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**Clinical Trial Protocol**

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Trial Title: Full Title of the Trial

Protocol Number: A protocol code number should be allocated that is unlikely to have been used for other trials, e.g. trial acronym and year (MAG98)

EudraCT Number:

ISRCTN Number:

Investigational Product:

Protocol Version:

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Chief Investigator:

CI Address:

Telephone:

Trial Sponsor: Name and Address

SAE Reporting: This should be the phone/fax/email number of the relevant person/team

**Instructions:**

Instructional text – requires you to complete the information. Prior to finalising the protocol, ensure all text is black.

Optional text – requires you to choose one of the options and delete the other as applicable to your trial, prior to finalising the protocol, ensure all text is black.

Standard wording – not to be removed or changed without prior consultation with the Clinical Trials Office

*CCTU/TPL001 version 3; November 2011*

**1 Protocol Signatures:**

I give my approval for the attached protocol entitled **add full trial title here** dated.....

**Chief Investigator**

Name:

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Site Signatures

I have read the attached protocol entitled "add full trial title here" dated ..... and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice; The European Clinical Trials Directives 2001/20/EC and 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

**Principal Investigator**

Name:

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**2 Trial Management Committee and Protocol Contributors**

Include names and contacts of personnel running the trial (e.g. coordinator, scientific and medical collaborators)

Also names of contributors to the study protocol including trials pharmacist and statistician.

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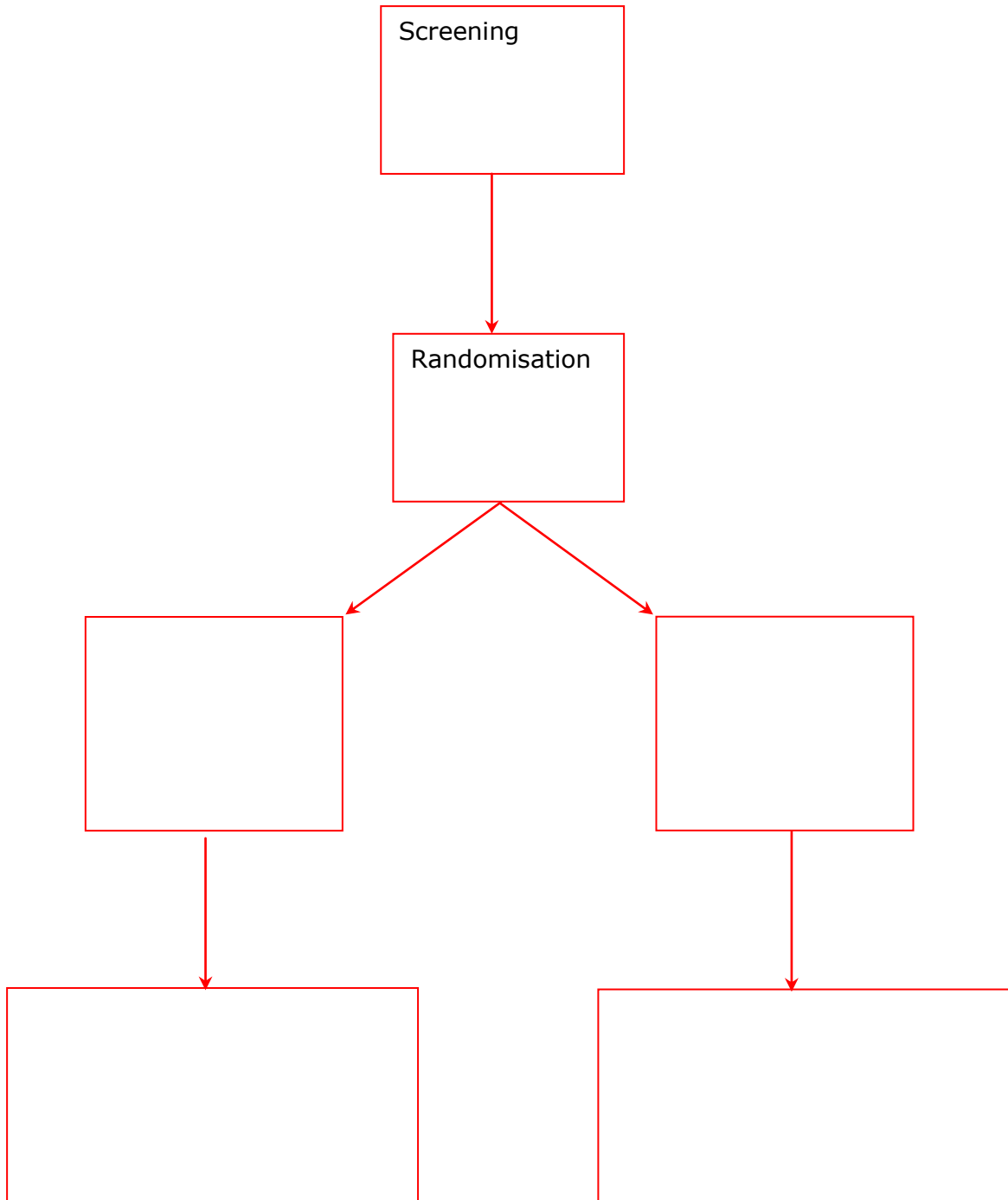
#### 4 Abbreviations

CRF	Case Report Form
GP	General Practitioner
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
MHRA	Medicines and Healthcare products Regulatory Agency
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
Add	Add as necessary

#### 5 Trial Synopsis

Title of clinical trial
Sponsor name
Eudract number for proposed trial
Medical condition or disease under investigation
Purpose of clinical trial
Primary objective
Secondary objective (s)
Trial Design
Trial Endpoints
Sample Size
Summary of eligibility criteria
Investigational medicinal product and dosage
Active comparator product(s)
Route(s) of administration
Maximum duration of treatment of a subject
Procedures: Screening & enrolment
Baseline
Treatment period
End of Trial
Procedures for safety monitoring during trial
Criteria for withdrawal of patients on safety grounds
Regulatory submissions on safety grounds

## 6 Trial Flow Chart



## 7 Introduction

### 7.1 Background

This should be concise but assume that none of the background information is known to the reader. Include the IMP and its mechanism of action

### 7.2 Data from non-clinical studies

Efficacy, tolerability, pharmacokinetics etc

### 7.3 Clinical Data

#### 7.3.1 Efficacy

#### 7.3.2 Safety and tolerability

#### 7.3.3 Pharmacokinetics & pharmacodynamics

## 8 Rationale for Trial

This should include a clear explanation of the research question/hypothesis and the justification of the trial.

## 9 Trial Design

### 9.1 Statement of design

For example: This is an open, uncontrolled non-randomised trial.

### 9.2 Number of Centres

### 9.3 Number of Subjects

### 9.4 Trial duration

Include expected duration of subject participation, and description of the sequence and duration of all trial periods including recruitment, active treatment phase and follow-up periods.

### 9.5 Trial objectives

#### 9.5.1 Primary objective

#### 9.5.2 Secondary objective

### 9.6 Trial endpoints

#### 9.6.1 Primary endpoint

This should be a simple concise statement of the observation(s) from the CRF that will be the focus of the primary analysis and thus will drive the choice of sample size. It should not make any statements about the anticipated results, analyses, or describe the objectives. Less is more.

For example: "The primary endpoint is overall survival."

Since there is only one choice of sample size, which may be based on the statistical power for the single primary analysis, there can only be one primary endpoint.

The exception to this is in a study that is comparing a new diagnostic or measurement technique to an existing standard. In which case, it is acceptable to have two co-primary endpoints: the old and the new technique.

#### 9.6.2 Secondary endpoint

This should be a sequence of concise statements referring to observations in the CRF that say nothing about the trial objectives or analysis. These are normally a set of endpoints that are well established as being of clinical importance, and could in theory be the primary endpoint in another trial.

#### 9.6.3 Exploratory endpoints

Any other endpoints that are not well established.

### **10 Selection and withdrawal of subjects**

#### **10.1 Inclusion Criteria**

To be included in the trial the patient must have: (provide in a bulleted list)

- 

#### **10.2 Exclusion Criteria**

The presence of any of the following will preclude patient inclusion: (provide in a bulleted list)

It will be important to consider the strictness of the eligibility criteria and consider whether any flexibility should be incorporated into the protocol to minimise the need for protocol amendments that are considered substantial by the MHRA's definition, but that are not substantial in terms of the safety or physical or mental integrity of the subjects, the scientific value of the trial, the conduct or management of the trial and/or the quality or safety of any IMP used in the trial. For example, changing the age range in a trial from, say, 18-65 to 18-75 in order to increase the rate of accrual in a trial is less likely to affect the risk/safety profile of a trial than lowering the entry age range which has paediatric implications.

#### **10.3 Assignment and Randomisation Number**

Provide a full description of the process of how treatments will be allocated between subjects (and within subjects for crossover trials). If minimisation, stratification randomisation or block randomisation is used then give full details. It should provide enough details to theoretically enable a full reproduction of the process.

Explain if any blinding will be used to avoid bias. Describe the process in detail. Do not loosely use vague terms such as "single blind" without explicitly stating who will remain blinded and who will not. If blinding is not to be used then provide a justification.

If an un-equal treatment allocation will be used, then provide a justification. If the allocation ratio may adaptively evolve over the course of the trial, then provide a short overview statement to that effect and refer to the full description in the "Interim Analysis" section.

#### **10.4 Method of Blinding**

Delete if not applicable for your trial

**10.5 Emergency Unblinding**

Delete if not applicable for your trial

**10.6 Subject withdrawal criteria**

It is always within the remit of the physician responsible for a patient to withdraw a patient from a trial for appropriate medical reasons, be that individual adverse events or new information gained about a treatment.

When and how to withdraw subjects from the trial / investigational product treatment

Type and timing of data collection for withdrawn subjects

Whether and how subjects are to be replaced

The follow up of subjects that have withdrawn from the treatment / trial

**11 Trial Treatments**

Dosage / regimen of investigational product

Plus comparator product / regimen

**11.1 Dosage schedules**

Describe the intended drugs and the dosing schedule for each

11.1.1 Route of Administration

11.1.2 Maximum dosage allowed

Specify total or daily amount

11.1.3 Maximum duration of treatment of a subject

11.1.4 Active comparator products

11.1.5 Procedures for monitoring subject compliance

**11.2 Presentation of the drug**

Include details on the packaging, labelling and form of the drug including placebos if used in the trial.

**11.3 Known drug reactions & interaction with other therapies**

Cross-reference with section 13.2 if applicable and/or SmPC and/or IB.

**11.4 Dosage modifications**

For Example Myelosuppression

If haematological toxicity is unacceptable then the following dosage reduction scheme (based on nadir blood counts) should be used. If the blood count has not returned to pretreatment levels by the time the treatment is due, the next course is to be delayed until the blood count has recovered, rather than given in reduced dose.

Neutrophils	Platelets	Dose to be given
<500 for <2 days	10-20,000	75%
<500 for >2 days	<10,000	50%

### 11.5 Legal status of the drug

The trial is being carried out under a Clinical Trial Authorisation. The drug is therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial.

### 11.6 Drug storage and supply

Include details on how the drug should be stored, who will supply and how eg 'upon receipt of a suitably signed trial specific prescription' and also accountability and destruction.

### 11.7 Concomitant therapy

Add as necessary

## 12 Procedure and assessments

### 12.1 Screening evaluation

Include details of the screening process up to the registration of the patient in the trial.

### 12.2 Baseline data

All patients will have a full medical history taken and a clinical examination .The following are to be recorded:

- a) Weight
- b) Sex
- c) Age and date of birth
- d) Any significant past medical history
- e) WHO performance score (see Appendix 2)
- f) Full blood count (including platelets and differential white cell count)
- g) Biochemical series (including urea, creatinine, uric acid, electrolytes, calcium, alkaline phosphatase, AST)
- h) 12 lead ECG
- i) Chest X-ray
- j) etc

However, please review the relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable.

### 12.3 Trial assessments

#### 12.3.1 Timing of assessments

For example: Patients are to be seen at Addenbrooke's Hospital least every 4 weeks for the first 6 months and at least every 3 months thereafter.  
Define the follow up intervals

#### 12.3.2 Assessment data at time point x, y or z (repeat if necessary)

The following are to be recorded each month for the first 12 months and every three months afterwards:

- a) History and clinical examination
- b) Assessment of the toxicity of the previous course

- c) Weight
- e) Full blood count
- f) Biochemical series (as in 7.1.g)
- g) Chest X-ray
- h) etc

## 12.4 Long-Term Follow-up Assessments

After the active treatment phase has closed and you wish to continue to monitor patients long term (survival data in terminal diseases etc). Include frequency of follow-up visits, duration of follow-up period and assessments to be carried out.

## 12.5 Schedule of Assessments

Insert table format of all trial related assessments here. This is the preferred method of review by RECs for understanding the participant's involvement in the trial.

## 12.6 Trial restrictions

Consider any contraindications whilst on the active phase of the trial including dietary requirements/restrictions.

## 13 Assessment of Safety

### 13.1 Definitions

#### 13.1.1 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.

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

#### 13.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship

#### 13.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

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 patient/event outcome or action criteria.

#### 13.1.4 Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### 13.2 **Expected Serious Adverse Drug Reactions**

In order to minimise unnecessary work, it is recommended that all **expected serious adverse drug reactions** (Suspected Serious Adverse Reactions/SSARs) are listed in the protocol with specific reference to the SmPC or IB (otherwise they will have to be reported as SUSARs). Cross-reference to 11.3 if applicable.

Sometimes, unexpected adverse drug reactions become 'expected' during the trial, in which case the protocol should be amended and such reactions would not need reporting. The Chief Investigator and Data Monitoring Committee (if applicable), should determine whether any reactions become 'expected' during the course of the trial and apply for MHRA and Ethics Committee approval for a substantial amendment.

### 13.3 **Expected Serious Adverse Events**

In order to minimise unnecessary work, it is recommended that all expected serious adverse events are listed in the protocol which are known to happen in patients with this condition.

### 13.4 **Recording and evaluation of adverse events**

Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, causality and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

#### 13.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 15.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

#### 13.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

#### 13.4.3 Clinical assessment of severity

- Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated
- Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
- Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

**For Oncology Trials only – replace this with the NCI CTCAE criteria for reporting severity (Grade 1-5)**

### 13.5 Reporting serious adverse events

This section is to explain in detail how adverse events are recorded and reported in this trial. It needs to define the flow of information from the PI to CI to Sponsor. For example:

Each Principal Investigator needs to record all adverse events and report these to the Chief Investigator. The Chief Investigator is responsible assessing all AE's and SAEs for expectedness and the prompt notification of all SAEs to the Sponsor. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting off all serious adverse event reporting to the competent authority (e.g. MHRA) of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

An adverse event or reaction that meets serious criteria irrespective of consistency (expected or unexpected) with the applicable product information (e.g. investigators brochure for unapproved investigational product or summary of product characteristics) must be reported to the sponsor unless explicitly listed within the protocol.

### 13.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

#### 13.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification to the MHRA, REC and any other investigators to the Chief Investigator. The Chief Investigator should report all the relevant safety information previously described, to the Sponsor, concerned competent authorities and to the Ethics Committee concerned. The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

#### 13.6.2 When to report?

##### 13.6.2.1 Fatal or life-threatening SUSARs

The MHRA, Research Ethics Committee and Sponsor should be notified as soon as

possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the MHRA, Ethics Committee and Sponsor within an additional **8 calendar days**.

#### 13.6.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and Ethics Committee in the concerned Member States as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

#### 13.6.3 How to report?

##### 13.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

- a) a suspected investigational medicinal product,
- b) an identifiable subject (e.g. trial subject code number),
- c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- d) an identifiable reporting source,

and, when available and applicable:

- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

##### 13.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

##### 13.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the MHRA. The format and content as defined by the MHRA should be adhered to.

## **14 Toxicity – Emergency Procedures**

Procedures in the event of toxicity reactions **if applicable**

## **15 Evaluation of Results (Definitions and response/evaluation of endpoints)**

Assessment of Efficacy. Methods and timing for assessing, recording and analysing of efficacy parameters

### **15.1 Response criteria**

Define here the values/scores that will determine success of failure and how they will be assessed.

### 15.1.1 Survival (patient and graft)

**Add here if required eg:** These will be measured from the date of randomisation and will be reported for all deaths and graft failures both due to rejection and due to all causes. The cause of death or graft failure is thus to be recorded in all instances.

### 15.1.2 Quality of life

**Add here if required or amend headings accordingly**

## 16 Statistics

### 16.1 Statistical methods

This should provide an overview of how the primary endpoint will be analysed and what explicit hypotheses are to be considered. There should be a clear link to the "Number of subjects to be enrolled and Objectives" sections.

An overview of further summary statistics to be presented for the secondary and exploratory variable should be presented.

Any subgroup analyses that are desired should be stated here to avoid the addition of undocumented ad hoc analyses at a later stage, which are of a low scientific credibility.

State that a detailed statistical analysis plan will be produced before the final data base lock.

### 16.2 Interim analyses

Include details of the timing of such analyses. What rules are in place to determine what actions are taken from an interim: e.g. stopping rules, sample size adjustments, stopping recruitment in certain sub-groups. What is the scope of any future adaptations to the trial?

### 16.3 Number of Subjects to be enrolled

Reason for choice of sample size, including reflections on the power of the trial and clinical justification. [ This section will be copied and used in IRAS applications forms, which state "How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation" ]

Formal sample size calculations typically require the following values with justification

- Treatment Effect- or – Alternative Hypothesis: is this the smallest size of effect that would be of clinical interest- how is this justified
- Null Hypothesis: A clear statement of the hypothesis, in terms of numerical values, of the treatment being ineffective. For example: an absolute difference in response rates between arms of zero.
- Significance level: what risk is acceptable of concluding the treatment is effective, when in reality the treatment is ineffective.
- Power: what risk is acceptable of concluding the treatment is not effect, when in reality the treatment is effective (as specified by the "Treatment Effect" above)
- Standard deviation of the primary endpoint: if previous studies or literature is used to estimate this parameter, or any other parameters relevant to the design (e.g. dropout rate, median survival rate, response rate), provide references.

If key parameters are genuinely unknown, but interim analyses or preparatory trials are not practical, then it may be appropriate to present a selection of power calculations across different values for the unknown parameters.

For studies that are not confirmatory in nature, a formal sample calculation may not be required. However, justification is still required as to why the trial will provide sufficient accuracy to enable reliable decisions to be taken following the trial. This can be achieved by presenting the predicted confidence intervals under a set of plausible assumptions. Also it may be acceptable to raise the significance level for a phase II trial assessing efficacy: explicitly stating this is advised. Repeating the design of a preceding trial is not acceptable justification alone.

#### **16.4 Criteria for the termination of the trial**

This section should generally be used sparingly. Once criteria are stated in the protocol it is difficult to change.

#### **16.5 Procedure to account for missing or spurious data**

Procedure for reporting deviations from original statistical plan

Selection of subjects to be included in the analyses (eg all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects)

#### **16.6 Definition of the end of the trial**

The sponsor must notify the MHRA of the end of a clinical trial within **90 days** of its completion. The definition of the end of the trial must be provided in the protocol. Any change to this definition for whatever reason should be notified as a substantial amendment. In most cases, the end of the trial will be the date of the last visit of the last patient undergoing the trial (please note, for long term follow-up the trial can be declared ended to the MHRA, but remain open to the REC). Any exceptions to this should be justified in the protocol. **Consider the requirements for other participating countries.**

### **17 Data handling and record keeping**

#### **17.1 CRF**

All data will be transferred into a Case Report Form (CRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers and the investigators as required.

For multi-centre trials:

Completed originals of the CRFs should be posted to the trial coordination centre (detail here) within (timeframe here) of the pages being completed.

The investigator will retain a copy of each completed CRF page at site. The investigator will also supply the trial coordination centre with any required, additional, background information from the medical records as required.

The investigators must ensure that the CRFs and other trial related documentation is sent to the trial coordination centre containing no patient identifiable data.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections

should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used. Changes must not be made to the CRF pages once the original has been returned to the trial coordination centre.

### **17.2 Source Data**

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Provide a list of source data/documents here, including items like: Patient Medical Records, On-line test results (especially if only held electronically) etc.

### **17.3 Data Protection**

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

### **18 Data Monitoring Committee/Trial Steering Committee**

Give details of the committees, their remit, when review of data will take place (time points or enrolment points) and what data they will review. Also detail the feedback process and whether they will have any input in the early termination of the trial for safety reasons.

### **19 Ethical & Regulatory considerations**

#### **19.1 Consent**

The Informed Consent form must be approved by the REC and must be in compliance with ICH GCP, local regulatory requirements and legal requirements. The investigator must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each patients signed informed consent form.

Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

If the trial requires documentation in a different language (other than English) the translation and back translation documents need to be reviewed and approved by the Sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and include version control.

#### **19.2 Ethical committee review**

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other

relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

Add any reporting requirements for other participating countries

### 19.3 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA (**list any other RAs in participating countries**). The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

**Development Safety Update Reports** will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

Add any reporting requirements for other participating countries

### 19.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or MHRA **add regulatory bodies for other participating countries as necessary**.

The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In the case, accrual of new patients will be halted until the REC and/or MHRA approval has been obtained. **Add regulatory bodies for other participating countries as necessary**.

### 19.5 Peer Review

**Provide details on who has reviewed this trial protocol – this may be funder specific or involve an internal Trust department/committee. It is OK to be general and not include individual names unless the person in question gives their express permission for you to do so.**

### 19.6 Declaration of Helsinki and ICH Good Clinical Practise

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the ICH Good Clinical Practice Guidelines, the protocol and applicable local regulatory requirements and laws.

### 19.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

## 20 Sponsorship, Financial and Insurance

The trial will be sponsored by Cambridge University Hospitals NHS Foundation Trust **(and University of Cambridge or other co-sponsor)**. The study will be funded by.....

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising thorough participation in the clinical trial.

## **21 Monitoring, Audit & Inspection**

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All patient data must be handled and treated confidentially.

**Include here any trial specific monitoring arrangements in place.**

## **22 Protocol Compliance and Breaches of GCP**

The investigator must not implement any deviation from the protocol without formal written agreement from the Sponsor and Chief Investigator. If this necessitates a subsequent protocol amendment, or halt to the trial this should be submitted to the REC, MHRA & R&D Department for review and approval if appropriate. **Add regulatory bodies for other participating countries as necessary.**

Potential/suspected serious breach of GCP must be reported immediately to the Sponsor.

## **23 Publications policy**

Ownership of the data arising from this trial resides with the study team. On completion of the trial the data will be analysed and tabulated and a Clinical Study Report prepared.

**Also include whether any of the participating investigators will have rights to publish any of the trial data.**

## **24 References**

## **25 Appendices**

## **25.1 Appendix 1 - Study Management / Responsibilities**

### 25.1.1 Patient registration/ Randomisation procedure

Give explicit details in this section including the centralised phone/fax/email which needs to be contacted for patient registration, details of the forms for completion if being faxed and the timeline for the registration process.

### 25.1.2 Data management

Include who is responsible for DM if any part of the trial coordination is outsourced. Also include what data management will entail (CRF checking, data queries/clarifications etc).

### 25.1.3 Preparation & submission of amendments

Include details here who will be responsible for amendments if any part of the trial coordination is outsourced

### 25.1.4 Preparation and submission of Annual Safety Report/Annual Progress Reports

Include details here who will be responsible for annual reporting if any part of the trial coordination is outsourced

### 25.1.5 Data protection/ confidentiality

### 25.1.6 Trial documentation & archiving

## **25.2 Appendix 2 – Authorisation of Participating Sites**

### 25.2.1 Required Documentation

List here all the documentation you require prior to initiating a participating site.

### 25.2.2 Procedure for initiating/opening a new site

Include details on when, how and who will perform the initiation and the release of drug to the participating sites.

### 25.2.3 Principal Investigator Responsibilities