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| This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended). | | | | | |
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| TABLE OF CONTENTS |
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| **Once protocol draft is complete, left click on the table of contents below, press F9 and update the entire table** |
|  |
|  |
| [LIST OF ABBREVATIONS 13](#_Toc448481756)  [STUDY SYNOPSIS 14](#_Toc448481757)  [GLOSSARY OF TERMS 15](#_Toc448481758)  [STUDY FLOW CHART 16](#_Toc448481759)  [SCHEDULE OF ASSESSMENTS 17](#_Toc448481760)  [1 INTRODUCTION 18](#_Toc448481761)  [1.1 BACKGROUND 18](#_Toc448481762)  [1.2 RATIONALE 18](#_Toc448481763)  [1.3 IMP: PRIOR EXPERIENCE IN [DISEASE AREA] (if applicable) 18](#_Toc448481764)  [1.4 STUDY HYPOTHESIS 19](#_Toc448481765)  [2 STUDY OBJECTIVES 20](#_Toc448481766)  [2.1 PRIMARY ENDPOINT 20](#_Toc448481767)  [2.2 SECONDARY ENDPOINT(S) 20](#_Toc448481768)  [3 STUDY DESIGN 21](#_Toc448481769)  [3.1 STUDY POPULATION 21](#_Toc448481770)  [3.2 INCLUSION CRITERIA 21](#_Toc448481771)  [3.3 EXCLUSION CRITERIA 21](#_Toc448481772)  [3.4 INDENTIFICATION OF PARTICIPANTS AND CONSENT 22](#_Toc448481773)  [3.5 WITHDRAWAL OF SUBJECTS 22](#_Toc448481774)  [4 TRIAL PROCEDURES 23](#_Toc448481775)  [4.1 STUDY SCHEDULE 23](#_Toc448481776)  [4.1.1 VISIT 1: VISIT DESCRIPTION (e.g. SCREENING) 23](#_Toc448481777)  [4.1.2 VISIT 2: VISIT DESCRIPTION (e.g. RANDOMISATION) 23](#_Toc448481778)  [4.1.3 VISIT X: ADD ADDITIONAL VISITS AS REQUIRED 23](#_Toc448481779)  [4.2 STUDY OUTCOME MEASURES 24](#_Toc448481780)  [4.2.1 PRIMARY OUTCOME MEASURE(S) 24](#_Toc448481781)  [4.2.2 SECONDARY OUTCOME MEASURE(S) 24](#_Toc448481782)  [4.3 LABORATORY TESTS 24](#_Toc448481783)  [5 ASSESSMENT OF SAFETY 25](#_Toc448481784)  [6 DRUG INFORMATION (if applicable) 26](#_Toc448481785)  [6.1 DRUG A 26](#_Toc448481786)  [6.1.1 DRUG A TREATMENT SCHEDULE 26](#_Toc448481787)  [6.1.2 RATIONALE FOR CHOSEN DOSE 26](#_Toc448481788)  [6.1.3 INVESTIGATIONAL PRODUCT ADMINISTRATION 26](#_Toc448481789)  [6.2 DRUG B 27](#_Toc448481790)  [6.2.1 DRUG B TREATMENT SCHEDULE 27](#_Toc448481791)  [6.2.2 RATIONALE FOR CHOSEN DOSE 27](#_Toc448481792)  [6.2.3 INVESTIGATIONAL PRODUCT ADMINISTRATION 27](#_Toc448481793)  [6.3 STUDY SUPPLIES 28](#_Toc448481794)  [6.3.1 SUPPLY OF STUDY TREATMENT 28](#_Toc448481795)  [6.3.2 LABELLING OF STUDY TREATMENT 28](#_Toc448481796)  [6.3.3 STORAGE OF STUDY TREATMENT 28](#_Toc448481797)  [6.3.4 DRUG ACCOUNTABILITY 28](#_Toc448481798)  [7 PHARMACOVIGILANCE 29](#_Toc448481799)  [7.1 DEFINITIONS OF ADVERSE EVENTS 29](#_Toc448481800)  [7.2 SERIOUS ADVERSE EVENT (SAE) 29](#_Toc448481801)  [7.3 RECORDING AND REPORTING OF ADVERSE EVENTS 30](#_Toc448481802)  [7.4 ANNUAL SAFETY REPORTING 30](#_Toc448481803)  [8 STATISTICS AND DATA ANALYSIS 31](#_Toc448481804)  [8.1 STATISTICAL ANALYSIS PLAN 31](#_Toc448481805)  [8.2 PRIMARY EFFICACY ANALYSIS 31](#_Toc448481806)  [8.3 SECONDARY EFFICACY ANALYSIS 31](#_Toc448481807)  [8.4 SAFETY ANALYSIS 31](#_Toc448481808)  [8.5 SOFTWARE FOR STATISTICAL ANALYSIS 31](#_Toc448481809)  [8.6 SAMPLE SIZE 31](#_Toc448481810)  [8.7 MANAGEMENT AND DELIVERY 31](#_Toc448481811)  [9 TRIAL CLOSURE / DEFINITION OF END OF TRIAL 32](#_Toc448481812)  [10 DATA HANDLING 33](#_Toc448481813)  [10.1 RANDOMISATION 33](#_Toc448481814)  [10.2 CASE REPORT FORMS / ELECTRONIC DATA RECORD 33](#_Toc448481815)  [10.3 RECORD RETENTION 33](#_Toc448481816)  [11 TRIAL MANAGEMENT 34](#_Toc448481817)  [11.1 ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP 34](#_Toc448481818)  [11.2 TRIAL STEERING COMMITTEE (TSC) 34](#_Toc448481819)  [11.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) 34](#_Toc448481820)  [12 STUDY MONITORING 35](#_Toc448481821)  [13 PROTOCOL AMENDMENTS 36](#_Toc448481822)  [14 ETHICAL CONSIDERATIONS 37](#_Toc448481823)  [14.1 ETHICAL CONDUCT OF THE STUDY 37](#_Toc448481824)  [14.2 INFORMED CONSENT 37](#_Toc448481825)  [15 INSURANCE AND INDEMNITY 38](#_Toc448481826)  [16 FUNDING 39](#_Toc448481827)  [17 ANNUAL REPORTS 40](#_Toc448481828)  [18 DISSEMINATION OF FINDINGS 41](#_Toc448481829)  [19 REFERENCES 42](#_Toc448481830)  [APPENDIX 1. 43](#_Toc448481831) |
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| LIST OF ABBREVIATIONS | |
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| **Complete as required, all abbreviations used in the protocol should be defined upon first mention and added to this table** | |
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| AE | Adverse Event |
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| REC | Research Ethics Committee |
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| SAE | Serious Adverse Event |
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| STUDY SYNOPSIS | |
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| **This section briefly outlines the study. Enter a concise description in each of the boxes below** | |
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| *Duration of Study* |  |
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| *Objectives* |  |
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| *Primary Endpoint* |  |
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| *Rationale* |  |
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| *Methodology* | e.g. Randomised, placebo-controlled study |
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| *Sample Size* |  |
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| *Screening* |  |
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| GLOSSARY OF TERMS | |
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| STUDY FLOW CHART |
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| **Insert a study flow chart that summarises the participant journey through the study. Participant identification, point of consent, randomisation, treatment arms and follow-up should always be shown on the flow chart** |
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| SCHEDULE OF ASSESSMENTS | | | | | | | | | |
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| **This schedule is vitally important and shows the procedures required at each visit. All procedures should be listed in the table and footnotes added as required** | | | | | | | | | |
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| 1. SCHEDULE OF ASSESSMENTS | | | | | | | | | |
| **Study Procedure** | **Visit 1[[1]](#footnote-1)**  **TIME** | **Visit 2**  **TIME** | **Visit 3**  **TIME** |  |  |  |  |  |  |
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| Obtain Informed Consent | ✓ |  |  |  |  |  |  |  |  |
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| Review Inclusion/Exclusion Criteria | ✓**[[2]](#footnote-2)** |  |  |  |  |  |  |  |  |
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| INTRODUCTION |
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| This section is vitally important and outlines the reasons for doing the study.  This section should make full use of the headers below and provide an in-depth description of the proposed study, a description of the participant population and the problem, any IMP, a summary of findings from non-clinical studies that potentially have clinical significance, and from previous clinical trials that are relevant to this study.  A summary of the known and potential risks and benefits to participants should be clearly outlined, together with, if applicable, a justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s). This information should be supported by appropriate references[[3]](#endnote-1) to published literature on the disease condition, its treatment and, if applicable, the use of the study drug for the indication. Data from previous studies as well as other information that provides background for the trial should be included. |
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| BACKGROUND |
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| RATIONALE |
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| IMP: PRIOR EXPERIENCE IN [DISEASE AREA] (if applicable) |
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| STUDY HYPOTHESIS |
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| STUDY OBJECTIVES |
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| This section should state the type of study (e.g. a double blind, multi-centre, parallel group study) and the overall purpose, aims and objectives of the study (e.g. to compare the efficacy of Drug A to Drug B in participants with X), along with details of the primary, secondary and tertiary (if applicable) endpoints. |
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| PRIMARY ENDPOINT |
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| * Measurement that will form the PRIMARY endpoint(s) |
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| SECONDARY ENDPOINT(S) |
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| * Measurement that will form the SECONDARY endpoint(s) |

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| STUDY DESIGN |
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| A description of the trial design along with standard statements on the conduct of the trail.  This study (INSERT TRIAL TYPE) will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006). |
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| STUDY POPULATION |
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| Outline the total number of participants that will be recruited to the trial and the setting where they will be identified.  Briefly describe the participant group and how eligibility to enter the trial will be assessed.  If applicable, outline the randomisation regimen (e.g. eligible participants will be randomised (1:1) to receive either Intervention A or Intervention B). |
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| INCLUSION CRITERIA |
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| An exhaustive list of trial inclusion criteria should be outlined here. If applicable, inclusion criteria for each study “group” should be fully defined in separate lists.  Written informed consent should be included as an inclusion criterion.  It is preferable that the criteria are provided in a bulleted list, as per the example below.   * Written informed consent * Male or non-pregnant female ≥ 18 years of age * ADD OTHERS AS REQUIRED |
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| EXCLUSION CRITERIA |
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| As outlined above, an exhaustive list of trial exclusion criteria should be outlined here.  It is preferable that the criteria are provided in a bulleted list, as per the example below.   * Contraindications to treatment X   + List of contraindications as sub-list   + ADD OTHERS AS REQUIRED * History of allergies to active substances in either trial medication, or to excipients * Severe concurrent medical condition that would prevent participation in study procedures (e.g. cardiac failure with severe pulmonary oedema) or life expectancy ≤ 3 months * ADD OTHERS AS REQUIRED |

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| INDENTIFICATION OF PARTICIPANTS AND CONSENT |
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| Clearly state how participants will be identified, screened for eligibility and approached for informed consent. It is preferable that participants are given a minimum of 24 hours to consider participation and it should be stated that all efforts will be made to ensure participants understand the commitment required to fulfil the study requirements. In addition, participants should be made aware that participation is voluntary and they can leave the study at any time without their standard care being affected.  If participants may lack the capacity to consent, the procedure to obtain informed assent from relatives or independent clinicians should be clearly outlined as well as the procedure to obtain informed consent from the participant for continued participation should they regain capacity.  Consent/assent procedures for trials involving children should also be clearly outlined and age-appropriate consent/assent forms prepared. |
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| WITHDRAWAL OF SUBJECTS |
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| Details of when and how to withdraw subjects from the trial should be included in this section.  Information should be included on how data from participants who withdraw should be included here along with decision to replace participants. Arrangements for safety follow-up of participants who withdraw due to adverse events should also be outlined.  Participants have the right to withdraw from the trial at any point for any reason. The investigator can also withdraw participants from the study intervention in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations or any other relevant reasons. |

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| TRIAL PROCEDURES |
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| STUDY SCHEDULE |
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| A brief overview of the study visits should be outlined here.  In the sections below, procedures that will be performed as part of the study should be listed in detail as per the examples below. It is important to check that the information listed below is consistent with the study flowchart. It may also be helpful to outline which measurements are considered standard of care and which are performed for the study only. Specific study procedures should only be carried out after written informed consent has been obtained |
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| VISIT 1: VISIT DESCRIPTION (e.g. SCREENING) |
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| **For example:**   * Medical history * CT Brain * Blood samples for biochemistry (including eGFR and blood glucose) and haematology (including coagulation) * Blood pressure, pulse and temperature * Capillary blood glucose * Weight * Physical examination * Completion of CRF |
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| VISIT 2: VISIT DESCRIPTION (e.g. RANDOMISATION) |
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| VISIT X: ADD ADDITIONAL VISITS AS REQUIRED |
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| STUDY OUTCOME MEASURES |
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| A description of the measures that will be used to determine efficacy of treatment (e.g. blood pressure, infarct size) should be outlined here. The measurement and the processing of the information should be described in detail starting with the primary efficacy parameters first then any secondary parameters. |
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| PRIMARY OUTCOME MEASURE(S) |
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| SECONDARY OUTCOME MEASURE(S) |
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| LABORATORY TESTS |
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| Laboratory measurements required should be outlined here including details of handling, storage and packaging instructions. Details of the labs conducting the analysis should be included here, if appropriate and available. Laboratory tests should be categorised as 1, 2 or 3. For NHS laboratories Category 1 is central laboratories, 2 is routine laboratory test that is non standard for that patient group and 3 is a non standard laboratory test.  Some studies will develop a separate laboratory manual; if this is the case, please state here. |

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| ASSESSMENT OF SAFETY |
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| Any specific measures that will be used specifically to determine participant safety during the study should be outlined here. These may include physical examinations, blood tests and adverse event reporting.  Timings of safety measurements should be outlined here. |

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| DRUG INFORMATION (if applicable) |
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| This section is usually completed by the Sponsor Pharmacy team. Suggested headings and information are included below.  Participants who are eligible for the study will be randomised to receive either:   * **TEST DRUG**   or   * **PLACEBO**   Further details of treatment schedules are given below. |
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| DRUG A |
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| DRUG A TREATMENT SCHEDULE |
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| RATIONALE FOR CHOSEN DOSE |
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| INVESTIGATIONAL PRODUCT ADMINISTRATION |
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| DRUG B |
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| DRUG B TREATMENT SCHEDULE |
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| RATIONALE FOR CHOSEN DOSE |
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| STUDY SUPPLIES |
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| SUPPLY OF STUDY TREATMENT |
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| LABELLING OF STUDY TREATMENT |
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| STORAGE OF STUDY TREATMENT |
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| DRUG ACCOUNTABILITY |
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| PHARMACOVIGILANCE |
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| This section currently contains standard text. R&D will liaise with the Pharmacovigilance team to ensure that this section is study specific. |
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| DEFINITIONS OF ADVERSE EVENTS |
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| **Adverse Event (AE) –** Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
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| SERIOUS ADVERSE EVENT (SAE) |
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| Any adverse event or adverse reaction that:   1. Results in death 2. Is life threatening 3. Requires hospitalisation or prolongation of existing hospitalisation 4. Results in persistent or significant disability or incapacity 5. Consists of a congenital anomaly or birth defect 6. Is otherwise considered medically significant by the investigator 7. Important adverse events/reactions 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 |

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| RECORDING AND REPORTING OF ADVERSE EVENTS |
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| This section should include study specific information on what SAEs will be reported. For example, in stroke trials it is likely that the participants will have a number of co-morbidities and therefore adverse events and reporting of all of the expected outcomes may be an onerous task. Therefore the Pharmacovigilance office can help outline levels of reporting appropriate for this study.  If safety reporting is required, then R&D will liaise with the Pharmacovigilance office to ensure this section is updated appropriately. |
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| ANNUAL SAFETY REPORTING |
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| Details on safety reporting will be completed by the Research Co-ordinator or Pharmacovigilance based on study requirements. |

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| STATISTICS AND DATA ANALYSIS |
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| Researchers should gain input on the statistical section of the protocol from the study statistician. This section of the protocol should contain a description of how the trial data will be managed. |
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| STATISTICAL ANALYSIS PLAN |
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| The study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be authored by the Trial Statistician and agreed by the Trial Steering Committee (TSC) before any unblinded data is seen (if appropriate). |
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| PRIMARY EFFICACY ANALYSIS |
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| Outline the primary efficacy variable and how the data will be processed. |
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| SECONDARY EFFICACY ANALYSIS |
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| Outline each of the secondary efficacy variables and how they will be processed. |
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| SAFETY ANALYSIS |
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| **Example text:** The safety data (adverse events) – both numbers of subjects and events – will be summarised by randomisation group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified. |
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| SOFTWARE FOR STATISTICAL ANALYSIS |
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| **Example text:** The statistical software to be used will be specified in the Statistical Analysis Plan. It is likely to be SAS 9.2 for Windows, Cary, NC, USA. |
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| SAMPLE SIZE |
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| It is important that adequate consideration of sample size is presented and the calculations are accurate and well founded. |
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| MANAGEMENT AND DELIVERY |
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| **Example text:** The Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit, a fully registered UK CRN Clinical Trials Unit, will manage and analyse trial data. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan. |

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| TRIAL CLOSURE / DEFINITION OF END OF TRIAL |
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| The end of the trial should be outlined clearly.  Please see example text below.  The trial will end when the TSC agrees that one or more of the following situations applies:   * Last participant, last study visit;   OR   1. The planned sample size has been achieved; 2. The Independent Data Monitoring Committee (IDMC) has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatments; 3. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained; 4. New information makes it inappropriate to continue to randomise participants to one or other arm of the trial; 5. Recruitment is so poor that completion of the trial cannot reasonably be anticipated. |

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| DATA HANDLING |
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| A description of how data generated by the study will be handled and the process for randomisation should be included here.  Please see example text below. |
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| RANDOMISATION |
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| A central randomisation facility (interactive voice response system, IVRS) will allocate the randomised therapy per participant. The IVRS, based at the Data Centre, will be available by telephone. A central unblinding facility based at the Data Centre will also be available by telephone. Notification of any unblinding will be sent to the CI. |
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| CASE REPORT FORMS / ELECTRONIC DATA RECORD |
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| An electronic case report form (eCRF) will be used to collect study data. The eCRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow and access to the eCRF will be restricted, with only authorised, site-specific personnel able to make entries or amendments to their participants’ data. It is the investigator’s responsibility to ensure completion and to review and approve data captured in the eCRF.  All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change). |
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| RECORD RETENTION |
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| To enable evaluations and/or audit from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link record), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years. |

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| TRIAL MANAGEMENT |
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| This section should outline the systems in place to manage the trial such as the local trial management group, the TSC and the IDMC, how they will be provided information and how decisions will be made. |
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| ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP |
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| The trial will be co-ordinated from INSERT UNIT by the Trial Management Group. The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, trial manager, research nurse, and data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. |
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| TRIAL STEERING COMMITTEE (TSC) |
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| IF REQUIRED  The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC should:   * Agree the trial protocol and any amendments * Provide advice to the investigators on all aspects of the trial * Have members who are independent of the investigators, in particular an independent chairperson   Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC. |
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| INDEPENDENT DATA MONITORING COMMITTEE (IDMC) |
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| IF REQUIRED  The role of the IDMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants’ attention or any reasons for the trial not to continue. The IDMC will be independent of both the investigators and the funder/sponsor and will be the only body that has access to unblinded data. It will make recommendations to the TSC. |

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| STUDY MONITORING |
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| This section will normally be completed by the NHS GG&C Monitoring team. The Research Co-ordinator will liaise with the Monitoring department to ensure this section is study specific. |

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| PROTOCOL AMENDMENTS |
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| Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, REC and sponsor.  The CI and TSC will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.  Before the amended protocol can be implemented, favourable opinion/approval must be sought from the original reviewing REC, and Research and Development (R&D) office(s). |

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| ETHICAL CONSIDERATIONS |
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| ETHICAL CONDUCT OF THE STUDY |
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| The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).  Favourable ethical opinion will be sought from INSERT REC NAME before participants are entered into this clinical trial. Participants will only be allowed to enter the study once they have provided written informed consent or their next of kin have provided written informed assent (if required).  The CI will be responsible for updating the REC of any new information related to the study. |
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| INFORMED CONSENT |
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| The process for obtaining informed consent should be included and made specific for the study, focussing on any ethical considerations related to informed consent. Section 3.4 can be referenced as appropriate.  **Example text:** Written informed consent should be obtained from each trial participant. Alternatively, if the participant is unable to consent for themselves, then written informed assent should be provided by the next of kin.  The research nurse or investigator will explain the exact nature of the study in writing, provision of participant information sheet, and verbally. This will include the known side-effects that may be experienced, and the risks of participating in this clinical trial. Trial participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.  In the case of participants who were unable to consent at the start of the study, written informed consent will be sought once they regain capacity. |

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| INSURANCE AND INDEMNITY |
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| This section should be completed by the sponsor representative (R&D Co-ordinator). Any requirements for additional insurance by the University of Glasgow will be assessed via interaction with the University of Glasgow Research Governance office if required.  **Example text:**  The XXX trial is sponsored by NHS Greater Glasgow and Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).  The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care. |

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| FUNDING |
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| Include information on the Funder, grant award number and any other relevant reference numbers and dates. |

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| ANNUAL REPORTS |
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| The Research Co-ordinator will advise on the content of this section as requirements may vary depending on the Funder.  **Example text:** A biannual progress report will be submitted to the Funder, the first being submitted 6 months from the date that all trial related approvals are in place. Annual reports will be submitted to the REC, regulatory authority and Sponsor with the first submitted one year after the date that all trial related approvals are in place. |

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| DISSEMINATION OF FINDINGS |
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| The section should outline how the findings from the trial will be disseminated. This would normally include presentation at conferences and publications of papers and may include student theses in the case of studies contributing towards educational qualifications. Consideration should also be given to notifying study participants of the findings. |

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| REFERENCES |
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| All references within the protocol should be outlined here and use the style below. |
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| INSERT TITLE |
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| Additional appendices should be added as required. Normally, copies of standard tests used in the study should be added as appendices. In addition, diagnostic criteria and definitions of adverse event reporting (e.g. CTCAV v3.0 [as used in cancer studies]) could also be added to the protocol as appendices. |

1. As appropriate [↑](#footnote-ref-1)
2. Only at initial visit [↑](#footnote-ref-2)
3. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;**375**:1695-703 [↑](#endnote-ref-1)