

## **PROTOCOL TEMPLATE FOR CLINICAL TRIALS WITHIN THE SIOPE/ENCCA NETWORK**

### **WORK INSTRUCTION:**

This template provides the minimum information required for trials involving an Investigational Medicinal Product (IMP).

For trials not employing an IMP, information relating to the chemotherapy, IMP, co-medication etc. may be removed and replaced with more relevant information for the research treatment being investigated. The template contains references to ICH GCP as well as any EU Clinical Trials Directive (EU CTD) regulations. ICH GCP section 6 describes what items should be covered in the protocol, however, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed may be contained in other protocol referenced documents, such as an Investigator's Brochure or Pharmacy File (ICH GCP section 7)

### **DEVELOP PROTOCOL**

Refer to this template when developing a protocol to ensure all the minimum requirements are met and ensure all the main headers are included.

Follow the instructions below when developing a protocol using this template:

- Delete the first two sections of this document, i.e. the header page and the pages containing these instructions
- Update header and footer as appropriate
  - o Ensure page numbering (page x of y) is used and appears on each separate page
  - o Ensure the protocol version number (e.g. version 0.1, version 0.2 (for drafts) or version 1.0, version 2.0 etc (for final versions)) and date (e.g. 12<sup>th</sup> May 2007) appears on each separate page
  - o For non-substantial amendments consider using a suffix e.g. version 1.0a
- Ensure the header and footer are deleted from the protocol coversheet
- Ensure all the main headers are included (with the exception of the header 'Amendments' for the first version of the protocol); maintain the order of the headings, where possible
- Add/delete sub-headings as applicable: the sub-headings are optional and should be used only if relevant to the particular trial
- Follow the instructions in *red italic text* given under the headings
- Remove the instructions whilst inserting the information required under each heading
- Text highlighted **grey** refers to ICH GCP and EU CTD regulations and offers guidance on the type of information that may be included in that section
- Wherever brackets < > are seen around a word, insert the relevant information into the text, delete the brackets and correct the font

## Protocol template for Clinical Trials within the SIOPE/ENCCA network

---

- All passages in black ink are suggested text for inclusion in the protocol, however changes should be kept to a minimum
  - o Where the protocol is not being developed for a clinical trial the word 'trial' may be substituted with 'study' or 'research project'
  - o Adapt to the treatment being studied e.g. chemotherapy maybe substituted with radiotherapy
- Ensure any instructions in *red italic text* and/or grey highlighted text are removed prior to finalising the protocol
- Ensure the use of abbreviations and terminology is consistent throughout the protocol
- If logos are used (e.g. funders) ensure prior permission is sought

The lay-out used in this template may be adjusted to bring the document in line with other trial specific documents. Changes should be kept to a minimum as this will help users of the SIOPE /ENCCA protocols to become used to a standard template protocol, regardless of the trial that the protocol is used in.

*<insert protocol cover sheet here; do not include header and footer>*

---

## INTRODUCTORY PAGES

*The following should be included in the introductory pages of the protocol (where applicable):*

- Protocol title
- Protocol short name or acronym
- Protocol version and date
- Protocol identifying number
  - o *The protocol should include:*
    - *EudraCT number (for IMP trials)*
    - *Sponsor number (a unique identifier assigned by the Sponsor to the trial)*
    - *ISRCTN reference number (The ISRCTN is a simple numeric system for the unique identification of randomised controlled trials worldwide and is available via <http://www.isrctn.org/>)*
    - *Other identifiers in accordance with the regulatory requirements of the nation state(s)*
- Any amendment(s) should also bear the amendment number(s) and date(s) and need to be provided also with tracked changes
- Name and address of the Sponsor and monitor (if other than the Sponsor)
- Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the Sponsor
- Name, title, address, and telephone number(s) of the Sponsor's medical expert for the trial
  - o *This would typically be the Chief Investigator in the lead nation state*
- Name and title of the Lead Principal Investigators who are responsible for conducting the trial in the respective nation states, and the address and telephone numbers of any relevant advisory groups, committees or panels related to the running of the trial study committee, name etc. → experts involved in protocol design and writing
- Name, title, address, and telephone number(s) of the qualified physician who is responsible for all trial-site related medical decisions (if other than investigator)
  - o *This would typically be the Chief Investigator and any Clinical Coordinators*
- Name and address of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial
  - o *E.g. Pathology, laboratories conducting translational sub-study analysis, regional coordinating centres, Quality of Life centres*
- The protocol should be signed by the Sponsor and Chief Investigator

*All contacts should only be listed according to their role in the trial; ie Trial Management Group, DMC, etc. even where listed in multiple indications above.*

*Telephone numbers of medical personnel would normally be listed as that of a switchboard or a secretary, not personal or mobile numbers.*

*Ensure the protocol cover sheet does not include the header and footer. Note: As per EC guidance (ENTR/CT 2) the protocol should be signed by the CI of the nation state and by the Sponsor.*

**SIGNATURE PAGE**

<insert trial name> Trial Protocol <insert version number and date>

This protocol has been approved by:

**Name:** <insert name of Chief Investigator> **Trial Role:** Chief Investigator

**Signature:** \_\_\_\_\_ **Date:** DD / MON / YYYY

**Name:** <insert name of Sponsor's representative> **Trial Role:** <insert role of Sponsor's representative >

**Signature:** \_\_\_\_\_ **Date:** DD / MON / YYYY

*Consider having the signature page immediately inside the front cover of the protocol.*

This protocol describes the <insert trial name> trial and provides information about procedures for patients taking part in the <insert trial name> trial. **The protocol should not be used as a guide for treatment of patients not taking part in the <insert trial name> trial.**

---

*Where appropriate include a summary of protocol amendments; this section should be omitted in the first version of the protocol*

**AMENDMENTS**

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

e.g. Sponsor & CI need to keep tracked changes versions of each amendment even if cleared for distribution

<b>Amendment number</b>	<b>Date of amendment</b>	<b>Protocol version number</b>	<b>Type of amendment</b>	<b>Summary of amendment</b>
<i>1</i>	<i>28th Oct 2005</i>	<i>2.0</i>	<i>Substantial amendment</i>	<i>Change in eligibility criteria</i>
<i>N/A</i>	<i>15th Sep 2006</i>	<i>2.0a</i>	<i>Non-substantial amendment</i>	<i>Change in trial contact details</i>
<i>2</i>	<i>16th Oct 2007</i>	<i>3.0</i>	<i>Substantial amendment</i>	<i>Change in max. number of chemotherapy cycles a patient may receive from 6 to 10</i>

## **TRIAL SYNOPSIS**

*As a guide this should be no longer than 2 sides of A4*

Example sub-headers include:

**Title**

**Name of Chief Investigator**

**Name Sponsor**

**Trial Design**

*E.g. prospective, phase III, international, 2 arm, multicentre, randomised, double-blinded clinical trial*

**Objectives (primary, secondary)**

**Outcome Measures**

**Treatment details**

**Patient Population**

**Sample Size**

**Main Inclusion and Exclusion Criteria**

**Trial Duration**

**Trials Office Contact Details**

**Trial Schema**

*E.g. Diagrammatic representation e.g. from screening through to follow up, treatment allocation*

**Schedule of Events**

*In complex multi-arm trials a schema should direct the reader to the relevant schedule of events. This can be best presented in a table. Each schedule should include all trial investigations and assessments.*

**Abbreviations**

*Include a list of all abbreviations used in the main text*

---

**Table of contents**

<b>1. Background and Rationale</b> .....	<b>3</b>
1.1 Background.....	3
1.2 Trial Rationale.....	3
1.2.1 Justification for patient population .....	<b>Error! Bookmark not defined.</b>
1.2.2 Justification for design .....	<b>Error! Bookmark not defined.</b>
1.2.3 Choice of treatment .....	<b>Error! Bookmark not defined.</b>
<b>2. Aims, Objectives and Outcome Measures</b> .....	<b>3</b>
2.1 Aims and Objectives.....	3
2.2 Outcome Measures .....	3
<b>3. Trial Design</b> .....	<b>3</b>
<b>4. Eligibility</b> .....	<b>4</b>
4.1 Inclusion Criteria.....	4
4.2 Exclusion Criteria.....	4
<b>5. Screening and Consent</b> .....	<b>4</b>
5.1 Screening.....	4
5.2 Informed Consent .....	4
<b>6. Trial Entry</b> .....	<b>5</b>
<b>7. Treatment Details</b> .....	<b>5</b>
7.1 Trial Treatment .....	6
7.2 Treatment Schedule .....	6
7.3 Assessments <i>Use of tables is encouraged</i> .....	6
7.3.1 Blood chemistry .....	<b>Error! Bookmark not defined.</b>
7.3.2 Haematology.....	<b>Error! Bookmark not defined.</b>
7.3.3 Physical examination/symptom assessment.....	<b>Error! Bookmark not defined.</b>
7.4 Sample Collection.....	<b>Error! Bookmark not defined.</b>
7.4.1 Archival Tumour samples <i>Including address/site of collecting centre &amp; make sure informed consent is given for sample collection!</i> .....	<b>Error! Bookmark not defined.</b>
7.4.2 New blood or tissue samples.....	<b>Error! Bookmark not defined.</b>
7.5 Dose Modifications .....	6
7.6 Treatment Compliance <i>Consideration should be given as to how this will be monitored, particularly if oral formulations are used. Patient diaries and drug reconciliation by pharmacy</i> .....	6
7.7 Supportive Treatment.....	6
7.8 Concomitant Medication .....	6
7.9 Patient Follow Up .....	6
7.10 Patient Withdrawal.....	6
<b>8. Adverse Event Reporting</b> .....	<b>6</b>
8.1 Reporting Requirements.....	7
8.1.1 Adverse Events.....	7
8.1.2 Serious Adverse Adverts .....	7
8.1.3 Reporting period .....	10
8.2 Reporting Procedure .....	10
8.2.1 Site.....	10
8.2.2 Trials Office <i>e.g. either the national co-ordinating centre or Sponsor</i> .....	11
8.2.3 Reporting to the CA(s) and EC(s).....	11
8.2.4 Investigators .....	12
8.2.5 Data Monitoring Committee.....	12
8.2.6 Manufacturer of Investigational Medicinal Product.....	12



---

8.2.7	Reporting to the Ethics Committee(s) according to national requirements.....	12
8.2.8	Investigators .....	12
8.2.9	Data Monitoring Committee.....	12
<b>9.</b>	<b>Data Handling and Record Keeping .....</b>	<b>12</b>
9.1	Data Collection .....	13
9.2	Archiving.....	14
<b>10.</b>	<b>Quality Management .....</b>	<b>14</b>
10.1	Site Set-up and Initiation .....	14
10.2	On-site Monitoring .....	14
10.3	Central Monitoring .....	15
10.4	Audit and Inspection .....	15
10.5	Notification of Serious Breaches .....	15
<b>11.</b>	<b>End of Trial Definition .....</b>	<b>15</b>
<b>12.</b>	<b>Statistical Considerations .....</b>	<b>16</b>
12.1	Power Calculations .....	17
12.2	Definition of Outcome Measures .....	<b>Error! Bookmark not defined.</b>
12.2.1	Primary outcome measures.....	<b>Error! Bookmark not defined.</b>
12.2.2	Secondary outcome measures.....	<b>Error! Bookmark not defined.</b>
12.3	Analysis of Outcome Measures.....	17
12.4	Planned Sub Group Analyses .....	17
12.5	Planned Interim Analysis .....	17
12.6	Planned Final Analyses .....	17
<b>13.</b>	<b>Trial Organisational Structure.....</b>	<b>17</b>
13.1	Sponsor .....	17
13.2	Coordinating Centre .....	17
13.3	Trial Management Group.....	18
13.4	Trial Steering Committee.....	18
13.5	Data Monitoring Committee.....	18
13.6	Finance .....	18
<b>14.</b>	<b>Ethical Considerations .....</b>	<b>18</b>
<b>15.</b>	<b>Confidentiality and Data Protection .....</b>	<b>19</b>
<b>16.</b>	<b>Insurance and Indemnity .....</b>	<b>19</b>
<b>17.</b>	<b>Publication Policy .....</b>	<b>20</b>
<b>18.</b>	<b>Reference List.....</b>	<b>20</b>
	<b>Appendix 1 - Tumour Staging - .....</b>	<b>20</b>
	<b>Appendix 2 - WMA Declaration of Helsinki .....</b>	<b>20</b>
	<b>Appendix 3 - Definition of Adverse Events.....</b>	<b>20</b>
	<b>Appendix 4 - Common Toxicity Criteria Gradings .....</b>	<b>22</b>
	<b>appendix 5 – definitions.....</b>	<b>22</b>

---

## 1. BACKGROUND AND RATIONALE

*ICH GCP and the EU CTD specify that the following should be included:*

- ICH GCP section 6.2.1 Name and description of the investigational product(s). 4
- ICH GCP section 6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial. 1B
- ICH GCP section 6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects. 5 IMP only
- ICH GCP section 6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).6 IMP only
- ICH GCP section 6.2.6 Description of the population to be studied. 2B
- ICH GCP section 6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial. 1A
- EU CTD requirement: A discussion of the relevance of the clinical trial and its design 2A
- EU CTD requirement: An evaluation of the anticipated benefits and risks 3
- EU CTD requirement: A justification for including subjects who are incapable of giving informed consent or other special populations 2C

### 1.1 Background

### 1.2 Trial Rationale

## 2. OBJECTIVES AND OUTCOME MEASURES

*ICH GCP specifies that the following should be included:*

- ICH GCP Section 6.3 A detailed description of the objectives and the purpose of the trial.
- ICH GCP section 6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

*Provide a succinct overview of the aims/goals of the trial and then define the primary and secondary objectives to be answered by the trial*

*Example sub-headers include:*

### 2.1 Objectives

### 2.2 Outcome Measures

*Include trial endpoints*

## 3. TRIAL DESIGN

ICH GCP section 6.4 states that the scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include (if not covered in other sections):

- ICH GCP section 6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- ICH GCP section 6.4.3 A description of the measures taken to minimize/avoid bias, including:
  - o Randomization.
  - o Blinding.

- 
- ICH GCP section 6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
  - ICH GCP section 6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

## 4. ELIGIBILITY

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.5.1 Subject inclusion criteria.
- ICH GCP section 6.5.2 Subject exclusion criteria.

*In complex multi-arm trials consistency should be maintained for all arms wherever possible and these should form the core criteria. Specific criteria for individual arms should be clearly identified as additional to the core criteria.*

*Example sub-headers include:*

### 4.1 Inclusion Criteria

### 4.2 Exclusion Criteria

## 5. SCREENING AND CONSENT

*EU CTD indicates that the following should be included:*

- EU CTD requirement: a description of the recruitment and informed consent procedures, especially when subjects who are (temporarily or permanently) incapable of giving informed consent are included or when a procedure with witnessed consent is to be used

*Example sub-headers include:*

### 5.1 Screening

*If relevant*

### 5.2 Informed Consent

*If there are multiple Patient Information Sheets (PIS) and Informed Consent Forms (ICF) the text should be amended to reflect this fact. In addition a paragraph explaining the purpose of the different Patient Information Sheets and Informed Consent Forms may be required.*

It is the responsibility of the Investigator *<specify in parenthesis any others allowed to take consent (e.g. Research Nurse if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the Site Signature and Delegation Log)>* to obtain written informed consent from the patient or an approved guardian prior to performing any trial related procedure. A Parent/guardian and age-specific patient Information Sheets are provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The parent/approved guardian and /or patient should be given ample time (e.g. 24 hours *<or specify trial specific alternative>*) to read the Information Sheet and to discuss their participation with others outside of the site research team. They must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the parent/approved guardian and/or patient to refuse to participate in the trial without giving a reason must be respected.

If the parent/approved guardian and/or patient expresses an interest in the patient participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator *<and if applicable specify "or designate">* must then sign and date the form. A copy of the Informed Consent Form should be given to the parent/approved guardian and/or patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once

the patient is entered into the trial the patient's trial *<or specify registration>* number should be entered on the Informed Consent Form maintained in the ISF.

*<If review of Informed Consent Forms is being performed by a centralised body such as a national co-ordinating centre, the following text should also be included "In addition, if explicit consent has been obtained, a copy of the signed Informed Consent Form must be sent in the post to the <insert relevant body> for review"*

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include who was present, date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Parent/patient Information Sheet and Informed Consent Form. Throughout the trial the parent/approved guardian and/or patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Parent/approved guardian and/or patient Information Sheets and Informed Consent Form are available from the *<insert relevant body>* and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General/Medical Practitioner should also be informed that they are taking part in the trial. A Letter to their General/Medical Practitioner should be provided for this purpose.

## 6. TRIAL ENTRY

## 7. TREATMENT DETAILS

This section should include a description of the treatment details including IMPs and NIMPS. The IMPs should be clearly identified in the trial protocol

Below are details of the information required by ICH GCP and the EU CTD for the IMPs defined in the trial protocol

*ICH GCP and the EU CTD specify that the following should be included:*

- ICH GCP section 6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- ICH GCP section 6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- ICH GCP section 6.6.3 Procedures for monitoring subject compliance.
- ICH GCP section 6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- ICH GCP section 6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- EU CTD requirement: a description of the plan for the provision of any additional care of the subjects once their participation in the trial has ended, where it differs from what is normally expected according to the subject's medical condition.
- ICH GCP section 6.7.1 Specification of the efficacy parameters.
- ICH GCP section 6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.
- ICH GCP section 6.8.1 Specification of safety parameters.

- 
- ICH GCP section 6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.
  - ICH GCP section 6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
    - o When and how to withdraw subjects from the trial/ investigational product treatment.
    - o The type and timing of the data to be collected for withdrawn subjects.
    - o Whether and how subjects are to be replaced.
    - o The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

*Examples of sub-headers include:*

## **7.1 Trial Treatment**

*Ensure details of IMPs and NIMPs are included;*

*Consider method for calculating Body Surface Area (BSA) and/or consider asking sites to confirm method used.*

## **7.2 Treatment Schedule**

## **7.3 Assessments**

*Use of tables is encouraged*

## **7.4 Dose Modifications and delays**

## **7.5 Supportive Treatment**

## **7.6 Concomitant Medication**

## **7.7 Patient Follow Up**

## **7.8 Treatment Compliance**

*Consideration should be given as to how this will be monitored, particularly if oral formulations are used. Patient diaries and drug reconciliation by pharmacy*

## **7.9 Patient Withdrawal**

# **8. SUB-STUDIES**

*Description of any sub-studies and biological studies could be included here*

# **9. ADVERSE EVENT REPORTING**

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.
- ICH GCP section 6.8.4 The type and duration of the follow-up of subjects after adverse events

*Reference appropriate product information against which SAEs will be categorised e.g. (compendium of) Summary of Product Characteristics, Investigator Brochure, protocol (non-IMP)*

---

*Refer to Appendix 3 for standard definitions of all types of Adverse Events. This should be specifically included either within the body of the protocol or as an appendix referred to within the body of the protocol.*

*IMP trials*

The collection and reporting of Adverse Events (AEs) will be in accordance with the requirements of the Competent Authority. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the *<insert appropriate Summary of Product Characteristics or Investigator Brochure>*..

*Non-IMP trials*

The collection and reporting of Adverse Events (AEs) will be in accordance with the appropriate competent authorities. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

## 9.1 Reporting Requirements

*This section should include information about the types of AEs for which data will be collected and any exclusions to the reporting process.*

*The type and extent of AE data collected for an individual trial should be risk based. For example it is anticipated that all early phase trials will collect all AEs however phase III trials utilising well characterised IMPs may choose to collect data on selected Adverse Reactions or SAEs only.*

*Standard sub-headers are shown below with examples of text which can be utilised in different scenarios.*

### 9.1.1 Adverse Events

*Example of text for trials collecting all AEs*

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this includes abnormal laboratory findings.

*Example of text for trials collecting selected ARs*

AEs (see Appendix 3 for definition) are commonly encountered in patients receiving chemotherapy. As the safety profiles of the Investigational Medicinal Products used in this trial are well characterised, only Adverse Reactions (ARs) experienced during treatment will be reported (*see section 9.2.1.1 for definitions*).

### 9.1.2 Serious Adverse Advents

***SAEs must be collected for all trials, for example:***

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) *<and are not excluded from the reporting process as described below>*.

#### 9.1.2.1 Events that do not require expedited reporting

*It is possible to excluded SAEs from expedited (immediate) reporting by sites. SAEs which are to be excluded from expedited reporting process must be clearly defined in the protocol and the type of event that is excluded should be restricted to those events which generate large volumes of SAEs.*

*An example is given below:*

Patients receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial:

- Admissions to control symptoms of nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression, for example an episode of febrile neutropaenia, unless this proves fatal or requires admission to a high dependency or intensive care facility

---

An SAE should be reported according to the specific reporting requirements of the trial and in compliance with national/international regulations.

### 9.1.2.2 Events that do not require reporting on a Serious Adverse Event Form

*This section should be used to list SAEs which will not be captured using an SAE form.*

*Events that do not require reporting on an SAE Form include*

- A) Those events that do not require reporting because they fall outside of the definition of an SAE (see Appendix 3).
- B) SAE related to IMPs (Serious Adverse Expected Reactions SAR) that has been defined in the protocol as expected. Expected Serious Adverse Reactions (SARs) can be captured on an Expected SAR Form or on a toxicity form rather than an SAE Form/reporting procedure. These events do not require expedited (immediate) reporting by sites.

The data collected for this type of event is significantly less than that collected for an SAE. Such events do not require expedited reporting by site and do not require evaluation by the clinical co-ordinators (as they are by definition expected). Again the number of Expected SARs should be restricted to common events

*For example:*

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - o Protocol defined treatment
  - o Pre-planned elective procedures unless the condition worsens
  - o Treatment for progression of the patient's cancer
- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

The following events should be reported on an Expected SAR Form rather than an SAE Form:

- Admissions to control symptoms of nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression unless this proves fatal or requires admission to a high dependency or intensive care facility; for example; an uncomplicated febrile neutropenic episode

Expected SAR Forms should be completed and returned in the post as soon as possible.

### 9.1.2.3 Expected Serious Adverse Events

*This section is compulsory for non-IMP trials.*

*This section can be used to list expected and related SAEs that will not be reported for the purposes of the trial. It would replace the section "Events that do not require reporting on a Serious Adverse Event Form" listed above.*

*For example:*

We are not expecting any SAEs to occur as a result of participation in this non-interventional study.

The following are regarded as expected SAEs for the purpose of study and should not be reported on an SAE form:

- SAEs that are thought to have occurred as a result of the patient's cancer treatment
- SAEs that are related to a pre-existing condition
- SAEs that are related to symptoms or progression of the patient's cancer
- Death from cancer, as a result of the patient's cancer treatment or from a pre-existing medical condition

---

This is not an exclusive list and Investigators should only report SAEs that are attributable to the study protocol.

#### 9.1.2.4 Monitoring pregnancies for potential Serious Adverse Events

*This section should be included for all trials where there is a risk of congenital anomalies or birth defects in the offspring of patients as a result of their participation in the trial. If relevant, for female patients consent to collect this information may be addressed in the main trial Patient Information Sheet or a separate pregnancy release of information form for pregnant trial patients and/or partners of trial patients may be used.*

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

*Examples of possible text:*

*For trials involving females only (and where pregnancy is addressed in the main trial PIS) include:*

In the event that a patient becomes pregnant during the SAE reporting period it should be reported to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* as soon as possible. Provide details of the subsequent outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving females only (and where pregnancy is not addressed in the main PIS) include:*

In the event that a patient becomes pregnant during the SAE reporting period please notify the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* as soon as possible. The patient should be given a *<insert pregnancy release of information form or appropriate form name>*. If the patient is happy to provide information on the outcome of their pregnancy they should sign the *<insert pregnancy release of information form or appropriate form name>*. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving males only include:*

In the event that a patient's partner becomes pregnant during the SAE reporting period please notify the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* as soon as possible. The patient should be given a *<insert pregnancy release of information form or appropriate form name>* to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the *<insert pregnancy release of information form or appropriate form name>*. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving both genders (and where pregnancy is addressed in the main trial PIS) include:*

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* as soon as possible. If it is the patient who is pregnant provide outcome data on *<insert pregnancy release of information form or appropriate form name>*. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a *<insert pregnancy release of information form or appropriate form name>* to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the *<insert pregnancy release of information form or appropriate form name>*. Once consent has been obtained provide details of the outcome of the pregnancy and if appropriate also complete an SAE Form as detailed below.

*For trials involving both genders (and where pregnancy is not addressed in the main trial PIS) include:*

In the event that a patient or their partner becomes pregnant during the SAE reporting period please notify the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* as soon as possible. The patient should be given a *<insert pregnancy release of information form or appropriate form name>* or the patient should be asked to give this to their partner. If the patient/partner is happy to provide information on the outcome of their pregnancy they should sign the *<insert pregnancy release of information form or appropriate form name>*. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.



---

### 9.1.3 Reporting period

*This section is mandatory and should include information on the length of the AE reporting period. This should be defined on a trial specific basis.*

*Careful consideration should be given as to when the reporting period will commence. It can be when the patient begins trial treatment or on entry into the trial. However for trials where the screening period includes trial specific tests which may impact on the safety of patients the start date can be the date of informed consent. If the protocol is mandating specific standard chemotherapy prior to trial treatment it may be necessary to include the standard chemotherapy drugs as NIMPs. It is preferable therefore to mandate such standard chemotherapies as inclusion criteria and place the trial entry point as close to possible to the start of the actual trial-mandated treatment.*

*Typically the reporting period will cease 30 days after the patient's last protocol defined treatment, unless there are trial specific assessments that may impact on patient safety scheduled to take place after this 30 day window. If the latter is the case, consider setting the end date in such a way that it allows for reporting of any AEs that may be related to this trial specific assessment.*

*For example:*

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

## 9.2 Reporting Procedure

### 9.2.1 Site

#### 9.2.1.1 Adverse Events

*The version of the CTCAE quoted should be agreed by the Trial Steering Committee.*

*If the CTCAE document is also provided in the Investigator Site File reference can be made to this also.*

*Example of text for trials collecting all AEs:*

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version *<insert appropriate version number>*. Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

*Example of text for trials collecting selected ARs:*

AEs experienced during treatment should be recorded in the toxicity section of the Treatment Form.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version *<insert appropriate version number>*. Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

#### 9.2.1.2 Serious Adverse Events

*This section is used to describe the SAE reporting process.*

*For example:*

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section *<insert section name or number>* of the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE *<insert appropriate version number>*.

---

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be transmitted as defined within the protocol, < insert trial specific details fax, e-mail, RDE database> to <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE < insert details of fax number or email or RDE process >

On receipt the <insert relevant body, eg. National co-ordinating centre, Sponsor> will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the <insert relevant body, eg. National co-ordinating centre, Sponsor>. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the <insert relevant body, eg. National co-ordinating centre, Sponsor> should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the <insert relevant body, eg. National co-ordinating centre, Sponsor> in the post and a copy kept in the ISF.

Investigators should also report SAEs to the relevant bodies in accordance with local practice.

### 9.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

### 9.2.2 Trials Office e.g. either the national co-ordinating centre or Sponsor

#### *For IMP Trials*

Unexpected Serious Adverse Reaction (SUSAR).

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Co-ordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the <insert (compendium of) Summary of Product Characteristics, or Investigator Brochure as applicable>) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

#### *For non-IMP trials*

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

*The following headings can be used for IMP trials*

### 9.2.3 Reporting to the CA(s) and EC(s)

#### 9.2.3.1 Suspected Unexpected Serious Adverse Reactions

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the CA(s) and EC(s) in accordance with current regulations i.e. 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

---

### 9.2.3.2 Serious Adverse Reactions

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report details of all SARs (including SUSARs) to the relevant CAs and ECs annually from the date of the initial Clinical Trial Authorisation, in the form of an Annual Safety Report.

### 9.2.3.3 Adverse Events

Details of all AEs will be reported to the CA(s) on request.

### 9.2.3.4 Other safety issues identified during the course of the trial

The CA(s) and EC(s) will be notified immediately if a significant safety issue is identified during the course of the trial.

### 9.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

### 9.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs

### 9.2.6 Manufacturer of Investigational Medicinal Product

*If a pharmaceutical companies supplying an Investigational Medicinal Product will usually wish to be notified of either: all SAEs, SARs or SUSARs. This may not be relevant for many paediatric oncology trials however, if there is any such requirement, it should be defined contractually with the pharmaceutical company. Such contracts will not be contained within the body of the protocol but may be referred to in order clarify delegated task roles to national co-ordinating centres.*

*Example text:*

All SAEs will be reported to the manufacturer of the Investigational Medicinal Product within 24 hours by fax.

*The following headings should be used for non-IMP trials:*

### 9.2.7 Reporting to the Ethics Committee(s) according to national requirements

#### 9.2.7.1 Unexpected and Related Serious Adverse Events

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report all events in accordance with national requirements

#### 9.2.7.2 Other safety issues identified during the course of the trial

The EC(s) and CA(s) will be notified in accordance with national requirements if a significant safety issue is identified during the course of the trial.

*Needs clarity of the different national roles of Ethics Committee and Competent Authorities*

### 9.2.8 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File

### 9.2.9 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

## 10. DATA HANDLING AND RECORD KEEPING

Required as per ICH GCP section 6.13

*ICH GCP also specifies that the following should be included*

- ICH GCP section 6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

### 10.1 Data Collection

*It is good practice to include a list or table of forms and indicate the timeframe in which each form should be completed. A reference to the relevant protocol section may be required. For example:*

The Case Report Form (CRF) will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist	Confirmation of eligibility and satisfactory staging investigations where necessary	Transmitted at point of randomisation
Randomisation	Patient details; details of stratification variables; optional consent issues	As soon as possible after randomisation
Baseline	Details of biopsy histology; (with copy of diagnostic biopsy report); details of planned surgery	Within 1 month of randomisation
Relapse Form	Date and site of relapse	Immediately upon patient relapse
Death Form	Date and cause of death	Immediately upon notification of patient's death
Deviation Form	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Withdrawal Form	Used to notify the <i>&lt;insert relevant body, eg. National co-ordinating centre, Sponsor&gt;</i> of patient withdrawal from the trial	Immediately upon patient withdrawal
Serious Adverse Event Form		Immediately on becoming aware of the event
Pregnancy Notification Form		
Others?		

*Many international trials will have remote electronic data capture (REDC). Such electronic systems should have mechanisms built in to record and track changes to the data set.*

*For paper CRFs, the following text must be entered and/or a paragraph referring to additional CRF completion guidelines should be used:*

The CRF must be completed, signed/dated and returned to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above *<indicate any exceptions to this, for example "The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator">*

Entries on the CRF should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

*<If applicable, provide information on data, which may not be captured in the source data, e.g. Quality of Life or health economic data which will be recorded directly onto the CRF>.*

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

*<Select one of the following as appropriate (a) The completed originals should be sent to the <insert relevant body, eg. National co-ordinating centre, Sponsor> and a copy filed in the Investigator Site File OR (b) On completion, the top copy of each form must be submitted to the <insert relevant body, eg. National co-ordinating centre, Sponsor> and the bottom copy filed in the Investigator Site File.>*

Trial forms may be amended by the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

## 10.2 Archiving

It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc) at their site are securely retained for at least 5 years *<if trial results are to be used for licensing, then the number of years should be increased to at least 15; consult the Chief Investigator to discuss this possibility. Also refer to relevant regulatory guidelines>* after the end of the trial *<or following the processing of all biological material collected for research, whichever is the later>*. Do not destroy any documents without prior approval from the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

## 11. QUALITY MANAGEMENT

Required as per ICH GCP section 6.11

*ICH GCP also specifies that the following should be included*

- ICH GCP section 6.10 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

### 11.1 Site Set-up and Initiation

All sites will be required to sign a *<insert "Clinical Study Site Agreement" or other appropriate Sponsor's term>* prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements *<specify other documents as appropriate for the trial e.g. registration forms>* and supply a current CV to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

All members of the site research team will also be required to sign the *<insert "Site Signature and Delegation Log" or appropriate external Sponsor term>*, which should be returned to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference *<if required amend to specify only "meeting" or only "teleconference">* covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping.

Sites will be provided with an Investigator Site File *<where applicable insert "and a Pharmacy File">* containing essential documentation, instructions, and other documentation required for the conduct of the trial. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* must be informed immediately of any change in the site research team.

### 11.2 On-site Monitoring

*Monitoring will be carried out as required by the regulations of the nation state and as defined in the trial protocol. The Sponsor will define the monitoring requirement based on a risk analysis of the trial. The minimum requirements for on-site monitoring should be described,*

If a monitoring visit is required the <insert relevant body, eg. National co-ordinating centre, Sponsor> will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the <insert trial name> trial staff access to source documents as requested.

### 11.3 Central Monitoring

*Where applicable include the following paragraph:*

*<Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.>*

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check data received for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests missing data or clarification of inconsistencies or discrepancies. For REDC trials these requests may be generated by automated data validation checks.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to <specify trial specific committees and/or stakeholders e.g. Trial Management Group, Trial Steering Committee> and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the EC(s) and CA(s).

### 11.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> of any CA inspections.

### 11.5 Notification of Serious Breaches

*The following should be included either in the body of the protocol or as an appendix referred to within the body of the protocol:*

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach, which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the <insert relevant body, eg. National co-ordinating centre, Sponsor> is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the <insert relevant body, eg. National co-ordinating centre, Sponsor> in providing sufficient information to report the breach to the CA where required and in undertaking any corrective and/or preventive action.

## 12. END OF TRIAL DEFINITION

Required as per EU CTD

*The definition of end of a trial must be clearly defined in the protocol. Definitions of end of trial will differ according to whether the trial is an Investigational Medicinal Product (IMP) or non-IMP trial and whether the trial involves long-term follow-up.*

*For all types of trial, where ethical approval for a sub-study (e.g. sample collection) has been (or will be) granted as part of the main protocol, the date of last data capture must also include the final*

---

*processing / testing of all samples, as specified in the protocol. Note: where analysis is not expected to be completed in an acceptable timeframe (e.g. sub-study does not form part of primary or secondary endpoints) it is preferable to have a separate protocol and ethics approval for the sub-study.*

*The following text should be used according to the type of trial and modified as appropriate:*

*Non-IMP trial*

The end of trial will be *<the date of or x months after>* the last data capture. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the EC(s) that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

*IMP trial without long-term follow-up*

*When calculating the end of trial date for IMP trials without long-term follow-up the end of trial date should be defined as the same date for both the CA(s) and EC(s). Allow sufficient time following the last patient visit for all relevant trial data to be received and entered onto the trial database. Consider the size of the trial and anticipated rate of data return.*

The end of trial will be *<the date of or x months after >* the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the CA(s) and EC(s) that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

*IMP trial with long-term follow-up*

*When calculating the end of trial date allow sufficient time following the last patient visit for all relevant trial data to be received and entered onto the trial database. Consider the size of the trial and anticipated rate of data return.*

For the purposes of the CA(s) the end of trial will be *<x>* months after the last patient has completed *<insert last protocol defined interventional treatment e.g. chemotherapy, radiotherapy, surgery>*. This will allow sufficient time for the completion of protocol procedures, data collection and data input. For the purposes of EC(s) approval, the trial end date is deemed to be *<the date of or x months after>* last data capture following *<x>* years of long-term follow-up.

After closure of the trial with the CA(s) the Sponsor is no longer required to notify the CA(s) and EC(s) of changes of Principal Investigator. However, sites should continue to notify the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV.

The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the CA(s) and EC(s) that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

### 13. STATISTICAL CONSIDERATIONS

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- ICH GCP section 6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- ICH GCP section 6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- ICH GCP section 6.9.3 The level of significance to be used.

- 
- ICH GCP section 6.9.4 Criteria for the termination of the trial.
  - ICH GCP section 6.9.5 Procedure for accounting for missing, unused, and spurious data.
  - ICH GCP section 6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
  - ICH GCP section 6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

*Example sub-headers include:*

### **13.1 Power Calculations**

*Provide a rationale for the sample size, i.e. a statement of the size of difference and significance level and power that contributed to the sample size calculations for the primary outcome measure(s) and any other measures (secondary or subgroups).*

*Specify any adjustments that have been made for drop-outs (e.g. inflation by X%) or interim analyses (e.g. adjustment of p-values)*

### **13.2 Analysis of Outcome Measures**

*Full details will be specified in a Statistical Analysis Plan but an outline of the plan will be given here.*

*Give details on the following:*

- *The statistical analysis by describing the comparisons that are planned between treatment arms and any adjustments being made for multiple comparisons and by describing the methods that may be used to compare each outcome measure, i.e. summary measures and hypothesis tests*
- *Selection of patients to be used in the analyses (if not intention to treat) e.g. definition of evaluable*
- *Rationale for the analysis of stratification factors*
- *If applicable, give the criteria for the termination (“stopping rules”) of the trial and cross reference the DMC and TSC*

### **13.3 Planned Sub Group Analyses**

*Give details of any subgroup analysis by describing in which subgroups the treatment effects will be investigated and the statistical methods that will be used*

### **13.4 Planned Interim Analysis**

*Give trial milestones with the number of participating sites (approximate) and the timing of interim analyses*

*Specify the type of analyses that will be presented at the interim analyses*

### **13.5 Planned Final Analyses**

*Give the timing of final analysis (there may be several final analyses that relate to different outcome measures or to different lengths of follow-up)*

*If applicable, give the criteria for the termination (“stopping rules”) of the trial and cross reference the DMC and TSC*

## **14. TRIAL ORGANISATIONAL STRUCTURE**

### **14.1 Sponsor**

### **14.2 Coordinating Centre**

*Can also include a list of National coordinating centres*



---

### 14.3 Trial Management Group

*Do not need to list the names of the members as they may change over the period of the trial but describe the oversight role of the Trial Management Group*

### 14.4 Trial Steering Committee

*Do not need to list the names of the members as they may change over the period of the trial but describe the oversight role of the Trial Steering Committee*

### 14.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with appropriate regulatory guidelines. *<In consultation with the Trial Statistician insert details of when the DMC will meet. Unless there is a specific reason (e.g. safety phase) avoid stating that the DMC will meet following the recruitment of XX patients, because if the recruitment rate is not as predicted the DMC may meet too early or too late which may affect their ability to effectively monitor the trial. Instead consider a time-based schedule. For example consider the following text for trials involving Investigational Medicinal Products (IMPs) "During the recruitment phase of the trial the DMC is scheduled to meet one month prior to the due date of the Annual Safety Report and annually thereafter". For a non-IMP trial consider "The DMC will be scheduled to meet one year after the trial opens to recruitment and then annually thereafter until the trial closes to recruitment.">*

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the *<insert Trial Management Group (TMG) or Trial Steering Committee as applicable>* who will convey the findings of the DMC to *<specify to whom the report will be sent e.g. Trial Steering Committee, CA, funders, and/or sponsors as applicable>*.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial may stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. *<If the trial includes stopping rules indicate here and reference the relevant section of the protocol>*.

### 14.6 Finance

*Where payments are made e.g. pathology payments, amend accordingly.*

This is a clinician-initiated and clinician-led trial funded by *<list all relevant funders, and acknowledge companies that provide free drug>*.

No individual per patient payment will be made to healthcare providers, Investigators or patients.

## 15. ETHICAL CONSIDERATIONS

*ICH GCP specifies that the following should be included*

- ICH GCP section 6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- ICH GCP section 6.12 Description of ethical considerations relating to the trial.

### *IMP trials*

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48<sup>th</sup> World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance with the relevant legislation in the nation state and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP).

---

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain all applicable regulatory approval(s). Sites will not be permitted to enrol patients until written confirmation of such approval(s) have been received by the *<National Co-ordinating Centre/Sponsor>*.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

#### *Non-IMP trials*

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance national regulations for conducting non-IMP trials and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP).

The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

## 16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the National Data Protection Laws. With the patient's consent, their *<specify patient identifiers e.g. full name, date of birth, hospital identifying number>*, *address, post code, hospital number, general/medical practitioner details>* will be collected at trial entry *<indicate why e.g. to assist with long-term follow-up via other health care professionals>*.

Patients will be identified using only their unique *<insert registration/trial>* number, *<insert other identifiers e.g. initials, hospital number and date of birth>* on the Case Report Form and correspondence between the Trials Office and the participating site.

*<For trials collecting consent forms specify "However patients are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process". Trials with long term follow-up may also wish to add "and may also be forwarded to other health care professionals involved in the treatment of the patient.>*

The Investigator must maintain documents not for submission to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party *<include exceptions to this e.g. "other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff)">*. Representatives of the *<insert trial name>* trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

## 17. INSURANCE AND INDEMNITY

*This is the standard text for a University of Birmingham sponsored UK clinical trial, and will need to amended as appropriate for other sponsors.*

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

---

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The Sponsor cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

## 18. PUBLICATION POLICY

Required as per ICH GCP section 6.15

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of <specify name of Sponsor>. Intellectual property rights will be addressed in the <insert "Clinical Study Site Agreement" or appropriate external Sponsor term> between Sponsor and site.

<For international trials taking place in more than one country and coordinated at a national level the following text may also be inserted, "Individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.">

## 19. REFERENCE LIST

Examples for tables/appendices include:

### APPENDIX 1 - TUMOUR STAGING

Include here the tumour staging scheme relevant to the disease

### APPENDIX 2 - WMA DECLARATION OF HELSINKI

At the time of writing the 1996 version is the legally required version in the EU; see link to shared drive: <S:\General\Reference documents\WMA Declaration of Helsinki version 1996.docx>

### APPENDIX 3 - DEFINITION OF ADVERSE EVENTS

For IMP trials

#### Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

#### Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

#### Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- 
- Results in death *<for phase III trials with long term follow-up where survival is an endpoint consider adding text "(unrelated to original cancer)">*
  - Is life-threatening\*
  - Requires hospitalisation\*\* or prolongation of existing inpatients' hospitalisation
  - Results in persistent or significant disability or incapacity
  - Is a congenital anomaly/birth defect
  - Or is otherwise considered medically significant by the Investigator\*\*\*

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

\* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

\*\*\* Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

### **Serious Adverse Reaction**

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

### **Suspected Unexpected Serious Adverse Reaction**

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information, such as drug monograph, SmPC or Investigator Brochure.

A SUSAR should meet the definition of an AR, UAR and SAR.

### **Unexpected Adverse Reaction**

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

### *For non-IMP trials*

#### **Adverse Event**

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

#### **Related Event**

An event which resulted from the administration of any of the research procedures.

#### **Serious Adverse Event**

---

An untoward occurrence that:

- Results in death *<for phase III trials with long term follow-up where survival is an endpoint consider adding text "(unrelated to original cancer)">*
- Is life-threatening\*
- Requires hospitalisation\*\* or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator\*\*\*

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

\* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

\*\*\* Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

### **Unexpected and Related Event**

An event which meets the definition of both an Unexpected Event and a Related Event.

### **Unexpected Event**

The type of event that is not listed in the protocol as an expected occurrence.

## **APPENDIX 4 - COMMON TOXICITY CRITERIA GRADINGS**

*The version of the CTCAE quoted should be the one currently being used at a unit level. At the time of finalisation of this document this was <insert appropriate version number>.*

*If the CTCAE document is also provided in the Investigator Site File reference can be made to this also.*

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), *<insert appropriate version number>*. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

## **APPENDIX 5 – DEFINITIONS**

**IMP** - An investigational medicinal product is any medicinal product which is being tested within a trial or any product, including placebo, used as a reference in a clinical trial. This includes products with a marketing authorisation where the product is:

- used in a different form from the marketing authorisation
- used for an indication not included in the summary of product characteristics for that product or
- used to gain further information about the product as authorised in the clinical trial authorisation.

*Consider adding Trials Office and national co-ordinating centre contact details to the back page of the protocol.*