REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request:	Date of request for additional information:	Grounds for non acceptance / negative opinion :
Date of request for information to make it valid:		Give date:
Date of valid application :	Date of receipt of additional / amended information :	Authorisation / positive opinion:
Date of start of procedure :		Give date:
Competent authority registration number :		Withdrawal of application :
Ethics Committee registration number :		Give date :

A: Trial identification

A1. National Competent Authority:

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number:

2021-006886-39

A3. Full title of the trial:

Early vasopressors in Sepsis

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

Early vasopressors in Sepsis

A3-2. Name or abbreviated title of the trial where available:

EVIS

A4. Sponsor's protocol:

Number: GN20AE342
Version: 4.0
Date: 09/12/2024

A5-1. ISRCTN number, if available :

A5-2. US NCT number:

NCT05179499

A5-3. Who Universal Trial Reference Number (UTRN)

A5-4. Other Identifiers:

Name	Identifier

A6. Is this a resubmission?

○ Yes ◉ No

A7. Is the trial part of a Paediatric Investigation Plan?

○ Yes ○ No ◉ Not Answered

B: Identification of the sponsor responsible for the request

B1. Sponsor

SP1
Contact person

Name of organisation	NHS Greater Glasgow & Clyde
Given name	Louise
Family name	Ner
Address	Research & Development, Admin Building, Level 2, Gartnavel Royal Hospital, 1055 Great Western Road
Town/city	Glasgow
Post code	G12 0XH
Country	United Kingdom
Telephone	01413144407
Fax	
E-mail	louise.ner@nhs.scot

B2.Legal Representative for the purpose of this CTIMP.
A legal representative must be appointed for a clinical trial of an investigational medicinal product (CTIMP) if the sponsor is not established in the UK or on the MHRA approved country list (please refer to question specific guidance).

Legal Representative 1

Contact person

Name of organisation
Given name

Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

B3. Status of the sponsor: Non-Commercial

B.4 Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):

B.5 Contact point designated by the sponsor for further information on the trial:

Name of organisation	NHS Greater Glasgow & Clyde
Functional name of contact point	Louise Ner
Street Address	Research & Development, Admin Building, Level 2, Gartnavel Royal Hospital, 1055 Great Western Road
Town/city	Glasgow
Post code	G12 0XH
Country	United Kingdom
Telephone	01413144407
Fax	
E-mail	louise.ner@nhs.scot

C: Applicant identification

C1. Request for the competent authority

C1-1. Who is responsible for the Clinical Trial Authorisation Application?

Sponsor

C1-4. Complete the details of the applicant below even if they are provided elsewhere on the form:

Contact person

Person or organisation name:	NHS Greater Glasgow & Clyde
Contact person Given name	Louise
Contact person Family name	Ner
Address	Research & Development, Admin Building | Level 2, Gartnavel Royal Hospital, 1055 Great Western Road

Town/city	Glasgow
Post code	G12 0XH
Country	United Kingdom
Telephone	01413144343
Fax	
E-mail	louise.ner@nhs.scot

C1-5. Do you want a xml file copy of the CTA form data saved on EudraCT?

◯ Yes ◉ No ◯ Not Answered

C2.Request for ethics commitee

C2-1. Who is responsible for the Clinical Trial Authorisation Application?

.....

C2-5. Complete the details of the applicant below even if they are provided elsewhere on the form

Person or organisation name:	.....
Title:	.....
Forename/Initials:	.....
Surname:	.....
Middlename:	.....
Address:	.....
Town/city:	.....
Post code:	.....
Country:	.....
Telephone:	.....
Fax:	.....
E-mail:	.....

Part D: Investigational Medicinal Products

D: Information on the IMPs

Information on each "bulk product" before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable. If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.

Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question D7 using the navigation screen.

D. Investigational medicinal products

PR1 No Marketing Authorisation - needed to answer D2-2

PR2 Plasma-Lyte® 148

PR3 No Marketing Authorisation - needed to answer D2-2

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
No Marketing Authorisation - needed to answer D2-2
EV Product Code
Does not apply
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

Is this the Member State concerned with this application?
○ Yes ○ No ◉ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group

◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :

○ Yes ◉ No ○ Not Answered

D2-3. IMPD submitted:

Full IMPD

○ Yes ◉ No ○ Not Answered

Simplified IMPD

○ Yes ◉ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ○ No ○ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

○ Yes ◉ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

○ Yes ◉ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	No Marketing Authorisation - needed to answer D2-2
D.3.2 Product code where applicable	Noradrenaline (Norepinephrine)
D.3.3 ATC codes, if officially registered	C01CA03
D.3.4 Pharmaceutical form (use standard terms)	Concentrate for solution for infusion
D.3.4.1 Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	48 hours

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	○ per day ○ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	

D.3.6.2 Maximum dose allowed	0.15 micrograms/kg/minute titrated as appropriate to target MAP 65 mmHg. Max total 0.43mg/kg based on maximum rate for 47h after 1h of titration from start rates
D.3.6.2 Specify per day or total	○ per day ○ total ◉ Not Answered
D.3.6.2 Specify total dose (number and unit)	0.43 mg/kg milligram(s)/kilogram
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous use

D.3.7 Routes of administration for this IMP

Intravenous use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Noradrenaline
CAS number:	51-41-2
Current sponsor code:	Noradrenaline
Other descriptive name:	Norepinepherine
Full Molecular formula	C8H11NO3
Chemical/biological description of the Active Substance	(R)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	1.0

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ○ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes ◉ No ○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.
Noradrenaline has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. NORADRENALINE (NOREPINEPHRINE) 1 MG / ML causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. This results in an increase in the force (and in the absence of vagal inhibition) in the rate of myocardial contraction. Peripheral resistance increases, and diastolic and systolic pressures are raised.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

(1,2,3,4,5)Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Comparator

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Plasma-Lyte® 148
EV Product Code
Name of the MA holder:
Baxter Healthcare Ltd
MA number (if MA granted by a Member State):
PL 00116/0332
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UK - MHRA
Is this the Member State concerned with this application?
○ Yes ○ No ◉ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

D2-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Plasma-Lyte® 148
D.3.2 Product code where applicable	Balanced Crystalloid IV fluids
D.3.3 ATC codes, if officially registered	B05BB01
D.3.4 Pharmaceutical form (use standard terms)	Infusion
D.3.4.1 Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	48 hours

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial

D.3.6.1 Specify per day or total: ◯ per day ◯ total ◯ Not Answered

D.3.6.1 Specify total dose (number and unit)

D.3.6.1 Route of administration (relevant to the first dose):

D.3.6.2 Maximum dose allowed: none specified

D.3.6.2 Specify per day or total: ◯ per day ◯ total ◉ Not Answered

D.3.6.2 Specify total dose (number and unit)

D.3.6.2 Route of administration (relevant to the maximum dose): Intravenous use

D.3.7 Routes of administration for this IMP

Intravenous use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Sodium Chloride
CAS number:	7647-14-5
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	NaCl
Chemical/biological description of the Active Substance	Sodium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	5.26

Active Substance 2

Name of active substance (INN or proposed INN if available):	Potassium Chloride
CAS number:	7447-40-7
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	KCl

Chemical/biological description of the Active Substance	Potassium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.37

Active Substance 3

Name of active substance (INN or proposed INN if available):	Magnesium Chloride hexahydrate
CAS number:	7791-18-6
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	MgCl2,xH2O
Chemical/biological description of the Active Substance	magnesium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.30

Active Substance 4

Name of active substance (INN or proposed INN if available):	Sodium Acetate trihydrate
CAS number:	6131-90-4
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	CH3.CO2Na,3H2O
Chemical/biological description of the Active Substance	Sodium Acetate trihydrate produces bicarbonate and is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	3.68

Active Substance 5

Name of active substance (INN or proposed INN if available):	Sodium Gluconate
CAS number:	527-07-1
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	C6H11NaO7
Chemical/biological description of the Active Substance	Sodium Gluconate produces bicarbonate and is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	5.02

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(•) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (•) No ( ) Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	( ) Yes (•) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (•) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (•) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (•) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (•) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (•) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (•) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (•) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (•) No ( ) Not Answered
Homeopathic medicinal product?	( ) Yes (•) No ( ) Not Answered
Another type of medicinal product?	( ) Yes (•) No ( ) Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Plasma-Lyte 148 is an isotonic solution of electrolytes. The electrolytes constituents of their concentrations are designed to match those of plasma. The pharmacological properties of Plasma-Lyte 148 are those of its components (water, sodium, potassium, magnesium, chloride, acetate and gluconate). The main effect is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid. Sodium acetate and gluconate are bicarbonate-producing salts.

Is it an IMP to be used in a first-in-human clinical trial? ( ) Yes (•) No ( ) Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR3**
Investigational medicinal product category:
Comparator

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
No Marketing Authorisation - needed to answer D2-2
EV Product Code
Does not apply
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

Is this the Member State concerned with this application?
○ Yes ○ No ◉ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered
If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

D2-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◯ Yes ◉ No ◯ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	No Marketing Authorisation - needed to answer D2-2
D.3.2 Product code where applicable	Compound Sodium Lactate Solution for Infusion
D.3.3 ATC codes, if officially registered	B05BB01
D.3.4 Pharmaceutical form (use standard terms)	Infusion
D.3.4.1 Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	48 hours

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	◯ per day ◯ total ◯ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	

D.3.6.2 Maximum dose allowed	no maximum
D.3.6.2 Specify per day or total	◯ per day ◯ total ◉ Not Answered
D.3.6.2 Specify total dose (number and unit)	
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous use

D.3.7 Routes of administration for this IMP

Intravenous use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Sodium Chloride
CAS number:	7647-14-5
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	NaCl
Chemical/biological description of the Active Substance	Sodium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	6.0

Active Substance 2

Name of active substance (INN or proposed INN if available):	Potassium Chloride
CAS number:	7447-40-7
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	KCl
Chemical/biological description	Potassium chloride is the principal sodium salt used as a source of sodium

of the Active Substance	ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.40

Active Substance 3

Name of active substance (INN or proposed INN if available):	Calcium Chloride dihydrate
CAS number:	10035-04-8
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	CaCl2,2H2O
Chemical/biological description of the Active Substance	Calcium chloride dihydrate is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.27

Active Substance 4

Name of active substance (INN or proposed INN if available):	Sodium Lactate
CAS number:	72-17-3
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	C3H5NaO3
Chemical/biological description of the Active Substance	sodium lactate is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	3.20

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes	○ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes	◉ No	○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered

Radiopharmaceutical medicinal product?	◯ Yes ◉ No ◯ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	◯ Yes ◉ No ◯ Not Answered
Plasma derived medicinal product?	◯ Yes ◉ No ◯ Not Answered
Extractive medicinal product?	◯ Yes ◉ No ◯ Not Answered
Recombinant medicinal product?	◯ Yes ◉ No ◯ Not Answered
Medicinal product containing genetically modified organisms?	◯ Yes ◉ No ◯ Not Answered
Herbal medicinal product?	◯ Yes ◉ No ◯ Not Answered
Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Compound Sodium Lactate solution is an isotonic solution of electrolytes. The constituents their concentrations are designed to match those of plasma. The pharmacological properties of the Compound Sodium Lactate solution are those of its components (sodium, potassium, calcium, chloride and lactate). The main effect is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid.

Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D8. Information on placebo *(if relevant; repeat as necessary)*

D8. Is there a placebo:

◯ Yes ◉ No ◯ Not Answered

D9. Sites responsible for final QP release for distribution to investigators.

D9-1. IMPs and placebos for which no responsible site needs to be identified.

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR1

Finished IMP
PR2

Finished IMP
PR3

Index of Sites where the qualified person certifies batch release

In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union

D9-2. Who is responsible in the Community for the certification of the finished IMP or placebo?
This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D1 or D7 In the case of multiple sites indicate the product certified by each site.

RS1

Name of the organisation:
Address
Town/city
Post code
Country
Give the manufacturing authorisation number

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

E: Design of the Trial.

E.1 Medical Condition or Disease under Investigation

E1-1. Medical condition or disease under investigation (1)

Specify the medical condition(s) to be investigated (free text) :
Sepsis

Medical condition in easily understood language
Blood infection

Identify the therapeutic area
Diseases [C] - Bacterial Infections and Mycoses [C01]

(1) In the case of healthy volunteer trials, the intended indication for the product under development should be provided.

E1-2. MedDRA information (2)

MR1

Version	23
Level	LLT
Classification Code	10040047
Term	Sepsis
SOC	10021881 - Infections and infestations

(2) Applicants are encouraged to provide the MedDRA lower level term (LLT) if applicable and classification code.

E1-3. Is any of the conditions being studied a rare disease? (3)

○ Yes ◉ No ○ Not Answered

(3) Refer to "Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation": COM/436/01 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003773.pd

E2. Objective of the trial

E2-1. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To determine whether early peripheral vasopressor infusion (PVI) targeted to MAP of ≥65 mmHg improves clinical effectiveness (Days Alive and Out of Hospital at 90 days) in hospitalised adult participants with septic shock compared with usual care, in the first 48 hours.

E2-2. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

Secondary objectives are to assess the effects of PVI, compared with usual care, on clinical, patient centred, health service and economic outcomes in the acute hospital setting and during three months follow-up post randomisation. These will include protocol adherence and safety outcomes.

E2-3. Is there a sub-study?

○ Yes ◉ No ○ Not Answered

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Age 18 years and over
Clinically suspected or proven infection resulting in principal reason for acute illness
SBP<90mmHg or MAP of < 65mmHg
Measured serum lactate of >2mmol/L at the time of eligibility assessment. The serum lactate should be measured 2 hours prior to determination of eligibility, where possible. Longer timeframes may be used and justified within the medical notes if, in the opinion of the investigator, the clinical status of the patient has not significantly improved in the time interval between lactate measurement and eligibility assessment. Lactate measurements more than 4 hours prior to eligibility assessment should not normally be used.
Hospital presentation within last 12 hours

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters).

>1500ml of intravenous fluid prior to screening
Clinically judged to require immediate surgery (within one hour of eligibility assessment)
Immediate (<1 hour) requirement for central venous access
Chronic renal replacement therapy
Known allergy/adverse reaction to norepinepherine
Palliation/end of life care (explicit decision by family/care in conjunction with clinical team that active treatment beyond symptomatic relief is not appropriate)
Previous recruitment in the trial
Patients with permanent incapacity
Pregnancy. All women of childbearing potential (WoCBP) must have a negative urine or serum pregnancy test result completed as part of screening requirements. WoCBP are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Other primary causes of shock (e.g. suspected cardiogenic shock, haemorrhagic shock, etc)
History or evidence of any other medical, neurological or psychological condition that would expose the subject to an undue risk of a significant Adverse Effect as determined by the clinical judgement of the investigator
Participation in other clinical trials of investigational medicinal products

E5-1. What is the primary outcome measure for the study?(max 5000 characters)

The primary outcome is Days Alive and Out of Hospital at 90 days (DAOH-90) following randomisation.

The primary objective is to determine whether early PVI (within 12 hours of admission) targeted to MAP of ≥65 mmHg improves clinical effectiveness (DAOH-90) in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours.

Timepoint(s) of evaluation of this end point (max 800 characters)
The main analysis will be according to the intention to treat principle and use an ordinal logistic regression model for the primary outcome of DAOH-90 adjusting for centre as a random effect (or e.g. centres combined at a regional level if there are many small centres) and any pre-specified baseline covariates strongly predictive of outcome. A sensitivity analysis using imputation of missing values will be considered only if the proportion of cases with missing values is sufficiently large.

The protocol will usually identify a single primary end point but there may be a co-primary end point in some cases and/or a number of secondary end points.

E5-2. Secondary end point(s) (max 5000 characters)

Secondary objectives are to assess the effects of PVI, compared with usual care, on clinical, patient centred, health service and economic outcomes in the acute hospital setting and during the three months after participant randomisation. These will include protocol adherence and safety outcomes.

Timepoint(s) of evaluation of this end point (max 800 characters)

The secondary outcomes will be analysed in a similar way to the primary analysis, using statistical models appropriate to the distribution of the outcome (mainly linear or logistic mixed effects models).
Protocol Adherence and safety outcomes will be summarised descriptively.

E6. What is the scope of the trial?

Diagnosis	○ Yes	◉ No	○ Not Answered
Prophylaxis	○ Yes	◉ No	○ Not Answered
Therapy	◉ Yes	○ No	○ Not Answered
Safety	◉ Yes	○ No	○ Not Answered
Efficacy	◉ Yes	○ No	○ Not Answered
Pharmacokinetic	○ Yes	◉ No	○ Not Answered
Pharmacodynamic	○ Yes	◉ No	○ Not Answered
Bioequivalence	○ Yes	◉ No	○ Not Answered
Dose Response	○ Yes	◉ No	○ Not Answered
Pharmacogenetic	○ Yes	◉ No	○ Not Answered
Pharmacogenomic	○ Yes	◉ No	○ Not Answered
Pharmacoeconomic	◉ Yes	○ No	○ Not Answered
Others	○ Yes	◉ No	○ Not Answered

Specify:

E7-1. Trial type and phase [(1)]

Human pharmacology (Phase I)	○ Yes	◉ No	○ Not Answered
Therapeutic exploratory (Phase II)	○ Yes	◉ No	○ Not Answered
Therapeutic confirmatory (Phase III)	◉ Yes	○ No	○ Not Answered
Therapeutic use (Phase IV)	○ Yes	◉ No	○ Not Answered

(1) The descriptions of the trial types provided are those recommended in preference to Phases. See page 5 of Community guideline CPMP/ICH/291/95. The development of a new indication after initial approval of a medicine should be considered as a new development plan.

E8. Design of the Trial.

E8-1. Is the trial design controlled?

◉ Yes ○ No ○ Not Answered

Specify:

Randomised	◉ Yes	○ No	○ Not Answered
Open	◉ Yes	○ No	○ Not Answered
Single blind	○ Yes	◉ No	○ Not Answered
Double blind	○ Yes	◉ No	○ Not Answered
Parallel group	◉ Yes	○ No	○ Not Answered
Cross over	○ Yes	◉ No	○ Not Answered
Other	○ Yes	◉ No	○ Not Answered

E8-2. If controlled, specify the comparator:

Other medicinal product(s)	◉ Yes	○ No	○ Not Answered
Placebo	○ Yes	◉ No	○ Not Answered
Other	○ Yes	◉ No	○ Not Answered

Number of treatment arms in the trial
2

E8-3. Single site in the Member State concerned (see also section G):

○ Yes ◉ No ○ Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G):

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in Member State concerned
30

E8-5. Multiple Member States

○ Yes ◉ No ○ Not Answered

Number of sites anticipated in the Community.

E8-6. Trial being conducted both within and outside the EEA

○ Yes ◉ No ○ Not Answered

Trial conducted completely outside EEA

○ Yes ◉ No ○ Not Answered

E8-7. Will a data monitoring committee (DMC) be convened?

◉ Yes ○ No ○ Not Answered

E8-8.

Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial.
If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.
12 months after last patient last visit in order to allow for data cleaning and resolution of queries and final study report

E8-9. How long do you expect the study to last? (1)

In all countries concerned by the trial
Years: 6 Months: 0 Days: 0

In the MS concerned
Years: 6 Months: 0 Days: 0

(1) From the first inclusion until the last visit of the last subject.

E8-10. Recruitment start date

Recruitment start date in MS
01/03/2022
In any country

(1) If not provided in the protocol.

F: Population of Trial Subjects

F1. What is the age span of the trial subjects?

Less than 18 years	○ Yes ◉ No ○ Not Answered	Approx no of participants: 0
Adult (18-64 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 2800
Elderly (geater than 65 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 1000

The number of participants will be initial estimates. Applicants will not be required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial.

F2. What is the gender of the trial subjects?

Female	◉ Yes ○ No ○ Not Answered
Male	◉ Yes ○ No ○ Not Answered

F3. Please select the categories of the trial subjects:

Healthy volunteers	○ Yes ◉ No ○ Not Answered
Patients	◉ Yes ○ No ○ Not Answered
Specific vulnerable populations	◉ Yes ○ No ○ Not Answered
Women of childbearing potential not using contraception	◉ Yes ○ No ○ Not Answered
Women of child bearing potential using contraception	◉ Yes ○ No ○ Not Answered
Pregnant women	○ Yes ◉ No ○ Not Answered
Nursing women	◉ Yes ○ No ○ Not Answered
Emergency situations	◉ Yes ○ No ○ Not Answered
Subjects incapable of giving consent personally	◉ Yes ○ No ○ Not Answered

If yes, please specify:
Due to the nature/severity of the presenting condition, patients with sepsis may not always be able to give personal consent.

Others	○ Yes ◉ No ○ Not Answered

F4. Planned number of subjects to be included:

In the member state 1005

For a multinational trial:

In the European community:

In the whole clinical trial: 1005

F5. Plans for treatment or care after a subject has ended his/her participation in the trial. ***If it is different from the expected normal treatment, please specify:***

At the end of the trial, participants will return to usual care as defined by local and national guidelines which may include continuation of the protocol assigned treatment.

G1. and G2. Investigator Details

G1. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Alasdair
Family name	Corfield
Qualification (MD...)	MBCHB, MRCP(UK), FRDEM< MPH
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Institution department name	Royal Alexandria Hospital
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Fax	
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G2. Other principal Investigators *(for a multicentre trial)*

IN2

Given name	Kevin
Family name	Rooney
Qualification (MD...)	MBChB, MPH, MRCP(UK),FRCEM, DipIMC (RCSEd), Dip RTM
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Fax	
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IN3

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IN4

Given name	Benjamin
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IN5

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IN6

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IN7

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IN8

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IN9

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IN10

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IN11

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Fax	
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IN12

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IN13

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IN16

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IN17

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IN18

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IN19

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IN20

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Fax	
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IN21

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IN22

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IN23

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IN24

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IN25

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IN26

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Institution department name	
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Post Code	L9 7AL
Country	
Telephone	
Fax	
E-mail	Ben.Morton@liverpoolft.nhs.uk

For multi-centre trials where the CI is also a local PI, please list the CI as a PI at G2 (single-centre).

G3. Central Technical Facility Details

G3. Central technical facilities to be used in the conduct of the trial. *Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised.*

Organisation

Central technical facility organisation name	
Central technical facility organisation department	
Contact person Given name	
Contact person Family name	
Street address	
Town/city	
Post code	
Country	
Work Telephone	
Fax	
E-mail	

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes ◉ No ○ Not Answered
Clinical chemistry	○ Yes ◉ No ○ Not Answered
Clinical haematology	○ Yes ◉ No ○ Not Answered
Clinical microbiology	○ Yes ◉ No ○ Not Answered
Histopathology	○ Yes ◉ No ○ Not Answered
Serology / endocrinology	○ Yes ◉ No ○ Not Answered
Analytical chemistry	○ Yes ◉ No ○ Not Answered
ECG analysis / review	○ Yes ◉ No ○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	○ Yes ◉ No ○ Not Answered
Primary/ surrogate endpoint test	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

Network organisation details

G4. Network organisation details

Organisation
Contact person Given name
Contact person Middle name
Contact person Family name
Street address
Town/city
PostCode
Country
Telephone number
Fax number
E-mail

Activities carried out by the network

G5. Organisations to whom the sponsor has transferred trial related duties and functions

G5. Subcontractor organisations.
Enter details of central CRO facilities supplying services for at least this Member State.

Organisation	Edinburgh Clinical Trials Unit
Department	Edinburgh Clinical Trials Unit
Contact person Given name	Jacqueline
Contact person Family name	Stephen
Street address	9 Little France Crescent
Town/city	Edinburgh
PostCode	EH1 4UX
Country	United Kingdom
Telephone number	
Fax	
E-mail	Jacqueline.Stephen@ed.ac.uk

Enter the details of any duties/ functions subcontracted to this sponsor's subcontractor facility in this trial

All tasks of the sponsor:	○ Yes	◉ No	○ Not Answered
Monitoring:	○ Yes	◉ No	○ Not Answered
Regulatory (e.g. preparation of applications to CA and Ethics Committee):	○ Yes	◉ No	○ Not Answered
Investigator recruitment:	○ Yes	◉ No	○ Not Answered
IVRS(1) - treatment randomisation:	◉ Yes	○ No	○ Not Answered
Data management:	◉ Yes	○ No	○ Not Answered
E-data capture:	◉ Yes	○ No	○ Not Answered
SUSAR reporting:	○ Yes	◉ No	○ Not Answered

Quality assurance auditing:	○ Yes ◉ No ○ Not Answered
Statistical analysis:	◉ Yes ○ No ○ Not Answered
Medical writing:	○ Yes ◉ No ○ Not Answered
Other duties subcontracted:	○ Yes ◉ No ○ Not Answered

H: Ethics Committee

H1-1. Type of application
Please tick the Ethics Committee box and give information of the Ethics committee concerned.

Ethics committee ☑

H2-1. Limited Name and address of ethics committee:

Organisation Scotland A REC
Work Address

PostCode
Country
Fax

H2-2. Date of submission:

30/12/2021

H2-3. Current status of Ethics Committee Opinion at the time of submission to the National Competent Authority:

○ To be requested ○ Pending ◉ Given

If "Given", please specify:
Date of opinion: 25/04/2022
State opinion: ◉ Accepted ○ Not Accepted

I: Signature Of The Applicant In The Member State

I1. I hereby confirm that /confirm on behalf of the sponsor (tick which is applicable) that:

- [x] The information provided is complete;
- [x] The attached documents contain an accurate account of the information available;
- [x] the clinical trial will be conducted in accordance with the protocol;
- [x] The clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I2. Applicant of the request for the competent authority (as stated in section C.1):

This section was signed electronically by Ms Louise Ner on 12/12/2024 12:34.

Job Title/Post:	Sponsor Research Coordinator
Organisation:	NHS GGC
Email:	louise.ner@nhs.scot

J: Checklist

J3. ***For details of the documents required for applications to the MHRA in the UK please see*** ***http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Whattosend/index.htm***