Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	EVIS
IRAS project ID* (or REC reference if no IRAS project ID is available):	307862
Sponsor amendment reference number*:	SA_09
Sponsor amendment date* (enter as DD/MM/YY):	13 December 2024
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	1). Addition of Sites undertaking the same activities as existing sites 2). Early closure of Royal Blackburn Hospital as a participating site, PI Dr Nick Truman. 3). Endpoint/Objective - The EVIS Funder (NIHR) approved a Re-design to the EVIS Trial on the 13/08/2024, to update the primary objective. The primary objective is to determine whether early PVI (within 12 hours of admission) targeted to MAP of ≥65 mmHg improves clinical effectiveness in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours. The primary objective is currently measured by the Primary outcome of 'All-Cause Mortality at 30 Days', the proposed re-design revises the Primary Outcome of 'Days Alive and Out of Hospital at 90 Days'. The EVIS independent study Statistician, IDMC, TSC and Sponsor are all aware and in support of this change. The NIHR conducted a formal internal and external review of the revised primary outcome prior to approval, with justication for the change submitted by the EVIS Trial team. 4). Reduction to the Sample Size from 3286 to 1005 participants overall. 5). Extension to study duration - new recruitment end date 31/11/2026, a 3 month follow up period ending on the 28/02/2027 and the end date for all study activities to be 31/10/2027. 6). Substantial Changes to the EVIS Protocol to apply change to the Primary outcome and all associated changes. 7). Non-Substantial Changes to the Protocol 8). Minor update to the clinical information sheets, to match the updated protocol wording. 9). Minor updates to the; Main PIS/ICF, PIS Summary, Welfare Attorney/Guardian, Professional Legal Rep (Scotland & England), Recovered Capacity (Scotland & England) and Personal Legal Rep PIS/ICF's to; A) Update to the follow up period, to match the updated windows in the protocol. B). Include additional wording on the legal basis for the processing of participant data. 10). Minor Changes to the EVIS Sub-Study Consent Form, PIS and Interview Guide to; A). Provide further information regarding how the data will be collected and stored. B). Include additional wording on the legal basis for the processing of participant data.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**	No		
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	No	No	**Yes**	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	**Yes**		No	
EudraCT number*:	2021-006886-39			
Was this clinical trial of an investigational medicinal product (CTIMP) processed under the CTIMP combined review service (formerly known as the Combined Ways of Working (CWoW) pilot)?:	**Yes**		No	
Did the study receive Pharmacy Assurance?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	

Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes	**No**
Did the study involve adults lacking capacity OR does the amendment introduce this?:	**Yes**	No
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes	**No**
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes	**No**
Did the study involve children OR does the amendment introduce this?:	Yes	**No**
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**	No
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes	**No**

	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	No	No	**Yes**	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	**Yes**	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	**Yes**	No

Section 2: Summary of change(s)

What do you want to update?:	Chief Investigator Sponsor Group Administrative
	Project information

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Participating Organisations			
Specific change (select - only available when area of change is selected first)*:	Addition of sites undertaking the same activities as existing sites			
Further information (free text - note that this field will adapt to the amount of text entered):	1). Addition of Queen Elizabeth Hospital, King's Lynn as a participating site, PI Dr Angelo Giubileo 2). Addition of Kings College Hospital, London as a participating site, PI Dr. Ahsen Ikram			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	All		**Some**	
			Remove all changes below	

Change 2				
Area of change (select)*:	Participating Organisations			
Specific change (select - only available when area of change is selected first)*:	Early closure or withdrawal of research sites			
Further information (free text - note that this field will adapt to the amount of text entered):	2). Early closure of Royal Blackburn Hospital as a participating site, PI Dr Nick Truman.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	All		**Some**	
			Remove all changes below	

Change 3	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Endpoint/objective - Change to the endpoint or the main objective
Further information (free text - note that this field will adapt to the amount of text entered):	Endpoint/Objective - The EVIS Funder (NIHR) approved a Re-design to the EVIS Trial on the 13/08/2024, to update the primary objective. The primary objective is to determine whether early PVI (within 12 hours of admission) targeted to MAP of ≥65 mmHg improves clinical effectiveness in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours. The primary objective is currently measured by the Primary outcome of 'All-Cause Mortality at 30 Days', the proposed re-design revises this Primary Outcome to 'Days Alive and Out of Hospital at 90 Days'. This decision has the support of the EVIS independent study Statistician, IDMC, TSC and Sponsor. The NIHR conducted a formal internal and external review of the revised primary outcome prior to approval. The justification for the change has been enclosed seperately in this amendment pack "Justification for the EVIS change to the Primary Outcome V1.0 09.12.24" which provides a summary of the justification provided to the Funder for review. The approval by the EVIS Funder to proceed with the change/suggested re-design has also be included in this amendment pack (13.08.24 - HTA Contract Variation Request Outcome).

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 4	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Participant numbers - Significant change to sample size
Further information (free text - note that this field will adapt to the amount of text entered):	4). Based on the updated sample size calculations for the new primary outcome the sample size is being reduced from 3286 to 1005 participants overall.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 5	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	5). As part of the approval to revise the primary outcome, the EVIS Funder (NIHR) approved an extension on the 13/08/2024. Current recruitment end date is 30/06/2025, with current study end date 30/09/2025. This amendment will extend the recruitment period, with the new recruitment end date 31/11/2026, a 3 month follow up period ending on the 28/02/2027 and the end date for all study activities to be 31/10/2027. As a result of a reduction in sample size, EVIS' new targets are now to open 30 participating sites across the UK (a reduction of 30 from the previous target of 60). The monthly recruitment target for participating organisations is also being reduced from 2 participants, per site, per month, to 1 participant, per site, per month. Participating sites can implement this change within existing resource, as although the duration of the Trial has been extended, the reduction in sample size results in the monthly recruitment target being cut in half, reducing monthly recruitment from 2 participants per site per month, to 1. Furthermore, the overall average total recruitment target per site, is reduced by this change from 55 participants required overall, to 33.5 recruited overall per site.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No

Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**	Some
		Remove all changes below

Change 6	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Protocol - Substantial changes (e.g. affecting safety or the scientific value of the trial)
Further information (free text - note that this field will adapt to the amount of text entered):	6). Substantial changes to the EVIS protocol to implement the change to the primary outcome. Namely; A). A reduction to the planned sample size. B). Extension to the planned trial period. C). Revision to the primary Objective/Outcome (see change 3 above for further information on this change). D). Reduction in number of UK NHS Sites from 60 to 30. E). Revised the Statistics and data analysis section of the protocol for the change to the primary outcome. Includes updated sample size calculations, recruitment rate and primary outcome analysis for the new primary outcome.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 7	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Protocol - Non-substantial changes (e.g. not affecting safety or the scientific value of the trial)
Further information (free text - note that this field will adapt to the amount of text entered):	7). Non-Substantial Changes to the Protocol: A) Administrative updates: versioning. B). Updated Schedule of Assessments for clarity and to match the change to the primary objective/outcome. C). Updated wording from Patients and Participants used interchangeably throughout the protocol, to Participants throughout for consistency. D). Additional description added to the Co-enrolment process, to provide further guidance when a patient would be eligible to co-enrol with more than one additional approved study. E). Additional clarity added to the Withdrawal process for patients. F). Updated Study Visits to ensure consistency with the updated Schedule of Assessments. G). Updated the description of the imbedded process evaluation in Appendix H and the main body of the protocol, to provide further information regarding how the data will be collected and stored. H). Included information regarding the National Data Opt Out and how this applies to EVIS Participant data. (I). Standardisation of

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 8	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	8). Minor update to the clinical information sheets, to match the updated protocol wording of titrating to a MAP of greater than or equal to (≥) 65mmHG.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 9	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below

Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	9). Minor updates to the EVIS; Main PIS/ICF, PIS Summary, Welfare Attorney/Guardian, Professional Legal Rep (Scotland & England), Recovered Capacity (Scotland & England) and Personal Legal Rep PIS/ICF's to; A) Update the stated follow up period, to match the updated windows in the protocol. B). Include additional wording on the legal basis for the processing of participant data.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
				Remove all changes below

Change 10	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	10). Minor Changes to the EVIS Sub-Study Consent Form, PIS and Interview Guide for the Qualitative Research in the context of the Early Vasopressors in Sepsis (EVIS) Trial imbedded EVIS Process Evaluation to; A) Explicitly ask for consent to record the staff interviews. B). Provide further information regarding how the data will be collected and stored. C). Include additional wording on the legal basis for the processing of participant data.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	**Yes**	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Applicant identification:	**Sponsor** Legal representative of the sponsor Person or organisation authorised by the sponsor
Organisation:	R&I NHS GG&C
Name [first name and surname]:*	Louise Ner
Address:	Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH
Telephone number:	
Fax number:	
Purchase Order (PO) number for MHRA invoicing:	
Email address:*	louise.ner@nhs.scot

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, amendments to trials processed under the combined review service should be made using the new part of IRAS. Further information can be found on the "Submission Guidance" tab.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

Review bodies			
UK wide:	England and Wales:	Scotland:	Northern Ireland:

	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWIA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:	N	N				(Y)				(Y)				(Y)					New site
Change 2:	N	N				(Y)				(Y)				N					B
Change 3:	Y	Y				(Y)				(Y)				(Y)					A
Change 4:	Y	N				(Y)				(Y)				(Y)					A
Change 5:	N	N				(Y)				(Y)				(Y)					C
Change 6:	Y	Y				Y				(Y)				(Y)					A
Change 7:	N	N				(Y)				(Y)				(Y)					A
Change 8:	N	N				(Y)				(Y)				(Y)					C
Change 9:	N	N				(Y)				(Y)				(Y)					C
Change 10:	N	N				(Y)				(Y)				(Y)					C
Overall reviews for the amendment:																			
Full review:	Y	Y				Y				N				N					
Notification only:	N	N				N				Y				Y					
Overall amendment type:	Substantial for review																		
Overall Category:	A																		