20-06-2017

HOT-ICU

Arterial Oxygen Tensions and Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

Agreement between:

Sponsor

Centre for Research in Intensive Care (CRIC)
Rigshospitalet, Dept. 7812
Blegdamsvej 9, 2100 Copenhagen Ø
Denmark
Represented by Bodil Steen Rasmussen
E-mail: bodil.steen.rasmussen@rn.dk
Phone: +45 97 66 18 64
Hereinafter CRIC or sponsor

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
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Hereinafter CTU

Signature:
Bodil Steen Rasmussen
President of EACTA
Chair of Steering Committee, Centre for Research in Intensive Care (CRIC)

_____

Date: __ __ /__ __ /__ __ __ __

Signature:
Jørn Wetterslev
Chief Physician

_____

Date: __ __ /__ __ /__ __ __ __

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Tick if relevent	#	Services and responsibilities	Responsible party		Overhead	Price	Billing	Comment
			Sponsor	CTU				
	1	**PRE-INITIATION OF TRIAL**						
	2	**PROTOCOL DEVELOPMENT AND REGULATORY APPROVAL**						
✓	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 periode 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				
✓	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 periode 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 storing/archiving [3]	X					
		Completed, signed and dated paper Case Report Forms (pCRF)						
		Data cleaning based on defined variable-list		X				
		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						
	5	**COMMITTEES**						
	6	**STATISTCAL ANALYSES**						
	7	**TRIAL MATERIAL AND DRUG ACCOUNTABILITY**						
	8	**PHARMACOVIGILANCE AND SAFETY REPORTING**						
	9	**MONITORERING**						
	10	**TRIAL REPORTING**						
	11	**TRIAL CLOSURE**						
		TOTAL						
		TOTAL	**See paragraph: 'Price specification and billing'**					

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Price specification and billing

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 of the literature, submission of trial pertinent documents to relevant authorities, data management, randomisation, statistical analyses, etc. CTU should receive the final trial protocol and if relevant later amendments, 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 as listed in the table provided herein.

Role allocation of agreement

CTU coordinator:
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Coordinating investigators:
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Denmark

See specifications and split of responsibilities in the associated table provided herein and according to the current trial protocol version 1.2, 24th of May 2017 (http://www.cric.nu/hot-icu-protocol-approved/). Any changes that may occur at a later stage will prevail, and will be amended to the present agreement.

Scope of agreement
By signing the present agreement, CTU assumes the following tasks:

- Randomisation
- Data management

The table provided herein specifies the contracted services and split of responsibilities between CTU and CRIC.

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

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.

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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. If appropriate, amendments to the protocol and new approvals from the relevant authorities must also be forwarded to CTU.

In case of an 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

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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.

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 effected 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.

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

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 compliant.

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Jørn Wetterslev (Jun 26, 2017)

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