*Note to authors – this template is a guide – all the sections below must be included however this is not exhaustive, other sections may be added. Don’t forget to delete the blue “guides” from each section! Once your protocol content is complete, update the index by clicking in the left of the field and pressing F9*

# PROTOCOL FULL TITLE

|  |
| --- |
| **Protocol Short Title/ Acronym:** |

Trial Identifiers

|  |  |  |  |
| --- | --- | --- | --- |
| **ISRCTN:** |  | | |
| **REC Number:** |  | | |
| **UKCRN Number:** |  | | |
| **Protocol Version Number:** |  | Date: |  |

(Co) Sponsor(s)

*This is usually the substantive employer of the CI. If this is KCL then co-sponsorship with the participating NHS Trust may be required.*

|  |  |
| --- | --- |
| **Name:** |  |
| **Address:** |  |
| **Telephone:** |  |
| **Fax:** |  |
| **Email:** |  |

Chief Investigator

|  |  |
| --- | --- |
| **Name:** |  |
| **Address:** |  |
| **Telephone:** |  |
| **Fax:** |  |
| **Email:** |  |

**Name and address of Co-Investigator(s), Statistician, Therapy Service, Laboratories etc**

|  |  |
| --- | --- |
| **Name:** |  |
| **Position/ Role:** |  |
| **Address:** |  |
| **Telephone:** |  |
| **Fax:** |  |
| **Email:** |  |

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| --- | --- |
| **Name:** |  |
| **Position/ Role:** |  |
| **Address:** |  |
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| **Name:** |  |
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| **Name:** |  |
| **Position/ Role:** |  |
| **Address:** |  |
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| **Email:** |  |

# Study Synopsis

|  |  |
| --- | --- |
| **Title Of Clinical Trial:** |  |
| **Protocol Short Title/ Acronym:** |  |
| **Study Phase If Not Mentioned In Title:** |  |
| **Sponsor Name:** |  |
| **Chief Investigator:** |  |
| **UKCRN Number:** |  |
| **REC Number:** |  |
| **Medical Condition Or Disease Under Investigation:** |  |
| **Purpose Of Clinical Trial:** |  |
| **Primary Objective:** |  |
| **Secondary Objective(s):** |  |
| **Trial Design:** |  |
| **Endpoints:** |  |
| **Sample Size:** |  |
| **Summary Of Eligibility Criteria:** |  |
| **Intervention (Description, frequency, details of delivery)** |  |
| **Comparator Intervention:** |  |
| **Maximum Duration Of Treatment Of A Subject:** |  |
| **Version And Date Of Final Protocol:** |  |
| **Version And Date Of Protocol Amendments:** |  |

# Revision History

|  |  |  |
| --- | --- | --- |
| **Document ID - (Document Title) revision X.Y** | **Description of changes from previous revision** | **Effective Date** |
| Document2 | New Protocol | May 2012 |
|  |  |  |

# Glossary of terms (Optional)

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# Background & Rationale

*This should comprise a brief description of the proposed study, a description of the population to be studied, the investigational product(s), device(s) or radiation exposure, a summary of findings from non-clinical studies that potentially have clinical significance, and from previous clinical trials that are relevant to the trial. A summary of the known and potential risks and benefits to human subjects should be presented, together with a justification for the choice of comparator, route of administration, dosage, dosage regimen, and treatment period(s). This should be supported by appropriate references to the published literature on the disease or condition, its treatment and the use of the study drug for the indication. Data from previous studies as well as any other information that provides background for the trial should be cited.*

# Trial Objectives and Design

## Trial Objectives

*This should comprise specific statements of the purpose (i.e. aims and objectives) of the study, together with a definition of the primary (and secondary) endpoints of the study.*

### Primary endpoints

### Secondary endpoints

## Trial Design

*A description of the design of trial to be conducted (e.g. double-blind, single-blind, open label, placebo-controlled, parallel-group, double-dummy, cross-over, etc.) should be given together with a framework of the study in the description (e.g., superiority, equivalence, noninferiority, exploratory).*

## Trial Flowchart

*Please include a time/event matrix (flow chart) of trial procedures and stages. This desirable is it is particularly useful for determining activities involved during each clinic visit (eg blood tests or scans, treatment, diary completion, adverse event monitoring, physical examination etc).*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Screen Visit | Pre dose | Day 1 |  |  |  |  |  |  |
| Patient information and informed consent | X |  |  |  |  |  |  |  |  |
| Physical examination |  |  |  |  |  |  |  |  |  |
| Pre dose PK sample |  |  |  |  |  |  |  |  |  |

# Trial Intervention

## Therapy/Intervention Details

*Provide a description of the trial treatment, (specify the type of therapy) including any sham therapy doses, include a description of the frequency, duration and method of administration of therapy. Provide details of how and when the intervention will be administered.*

## Frequency and duration of intervention

*It is necessary to define the expected duration of subject participation, and to describe the sequence and duration of all trial periods (e.g. “wash-out”, “treatment”, “follow-up” etc).*

## Intervention records

*Specify the process for recording therapy sessions*

## Subject Compliance.

*State here the procedures for determining compliance with therapy. (This can be attendance at stipulated visits, or by subjects completing diaries, or by compliance with tasks specified by the intervention).*

## Study adherence

*Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence and assessments (e.g., drug tablet return, laboratory tests).*

## 5.5 Concomitant Medication

*Describe what (if any) medications or treatments will be permitted concurrently with the intervention. Also stipulate those drugs or therapies that will not be permitted during treatment with the intervention. The section should also include reference to any medication that may be prescribed as an adjunct to therapy in both trial arms*

*A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF.*

# Research environment

*A description of the study setting (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained.*

# Selection and Withdrawal of Subjects

## Inclusion Criteria

*This section should contain details of age, sex, disease, prior treatment constraints etc., under which a subject is deemed to be suitable (eligible) to participate in the trial. This also includes healthy volunteers and any “control” groups etc. Each such “group” should be defined separately. Informed consent to participate (preferably written and witnessed) must be stated as an inclusion criterion. A simple list format is the preferred style. It should be stated if women of child bearing age will be included or excluded and suitable methods of contraception to enable inclusion into the trial.*

## Exclusion Criteria

*This section should contain details of age, sex, disease, prior treatment constraints etc., under which a subject is considered to be unsuitable for inclusion into the study population. A simple list format is the preferred style.*

## Selection of Participants

*State where participants will be recruited from, i.e. from clinic or referred from GP surgeries/other hospitals etc.*

## Randomisation Procedure / Code Break

*Provide details of the randomisation procedure to be used for each subject (methodology to go in section 12.2)*

## Withdrawal of Subjects

*Please provide details of when and how to withdraw subjects from the trial or therapy. It is essential that you specify the type and timing of the data to be collected for withdrawn subjects as well as arrangements for safety assessment follow-up of any subjects withdrawn from trial treatment as the result of (Serious) Adverse Events. Also include if patients will be withdrawn due to poor compliance and what the rules for this are e.g.*

* *Therapy must be discontinued if:*
  + *the participant misses xx consecutive courses of treatment*
  + *the participant decides they no longer wish to continue*
  + *recommended by the investigator*

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE’s, SUSAR’s, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

*Participants who wish to withdraw from therapy will be asked to confirm whether they are still willing to provide the following.*

* *study specific data at visits xxx*
* *xxx data collected as per routine clinical practice at visits xxx*

## Expected Duration of Trial.

*Specify the expected clinical participation and define the end of the trial . This can be the full study duration e.g. first patient first visit to last patient last visit including follow up.*

# Trial Procedures

## By Visit

*Describe the sequence of procedures to be performed at each visit as detailed in the time/event flowchart in section.2.3.*

## Laboratory Tests

*Detail any laboratory measurements required, detailing any handling, storage and packaging instructions. Include details of the Lab conducting analysis.*

# Assessment of Efficacy

*Describe the measures that will be used to determine the efficacy of treatment (eg glucose, blood pressure, tumour reduction etc).Give a rational for the selection of the efficacy methods (e.g. reasons for the choice as opposed to other possible methods). Primary efficacy parameters should be stated first, then any secondary parameters*

## Primary Efficacy Parameters

## Secondary Efficacy Parameters

## Procedures for Assessing Efficacy Parameters

*Describe here the procedures for determining the primary (and secondary) efficacy parameters (eg venepuncture, 25 mls to be drawn 12 hrs post treatment for full blood count, SMAC and glucose, or CT scan at 6 months, etc). State also here what is to be recorded in the CRF (eg WBC, Hb, Urea, Glucose etc rather than “FBC” or “SMAC”) – ie stipulate the parameters that are actually to be used for the analysis of efficacy. (See also Safety Parameters, 5.1 below)*

# Assessment of Safety

## Specification, Timing and Recording of Safety Parameters.

*Describe the measures that will be used to determine subject safety during the study. These will include physical examination, blood tests and adverse event reporting. Obviously, there will be close correlation with efficacy testing intervals and efficacy blood tests etc. In this section the tests that to be performed for assessing the safety of the subject should be appropriate to the treatment (eg WBC and platelets in chemotherapy, LFTs if there is a known or suspected risk of hepatotoxicity, U&Es if there is a risk of renal problems etc), although “general” assessments from FBC or SMAC would be acceptable. As with efficacy measures, please stipulate (ie repeat even if given above) the times at which safety evaluations will be conducted (Please do not write “see above” in this section; please copy & paste from 4.2 as and where appropriate).*

## Procedures for Recording and Reporting Adverse Events

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Adverse Event (AE):** Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences which are not necessarily caused by or related to that therapy.  **Adverse Reaction (AR):** Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.  **Unexpected Adverse Reaction** (UAR): An adverse reaction the nature and severity of which is not consistent with the information known about the therapy in question in the view of the investigator  **In non-CTIMPs, a serious adverse event (SAE) is defined as an untoward occurrence that:**  (a) results in death;  (b) is life-threatening;  (c) requires hospitalisation or prolongation of existing hospitalisation;  (d) results in persistent or significant disability or incapacity;  (e) consists of a congenital anomaly or birth defect; or  (f) is otherwise considered medically significant by the investigator**.**  **An SAE occurring to a research participant should be reported to the main REC, where in the opinion of the Chief Investigator (CI) the event was:**   * Related – that is, it resulted from administration of any of the research procedures, and * Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.   Reporting Responsibilities  All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) should be reported immediately to the Chief Investigator and to the Sponsor.  Reports of Serious Adverse Events (SAEs) that are:   * **related**to the study (ie they resulted from administration of any of the research procedures) and * **unexpected**(ie not listed in the protocol as an expected occurence)   Should be submitted to the REC using the [Non-CTIMP safety report to REC form](https://www.hra.nhs.uk/documents/1087/safety-report-form-non-ctimp.docx).  These should be sent within 15 days of the chief investigator becoming aware of the event. Reports of  SAEs in double-blind trials should be unblinded.  There is no requirement for annual safety reports in addition to the information provided through the annual [progress report](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/). | | | | |
|  | | **Who** | **When** | **How** | **To Whom** | |
| **SAE** | | Chief Investigator | Within 15 days of CI becoming aware of the event | SAE Report form for Non-CTIMPs, available from NRES website. | Main REC with a copy to the sponsor | |
| **Urgent Safety Measures** | | Chief Investigator | Immediately  Within 3 days | By phone  Notice in writing setting out reasons for the urgent safety measures and the plan for future action. | Main REC  Main REC with a copy sent to the sponsor. The MREC will acknowledge this within 30 days of receipt. | |
| **Progress Reports** | | Chief Investigator | Annually (starting 12 months after the date of favourable opinion) | Annual Progress Report Form (non-CTIMPs) available from the NRES website | Main REC with a copy to the sponsor | |
| **Declaration of the conclusion or early termination of the study** | | Chief Investigator | Within 90 days (conclusion)  Within 15 days (early termination)  *The end of study should be defined in the protocol* | End of Study Declaration form available from the NRES website | Main REC with a copy to the sponsor | |
| **Summary of final Report** | | Chief Investigator | Within one year of conclusion of the Research | No Standard Format  However, the following Information should be included:-  Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to subjects | Main REC with a copy to be sent to the sponsor | |

### Adverse events that do not require reporting

*Define here any AE’s or SAE’s that are expected and do not require reporting for this trial. . Please define the period for AE reporting – eg consent or randomisation, or first therapy session until 30 days post final therapy session*

## Stopping Rules

*Define rules e.g.*

|  |
| --- |
| The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee regulatory authority or ethics committee concerned.  The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. |

# Statistics

*A description of the measures taken to avoid, or at least minimize, bias should be given*

## Sample Size

*The number of subjects to be enrolled (in multicentre trials, the numbers of subjects for each site) should be stated, together with the rationale for the sample size (the “power calculation”).*

## Randomisation

*Describe statistical basis of the randomisation (e.g. stratified etc.) and blinding, details of randomisation process to be included in section 6.4.*

## Analysis

*A description of the statistical methods to be employed, including timing of any planned interim analyses should also be provided The level of significance that is to be used in each trial analysis must be stipulated, together with the procedure(s) for accounting for any missing, unused, and spurious data. Procedures for reporting any deviation from the original statistical plan should be described and justified. The data set for any analysis must be clearly stipulated (eg “all subjects”, “randomised subjects”, “intent to treat”) and the population(s) should be clearly defined. Define the trial stopping rules if appropriate.*

# Trial Steering Committee

*Detail composition and function of the Committee (if used). The Committee Chair should be independent (ie not a co-investigator). Lay members or patient population representative are desirable*

# Data Monitoring Committee

*Detail composition and function of the Committee (ie - to assess trial progress, occurrence of adverse events and all other aspects). Define how often the committee will meet.*

# Direct Access to Source Data and Documents

*It wil be specified, (or reference is made to another written agreement) that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients’ case sheets, blood test reports, X-ray reports, histology reports etc).*

|  |
| --- |
| e.g.  The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (eg patients’ case sheets, blood test reports, X-ray reports, histology reports etc). |

# Ethics & Regulatory Approvals

*A statement that the trial will be conducted in compliance with the principles of the Declaration of Helsinki (specifying which amendment), the principles of GCP and all of the applicable regulatory requirements (specify current legislation) is essential. State the name and address of the REC to which the study protocol and other documentation will be submitted (eg Liverpool Adult Research Ethics Committee or Liverpool Children’s Research Ethics Committee). You should also state that any subsequent protocol amendments will submitted to the REC and Regulatory Authorities for approval, and that you will comply with regulations, particularly specifying, Pharmacovigilance reporting and providing the REC & MHRA with progress reports, and a copy of the Final Study Report*

e.g.

|  |
| --- |
| The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK policy framework for health and social care research and the Mental Capacity Act 2005.  This protocol and related documents will be submitted for review to XXXXXX Research Ethics Committee (REC)  The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor |

# Quality Assurance

*Give details as to how QA will be maintained,*

|  |
| --- |
| e.g.  Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team (DETAIL METHODS) |

# Data Handling

*Give details regarding the data handling procedures.*

|  |
| --- |
| e.g.  The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:  Patient data will be anonymised.(amend as required)   * All anonymised data will be stored on a password protected computer. * All trial data will be stored in line with the Data Protection Act. * and archived in line with Sponsor requirements |

# Data Management

*Give details of whether paper or electronic CRF will be used, describe the proposed database etc*

# Publication Policy

*State how you intend to put the results of the trial into the public domain*

|  |
| --- |
| e.g.  It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. |

# Insurance / Indemnity

*Give details of the insurance/ indemnity arrangements for the trial.*

# Financial Aspects

*Describe how the trial is to be funded.*

|  |
| --- |
| e.g.  Funding to conduct the trial is provided by XXXXXXXXXXXXXXXX |

# Signatures

*To be signed by Chief Investigator minimum and statistician if applicable.*

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Chief Investigator Date

*Print name*

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Statistician (if applicable) Date

*Print name*

# References

*Provide citations for all publications referenced in the text. References should show thoughtful consideration of the research topic. Publications should be recent and organized in the format required by major journals. It should be organized as any standard bibliography.*

1. Author(s) Last Name, Initial(s). Title of Reference Article, Year Journal, Volume, Page(s)
2. Author(s) Last Name, Initial(s). Title of Reference Article, Year Journal, Volume, Page(s)

# Appendixes

*This section should contain all pertinent documents associated with the management of the study. The following lists a few examples of potential attachments:*

* Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
* Patient Information Sheet
* Sample Consent Form
* Study Procedures Flowchart/Table
* SAE Reporting Flow Chart

# Confidentiality agreement ???