Title	
	SOP 02- Data management – CRF completion
Document type	SOP
Version N.	3.0
Date	February 20th 2020

	NAME	**DATE**
PREPARED BY	RM/AE	July17th2019
REVIEWED BY	Site PIs	
APPROVED BY	Site PIs	

PURPOSE: To outline the process for data management and CRF completion for the G-DEFINER study conducted by INT, Onk-Pat KI, OUH and DCU-SVUH.

Abbreviations

Acronym	Description
CI	Clinical investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Capture Forms
DM	Data Manager
eCRF	Electronic Case Report Form
G-DEFINER	Gender Difference in sidEeFfects of ImmuNotherapy: a possible clue to optimize cancErtReatment
GDPR	General Data Protection Regulation
INT	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Onk-Pat KI	Dept of Oncology-Pathology, Karolinska University Hospital, Sweden
OUH	Oslo University Hospital – The Radium Hospital, Norway
PI	Principal investigator
DCU- SVUH	Dublin City University, Dublin -St Vincent's University Hospital, Ireland

Related documents

Document type	Title
FORM	CRF 01 - Informed consent and screening CRF 02 - Registration and baseline CRF 03 - Immune Related Adverse Event Log CRF 04 - Lab tests and concomitant medications CRF 05 - Questionnaires distress and health CRF 06 - Follow up log CRF 07 - Study specific blood and stool samples CRF 08 – Off study CRF 09 - ICI and oncologic treatments log CRF 10 - Diet form CRF11 - Pre-Screening form
SOP	SOP 03 - Study conduction
SOP	SOP 04 - AE registration

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Appendices:

Document type	Title
Annex	SOP 02 - Annex - [ISO-IEC 27001-2013] Certificate (2019-02-26 EN) (Nubilaria ISO certificate)
Annex	SOP 02 - Annex - ACTide_presentation-en-20190701 (ACTide presentation)

1. Scope and applicability

To describe the procedure for data management and CRF entry for the study "Gender Difference in sidEeFfects of ImmuNotherapy: a possible clue to optimize cancErtReatment (G-DEFINER)" conducted by INT, Onk-Pat KI, OUH and DCU-SVUH.

2. Glossary/definitions

Case Report Form

The Case Report Form (CRF) is a paper or electronic document (eCRF)used to record patients data.

Source documents/data
Source data

Source data is all information contained in source documents which is necessary for the reconstruction and evaluation of the study. Source documents include patient hospital files which record all patient history and clinical findings data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, accurate copies or transcriptions , microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

3. Responsibilities

Clinical investigator. The clinical investigator is ultimately responsible for the accuracy, completeness, legibility and timeliness of the data entered in the CRF/eCRF and all required reports.
Data Manager. Data collection and CRF/eCRFentry is the responsibility of the DM, with close cooperation between other members of the G-DEFINER research staff.

4. Procedure

The present SOP reports the general istructions for data management and CRF completion. The user manual of the eCRF (study database) is a separate document. Please refer to "SOP 03 - Study conduction" for all the details related to the study conduction.

4.1 General principles

- G-DEFINER data must be entered in the eCRF; paper CRF may be also used.

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- CRF**/**eCRFs should be completed according to the fundamental elements of data integrity; attributable, legible, contemporaneous, complete, original and accurate**.**
- Only research staff trained on the remote eCRF system will enter data for the study using their unique and private username and password.
- The entered data must be reviewed by a CI and should be an accurate reflection of the patient's medical notes.
- The entered data must be source verifiable.
- The CIs and the DM must ensure that all required G-DEFINER data is collected and all CRFs completed.
- Any discrepancies between the CRF/ eCRFs and the source documents must be corrected, or the discrepancies explained.

4.2 Prior to the patients accrual
- At each site DM/s will be assigned to the study, who will work as a team with the CIs.
- The CIsand DM/s will be initiated on the protocol, protocol amendments (if any), and undergo eCRF completion training.

4.3 Prior to CRF Completion
- **Pre-screening phase** (see **"**SOP 03 - Study conduction")**.** The site will identify potentially eligible patients who meet the protocol entry requirements.
- The DM/s will be informed by the CIs when a new patient is identified as potentially eligible.
- In the pre-screening phase no data are entered in the eCRF (study database). The paper DCFs "CRF 11- Pre-Screening form" must be used to document reasons why a patient does not enter the further screening phase.

4.4 CRF compilation

4.4.1 General instructions
- eCRF entry will commence at the "**Screening phase**", before the patient commences the ICI treatment (see "SOP 03 - Study conduction").
- The eCRF will allow to register all the study data of patients who signed the informed consent. Moreover, the eCRF will also allow to register age, sex, type of disease and reason for refusal of patients who are not willing to participate to the study but specifically consent to register te above personal information.
- If data is unavailable there is the option to select 'unknown', 'not applicable' or 'missing'.
- The free text (when requested) should be kept to a minimum, as it is complex to analyse.

4.4.2 Data capture forms compilation

DCFs are templates that may be used to collect patient information or to collate information which has been documented elsewhere in the patient's chart for a later entry in the eCRF (study database), thus they may be considered as an aid for eCRF completion. The same information is included in the DCFs and in the eCRF.

- The templates should be stored according to the data protection policy of the Center.
- Patient identifiers must not be written on the templates. These documents must be labeled with the subject identification code.
- Additional fields must not be created on the templates. If it emerges that additional information is needed, please make a request to the Coordinating Center.

The following templates can be used:

CRF 01 - **Informed consent and screening**. Can be used to capture the date of informed consent signature, the rational for screen failure, and the age, sex, type of disease and reason for refusal of patients who are not willing to participate to the study but specifically consent to register te above personal information.

CRF 02 - registration and baseline. Can be used to capture data such as: patient characteristics; cancer type, stage and histology; ICI treatment type, dose, schedule and setting; concomitant oncologic treatments; concomitant medications; gender-related characteristics.

CRF 03 - Immune Related Adverse Event Log. Can be used to capture ICI-related adverse events, start date, grade, frequency, treatment required, casualty and action taken with the study medication. Multiple records can be registered, one record at the occurrence of an immune related adverse event.

CRF 04 - Lab tests and concomitant medications. Can be used to capture specific information on hematology, chemistry and hormones lab test at different pre-specified times: baseline (before starting treatment), at 2nd infusion, at occurrence of fist irAE G≥3, or different not scheduled times (if wishing to register data pertaining to a time period other than baseline, 2nd infusion, 1st irAE G≥3). . Multiple records can be registered, one record at each pre-specified time.

CRF 05 - Questionnaires distress and health. Can be used to capture patients' answer on the "Distress questionnaire" (distress thermometer and problems list) and on the "Health questionnaire" at different pre-specified times: baseline (before starting treatment), at 2nd infusion, at occurrence of fist irAE G≥3 and, if records are available in the hospital charts, at first year (+ / - 3 months) after enrolment, and optionally at second year (+ / - 3 months) after enrolment. Multiple records can be registered, one record at each pre-specified time.

CRF 06 - Follow up log. Can be used to capture patients follow-up information at different times (withdrawal information, ocurrence of disease recurrence or progression, death date and cause). .

Multiple records can be registered, one record at each follow-up time.

CRF 07 - Study specific blood and stool samples. Can be used to capture specific information on collection date, storage date, freezing and defrost date for the different biological samples (blood for gene expression, SNPs and cytokines stool for microbiota) at different pre-specified times: baseline (before starting treatment), at 2nd infusion, at occurrence of fist irAE G≥3. Multiple records can be registered, one record at each pre-specified time.

CRF 08 - Off study. Can be used to capture the date of off study, the causes of interruption (during screening phase or during the study), and best/first response to treatment.

CRF 09 - ICI and oncologic treatments log. Can be used to capture information on ICI and other treatments at different times: date of administration, cycle and week, and the possibile reason of interruption (if any) or dose reduction. Multiple records can be registered, one record at each cycle/week.

CRF 10 - CRF 10 - Diet form. Can be used to capture patient answers to the dietary questionnaires. This is to be compiled only once, preferentially at baseline.

CRF 11 - Pre-Screening form. Can be used to record the date of pre-screened and the reason why the patient was not entering the screening phase. Do not document any patient specific information on this form.

4.4.3 Recording of Immune Related Adverse Events

- The corresponding DCF is "CRF 03 - Immune Related Adverse Event Log."
- The CI captures and grades (using NCI's 5.0 version of CTCAE) all immune related adverse events/toxicities.
- The CI will assign causality accordingly.
- Immune Related Adverse events (toxicities) can be captured on the DCFs.
- All immune related adverse events (toxicities) of any grade will be registered onto the eCRF/CRF.
- The DM shall review the patient's chart to ensure that all immune related adverse events/ toxicities are transcribed onto the eCRF. Any inconsistencies in the patient's chart will be discussed with the PIs or designee.
- The CIs are responsible for resolving inconsistencies between the patient's chart and the eCRF/CRF..

4.4.4 Data protection

In keeping with the Directive (2001/20/EC) and GDPR, confidentiality of patient data will be ensured at all times (ANNEX 03 - Administrative and regulatory details). In the G-DEFINER study all the data will be electronically

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registered in a secure validated GDPR compliant web platform (*study database*) allowing data registration and management. The database has been created by Nubilaria S.R.L. (ISO certificate: "SOP 02 - Annex - [ISO-IEC 27001-2013] Certificate (2019-02-26 EN).pdf"), using "ACTide application service" a proprietary, web native platform managed since2009, validated since2011 ("SOP 02 - Annex - ACTide_presentation-en-20190701.pdf"). The database is password protected and access is limited to the authorized users. Security of the password is to be maintained by the users. For further security only the year of birth and age at registration will be collected.

4.4.5 Training
Specific training on the study database:

- Support study crew 36 months.
- Help Desk Investigators for the first 6 months from the first patient accrual.
- Database manual.
- On demand: training remotely for user groups (Es. center PIs): a session of 8 users for 2 hours.
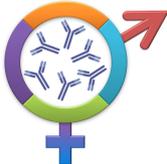
4.4.6 Approval process and amendment
eCRFs should be reviewed by the CIs and PIs at each Center and the approval process should be well documented via a note to file. Amendments to the eCRFs/CRFs may be triggered by a change in study design or data requirements. These amendments should be tracked through version numbers and dates.

5. Dissemination
The SOP will be disseminated according to the G-DEFINER "SOP 01 - Development, Approval and Review documents", and the PI at each site will ensure implementation of the SOP.

6. References
- Directive 2001/20/EC & 2005/28/EC.
  DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001. Official Journal of the European Communities.http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf
- ICH/GCP Guidelines (http://www.ich.org/)
- GDPR EU 2016/679
- Good Clinical Practice (GCP)

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7. Document history

Version No.	Date	Reviewer	Details of changes
0.1	May 8th 2019	RM	First version
0.2	May 23rd2019	RM	First revision
0.3	July17th 2019	RM	References to the data capture forms
1.0	August 16th 2019	Naoise Kelly	Substantial text revision. Suggestion CTCAE
2.0	October 8th 2019	RM	Modified par 4.4.2 Data capture forms compilation with the new forms, and par , and par. 4.4.3 Recording of Immune Related Adverse Events
3.0	Febrary 20th 2020	RM	Sections modified: 4.3 Prior to CRF Completion , 4.4. CRF compilation . 4.4.1 and 4.4.2 CRF list and information update