SECTION 1 – SPONSORSHIP AND RESEARCH GOVERNANCE RISK ASSESSMENT

Proposed Study: Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program			
Proposed Co-Sponsors: Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool L8 7SS and University of Liverpool, The Foresight Building, Brownlow Street, Liverpool L69 3GL			
Risk Assessment Conducted by:			
Date of Risk Assessment:		**Document Version:**	
Risk/Hazard identified	**Likelihood** Low Medium or High	**Impact** Low Medium or High	**Concerns and Recommendations for Mitigation & Management**
Compliance with regulations	**L**	**M**	The trial is of an investigational medicinal product. The sponsors (Trust) will need to assure compliance with the Clinical Trial Regulations 2004/1031 (as amended).
Organisational Accountability	**M**	**L**	**Contracts**: Co-sponsorship is confirmed by Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool L8 7SS and University of Liverpool, The Foresight Building, Brownlow Street, Liverpool L69 3GL. A co-sponsorship agreement will be put in place between LWFT and University of Liverpool. An Agreement exists for the provision of Research Management Services between the University and Trust detailing the clinical research management of the study by the Trust (as the Co-ordinating Centre). Clinical Trial Site Agreement will be prepared and signed at each recruiting site and the specialist analyst laboratory. No contract is required for the continuing care sites however a statement of responsibilities will be submitted through the Comprehensive Research Network service for Central NHS Permissions. Standard operating procedures will be prepared specifically for recruiting and non recruiting (follow up) sites to ensure the guidance is specific to their responsibilities.

			A **Material Transfer Agreement** will cover the transfer of samples to the laboratory for PK and DNA analysis.
Inadequate /poorly documented delegation to sites	**L**	**M**	**Recruiting sites:** Principal Investigators at recruiting sites will be take responsibility for the delegation of roles to the research team confirming each member is 'confident, competent, delegated and trained'. GCP certificates and curriculum vitae of team members will be held on the site trial file and the delegation log will be signed by both the PI and the team member specifying the roles they are delegated to do. Principal Investigators will meet with the Chief Investigator every 3 months to review recruitment and compliance with the protocol. **Follow Up Sites**: a 'statement of responsibilities' and generic Site Specific Information form will be provided for follow up sites outlining governance requirements and the role of the PI in accordance with the Research Governance Framework (2005), transfer of Site-Specific Assessment to NHS R&D, and Centralised NHS Permissions CSP National Guidelines.
Poor quality control and quality assurance	**M**	**M**	The PI and CLRN nurse will be GCP trained and familiar with the protocol thereby able to ensure SAEs and SUSARs are reported within the time line stated in the protocol. Also, knowledgeable of the standard operating procedures specific to follow up sites. The recruiting sites will liaise closely when a baby is transferred to other hospitals to ensure the site team are given guidance on follow up requirements.
Inadequate monitoring & auditing	**M**	**M**	Monitoring by the Sponsor (Trust) will be undertaken according to a monitoring plan based on the outcome of the bespoke risk assessment. It is assumed that on site monitoring will be required. This will include GCP, Research Governance, source data checks, laboratory handling of samples and data reliability. Data reliability is the greatest risk of this study and it will be important to review the 1st 10 Pharmacokinetic samples for quality control to ensure data is within the expected range. There is a risk that the data is not precise and that the audit tools are not sensitive to detect errors therefore trial tools will be developed to provide more than one source of data verification.
Poor archiving of study related information	**L**	**L**	Patient data will be managed in accordance with GCP, the Caldecott Guardian /National Information Governance Board and the Data Protection Act. Following the study the medical notes are archived using the NHS hospital appointed archiving services. The medical notes will be labelled as requiring archiving for 15 years (protocol requirement). The Sponsor (Trust) will monitor the storage of data is compliant with these regulations. TMF will include essential documents and version control ICH GCP section 8 [1]

Inadequate patient safety monitoring	**L**	**L**	The Independent Data Safety Monitoring Committee will need to be put in place. The Chief Investigator will need to provide a summary of adverse events and the anticipated incidence for this patient population.
Study Design: , inadequate study powered recruitment	**L**	**L**	The TINN Consortium of Neonatal experts across Europe have contributed to the design of this study (www.tinn-project.org). Trial Adoption will be requested from Medicines for Children Research Network providing independent peer review of the study design and methods. A European Ethics Advisory Group is set up to ensure the study is designed to meet the requirements of this vulnerable patient group. Feasibility will be undertaken to identify the number of babies for recruitment but if the target is not met further sites will be opened. Due to high mortality in this group babies will be over recruited to ensure the minimum target is met for Day 1 and Day 5 samples.
Inadequate costing of the study	**M**	**M**	The funding for the study includes a contingency allowance. A monthly report will be provided to the Investigator and reviewed by the Research Support Office a quarterly basis Research Support Office
Insurance/Indemnity	**L**	**L**	The NHS Sponsor's indemnity is provided by the NHS Litigation Authority As Co-sponsor the University of Liverpool (there is no exclusion for neonates or children in the University insurance policy)

Approval

Chief Investigator:		**Date:**		**Sponsor:**		**Date:**	
				Sponsor:		**Date:**	

SECTION 2 – IMP RISK ASSESSMENT AND SAFETY MONITORING

Risk Assessment of the Investigational Medicinal Product

(Drug risk assessment based on SmPC, BNF Children, protocol background papers, data on other quinolones, British National Formulary for Children and the MHRA Public Assessment Report)

Study Title: LW0852: To evaluate the pharmacokinetics, tolerability and short-term safety of ciprofloxacin in neonates with suspected (or proven) Gram Negative infection. Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program

Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program

EudraCT: 2010-019955-23

Co-Sponsors: Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool L8 7SS and University of Liverpool, The Foresight Building, Brownlow Street, Liverpool L69 3GL

Risk Assessment Conducted by:	**Date of Risk Assessment:**	**Document Version:**

Risks associated with trial IMP/interventions ☑ **Type A ≡** Comparable to the risk of standard medical care ☐ **Type B ≡** Somewhat higher than the risk of standard medical care ☐ **Type C ≡** Markedly higher than the risk of standard medical care	Ciprofloxacin is prescribed by the clinical team as part of standard medical care not for the purpose of research. This is a Pharmacokinetic clinical trial that requires additional monitoring and collection of safety data therefore the risks from the study interventions are associated with monitoring but additional safety aspects of the IMP will be monitored in detail. Patients will be intensively monitored as per standard of care as they are critically ill. **Ciprofloxacin Guidelines:** The SmPC dated 2/1011 includes the use of this drug indicated for severe infection in children. Ciprofloxacin (intravenous) is licensed for use in children over 1 year of age in the British National Formulary for Children 2011, the neonatal use is off label, but the neonatal dose is included in the British National Formulary for Children. The Liverpool Women's Neonatal Late onset Sepsis policy includes the use of Ciprofloxacin. **Published Evidence:** A systematic review of adverse effects in paediatrics identified 105 articles involving 16 184 paediatric patients (they found that the musculoskeletal adverse events were reversible) [2]. A prospective study of adverse events found that treatment of neonatal sepsis with ciprofloxacin resulted in no short term hematologic, renal or hepatic adverse effects and did not appear to be associated with clinical arthropathy or growth impairment at 1 year follow up evaluation [3]. A Systematic review specific to neonates found 32 cohort studies or case reports[4] . **Established Practice:** Survey: 26% (50 /193) neonatal units use Ciprofloxacin at least occasionally in Europe (http://www.tinn-project.org/). Ciprofloxacin has been administered off label to neonates for over 20 years as part of clinical care and published evidence [3-8]. **Off label use** is established practice for children and neonates, 55% drugs are administered off label to neonates [9]. This study will contribute to a non-commercial Paediatric Investigational Plan to contribute to licensing this drug specifically for neonates and influencing prescribing guidelines for neonates internationally. A study to evaluate the pharmacodynamic microbiological and clinical outcome of babies administered a lower dose 5mg/kg 12hourly is being evaluated by the research team at present. An Investigator Brochure is replaced by the SmPC. As the IMP is used off label, the trial will require authorisation by MHRA, rather than notification to MHRA.

IMP/ Intervention	Body System	Hazard	Likelihood Rare, Low Medium or High	Mitigation	Comments
Ciprofloxacin administered Intravenously	Joints	Arthropathy/ tendinopathy	M	Assess mobility pain redness prior to IMP administration and on set days during infusion and follow up for 6 weeks Nurses /parents are asked to report any signs of tenderness in joints when handling the baby	Neonates are not weight bearing so it is difficult to assess arthropathy. The patients may be recruited to a separate MRI study to assess joints. Pre clinical studies to assess joints in mice. Further examination will be undertaken by the Consultant Neonatologist if tenderness is reported.
	Vein	Phlebitis	L	Validated Visual Infusion Phlebitis Score monitored by the nurse during after infusions for 6 hours	Recorded in CRF
	Liver Function	Failure /pancreatitis	L *	Base line bloods and day 1-7 and day 10 and >daily clinical assessments are part of intensive care management	Daily clinical blood results are required for clinical care used for monitoring to minimise blood sampling. Reference ranges for neonates stated in the protocol. Values out with the normal range are associated with critical illness therefore may not be related to the intervention.
	Renal Function	Failure Crystalluria	L *		
	Blood cells	Deranged	L*		
	Gastro-intestinal	Colitis if severe and persistent consider Clostridium Difficile	M	Nappies are routinely weighed to estimate urine output and faeces when stools are watery. Stool samples sent to microbiology if colitis suspected Weekly surveillance of rectal swabs by bacteriology.	
	Anaphylaxis /Allergy		R	Intensive or High Dependency Level of Monitoring Daily + Clinical Assessments Vital signs monitored frequently /continuously	Signs or allergic reaction, rash/photosensitivity/ cardiac arrhythmias /convulsions and other conditions are systematically reported by nursing staff in the electronic patient data system and can be monitored daily as required by the researcher.
	Skin:	Rash/photosensitivity	M		
	Cardiac	ventricular arrhythmia, QT interval prolongation	R		
	Neurological	Convulsions	M		
	Syndromes	Stevens Johnson /Lyell	R		

Pharmacovigilance and processes that have been put in place to mitigate risks to participant safety (IDMC, independent data review,...)

Ciprofloxacin is considered a low risk as the drug is given for clinical care, the decision to prescribe is independent of the decision to enrol a baby into the trial. The study population are a vulnerable group who are critically ill therefore many adverse events are anticipated due to the nature of critical illness triggered by 1) clinical condition 2) clinical interventions 3) other drugs 'poly pharmacy' therefore causality is difficult to determine. There is an anticipated high mortality of 44% based on retrospective data of babies with Gram negative Sepsis over the last 6 years at this site.

Due to the anticipated high number of Adverse events (AE) and Serious Adverse Events (SAE) for reasons outlined above and the logistics of the trial, the protocol will outline which events need to be recorded by the investigator onto the CRF and which need to be reported immediately to the Sponsor (as per Regulation 32 (4)[10], ICH GCP 4.11.1 [1] and CT3 5.1.9 [11]) . The investigator is required to record all SAEs in the CRF and those AEs identified during the risk assessment as requiring recording. The investigator must report immediately to the Sponsor all SAEs, except those that are identified in the protocol as 'anticipated' events.

The process for reporting anticipated Serious Adverse Events (whether related to the IMP or not) to the Sponsor (Trust) will be defined in the protocol and standard operating procedure. The Sponsor (Trust) will monitor the incidence of anticipated SAE, if this increases during the trial they are required to report this as a SUSAR to the MHRA and NRES. All SAE whether related to the IMP or not will be recorded in the case report form and a summary provided for the Sponsor (Trust) and DMC.

The protocol will list the anticipated Serious Adverse Events (SAE) commonly seen in extremely premature babies less than 28 week and 34 weeks based on the incidence at Liverpool Women's NHS FT between 1980 and 2004.

SAE anticipated in critically ill /premature neonates		
SAE	**Estimated Incidence < 28 weeks gestation**	**Estimated Incidence 28 - 34 weeks gestation**
Death	20%	8%
Necrotising Enterocolitis	15%	3%
Intracranial abnormality	15%	6%
Supplementary Oxygen	55%	6%
Patent Ductus Arteriosus	25%	8%
Retinal Surgery	5%	0.14
Pulmonary Haemorrhage	5%	0.5%

Serious Adverse Events that are not 'anticipated' or **Suspected Unexpected Serious Adverse Reaction** (SUSAR) will be reported to the sponsor (Trust) within 24 hours by the Principal Investigator (LWH R&D Office). SUSARs require expedited reporting to the MHRA and REC within 7 or 15 days in accordance with regulation 33 [10].

Adverse Events (non-serious) that are identified by the Sponsor as requiring recording in the CRF following a risk assessment of the IMP will be recorded in the CRF (SmPC for all quinolones, protocol back ground papers, British National Formulary for Children and the MHRA Public Assessment Report). These include

arthropathy /phlebitis / altered liver or renal function/pancreatitis/deranged blood cells, gastro intestinal, skin, cardiac and fitting. The case report form and trial monitoring tools are designed to collected these events systematically; they only require immediate reporting to the Sponsor (Trust) if they are assessed by the Principal Investigator as Serious (regulation 32 (5) [10]).

Adverse events (non-serious) that have been identified in the risk assessment as uncommon but may be relevant are identified in the standard operating procedure and should also be included in adverse event summary reports/case report forms including: Gastro intestinal, anaphylaxis /allergy /skin: rash/photosensitivity /cardiac arrhythmias: ventricular arrhythmia, QT interval prolongation Syndromes: Stevens Johnson /Lyell /Neurological: convulsions. As these are not critical to the evaluation of the safety of the trial (regulation 32 (5) [10]) they are only recorded in case report forms and included in DMC reports unless they are serious when they are reported as above.

All other adverse events in this patient population that are common during critical illness including for example altered desaturations (oxygen levels), diarrhoea, vomiting and tachycardia will not be recorded as the Sponsor (Trust) does not feel these are critical to the evaluation of safety (regulation 32 (5) [10]), unless the attending clinician assesses the event as serious or has a temporal relationship to the administration of Ciprofloxacin

Concomitant Medications - Critically ill patients are likely to be administered many medicines simultaneously, which make an assessment of relatedness to Ciprofloxacin difficult. All concomitant medications will be recorded in the CRF. Drugs that are known to interact have been identified in the SmPC; these include drugs metabolised by CYPIA2 that can increase serum concentration of drugs including Theophylline. Other drugs administered to neonates that can alter levels include Caffeine, Phenytoin and oral anticoagulants (including Warfarin). Concurrent administration with NSAID can provoke convulsions. These groups of drugs and others relevant to covariate analysis including antimicrobials, analgesia and inotropes will be recorded within the CRF.

Monitoring Period: monitoring of adverse events will commence on the first day the baby is eligible and when Ciprofloxacin has been administered and for the following 42 days (the last study procedure). Section 3.0 [12]

Summary Report of Adverse Events: The Investigator will assess all AEs and SAEs on monthly basis. A summary of SAE (including anticipated SAE) will be sent to the Sponsor (Trust) every 3 months. The Data Monitoring Committee will assess SAEs on a 6 monthly basis. Any potential increase in severity or incidence that is detected will then require a report to be made to the sponsor. Annual report will be made to NRES/MHRA/Data Monitoring Committee in accordance with Regulation 35 [8].

The protocol will specify the safety monitoring procedures as described above and there will also be a trial specific SOP.

Approval

Chief Investigator:		**Date:**		**Sponsor:**		**Date:**	
				Sponsor:		**Date:**	

SECTION 3 – BESPOKE TRIAL RISK ASSESSMENT

Bespoke Risk Assessment (participant safety relating to the IMP, study design, methods, safety and rights and reliability of results)	
Study Title: LW0852: To evaluate the pharmacokinetics, tolerability and short-term safety of ciprofloxacin in neonates with suspected (or proven) Gram Negative infection. Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program **Phase I, open-label pilot PK Study -TINN Treat Infections in Neonates Program**	
EudraCT: 2010-019955-23	
Co-Sponsors: Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool L8 7SS and University of Liverpool, The Foresight Building, Brownlow Street, Liverpool L69 3GL	
Risk Assessment Conducted by:	
Date of Risk Assessment:	**Document Version:**

1. IMP

	Risk identified	Likelihood Low Medium High	Concerns	Mitigation or Adaptation	Monitoring methods to address
Drug is administered off label (licensed for children over 1 year)	Drug dose	M	Yes. Dose is insufficient to treat the infection or toxic to the baby	• The dose is estimated on paediatric licensed doses for children over 1 year of age • Previous experience of use in neonates(see section 2) • Interim data will be analysed by comparing PK/PD data to determine whether a change in dose is required (after 1st 10 babies) • The TINN consortium of neonatal experts will evaluate interim data (based on optimal dosing model from adult studies). • Intensive care babies have continuous or regular clinical monitoring and daily assessments of vital signs, biochemistry and haematology. • DMC will review the 1st 10 babies adverse events and at 6 monthly intervals. • Case report form will systematically collect data on vital signs during the 1st 10 days of administration.	• The Sponsor (Trust) /Monitor will ensure an interim analysis takes place as planned. • Monitor to confirm that a charter is in place for TINN consortium and the DMC to outline their duties and functions in the trial conduct. •

Storage	Hospital stock of IMP may be stored in up to 30 wards between both sites. Impractical to monitor temperature.	L	None.	• Stability Data from pharmaceutical company for safe storage up to 40oC • The standard hospital pharmacy practice does not require the temperature of drugs to be monitored outside of pharmacy in ward stock cupboards (Duthie Report - the safe and secure handling of medicines issued by the Royal Pharmaceutical Society 2005) • Store as per standard hospital practice exempt from temperature monitoring.	• No checks required on storage areas by on site monitoring.
Drug Labelling	Impractical to label. Used as normal clinical practice. No risk.	L	None.	• Annex 13 labelling is not required as the drug is supplied by the NHS hospital as standard care. Regulation 46 applies. This is covered in protocol/CTA application.	• None.
Drug Accountability	Records must be maintained for the precision of the dose and exact time given otherwise PK results will be invalidated.	H	Yes. Impact on reliability of results from PK analysis.	• Hospital pharmacy will dispense the IMP. • There are no requirements to record the batch number or expiry date or site level accountability records. • Patient level accountability records are essential, precise documentation for recording infusions, dosage and exact time the drug is administered. • Training of clinical staff (200+- per unit) will be undertaken and recorded. • Generic drug - the same product , Claris, used at both recruiting sites • No requirement for full accountability records, as the drug is prescribed as part of clinical care.	• Monitor to ensure completion of patient infusion records. SDV of this data recommended. • Training records review (could be centrally done)
Infusion Practice – exact time the drug reaches the blood is required	Small volumes in neonates mean the drug rate is low and may not reach the blood for a long period (up to 24 minutes)	M	Yes. Incorrect time recorded for dosing – impact on PK analysis.	• Standard operating procedures are prepared specific to the recruiting site's drug infusion practice – the infusion line will be primed with ciprofloxacin to prevent delays in the drug reaching the blood. • Record which IV line the drug is infused (particularly when a long line or central Broviac lines are in place with large dead space) • Calculate the volume in the line between the patient and the drug prior to infusion and the rate of the infusion to correct the time the drug reaches the blood.	
	Lines not	**M**			

	flushed after the infusion within the 3 minutes sampling period			• If there is a deviation from the planned time due to other clinical priorities details will be recorded on the sample schedule. • Trial Training all 200 clinical nurses for each site (consistent with GCP for that task)	
	Dead space in infusion lines /broviac lines can be >2mls which takes 20 minutes to reach the blood if infused at 6ml/hour	**M**			

2. Patient Safety

Area	Particular risk identified	Likelihood Low Medium High	Concerns	Mitigation or Adaptation	Monitoring methods to address
Blood sampling 3 samples on day 1 3 samples on day 5 Scavenged when a biochemistry samples is collected for clinical care	Skin trauma	L	Yes. Heels already pricked /bruised	• Skilled staff trained in sampling neonates for clinical care • Use of neonatal lancet • Trust training policy for blood sampling	• Sample of Training records review (could be centrally done)
	Pain	L	Yes. Distress to parent and baby	• Use arterial or central line when possible • Sample taken when clinical samples are required when possible from one heel prick planned with other cares when possible • Sample planner agreed with the clinical team to ensure samples are collected at the same time as clinical bloods when possible by selecting the sample schedule in line with clinical blood times.	• Monitor to review sample planner and sample times to confirm baby is not having unnecessary sampling times. • To monitor a selection of patients (not 100%).
	Blood loss	L	Yes. Increased risk of transfusions (For a neonate 500g weight the total blood volume	• Minimum volume 0.2 ml and sampling episodes reduce from 3 to 2 samples per day samples for babies less than 1000grams weight • Limit participation to one study that requires blood samples or within the volume allowed by the MCRN EMA guidance	• Monitor to confirm not participating in another trial involving blood draw as part of eligibility check.

			is only 40mls +-)	for neonatal sampling in clinical trials [13, 14]. For research - 3% total blood volume during 4 weeks or 1% at any single time based on a total volume of blood 80- 90 ml/kg body weight.	
Lumbar Puncture for CSF sample.	CSF sample – lumbar puncture Pain Loss of CSF volume Precision for the time the sample is collected	L	Yes. Disturbing the baby Dehydration PK analysis of CSF	• CSF samples will only be collected if the procedure is required clinically –additional CSF taken during the same procedure • 0.2ml will be collected after the clinically required samples are taken. • Trial label and sample bottle left on the cot with instructions for the person performing the procedure to add the time collected and store in the freezer -20oC	Freezer temperature monitored daily
DNA Sample	Mouth swab /blood volume	L	Yes. Disturbs the baby Dislodging endotracheal tube	• Buccal sample taken with other cares. Minimal handling is required to allow neonates maximum rest for growth and development. • Check with the clinical team if an endotracheal tube is in place that it is secure –samples taken by intensive care trained staff for ventilated babies. • Blood scavenged from EDTA samples	
Faeces	Required week 4 -6, possibly after discharge	L	Yes. Baby may be at another hospital or at home	• R&D approvals for 40 other hospitals and PI at each follow up site to allow samples to be collected • Parents to send from home in Category B packaging provided by the trial staff conforming to the Health and Safety Executive Guidance[15].	Collation and checks of approvals (central monitoring). Maintenance of approved site list. Monitoring to check follow up at approved sites (can be done centrally).

Drug adverse effect or reaction	Complexity of pharmacovigilance in critically ill babies	L	The IMP is used off label and risks associated with the drug relate to data from adult studies. Due to the complexity of adverse effects or reactions in critically ill babies there is a risk of not being able to identify events related to the IMP.	• A safety monitoring plan is in place and a DMC is established with charter/procedures. All adverse event reported to the sponsor (Trust) as per protocol are summarised for DMC at 6 monthly intervals to ascertain whether the risk of expected SAE has increased above the anticipated incidence (see Section 2). • Pharmacovigilance procedures are based on a risk assessment of the IMP and anticipated adverse events in critically ill babies. • SAE/SAR/AE/AR record and reported as they occur by the Principal Investigator as per protocol. SAE/SAR reports are sent to the Sponsor (Trust) and checked by an independent clinician (to assess expectedness for SAR). • The protocol includes reference safety information (RSI) for the expectedness of suspected adverse reactions (serious and non-serious) to allow comparison with the actual incidence –reviewed 6monthly by the DMC. The RSI will be as per table section 2 Pharmacovigilance • Routine clinical monitoring is continuous or at frequent intervals in intensive care patients to detect potential reactions • Concomitant medications are recorded in the CRF for the period the IMP is administered	• Monitor to sample Source verification Data for AEs being reported as per protocol • Monitor to check DMC undertaking regular safety reviews.
Eligibility	Ineligible patients recruited	L	Patients are eligible if prescribed ciprofloxacin and less than 52 weeks post menstrual age. They are excluded if under 5 days age post birth or not likely to survive in the judgement of	• Prior to any study procedure a doctor looking after the baby will determine whether the baby meets the eligibility criteria and that they have made a clinical decision to allow the baby to participate in the trial. • A form 'Determine Eligibility' includes the eligibility and exclusion criteria is completed by the doctor looking after the baby on the day the study starts and filed in the case notes. • Staff training tools and a log of training. • Recruitment checklist (version controlled and consistent with protocol).	The Monitor will confirm a medical review of criteria has been completed by checking the 'determining eligibility form'. The eligibility will also be confirmed against the electronic patient data system for 30% of babies recruited.

			an attending physician.		
	Recruitment into more than one study allowed in the eligibility criteria	L	Yes. Risk to PK analysis if other medications administered as part of other trials not recorded.	• Review other trials taking place at recruiting sites to assess whether they present any issues for this trial. • (see drug interactions section2)	

3. Patient Consent, Rights and Confidentiality

Area	Particular risk identified	Likelihood Low Medium High	Concerns	Mitigation or Adaptation	Monitoring methods to address
Consent	Yes. Vulnerable subjects: premature baby. Multiple trials in place at the same time	M	Yes. Parents concerned about allowing further procedures to their baby when their baby is critically ill. Stress due to requests for many trials.	• Information sheet includes 20 elements of consent ICH GCP (4.8.10) [1]. The consent form asks parents to sign to say they have read the information sheet. • Consent processes and documents are approved by the REC and Patient Public Involvement representatives. • Ethical issues are monitored by a European Ethics Advisory board in addition to NRES to ensure the protocol is ethically approved across Europe • Staff trained in paediatrics /neonates will describe the procedures and discuss specific concerns regarding sampling [16] • Consent processes are described in the protocol - prospective consent is preferred but deferred 'emergency consent' may be obtained according to regulation 2006 No 2984 [17] with approval by NRES. • Researchers will co-ordinate their approach to parents and advise parents how many trials they are likely to be approached about during the admission. • Researchers will be trained in paediatric consent/GCP/Trial protocol and law on parental responsibility (Children's Act 1989 /Adoption and Children Act 2002 www.opsi.gov.uk/acts/acts2002/kpga) • The Principal Investigator and the research doctor/nurse will	• Check of records to ensure consent was given by someone with parental responsibility. • Record time/date consent taken prior to procedures or record the use of deferred consent • Check of 30% consent forms • Check delegation log • Check training record for the research team (above could be achieved without a site visit)
	Parental responsibility	L	Yes. Failure to obtain consent from someone with parental responsibility.		
	Parents not informed adequately about the study	L	Yes. Parent/Guardian stress due to critically ill baby impacts on capacity to consent - unable to concentrate on the informed		

			consent process	jointly determine that they are 'confident competent and delegated' to undertake consent. • The PI will sign the delegation log for each site. • Prospective consent allows parents more time to consider the information fully. • Clinical team trained in the study able to answer parents questions • Assess parental capacity to consent at the time by asking parents open questions • Provide information to both partners when possible. • Documented check on parental responsibility (if unmarried fathers sign the consent form they will be asked to add that they are named on the birth certificate. • Explain the study is voluntary participation • Telephone consent may be requested if parents are not available but researchers will attempt to provide them with the information first. Clinical team member will phone parents then witness the researcher consenting. • Parents may opt to consent separately for 1) drug levels, 2) CSF and 3) DNA by signing separately for each component on the same form.	
	Coercion. Parents feeling obliged to participate due to the care given by the clinical team.	L	No.		
	The study drug can be prescribed at any time of the day or night when parent may not be available – sampling required within 3 minutes	M	Yes. Parents not present at the time consent is required. Failure to obtain consent or loss of recruitment of subject.		

Information leaving the hospital & Data Protection	Medical data required by external teams in UK and Europe Samples are labelled and sent to other laboratories and hospitals with documents.	L	Yes. Breach of subject confidentiality.	• Data will be anonymised before sending to any external hospital or laboratory. • Data protection process are approved by NRES, Trust R&D and consistent with NIGB guidance. • Parents are aware that we will contact their GP • Clinical data is anonymised when used outside the clinical environment. • The information sheet describes to parents how data is anonymised • Data stored on a clinical database- this electronic CRF does not contain any patient identifiers and is password protected. • DNA samples are anonymised prior to sending them to the genetics laboratory • DNA extraction methods prevent information relating to other clinical conditions being identified prior to being anonymised. • Process in place at labs to raise alert and implement corrective actions if labels contain patient identification data. • Laboratory staff are GCP trained and employed by the NHS Trust. • Medical notes are labelled to be archived by the Trust archiving services for 15 years • Trial data is stored in a lockable cabinet in a lockable room GCP compliant	Check all sample labelling procedures and sample labels to confirm no fields for patient identifiers (centrally)

4. Reliability of Trial Results					
Area	**Particular risk identified**	**Low Medium High**	**Concerns**	**Mitigation or Adaptation**	**Monitoring methods to address**
CRF data	Reliability of recording data Covariates: weight, postmenstrual age, postnatal age and serum creatinine needed for PK analysis.	M	Inaccurate data. Electronic CRF not fit for purpose. Yes. Inaccurate covariate data – incorrect PK analysis. Weight varies daily/weekly in babies due to growth, altered nutrition and fluid shift or renal failure.	• The electronic CRF Designed and validated. The electronic CRF is approved by the Trial Team. System has password access, audit trail and back up. • Hard copy of the CRF is completed in the clinical area then entered onto the ECRF. • Hard copies are stored as source data stored at the recruiting sites	The monitor will check the E CRF against source data and the paper CRF for 30% of recruits. A written statement from the ECRF company regarding GCP compliance will be filed on the TMF
		L		• PK Model developed by expert neonatal PK team within the TINN consortium • Weight recorded at birth, start of study, the end of PK samples and on discharge.	Source data verification of covariates required as important for trial results.
Con Meds	Poly pharmacy	L	Yes. Up to 20 medicines administered concomitantly to each baby. There is a risk of metabolism interactions - potential to impact on PK analysis.	• All concomitant medications recorded during the administration of the IMP are recorded • Specific drugs administered to neonates identified as having potential interactions for quinolones by the SmPC and Public Assessment Report (MHRA) are identified in section 2 • Caffeine and phenytoin are drugs with known interactions and are commonly prescribed therefore we are recording further details regarding the dose and time of administration. • Analgesia may mask arthralgia therefore will be recorded in the CRF • Analysed as covariates	Source data verification of concomitant medications – (sample to assure reliability of CRF data.)
Group Allocation at Recruitment	To achieve the minimum 5 babies per age group – distributed over Groups A and C or B and D	L	None. Potential risk of allocation errors result in imbalanced groups.	• The sampling group is allocated by the researcher following discussion with the clinical team regarding the best time for sampling the baby to coincide with the clinically required samples (to minimise disturbing the baby). Also based on whether the dose is prescribed 8 or 12 hourly. • Record the number of recruits allocated to each sub group aiming to balance the groups throughout the study. • The study is not comparing outcomes of one group with the other, groups are chosen to provide representation of drug	Summary of recruitment allocation maintained throughout the study.

				levels at different time points.	
Blood Sampling	Precise timing of samples necessary Administering the drug infusion and taking samples sampling requires high level of precision and accurate timing	H	Yes. Samples collected out with the tight time frame of 3 or 10 minutes – PK analysis invalid. Yes. Training large clinical teams – ensuring all those involved have appropriate training to ensure timings are recorded correctly.	• Advice to avoid sampling during an infusion • Cot side guide for 5 main point of the study • Cot side recording charts • Record of times can be cross checked on multiple sources (blood gas analyser/phlebotomist record nursing notes/ arrival time in the laboratory recorded). • Training for laboratory staff, phlebotomist and all clinical staff 200 at each intensive care unit • Hand holding by researchers and research network staff to ensure a named clinical nurse /doctor is responsible and updated on each shift covering each patient. • Label designed for the study are completed with the time the sample was taken • Detailed SOPs and monitoring tools to ensure precision is achieved, monitored, recorded CRF and cross checked for quality control • Time sample collected written on the form and a back up log • Clocks checked in clinical areas/season changes • Standard operating procedure for scavenging samples • Scavenged from clinically required biochemistry samples • Phlebotomists are trained in the study and add a label to the scavenged sample when they take the blood and hand write the time on the label and keep as record on site. • The laboratory record the study ID number / time /date on the bottle on the label with the patient study ID (scavenged samples)	• Monitor to check records and undertake SDV to confirm sampling time accurate and procedures followed. Onsite visit needed. • .PK analysts adjust the modelling based on the data but the team will aim to balance recruitment among groups
	Scavenged Samples Precise Timing	H			

	Storage/preparation /transfer	L	Yes. Invalid assay results from inappropriately stored samples.	• Standard operating procedures detail the storage and handling of samples • Blood samples are stored at -20oC CSF samples stored at -80oC. Laboratory freezers are alarmed to the central switchboard system and temperatures recorded daily. • Hospital approved courier transported within Category B standards and for transport on dry ice [15] • The courier agrees to deliver by 12 noon the following day and sufficient dry ice is provided for 3 days in case of delay. In the event no dry ice present on arrival then the samples are not included. • The Laboratory is certified by Clinical Pathology Accreditation Standards for Medical Laboratories ISO 15189. and authorised to store and process samples • Clinical samples are centrifuged for clinical analysis and any remaining plasma is scavenged for additional data when the time has been recorded on the clinical sample with a study label – nurses and phlebotomists are trained to provide this information. • Laboratory staff GCP and trial trained. • Controls in place for shipment, receipt & chain of custody records	• Monitoring to check temperature records of sample storage and see evidence of receipt at labs confirming conditions satisfactory in transit.
PK Analysis	Blood sample analysis	M	Yes. Invalid assay values.	• Sponsor (Trust) to confirm that assay method (Analytical Liquid Chromatography Mass Spectrometry (LC-MS)) has been validated. • Assessment of laboratory undertaken (e.g. audit of facilities to confirm standards be adhered to (e.g. GCP Labs) • The Laboratory are certified by Clinical Pathology Accreditation Standards for Medical Laboratories ISO 15189. • Specialised laboratory experienced in Neonatal PK analysis and measuring small assay volumes • Contract in place with laboratories as part of the CTA and Material Transfer Agreement • Cross check the timing of source data using blood gas analyser times, arrival in the laboratory and ask phlebotomists to record the time they take scavenged	• Check laboratory facilities contracts in place and confirm assay validation report available. (could be done centrally)

				samples.	
	PK data analysis	M	None, provided the data are accurate.	• Specialist PK Laboratory (Paris) Accredited with PK Analysis experience in neonatal sampling (Trust sponsor has made an assessment) and Specialised statistical Modelling	
Other sample analysis	Microbiology analysis	L	None	• Standard operating procedure for testing faeces and MIC to Ciprofloxacin • Minimum inhibitory concentration – based on EUCAST method and standards (European Committee on Antimicrobial Testing)	
	Biochemistry/ Haematology etc.	L	None. Use of hospital labs as per normal clinical practice	• No need for normal ranges for these to be filed in TMF.	

5. Facilities, Equipment and Resources

Area	Particular risk identified	Low Medium High	Concerns	Mitigation or Adaptation	Monitoring methods to address
Facilities	2 recruiting sites, but complex follow up as neonates are transferred nearer home and thus 40 follow up sites for Pharmacovigilance reporting for 6 weeks – failure to obtain follow up info.	L	None regarding recruiting sites provided other risks mitigated. Facilities for the trial appropriate. Yes. Collection of faeces samples and obtaining reliable safety information from 40 follow up sites	• Standard operating procedures are prepared for recruiting sites and separate ones for follow up sites. • Recruiting Site assessment process in place. Site contracts and R&D approvals in place at recruiting sites, an induction programme is provided for the research team and trial tools provided. • Follow up sites -. The R&D will take responsibility for GCP and CV at their site. A statement of responsibilities replaces a contract as this is simply data collection and a faeces sample. • Principal Investigator at each site will report pharmacovigilance for up to 6 weeks • R&D approvals and statement of responsibilities for follow up sites • Accredited hospital laboratory are trained by the trial team and a dummy run of samples to test the systems.	Check contracts on TMF Follow up sites are assessed remotely on receipt of R&D approval and acceptance of the role by a neonatal Principal Investigator CLRN will check the Statement of Responsibilities

				• Follow up data is recorded in the CRF and the discharge letter is filed to cross check the incidence of adverse events	
Staff Training	Precision of samples and compliance with processes	H	Yes. Large clinical team involvement (200). Risk that proper process not followed and lack of precision in dosing and blood sample taking etc.	• Detailed SOPs • Formal training of clinical staff 200+ per site in protocol and trial specific SOPs • The research team will hand hold the procedures and speak to the nurse on duty each shift. • GCP training for Investigators and those with substantial roles (recruiting and pharmacovigilance reporting) • Training delivered to the clinical teams by staff who are GCP trained Training packs for the bedside • The clinical team are not GCP trained but will be trained in the tasks they are required to do consistent with GCP standards. • Formal Trial Training presentation/initiation visit to explain trial tools at recruiting sites. • Ensure SOP are consistent with the sites clinical practice. • Training log for day/night staff • Delegation log – PI approves research team are appropriately trained prior to involvement in trial activities.	• Review of training and delegation logs. Cross check trained individuals taking consent, dosing and blood sampling,
Follow Up	Loss to Follow up - babies may be transferred to any hospital within 200 miles during follow up	L	Yes. Loss of follow up data and PV data.	• Principal Investigator at follow up site with GCP training is required for safety reporting during 6 week follow up • Generic SSI used for R&D approvals for 40 sites administered by the Comprehensive Local Research Network • Standard operating procedure specifically for follow up sites including pharmacovigilance reporting and transfer of Category B faeces samples • Follow up with 'discharge letter from each site.'	• Collation and checks of approvals (central monitoring). Maintenance of approved site list. Monitoring to check follow ups at approved sites (can be done centrally).

6. Documentation, Governance and GCP Compliance

Area	Particular risk identified	Low Medium High	Concerns	Mitigation or Adaptation	Monitoring methods to address
TMF	Lack of documentation to reconstruct trial and confirm compliance with CT regulations, the protection of subject's rights/well being/safety and the reliability of the trial results.	L	None.	• TMF centralised at the Chief Investigator recruiting sites (ICH GCP Section 8.2) and a Site Trial File at the other recruiting site containing essential documents • CV and GCP certificates are filed centrally at the NIHR site for the investigating team, which are accessible long term. • Retention of TMF 21 years supporting Paediatric Investigation Plan (required for neonates growth and development issues) stored by NHS approved archiving (ICH GCP Compliant). • Trial files are not required at non recruiting follow up sites • The Statement of Responsibilities (section 1) states that a trial file is not required at the non recruiting follow up sites as approved by the R&D Forum	• Monitor to review recruiting site TMF at least once during trial conduct to ensure adequately maintained. • Monitor to confirm suitable archiving arrangements for all TMF
Monitoring	Inadequate monitoring. 1) Regulatory 2) Source data 3) Data reliability	 L L H	Yes. Lack of monitoring appropriately could result in non-compliance and inaccurate data for the PK objective. Minimal risk of loss to follow up data	• Recruiting sites: Sponsor (Trust R&D Department) monitor the study and undertake source data verification (SDV) based on risks identified – process to be documented in a Monitoring Plan. • Compliance with trial SOP are assessed daily by the researcher during the study and on completion of the case report forms by checking sample times /infusions/ or protocol deviations. Serious breaches are risk managed by detailed standard operating procedures, detailed trial tools and staff training. • Serious Breaches that affect the safety of the subject or the scientific integrity of the trial are reported to the Sponsor (Trust R&D Policy) as per Regulation 29A [8] A root-cause analysis, corrective and preventive actions will be undertaken. If defined as a serious breach by the Sponsor (Trust) it will be reported to the MHRA within 7 days. • Monitoring is not required at follow up sites – data will be recorded according to the SOP and further information	• There will be a need for onsite monitoring at the recruiting sites with targeted Source Data Verification. Some central review of documentation may be possible. • The monitor will design tools to assess 1) Governance 2) Source data 3) data reliability for SOP compliance in the ward and laboratory.

				requested from the Principal Investigator at the site when required.	
Sponsors	Inadequate oversight.		None, but potential if there is a lack of clear sponsor responsibilities that could result in non-compliance.	• Trial Sponsored by Liverpool Women's NHS FT and University of Liverpool. • Sponsor and Co-Sponsor roles and responsibilities will be defined & Co-sponsorship contract in place. • An Agreement exists for the provision of Research Management Services between the University and Trust detailing the clinical research management of the study by the Trust (as the Co-ordinating Centre). • All trial procedures undertaken by both hospital sites and contracts or agreements in place.	• Check contracts in place and they cover all responsibilities under the legislation.

Approval

Chief Investigator:		**Date:**		**Sponsor:**		**Date:**	
				Sponsor:		**Date:**	

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