



## COLLABORATE Study

### Safety Reporting Manual for Participating Sites

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# IMPERIAL

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## Associated Documents

**Document Title:**

Protocol

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## 1. Introduction

The purpose of this document is to describe the procedures involved in detecting, recording and reporting unexpected and study-related Serious Adverse Reactions (SARs) for the COLLABORATE study at the participating sites.

## 2. Scope

This procedure manual is applicable to all delegated personnel working on the COLLABORATE Study at all participating sites when safety events require notification to the Imperial Clinical Trials Unit (ICTU) study team.

It is not the intention that this manual be read as a standalone document, and the current version of the protocol should also be read in conjunction.

## 3. Abbreviations

|      |                                      |
|------|--------------------------------------|
| AE   | Adverse Event                        |
| AR   | Adverse Reaction                     |
| CRF  | Case Report Form                     |
| CI   | Chief Investigator                   |
| DMEC | Data Monitoring and Ethics Committee |
| eCRF | Electronic Case Report Form          |
| HRA  | Health Research Authority            |
| ICTU | Imperial Clinical Trials Unit        |
| PI   | Principal Investigator               |
| REC  | Research Ethics Committee            |
| SAE  | Serious Adverse Event                |
| SAR  | Serious Adverse Reaction             |
| TSC  | Trial Steering Committee             |

## 4. Responsibilities

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chief Investigator (CI)</b>       | <ul style="list-style-type: none"> <li>• Review the SAR report form from site</li> <li>• Determine whether SAR is related to the study/study-related activities</li> <li>• Responsible for sign-off of SAR</li> <li>• Provide advice and guidance to participating sites where required</li> </ul>                                                                                                                                                                                                                                                                      |
| <b>Principal Investigator (PI)</b>   | <ul style="list-style-type: none"> <li>• Responsible for immediately reporting all unexpected study-related SARs</li> <li>• If medically qualified, reviewing unexpected study-related SARs for causality and severity, unless this is delegated to a/another study doctor on the study delegation log</li> <li>• Signing off documentation i.e. SAR CRFs, unless this is delegated to a/another study doctor on the study delegation log</li> </ul>                                                                                                                    |
| <b>Study Doctor/Sub-Investigator</b> | <ul style="list-style-type: none"> <li>• Safety-recording and reporting duties delegated by the PI</li> <li>• Responsible for immediately reporting all unexpected/study-related SARs</li> <li>• Reviewing SARs for causality and severity</li> <li>• Ensuring the relevant documentation is obtained to ensure a correct judgement regarding an event</li> <li>• Signing off documentation i.e. SAR CRFs</li> </ul>                                                                                                                                                    |
| <b>Study Nurse/Coordinator</b>       | <ul style="list-style-type: none"> <li>• Duties delegated by the PI</li> <li>• Responsible for immediately reporting all unexpected study-related SAR on the eCRFs in OpenClinica</li> <li>• Identify at each evaluation of the participant whilst on study if any expected and unexpected study-related SARs have occurred</li> <li>• Ensure safety events (expected and unexpected) are recorded in the participant's medical records</li> <li>• Ensure any follow up information on unexpected and study-related SARs are reported in the OpenClinica CRF</li> </ul> |
| <b>Trial Manager/Monitor</b>         | <ul style="list-style-type: none"> <li>• Review all SAR Report forms to ensure all available information has been entered into OpenClinica</li> <li>• Confirm the SAR report matches what is documented in the participant's medical records (where Source Data Verification has been triggered)</li> <li>• Ensure unexpected and study-related SARs are reported to the study TSC/DMEC</li> <li>• Report all unexpected and study-related SARs to the approving Research Ethics Committee (REC)</li> </ul>                                                             |

## 5. References

- COLLABORATE Protocol V3.0 dated 09 Jan 2026

## 6. Definitions of Safety Events

### 6.1. Adverse Event (AE)

Any untoward medical occurrence in a participant, whether or not related to the study protocol.

### 6.2. Serious Adverse Event (SAE)

Any adverse event that:

- results in death;
- is life-threatening;
- requires prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### 6.3. Adverse Reaction (AR)

All untoward and unintended responses to the study intervention. All AE judged by either the reporting investigator or the sponsor as having reasonable causal relationship to the study intervention qualify as AR.

### 6.4. Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any study intervention given to the participant.

### 6.5. Definition of Severity

The assignment of severity should be made by the investigator responsible for the care of the participant using the definitions listed in Table 1 below.

If any doubt about the seriousness/severity exists, the local investigator should notify ICTU who will notify the CI.

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**Table 1. Definitions for assessment of severity**

|                 |                                                       |
|-----------------|-------------------------------------------------------|
| <b>MILD</b>     | Appears easily tolerated                              |
| <b>MODERATE</b> | Discomfort to cause interference with usual behaviour |
| <b>SEVERE</b>   | Not demonstrating usual activity                      |

## 6.6. Assignment of Causality

The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions listed in Table 2 below. If any doubt about the causality exists, the local investigator should notify ICTU who will notify the CI. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the approving NHS Research Ethics Committee (REC) will be informed of both points of view.

**Table 2. Definitions for assessment of causality**

|                  |                                                                                                                                                                                                                                                                                                    |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>UNRELATED</b> | No evidence of any causal relationship                                                                                                                                                                                                                                                             |
| <b>UNLIKELY</b>  | Little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after the study intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment)                     |
| <b>POSSIBLE</b>  | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the study intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments) |
| <b>PROBABLE</b>  | There is evidence to suggest a causal relationship and the influence of other factors is unlikely                                                                                                                                                                                                  |
| <b>DEFINITE</b>  | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out                                                                                                                                                                                  |

## 7. Safety Reporting Procedure for Participating Sites

The use of pasteurised Human Donor Milk, Preterm Formula and fortifier are established in routine care. In this extremely preterm population, we anticipate frequent foreseeable AE, SAE and AR, and a mortality rate to discharge from neonatal care of around 10%. For these reasons, AE, SAE, and AR will not be recorded.

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All expected SAR have been listed as study endpoints, hence these events will be excluded from safety reporting. Any other SAR will be unexpected and extremely rare. **All unexpected SARs will be reported.**

**The safety reporting window for this study will be from randomisation (1 or 2) until 34 weeks Post Menstrual Age, discharge from neonatal care, or death, whichever is sooner.** The reporting timelines are the same for infants participating in the mechanistic sub-study.

## 7.1. Expected Serious Adverse Reactions (SARs)

The following are serious adverse reactions that could be reasonably anticipated to occur in this population of infants during the course of the study or form part of the outcome data. All expected SARs have been listed as study endpoints, these events will be excluded from safety reporting:

- Spontaneous intestinal perforation (SIP)
- Bronchopulmonary dysplasia (BPD)
- Necrotising Enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Severe brain injury
- Milk-curd obstruction
- Bacterial or fungal bloodstream infection
- Bacterial or fungal cerebrospinal fluid infection
- Bacterial or fungal urinary tract infection
- Short bowel syndrome
- Intestinal failure-associated liver disease
- Moderate–severe cognitive–language impairment
- Gross motor function
- Hearing impairment
- Vision impairment
- Death

**Expected SARs will not be reported by participating sites but will be recorded in the participant’s medical records, as per routine clinical care.**

These events should be recorded in the participant’s medical records from the time of consent to final study assessment.

If the participant experiences an SAR that is not on the above list, this would therefore be ‘unexpected’ and must be reported urgently in line with the study protocol. Please refer to section 7.2 for reporting procedures of unexpected SARs.

## 7.2. Unexpected Serious Adverse Reactions (SARs)

**All unexpected and related SARs must be reported to ICTU by a member of site staff within 24 hours of becoming aware of the event.**

Related and unexpected SARs are defined as:

- ‘Unexpected’ means the event is not already listed as an expected occurrence in the protocol (see section 7.1)
- ‘SAR’ means it is a ‘serious’ event, that is ‘related’ to (and resulted from) the study intervention or procedure (see definitions in sections 6.5 and 6.6)

Site staff should record the unexpected SAR in the OpenClinica eCRF within 24 hours of becoming aware of the event. If after reporting the SAR additional information becomes available, the original SAR form should be updated.

The PI (or study doctor) at the site will assess the event to confirm the severity, causality and expectedness.

Once a SAR form has been completed on the eCRF, ICTU will notify the CI as soon as possible. The CI (or ICTU delegate) will also review the SAR to determine expectedness and relatedness.

If the assessments of the PI and CI do not agree, further discussion can take place. If either the PI or CI confirm the event was serious, related **and** unexpected it will be further reported as below.

All unexpected SARs will be submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the study within 15 working days of the CI becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form (see HRA website).

## **To report an unexpected study-related SAR:**

**Complete an SAR form in OpenClinica and notify Imperial Clinical Trials Unit (ICTU) as soon as possible (within 24 hours).**

**COLLABORATE Trial Manager:**

**[collaborate@imperial.ac.uk](mailto:collaborate@imperial.ac.uk)**

### **7.3. Guidance on reporting unexpected/study-related SARs**

- Each completed SAR CRF in OpenClinica should systematically be reviewed and signed by the site PI to ensure that relationship and causality are assessed and documented in the source notes. See section 6.6 for causality assessment definitions.
- If any further information becomes known regarding an existing SAR, the investigator must report it by updating the original SAR CRF in OpenClinica.
- At each contact with the participant during the study intervention and follow-up period, the investigator must seek information on adverse events by examination.
- All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the participant medical records.
- The clinical course of each event should be followed until resolution or stabilisation.
- The completed SAR CRF will be signed off by the PI.
- The CI or delegate will review the SAR CRF as soon as possible, in OpenClinica. In the event of missing information, the CI or delegate will contact the COLLABORATE Trial Manager or the site staff with any queries.
- The Trial Manager will contact the site to obtain further information about the SAR, as soon as possible following the event being reported and during the follow-up phase of the event, to obtain any missing or other relevant information.

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- Any follow-up information regarding a SAR must also be recorded in the participant medical notes and within the same SAR previously reported in OpenClinica.
- All unexpected study related SARs should be recorded and reported from the time of randomisation to 34 weeks post menstrual age, discharge from neonatal care, or death, whichever is sooner.
- An SAR that is considered completely unrelated to a previously reported one should be reported separately as a new event.
- All unresolved SARs should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At neonatal discharge, the investigator should document any ongoing SARs, and these should be managed as per local practice.

## 8. Safety Reporting Timelines

| Event                                                                            | Reported by    | Reported to                                     | Time            |
|----------------------------------------------------------------------------------|----------------|-------------------------------------------------|-----------------|
| Unexpected Serious Adverse Reactions                                             | Site staff/PI  | COLLABORATE study team via OpenClinica SAR form | Within 24 hours |
| Unexpected Serious Adverse Reactions (once assessed by investigator or delegate) | CI or delegate | REC and Sponsor                                 | Within 15 days  |

## 9. Revision History

| Version | Date Effective                | Reason for update (page and section of change) |
|---------|-------------------------------|------------------------------------------------|
| 1.0     | 9 <sup>th</sup> February 2026 | First version of document                      |