Academic and Clinical Central Office for Research and Development

RISK ASSESSMENT TOOL

SNAP study (Ref: 2010/R/AE/02)

Investigational Product/Agent

	Risk Adaption Categorisation	Justification	Mitigation	Management Strategy comment
1	Study interventions e.g. *- Comparable to the risk of standard care (A)* *- Risk somewhat higher than standard care (B)* *- Risk markedly higher than standard care (C)*	This trial has been categorised as 'Type B'. Ondansetron is marketed and indicated for nausea/vomiting in other patient groups e.g. chemotherapy and post-operative patients thus is being used for a new indication and presents a risk somewhat higher than standard care. Ondansetron will be administered prophylactically and its safety profile is well characterised. Ondansetron will be compared with a sodium chloride placebo. The placebo presents a risk not higher than standard care. Acetylcysteine (antidote) will be used for its indicated use however, a modified regimen of acetylcysteine will be used in some subjects. The modified regimen has an identical total dose to the conventional regimen but with a steady-state concentration and a lower peak concentration therefore, this is not a substantial dose modification and acetylcysteine presents a risk comparable to standard care.		None

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
2	Expected hazards related to study investigations e.g. *- side effects* *- high risk dosing procedure e.g. cohort, MTD* *- high level of treatment interception* *- e.g. frequent PKs* *- Interactions with concomitant/permitted medications* *- Interactions between IMPs/NIMPs* *- Risk carrying interventions e.g. open heart surgery* *- Other known or anticipated safety issues* - Precautions and impact on eligibility - congenital anomalies	Minor side effects that if occur, the impact would be relatively non-substantial in this patient group: Ondansetron - headache, flushing and constipation as defined by the SPC. Acetylcysteine - nausea, vomiting, flushing and skin rash as defined by the SPC.	Moderate	An independent DMC will be established before the study begins to oversee the safety of trial subjects. The modified dose of acetylcysteine may reduce the instance of AEs according to previous research.	Monitoring: Of those participants selected for monitoring, all AEs will be reviewed
		Side effects that could have a substantial impact in this patient group: Ondansetron - Hypersensitivity reactions, transient ECG changes, seizures as defined by the SPC. Acetylcysteine - more serious anaphylactoid reactions have been reported that include angioedema, bronchospasm/respiratory distress, hypotension, tachycardia and hypertension as defined in the SPC.	Very low	Literature indicates that Ondansetron will be the safest choice of anti-emetic. Subjects with a known hypersensitivity to Ondansetron or other 5HT3 antagonists will not be included. The researchers believe the potential benefits outweigh the potential risks for the trial subjects. The risk of transient ECG changes is sufficiently low that ECG monitoring is not required in the opinion of the investigators. Acetylcysteine will be used according to its indication except in the modified dose arm. The modification is unsubstantial and the total dose will not be altered. Some research indicated that the modified dose may reduce the instance of AEs.	
		Risk of Interactions of the IMPs causing harm to subjects. A modified regimen, compared with the regimen	Very low	There are no known interactions between the IMPs or permitted medications recorded in the SPCs.	

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
		stated in the SPC, of acetylcysteine will be used in some subjects. No risk as the modified acetylcysteine regimen has an identical total dose to the conventional regimen but with a steady-state concentration and a lower peak concentration which may reduce the instance of AEs according to previous research. Previous research indicates that the traditional very high initial concentration is not necessary for clinical efficacy	n/a		
		Risk of harm to foetus.	Very low	To date, the safe use of ondansetron during pregnancy has not been established. Patients that are known to be pregnant will not be included. The treatment period is 20.25 hours and is under supervision thus subjects cannot become pregnant during the study. All pregnant female participants and partners of male participants will be followed up until post-birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to the sponsor.	
		Risks identified potentially impact patient wellbeing and safety.			

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
3	Pharmacovigilance e.g. *- AE reporting* *- USMs* *- SUSAR reporting* *- Safety monitoring committee*	Standard reporting and DMC set up as noted in section 2 except: Liver function abnormality and renal impairment SAEs will not be reported to the sponsor in an expedited fashion. GCP dictates that SAEs should be reported to the sponsor immediately. Risk that not reporting stated SAEs to the sponsor could result in potential safety issues not being identified.	Very low	Stated events will be recorded in the CRF, thus will be available to the sponsor to review via the CRF. Stated events will also be reviewed by the DMC. It is anticipated that liver abnormality and renal impairment may be an outcome for patients as a result of paracetamol toxicity as opposed to a reaction to study treatment.	None
4	Manufacture and distribution of the product(s) e.g. *- licence status* *- QP certification: packaging, labelling, distribution,*	Assembly and distribution of ondansetron and placebo delegated to a commercial contractor. Risk is that procedures and quality systems are unknown to the sponsor. If the products are compromised, study outcomes could be compromised. Acetylcysteine is taken from hospital stock and overlabelled. Risk that products will not be labelled as required according to annex 13.	Very low Very low	Pre-qualification checks will be performed of the commercial contractor by QA representatives of the sponsor. An agreement describing arrangements and responsibilities will be put in place. QP certification and related documents will be reviewed by the sponsor. Over-labelling is routinely performed by qualified clinical trials pharmacists with routine QC check systems in place. IMP will be labelled for trial use.	QA: Pre-qualification check/audit

Study Participants

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
	Difficulties or incapacity to give consent in comparison with a fully cognisant adult e.g. *- language, emergency situation, age, legal incapacity, cognitive impairment. AWI, coercion* *- Vulnerable target population e.g. babies, elderly*	Depending on the effects of the paracetamol overdose, subjects may lack capacity to provide informed consent. Also risk that a subject is incorrectly assessed as having capacity to provide consent. Risk that the informed consent process is not undertaken as per the protocol/GCP/REC approval.	Very low	Informed consent will be sought according to methods approved by an independent REC and local NHS management organisation. The researchers have experience in taking informed consent, and assessing capacity of subjects, in trials of this nature. If a potential subject lacks capacity, consent will be obtained from the subject's legally accepted representative.	Monitoring: All subject consent forms will be reviewed and the consent process will be closely examined through on-site visits.
5		Due to the emergency situation, subject/representatives may have a very short time to consider participation (10-60mins) thus, patients/representatives may not give due consideration to the decision to participate. This is further complicated by consideration of participation in the sub-study (entails an extra blood sample).	Very Low	Subjects that are unlikely to complete the full course will not be included. If it is considered that lack of capacity is not temporary (lasting more than 12 hours), patients will not be considered for inclusion. When capacity is recovered, consent from the subject will be sought as soon as possible. If the subject withholds consent, they will be withdrawn from the study and their data will not be used in analysis. Consent for the sub-study will only be sought when subjects have fully recovered capacity. The sample for the sub-study will only be obtained subsequent to consent.	
		Due to the emergency	Low	Eligibility criteria mainly consist of factors that	Monitoring: eligibility checks

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
		situation, researchers may have a relatively short time in which to confirm eligibility (10-60mins). Risk that an ineligible patient is recruited.		must be considered in normal clinical care for this patient group. Accounting for the risk-benefit balance of the modified acetylcysteine regimen, participation in the study is largely consistent with standard treatment from the perspective of the subjects.	(100% of criteria will be performed for all subjects monitored).
		Risk of insufficient availability of qualified researchers to perform consent and capacity decisions, and that the informed consent process is not undertaken as per the protocol/GCP/REC approval.	Very low	Members of the research team routinely work with this patient group and a sufficient number of staff will join the research team. If for an unforeseen reason, there is insufficient staff availability to perform and oversee all study procedures when a potential subject presents, the potential subject will not be enrolled in the study.	
		Risks could impact on subject rights, safety and well-being and could impact study outcomes.			
6	Collection of indirectly identifying or sensitive characteristics e.g. *- phone number, address, place of work, CHI number* *-sensitive characteristics, ethnic origins, sexual or religious orientation* *- data sent outside EU*	None – no indirectly identifying or sensitive characteristics will be collected.	n/a	n/a	n/a
7	Participant well-being e.g. *- risk-benefit balance* *- burden of study visits* *- Lifestyle requirements* *- Study specific procedures which carry risk additional to standard care*	Risk of causing distress to subjects who are initially entered into the study with consent from a legal representative but do not wish to take part in the study when they recover capacity.	Unknown	The study team have identified the most likely cause of such a reaction from the subject would be a lack of information. In response, the importance of good, clear and full communication, with subjects and legal representatives, will be highlighted to the study team in training before and during the study. In addition, capacity will be re-assessed prior to	Monitoring: eligibility checks (100% of criteria) will be performed for all subjects monitored

	Risk Factor	ID of Risks	Likelihood	Mitigation	Management Strategy comment
				every trial related procedure.	
		Potential risk compared with standard care is if treatment is delayed in order to assess eligibility and perform randomisation.	Very low	Researchers are familiar with the eligibility criteria and with randomisation procedures and do not expect any delay in evaluating eligibility in comparison to standard care. If unforeseen delays occur, due to randomisation procedures or study specific eligibility criteria evaluation, the subject will not be included in the study and instead proceed with standard treatment.	
		No other risks identified. Normal clinical practice is applied to participants thus no additional requirements or visits for patients. Survival data will be collected from hospital notes only.			

Study Design and Methods

	Risk Factor	ID of risks	Likelihood	Mitigation	Management Strategy Comment
8	Feasibility assessment of the study recruitment based on reliable sources e.g. *- estimation based on clinical department activity, documented pre-registry*	Sites may not have suitable/sufficient patients to meet the recruitment targets..	Low	Site selection and recruitment targets will be based on known, robust clinical department activity data.	n/a
9	Blinding of randomisation procedures e.g. *-blinded during allocation* *-centralised allocation* *-study double blinded* *-blind maintained during investigations* *-blind maintained throughout data analysis*	Allocation to treatment arm (ondanstron or placebo with acetylcysteine) will be randomised but not completely blinded. Medical and nursing staff will be blinded to the anti-emetic treatment/placebo allocation. Subjects will be blinded. Complete blinding is not possible during treatment allocation due to the nature (body weight dependent) of acetylcysteine dosing. acetylcysteine is included in all 4 treatment arms. There is a risk that the incomplete blinding could compromise the impartiality of certain researchers. This could impact study outcomes.	Low	Blind will be implemented during data analysis. Randomisation will be performed from a central trial office. Placebo will be matched to ondansetron. Doses were designed to run over 20.25hrs in both treatment arms to make treatment allocation less obvious. Distinct, clear roles for study staff	Monitoring: randomisation activities and staff roles will be subject to monitoring
10	Objective assessment of primary and the main secondary outcomes and verifiability e.g. *-objective vs. subjective assessment,* *- independent assessor of study outcomes* *-location of sample analysis* *-data points entered straight into CRF*	Clearly defined empirical endpoints (retching/vomiting recorded continuously up to 2hrs and 12hrs by nurses) described in the protocol. Potential	Very low	Nursing staff have experience in dealing with scenarios involving this patient group and retching/vomiting and will record in an objective fashion as nurses will be blinded to anti-emetic treatment/placebo. Nursing staff will be adequately trained and will understand the	Monitoring: Ensure nurses are appropriately blinded during on-site monitoring.

	Risk Factor	ID of risks	Likelihood	Mitigation	Management Strategy Comment
	-Voluminous and/or complex data collection	risk of bias or mistakes in recording retching/vomiting as interpretation and classification of events will be required as well as continuous subject monitoring. This could impact study outcomes. Adverse events will be measured via an 11 point Likert scale on a set of 9 symptoms. This is completed by the subject if they are able. Risk of mis-interpretation or miscommunication of symptoms and risk of inconsistent application. No samples collected in relation to 1˚ and 2˚ endpoints. Simple data collection. No further risks identified.	Low	importance of continuous monitoring over the whole period. Adequate numbers of staff will be provided for this task. The Likert scale is a popularly used measurement tool. Nursing staff are experienced in dealing with this patient group and are therefore experienced in interpreting the symptoms that are likely to occur. Nursing staff will be adequately trained to interpret symptoms in a consistent fashion.	
11	Complexity of study procedures e.g. *-study procedures: recruitment, design, follow-up* *-complex recruitment: cluster accrual* *-complex designs: crossover design, dose escalation, structured therapeutic interruption* *-complex follow-up: different types of follow-up visit, additional investigations as compared to standard of care*	None. Study has a simple 2x2 factorial design, incorporating the normal and modified acetylcysteine regimen and aims to provide a simpler dose calculation. Study procedures do not include any degree of complexity.	n/a	n/a	n/a

Study Organisation

	Risk Factor	ID of risks	Likelihood	Mitigation	Management Strategy Comment
12	Education, training, experience and resources of all investigator site staff in GCP and study procedures e.g. *-GCP procedures, informed consent, anonymisation, SAE reporting, queries management* *- Previous negative audit/inspection observations or other issues with the investigator(s) or investigator site* *- Adequate resources available for the duration of the study* *-Knowledge of study procedures: trial interventions, trial investigations* *-Experience in the study phase and therapeutic area.* *-Awareness of sponsor SOPs*	Multiple investigator sites (3) – 2 sites have no collaborative history with the sponsor. Such sites present a risk of non-compliance with sponsor SOPs. This could impact study outcomes and patient safety.	Moderate	Monitors will ensure that initiation procedures involve training in sponsor SOPs and study specific procedures including ISF, Serious breaches, IMP handling, SAE reporting, data reporting, deviation reporting, archiving. Training will include any staff that may be involved in study procedures. Initiation procedures will also determine if adequate resources are available. Sponsor SOPs will be provided to research site teams and are publically available on the world wide web.	Monitoring: On-site monitoring visits will be conducted and will include any staff not already trained that may become involved in study procedures.
13	Intervention management at site e.g. *-for drugs: restocking, dispensing, accountability, expiry date, re-labelling, storage conditions* *- Robustness of dose calculation* *- Technical agreement*	Possibility of staff using ward stock (acetylcysteine) instead of IMP. This would distort accountability and could impact overall intervention management. Risk that section 4.6.3 of ICH-GCP will not be complied with. Ondansetron/placebo will be labelled according to Annex 13 requirements and with specific dose thus no risks have been identified, in terms of intervention management, except the possibility of temperature excursions. Possibility of mistakes in dosing calculation	Low Low	Training will be given on compliant ward storage. Storage areas will be inspected prior to use. IMPs will be secured together to reduce risk of clinical stock being used in error. Study acetylcysteine will be over-labelled with “for trial use only”. Similar to standard of care in dose calculation thus, study team will have experience in this	Training at site set up regarding products storage and dosing preparation. Work sheets will also be reviewed remotely before the set up visit.

	Risk Factor	ID of risks	Likelihood	Mitigation	Management Strategy Comment
		(acetylcysteine) or that the standard regimen is given instead of the modified regimen in error. This could result in a patient receiving the wrong dose which could impact patient safety and study outcomes. Possibility of temperature excursions for all products. This could result in compromised products being administered to patients which could impact patient safety and study outcomes.	 Low	area and will use work sheets to calculate and record the dose. The study team will be given study specific training, including delivery of the modified regimen and the importance of the delivering the correct regimen Temperatures monitored daily in storage facilities by clinical trials pharmacists. Systems in place to report temperature excursions to the sponsor and the manufacturer and to quarantine affected products.	
14	Quickness, security and quality of data in the database e.g. *-quick data entry, e-CRF* *-secure data entry: secured websites ,passwords* *-appropriate storage of identifiable data* *-validation checks* *-QC checks*	None - paper based CRF used and then data entered into secure access database. Validation checks in place. QC checked by member of study team. No risks identified as established systems ensure the security and quality of data in the database.	n/a	n/a	n/a
15	Responsibilities e.g. *-trial unit involvement* *-Clinical Research Facility involvement* *- CI and sponsor duties defined*	Lack of clarity of roles and responsibilities. Risk of protocol or GCP non-compliance	Low	All responsibilities will be clearly defined and allocated. - The Trials Unit will be involved in trial management of all 3 sites including green light oversight, statistical consideration and data analysis. An agreement will be initiated between both the sponsor and the CI with clear delegation of roles. Agreements will also be in	Sponsorship: The sponsor will ensure regular communication is maintained with Trials Unit

	Risk Factor	ID of risks	Likelihood	Mitigation	Management Strategy Comment
				place between the sponsor and each research site with clear delegation of roles and responsibilities.	
16	Facilities e.g. *- Sufficient clinical area* *- Clinical equipment maintenance* *- Laboratories*	Study involves emergency patients thus resuscitation equipment must be maintained in good working order. Risk that unreliable resuscitation equipment could compromise patient safety.	Very low	Study will be conducted in emergency departments where it is necessary in clinical practice to have working safety equipment.	Monitoring: Monitors will verify that safety equipment has an appropriate maintenance schedule and correct equipment for the study is always available.
		The sub-study involves the collection of a blood sample that is relatively unstable. Risk of samples not handled appropriately resulting in non-viable samples and insufficient data.	Low	Sample collection will be confined to patients who present in daylight hours. Collection under these circumstances will ensure samples are processed while stable.	QA: Pre-qualification audit of the laboratory will be conducted to examine if facilities and equipment are adequate and to examine if methods are robust with descriptive procedures and lab staff are suitably trained and qualified.
		Sub-study samples are also non-routine, therefore there is a risk that samples will not be collected as required for the sub-study. This could manifest as a risk of samples not handled appropriately resulting in non-viable samples or inaccurate data.	Low	Methods are not complex however, staff involved in sample collection will be adequately trained on study specific collection methods and circumstances. The difference with routine collection and processing will be highlighted.	

Risk Factor		ID of risks	Likelihood	Mitigation	Management Strategy Comment
		No further risks identified in regards to laboratories as samples, in the main study, will only be collected for routine clinical analysis and will be processed at accredited local clinical laboratories used according to normal clinical practice.			

Outcome

Topic	Monitoring strategy	Facilitation/Sponsorship	Audit
Investigational product/agent	**Dose adjustments** (RA section 11) – reduced level of monitoring according to appendix 2 **AE Assessment** (RA section 2, 3) – regular level of monitoring according to appendix 2 **IMP Accountability** (RA section 4, 13) – regular level of monitoring according to appendix 2	**IMP management** (RA section 4, 13) **–** Risk adaption applied according to appendix 1 **Labelling** (RA section 4) – Risk adaption applied according to appendix 1 **Submission & approval** (RA section 1) – Type B	*Select 1 of 3:* *1) No audit required unless cause arises.* ***2) Monitoring reports and feedback will be reviewed to ascertain if audit is required*** *3) An audit plan will be prepared and agreed with the monitors and the sponsor(s)*
	State strategy towards each area. Intensity and nature of monitoring will be greater if for a type C study compared with type B and greater for a type B study compared with a type A study. Intensity and nature of monitoring will also be increased depending on the likelihood associated with identified risks and mitigation strategies.	*State strategy towards each area. Requirements will be reduced for type A studies compared with type B and reduced for type B studies compared with type C studies in accordance with competent authority guidelines. Type A studies will qualify for reduced submission (MHRA notification scheme) and reduced labelling requirements. Facilitation/sponsorship actions will be increased depending on the likelihood associated with identified risks and mitigation strategies. For phase I studies at the WTCRF, the role of the WTCRF phase I committee.*	
Study participants	**Participant eligibility** (RA section 5, 7,) – reduced level of monitoring according to appendix 2 **Participant calendar** (RA section 7, 11) – reduced level of monitoring according to appendix 2 **Participant consent** (RA section 5) - regular level of monitoring according to appendix 2	n/a	
	State strategy towards each area. Intensity and nature of monitoring will be increased depending on the likelihood associated with identified risks and mitigation strategies.		

Topic	Monitoring strategy	Facilitation/Sponsorship	Audit
Study Design and Methods	**Data QC checks** (RA section 14) – reduced level of monitoring according to appendix 2 **CRF completion** (RA section 10, 11, 14) – reduced level of monitoring according to appendix 2 **Protocol/regulatory compliance** (RA section 8, 11, 15, 16) – reduced level of monitoring according to appendix 2 **SDV** (RA section 10, 11, 14) – reduced level of monitoring according to appendix 2	**Safety surveillance** (RA section 2, 3) – Risk adaption applied according to appendix 1	
	State strategy towards each area. Intensity and nature of monitoring will be increased depending on the likelihood associated with identified risks and mitigation strategies.	*State strategy. Facilitation/sponsorship actions and surveillance requirements will be determined depending on the likelihood associated with identified risks and mitigation strategies.*	
Study organisation	**Staff training** (RA section 11, 12) – regular level of monitoring according to appendix 2 **Recruitment reporting** (RA section 8, 11) – reduced level of monitoring according to appendix 2 **Facilities & resources** (RA section 8, 15, 16) – reduced level of monitoring according to appendix 2 **Records and delegation** (RA section 6, 11, 15) – reduced level of monitoring according to appendix 2	**Documentation** – (RA section 3, 5, 6,) No risk adaptions applied **Archiving** (RA section 1) – Risk adaption applied according to appendix 1	
	State strategy towards each area. Intensity and nature of monitoring will be increased depending on the likelihood associated with identified risks and mitigation strategies.	*State strategy towards each area. Facilitation/sponsorship actions and documentation/archiving requirements will be determined depending on the likelihood associated with identified risks and mitigation strategies. Type A studies can qualify for reduced requirements*	

Sponsor representative…….. Printed Name……. Date…….

QA representative…….. Printed Name……. Date…….

Monitoring representative…….. Printed Name……. Date…….

Other…….. Printed Name……. Date…….

Contributors (state sections contributed to):

Facilitation/Sponsorship Risk Adaptions Appendix 1

Document	Type A		Type B		Type C	
	Risk Adaption Possible	**Risk Adaption Applied?**	**Risk Adaption Possible?**	**Risk Adaption Applied?**	**Risk Adaption Possible?**	**Risk Adaption Applied?**
Investigators Brochure	Yes		(Yes)	Yes –, SPCs used, relates to RA section 1	No	
IB annual update	No		No	N/a	No	
Sample label	Yes		(Yes)	Yes (Ach only) - , reduced labelling. Hospital stock will be over-labelled, relates to RA section 1, 4	No	
Certificate(s) of analysis	Yes		(Yes)	Yes – (Ach only) no CoA provided , hospital stock will be used, relates to RA section 1	No	
IMP shipments	Yes		Yes	No	No	
IMP handling instructions	Yes		(Yes)	No	No	
Master randomisation list	No		No	N/a	No	
Unblinding procedures	No		No	N/a	No	
Site IMP accountability	Yes		(Yes)	No	No	
IMP return/destruction	Yes		(Yes)	No	No	
IMP dossier	Yes		(Yes)	Yes – no IMP dossier for all products are licensed and relevant information is covered in other documents, justification in RA section 1	No	
MIA for IMP	Yes		(Yes)	No	No	
Manufacturing Authorisation	(Yes)		No	N/a	No	
IMP importation authorisation	No		No	N/a	No	
QP certification	N/a		(Yes)	Yes (Ach only) – no QP certification provided, hospital stock will be used, relates to RA section 1, 4	No	
GMP compliance statement	Yes		(Yes)	Yes(Ach only) – no GMP compliance statement provided, hospital stock will be used, relates to RA section 1	No	
AE/AR recording	Yes		(Yes)	No	(Yes)	
AE/AR reporting to sponsor	Yes		(Yes)	No	(Yes)	

SAE/SAR reporting to sponsor	(Yes)		(Yes)	Yes – Selected SAEs will not be reported to the sponsor in an expedited fashion, relates to RA section 3	(Yes)	
SUSAR reporting to MHRA/REC/investigators	No		No	N/a	No	
Annual safety report	No		No	N/a	No	
Trial level IMP accountability	Yes		(Yes)	No	No	
Subject level IMP accountability	Yes		(Yes)	N/a	No	
Storage conditions records	(Yes)		(Yes)	No	No	
Deviation impact assessment	(Yes)		(Yes)	No	No	
Combined/centrally held documentation	(Yes)		(Yes)	No	(Yes)	
Document retention time	(Yes)		(Yes)	Yes – documents will be retained for a minimum of 5 years as data will not support an MA application.	No	
Reduced MHRA role for approval	Yes		No	N/a	No	

Monitoring Strategy Template Appendix 2

Reduced level of monitoring			
IMP / Agent (A)	**Study Participants**	**Study Design and Methods**	**Study Organisation**
Dose Assessment: Study dose may be assessed via electronic case report forms by clinical monitors.	Participant Eligibility: Eligibility can be confirmed remotely via eligibility checklists by a trial manager or clinical monitor.	Data QC checks: May be checked remotely via electronic CRFs by a data monitor/clinical monitor.	Staff Training: Study team will receive training in the sponsor's SOPs, and conducting a study to GCP and study protocol as required.
AE Assessment: DSURs will describe safety information to maintain oversight. DMC may review safety information	Participant Calendar: Participant attendance may be checked remotely via electronic CRF by a trial manager/clinical monitor. Study teams can send deviation logs directly to clinical monitors to capture when participants have not attended visits.	CRF Completion: May be checked, by the DMC/data monitor/clinical monitor remotely via electronic CRF if applicable. Clinical monitors can be alerted of poor completion of data by DMC, data monitor and study team.	Recruitment and Reporting: Levels of recruitment discussed between the study team and the sponsor as necessary.
IMP Accountability: IMP accountability may be conducted by delegated study team members and pharmacy and reported to monitors. Batch numbers and expiry dates may be checked by delegated study team members and reported to monitors.	Participant Consent: Forms may be reviewed remotely by clinical monitors. Process can be discussed at SIV and at other time if necessary.	Protocol / Regulatory Compliance: Deviations may be faxed to clinical monitors at intervals agreed with study team. Violations will be faxed to the clinical monitors. Study teams able to contact clinical monitors via telephone/email during the study to discuss compliance.	Records and Delegation: Guidance on Investigator Site File provided by clinical monitors. Delegation logs provided by clinical monitors, for completion by the PI.
IMP storage: Checking temperature logs may be performed by delegated study team members and reported to clinical monitors.		SDV of study outcomes: SDV for primary and secondary endpoints will be carried out remotely where possible and necessary by monitors.	
Reduced monitoring guide: Remote SIV. Remote close-out. Central monitoring will be conducted as described. Onsite monitoring visits will only be conducted if issues are identified during central monitoring that require resolution/investigation via on-site monitoring.			

Regular level of monitoring			
IMP / Agent (B)	**Study Participants**	**Study Design and Methods**	**Study Organisation**
Dose Assessment: Actions described in "reduced level" in addition to: Onsite monitoring: selected participants will have their batch numbers traced from their medical notes to pharmacy. Study dose of IMP will be compared with medical notes and any randomisation documentation for those. Of those participants whose notes are reviewed, it will be confirmed that 100% of the dose was correct.	Participant Eligibility: Actions described in "reduced level" in addition to: Onsite monitoring: for those participants selected for SDV monitors will SDV 100% of eligible criteria where possible or unless otherwise stated in the monitoring plan.	Data QC checks: Actions described in "reduced level" in addition to: Onsite monitoring: sample of CRFs checked during routine monitoring visits.	Staff Training: Actions described in "reduced level" in addition to: Onsite monitoring: additional training needs will be reviewed during the course of routine monitoring and addition training will be provided to the study team as necessary.
AE Assessment: Actions described in "reduced level" in addition to: Onsite monitoring: for selected participants monitors will review medical records and any other applicable records onsite for adverse events and will ensure that they are noted.	Participant Calendar: Actions described in "reduced level" in addition to: Onsite monitoring: for those participants selected for monitoring monitors will check 100% of attendance data where possible or unless otherwise stated in the monitoring plan.	CRF Completion: Actions described in "reduced level" in addition to: Onsite monitoring: paper CRFs will be checked for completion.	Recruitment and Reporting: Actions described in "reduced level" in addition to: Onsite monitoring: Screening / pre-screening logs will be checked during monitoring visits. Recruitment will be recorded and discussed during any monitoring visits.
IMP Accountability: Actions described in "reduced level" in addition to: Onsite monitoring: during routine onsite monitoring, a visit to pharmacy may be conducted to carry out an accountability check of the IMP. Batch numbers and expiry dates of any IMP will also be checked for a sample of participants.	Participant Consent: Actions described in "reduced level" in addition to: Onsite monitoring: all participant consent forms will be checked during monitoring visits. For those participants selected for monitoring medical notes will also be checked to ensure all the correct documentation has been completed and the person taking consent is delegated to do so. Process can be reviewed at monitoring visits and in dialogue.	Protocol / Regulatory Compliance: Actions described in "reduced level" in addition to: Onsite monitoring: confirm/observe compliance with study team. Deviations log will be reviewed by monitor during monitoring visit.	Records and Delegation: Actions described in "reduced level" in addition to: Onsite monitoring: study team may be provided with prepared Investigator Site file by the clinical monitors if possible. Delegation log checked at monitoring visit along with ISF.
IMP Storage: Actions described in "reduced level" in addition to: Onsite monitoring: temperature logs will be reviewed at routine monitoring visits to pharmacy.		SDV of study outcomes: Actions described in "reduced level" in addition to: SDV will be carried out for primary and secondary endpoints'. These will be checked for 100% of selected participants where possible or unless otherwise stated in the monitoring plan.	
Regular monitoring guide: Onsite SIV. Remote close-out if no participants recruited or if all close-out requirements have been verified at a previous visit – otherwise, onsite close-out. Central monitoring will be conducted as described. At least 1 onsite monitoring visit (per site) will be conducted during the trial. Further triggered visits will be conducted if issues are identified during central/onsite monitoring that require resolution/investigation via on-site monitoring.			

Increased level of monitoring			
IMP / Agent (C)	**Study Participants**	**Study Design and Methods**	**Study Organisation**
Dose Assessment: Actions described in "reduced level" in addition to: Onsite monitoring: selected participants will have their batch numbers traced from their medical notes to pharmacy. Study dose of IMP will be compared with medical notes and any randomisation documentation for those. Of those participants whose notes are reviewed, it will be confirmed that 100% of the dose was correct.	Participant Eligibility: Actions described in "reduced level" in addition to: Onsite monitoring: for those participants selected for SDV monitors will SDV 100% of eligible criteria unless otherwise stated in the monitoring plan.	Data QC checks: Actions described in "reduced level" in addition to: Onsite monitoring: sample of CRFs checked during routine monitoring visits.	Staff Training: Actions described in "reduced level" in addition to: Onsite monitoring: additional training needs will be reviewed during the course of routine monitoring and addition training will be provided to the study team as necessary.
AE Assessment: Actions described in "reduced level" in addition to: Onsite monitoring: for selected participants monitors will review medical records and any other applicable records onsite for adverse events and will ensure that they are noted. All adverse events will be reviewed.	Participant Calendar: Actions described in "reduced level" in addition to: Deviation logs will be forwarded to monitors at a greater frequency Onsite monitoring: for those participants selected for monitoring monitors will check 100% of attendance data unless otherwise stated in the monitoring plan.	CRF Completion: Actions described in "reduced level" in addition to: Onsite monitoring: paper CRFs will be checked for completion.	Recruitment and Reporting: Actions described in "reduced level" in addition to: Onsite monitoring: Screening / pre-Screening logs will be checked during monitoring visits. Recruitment will be recorded and discussed during any monitoring visits.
IMP Accountability: Actions described in "reduced level" in addition to: Onsite monitoring: during routine onsite monitoring, a visit to pharmacy may be conducted to carry out an accountability check of the IMP. Record of receipt, dispensation, return and destruction will be reviewed. Batch numbers and expiry dates of any IMP will also be checked for a sample of participants.	Participant Consent: Actions described in "reduced level" in addition to: Onsite monitoring: all participant consent forms will be checked during monitoring visits. All participants' medical notes will also be checked to ensure all the correct documentation has been completed and the person taking consent is delegated to do so. Process can be reviewed at monitoring visits and in dialogue.	Protocol / Regulatory Compliance: Actions described in "reduced level" in addition to: Onsite monitoring: confirm/observe compliance with study team. Deviations log will be reviewed by monitor during monitoring visit.	Records and Delegation: Actions described in "reduced level" in addition to: Onsite monitoring: study team may be provided with prepared Investigator Site file unless otherwise stated in the monitoring plan. Delegation log checked at monitoring visit along with ISF.
IMP Storage: Actions described in "reduced level" in addition to: Onsite monitoring: temperature logs will be reviewed at routine monitoring visits to pharmacy.		SDV of study outcomes: Actions described in "reduced level" in addition to: SDV will be carried out for primary and secondary endpoints. These will be checked for 100% of selected participants unless otherwise stated in the monitoring plan.	
Increased monitoring guide: Onsite SIV. Onsite close-out. Central monitoring will be conducted as described. At least 1 Onsite monitoring visit (per site) will be conducted every 6 months during the active stage of the trial. Further triggered visits will be conducted if issues are identified during central/onsite monitoring that require resolution/investigation via on-site monitoring.			