SPIRIT 2

STI571 Prospective International Randomised Trial

Serious Adverse Event (SAE) Completion Guidelines- Trial Sites

These guidelines are for site staff responsible for reporting SAEs to the SPIRIT 2 Trial Office.

Protocol Safety Reference

SPIRIT 2 SAE reporting criteria can be found in **Section 11.3** of the SPIRIT 2 protocol.

Definition of SAE in SPIRIT 2 Under the protocol a Serious Adverse Event is defined as

- **An event that is fatal or life threatening (life threatening is anything that would result in the patient's death if left untreated)**
- **An event that results in significant or persistent disability**
- **An event that leads to the hospitalisation of the patient (any overnight inpatient stay) or prolongs existing hospitalisation. This includes any elective (planned) admission (for example knee replacement etc.)**
- **Adverse pregnancy outcomes in a patient or partner of a male patient (including spontaneous abortion). Pregnancy itself is not an SAE however should be reported to the trial office via the Pregnancy Reporting Form downloadable from: http://www.spirit-cml.org/spirit-2-home/documents-and-downloads.aspx. This includes pregnancies in the partners of male patients**
- **Any other significant medical event (in the opinion of the Principal or Co-Investigator)**
- **A diagnosis of any malignancy (other than Chronic Myeloid Leukaemia (CML)) – as included in Protocol version 2.0**
- **The SPIRIT 2 protocol also defines CML disease progression (Section 12.5) as an SAE. Any progression of CML (to accelerated phase or blast crisis) whilst a patient is on randomised treatment should be reported as a SAE**

If a patient experiences a progression following discontinuation of Investigational Medicinal Product (IMP) , this does not require SAE reporting (unless it occurred within one month of the last dose of trial IMP). Any progressions occurring post discontinuation should be reported via the eCRF Annual Review Page

The SAE Reporting Form

The paper SPIRIT 2 SAE reporting form should be used to notify the Trial Office of a SAE. These guidelines relate to version 2.0 of the SPIRIT 2 SAE form.

Please refer to the SPIRIT 2 website www.spirit-cml.org and your ISF for details of the current version of the SAE reporting form. All new initial SAE reports should be reported on the current version at the time of reporting and the appropriate guidelines referred to.

Forms should be faxed to the Trial Office on **0191 376 0748**. If you do not have access to fax, forms can be scanned and securely emailed (nhs.net to nhs.net) to tnu-tr.spirittrials@nhs.net.

When providing an update to the SAE report you should use the original form (please do not complete a new form). This ensures that all the original information is preserved. The changes should be clearly marked on the form whilst ensuring that it is clear which data has been crossed out/amended. All changes should be dated and initialled by the person making the change.

When submitting a follow-up report please fax all pages of the form and not just the updated pages.

It is recommended that you keep fax sent confirmations and SAE receipt acknowledgement emails alongside each original SAE form as confirmation that the report/follow-up has been submitted.

Reporting Timelines

SAE reports MUST be submitted to the Trial Office within 24 hours of a site becoming aware of a serious event.

If notification of an initial SAE is submitted more than 24 hours after the start date, please add a comment to the SAE form to indicate the date you became aware of the event (or became aware that it met the 'serious' criteria).

We are required to ascertain the reasons for late reporting of any SAEs (i.e. outside the 24 hour timeframe). Delays in reporting should therefore be accounted for.

In the interests of timely reporting it is acceptable to submit an initial report without full details or a PI/Co-Investigator signature. These should then be provided as soon as possible in a follow-up report. The minimum acceptable information for an initial SAE report is:

- **Patient trial ID**

- **Event title**- ideally this should be an overall diagnosis however if not known at the time of reporting, presenting symptoms can be listed instead
- **IMP details**- drug and current dose
- The **expedited reporting (seriousness) criteria**
- **Causality Assessment-** this needs to be signed off by the PI or Co-investigator however it should be provided on the initial report wherever possible

The following **critical information** should be provided **as soon as possible**:

- **Onset Date**- please report the date of the first signs and symptoms even if this was not the date the event became serious)
- **Causality Assessment**- if this is not included in the initial report it must be assessed by the Principal Investigator or delegated Co-Investigator and provided as soon as possible
- **PI Signature or delegated Co-Investigator Signature**- we are unable to accept the causality assessment as valid until we have a signature and therefore it is vital that this is obtained as soon as possible
- **Action Taken-** this should be indicated in the tick boxes and further details added in the narrative section of the form

Causality Assessment (Site PI/Co-Investigator Activity)

All Adverse Events should be assessed for causality (whether or not thought to be related to the trial drug) by the Principal Investigator or a delegated Co-Investigator at your site (they must be on the delegation log with this role at the time of reporting).

Their causality assessment should be clearly documented in the source data (patient notes).

The PI or Co-Investigator is also required to sign-off the SAE form (either page 2 or page 3) to confirm the causality assessment provided for an SAE. The assessment is documented in section 14 (on page 1) of the form.

The form provides options of ‘Suspected’ or ‘Not Suspected’. If causality is not clear, assessors are encouraged to take a conservative approach (i.e. report as suspected) however it is acceptable for the investigator to write ‘unknown’ on the report next to the causality assessment section.

If the causality assessment of an SAE changes, the investigator must countersign and re-date the SAE form (ideally next to the changed causality) to confirm this. A reason for a change in causality should also be provided on the narrative section on the form.

If the event title/diagnosis changes the PI or Co-Investigator will need to counter-sign the form (next to the causality assessment)to confirm that the causality assessment is still valid (or they will need to change the assessment if necessary).

Expectedness Review (Central Sponsor Activity)

All initial SAE reports will be forwarded to the SPIRIT 2 CI or Medical Advisor for review.

Where the causality is 'Suspected', they will review the event for expectedness (whether or not the event is listed as a known side effect of the IMP in the Reference Safety Information-RSI).

A SUSAR is any event which is

SUSPECTED of being causally related to the IMP

And is also

UNEXPECTED (not listed in the RSI)

The approved Reference Safety Information (RSI) for SPIRIT 2 is:

Dasatinib	**Section 4.8 of the Sprycel SmPC dated 08 April 2015 (section 4.6 for pregnancy information)**
Imatinib	**Section 4.8 of the Glivec SmPC dated 02 April 2015 (section 4.6 for pregnancy information)**

Previously (before April 2016) the approved RSI for dasatinib was Dasatinib Investigator's Brochure (version 7.0) and the approved RSI for imatinib was the Glivec SmPC dated 20 November 2007.

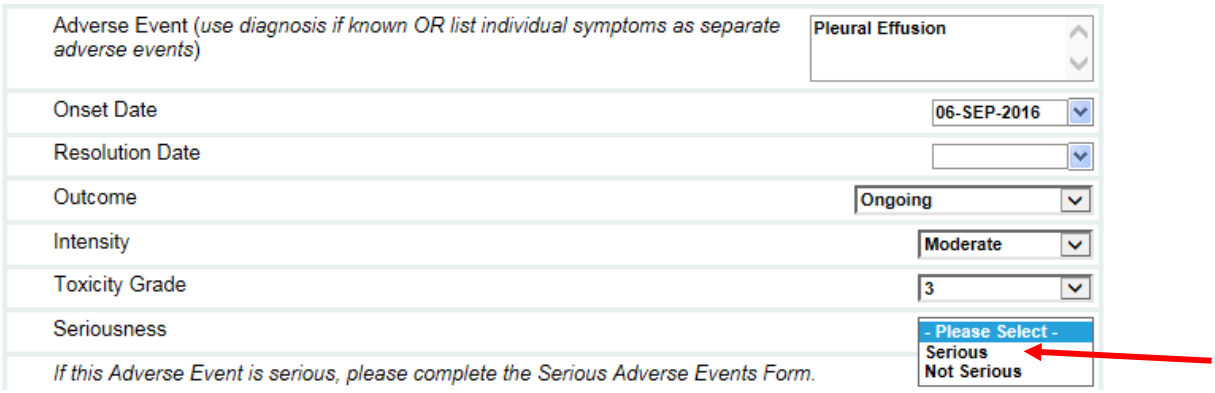
Only the approved RSI will be used for the expectedness assessment

- Any Serious Adverse Reaction (SAR) which is not listed in the approved RSI will be a SUSAR
- If an SAE from your site is reported as a SUSAR you may be contacted and asked to provide additional information
- The Sponsor and Trial Office will be responsible for reporting the SUSAR, however you should check your local policies and procedures to determine any local actions required (i.e. reporting to your R&D department)

Recording SAEs in the electronic Case Report Form (eCRF)

Once an SAE has been reported via the reporting form, it must also be recorded in the eCRF as an AE page marked as 'serious'.

This is because we require details of the event for the main trial analyses and also generate safety data listings using the eCRF; therefore, we need this record to be as current and as accurate as possible.



If an event is reported as 'Serious' in the eCRF we would expect to receive an SAE form.

A monthly status report is generated which flags any 'serious' eCRF events for which we have not received an SAE form. These will be followed up with site as will SAEs which have been reported via form but are not entered to the eCRF.

Event Title

The eCRF record of an event must match the SAE form exactly (where possible).

For example the event title should be the same for both. This is in order to assist in reconciliation between the eCRF and SAE receipt listings. Exact matching of terms allows automatic comparison between eCRF listings and SAE report listings. This reduces error and ensures consistency between the information in the eCRF listings and SAE listings.

However, if there is more than one overall diagnosis or if there is no diagnosis (just symptoms) these will need to be split for recording in the eCRF. For example 'Diarrhoea and Vomiting' may be the title of the SAE on the form. This will require two separate serious AE pages in the eCRF, one for 'Diarrhoea' and one for 'Vomiting'. The SAE report reference

number (i.e. S2 SAE N0000XXXX.XXXX.0X) should be added as a comment in the comment field of both AE eCRF pages to clarify that they are part of a single SAE report.

Event Dates and Resolution Status

Onset dates and resolution dates MUST be identical between the SAE form and eCRF (see below for certain exceptions).

Both should reflect the source data and therefore there should be no variation. Each need to be accurate for reporting and analysis.

Resolution Status must also be the same. If an event has not yet resolved there is only the option of ‘ongoing’ in the eCRF. This should therefore be selected- however if an SAE form records status of ‘present and unchanged’, ‘deteriorating or improving’ the eCRF will record the event as ‘ongoing’.

Action taken

This should match section 19 of the SAE form exactly.

Please note however that there is no option in the eCRF for ‘hospitalisation’. If hospitalisation is the only action selected in section 19- ‘No action taken’ will be selected in the eCRF. However in all other circumstances there should be no difference between entries.

Any action that is reported on the SAE form as being taken and detailed in the narrative should be reflected elsewhere in the eCRF e.g. drug interruptions should be recorded in the Study Drug Log, medications taken should be added to the eCRF list of concomitant medications. Once again details should match.

Multiple Admissions for a Single Event

A patient may experience a single adverse event that requires hospital admission on more than one occasion.

Unfortunately this type of repeat admission is not addressed in the protocol and therefore submission of a separate SAE reporting form is required for each admission. *However* please do not record each admission as a separate AE page in the eCRF as this would lead to over-reporting of the event in the trial data analysis. Please create one AE page with title of event with start date and end date when the event is finally resolved.

In the above cases, sites will be asked to submit a new SAE form for each admission however on each form the start and resolution dates, event title and action taken will be the same. This is because we ask that the entire duration of the event is captured on each form (rather than details relating to the admission only). Each SAE form for an event will therefore be virtually identical to the others. The only difference between forms should be the dates of admission and discharge (which should be recorded in the case description (Question 12 page 1 or narrative page 3 on each form). Ideally the multiple admissions should be flagged on the case description on page 1 so that the report is easily identifiable as relating to multiple admissions.

It is likely that every time a new SAE form is submitted existing forms for the same event will need to be updated.

In terms of eCRF recording- a single Adverse Event eCRF page should be entered for the event selecting 'Serious' option to record as SAE. The site should be asked to record a comment which states that multiple hospital admissions related to the event and listing all relevant SAE reference numbers.

Downgrading SAE Reports

On occasion it may be necessary to downgrade an SAE report to 'Not Serious'. For example in situations where additional information is received which confirms that the event does not meet the expedited reporting criteria.

In these situations, the PI or delegated Co-Investigator should add a comment to the SAE reporting form to confirm that the event has been downgraded. A reason for the downgrade should also be recorded on the form and this should be signed by the PI/Co-Investigator.

The form should then be re-faxed to the Trial Office where you will receive an email to confirm that the event has been downgraded. If the decision is taken to query or not accept the downgrade, this will be confirmed/queried via email.

Detailed Guidance on SAE Form Completion

Detailed guidance on each section of the SAE form and the data required can be found below.

SAE Form Completion

Key to Status	
C	Critical Data (must be provided on the SAE form and will be followed up completely)
N	Not critical data and not usually followed up
N*	Not critical data however if provided this will be followed up for accuracy (there is a slight exception for con meds see relevant section for details)

Field	Status	Requirement	Explanation
1. Report Type	**N**	Please tick to confirm if this is an Initial or Follow-up.	We need to know whether this is an initial report or contains follow-up information on a report that has already been submitted.
2. Local Case ID	**N**	You do not need to add anything here as we do not use this information however you can add your own reference if required for your systems.	
3. Country	**C**	This is Pre- Populated on the Form and will always be UK.	

Demographic Information

Field	Status	Requirement	Explanation
4. Date of Birth	**C**	Needs to be accurate and match eCRF data.	Is used by us to check that the age at onset is accurate.
5. Age	**C**	Should be the patient's age at the onset of the event (not their age on the date the report is submitted). The form requests years and months however if whole years only are reported (i.e. 55) this is acceptable.	The DOB is removed prior to onward reporting to the Sponsor and manufacturer therefore we require an accurate age at onset to be recorded.
6. Race	**N**	Requests that race is selected however can be left blank.	This is not an essential piece of data however it is important that when providing details of abnormal lab results- any relevant information regarding ethnicity is provided as a comment.
7. Sex	**C**	Should select Male or Female.	Necessary for medical review and onward reporting.
8. & 9. Height & Weight	**N**	Height in cm and weight in kg (to the nearest whole cm or kg is fine). However can be left blank.	You may not have current information (especially on weight). However we may need to request this if a SUSAR is reported.

Adverse Event Information

Field	Status	Requirement	Explanation
10. Onset of First Sign/ Symptoms of SAE	**C**	Should be the date of the very first signs or symptoms of the event (regardless of whether the event would be considered serious or not at that point). For example a patient may be admitted to hospital following a three day history of sore throat. The event start date would be start of the sore throat (i.e. three days prior to the admission date). Date can be in any format however wherever possible should be exact (i.e. avoid 'unknowns'). If the start is not know the first date reported or the date of a definitive diagnosis would be ok (as long as specified).	We are interested in the duration of the adverse event from the very start of symptoms to complete resolution (where applicable).
11. Date of Death	**C**	Date can be in any format however MUST be exact (i.e. no 'unknowns'). Can be left blank if not applicable**.**	Required information for onward reporting.
12. Serious Adverse Event in Medical Terms	**C**	Should be the **medical condition /overall diagnosis**. This may not be evident at the initial point of reporting and therefore it is acceptable to provide signs or symptoms until a diagnosis is confirmed or suspected. If a diagnosis is suspected but not confirmed record the event followed by 'suspected' e.g. 'Pneumonia (suspected)'. This can be updated and 'suspected' removed if the event is confirmed however for events that are never confirmed leaving the suspected comment is fine. Should be as specific as possible with diagnosis (in terms of infection type, location, severity (if the condition can occur with varying severity). 'Left pleural effusion' or 'bilateral pleural effusion' are preferable to just 'pleural effusion'. Where a patient has been admitted for a procedure (for example for elective surgery). The event will be the condition which the surgery is used to treat and not the surgery itself. For example 'Hip Replacement' would not be an acceptable event title however	We want to capture the underlying event rather than the symptoms, treatment or outcome (these are captured elsewhere on the form).

		'Osteoarthritis left hip' (if the condition being treated) would be acceptable. Details of the surgery and admission dates can then be added to the event narrative. Where a procedure is being used to treat a concurrent condition the event title should reflect the condition but also the reason that action has been taken. For example if the above patient had osteoarthritis in their left hip at trial entry, it may be that worsening of this condition led to the surgery. In this case the event title would be 'Worsening Osteoarthritis Left Hip'. If a hospital admission is for a combination of events- these can all be reported on one form (however they will need to be reported as separate AE pages when entered on the eCRF). Death is an outcome and therefore **should not be** reported as an event. Cause of death (or suspected cause until confirmed) should be reported as the event.	
Case Description	**N**	Details of signs and symptoms and admission dates etc. can be added here. However it can be left blank especially if further information is added on page 3.	
Efficacy and Progression of Underlying illness questions	**N**	Tick to select if due to these.	Details relating to contributing factors should be added in the narrative also.
13. Expedited Reporting Criteria	**C**	Must select all relevant criteria by ticking **all** relevant boxes. Multiple criteria can be selected.	This is required for onward reporting and also in determining reporting timelines for SUSARs. Failure to select all reporting criteria may lead to late reporting to the regulatory authorities.
14. Assessment of Causality	**C**	Must be completed by ticking against 'Suspected' or 'Not Suspected'. If unsure sites should take a conservative approach and tick 'Suspected'. Needs to be determined by PI or Co-Investigator (on delegation log. A signature on the SAE form (page 2 or 3) is acceptable authorisation however if causality is updated/changed they should counter sign and date against the update.	

Trial Drug Information

Field	Status	Requirement	Explanation
15. Trial Drug	**C**	The relevant drug must be selected by ticking the appropriate box.	Key data required for safety review and onward reporting.
16. Dose at or Before Onset of SAE	**C**	The dose of IMP the patient was taken at the time the event started should be specified i.e. this will be whatever dose they took the day before the event.	Key data required for safety review and onward reporting.
17. Trial Indication	**C**	Pre-Populated.	Always CML
18. Therapy Initiation Date	**C**	The date the patient first started to take the IMP (regardless of whether there have been any changes since then) should be recorded. If the patient was still taking IMP at the onset of the event there is no requirement to enter anything in the 'to' box however sites can enter 'ongoing'. If drug was interrupted prior to the event, the dose at onset should be marked as 0 and the narrative should refer to how long since interruption. If the IMP was interrupted or discontinued due to this event- the interruption date should **not** be recorded in the 'to' box. If the patient permanently discontinued prior to the event but the event occurred within the 28 day reporting period the date of discontinuation should be recorded in this box.	Provides details of how long the patient has been on the treatment as a whole. Having only the permanent discontinuation date in the 'to' box makes it easier to identify reports which relate to events occurring after treatment discontinuation.
19. Action Taken	**C**	All relevant boxes relating to the action taken should be ticked. If section 13 specifies hospitalisation as an expedited reporting criteria section 19 needs to have hospitalisation ticked. No Action Taken should only be selected where the patient was not admitted and no other actions have been taken. It is possible to select interruption and permanent discontinuation	This needs to accurate reflect what action has been taken as a direct result of the event being reported. Non-drug therapy includes procedures/interventions used to treat a condition (surgical treatments, transfusions etc.). However procedures that are exclusively for diagnostic purposes should not be

		(i.e. if a patient stops, briefly restarts but subsequently discontinues both would apply).	reported as non-drug therapy. If you indicate that action has been taken details must be provided on the SAE form narrative page 3. Including - Dates of admission and discharge from hospital (if applicable) - Details of any con meds used- name, dose, frequency and duration (where possible) - Details of any non-drug therapy- name, date of procedure (if applicable). Eg oxygen, IV fluids, insertion of chest drain - Details of any medication dose adjustment or any interruptions- including dates and doses.

Concomitant Drugs and Medical History

Field	Status	Requirement	Explanation
20. Concomitant Drugs	**N***	Any relevant medications the patient is taking for other conditions (i.e. not related to this event) should be specified. It is permissible to leave blank or to record a comment to state that the eCRF listing should be referred to. Anything listed here must be recorded on the eCRF list of con meds. Drugs listed on SAE forms but not on the eCRF will be followed up with site. However discrepancies in terms of dose, frequency or indication will not be followed up. Data in the eCRF will be treated as the accurate source of information on these factors.	If further information on con meds is required (for example for SUSAR reporting) this will be requested.
21. Patients Past Medical History	**N***	Any relevant medical history (including earlier AEs) should be recorded here. It is permissible to leave blank if none of the patient's medical history is relevant to the event.	If further information was needed (for example for SUSAR reporting) this will be requested

		Anything listed here must be recorded on the eCRF as medical history or an AE page and discrepancies will be followed up. However if the difference relates to the use of interchangeable names/terms only, this will not be followed up.	

Test Results and Event Outcome

Field	Status	Requirement	Explanation
22. Test/Laboratory Findings	**N***	These are not mandatory however it there are relevant abnormal results these should be provided. This includes X-ray results.	These are required for the safety review of the event and to provide context.
23. Comments on Tests/Laboratory Findings	**N***	See above.	See above
24. Outcome of the Patient/SAE	**C**	Must be provided via tick box. A resolution date must be provided for a status of 'Completely Recovered' or 'Recovered with Sequelae'. Where multiple boxes are ticked – for example where the status has changed between updates, the most recent tick will be taken as the correct status the previous status should be crossed through on any updates. For Death the Autopsy question must be answered by ticking the relevant box. The death date should be recorded on page 1 (field 13).	This is required for onward reporting and therefore needs to be accurate and up-to-date.

Information Source

Field	Status	Requirement	Explanation
25. Name, Address and Telephone Number of Investigator	**C**	We require the name and signature of the investigator (this can be the PI or a Co-Investigator who is on the delegation log). The address and telephone numbers do not need to be added. However if there is just a signature with no name this is not acceptable as it is not always possible to determine who the signature belongs to and whether they are on the site delegation log. The signature can be on the declaration box on page 2 or page 3 (or both). However if the event title or causality on the form are updated the form must be re-signed or the changed area countersigned by the PI or a Co-Investigator.	The form needs to be authorised by a delegated PI or Co-Investigator as this is a regulatory requirement In signing they are signing to agree with the event, the fact that it is serious and also the causality.
26. Reporting Date by Investigator/Person reporting the Event	**N**	It is helpful if a date is provided however in the absence of a date it will be assumed that the report was completed on the day of receipt. Again the site can enter details on page 2, page 3 or both. If information is on one of the pages it doesn't need to be added to the boxes on the other page. Any changes to the form MUST be initialled and dated with the date of change however a new date in this field is not required.	
Additional Information	**N**	On certain occasions it may be possible for all the relevant information to be included in the event title and case description fields. However it is likely that information will need to be included on page 3. If it has been indicated that con meds or non-drug therapies have been used for the event, these should be specified here. Dates of any study drug interruptions or discontinuations should also be added here. This section should also be used to record details of any changes	

		in condition.	

Study Drug Manufacturer Information- This does not require completion.

Other parts of the form

Field	Status	Requirement	Explanation
Site Name	**C**	Should be as recorded on the CTAg.	This will be used to confirm that the patient is registered at that trial site for SPIRIT 2. It also allows alternative contacts to be identified if the named contacts are not available.
Site Number	**N**	Should be the 7 digit site number (starting N00…….). This is useful as an additional.	
Subject Number	**C**	Should be the four digit trial ID number.	This will be used to confirm that this report is for the correct patient.
Subject Initials	**C**	Should be a minimum of two initials. If three initials are recorded in the eCRF as long as the first name and last name ones match this is ok (and vice versa). Note: If a patient has changed surname since they were initially recruited (i.e. if married) this should be flagged on the form.	This will be used to confirm that this report is for the correct patient.
Contact For Queries	**C**	Should be the name and email address at a minimum (ideally telephone number too) of the person submitting the initial report. There is no requirement for this to be updated if someone else updates the report (as there is limited room) however a cover sheet with contact details is advised. If it is not possible to contact the named contact and a cover sheet has not been provided. The site contacts in CTMS will be approached with queries (including the site PI). The contact should be on the delegation log however may be a clinical or administrative staff member.	We need a named contact for queries and to ensure that these are responded to in a timely manner.