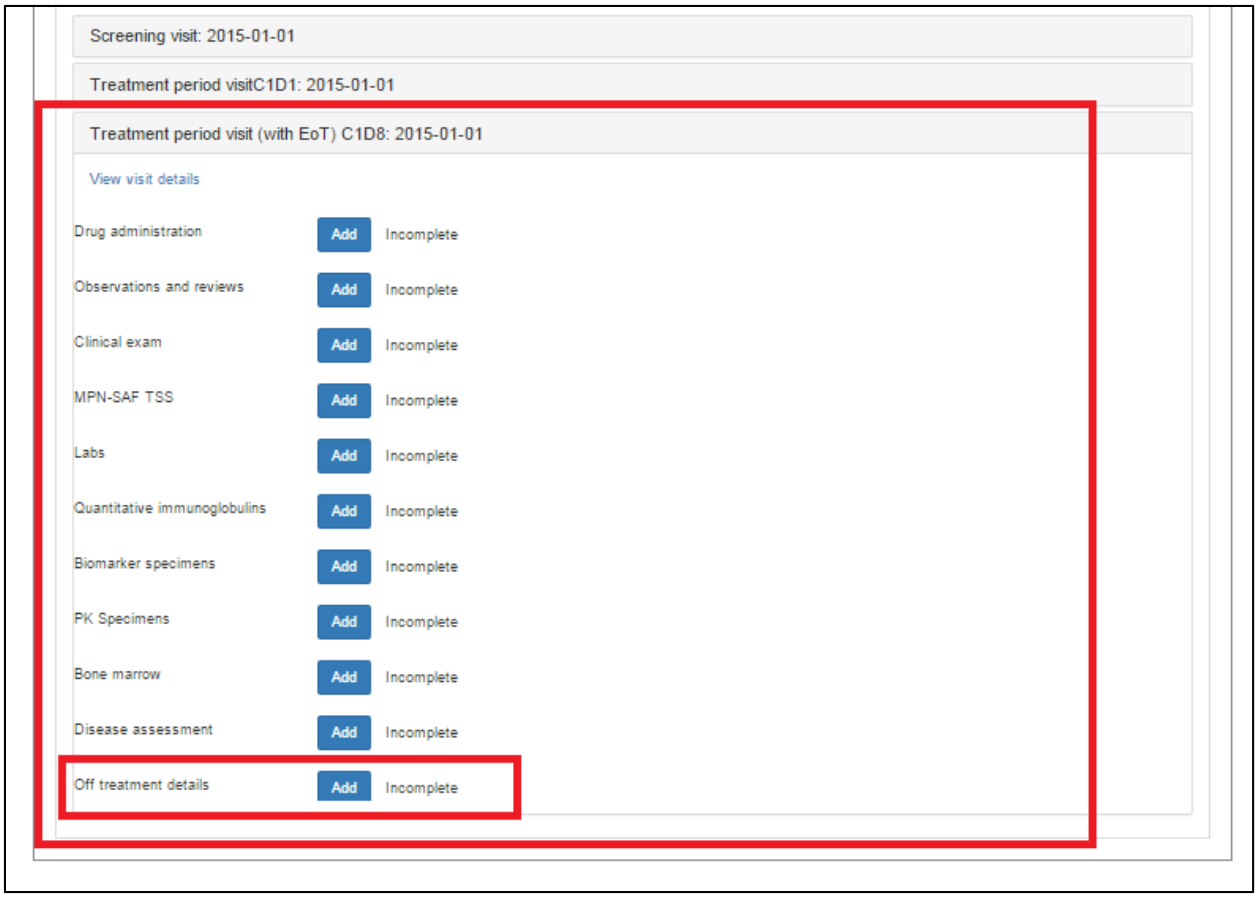
TIP:

- At C1D1, the full time course of PK specimens is collected.

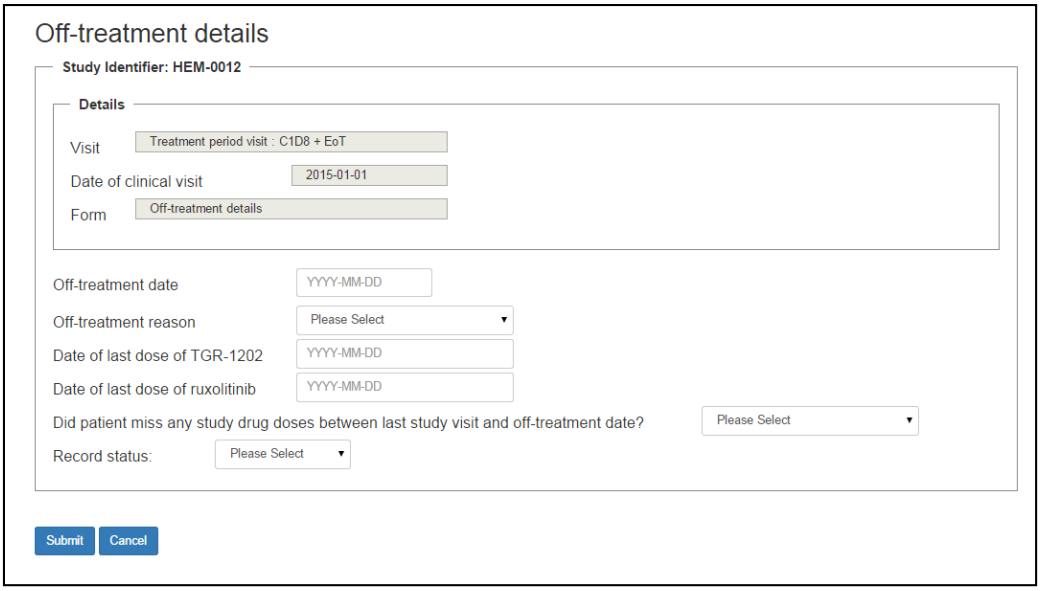


5.7.3.4 C1D8+EoT visit forms: Off-treatment details

a) Navigate to the *visit forms* tab. Toggle open the 'C1D8+EoT visit' section as needed. Click on the ADD button for the off-treatment details form.



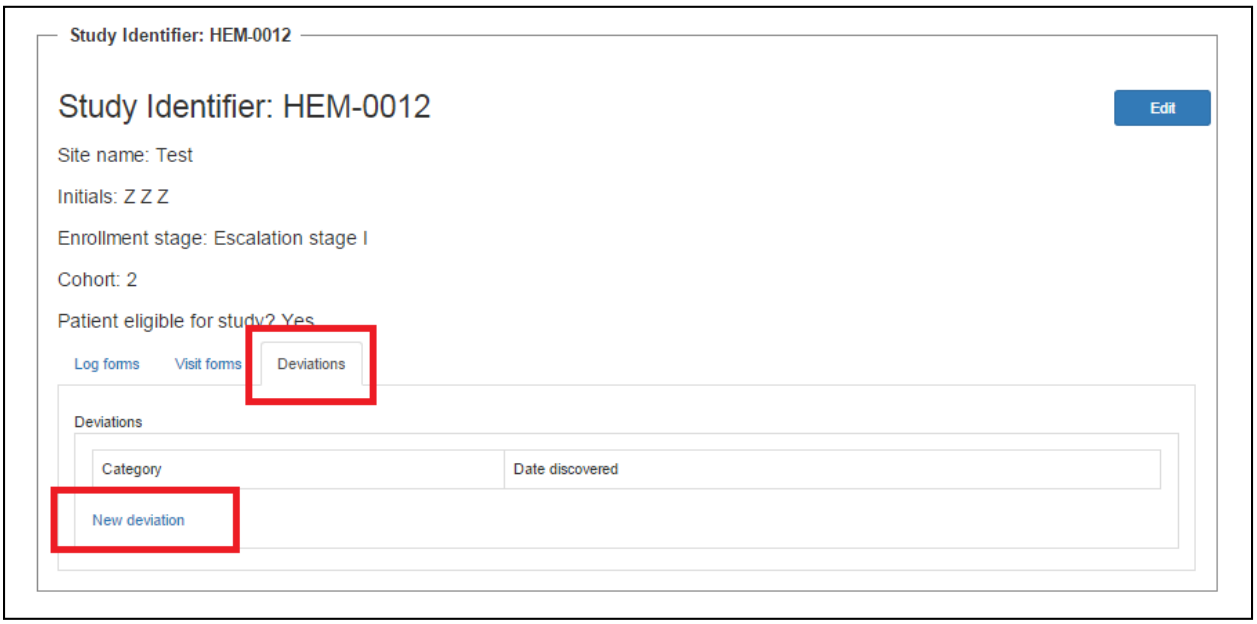
b) Complete the form in its entirety and click 'Submit'.



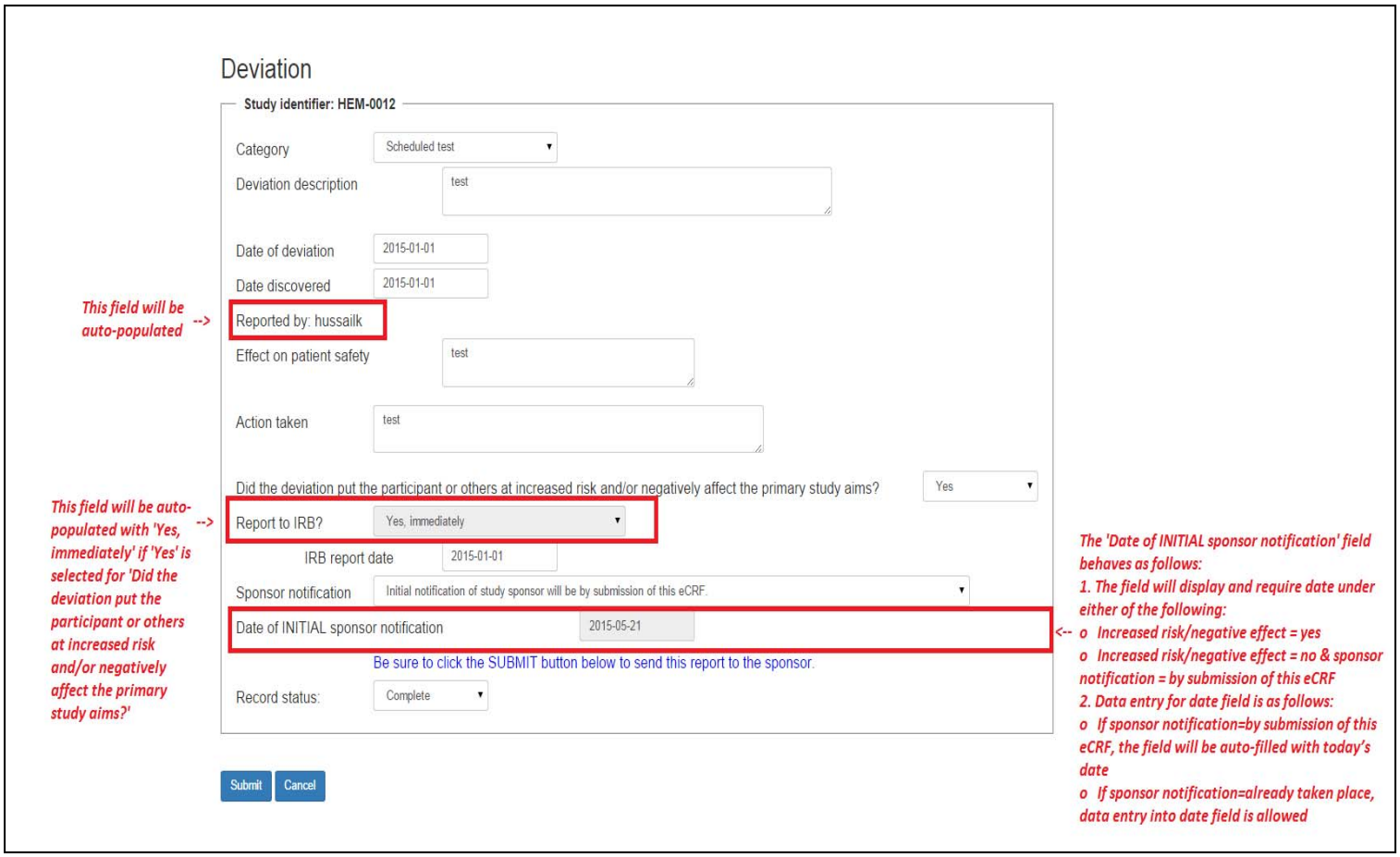
5.8 New entries: Deviation

To enter a new deviation, follow these steps:

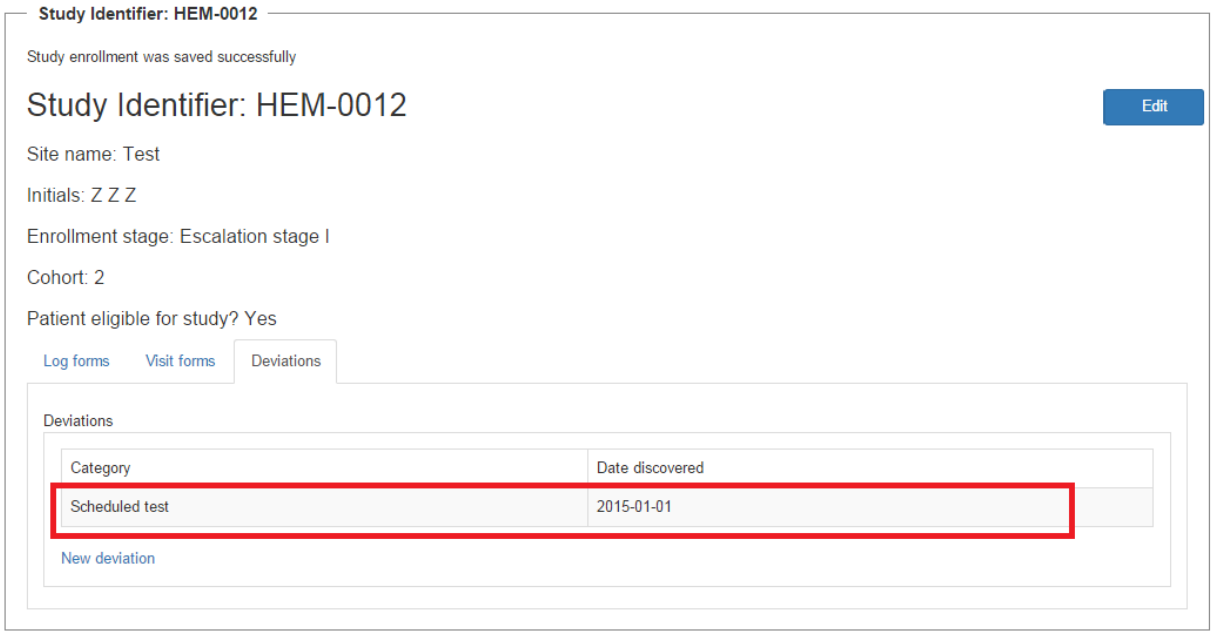
a) From the deviations tab on the *patient view page*, click on 'New deviation'



b) Complete the form and click the 'Submit' button.



c) After submitting, you will be redirected to the *patient view page*. A table will display the data you have submitted.



TIPS:

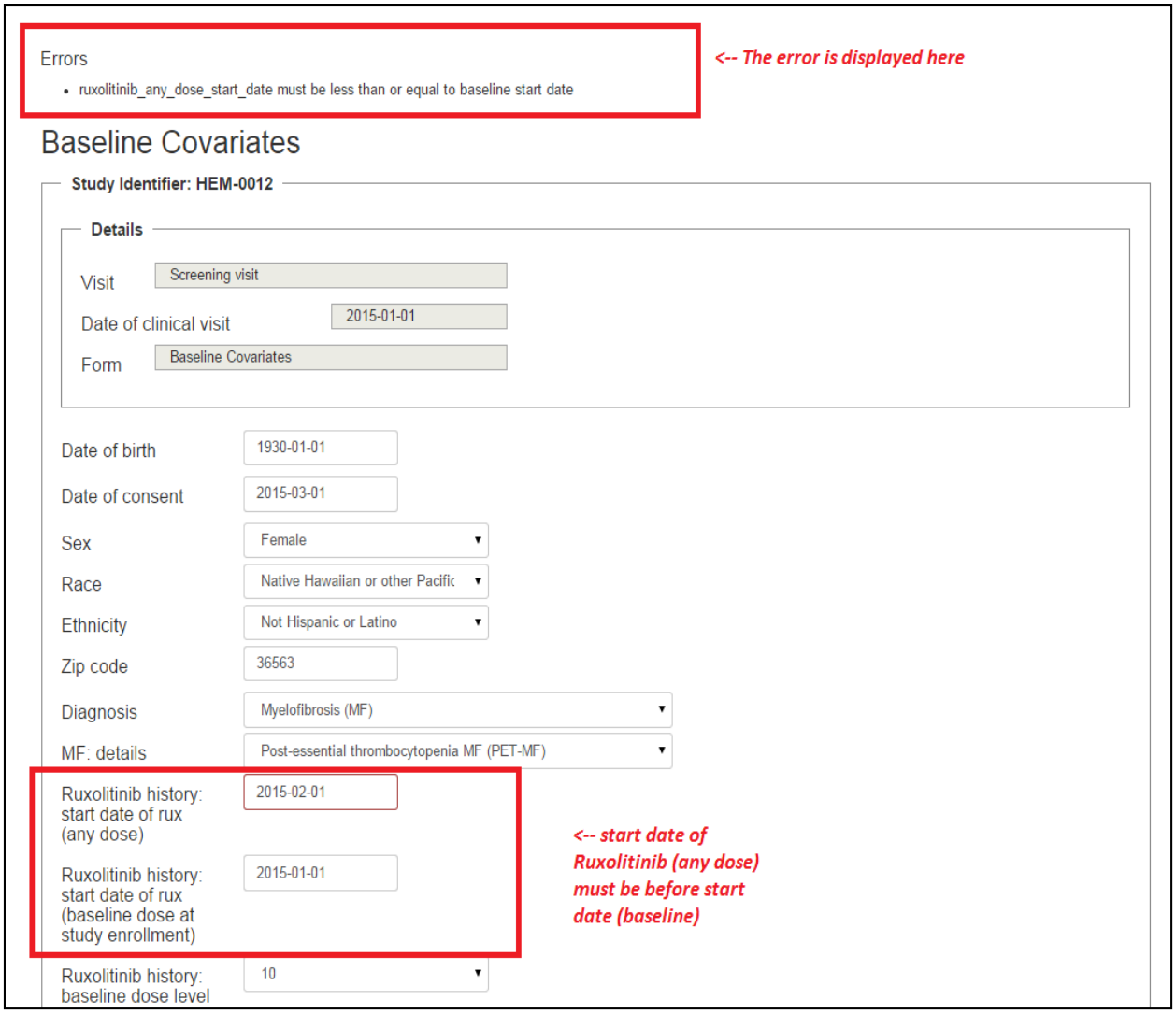
- When a deviation is submitted, the EDC generates an email alert to the trial coordinating center. You will be contacted as needed for additional information.

5.9 Correcting Errors

Whenever you submit a form with a status of 'complete', the EDC system will run a series of validations on the data you have submitted to help guard against data entry errors. If the system detects an error, submission of the form will fail, and the system will return an error message to you. The error may be flagged due to a logic check: for example, date of consent cannot be prior to date of birth. Other problems are flagged because they appear to deviate from protocol requirements: for example, study-calendar visits must occur within three days of schedule per calendar. The following illustrates examples of the types of error messages you may see.

Example

Suppose a baseline covariates form is submitted with a ruxolitnib start date (any dose) that post-dates the start date of the patient's ruxolotinib dose at study enrolment. This is an error in logic. The system will flag the error with an error message at the top of the form, along with red outlines to demarcate the field involved in the error. Please check your data entry, and correct the date or dates that was entered erroneously.



TIPS:

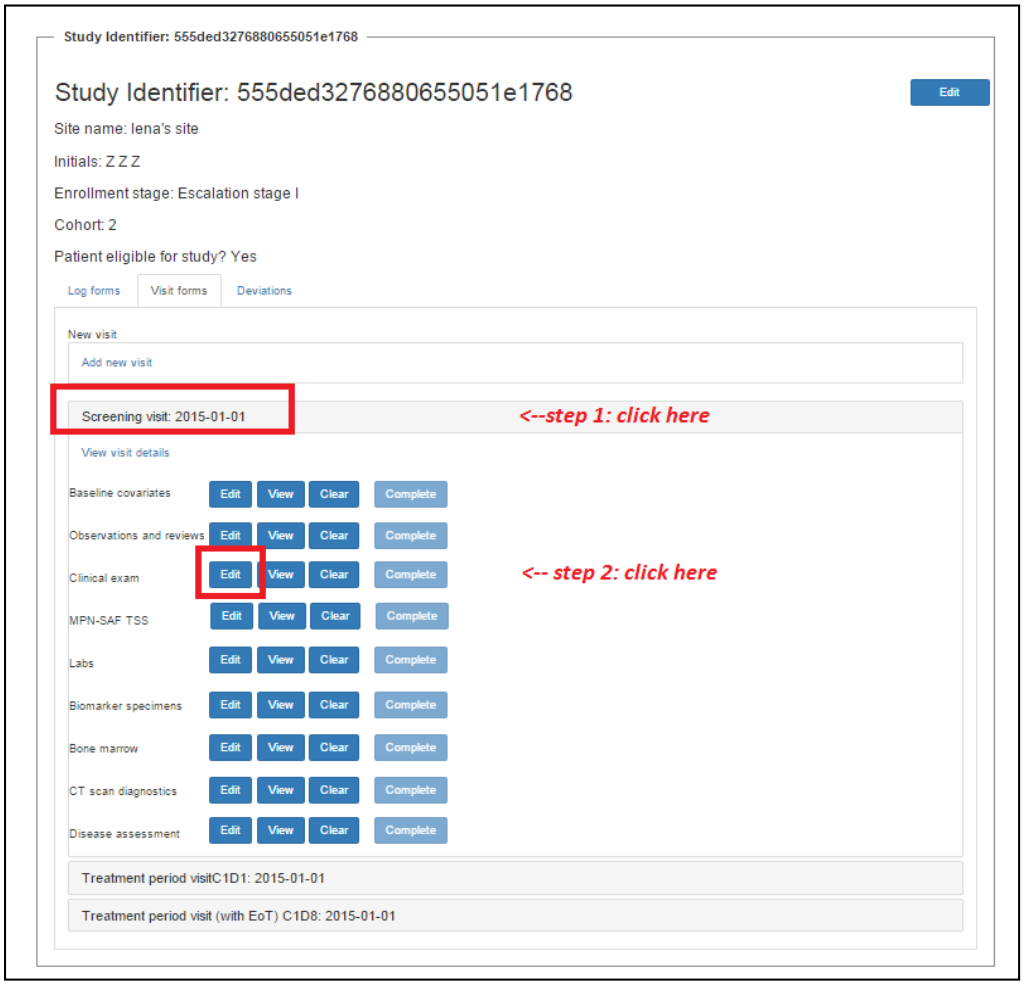
- Validations are only run when forms are submitted in 'complete' status. Forms submitted in draft ('incomplete') status are not run through validations, and can be submitted even with errors or incomplete data. When you return to the form to submit in complete status, any errors will be flagged at that time.
- In addition to errors with hard stops (the form cannot be submitted without correcting the error), the HEM1538db utilizes warning message with soft stops (the user is prompted to review the data and correct as needed, or override the warning and submit if the data are correct). For example, if a new visit is entered with a visit date outside the +/-3-day window from study calendar permitted per protocol, the system will return a warning message. If the date was entered in error, this error should be corrected. If the visit did, in fact, deviate from protocol, the original data entry should stand, and the user can override the warning message and submit the form.

5.6 Making Edits

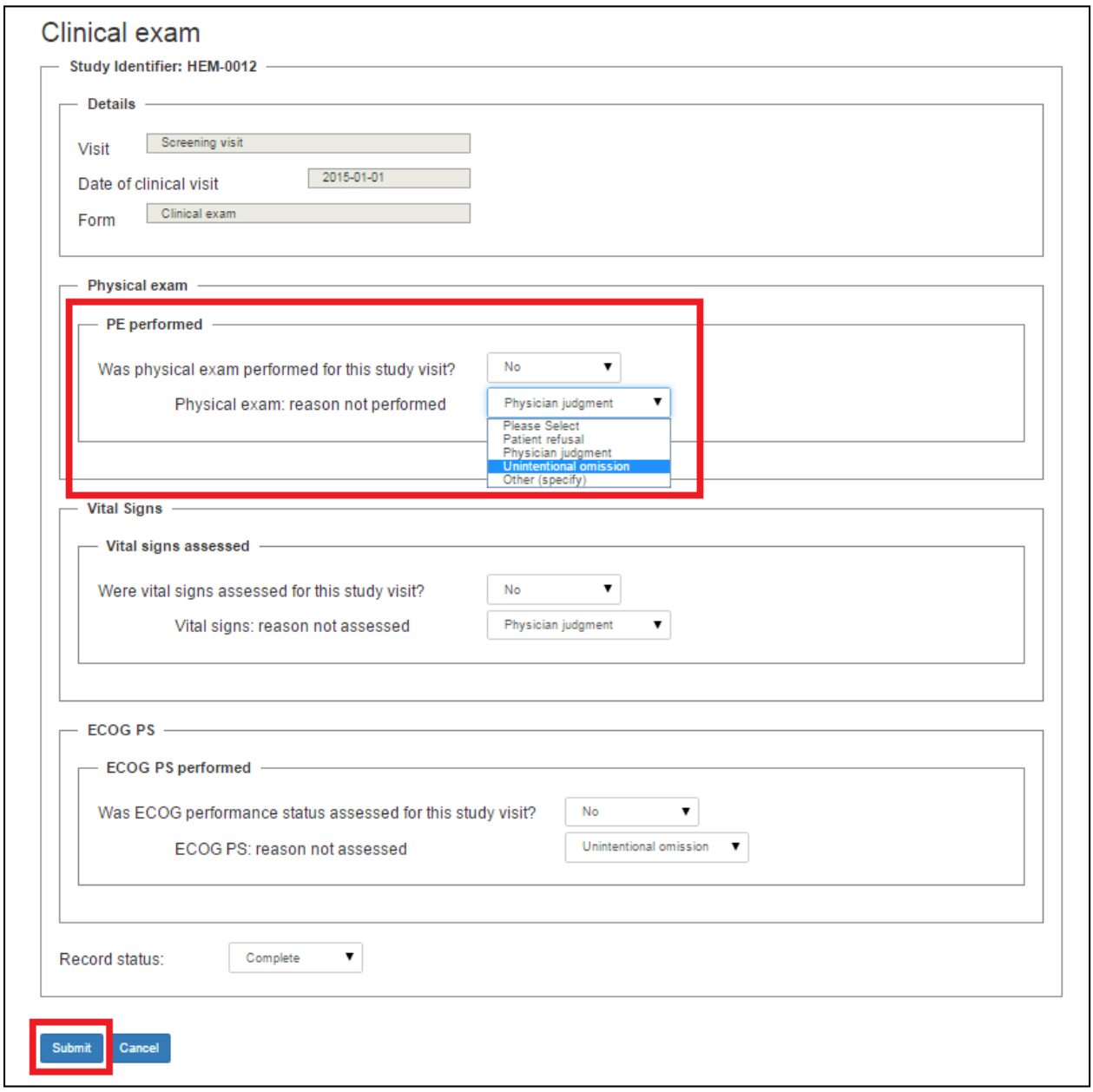
The following example will illustrate making an edit to the clinical exam form for the screening visit. In this example, we realize that the reason for omission of physical exam at this visit was entered incorrectly, and needs to be changed. To make edits to other forms, the process follows similar steps.

a) Navigate to the *visit view page* for the patient of interest.

b) Toggle open the screening visit, and click the edit button for the clinical exam form.



c) When the form loads, make the desired change and then click the submit button to save the change into the database.



TIPS:

- For log forms, the edit button is located within the form; click on the view button for the appropriate record from the log-form tab to access the record, then click on the edit button on the eCRF to make edits.
- For deviations, the edit button also is located within the form; click on the deviation of interest from the deviation tab to access the record, then click on the edit button on deviation eCRF to make edits.

Query feature

For data monitor

1. Within each form, you will now have access to two different buttons: VERIFY and QUERY. Note that you also will still have access to the VERIFY button in the forms lists (i.e., list of forms attached to each visit; list of concom meds, etc.); the QUERY button, however, is available only within the form, after accessing the form by clicking the VIEW button (for visit forms) or clicking on the row for the record of interest (for log forms: medical history, concom meds, comments, deviations, AEs/SAEs).

2. If you need to query something on a form, click the QUERY button. This will open a comment box. Type the query into the comment box, and click ADD COMMENT.

   IMPORTANT! Do not forget to click the ADD COMMENT button after typing your comment in the query-comment box. Your comment will not be saved if you do not click this button, and the data entry user will not receive notification of your query.

3. After you type a comment in the query-comment box, and click ADD COMMENT, an automated email will be generated, to alert the site entry user to review the comment and proceed accordingly – whether to explain an apparent discrepancy, make a correction as requested, etc. When the site entry user takes the appropriate action, he or she should comment accordingly in the query-comment box. This will generate an automated email to you to review the response to your query.

4. If the data entry personnel has responded to the query to your satisfaction, close the query and verify the record by clicking VERIFY. The query-comment trail will still be visible, but no further comments may be entered. However, the QUERY button will reappear, so if you discover that you need to make additional queries on the record, you may open another query.

5. If the data entry personnel has NOT responded to the query to your satisfaction, enter a follow-up comment by typing in the comment box and clicking the ADD COMMENT button. This will again generate an automated email to the data entry personnel to respond to your query.

IMPORTANT: Automated emails will come from the email address noreply@vanderbilt.edu . To ensure the automated emails are directed to your inbox and not your junk mail, you may wish to add this email address to your list of safe senders.

For data entry users

1. If the data monitor has a query on one of your forms, she will open a query and type a comment with the issue to be resolved. This will generate an automated email to you to review the query and respond accordingly.

2. After reviewing the query, determine the appropriate course of action: request clarification from the monitor; make a requested change; explain an apparent discrepancy, etc. Then document your course of action in the query-comment box on the form in question, just above the data monitor's comment.

IMPORTANT: You must access the form in VIEW mode to type in the query-comment box. If an edit to the form is required to respond to the query, you may (1) access the form in edit mode, (2) make the necessary change, (3) submit the form, (4) re-access the form in view mode, and (5) document the change/correction you have made by entering a response in the query-comment box.

IMPORTANT: After typing your response in the query-comment box, be sure to click the ADD COMMENT button to save the comment. If you do not click this button, your comment will be lost, and the data monitor will not receive notification that you have responded to the query.

3. When you enter a response to the query in the query-comment box on the form in question and click ADD COMMENT, the data monitor will receive an automated email to review your response. The monitor may be satisfied with the response, and close out the query by verifying the form. Alternatively, the monitor may have follow-up question(s), which she will enter in the query-comment section of the form in question. When she does so, you will receive another automated email. This cycle can continue for as many rounds as needed to resolve the query.

IMPORTANT: Automated emails will come from the email address noreply@vanderbilt.edu . To ensure the automated emails are directed to your inbox and not your junk mail, you may wish to add this email address to your list of safe senders.

Out-of-range flag feature

For data entry users

The out-of-range flag feature will prompt you to review any lab entries that fall outside the reference ranges entered in the EDC. Relevant labs are hematology labs (labs form), blood chemistry labs (labs form), coagulation labs (labs form), HbA1c (labs form), and quantitative immunoglobulins (quant. immunoglobulin form).

Please use this feature as follows:

1. During data entry into relevant fields, if you enter an out-of-range value, a pop-up window will appear, prompting you to review the field for possible data entry error; or, if the data entry is correct, to answer follow-up questions about the out-of-range value. Click 'OK' in the pop-up window to close the window and proceed with next steps.

2. If your entry was in error, please correct, and proceed with the form as usual.

3. If your entry was the correct value for the patient in question, please answer the follow-up question(s) that will appear.

    a. The first follow-up question asks whether the out-of-range value is clinically significant. If you indicate that the value is not clinically significant, no further follow-up questions will appear. If you indicate clinical significance, a second follow-up question will display. If you are not sure whether the value is clinically significant, please consult with the study PI.

    b. The second follow-up questions asks whether the out-of-range value is reportable as an AE. Select 'Yes' if the abnormal lab is reportable. If the abnormal lab is not reportable, select either 'No. Not reportable per protocol' or 'No. Not reportable for other reason.' For example, per protocol, no AEs of grade less than 3 are reportable, except for events of special interest. If the abnormal lab is not an event of special interest, and would represent a grade 1 or 2 AE, this is not reportable per protocol, and you would select this option. If the abnormal lab is not reportable for another reason, you will need to answer one more follow-up question. If you are not sure whether an abnormal lab is reportable, please consult with the study PI.

    c. The third follow-up question is free-text entry for abnormal labs, not reportable for 'other' reason. Here, please specify the reason not reportable.

Reports feature

The HEM1538 EDC has four pre-specified reports:

- AEs (summary statistics of all AEs by type and grade)
- SAEs (detailed data points from each SAE)
- Deviations (detailed data points from each SAE)
- Verifications (list of all records in EDC, with verification status of each)

For any additional reports needed, please contact the CQS for custom report generation.

To generate a pre-specified report from the HEM1538 EDC user interface:

1. Navigate to the reports page by clicking on REPORTS in the top navigation bar.
2. Select the report type you wish to run (AE, SAE, deviations, verifications).
3. For AE, SAE, deviations, select the date range for events to be reported.
    a. For AE and SAE, the date ranges will filter on event start date, i.e., events with start date in the specified date range will be returned.
    b. For deviations, the ranges will filter on deviation discovered date, i.e., events with discovered date in the specified date range will be returned.
4. Select the institutions for which events should be returned.
5. Click SUBMIT.
6. The report will generate and can be downloaded like any document download from a web page.