Registry eForm Data Entry Guidelines
Version 1.0 – 02 Apr 2014
Updated for eForm on 20 Jun 2016

Part 3
General recommendation for data entry in ProMISe and instructions of completion for the Follow up Form 6 and 12 Months post HSCT

PASS Protocol DF VOD-2013-03-REG

A multi-centre, multinational, prospective observational registry to collect safety and outcome data in patients diagnosed with severe hepatic VOD following hematopoietic stem cell transplantation (HSCT) and treated with Defitelio® or supportive care (control group)

Guideline for e-form completion of the VOD Registry is divided in 3 parts:

- Part 1: general recommendation for data entry in ProMISe and instructions of completion for the Registration Form and the Med-AB
- Part 2: instructions of completion for the Follow-up Form 100 days post HSCT
- **Part 3: instructions of completion for the Follow-up Forms 6 & 12 months post HSCT**

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I/ MEANS TO ENTER PATIENTS INTO THE REGISTRY

- **Patients to be included**

1. Any patient in which you have made a diagnosis of severe VOD post-HSCT

    - *Note: It is important that you include also patients not treated with Defitelio® (for example patients in which Defitelio® is not used due to the presence of contraindications or patients considered unsuitable as a result of the special warnings and precautions listed in the Defitelio® SmPC)*
    - *Note: All consecutive and consenting patients with a diagnosis of severe VOD should be entered into the Registry*

2. Any patient receiving treatment with Defitelio® for any other condition

    - *Note: If in your clinical practice you treat conditions other than severe VOD with Defitelio® you should also enter these patients in the Registry (VOD-Project + EBMT Med-AB)*

- **Contacts**

If you have any questions on this Registry, regarding the means to enter patients into it or questions around Defitelio®, please contact:

- **INFO ON REGISTRY:**

jessica.lemaitre@upmc.fr & emmanuelle.polge@upmc.fr

- **INFO ON DEFITELIO®:**

medical-enquiries@gentium.it

- **Forms to be reported**

The registration form to enter patients into the Registry can be accessed via the EBMT website at: http://www.ebmt.org/Contents/Research/EBMTStudies/CurrentResearch/Pages/Study%20Pages/VOD-Project.aspx

EBMT CICs will be asked to report information for patients included in the VOD project via Internet and e-forms, at Registration, Day 100, 6 and 12 months after transplant as described below:

Once patient has given his/her consent,

- At sVOD diagnosis or start of Defitelio® (if Defitelio® is administered for other reason than treatment of the sVOD)
    - Fill in VOD-Project Registration Form ;
- At 100 days post HSCT
    - Fill in Med-B and comorbidities Form (Med-AB project specific link)
    - Fill in VOD-Project 100 days Follow-up Form
- At 6 months post HSCT
    - Fill in VOD-Project 6 months Follow-up Form
- At 12months post HSCT
    - Fill in VOD-Project 12 months Follow-up Form

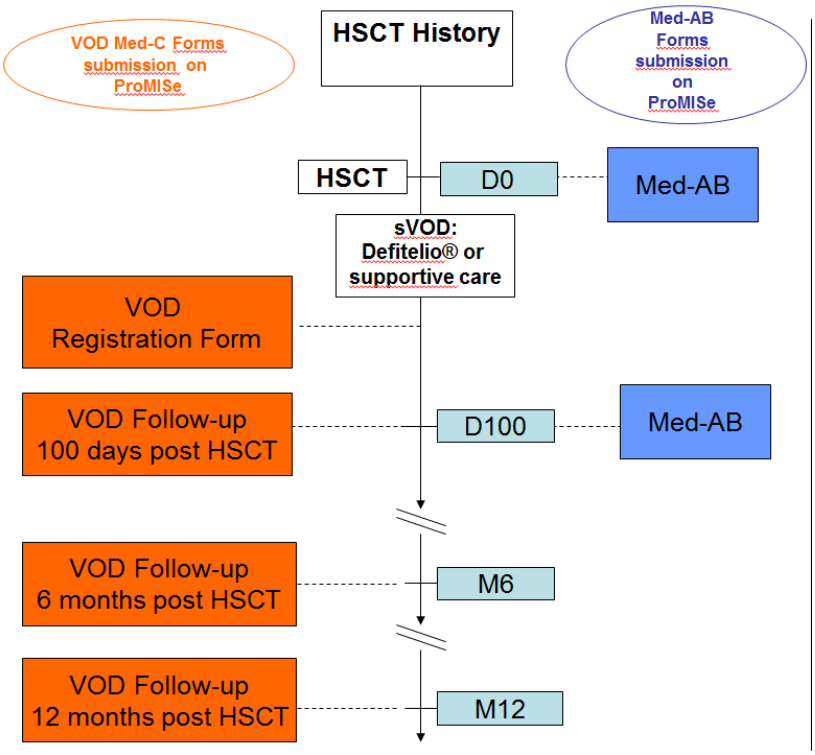


Figure 1 - Data Flow Chart

II/ e-Form Completion Instructions in ProMISe

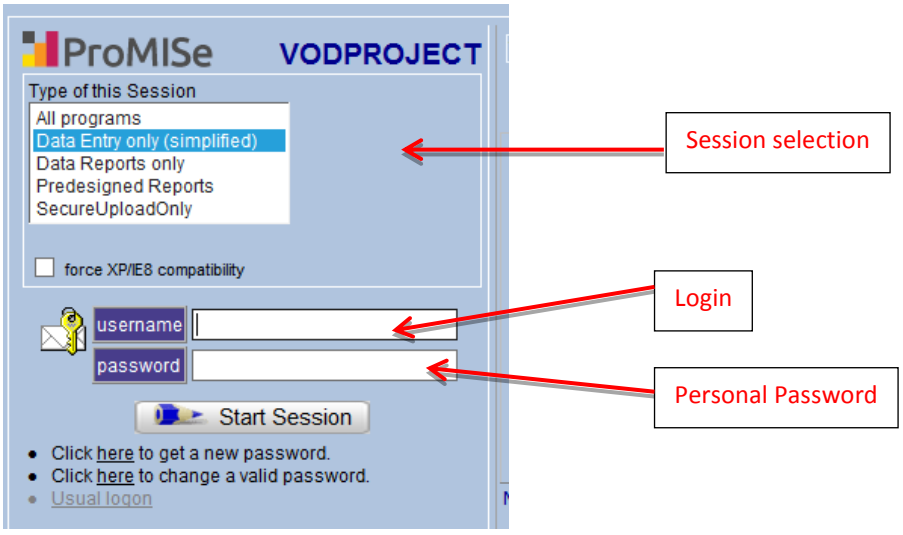
II-1/ Connection to VOD Project (Med C)

VOD-Project e-forms are available on Internet:

https://www.clinicalresearch.nl/PROMISE/S/HEIT/S_O_EBMT_C_NIS_VODPROJECT_/LOGON/INDEX.HEI

To connect for data entry:

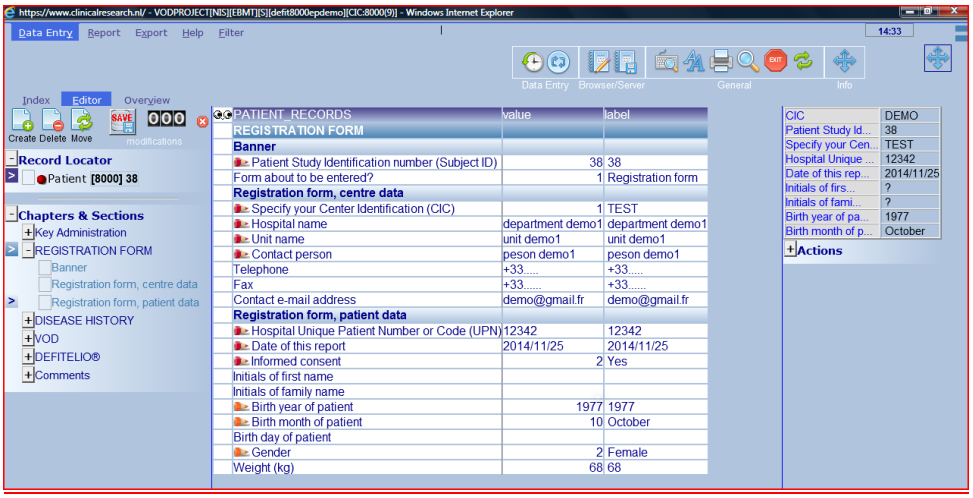
- 1st select either session “All programs” or session “Data entry only (simplified)”



- Then fill in the **username** and **password** fields then click on the "Start Session" button to enter the VOD Project.

Your password is personal. Please, keep it confidential. This personal password will be attributed and sent by email to the people in charge of the data entry after the training session. In case of loss or expiration or blocked account, please contact jessica.lemaitre@umpc.fr or emmanuelle.polge@upmc.fr

VOD Project opens on the Data Entry tab, and Editor sub-tab (screen copy below).

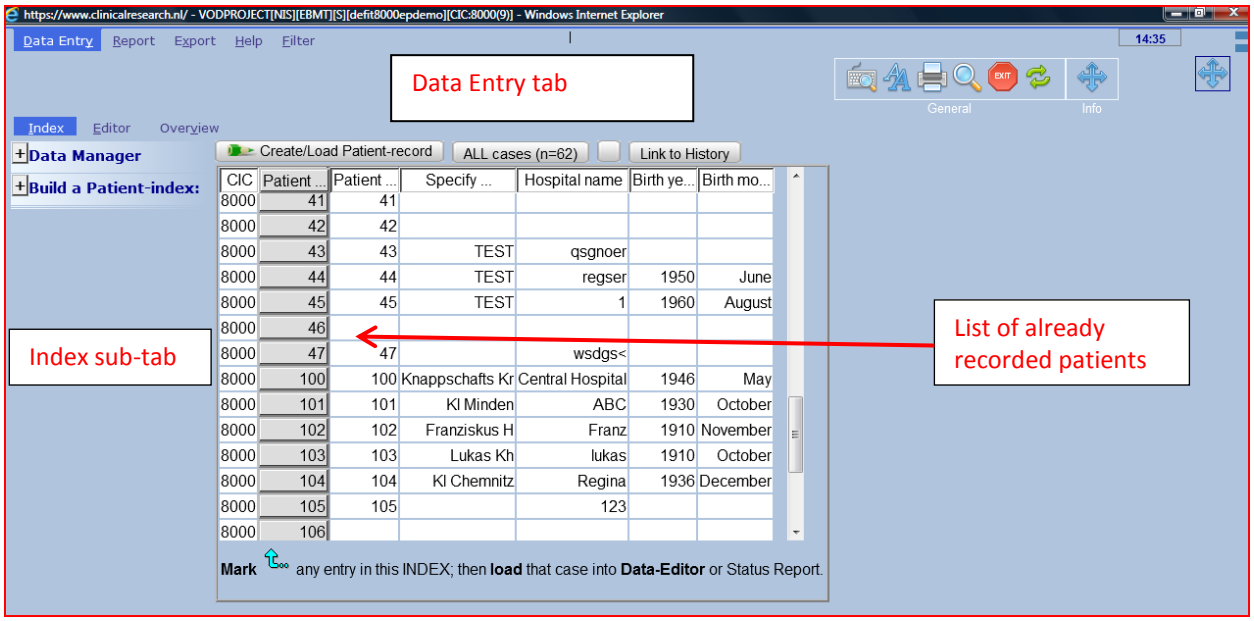


II-2/ List of patients already reported

The list of patients already reported in the VOD project is available on:

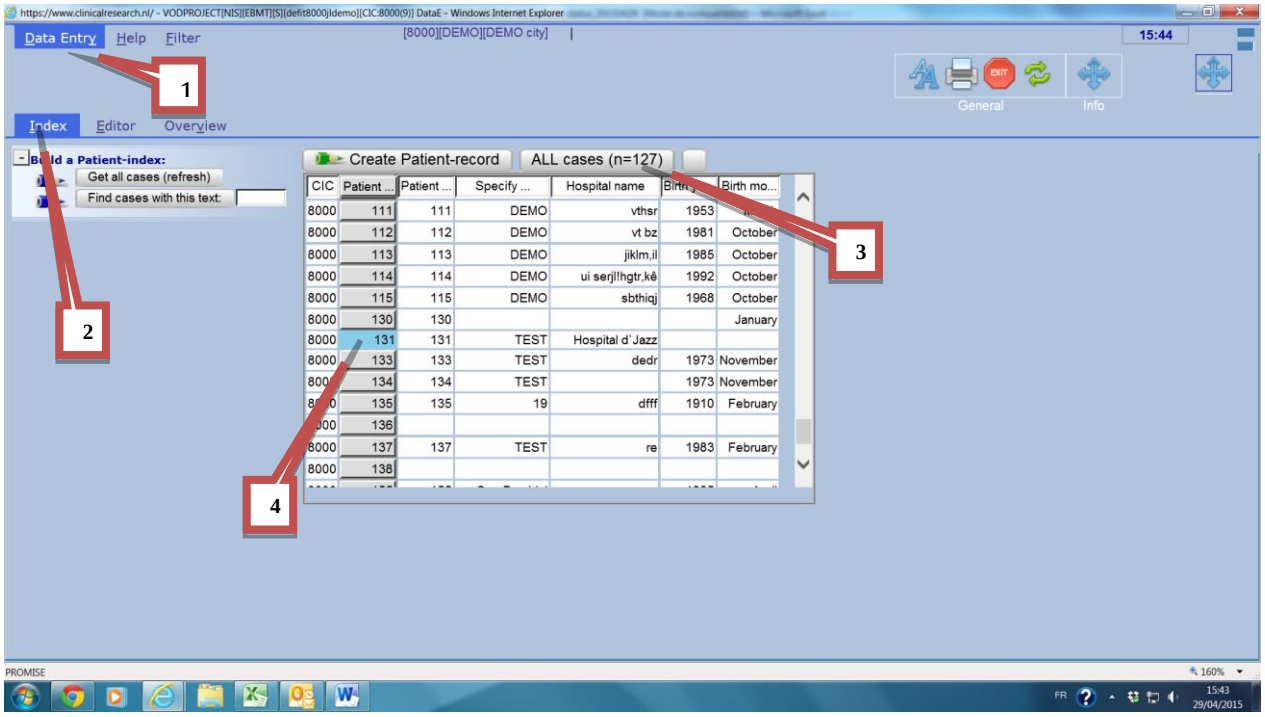
Tab: **Data Entry**

Sub-tab: **Index**



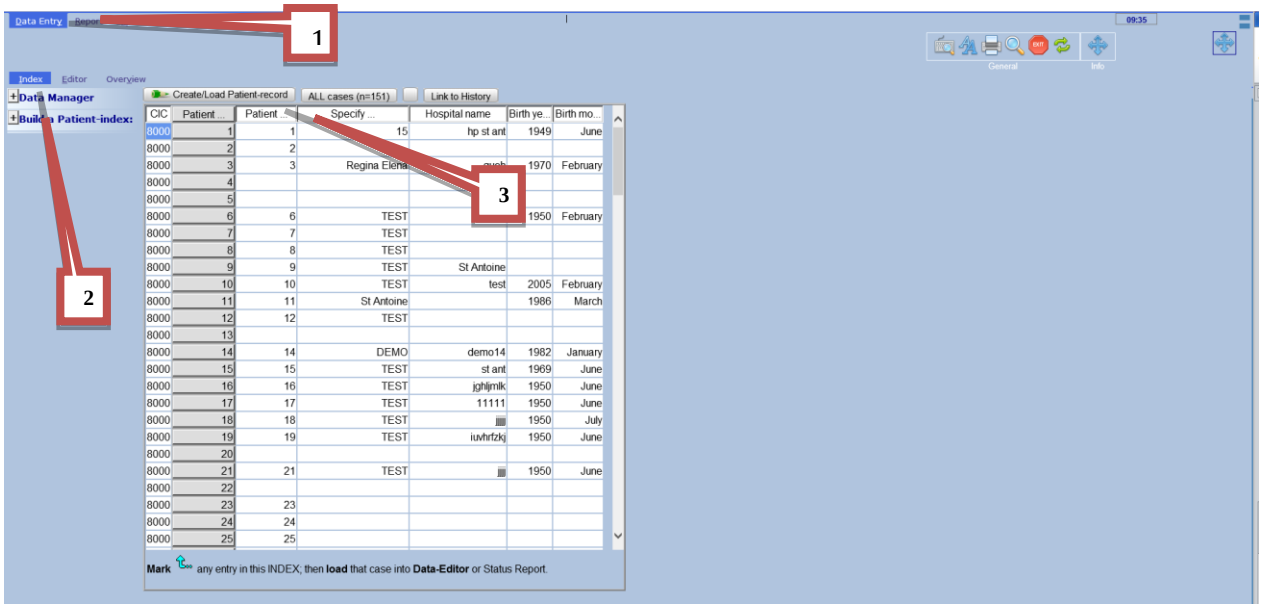
II-3/ Patient Record & Selection of the Form to be entered

1/ To load a patient already recorded, click on “Data Entry” Tab (1), then “Index” sub tab (2), followed by “All cases” list (3) and RIGHT click on the patient you want to report a follow up Form (4).

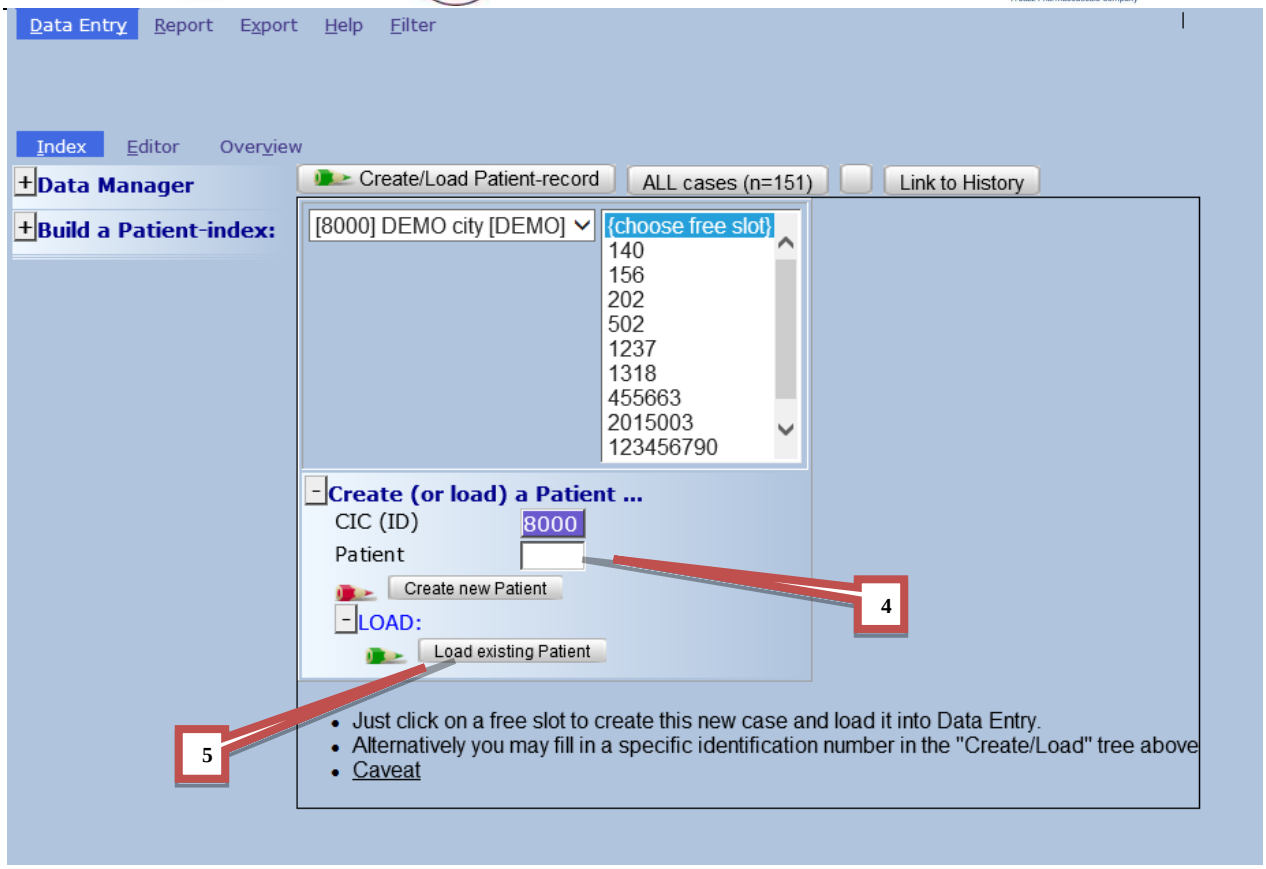


Or

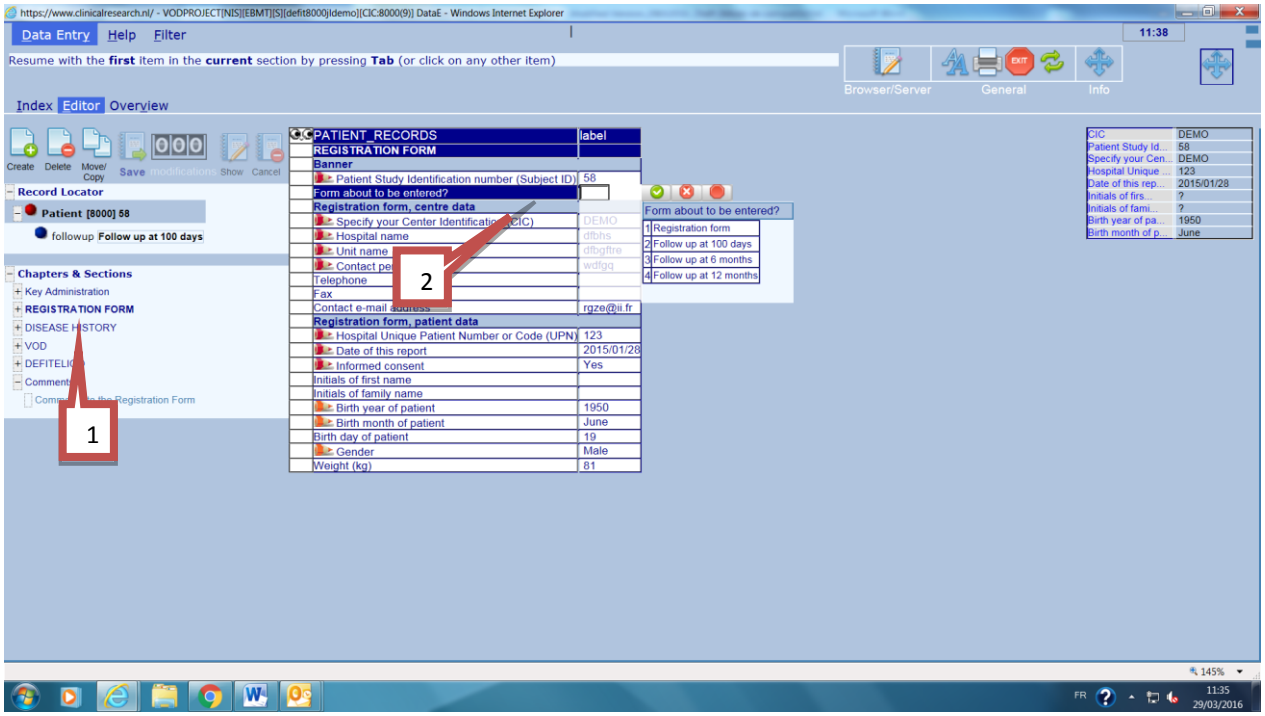
In “Data entry” tab and “Index” sub-tab, click on “Create/Load Patient-record” button



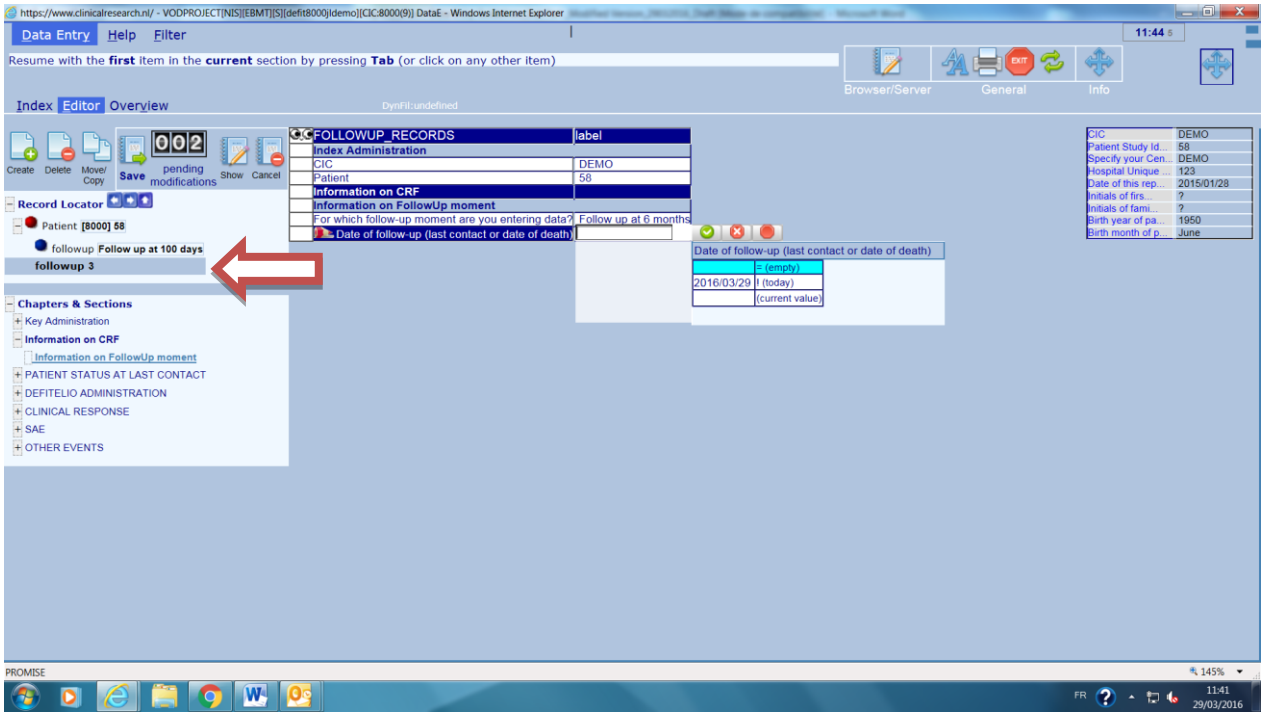
Enter the Study Number of the patient you want to complete the follow-up, and then click on “load existing patient”.



2/ To create the Follow up Form 6 or 12 Months, click on the menu “Registration form” (1), then select in “Form about to be entered?” the appropriate form you wish to create (2). Choose the follow up form you wish to report (6 months or 12 months).



You can see the follow up Form 6 months post HSCT is created below:



As the form is created, you can now start the data entry for this patient.

II-4/ Data entry navigation

Data entry in ProMISe is interactive: it means that the programmed navigation will follow your form order, while skipping any irrelevant questions for that particular patient according to data already reported.

IMPORTANT: To navigate within the eform from one item to the other, please use the <u>Tabulation key</u>.
Avoid using the mouse to go from one section to another, follow the cursor jump navigation.

II-5/ How to modify data in a form

Please note that when you want to change the data already recorded, this is possible, but the system will ask you the reason why you have decided to make any change. Please be careful and record, for any changed data, the reason as:

-Data Entry Error
-New data available
-Any other reason can be also specified here, as this is a free text field

And finalize the “Save action” by clicking on the pending modification button.

II-6/ How to save or remove pending modifications

It is very important to note that the data entered in the browser are not automatically stored in the database on the server. In order to save the data on the server, you have to explicitly give the command to save the data, which is done by clicking the Save button above the record locator (Fig. 1) or by using the shortcut ctrl + s. If you wish to cancel all pending modifications, you can click on the cross button in the save dialog.
The save dialog also shows a counter with the number of pending modifications. The pending modifications count the number of items that have been modified, filled or erased since the last save. You can review the pending modifications by using the function buttons shown in Fig. 2. This allows you to either view the pending modifications or view the original, unmodified data of the current case as stored on the server. The current case as on the server can also be viewed by selecting the Overview sub tab in Data Entry main tab and clicking Horizontal or Vertical.

Figure 1: Clicking the save button will save all pending modifications to the server. To cancel pending modifications, click the cross button on the right of the dialog.

Figure 2: Buttons for browser to server comparison. Clicking (1) will show a list of all pending (unsaved) modifications. Clicking (2) will show an overview of the current, unmodified data of the current case as on the server (without pending modifications).

II-7/ How to close ProMISe session

Finally, after a data entry session, you may wish to close the ProMISe application. To close the session, click the exit button in the upper right bar of the screen (Fig. 1). ProMISe will warn you if there are unsaved changes and give an option to save these changes before closing. You can also use the "x"-button on the browser window to close ProMISe, but then ProMISe will not be able to give warning messages with regard to unsaved data.
There may arise situations in which you wish to restart the session. To restart the session, click the refresh session button next to the exit button (Fig. 1).This will close the current session and build a new session. This option is not available if there are unsaved changes; you must first save or discard all pending modifications.

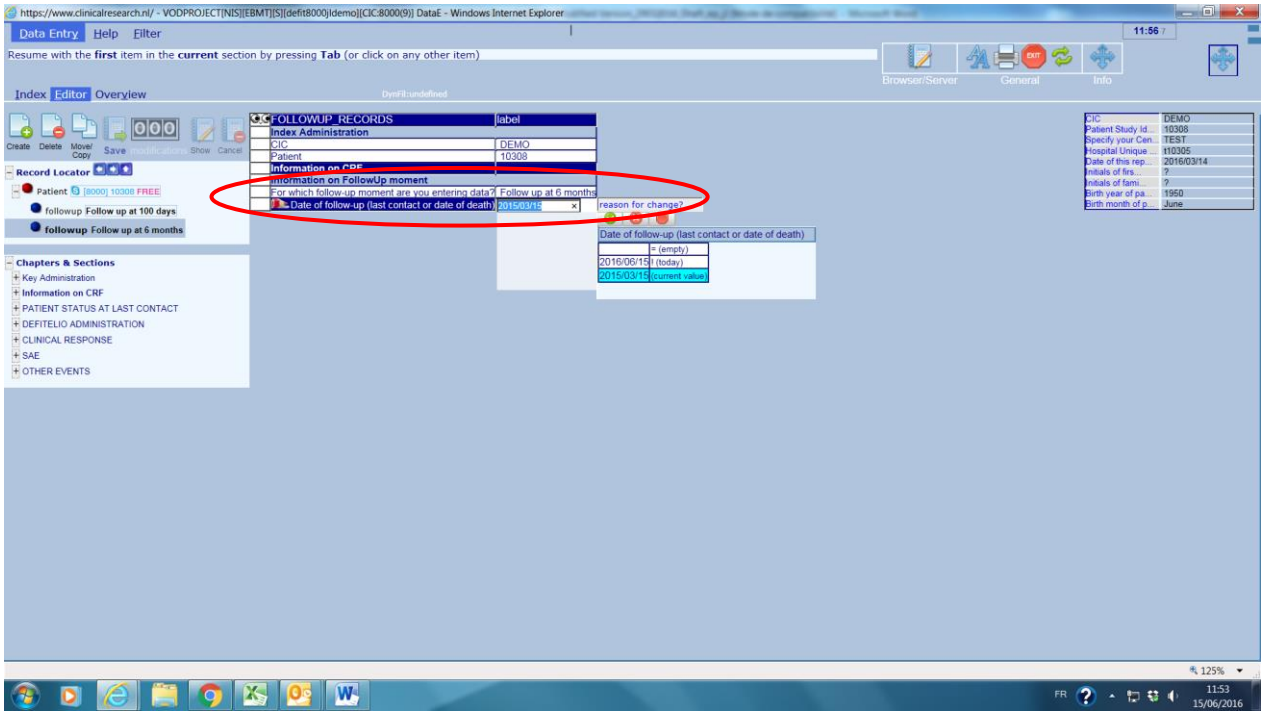
Figure 1: The Exit and Refresh session buttons

II-8/ READ ONLY status

In some rare case, you can see READ ONLY in watermark. This means that 2 persons are connected at the same time on the patient record. It can be 2 persons form the center if several persons have access (have personal password) to the VOD project data-base in you center, or it can be the data manager in charge of VOD Project at the EBMT Data Office in Paris.
In such cases, try to load the patient later or contact your colleague or the EBMT Data Office in Paris to disconnect the patient.

III/ FOLLOW UP FORM 6 or 12 MONTHS POST HSCT

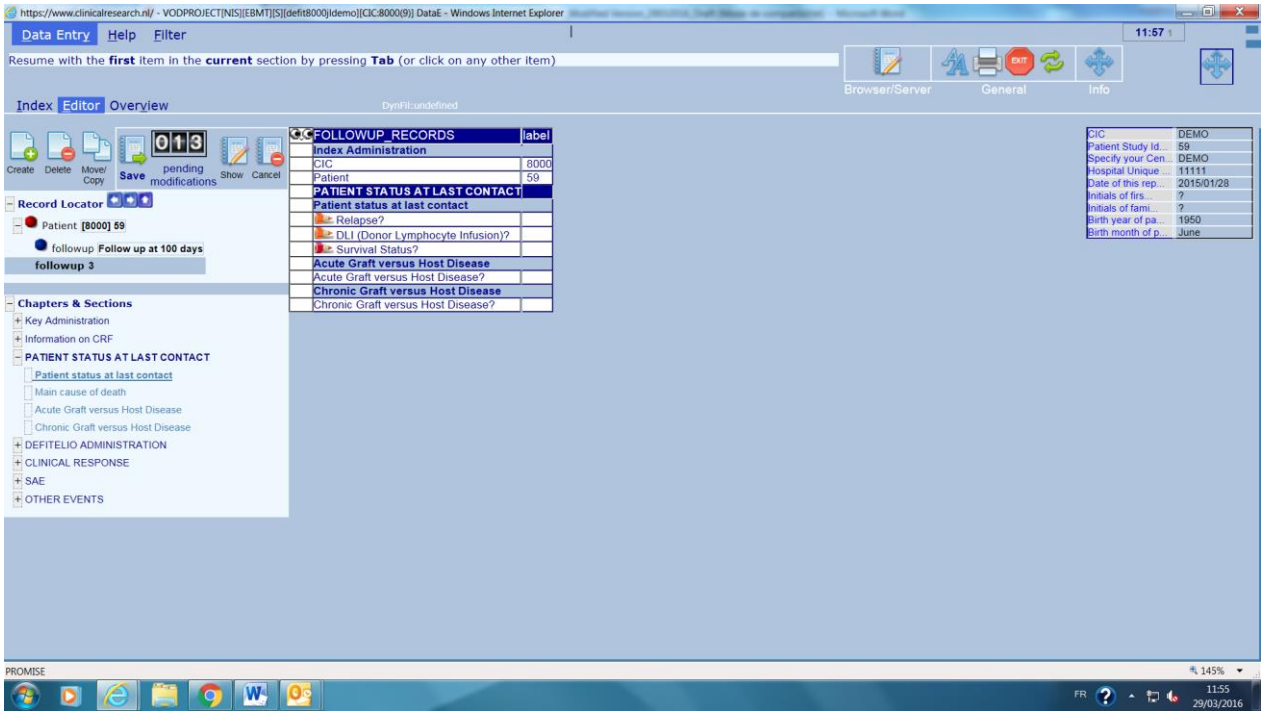
III-1/ Please complete the section INFORMATION ON CRF:



- **Subsection Information on follow up moment:**
  - Date of the follow up (Last contact or date of death): If the patient at last contact at 6 or 12 Months post HSCT is alive, please record the date closest to 6 or 12 Months follow-up after transplant when the patient contact happened; If the patient died before 6 or 12 Months, please record the date of death.

The data entry is dynamic; sections will appear if necessary
and according to information previously reported (in registration or in follow-up forms)

III-2/ Please complete the Section PATIENT STATUS AT LAST CONTACT:



- **Subsection Patient status at last contact:**

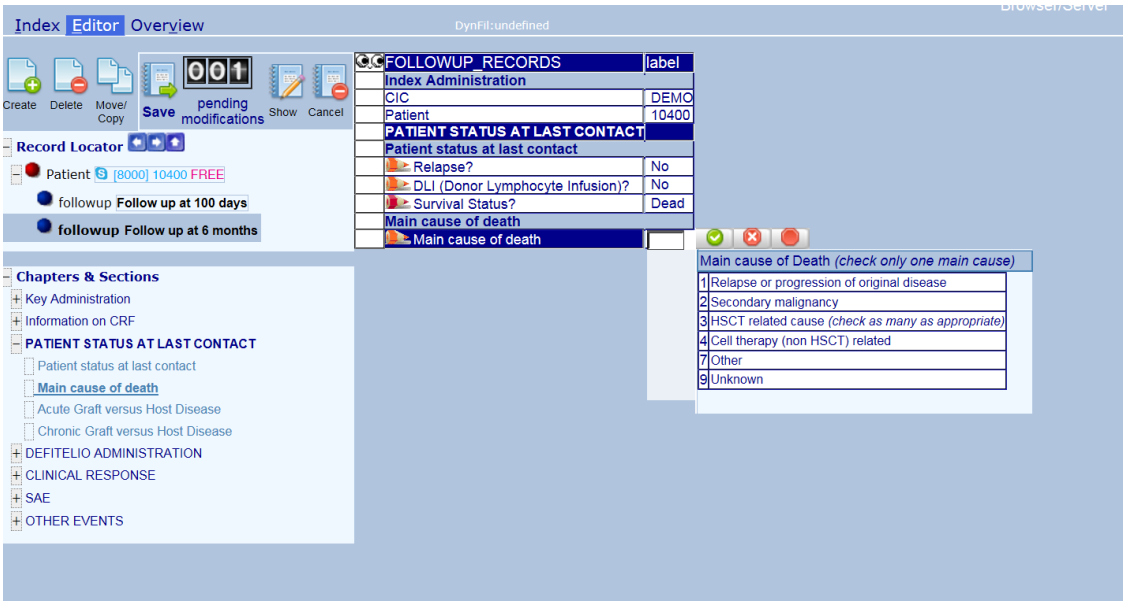
  - Relapse: Please record if the patient had a relapse of the underlying disease, by clicking the appropriate answer “No” or “Yes” or “Unknown”. If “Yes” is selected, please also record the first relapse date.

  - DLI (Donor lymphocyte infusion): Please record the date when the first DLI was performed, when known.

  - Has VOD been diagnosed since last visit: If defibrotide was administered initially for another reason than treatment sVOD then sVOD appeared, please tick Yes otherwise tick No.

  - Survival Status: Please provide the most recent information you have. The status must be the status at the date of last contact and the latter must be either the very last date the patient was known to be alive or the date of death if the patient is known to have died; so please choose the applicable answer “Alive”, “Dead”, “Died before HSCT and after start of conditioning” or “Lost to follow up” as applicable.

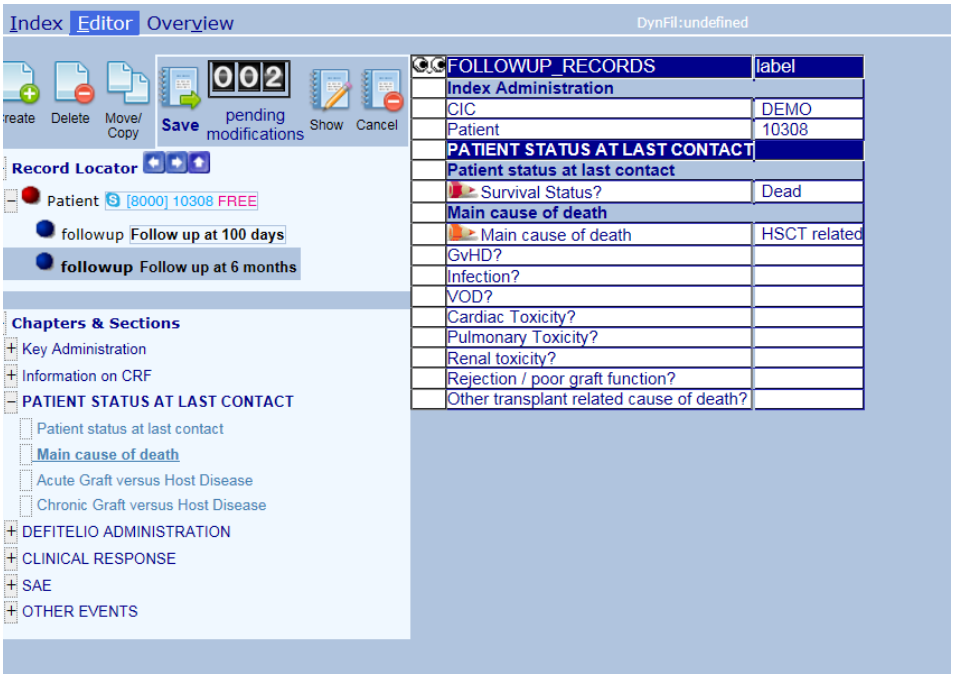
- **Subsection Main Cause of death:**



- Main cause of death (check only one main cause): If the patient status at 6 or 12 Months was “Dead”, please click only one major cause of death in the list to indicate the primary cause of death:

  - Relapse or progression of original disease
  - Secondary Malignancy
  - HSCT related cause: in this case, please also check all the applicable choices:
  - Cell therapy (non-HSCT related): please specify.
  - Other: please specify.
  - Unknown

Please note: if the patient died, a SAE form needs to be filled and sent to the contact details specified on the SAE form, 24 hours from the event awareness.



- If the death is HSCT related, check as many causes as are considered to have been contributing to the outcome:
  - GvHD
  - Infection
  - VOD
  - Cardiac Toxicity
  - Pulmonary Toxicity
  - Renal Toxicity
  - Rejection/poor graft function
  - Other transplant related cause of death: please also specify.

- Please check with your physician since this information is sometimes difficult to find in the patient's file. In the absence of clinical disease, a death caused by complications or infections after transplant is considered HSCT-related. In the presence of clinical disease, if the disease is progressing, the death will be considered as relapse or progression, even if there are complications or infections during the post-transplant period. However, if the disease was stable, or there had been an improvement after transplantation and the patient were to die of complications or infections, the death should be considered HSCT-related.

Paper CRF screen shot template is reported below for your reference only:

PATIENT STATUS AT LAST CONTACT

Relapse ☐ YES ☐ NO Date of relapse_____

DLI ☐ YES ☐NO, If yes, date of 1st DLI (Donor Lymphocyte Infusion)_____

Has VOD been diagnosed since last visit? ☐ YES ☐NO *(for off label use or absent at previous follow-up)*

Survival Status Alive ☐ Dead ☐ Lost to Follow-up ☐

Date of follow-up (last contact or Date of death): _____/___/___

Main cause of Death *(check only one main cause)*

Relapse or progression/persistent disease ☐

Secondary malignancy ☐

HSCT related cause *(check as many as appropriate)* ☐

☐ ☐

GvHD ☐ YES ☐ NO Cardiac toxicity ☐ YES ☐ NO Rejection/poor graft function ☐YES ☐ NO

Infection ☐ YES ☐ NO Pulmonary Toxicity☐ YES ☐ NO

VOD ☐ YES ☐ NO Other: ☐ YES ☐ NO Renal Toxicity ☐ YES ☐ NO

*Specify:*_____

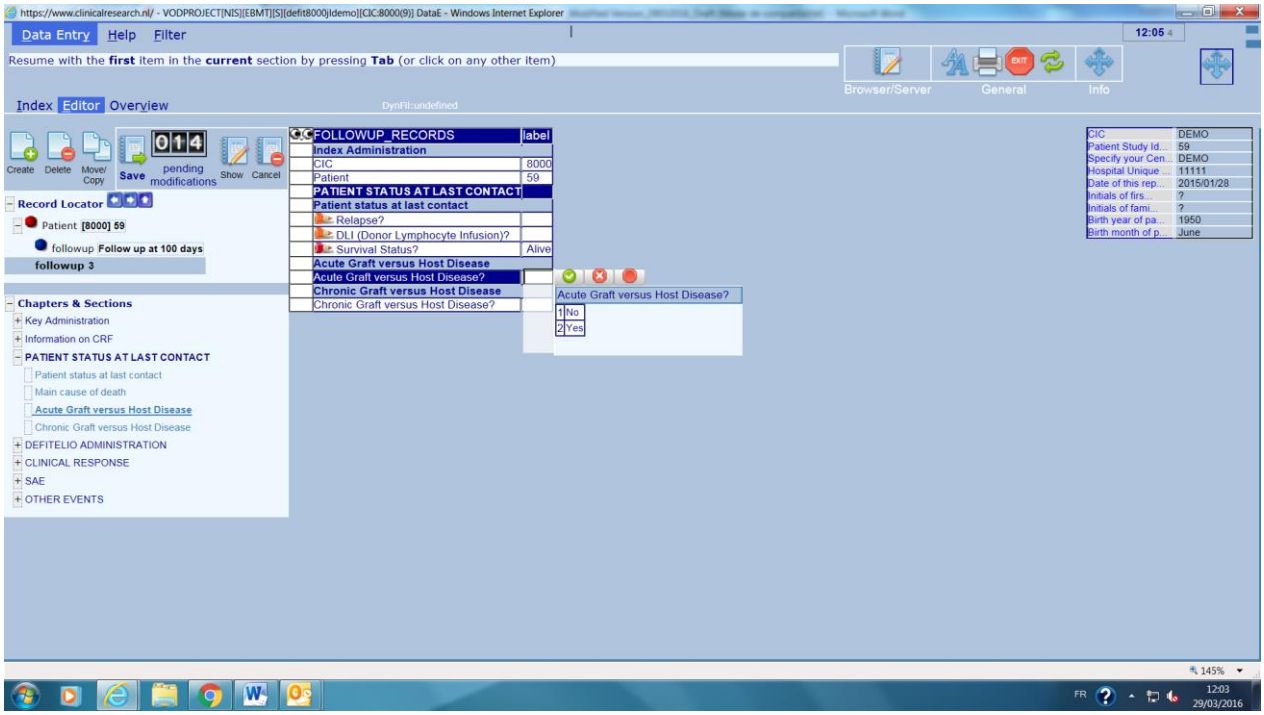
Cell therapy (non HSCT) related ☐

Unknown ☐

Other ☐

*Specify*_____

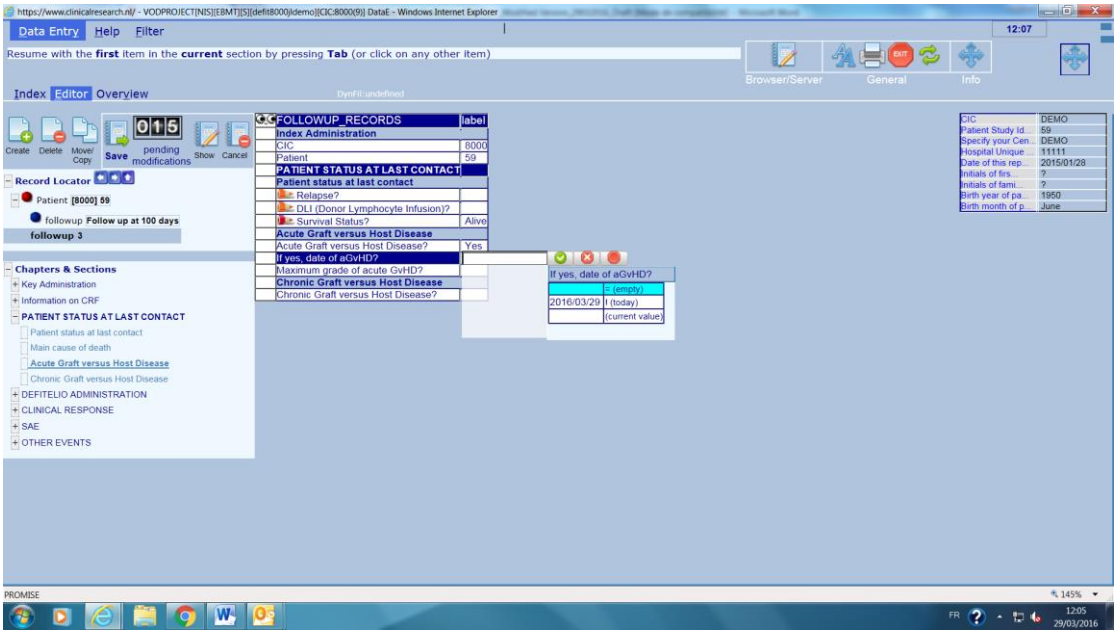
- **Subsection Acute graft *versus* host disease:**



This section will appear ONLY IF the patient underwent an allogeneic HSCT (please double check eForm Registration Form – Section HSCT):

- Please tick if the patient suffered from acute GvHD or not, by selecting the corresponding answer "Yes" or "No".

- Acute GvHD date of diagnosis: If "Yes" is selected, please add the diagnosis date. In a conventional transplant the onset of acute GvHD in T-cell depleted transplants or in non myeloablative transplants, the onset of GvHD may be later than D100.



- Maximum grade of acute GvHD: Please record the maximum GvHD grade, by selecting only one of the following:
  -I
  -II
  -III
  -IV

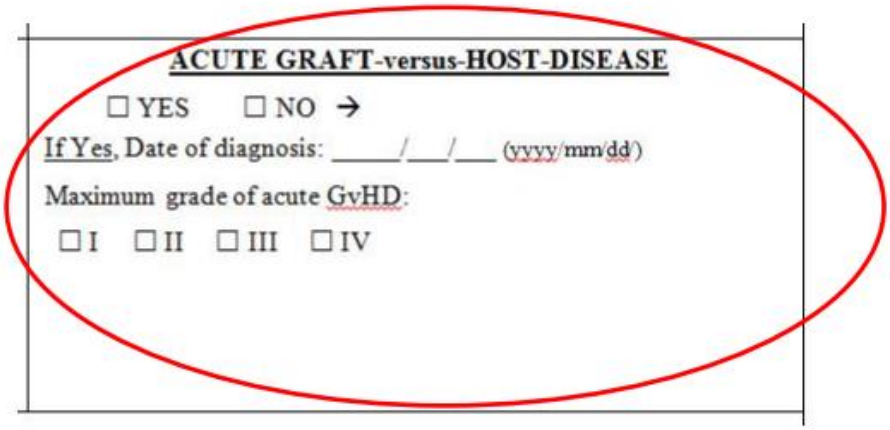
The overall grade (or the grade of skin, liver and or gut) should be mentioned in the patients' file. The maximum grade for acute graft *versus* host disease (aGvHD) is defined according to the stage presented by the skin, liver and gut.

ORGAN		STAGE
Skin	1	Skin rash < 25% body surface
	2	Skin rash 25-50% body surface
	3	Skin rash >50% body surface
	4	erythroderma
Liver	1	Bilirubin 34-50 micromol/L
	2	Bilirubin 51-102 micromol/L
	3	Bilirubin 103-255 micromol/L
	4	Bilirubin > 255 micromol/L
Gut	1	Diarrhoea volume 501 - 1000 ml/day
	2	Diarrhoea volume 1001 - 1500 ml/day
	3	Diarrhoea volume 1501 - 2000 ml/day
	4	Severe pain with or w/o ileus

grade 1: Skin stage 1 or 2	AND	Liver stage 0	AND	Gut stage 0
grade 2: Skin stage 3	OR	Liver stage 1	OR	Gut stage 1
grade 3:		Liver stage 2 or 3	OR	Gut stage 2, 3 or 4
grade 4: Skin stage 4	OR	Liver stage 4		

(Przepiorka et al, Bone Marrow Transplantation 1995;15; 825-828)

Paper CRF screen shot template is reported below for your reference only:

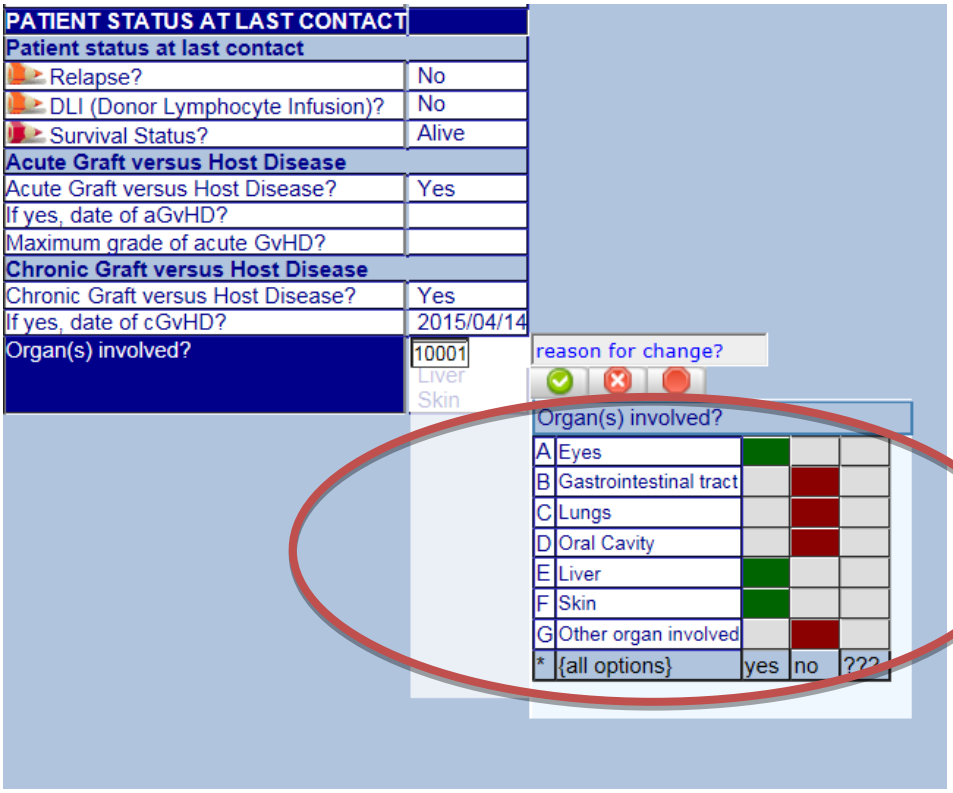


- Subsection Chronic graft *versus* host disease:

Please complete this section ONLY IF the patient underwent an allogeneic HSCT (please double check eForm Registration Form – Section HSCT):

- Please tick if the patient suffered from chronic GvHD or not, by selecting the corresponding check-box "Yes" or "No".

- Date of GvHD of diagnosis: If "Yes" is selected, please add the diagnosis date.
- Organ(s) involved: Please list all the organs involved by the chronic GvHD by selecting Yes or No in the table.



Paper CRF screen shot template is reported below for your reference only:

CHRONIC GRAFT-*versus*-HOST-DISEASE

☐ NO ☐YES

If Yes: Date of diagnosis: _____/___/___

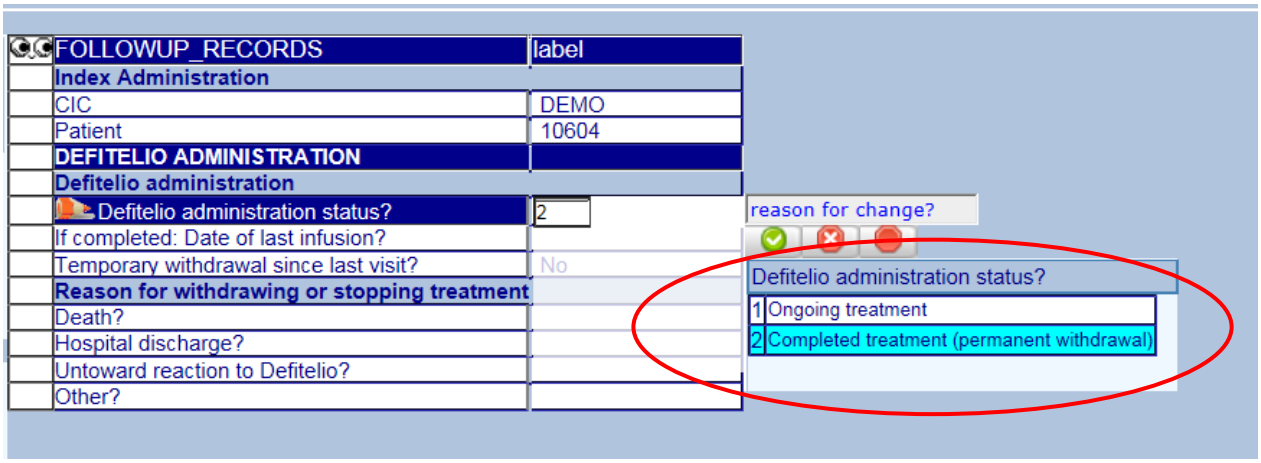
Organ(s) involved:

Eyes ☐ Gastrointestinal tract ☐ Lungs ☐ Oral cavity ☐

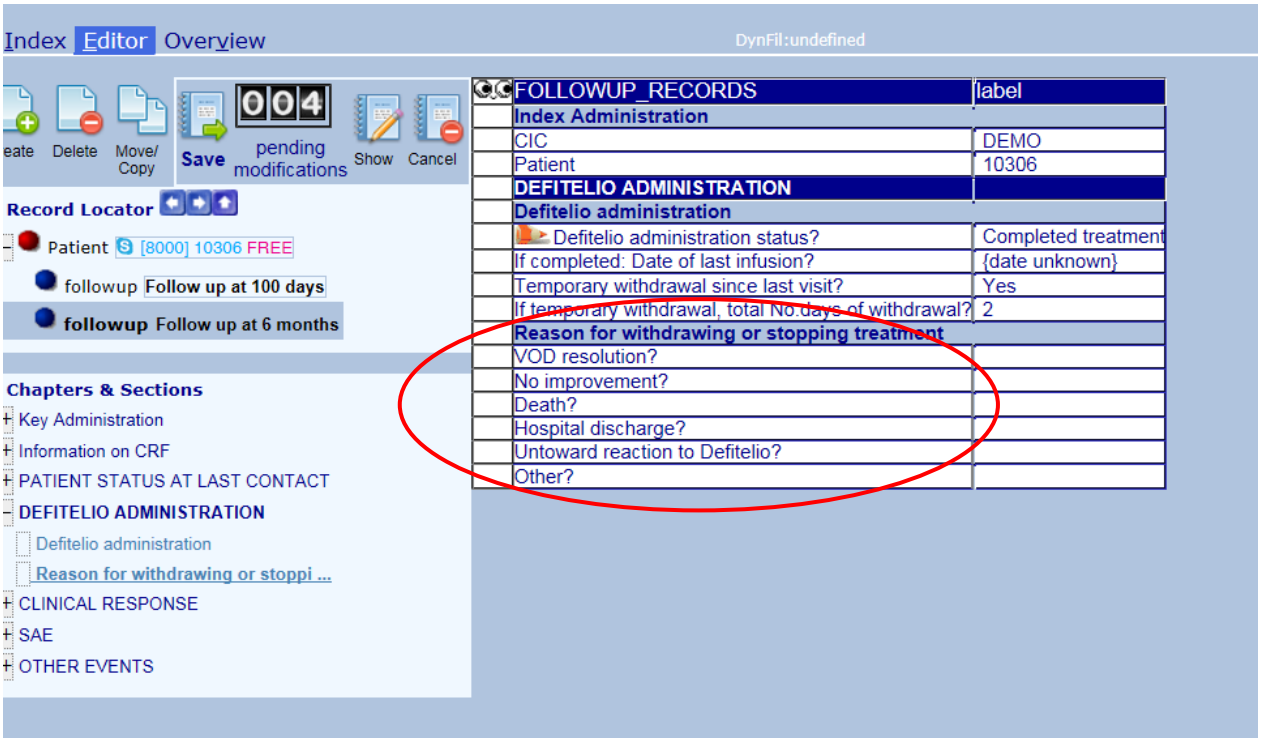
Liver ☐ Skin ☐ Other ☐: _ _ _ _ _ _ _

III-3/ Please complete the section DEFITELIO ADMINISTRATION: this section is completed ONLY IF the patient was treated with Defitelio®

- Defitelio® administration status: Check if Defitelio® treatment is ongoing or if it is completed. If it is completed, please also give the date when the last infusion was administered to the patient.



- If treatment is completed:
  Temporary withdrawal since last visit form: Please indicate if Defitelio® treatment has been withdrawn or not and, if applicable, the number of days for which the treatment was withdrawn.



If the drug has been withdrawn **or** stopped, please check "Yes" for only one reason (if more than one reason is existing, please check only the main one):

- VOD resolution (if applicable)
- No improvement (If applicable)
- Death
- Hospital Discharge

- Untoward reaction to Defitelio® (in this case, please specify which reaction took place. If the event is serious, please also complete and submit the SAE form for the details, please refer to the last version of the "Registry SAE Completion Guidelines")
- Other: please specify.

IMPORTANT: If a patient has been enrolled and treated with Defitelio® for another reason than sVOD and, in a second moment, developed sVOD after registration, for which a new Defitelio® treatment is planned.
In this case, you should consider the patient and his/her follow-up in the way outlined below:

- **Defitelio Administration: please select Defitelio® Administration: Completed Treatment.**
- **Complete the date of last infusion when Defitelio® was administered for another reason than sVOD**
- **For Reason for withdrawing or stopping treatment: Select Other and specify sVOD diagnosed after registration. Please record the patient in a new Registration Form (please refer to the most recent Registry eForm Data Entry Guidelines Part 1) with a new patient ID and report the patient as enrolled in the sVOD arm. Please in comment section, indicate the previous Patient Id used in the first Registration form.**
- **If the patient is re-enrolled after a new HSCT, he/she needs to re-sign the Registry ICF, otherwise this is not necessary.**

Paper CRF screen shot template is reported below for your reference only:

DEFITELIO® ADMINISTRATION
(Fill this Section if Defitelio administration continued after Day+100 post-HSCT)
Defitelio® administration status?

☐ Ongoing treatment ☐ Completed (permanent withdrawal)

If completed: Date of last infusion?
_____/___/___

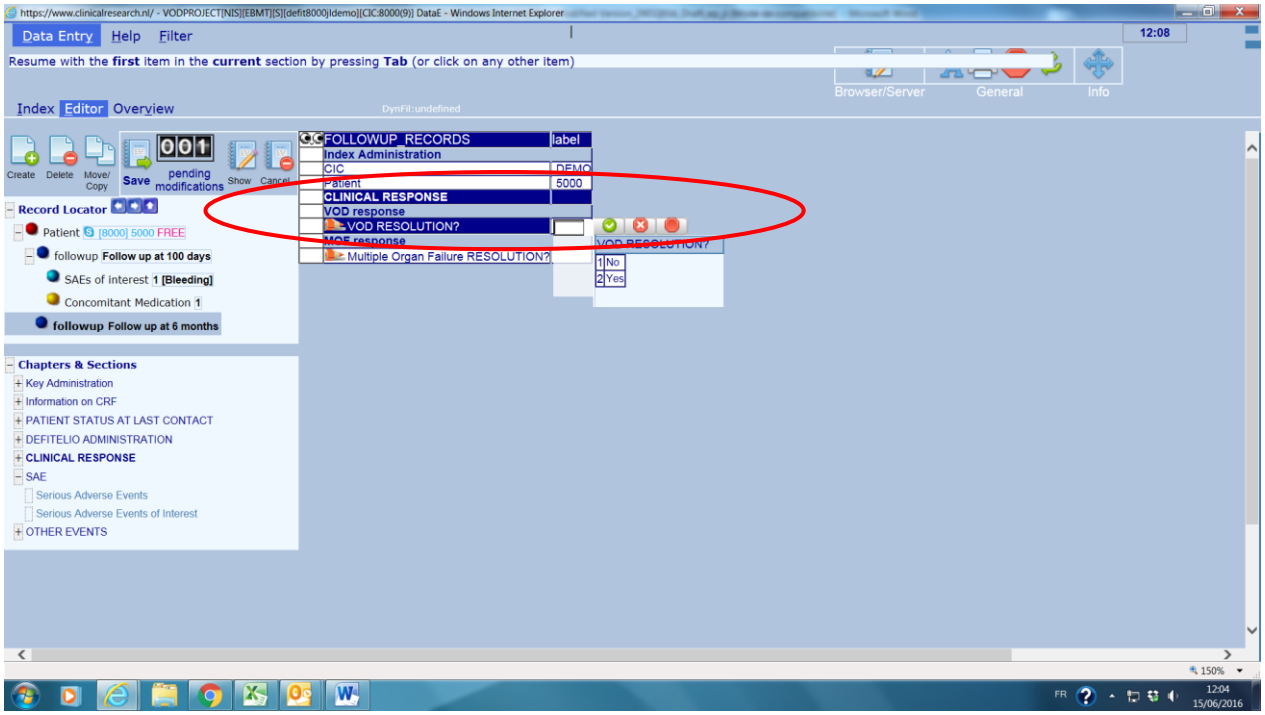
Temporary withdrawal since registration form?

☐ YES ☐ NO

If temporary withdrawal, Total No.days of withdrawal? _ _ _ _

Reason for stopping treatment: **temporary or permanent* VOD resolution ☐ YES ☐ NO
No improvement ☐ YES ☐ NO
Death ☐ YES ☐ NO
Hospital discharge ☐ YES ☐ NO
Untoward reaction to Defitelio® ☐ YES ☐ NO
Specify: _____
☐ Other ☐ YES ☐ NO
Specify: _____

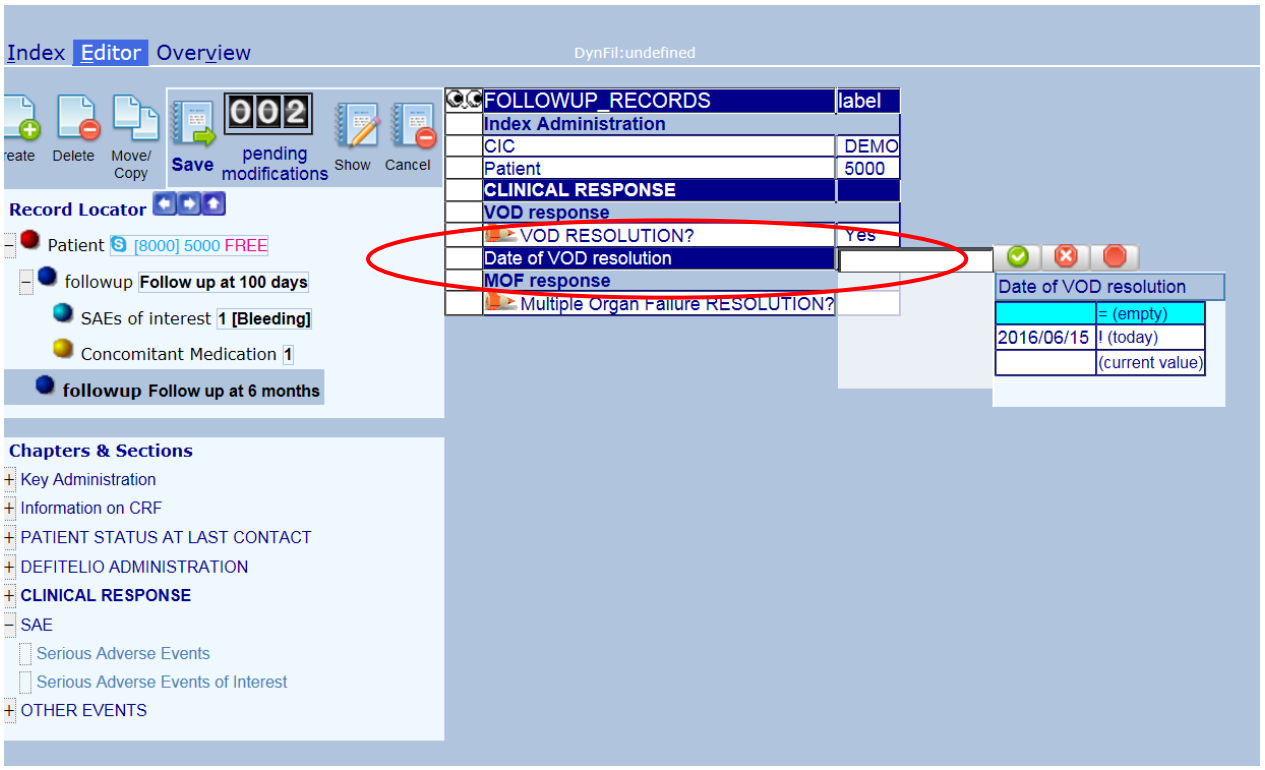
III-4/ Please complete the section CLINICAL RESPONSE:



- VOD Resolution: If the patient suffered from VOD (please double check the Registration Form), please check the appropriate answer "Yes" or "No", to record if the patient's VOD resolved:

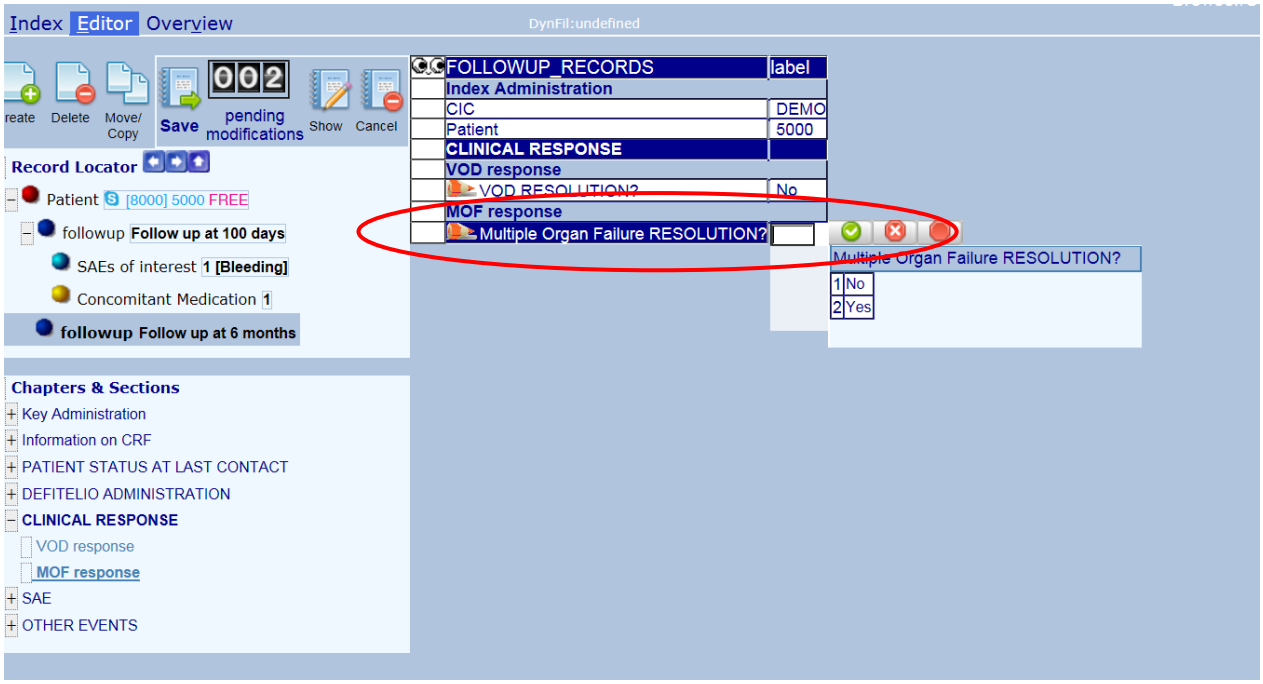
"Yes" should be checked if the patient suffered from VOD at the registration or D100 follow up and resolved within the next visit follow-up; If the patient had a VOD response, please also record the date when VOD resolved.

"No" should be checked if the VOD previously declared, didn't resolve within the current visit.



- Did the MOF developed after patient's last visit? Please check the appropriate answer "Yes" or "No".

"Yes" should be ONLY clicked if the patient didn't suffer from MOF previously, but he/she developed MOF after the previous visit.
"No" should be checked in all the other cases.

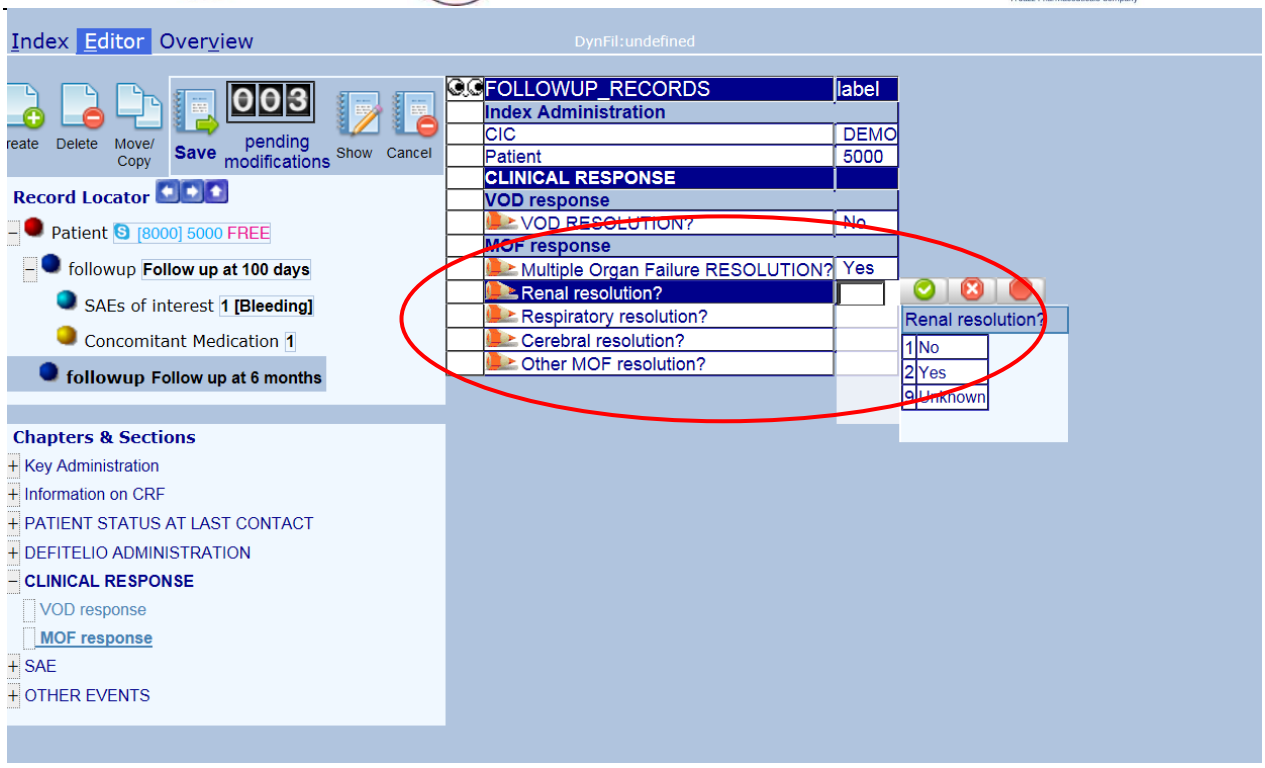


- MOF resolution: If the patient suffered from MOF at any time between the study entry and the current visit, please check the appropriate answer "Yes" or "No", to record if the patient's MOF resolved.

"Yes" should be checked if the patient suffered from MOF at any visit and resolved within the current visit;
In this case, please specify the affected system(s) and the date when the MOF dysfunctions resolved:

- Renal: If selected, please add also the renal dysfunction resolution date
- Respiratory: If selected, please add also the respiratory dysfunction resolution date
- Cerebral: If selected, please add also the cerebral dysfunction resolution date
- Other: If selected, please add the date of resolution

"No" should be checked if the patient suffered from MOF at any time between the study entry and the current visit, but his/her MOF didn't resolve within the current visit.



Paper CRF screen shot template is reported below for your reference only:

CLINICAL RESPONSE

☐ VOD RESOLUTION ☐ YES ☐ NO

Date: _____/___/___

Did MOF developed after patient's last follow-up? ☐ YES ☐ NO

☐ MOF RESOLUTION ☐ YES ☐ NO

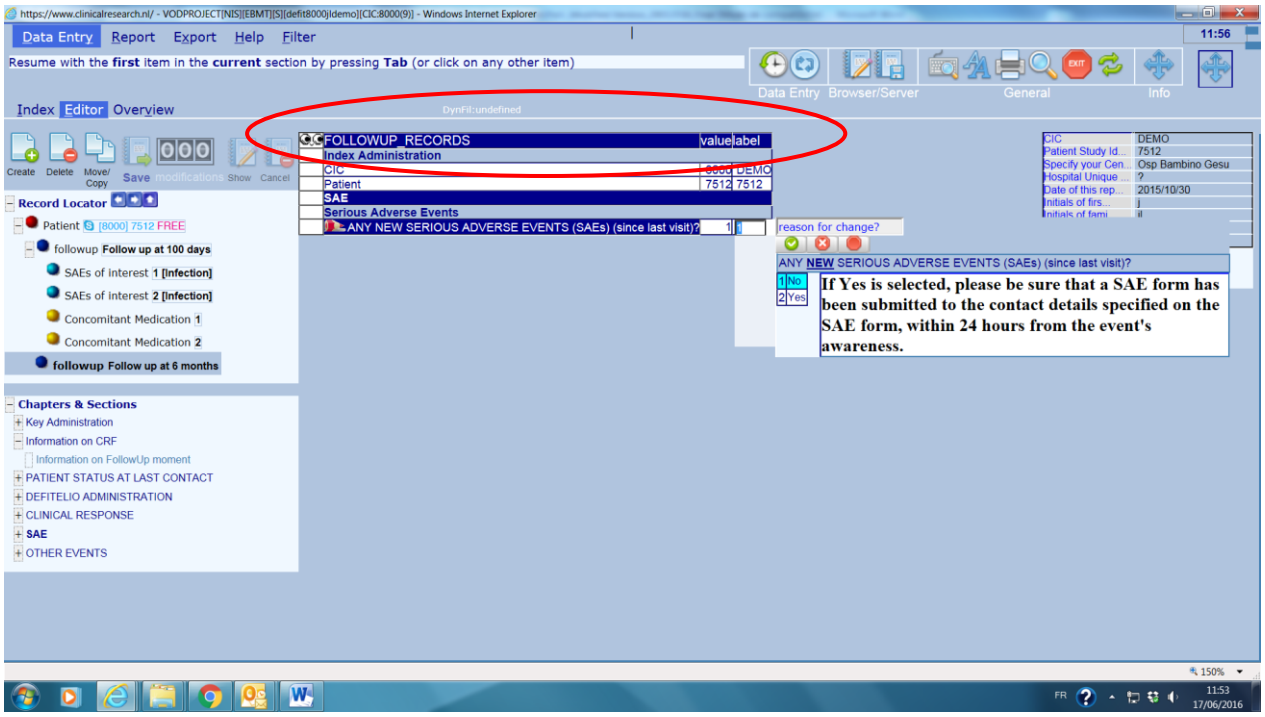
☐ Renal Date_____/___/___

☐ Respiratory Date_____/___/___

☐ Cerebral Date_____/___/___

☐ Other Date_____/___/___

III-5/ Please complete the section SAE:



- **Subsection Serious Adverse Event:**

Please indicate if one or more SERIOUS adverse events occurred within 100 days follow-up. Please note that all the serious events need to be reported, irrespective of the relationship with Defitelio® and also for patients treated with supportive or alternative care and not only for patients treated with Defitelio®.

If any, "Yes" is selected, please be sure that a SAE form has been submitted to the contact details specified on the SAE form, within 24 hours from the event's awareness.

For serious adverse event seriousness criteria and for SAE form completion guideline, please refer to the most current version of DF VOD-2013-03-REG SAE completion guideline.

Paper CRF screen shot template is reported below for your reference only:

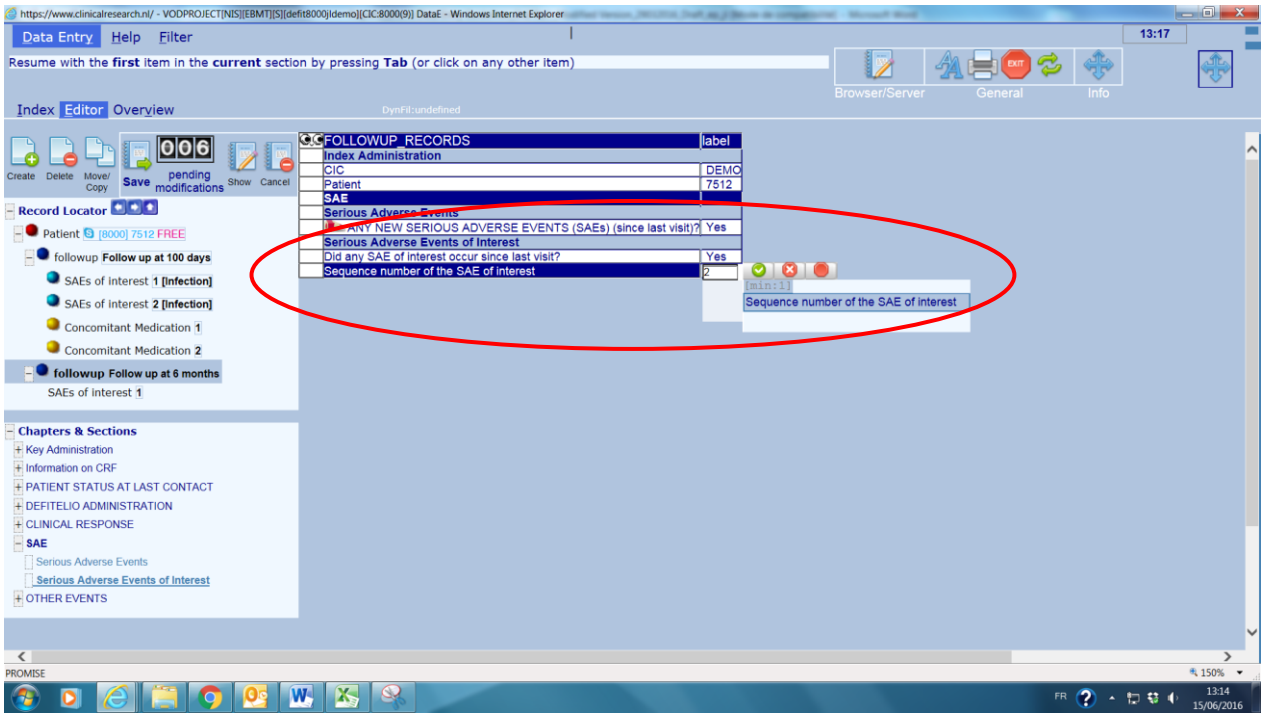
ANY SERIOUS ADVERSE EVENTS since last visit (SAEs)
?

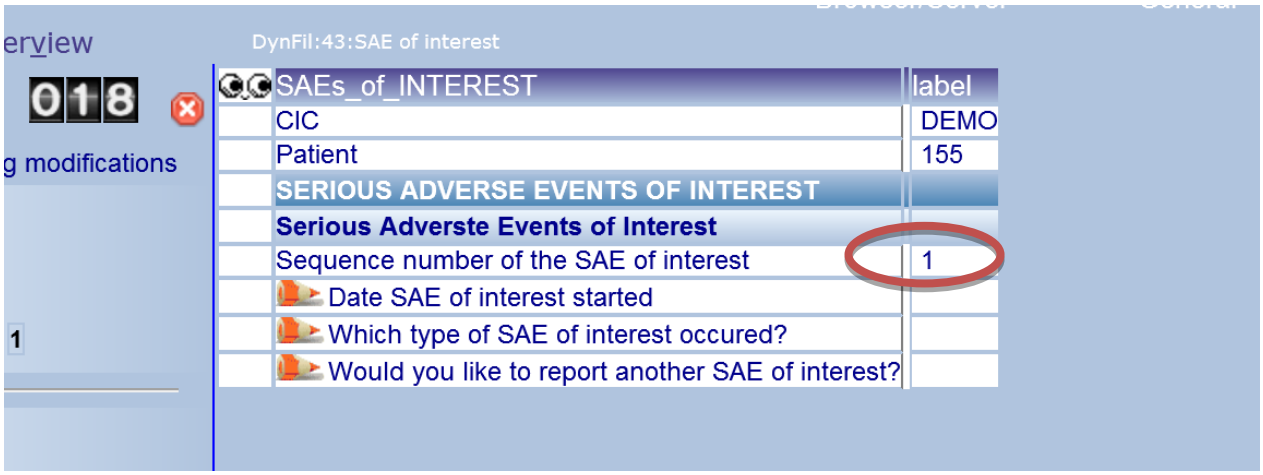
☐ NO ☐ YES

if YES complete in details the SAE FORM and SEND A FAX OR A SCANNED COPY TO THE CONTACT INFORMATION LISTED ON THE SAE FORM

- **Subsection Serious Adverse Event of Interest:**

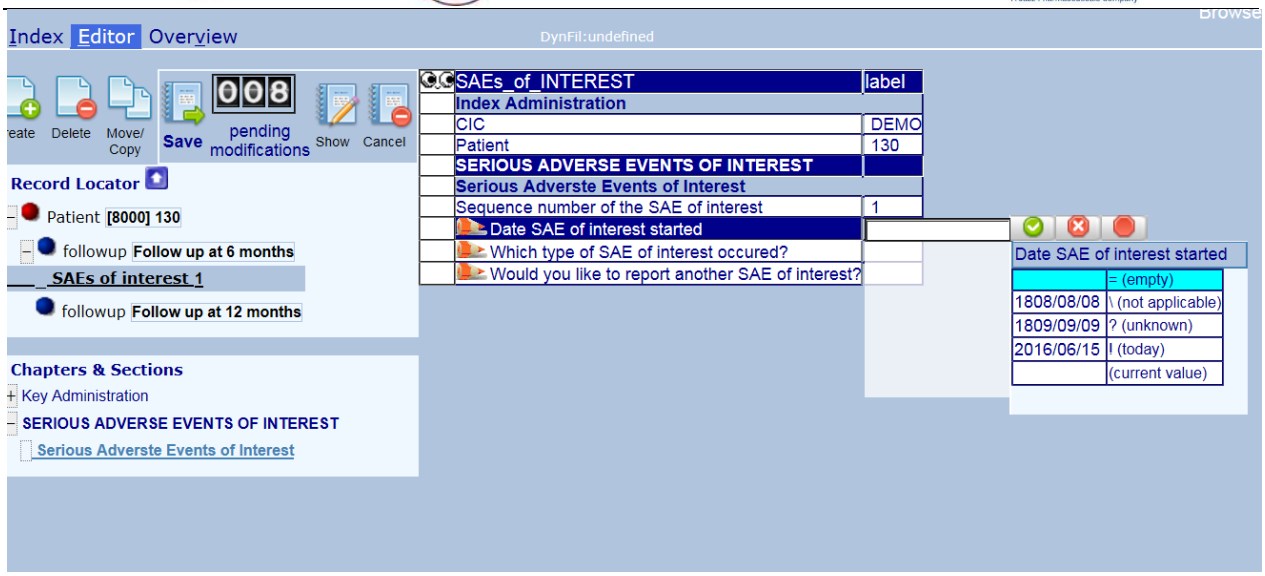
If "Yes" is selected, please indicate in "sequence number of the SAE of interest" a chronological number. So, please start numbering with "1" and if you need to declare another SAE of interest later on, please increment the number to "2" and "3", etc





Also record the onset date and the type of SAE of interest declared:

- Bleeding: If “Yes” is selected, please also specify the localization
- Hypotension
- Coagulopathy
- Allergic/Hypersensitivity reactions
- Injection site reaction
- Infection: If “Yes” is selected, please also specify the localization and the type of infection
- Thromboembolic events



If you have another SAE to declare, please do the same way again.

Paper CRF screen shot template is reported below for your reference only:

SERIOUS ADVERSE EVENTS OF INTEREST

Did a SAE of interest occur since last visit? ☐ YES ☐ NO

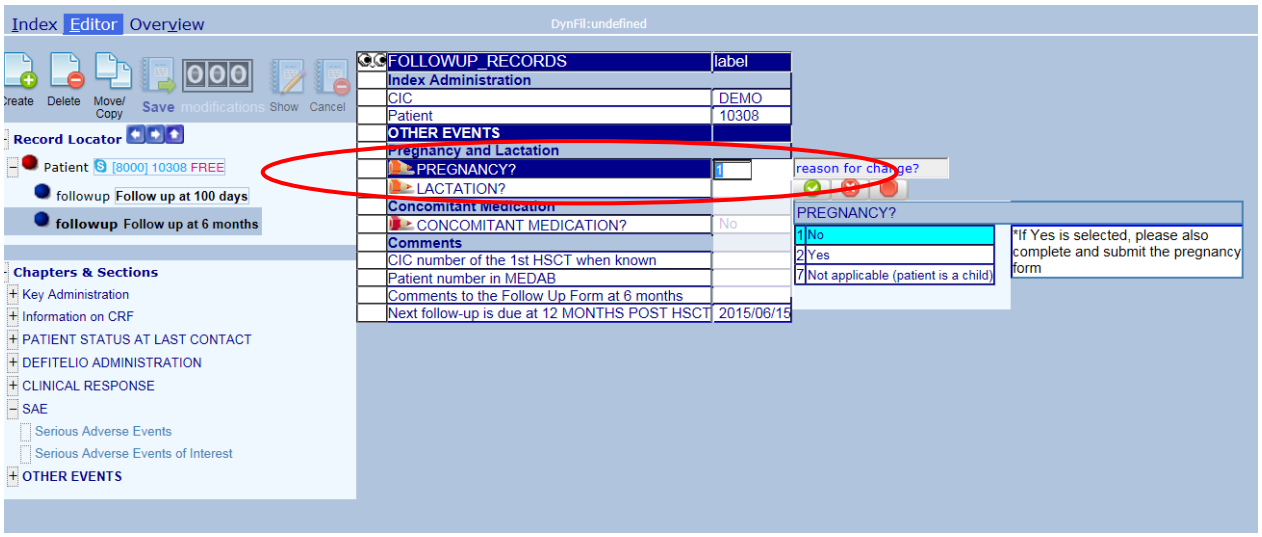
Sequence number of the SAE of interest : ___

Date SAE of interest started? ____/__/__

Bleeding	☐ Site:_____	
Hypotension	☐	
Coagulopathy	☐ Allergic/Hypersensitivity reactions	☐
Injection site reaction	☐	
Infection	☐	

III-6/ Please complete the section OTHER EVENTS:

- **Subsection Pregnancy and Lactation: (If the patient is a female)**



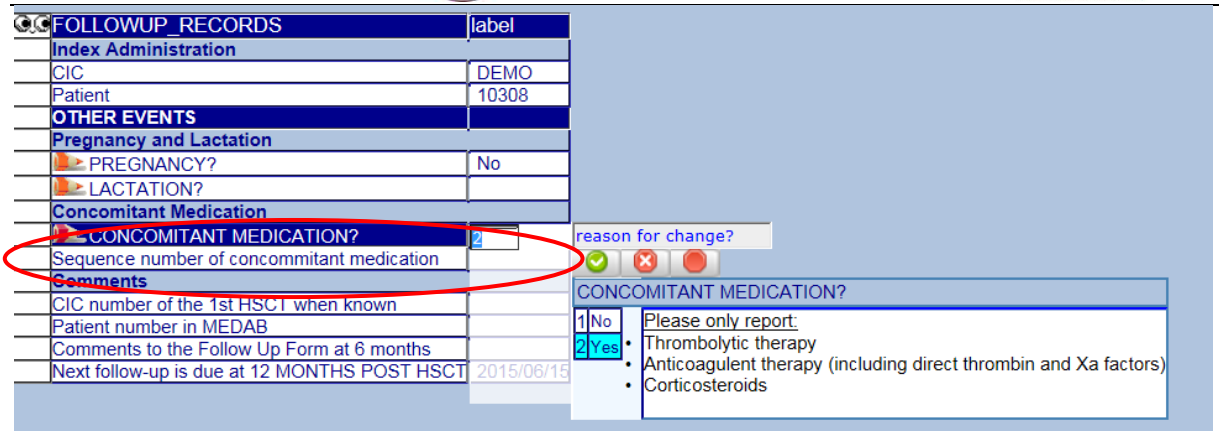
- Please check if the patient was pregnant or not at the current visit and please complete and submit the pregnancy form within 24 hours since the awareness in case of positive answer.
- Please check if the patient was lactating or not at the current visit and please complete and submit the pregnancy form within 24 hours since the awareness in case of positive answer.

Paper CRF screen shot template is reported below for your reference only:

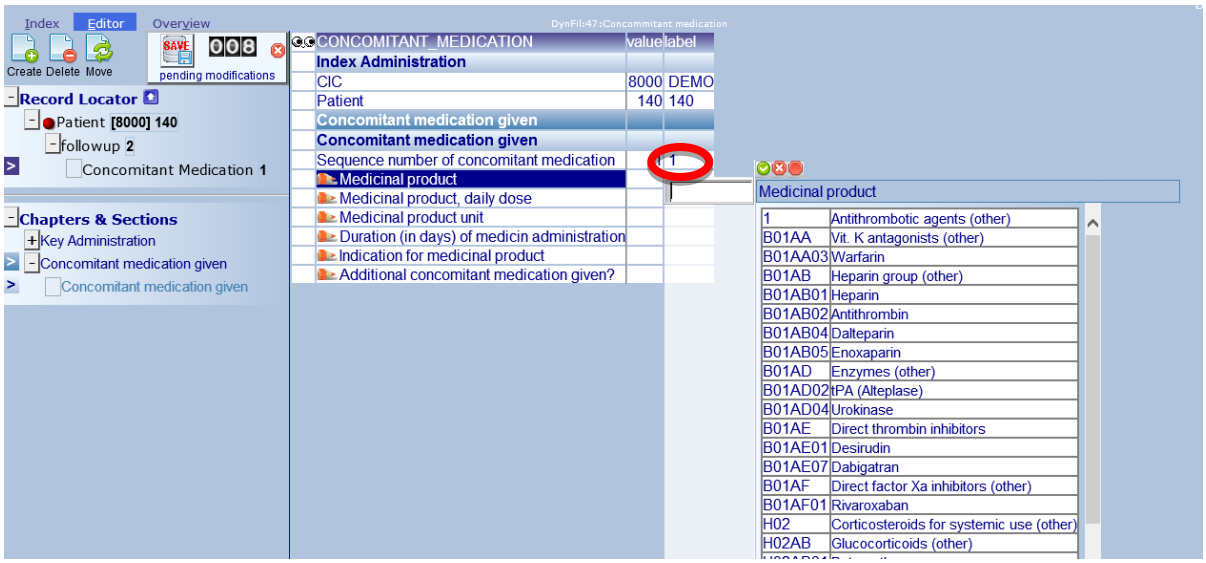
PREGNANCY*	LACTATION
☐ YES ☐ NO *If Yes is selected, please also complete and submit the pregnancy form	☐ YES ☐ NO

- **Subsection Concomitant medication:**

Please **only** report:
•**Thrombolytic therapy**
•**Anticoagulant therapy (including direct thrombin and Xa factors)**
•**Corticosteroids** that the patient is taking while VOD is under treatment (including supportive care) - or in general while the patient is enrolled in the study - until the current time.



If "Yes" is selected, please indicate in "sequence number of concomitant medication" a chronological number. So, start numbering with "1" and if you need to declare another concomitant later on, please increment the number to "2" and "3", etc



Please record the following details:

- Drug Name
- Daily Dose
- Dose Unit
- Treatment Duration (in days)
- Indication

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CONCOMITANT MEDICATIONS ☐ YES ☐ NO

Sequence number of the concomitant medication : ___

Medicinal product _ _ _ _ _ _ _

Medicinal product daily dose? _ _ _ _ _

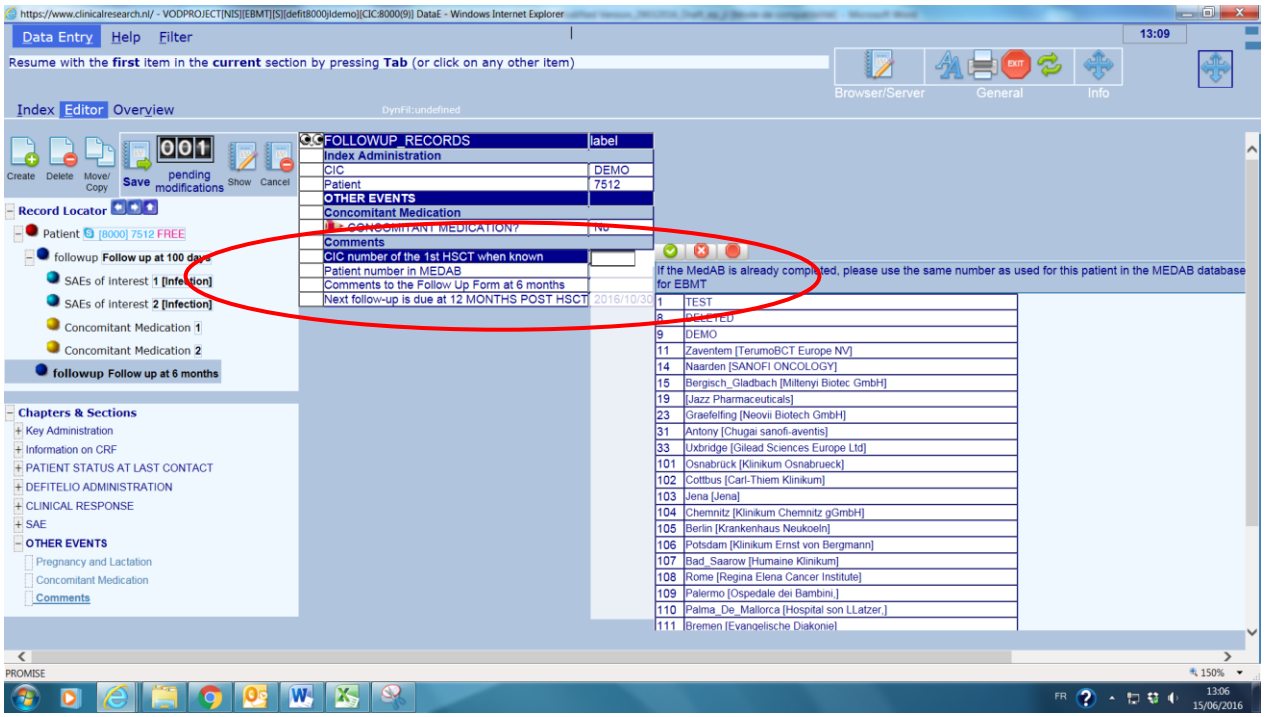
Medicinal product unit? _ _ _ _

Medicinal product duration (in days)? _ _ _

Medicinal product indication _ _ _ _

if several please indicate each

- **Subsection Comments:**



.

- **CIC number of the 1st HSCT when known:** If the patient is already recorded on the EBMT Med-AB project please enter here the code of this center. If the patient had a previous transplant in another center, the CIC number will be the one of the 1st Center.

- **Patient number in MEDAB:** If the patient is already recorded on the EBMT Med-AB project, please enter here the Patient Code used in the Med-AB project.

- **Comments to the follow up 6 or 12 Months:** Free text field

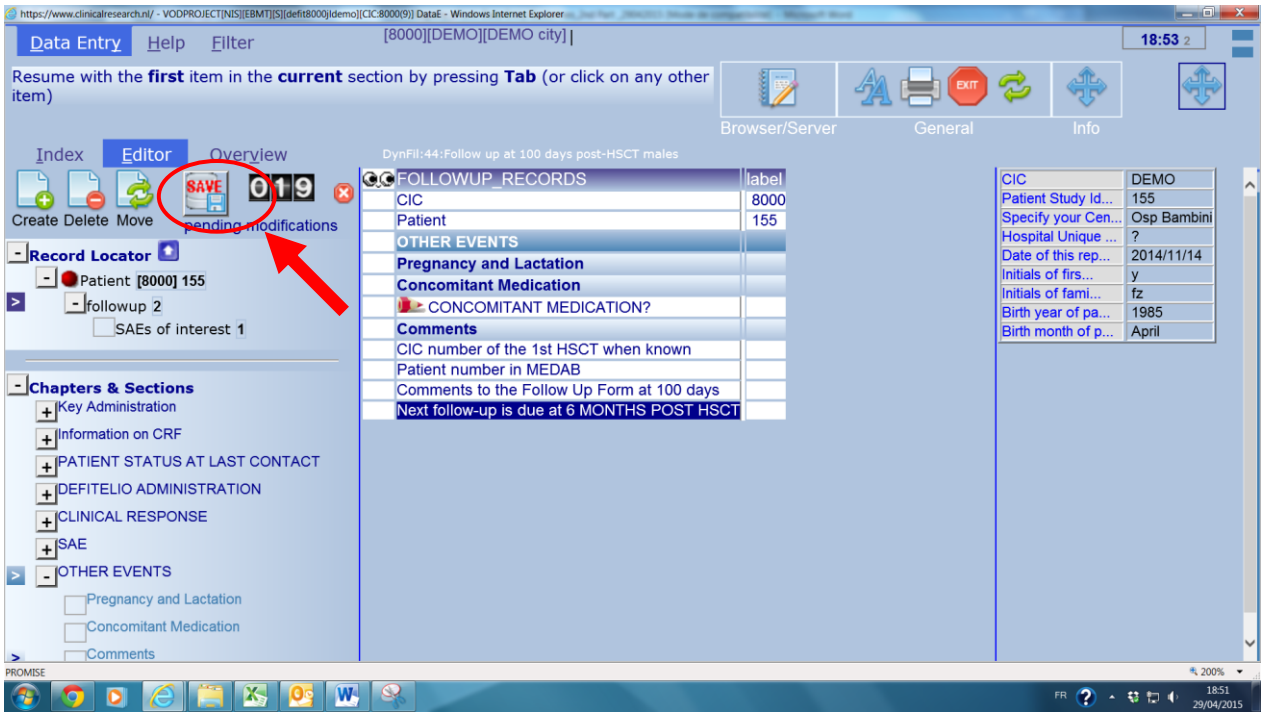
- **Next follow-up is due at 12 Months post HSCT:** Automatic variable calculating and giving the date for the next form to be filled in: "VOD project 12 months post HSCT Follow-up"

Paper CRF screen shot template is reported below for your reference only

Comments

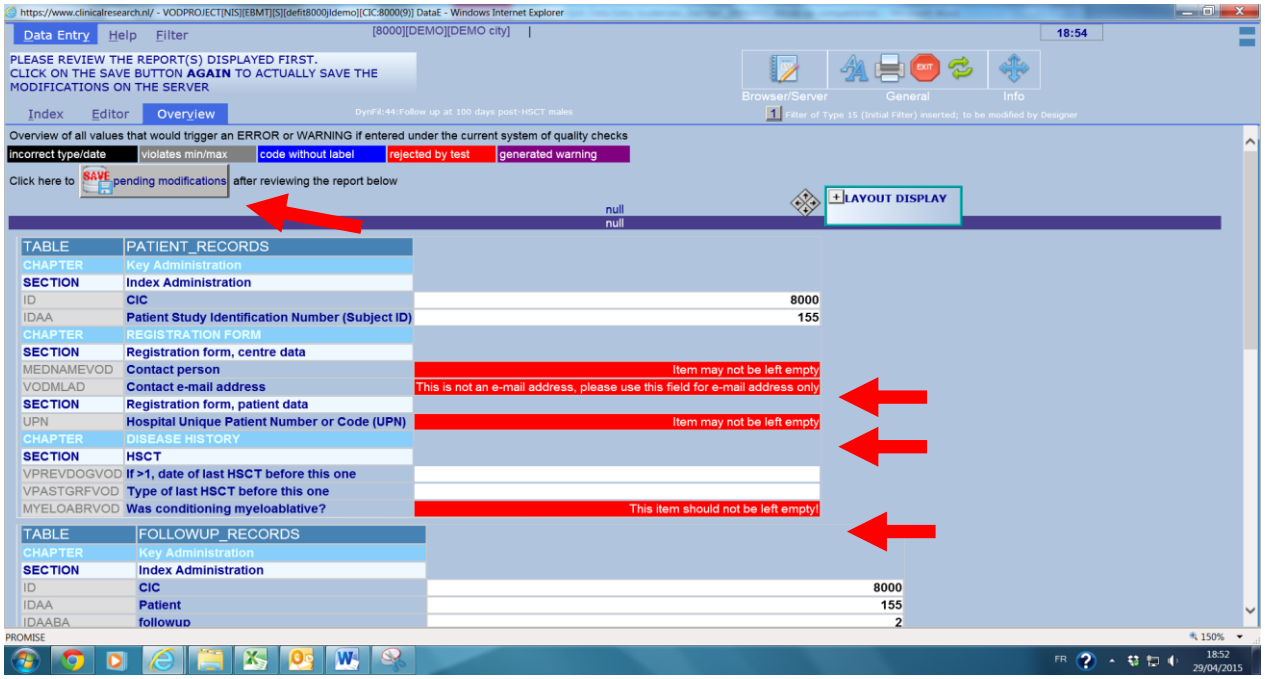
CIC number of the 1st HSCT when known : _ _ _ _ _ _ _ _
Patient Number in MEDAB : _ _ _ _ _ _ _ _
Comment to the Follow-up Forms at 6 or 12 months : _

III-7/ Please save the Follow up Form:



The total number of data entered since last saved, is written on the **pending modification counter.**
To save them, please click on the **Save Button** (floppy disk icon).

An overview of missing mandatory variables and rejected controls will appear:



Please complete missing or incorrect information by clicking on the corresponding red box cursor. This will jump directly to the variable to be corrected.

And finalize the “Save action” by clicking on the pending modification button.