EU-RESPONSE Project: EU-SolidAct

European DisCoVeRy for Solidarity:
An Adaptive Pandemic and Emerging Infection Platform Trial

Safety reporting: Safety Working Instructions for participating sites

Safety Working Instructions			
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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
DRE	Disease-Related Event
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
PV	Pharmacovigilance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
WI	Working Instructions

1. Purpose

This working instructions (WI) document describes the procedures the sites need to follow for reporting Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Event of Special Interest (AESI), Disease-Related Events (DREs) and Pregnancies for the EU-SolidAct trial.

All events and DREs should be processed in the eCRF, assessed and followed up.
SAEs, AESIs and Pregnancies must be reported promptly by sites to the sponsor, reviewed in a timely manner, and if required, submitted to the appropriate authorities by the sponsor within the regulatory timeframes.

2. Definitions

2.1 Investigational Medicinal Product

An investigational medicinal product (IMP) is defined as the tested investigational medicinal product and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision).

2.2 Adverse Events

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP and EU guidance ENTR/CT 3 apply to this trial protocol. These definitions are given in **Table 1**.
When requested, local requirements should apply.

Table 1: Definitions of Adverse Events

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant, which does not necessarily have a causal relationship with the research procedures or the investigational medicinal product (IMP).
Adverse Reaction (AR)	Any untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event or Reaction (SAE/SAR)*	Any AE/AR that, at any dose, results in: ▪ death; ▪ a life-threatening AE**; ▪ hospitalization or prolongation of existing hospitalization; ▪ a persistent or significant disability or incapacity; ▪ a congenital anomaly or birth defect; ▪ an important medical event***
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An unexpected adverse reaction is an AR of which the nature, outcome, frequency or severity is not consistent with the

	applicable Reference Safety Information (RSI): SmPC or Investigator's Brochure (IB).
Safety issue/Safety concern	An important identified risk, important potential risk or important missing information, *i.e.* includes the qualifier "important" in relation to missing information (see Annex IV, ICH-E2C (R2) Guideline).
Special situation	**Medication error**: an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient while the medication is in the control of the health care professional, patient or consumer. **Overdose**: more than the maximum recommended dose (in quantity and/or concentration), *i.e.* an excessive dose. **Abuse:** persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

**EXCEPTIONS: the following events are not considered as SAE requiring immediate reporting to the sponsor:*
-the participant is formally admitted to a hospital for medical reasons with no seriousness criterion and does not require overnight hospitalization
-elective or previously scheduled surgery or medical treatment;
-hospitalization for social or administrative reasons;
-pre-existing diseases or present conditions detected prior to start of study drug administration and which do not worsen.

***The term "life threatening" in the definition of a serious adverse event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might cause death if it were more severe, for example a silent myocardial infarction.*

****Medical judgment should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes in the definitions above; for example a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation, or development of drug dependency.*

2.3 Adverse Events of Special Interest (AESI)

Some adverse events of special interest (AESIs) are monitored during and after the administration of IMPs. All subjects enrolled in the study will be monitored for AESIs for the entire follow-up period. The occurrence of any of these adverse events requires an immediate notification to the sponsor via the *SAE form*, whether the AESI is serious or not.

For each IMP of the EU-SolidAct trial, AESIs will be listed in **Appendix 5** with corresponding adapted DRE list (if applicable), which will be reviewed and updated at each new arm or safety profile update.

Refer to **Appendix 7** for discontinuation strategies and treatment management.

2.4 Disease-Related Events and/or Disease-Related Outcomes not qualifying as AEs or SAEs

These events may refer to disease- or complication-related events that are common in Covid-19 patients and can be serious/life-threatening.
They are reported systematically in the eCRF in the pre-defined daily data and DRE sections. However, they will NOT required immediate reporting to the sponsor as SAE in the eCRF, even if the event may meet the definition of an SAE, **unless:**

- **the investigator suspects that there is a reasonable possibility that the study intervention (blinded investigational agent/ placebo or study-supplied SoC treatment) caused the event**
- **or the DRE is associated with a fatal outcome**

These events may occur during the initial hospitalization, lead to a re-admission, or occur during later hospitalization or at follow-up.

The general DREs from the *Master protocol* are listed in **Appendix 4**.

Some of these events can be recorded as AESI, depending on the IMP safety profile: in that case, the DRE list will be adapted (see **Appendix 5** for adapted DRE list).

2.5 Pregnancy

Pregnancy during hospitalization is highly unlikely, and no specific procedures will be undertaken to discover pregnancies during hospitalization except for the pregnancy test at screening.

Pregnancy is not an adverse event. However, reports where the embryo or foetus may have been exposed to the IMP should be reported immediately via the *Pregnancy form* and followed-up in order to collect information on the outcome of the pregnancy and the development of the child at birth.

While pregnancy itself is not considered to be an AE, any pregnancy complication, abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy for medical reasons will be reported with the same timeframe as an SAE.

Depending on the IMP safety profile, pregnancy occurrence involving the participant's partner will be also recorded.

3. Reporting Procedures and Requirements

The Investigator is responsible for detecting, documenting and reporting all adverse events and DREs occurring during the clinical trial, independently from the seriousness and the relatedness to the IMP. These should be recorded on the appropriate eCRF sections.
Refer to **Appendix 6** for general safety management leaflet.

SAE, AESI and PREGNANCY REPORTING

SAE/AESI and pregnancy must be reported **within 24 hours** of becoming aware of the event.
Investigators complete the corresponding *SAE* or *Pregnancy form* in the **eCRF**.

If eCRF is unavailable

Investigators send the signed paper SAE *or* Pregnancy form *(see **Appendices 1** and **2**) to:*
pharmacovigilance@anrs.fr
*Refer to the manual of instructions in **Appendix 3***
If an SAE is notified by paper circuit, investigator has to re-enter the form in the eCRF

3.1 Reporting of AE, SAE, AESI, DRE and Pregnancy

AE and AR	All non-serious AE and AR, whether expected or not, should be recorded in the participant's file of the eCRF **within 1 week** of becoming aware of the event. NOTE: - Only new AE/AR or aggravation of preexisting AE should be reported during the trial
SAE, SAR and AESI	All SAE, SAR and AESI should be notified by the Investigator by completing the *SAE form* in the eCRF **within 24 hours** of becoming aware of the event, with due care being paid to the grading, seriousness criteria and causality of the event. Participants will be followed up until resolution or clinical recovery is complete, and/or laboratory results have returned to normal or baseline, or until progression has been stabilised.
DRE	All DRE should be reported in the DRE section in the eCRF, with due care being paid to the grading, seriousness criteria and causality of the event. An *SAE form* should be reported within 24 hours: → If the DRE is serious and considered to be possibly related to the IMP → If the DRE is associated with a fatal outcome
Pregnancy	All pregnancies disclosed after inclusion should be reported by the Investigator using the *Pregnancy Form* in the eCRF **within 24 hours** of being aware of it. NOTE:

	- If a female participant becomes pregnant during the study, **the IMP will be discontinued** - Any SAE experienced during pregnancy should be reported via the *SAE form* - *Pregnancy Follow-up Form* should describe the outcome of the pregnancy, including details on the neonate. Any complication or abnormal outcome should be reported **as an SAE** (voluntary or spontaneous abortion, presence of any congenital abnormalities, birth defects, maternal or newborn complications), with the causal relationship evaluation to the IMP
If the eCRF is unavailable, the signed paper *SAE/Pregnancy form* (Appendices 1 and 2) should be sent by email to the Inserm-ANRS Pharmacovigilance Office within 24h *via* pharmacovigilance@anrs.fr	

The minimum criteria required for reporting an SAE are:

1. Identification of the participant: participant trial number
2. Name of Investigator/member of the site trial team reporting
3. Nature of the adverse event
4. Seriousness criteria (except for AESI)
5. Study treatment details
6. Causality assessment

Each SAE notification in the eCRF will result in an automatic email alert received at the Inserm-ANRS Pharmacovigilance Office and the *SAE form* will be available for downloading.

➢ **Relevant documentation related to SAE/AESI/Pregnancy:**

All relevant **anonymized** documentation related to the SAE/AESI/Pregnancy (hospitalization or medical report, laboratory results, autopsy report…) will be sent, along with the corresponding *SAE* or *Pregnancy form*, by email to pharmacovigilance@anrs.fr or fax: +33 1 53 94 60 02.

None of these documents should mention the participant's name and will thus be identified with the trial name and the participant identification code.

3.2 Follow-ups

➢ **Follow-up related to SAE/AESI:**

The investigator must document and report all new or additional information about an SAE/AESI already reported using the *Follow-up SAE form*.

Follow-up of SAEs/AESIs will continue after completion of protocol treatment. The trial monitoring team will continue to follow up sites until resolution of the events and/or laboratory results have returned to baseline, or until the event has stabilized, even if this continues beyond the planned trial follow-up period.

Additional information should be notified within 1 week for fatal or life-threatening events and 2 weeks for other events.

In some cases, e.g. chronic conditions, the event will not be resolved: such events can therefore be closed as unresolved upon agreement by the safety officer and Investigator.

- **Follow-up related to Pregnancy:**

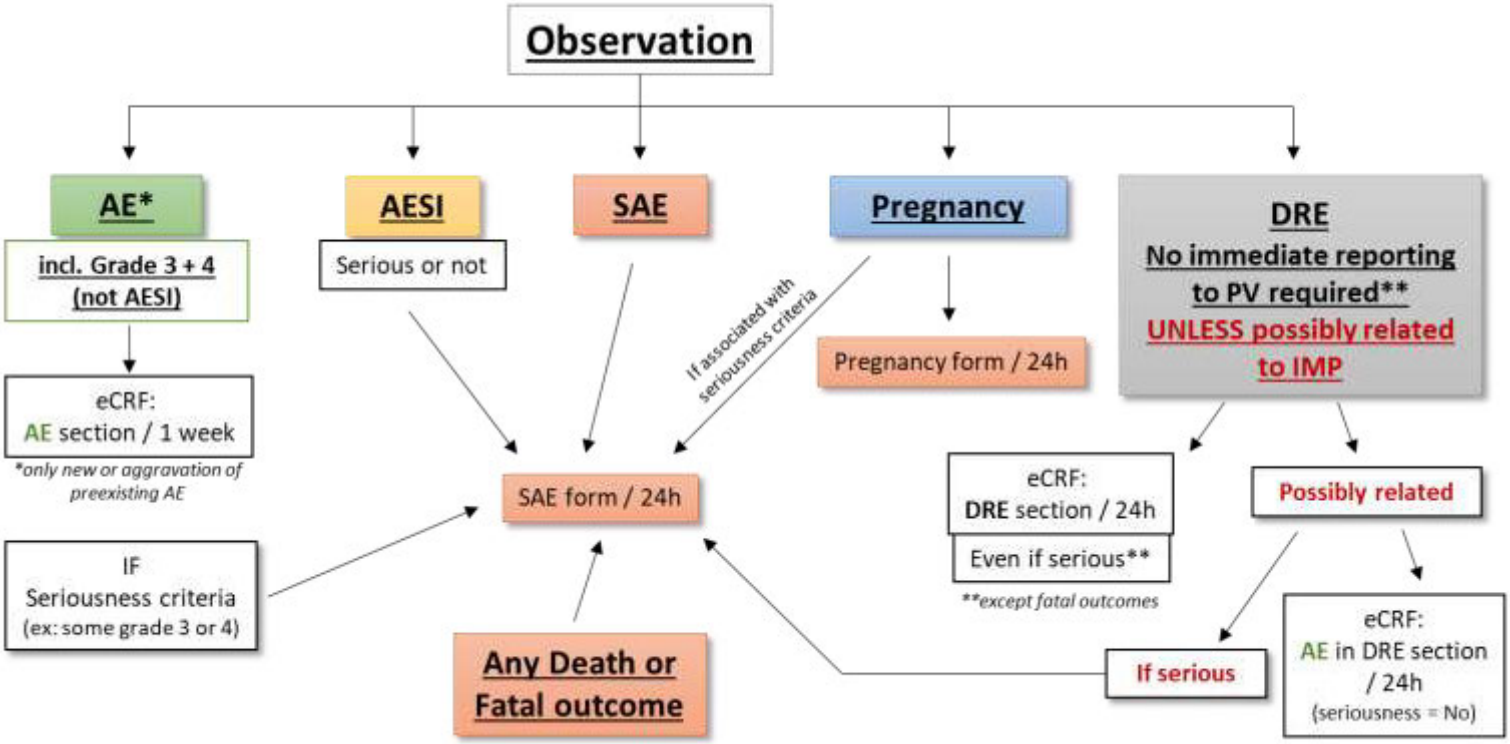
Each pregnancy outcome should be followed up and described using the *Follow-up Pregnancy Form*, including details on the neonate.
Any complication or abnormal outcome should be reported as an SAE (voluntary or spontaneous termination, presence of any congenital abnormalities, birth defects, maternal or newborn complications), with the causal relationship evaluation to the IMP.

3.3 Queries Management

When necessary, the Inserm-ANRS Pharmacovigilance Office or data and monitoring teams may request additional information on the notified SAE or Pregnancy sections.
Theses queries can be addressed directly in the corresponding section of the eCRF or by email to the investigator site. Once received, the site should provide the requested information or clarification as soon as possible for urgent queries or events requiring review, and within 2 weeks for general data queries.

When some minor corrections (e.g. error in a date, of typo, in drug dosage…) are made on the SAE/AESI form, a modification rank should be selected (at the bottom of the page).
Answers that can impact significantly the initial SAE report should be reported on the *complementary form* in the eCRF (e.g. evolution in outcome, change of causality assessment, new diagnosis…).

3.4 Summary of Investigator Reporting Timelines



4. Investigator Assessment of AE/SAE/AESI/DRE

4.1 Grading of Adverse Events (severity)

The severity of all AEs and DREs (serious and non-serious) in this trial should be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the DAIDS table, the following guidelines will be used to describe severity:

- **Grade 1 (Mild):** Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.
- **Grade 2 (Moderate):** Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
- **Grade 3 (Severe):** Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalization.
- **Grade 4 (Very severe):** Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting; events that are potentially life-threatening.

4.2 Seriousness Assessment

When an AE occurs or a DRE is observed, the investigator responsible for the care of the participant must first assess whether or not the event meets one or more of the seriousness criteria described in **Table 1**.
An SAE form must be completed and sent as per the process described in **section 3**:

- if the AE is serious or becomes serious
- if the AE is of special interest (AESI)
- if the DRE is serious and considered as possibly related to the IMP

4.3 Causality Assessment

The investigator must assess the causality of all events and DREs in relation to the trial treatment using the definitions below:

- ***Possibly Related*** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- ***Not Possibly Related*** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established.

All AEs/SAEs for which the investigator or the sponsor considers a causal relationship to be a reasonable possibility are considered suspected ARs/SARs.

Other causal relationships
The investigator should also give his opinion about other possible causal relationships, especially related to the:

- study procedure (exams, strategy…)
- progression of disease under study (Covid-19 pneumonia)
- pre-existing medical condition/illness
- concomitant medication
- or other explanations

Consensus
The causality assessment as reported by the local Investigator cannot be overruled.
In case of divergent assessments, both the local investigator's and sponsor's (*via* Inserm-ANRS Pharmacovigilance Office) opinions will be provided in any subsequent reports.

In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. Meanwhile, the Inserm-ANRS Pharmacovigilance Office will be responsible for this assessment.

All SARs for which the event is evaluated as unexpected are considered SUSARs (*i.e.* expedited reports). Consequently, each change in causality (following additional information or case review) may results in the new reporting or previous reporting nullification to the regulatory authorities.

5. Unblinding Procedure and Notes

During the course of the study, this procedure is **only authorized when**:

- Immediate management of the participant would be different if the trial allocation is known
- The outcome of a decision made by the participant depends on the treatment allocation (ex: pregnancy…)

Unblinding procedure is as follows:

- Investigator connects to the eCRF with his pre-defined access
- Investigator fills the required information, including the reason and finalizes the unblinding
- The result appears in a window that will remain unsaved
- Investigator must indicate the unblinding request in the patient's medical file
- In parallel, an automatic alert email is sent to the sponsor, data and PV teams (without the result)

For each unblinding, **an SAE should be reported consequently**.

No unblinded information should be provided to the patient during the course of the study.

Unblinding should remain an exceptional procedure to guaranty the best participants' security. It should occur in exceptional circumstances and in a responsive manner when it is clinically indicated and affect the medical care.

Only the sponsor *via* the Inserm-ANRS Pharmacovigilance Office will unblind a treatment allocation for reporting SUSARs to the regulatory authorities.

6. Appendices

- Appendix 1: Paper *SAE form* (initial and follow-up)
- Appendix 2: Paper *Pregnancy form* (initial and follow-up)
- Appendix 3: Manual of Instructions for *SAE form* Completion
- Appendix 4: Disease-Related Events (DREs) as per Master protocol
- Appendix 5: IMP-related AESIs and adapted DRE list
- Appendix 6: General safety management leaflet
- Appendix 7: Discontinuation strategies and treatment management

7. Revision history

Version	Date	Reason for Revision
1.0	23-Jun-2021	Writing
1.1	05-Jul-2021	Addition of Appendices: - 6 – *General safety management leaflet* - 7 – *Discontinuation strategies and treatment management*
1.2	13-Sep-2021	Section 3.1 Reporting of AE, SAE, AESI, DRE and Pregnancy: Change in non-serious AE and AR reporting: from 24 hours to 1 week.
2.0	18-Nov-2021	Update following amendment 1 to the protocol: • Appendix 5: update of the AESI and DRE lists for baricitinib/placebo arm ○ precision regarding hepatotoxicity (only grade 3 and 4 to be reported) and viral reactivation (CMV added) ○ Cardiac disorders and Stroke removed from DRE list and added in AESI list • Appendix 7: Reasons for permanent discontinuation modified: ○ Invasive fungal infection, including invasive pulmonary aspergillosis added ○ Active infection updated with inclusion of CMV and HSV
2.1	03-Dec-2021	• Appendix 7: Wording of the criteria for dose reduction in patients with eGFR ≥ 15 to < 30 mL/min/1.73 m² reformulated to match IB: ○ From "2 mg every other day" to "2 mg once every 48 h"
3.0	09-May-2022	• 3.3 Queries Management: clarification regarding the actions to take for the SAE form when queries are answered • Appendix 5: addition of the AESI and DRE lists for bemcentinib/placebo arm • Appendix 7: addition of the reminders for dose modification and permanent discontinuation for bemcentinib/placebo arm
4.0	28-Jul-2022	Update of: • Appendix 1 – Paper *SAE form* ○ EudraCT number from CTIS added ○ Wording changed in Section 6 • Appendix 2 – Paper *Pregnancy form* ○ Eudra CT number from CTIS added • Appendix 3 – Manual of Instructions for *SAE form* Completion ○ Precision on Date of hospitalization ○ Seriousness section specified ○ Precision on outcome "Unknown" use

		○ Precision on study treatment initiation / not administered Correction in Appendix 7 – Discontinuation strategies and treatment management: Bemcentinib/Placebo arm • Addition of the following permanent discontinuation reasons: ○ Ventricular arrhythmia ○ SARS CoV2 infection resolution but hospitalization maintenance for other reasons