Copenhagen Trial Unit
Centre for Clinical Intervention Research

May 4th, 2018

Collaboration agreement

AID-ICU

Agents Intervening against Delirium in Intensive Care Unit (AID-ICU) – A randomised, blinded, placebo-controlled trial.

Agreement between:

Sponsor

Lone Musaeus Poulsen
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Lykkebækvej 1
4600 Køge, Denmark
E-mail: lmp@regionsjaelland.dk
Phone: +45 4732 6451
Hereinafter CRIC or sponsor

Date: 04 / 05 / 2018

Signature:

Lone Musaeus Poulsen

Copenhagen Trial Unit

Copenhagen Trial Unit
Centre for Clinical Intervention Research,
Rigshospitalet, Dept. 7812
Blegdamsvej 9, 2100 Copenhagen Ø
Denmark
Represented by Jørn Wetterslev
E-mail: wetterslev@ctu.dk
Phone: +45 35 45 71 59
Hereinafter CTU

Date: 04/05/2018

Signature:

Jørn Wetterslev

Jørn Wetterslev | Copenhagen Trial Unit | Centre for Clinical Intervention Research
Rigshospitalet | Phone: +45 35 45 71 59 | E-mail: wetterslev@ctu.dk

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Services, price specification and billing

A complete list of services and split of responsibilities between CTU and AID-ICU can be found in the table at the end of the present agreement.

The nature of the partnership between CTU and the sponsor, Centre for Research in Intensive Care (CRIC), is based on a collaboration model, and the obligations to contribute to this partnership by both parties are described in the collaboration agreement between CTU and CRIC (not attached), alongside the grant provisions directed by the Innovation Fund Denmark. Billing will be made through Rigshospitalet and will include all services delivered once every year ultimo December.

Agreement specification

Collaboration model

The collaboration model requires that CTU is an active contributor in the development of the trial protocol, participates in the trial steering committee as a member, and performs one or more tasks associated with the trial, e.g., a conduct of systematic reviews, performs Trial Sequential Analysis, submission of trial pertinent documents to relevant authorities, data management, randomisation, statistical analyses, etc. CTU shall receive the final trial protocol including any later amendments, trial registration number, and copies of approvals from relevant authorities (i.e., the Danish Research Ethics Committee, the Danish Data Protection Agency, and possibly the Danish Medicines Agency).

Privacy act

If any services provided by CTU involve handling of personal data, CTU will play the role as data processor, while sponsor will be perceived as data controller and data responsible as per the Danish Act on Processing of Personal Data, section 3. CTU's legal liability extents to the data and data management, and the processing hereof is defined by the split of responsibility.

Role allocation of agreement

CTU coordinator:
Jørn Wetterslev, MD, PhD
Copenhagen Trial Unit
Centre for Clinical Intervention Research
Rigshospitalet, Dept. 7812
Blegdamsvej 9, 2100 Copenhagen Ø, Denmark
E-mail: wetterslev@ctu.dk
Phone: + 45 35 45 71 59

Sponsor:
Lone Musaeus Poulsen
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Lykkebækvej 1
4600 Køge, Denmark
E-mail: lmp@regionsjaelland.dk
Phone: +45 4732 6451

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Coordinating investigators:
Nina Christine Andersen-Ranberg, MD
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

Stine Estrup
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

See specifications and split of responsibilities in the associated table provided herein and in the current trial protocol version 3.6, 1th of December 2017 (http://www.cric.nu/aid-icu-protocol/). Any changes that may occur at a later stage will prevail and will be amended to the present agreement.

Reservation
Collaboration between CTU and sponsor requires approval of this agreement by the Research and Innovation Unit (EFI), Law and Contracts, Capital Region, Denmark.

With regards to the collaboration model, it is not a requirement that the full financing of CTU's services is achieved at the time the present agreement comes into force. If a partial financing is achieved, CTU and sponsor will seek funds conjointly for full coverage of the expenses described in the present agreement. If the remaining funding is not obtained, the current agreement shall be reassessed.

Jørn Wetterslev | Copenhagen Trial Unit | Centre for Clinical Intervention Research
Rigshospitalet | Phone: +45 35 45 71 59 | E-mail: wetterslev@ctu.dk

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General terms of agreement

Standards

CTU's work is performed in accordance to the Helsinki Declaration and the ICH-GCP guidelines as well as Danish regulations and legislation. CTU expects equal standards of sponsor.

Sponsor may audit CTU, and CTU may be inspected by relevant authorities.

Preparation of protocol

The approved protocol should be forwarded to CTU. All later amendments to the protocol and new approvals from the relevant authorities must also be forwarded to CTU.

In case of a collaboration agreement, CTU should be informed of any changes associated with the trial and be involved in the decision making prior to their adoption.

Terms of web-based systems

1.Development, validation, training

For randomisation systems

Sponsor must provide a list of the information to be collected and a list of all stratification variables. Concerning the validation process please refer to the paragraph: 'For electronic case report form – schedules'.

For electronic case report forms - system development

A requirement specification should be prepared prior to initiation of a trial. The final approval of developed or modified systems by sponsor will be based on the requirement specification.

CTU will continuously make the changed/newly developed systems available to sponsor, to ensure that its functionality can be evaluated throughout the development process.

For electronic case report form - schedules

The sponsor should disclose fully annotated paper copies of all forms that are to be included in an electronic case report form (eCRF). Sponsor must approve the forms as final, and these will serve as the basis for the eCRF. CTU can also participate in the development of CRFs. Each applicable paper CRF (pCRF) should be clearly annotated with the protocol version it belongs to.

Sponsor will test the eCRF for approval of workflow in the system, and correctness with regards to the provided final pCRFs. This testing must be completed within 7 working days after CTU has announced that the database is ready for review. Investigator should prepare a list of corrections sent to CTU in writing. The performance of this validation is not the responsibility of CTU. Upon a subsequent written approval from sponsor, the database is deemed correct, and the eCRF is to be prepared for data entry. Changes after this point may have additional costs than specified in the present agreement and will be billed by hourly rate.

CTU undertakes to prepare specific user manuals for the use of developed eCRF and/or randomisation systems, and training of sponsor in their use. Unless otherwise agreed and specified in the present agreement, it is the responsibility of sponsor to educate site investigators and other personnel in the use of these systems.

2. Security and IT environment

eCRF system and randomisation system are hosted on a server environment with the following characteristics:

- Fiber connection to the internet;
- Windows Server 2008R2 server environment;
- encrypted traffic between server and clients;
- daily backup of databases;
- monitored and locked server room only accessed by authorised personnel.

3. Availability

The systems will be available at all hours, except during service time slot periods, given that the client's connection to CTU's server is intact.

General service time slots will be of a duration less than 10 minutes and will be around 06 p.m. on weekdays. The number of normal service time slots is approximately 4 per month. CTU is not required to advertise normal service time slots.

Lost connection to the server due to an error on CTU hardware is the responsibility of CTU, as is solving the problem in a timely manner. CTU has a support agreement with IBM for this purpose with Next Business Day Service Level Agreement. If it is not possible to rectify the error within an acceptable time span, CTU offers alternative hosting of systems and data based on the latest available backup. The alternative hosting, set up of systems, and data transfer is free of charge.

If connection is lost due to hardware failure not belonging to CTU, and if it is not possible to rectify within an acceptable time span, CTU offers alternative hosting of systems and data based on the latest available backup. The alternative hosting, set up of systems, and data transfer will be billed according to the current hourly rate.

Lost connection due to software installed on CTU's server is the responsibility of CTU. The lost connection should be repaired within one working day after notification of the error. If it is not possible to rectify the error within an acceptable time span, CTU offers alternative hosting of systems and data based on the latest available backup. The alternative hosting, set up of systems, and data transfer is free of charge.

CTU takes reservations for unannounced hiatus between CTU and CTU's internet service provider (DeIC, Research Network). If possible, CTU will offer alternative hosting of systems and data based on the latest available backup. The alternative hosting, set up of systems, and data transfer is free of charge.

Terms of data entry from pCRF

Sponsor must provide an annotated pCRF to CTU, which will form the basis for the development of the CTU internal data entry system. Any changes to a pCRF must be announced to CTU, and the new CRF should be sent with clear annotation of all changes to previously applicable version.

Jørn Wetterslev | Copenhagen Trial Unit | Centre for Clinical Intervention Research
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Investigator is required to submit one or more filled test pCRFs, which will underlie CTU's validation of the data entry system.

CTU undertakes to retype the CRFs, and continually check completeness and quality of CRFs and entered data.

Force majeure

CTU is not responsible for failure to meet the obligations of CTU under the present agreement if fulfilment is hindered by extraordinary circumstances, which CTU could not prevent or overcome, and which CTU upon signing the agreement could not have foreseen, avoided or overcome. These exceptional circumstances include war, invasion, terrorism, epidemics, nuclear accidents, general strike and general lock out. In such cases, CTU should immediately inform the sponsor.

Serious non-compliance incidents occurring during the trial, are reported to the Danish Medicines Agency according to GCP guidelines, Danish legislation and CTU's standards.

Privacy

'Proprietary information' refers to the information relayed to CTU by sponsor in order to manage the services described in the first part of the present agreement.

Proprietary information must not be used by CTU for purposes other than those for which sponsor has given written consent, or which are necessary for CTU to perform the services under the present agreement. Upon termination for any reason, use of proprietary information by CTU will be discontinued immediately. Proprietary information must be kept confidential and should not, without prior written consent from sponsor, be disclosed to any third parties.

Confidential information does not include information that:

- at the time of receipt has been made public, and not due to a breach of confidentiality obligations by CTU;
- CTU received from a third party in good faith, unless the third party is already bound by confidentiality obligations as a sponsor and/or investigator;
- CTU has developed independent of, and unrelated to, any confidential knowledge delivered under the present agreement;
- pursuant to the law, must be published.

Confidentiality obligations must cease no later than 5 years after closure of the present agreement or ending of CTU services provided under the present agreement, whichever is affected first.

Termination

The present agreement may be terminated by the parties involved with one month's prior written notice. Minimum duration of services offered will not be shortened by termination of the present agreement.

Duration

The present agreement should come into force upon signature of the involved parties and continue until the end of the trial as stated in the agreement, unless the agreement is terminated by either party in accordance with the terms of termination of agreement.

Delivery of final data

After follow-up of the last included trial participant, it is CTU responsibility to hand over a full copy of the trial relevant data to sponsor. Moreover, it is CTU responsibility to hand over a full copy of site data, including changes made, to each site investigator.

Insurance

If not otherwise specified in the agreement, the responsibility of any insurance aspects always lies with the Sponsor.

Breach of agreement

Serious deviations from conditions described in the present agreement will possibly be regarded as a breach of agreement.

If CTU is suspected of breach of agreement:

- Sponsor should inform the CTU management of this in writing, so that the CTU management is given the opportunity to prevent the breach of agreement (typically 30 days);
- the agreement will be terminated;
- CTU should pay back funding, which has not yet been spent, and which CTU has received according to the agreement and budget for specific project-related services;
- if CTU is liable to pay compensation according to Danish law, the amount of compensation should not include indirect losses, consequential losses, operational losses, loss of earnings, and other consequential losses, including damages claimed by Sponsor.

If CTU suspects Sponsor of breach of agreement:

- The CTU should inform Sponsor as well as the management at Rigshospitalet in writing hereof;
- The CTU should seek advice and, if necessary, approval of dispositions regarding negotiation with Sponsor at Law and Contracts or the management at Rigshospitalet. If the conflict/breach of agreement is complicated, the negotiation should be handed over to the Director at Rigshospitalet or a delegated person, who ultimately has the responsibility of resolving the conflict.

Other

The present agreement should be interpreted and governed according to Danish Law.

The present agreement should take precedence over the trial protocol and other documents in those situations where the documents are not concurrent.

Jørn Wetterslev | Copenhagen Trial Unit | Centre for Clinical Intervention Research
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Table specifying services, prices and split of responsibility of the present contract

Contract-relevant?	#	Services and responsibilities	Responsible party		Price	Overhead	Billing	Comment
			Sponsor	CTU				
Yes	**1**	**PRE-INITIATION OF TRIAL**						
		Filing of relevant communication between sponsor and CTU	X	X				
		Documents regarding financing (budget, application for funding, etc.)	X	X				
		Curriculum vitae and/or other documentation for the qualification level of current and new trial personnel	X					
		List of personnel to whom the investigator has delegated trial-related responsibilities	X					
		Agreements (signed and legally approved) concerning specific services to be delivered by CTU	X	X				
		Other written agreements	X					
		Setting up and maintaining the Trial Master File (TMF) until end of trial	X					
Yes	**2**	**PROTOCOL DEVELOPMENT AND REGULATORY APPROVAL**						
		Development of trial protocol including trial amendments (two pieces)	X	X				
		Information material for trial participants (including trial information sheet, written informed consent form, power of attorney etc.) and update of these documents during trial period	X					
		Creating EudraCT number and preparation of Clinical Trial Application (CTA)	X					
		Translation of pertinent documents to applicable language (including trial information sheet, written informed consent form, power of attorney etc.)	X					
		Regulatory approval from Regional Ethics Committee and if necessary supplementary approvals	X					
		Regulatory approval from Danish Data Protection Agency and if necessary supplementary approvals	X					
		Regulatory approval from Danish Medicines Agency and if necessary supplementary approvals	X					

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		Registration of trial in publicly available registries/databases, e.g., clinicaltrials.gov	X					
Yes	**3**	**RANDOMISATION**						
		Set-up of a randomisation system (development and user testing) - total price covering services listed in the following marked with [2]		X				
		Generation of allocation sequences[2]		X				
		Development of a randomisation manual [2]	X					
		Training of site personnel	X					
		Hosting of the randomisation system (DKK 2.500 / month, minimum period of 6 months)		X				
		Procedure for emergency randomisation in case the primary system breaks down [2]		X				
		Procedure for code disclosure / unblinding in blinded trials		X				
		Identification log of participants		X				
		Screening log of potential participants		X				
		Final list of all included participants in a chronological order [2]		X				
Yes	**4**	**DATA MANAGEMENT**						
		Development and update of a trial-specific Case Report Form (CRF) template	X					
		Development and update of a trial-specific paper Case Report Form (pCRF)						
		Development and update of a trial-specific electronic Case Report Form (eCRF) - total price covering services listed in the following marked with [3]		X				
		Development of a data entry manual for eCRF [3]	X					
		Training of site personnel [3]	X					
		Hosting of clinical database (DKK 2.500 / month, minimum period of 6 months)[3]		X				
		Documentation for changes applied to CRFs [3]		X				
		Description of where source data is stored/archived (source data list) [3]	X					
		Source data [3]	X					
		Completed, signed and dated paper Case Report Forms (pCRF)						
		Data cleaning based on defined variable-list		X				

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		Extraction and delivery of data to statistician [3]		X				
		Archiving of depersonalised trial data including meta data in Danish Data Achieve and ZENODO		X				
		Quality assurance of information collected from public databases for the purpose of statistical analyses						
		Collection of events from public databases						
		Development, test, and maintenance of additional IT systems (Medicine module)		X				
Yes	**5**	**COMMITTEES**						
		Steering Committee	X					
		Independent data monitoring and safety committee (IDMSC)	X					
		Reporting to IDMSC		X				
Yes	**6**	**STATISTICAL ANALYSIS**						
		Development of a detailed statistical analysis plan	X	X				
		Definition of variables/derived variables relevant for the outcomes in the detailed statistical analysis plan	X					
		Statistical analyses	X					
		Statistical analysis report (included in 'statistical analysis')	X					
Yes	**7**	**TRIAL MATERIAL AND DRUG ACCOUNTABILITY**						
		Investigator's brochure or approval of summary of product characteristics and update of these during trial period	X					
		Instructions on handling medicinal products and other trial-related material	X					
		Example of labels and package leaflet of medicinal product	X					
		Documentation for delivery of trial material	X					
		Analysis certificates for new batches of medicinal products	X					
		Overview of final consumption of medicinal product	X					
		Destruction of medicinal product	X					
		Documentation regarding destruction of medicinal product						
Yes	**8**	**PHARMACOVIGILANCE AND SAFETY REPORTING**						
		Reporting of serious adverse events (SAEs) to sponsor	X					
		Reporting of suspected unexpected serious adverse reactions (SUSARs) to authorities	X					
		Status / annual reports to Danish Medicines Agency and the Regional Ethics Committee	X					

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Yes	**9**	**MONITORING**						
		Development of a trial-specific monitoring plan	X					
		Filing of essential documents (as defined by GCP and according to the protocol) in the Investigator Site File	X					
		Collection and filing of signed informed consent form and power of attorney	X					
		Monitoring visits (pre-initiation visit, initiation visit, regular visits and close-out visit)	X					
		Monitoring reports (pre-initiation visit, initiation visit, regular visits and close-out visit)	X					
		Follow-up letter to clinical site	X					
Yes	**10**	**TRIAL REPORTING**						
		Systematic reviews	X	X				
		Design paper	X	X				
		Paper on main results	X	X				
		Paper on any secondary or exploratory outcome	X	X				
Yes	**11**	**TRIAL CLOSURE**						
		Preparation of close-out trial report	X					
		Reporting to relevant authorities regarding trial close-out	X					
		Archiving of trial essential documents from TMF for 20 years after end of trial	X					
		Receipt for closing data archive (deletion of data) after archiving period	X					
		TOTAL						
		TOTAL	**See paragraph: ”Services, price specification and billing”**					

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