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| **Title** |  <br>**SOP 03- Study conduct** |
| **Document type** | SOP |
| **Version N.** | 5.0 |
| **Date** | March 1st 2020 |

| | **NAME** | **DATE** |
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| **PREPARED BY** | Rosalba Miceli | July 23rd2019 |
| **REVIEWED BY** | Site PIs | |
| **APPROVED BY** | Site PIs | |
| **PURPOSE** To outline the process for the G-DEFINER study conduct at INT, Onk-Pat KI, OUH and DCU-SVUH. | | |

**Abbreviations**

| **Acronym** | **Description** |
|---|---|
| AE | Adverse event |
| CI | Clinical investigator |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCF | Data Capture Forms |
| DCU- SVUH | Dublin City University, Dublin -St Vincent's University Hospital, Ireland |
| 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 |
| IEC | Institutional Ethics Committee |
| INT | Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy |
| irAE | Immune-related adverse event |
| Onk-Pat KI | Dept of Oncology-Pathology, Karolinska University Hospital, Sweden |
| OUH | Oslo University Hospital – The Radium Hospital, Norway |
| PI | Principal investigator |
| SOP | Standard Operating Procedure |

**Related documents**

| **Document type** | **Title** |
|---|---|
| Protocol | Protocol-G Definer-ENG |
| FORM | CRF 01 - Informed consent and screening<br>CRF 02 - Registration and baseline<br>CRF 03 - Immune Related Adverse Event Log<br>CRF 04 - Lab tests and concomitant medications<br>CRF 05 - Questionnaires distress and health<br>CRF 06 - Follow up log<br>CRF 07 - Study specific blood and stool samples<br>CRF 08 – Off study |

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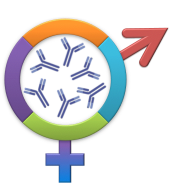
| **Title** |      **SOP 03- Study conduct** |
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|---|---|
| | CRF 09 - ICI and oncologic treatments log<br>CRF 10 - Diet form<br>CRF11 - Pre-Screening form |
| SOP | SOP 02 - Data management CRF completion<br>SOP 04 - AE registration<br>SOP 07 - Faeces sampling and microbiota analysis<br>SOP 08 - Blood sampling and SNP analysis<br>SOP 09 - Blood sampling and gene expression analysis<br>SOP 10 - Blood sampling and storing for cytokines - |

**Appendices:**

| Document type | Title |
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# 1. Scope and applicability

This SOP describes the G-DEFINER study conduct and is applicable to all study site staff involved in the study.

# 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 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).

### Good Clinical Practice (GCP)

An internationally recognized standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

### International Conference on Harmonization (ICH)

A joint collaboration between the United States, European Union (EU) and Japan that established the ICH GCP Guidelines aimed to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities of these jurisdictions.

### Standard Operating Procedure (SOP)

ICH defines a SOP as “detailed written instructions to achieve uniformity of the performance of a specific function.” (ICH GCP 1.55). A SOP is a written process for a clinical site to perform a task the same way each time it is completed.

# 3. Responsibilities

This SOP applies to all members of the clinical research team and others who may be involved in the G-DEFINER study initiation, conduct and close-out.

The overall responsibility for G-DEFINER study conduct rests with the study PI, together with the PIs at each Center. The CIs, research nurses, data managers and support staff delegated with study responsibilities by the PIs, in accordance with the study protocol, are legally and ethically bound to fulfill those responsibilities in compliance with GCP and this and other SOPs.

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*Responsibilities as outlined in the Annex 03 of the study protocol:*

| Responsibilities | Roles |
|---|---|
| Study protocol, CRFs, SOPs | Coordinating center, Study PI,Center PIs |
| Overall supervision of the study | Study PI, Center PIs |
| Data collection at each Center | Center Clinical Investigators |
| Study database | Coordinating center, Study PI |
| Statistical analysis | Coordinating center, Study PI |
| Results: participation in publications and communications | All Investigators |

# 4. Procedure

## 4.1 General issues

### 4.1.1 Standards

- The CIs, research nurses, DMs, and research staff will follow the G-DEFINER SOPs.
- G-DEFINER activities are completed using standardized methods and forms to ensure compliance and consistency.

### 4.1.2 Training

- The CIs participating in the G-DEFINER study should have evidence of ICH/GCP as per each sites policy.
- CI's and site staff will be initiated on the protocol, protocol amendments (if any) and the eCRF database.

### 4.1.3 Clinical data collection and recording

- Only those individuals with legitimate access to the study database will be able to view G-DEFINER clinical data records.
- Please refer to "SOP 02 - Data management CRF completion" for clinical data collection procedures.

### 4.1.4 Biological Samples

- Study specific biological samples must be handled, stored and transported as specified in the specific SOPs:
    - SOP 07 - Faecal sampling and microbiota analysis.
    - SOP 08 - Blood sampling and SNP analysis.
    - SOP 09 - Blood sampling and gene expression analysis.
    - SOP 10 - Blood sampling and storing for cytokines

### 4.1.5 Safety Reporting

- AEs must be assessed and reported according to the Center procedures and protocols in use.

- Participants enrolled in the G-DEFINER study should be instructed at the beginning of the study to contact the reference oncologist if they experience any untoward event, even outside scheduled oncologic visits.
- As regards the reporting specific for the G-DEFINER study, please refer to "SOP 04 - AE registration".

## 4.2 Preparing the Center

- The Center ensures that it has met with all the required regulatory requirements.
- The Center ensures that study protocol has been approved by the Institutional Ethics Committee (IEC).
- The Center has all essential documents in place to conduct the study in compliance with the approved protocol and applicable regulatory guidelines.
- The Center is aware of all the procedures and SOPs for study conduct.
- The Center ensures that the names and contact numbers of the relevant medical and study personnel are available and documented clearly.
- The Center checks that related supplies are available or are to be shipped to the Center at a later date, and that they are available in sufficient quantities.
- The Center checks that laboratory facilities and arrangements for the collection and storage of biological samples are organized and that any specialized equipment that may be required will be available throughout the period of the study, e.g. collection kits, centrifuge machine, freezer, etc.
- The Center confirms activation of the web-based study database.
- The patients unique code ("Code") is generated through the study database and registered together with information for patient identification (e.g. name, surname, clinical chart number, address,) is maintained as per GDPR requirements.

## 4.3 Center activation

- The Center will distribute protocol summaries and worksheets.
- The Center will notify all appropriate departments that the study is ready to enroll participants.
- The Center will initiate study recruitment strategies and begin enrolling study patients/participants.

## 4.4 Study initiation

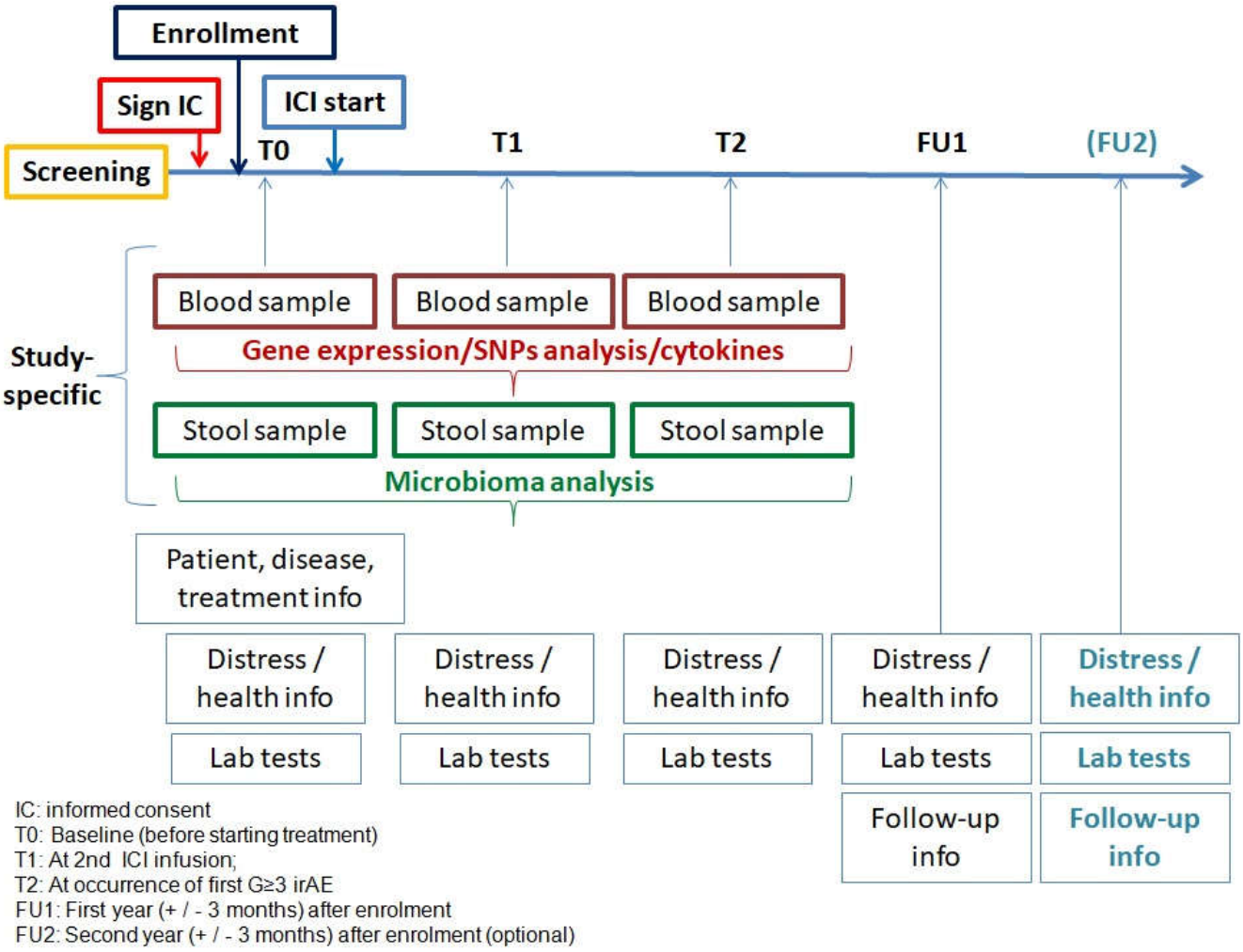
### 4.4.1 General principles

While the study is ongoing the CIs will ensure the following:

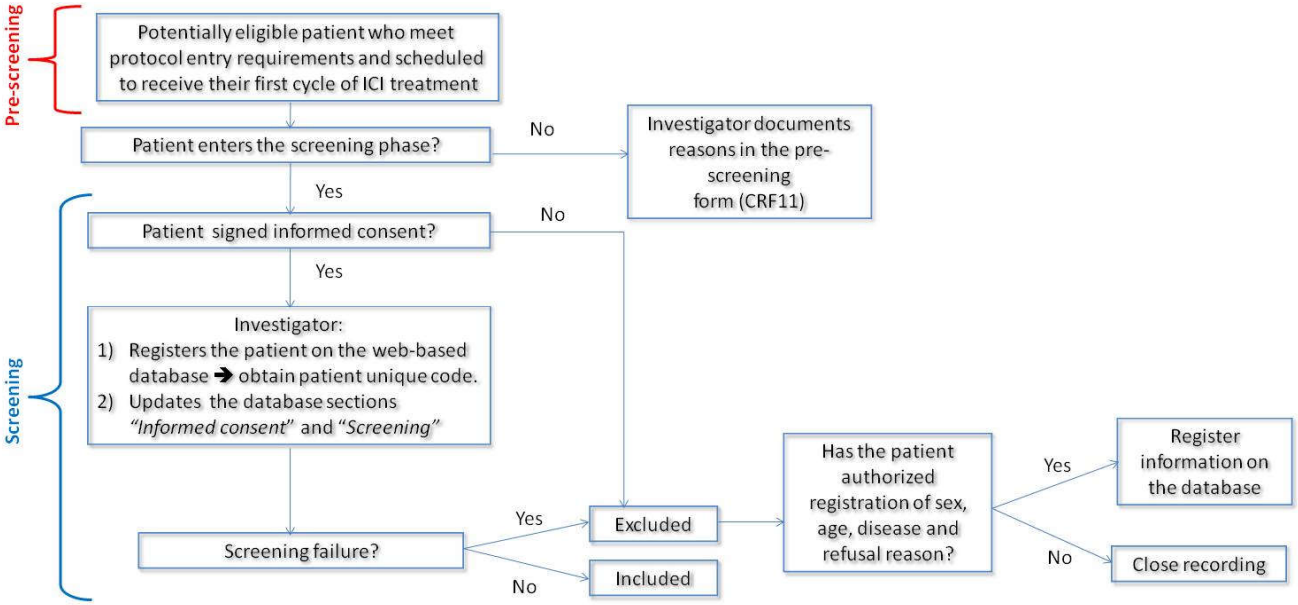
- All study activities are conducted in accordance with the protocol and applicable regulatory regulations.
- Patients sign the correct version of the consent form before any study-related procedures are commenced.
- Data collected in the eCRF is transcribed from source documents.
- Biological samples are obtained, handled, stored, and shipped appropriately as per SOP.
- Study supplies remain adequate.
- Study records remain confidential in accordance with local GDPR requirements.

### 4.4.2 Study conduct

Study flow-chart:



## Pre-screening, screening informed consent generation, and registration.




- **Pre-screening phase.**
  - The site will identify potentially eligible patients who meet the protocol entry requirements. The patients must be scheduled to receive their first cycle of ICI treatment.
  - The paper DCFs "CRF 11- Pre-Screening form" can be used to document reasons why a patient does not enter the subsequent screening phase.
- **Screening phase:**
  - **Informed consent assessment.**
    - The CI is responsible for the conduct of the informed consent process.
    - The CI/delegated team member will provide the patient with information on the study (Protocol Annex 01 in Italian, Annex 02 in English; translation in other languages is locally performed at each Center) and the patient informed consent form; each Center will use its own form(s).
    - The study will be discussed with the patient by the CI/delegated member of the study team and a signed copy of the current approved PIL/CF will be obtained if the patient wishes to proceed.
    - A signed copy of the informed consent must be kept secure according to the local privacy policy.
    - **Patient registration into the database and patient code.** Create a new record on the web-based study database and a unique code will be generated for the patient. The code is composed of 3 characters indicating the center (IRE-Ireland, ITA-Italy, NOR-Norway ,SWE-Sweden) and a a serial number from 001. The code can be reported in the paper DCFs used to collect screening information for a later entry in the study database.

- Open the database section *"Informed consent and Screening"* and fully check eligibility criteria (notice that inclusion criteria include the informed consent signing).

- **Consent obtained:**
  - Register the requested information on the study database in section "*Informed consent and Screening* ".
  - The patient will be given 3 kits for stool sampling, the related instructions and will be educated on when to collect the first stool sample (T0 sample). The patient will collect the stool samples at home and will bring the T0 sample at the next oncologic visit. Refer to "SOP 07 - Faeceal sampling and microbiota analysis".
  - **Screening failure (**"potential patient who was screened for the study participation, but was not enrolled").
    - If the patient has given explicit authorization authorization for registering information on sex, age, disease type and reason for refusal, such information must be registered in the study database in section "*Informed consent and Screening*". Otherwise, without patients' authorization no addidional data can be entered.
    - Update the database section "Off Study" with the causes of screening failure.
- **Consent not obtained:**
  - Open the database section *"Informed consent and Screening"* and register the date and information that consent was not obtained for that patient.
  - If the patient has given explicit authorization authorization for registering information on sex, age, disease type and reason for refusal, such information must be registered in the study database in section "*Informed consent and Screening*". Otherwise, without patients' authorization no addidional data can be entered.
- The paper DCFs "CRF 01 - Informed consent and screening**"** and CRF 08 - Off study**"** may be used to collect screening information for a later entry in the study database.

## Enrolled patient: time T0

Before starting ICI treatment:

- Register in the database the information on patient characteristics; cancer type, stage and histology; ICI treatment type, dose, schedule and setting; concomitant oncologic treatments; gender-related characteristics. The paper DCFs "CRF 02 - registration and baseline**"** may be used to collect data for a later database registration step.
- Provide the "Diet form" (general eating habits and questionnaire of Mediterranean diet adherence) to the patient. The paper DCFs "CRF 10 - Diet form**"** may be used to collect data for a later entry in the study database.
- Provide the "Distress questionnaire" (distress thermometer and problems list) and "Health questionnaire" to the patient. The paper DCFs "CRF 05 - Questionnaires distress and health**"** may be used to collect data for a later entry in the study database.
- Enter in the database the information on patient hematology, chemistry and hormones lab tests taken before ICI administration. Enter in the database the information on concomitant medications

(administered within 7 days), and their reason for use. The paper DCFs "CRF 04 - Lab tests and concomitant medications" may be used to collect data for a later entry in the study database.

- Blood collection: 3 tubes.
  - Tube 1: EDTA tube. For sample collection, preparation and storage please refer to "SOP 08 - Blood sampling and SNP analysis"
  - Tube 2: PaxGene (Qiagen) tube. For sample collection, preparation and storage please refer to "SOP 09 - Blood sampling and gene expression analysis".
  - Tube 3: EDTA tube. For sample collection, preparation and storage please refer to "SOP10 - Blood sampling and storing for cytokines".
  - All blood samples must be labeled with patient ID, timepoint and date of collection.
- Stool sample:
  - collect the T0 sample from the patient, give instructions on when to collect the second stool sample (T1 sample).
  - The patients will collect the stool sample at home and will bring the T1 sample at the next oncologic visit. Refer to "SOP 07 - Faecal sampling and microbiota analysis".
  - Stool samples must be labeled using the appropriate labels received from Sweden lab.

## Enrolled patient: time T1

- Provide the "Distress questionnaire" (distress thermometer and problems list) and "Health questionnaire" to the patient. The paper DCFs "CRF 05 - Questionnaires distress and health" may be used to collect data for a later entry in the study database.
- Enter in the database the information on patient hematology, chemistry and hormones lab tests taken before ICI administration. Enter in the database the information on concomitant medications (administered within 7 days), and their reason for use. The paper DCFs "CRF 04 - Lab tests and concomitant medications" may be used to collect data for a later entry in the study database.
- Blood collection: 2 tubes.
  - Tube 1: PaxGene (Qiagen) tube. For sample collection, preparation and storage please refer to "SOP 09 - Blood sampling and gene expression analysis".
  - Tube 2: EDTA tube. For sample collection, preparation and storage please refer to "SOP10 - Blood sampling and storing for cytokines".
  - All blood samples must be labeled with patient ID, timepoint and date of collection.
- Stool sample:
  - collect the T1 sample from the patient and give instructions on when to collect the possible third stool sample (T2 sample).
  - The patients will collect the stool sample at home in case of occurrence of G≥3 irAEs and will bring the T2 sample at the next oncologic visit. Refer to "SOP 07 - Faecal sampling and microbiota analysis".
  - Stool samples must be labeled using the appropriate labels received from Sweden lab.

### Enrolled patient: time T2

- Provide the "Distress questionnaire" (distress thermometer and problems list) and "Health questionnaire" to the patient. The paper DCFs "CRF 05 - Questionnaires distress and health**"** may be used to collect data for a later entry in the study database.
- Enter in the database the information on patient hematology, chemistry and hormones lab tests taken before ICI administration ( if scheduled). Enter in the database the information on concomitant medications (administered within 7 days), and their reason for use. The paper DCFs "CRF 04 - Lab tests and concomitant medications**"** may be used to collect data for a later entry in the study database.
- Blood collection: 2 tubes.
    - Tube 1: PaxGene (Qiagen) tube. For sample collection, preparation and storage please refer to "SOP 09 - Blood sampling and gene expression analysis".
    - Tube 2: EDTA tube. For sample collection, preparation and storage please refer to "SOP10 - Blood sampling and storing for cytokines".
    - All blood samples must be labeled with patient ID, timepoint and date of collection.
- Stool sample:
    - Collect the T2 sample from the patient. Refer to "SOP 07 - Faecal sampling and microbiota analysis".
    - Stool samples must be labeled using the appropriate labels received from Sweden lab.

## 4.5 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page; the paper DCFs "CRF 08 - Off study**"** may be used to collect data for a later entry in the study database. Patients will not be followed-up for any reason after consent has been withdrawn. If a patient has withdrawn from the study no more data can be collected on him/her unless he/she gives explicit consent to data collection. Patients who withdraw from the study will not be replaced.
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## 4.6 Premature termination of the study at a Center

If the study is prematurely suspended or terminated for any reason, the Center should:

- Inform the Cooordinating Center regarding the premature termination of the study with a detailed written explanation of the termination or suspension.
- Maintain the study documents and take measures to prevent accidental or premature destruction.
- Inform the approving Ethics Committee.

- Any decision is demanded to the General Assembly as the only and ultimate decision-making body of the consortium.

# 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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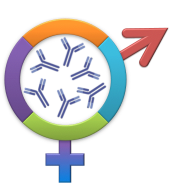
| **Title** |    **SOP 03- Study conduct** |
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# 7. Document history

| Version No. | Date | Reviewer | Details of changes |
|---|---|---|---|
| 0.1 | May5th 2019 | RM | First version |
| 1.0 | July 17th 2019 | RM | Conduction ➔ conduct. Addedd: 4.1 General issues |
| 2.0 | July 17th 2019 | RM | Addedd " Premature termination of the study at a Center" (with Paola Loro) |
| 3.0 | July 30th 2019 | RM | Added point in par 4. 1.5 Safety Reporting, modified stool kit provision time, blood ml in the tubes for cytokines and gene expression analysis |
| 4.0 | August 16th 2019 | Naoise Kelly | Substantial revisions: text, eliminated reference to SUSAR (as it is observational study), |
| 4.1 | October 8th 2019 | RM | Modifcations: Page 5 (id generation), study flow chart (inclusion informed consent and cytokines blood sampling), added screening figure and text corrections . |
| 5.0 | March 1st 2020 | RM | Modifications : see version with revisions. |