AGREEMENT FOR THE PERFORMANCE OF THE TRIAL

PROOF: "Penumbral Rescue by Normobaric O=O Administration in Patients with Ischemic Stroke and Target Mismatch ProFile: A Phase II Proof-of-Concept Trial"

Project ID : 2017-001355-31

INVOLVING

European Clinical Research Infrastructure Network (ECRIN-ERIC)

www.ecrin.org

Hereinafter referred to as "ECRIN"

and

Masaryk University

Hereinafter referred to as "ECRIN PARTNER"

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THIS AGREEMENT IS MADE BY AND BETWEEN (hereinafter referred to as the **"Agreement"**):

European Clinical Research Infrastructure Network (ECRIN-ERIC), registered under SIRET n°801 933 235 00021, established in 5-7 rue Watt, 75013 Paris, France, represented by Prof. Dr. Jacques Demotes, Director General of ECRIN ERIC

Hereinafter referred to as "ECRIN"

AND

Masaryk University, whose registered office at Zerotinovo nam. 617/9, Brno 601 77, Czech Republic, ID number 00216224, VAT num.: CZ00216224

Represented by: prof. MUDr. Martin Bareš, Ph.D., the dean of **Faculty of Medicine,** contact address: Kamenice 5, Brno-Bohunice, 625 00, Czech Republic

Hereinafter referred to as "ECRIN PARTNER"

Hereinafter individually or collectively referred to as the "Party" or the "Parties".

WHEREAS

A clinical trial entitled **PROOF: "Penumbral Rescue by Normobaric O=O Administration in Patients with Ischemic Stroke and Target Mismatch ProFile: A Phase II Proof-of-Concept Trial"** (hereinafter referred to as the "Clinical trial") is to be conducted in different European countries pursuant to the protocol current version (hereinafter referred to as the "Protocol").

The Clinical trial is the core part of a European Consortium Agreement (Final Version, ***07.04.2017***) which receives funding from the European Union Horizon 2020 program under Grant Agreement no. **733379**.

The **University Hospital Tübingen** is the Sponsor of the Clinical trial in the European Union (EU). The Sponsor has delegated specified tasks to ECRIN, as stated in a separate Agreement signed by the Sponsor and ECRIN on July 13th, 2018.

ECRIN will perform the tasks delegated by the Sponsor in the different EU countries through subcontracting to its Partners as stated in the above-mentioned agreement.

Masaryk University (hereinafter referred to as ECRIN PARTNER), hereby agrees to undertake the tasks specified for ECRIN PARNER in the Tasks list (see appendix 1) in the **Czech Republic** according to the Protocol current version (see Appendix 3) subject to the terms and conditions of this Agreement.

The purpose of this Agreement (hereinafter referred to as the "Agreement") is:

- to state the tasks (hereinafter referred to as the Tasks) subcontracted by ECRIN to ECRIN PARTNER;
- in particular, to set forth the terms and conditions governing the performance of the Tasks in the **Czech Republic**.

THEREFORE, IT IS HEREBY AGREED AS FOLLOWS:

1. PERFORMANCE OF CLINICAL TRIAL RELATED TASKS

The clinical trial-related tasks shall be conducted by the participating Parties:

1.1.1. in all respects in accordance with their respective roles and responsibilities as described in the present agreement and Tasks list (*see Appendix 1*)

1.1.2. in accordance with the protocol (*see Appendix 3*)

1.1.3. in accordance with the requirements laid down by laws and regulations applicable in the participating countries

1.1.4. Each Party has a duty to inform the other Party as soon as possible of any difficulties encountered in carrying out the Tasks assigned to it and which may compromise the objectives of the Clinical trial.

2. DUTIES

2.1. Obligations of ECRIN

2.1.1. ECRIN shall be responsible for the coordination of the Clinical Trial in the following countries: **Belgium, Czech Republic, Finland, France, Spain, Sweden and Switzerland**

2.1.2. ECRIN shall centralize and transmit clinical trial-related documents and information from the abovementioned countries to the Sponsor or to any person authorized by the Sponsor for the completion of the Clinical trial as described in the aforementioned Tasks list.

2.1.3. ECRIN shall transfer to ECRIN PARTNER the Monitoring manual and all documents necessary to perform the tasks

2.1.4. For the avoidance of doubt, ECRIN has no obligation to transfer to ECRIN PARTNER any data or information other than data and information strictly needed by ECRIN PARTNER for the performance of the Tasks assigned to ECRIN PARTNER

2.2. Obligations of ECRIN PARTNER

ECRIN PARTNER shall be responsible for carrying out its Tasks as described in the Tasks list (*see Appendix 1*). In particular, under ECRIN coordination, ECRIN PARTNER shall:

2.2.1. *in close collaboration with the Sponsor and the lead CTU (KKS Heidelberg, Germany) be responsible for applications to National Competent authorities, Ethics Committees and any relevant Authorities, in the* **Czech Republic**

2.2.2. *be responsible for monitoring of the Clinical trial in the trial sites in the concerning country according to the Monitoring Manual provided by the Sponsor*

2.2.3. *according to the local requirements and based on documents provided by the Sponsor and/or the Lead CTU, shall be responsible for the notification of SAEs/SUSARs and Safety reports to National Competent authorities, Ethics Committees and any relevant Authorities, in the* **Czech Republic**

2.2.4. *is responsible for ensuring that the tasks related to the Monitoring as described in the Protocol current version and Monitoring Manual are fulfilled strictly in accordance with the terms of this Agreement, and all applicable international and national laws, regulations and guidelines.*

2.2.5. *for all work involving databases of personal data, electronic or otherwise, including but not limited to medical information and genetic information the ECRIN PARTNER shall fully comply with prevailing data protection provisions, in particular the EU Data Protection Directive 95/46 CE of 25 October 1995 or when applicable, the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (the GDPR), and any related law and regulations applicable in the participating countries.*

In addition, ECRIN PARTNER represents and warrants to ECRIN that:

2.2.6. shall fulfill its obligations under this Agreement and during the term of this Agreement and will not enter into any agreement which would in any way prevent it from performing its Tasks under this Agreement.

2.2.7. has disclosed any existing relationship, which may adversely impact the execution of the Tasks.

3. COST AND PAYMENTS

For the avoidance of doubt, ECRIN PARTNER is considered as in kind contributor under the Grant agreement **733379**.

For the performance of the Tasks, both Parties agree on the costs, which are based on the assumptions described in Appendix 2, for a total maximum amount of EUR 22,105 (including indirect costs, excluding VAT). The tasks are exempt form Value added tax, based on the Commission implementing decision of 29 November 2013 on setting up the European Clinical Research Infrastructure Network (ECRIN) as a European Research Infrastructure Consortium (ECRIN-ERIC) 2013/713/EU and article 151 (1)(b) of Council Directive 2016/112/EC.

The tasks for this Study are provided under the non-economic activity model according to the Framework agreement signed on 16.11.2016. ECRIN PARTNER shall charge price at the level of costs (including overheads) without profit.

The remuneration and payment is agreed on under presumption that one site will be initiated in the Czech Republic. In case that more sites are initiated, the parties will enter into negotiation immediately regarding new payment schedule.

Payments will be made pro-rata for work completed. On a quarterly basis, ECRIN PARTNER shall submit original invoice and report summarizing the work completed to ECRIN at the address below. The clinical trials reference **PROOF** should be mentioned on the invoice. Invoices for the work completed will be paid within thirty (30) days of receipt.

INVOICING DETAILS:
ECRIN
Attn: [redacted]
5-7 RUE WATT
75013 PARIS - FRANCE
VAT N°: FR91 801933235

In the event of early termination of the Agreement, if payment (whether for salaries or otherwise) has been made by ECRIN to ECRIN PARTNER in advance for work not completed, funds received in advance at the exception of duly justified expenses already incurred by ECRIN PARTNER, shall be returned to ECRIN within thirty (30) days of the effective date of termination.

Misuse of funds, if discovered or suspected, will result in immediate suspension of the Tasks and reimbursement of the already received funds shall/may be expected.

4. CLINICAL TRIAL DATA& RESULTS

ECRIN PARTNER agrees not to make claims to possible intellectual property rights (the "IPR") from data and results obtained during the conduct of the Clinical Trial (hereinafter referred as to "Data" and "Results") and not to pursue IPR protection that would prevent or block access to or use of any data, conclusions drawn directly from those Data and Results.

5. CONFIDENTIALITY

For the purpose of this AGREEMENT, confidential information should include but not limited to any and all information related to the Clinical Trial which is disclosed by ECRIN to ECRIN PARTNER as a result of this AGREEMENT. (Hereinafter referred to as the "CONFIDENTIAL INFORMATION")

5.1. Confidentiality of Provided Information

5.1.1. ECRIN PARTNER hereby agrees that at all times during the term of this Agreement, ECRIN PARTNER with its professional staff, affiliates, independent consultants and any other cooperating partners, will hold and maintain in confidence all proprietary and CONFIDENTIAL INFORMATION related to the Clinical Trial, written or oral, provided by ECRIN.

5.1.2. ECRIN PARTNER undertakes to use such CONFIDENTIAL INFORMATION only in relation to the execution of the Tasks unless otherwise agreed with the disclosing Party.

5.1.3. ECRIN PARTNER agrees that it will not permit CONFIDENTIAL INFORMATION in its possession to be reproduced, disseminated or otherwise disclosed to any third party or used for any purpose not previously authorized in writing by ECRIN other than those contemplated by this Agreement.

5.1.4. In the event ECRIN PARTNER becomes legally compelled to disclose any confidential information, it shall immediately provide ECRIN with notice thereof prior to any disclosure, shall use its best efforts to minimize the disclosure of any CONFIDENTIAL INFORMATION, and shall cooperate with ECRIN.

5.1.5. The obligations set forth in this Article shall not apply to information for which the Party it is able to prove that:

-the Confidential Information becomes publicly available by means other than a breach of confidentiality obligations;

- the disclosing Party subsequently informs the recipient that the Confidential Information is no longer confidential;

-the Confidential Information is subsequently communicated to the recipient without any obligation of confidence by a third party who is in lawful possession thereof and under no obligation of confidentiality;

- that the disclosure or communication of the Confidential Information is foreseen by law or by other provisions of this grant agreement or the supplementary agreement;

- that the disclosure or communication of Confidential Information is required by the Laws and Regulations.

5.2. Confidentiality of Results

5.2.1. ECRIN PARTNER including its professional staff, agrees not to disclose or transfer or publish or commit to any third party the data, in whole or in part, and the results of the Clinical trial which are confidential information.

5.2.2. In the event ECRIN PARTNER's independent consultants or any other cooperating partners (hereinafter "PARTNERS") shall be involved, ECRIN PARTNER will undertake that such PARTNERS are obliged to respect the commitment specified in this Agreement to the same extent.

5.2.3. In any case, all CONFIDENTIAL INFORMATION containing personal data shall be handled in accordance with all applicable laws, including, but not limited to the European Data Protection Directive EC/95/46 and the locally applicable laws and regulations on Data Protection.

5.2.4. The terms and conditions of these obligations of confidentiality and restricted use contained herein are applicable during the term of the Agreement and shall survive its date of termination, whether by expiration or by earlier termination.

5.3. Specific obligations of ECRIN PARTNER under national law of the Czech Republic

5.3.1. ECRIN acknowledges that the ECRIN PARTNER is an obligated subject under the Czech act no. 340/2015 Coll. of the Czech Republic, on special conditions for the effectiveness of some contracts, the disclosure of these contracts and the Registry of contracts (Act on the Registry of contracts). Provisions of the Act on the Registry of contracts obligates public institutions (such as Masaryk university) to transparently publish a copy of this agreement (including metadata) in a central repository of contracts (Registry of contracts) before the agreement enters into force.

5.3.2. ECRIN and ECRIN PARTNER declare that they agree that this Agreement and all its amendments will be published by the ECRIN PARTNER in the Register of contracts under the conditions of the Act on the Registry of contracts.

5.3.3. ECRIN and ECRIN PARTNER declare that the confidential parts of this Agreement and its amendments, third party trade secrets and parts protected by intellectual property, such as the Protocol, will not be published in the Register of contracts.

5.3.4. The parties have agreed, that the annexes (appendices) of this Agreement will not be published, because they contain intellectual property, know-how and trade secrets of the Sponsor and/or ECRIN If ECRIN.

6. SUBCONTRACTING

6.1.1. ECRIN PARTNER represents and warrants to ECRIN that shall not sub-contract part of its Tasks to a third party in the framework of this Agreement without notifying ECRIN through a written notice and having received ECRIN's written consent and, if necessary, the authorization of the Sponsor. The prior information shall be notified to ECRIN at least thirty (30) days before the date of signature of any subcontracting agreement.

6.1.2. Notwithstanding such ECRIN consent, ECRIN PARTNER shall ensure that :

- its agreement with the subcontractor(s) is made on terms that reflect the requirements of this Agreement
- the subcontractor shall not claim any intellectual property right or right of use of Data and Results pertaining to Clinical trial.

6.1.3. In any event, ECRIN PARTNER shall remain fully liable for the completion of the share of the Tasks that it entrusts to said third party subcontractor as well as for the acts and omissions of any such permitted third party.

7. LIABILITY AND INDEMNITY

7.1.1. ECRIN PARTNER is exclusively and fully liable for its assigned Tasks related to the Clinical trial and for the implementation of all technical, organizational, human, material, legal operations, and safety rules required by the performance of its tasks.

7.1.2. ECRIN PARTNER shall take out appropriate insurance cover in respect of its potential liability and shall produce to ECRIN, on request, a copy of the insurance certificate as evidence to confirm that it has such coverage. Failure to maintain adequate insurance coverage does not relieve or reduce ECRIN PARTNER liability under this Agreement.

7.1.3. ECRIN PARTNER undertakes to carry out its assigned Tasks with outmost care, observing approved and recognized scientific standards.

7.1.4. ECRIN PARTNER shall indemnify and hold ECRIN harmless from any and all claims, demands, damages, liabilities and costs incurred by ECRIN which directly or indirectly result from, or arise in connection with, any negligent act or omission of ECRIN PARTNER, its agents, or employees, pertaining to its activities and obligations under this Agreement.

8. INSPECTION AND AUDIT

8.1.1. Should ECRIN PARTNER become aware of an upcoming inspection or audit related to the Clinical Trial, ECRIN PARTNER should inform ECRIN and Sponsor in writing within 72 hours.

8.1.2. ECRIN PARTNER hereby allows any Regulatory Authorities may inspect the facilities and all related documents being used by ECRIN PARTNER for the performance of the Tasks.

8.1.3. ECRIN PARTNER agrees that, during an audit or an inspection by a Regulatory Authority it will not disclose information and materials that are not required to be disclosed to such Regulatory Authority without the prior written consent of ECRIN

8.1.4. ECRIN PARTNER shall provide ECRIN with a copy of all correspondence related to such audit or inspection and a summary of the audit findings or the inspection report

8.1.5. If any inspection, audit or examination by a Regulatory Authority results in a finding that ECRIN PARTNER has failed to comply with the terms of this Agreement, ECRIN PARTNER promptly take such measures at its own cost and expense as are necessary to correct such default identified in any such inspection, audit or examination.

9. MODIFICATION

9.1.1. This Agreement, including the attached Annexes, constitutes the entire and only Agreement between the parties relating to the Clinical trial.

9.1.2. Any agreement to change the terms of this Agreement and its Appendices in any way shall only be valid if the change is made in writing and approved by mutual agreement of authorized representatives of all the Parties. Such amendments shall be assigned by all the Parties and annexed to this Agreement.

10. INTUITU PERSONAE

The Agreement is executed *intuitu personae*. Consequently, ECRIN PARTNER is not authorized to transfer all or part of the rights and obligations hereunder to a third party without the prior and written agreement of ECRIN and of the Sponsor.

11. TERM AND TERMINATION OF THE AGREEMENT

11.1. This Agreement is considered concluded as from the date of signature of the last Party to sign the agreement. The effective date is the date when a copy of this agreement has been published in a Registry of contracts pursuant to Art. 5.3. of this Agreement. The Agreement shall remain in effect up to 31.12.2021. The agreement may be extended by amendment. Any and all extension shall be subject to the drafting of an amendment to be signed by an authorized representative of each Party.

11.2. This Agreement can, only after discussing between the Parties, be terminated by written notice in case of

- early termination of the Study
- any technical, administrative cause (e.g. Study not authorized, suspended or prohibited by the Authorities) or methodological impossibility to pursue the Study
- termination for Breach

11.3. In the event of a breach by any Party of any of its obligations under this Agreement, the other Party may provide written notice to the breaching Party, such notice specifying the breach and requiring that the default be remedied within thirty (30) days. If the breach has not been remedied by the breaching Party to the satisfaction of the other Parties within thirty (30) days of receipt by the breaching Party of the notice identifying the breach and requiring its remedy, the Parties may terminate automatically, totally or partially, this Agreement with respect to the Defaulting Party with immediate effect. Such termination shall become effective with respect to such Defaulting Party as of the date of the notice of termination. Fees in relation with Tasks carried out up to this termination remain payable.

11.4. The defaulting Party concerned by the termination undertakes to communicate to the other Party or subrogated third parties, free of charge and immediately, all the files and information required to allow them to continue the implementation of the Study.

11.5. Exercising this cancellation right does not exonerate the defaulting Party from fulfilling its contracted obligations until the effective date of the termination and shall not, in any case be interpreted as a waiving, by the Party or Parties requesting the termination, of damages and interest in any way whatsoever.

12. FORCE MAJEURE

For the avoidance of doubt, force majeure means any unforeseeable and exceptional event affecting performance of the Agreement, which is outside the control of the Parties, and which cannot be avoided in spite of the efforts which the Parties may reasonably make.

No Party shall be considered to be in breach of this Agreement if such breach is cause by Force Majeure. Each Party shall notify the other Party of any Force Majeure as soon as possible. If impossibility or delay in fulfillment due to a case of force majeure continues for longer than three (3) months, the latter Party may automatically terminate the Agreement at any time by written notification sent to the other Party.

13. SURVIVAL

Upon termination of expiration of the Agreement for any reason, the provisions relating to the Clinical Trial Data and results, Confidentiality, Liability, Indemnity and Litigation shall survive termination of this Agreement.

14. WAIVER

No failure, delay, relaxation or indulgence by any Party in exercising any right conferred on such Party by this Agreement shall operate as a waiver of such right, nor shall any single or partial exercise of any such right nor any single failure to do so, preclude any other or future exercise of it, or the exercise of any other right under this Agreement.

15. NOTICES

All notices or other communications required or permitted to be made or given hereunder shall be deemed so made or given when hand-delivered or sent in writing by registered or certified mail, postage prepaid and return-receipt requested, or by a recognised courier service, charges prepaid and properly addressed to the representatives of the Parties at their addresses mentioned herein:

ECRIN-ERIC	ECRIN PARTNER
European Clinical Research Infrastructure Network (ECRIN-ERIC) **BioPark, 5-7 rue Watt** **75013 Paris, France**	**Masaryk University, Faculty of Medicine (CZECRIN)** **Kamenice 5** **625 00 Brno – Bohunice** **Czech Republic**

16. LITIGATION

In the event of any dispute arising between the Parties in relation to the terms of this Agreement, the parties shall use their best endeavors to resolve the matter on an amicable basis.

To initiate conciliation, a Party must give notice in writing to the other Party, requesting conciliation in accordance with this clause. Within thirty (30) days after this notification, the Parties shall try to appoint a single conciliator, but in the absence of agreement, each Party shall appoint one conciliator. The mission assigned to the Conciliator(s) by the Parties is to suggest a solution in order to resolve amicably such dispute within sixty (60) days after the notification.

In the event the Parties are unable to resolve the dispute informally within a reasonable time, any action brought by either party to this Agreement shall be heard by the appropriate court of competent jurisdiction.

17. GOVERNING LAW

This Agreement and all disputes arising hereunder will be governed by and interpreted in accordance with the laws of France without giving effect to the principles of conflict of laws. The parties hereby consent to and agree that the competent courts, where the ERIC has its statutory seat, shall have the sole and exclusive jurisdiction to resolve all such disputes.

18. GENERAL PROVISION

The invalidity of one or more provisions of this agreement does not affect the validity of the others. The invalid provision is to be replaced by a provision, which, in compliance with the legal prescriptions, suits the purpose best. The modification shall be made in writing and approved by mutual agreement of authorized representatives of all the Parties as specified in article 8.

19. APPENDICES

The following documents are appended to the Agreement and form an integral part hereof:

- **Appendix 1: Tasks list (Version n• 2.0, 02/07/2018)**
- **Appendix 2: Financial annex (Version n° 2.0, 15/08/2017)**
- **Appendix 3: Protocol (Version n° 1.0 , 10/04/2018)**

20. SIGNATURE

This Agreement is executed in two counterparts, depending on the number of the parties, each of which shall be considered an original hereof but which together shall constitute one agreement.

IN WITNESS WHEREOF, the parties, acting through their duly authorized representatives, have executed three (2) copies of this Agreement

1. For and on behalf of ECRIN
European Clinical Research Infrastructure Network (ECRIN-ERIC)
BioPark, 5-7 rue Watt
75013 Paris, France

LEGAL REPRESENTATIVE :
Prof. Dr. Jacques Demotes
Director General of ECRIN ERIC

DATE: 3-8-2018 SIGNATURE: [redacted]

2. For and on behalf of the ECRIN PARTNER
Masaryk University, Faculty of Medicine
Žerotínovo nám. 617/9, 601 77 Brno, Czech Republic

LEGAL REPRESENTATIVE:
Prof. MUDr. Martin Bareš, Ph.D.
The dean of Faculty of Medicine

DATE: -4 -10- 2018 SIGNATURE: [redacted]

❶ executive organ/primary ❷ executive organ/secondary (e.g. deputy) ↦ delegated 🗗 subcontracted		Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
PROJECTMANAGEMENT										
Clinical project management/ Coordinating investigator - Principal investigator										
1	**Medical/ clinical supervision**	Financing	❶							EU Grant: Horizon 2020
		Trial design and conception	❶	❷	❷					review by ECRIN Scientific Board
		Medical expert/contact person for medical questions	❶				❷			
		Medical training of contract partners (medical background, indication, treatment, evaluation tools (scores) etc. (if necessary) (e.g. training of clin. monitors).	❶	❷			❷ support only			KKS: Training of external CRAs
		Acknowledgment of deficiencies; introducing countermeasures (e.g. for cause monitoring) in case of incompliances of the sites/other contracting partners	❶							e.g. after having received monitoring-visit-reports from KKS/CRO or reports of otherwise observed deficiencies. Main responsibility for the review of monitoring visit reports stays with the Sponsor.
General Project management										
2	**Clinical Trial register**	Registration in an officially accepted public register and up-date (including publishing of final study results irrespective of findings)	❶	❷						KKS: support
3	**Organisation of co-operating partners**	Feasibility and site selection/site recruitment; identify and involve new sites	❶				❶			Feasibility: Sponsor only. Site selection / site recruitment: Sponsor and NCs
		Identify partners (CROs) in countries outside of Germany (for country specific application to EC/CA, monitoring, etc.)	↦		❶					Delegated from Sponsor to ECRIN
		Documented feasibility and CRO selection	↦		❶					Delegated from Sponsor to ECRIN: Feasibility will be checked based on Self Assessment Sheets (SAS); however, the completed SAS sheets are confidential and not for distribution to the sponsor (only for ECRIN internal decision procedure). In case of inspections by local authorities or in case of audits the possibility of SAS-disclosure will be clarified/discussed.
		Consent to provide Standard operating procedures or SOP-Index on demand from the CRO for contracted tasks where KKS SOPs are not applicable (e.g. EC/CA application)	↦		🗗	❶				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO.
		Provide current qualification documents of the involved members of the CRO (e.g. CV, study experience, (ICH-GCP) training certificates)	↦		🗗	❶				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO. e.g. CV/experience ofthe clinical monitor, project manager (responsible for EC/CA application/submission)

		Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
4	**DSMB members**	Identification of members; oversee regular meetings (according to DSMB charter)	1							
5	**Communication with the funding organisation (periodic reports)**	budget controlling, re-calculation	1	2	2					ECRIN is beneficiary in the project and has its own responsibility for reporting/budget control etc.
		regular status reports	1	2						KKS: support
		Translation of essential documents (e.g. EC/CA approvals) into English and forwarding to the funding organisation.	1							also see #30/31
6	**Audits**	Inducement/organization of audits (if necessary)	1							
7	**Meetings**	Organization and defining contents of project team meetings, investigator meeting	1	2	2					ECRIN organizes primarily regular telephone conferences with ECRIN partners and with representatives of the sponsor/lead CTU.
		Documents Development								
8	**Protocol and amendments[1] (in English)**	Writing (incl. English and German summary)	1							English summary also required as master template for translation by ECRIN partners into national language
		Support in writing and reviewing (e.g. for applicable tasks (pharmacovigilance, biometry, data management etc.)		1			2 support only			
		Additional reviewing			1					As agreed in the EU application (Horizon 2020): final review by ECRIN-ERIC Scientific board
		Final validation, release by signature	1	1						KKS: biometrician
		If applicable: summary in local language	↱		🗗	1				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO.
		If applicable: add local requirements (local version (addenda) of the protocol/ amendments)	↱		🗗	1				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO.
		Final validation, release of local versions by signature	1	1						KKS: biometrician
9	**Investigational product Manual (in English)**	describe processes concerning randomization, ordering, shipment, storage requirements (e.g. temperature control), preparation, administration, destruction or return; Provide all necessary documents/forms (e.g. ordering forms, temperature logs etc.)	1							
10	**Laboratory Manual (in English)**	If applicable: describe all laboratory processes (sampling, labeling, storage, shipment); provide necessary equipment/laboratory kits (e.g. tubes, labels) for the sites							x	processes for handling of biomarkers have to be provided to the sites by the WP 6 (Biomarkers) team

1 executive organ/primary
2 executive organ/secondary (e.g. deputy)
↱ delegated
🗗 subcontracted

❶ executive organ/primary ❷ executive organ/secondary (e.g. deputy) ↱ delegated 🗗 subcontracted		Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
11	Safety Manual (in English)	Describe management of SAEs/SUSARs, responsibilities, specific forms (e.g. SAE form)	↱	❶						Delegated from Sponsor to KKS. KKS provides DSUR Master template
		Forward/ describe country specific requirements for pharmacovigilance (e.g. via standard operating procedures of the CRO).	↱		🗗	❶				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO. Local, country specific modifications by ECRIN partners / local CRO
		Reviewing and release	❶	❶						KKS: safety officer
12	Information and Consent Form (ICF) (German version), ICF amendments, NCA/EC requests	Writing	❶							
		Support in writing and reviewing		❶						Delegated from Sponsor to KKS.
		Final validation, release	❶							
		Other material provided to the subjects (e.g. announcements, flyer, webpage), writing/release	❶							
		Translation into English (master template for other countries), final validation, release of the English translation	❶	❷						Certified translation of German ICF into English master document needed
13	National ICF, ICF amendments , NCA/EC requests,	Reviewing the English translation and commenting on parts to be changed/added according to local requests	↱		🗗	❶				Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO. Forward comments to KKS.
		Final validation, release of the commented version	❶							
		Translation of the English master template with necessary local modifications into national language(s)	↱		🗗	❶	❷ support only			Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO (translation according to local requirements).
		Final validation and release of national ICF	↱		🗗	❶	❷ support only			Delegated from Sponsor to ECRIN, and subcontracted from ECRIN to ECRIN partners / local CRO. The CRO is responsible for correct translation of the English master template into national language
		Acknowledgement of national ICF and formal release	❶							
		Other material provided to the subjects (e.g. announcements, flyer, webpage) (if applicable)	❶							
		Release of other material provided to the subjects	❶							
14	DSMB charter (in English)	Preparation and Reviewing	❶	❷						KKS provides template; final charter to be written by DSMB members
		Final validation, release							X	final charter to be written by DSMB members
15	ECRIN logistical feasibility and cost assessment	Regulatory submission	↱		❶	❷				Delegated from Sponsor to ECRIN
		Monitoring	↱		❶	❷				Delegated from Sponsor to ECRIN
		National project management	↱		❶	❷				Delegated from Sponsor to ECRIN

❶ executive organ/primary ❷ executive organ/secondary (e.g. deputy) ↱ delegated 🗗 subcontracted		**Clinical Trial: PROOF** **Responsibility Split** **V2 02.07.2018**	**Sponsor**	**KKS**	**ECRIN**	**ECRIN partner/ local CRO**	**National Coordinator (NC)**	**Participating sites**	**NA**	**Comments**
16	**Distribution of documents**	Shipment of relevant documents to partners (e.g. trial protocol and amendments, new investigator's brochure, up-dates for Investigator study file etc.) **based on documents provided by Sponsor** ; receipt must be confirmed in writing	↱	❶	🗗	❶				Delegated from Sponsor to ECRIN and to KKS. Subcontracted from ECRIN to ECRIN partners / local CRO. KKS: shipment within Germany CRO (after receipt from KKS): shipment within applicable country
		Contracts/ Agreements								
17	**Agreement between: Sponsor (University Hospital Tübingen) and Coordinating Investigator**	Preparation	❶							
		Reviewing and release	❶							
		Collecting	❶							
18	**Agreement ECRIN and Sponsor**	Preparation			❶					Agreement based on templates ECRIN ERIC
		Reviewing and release	❶							
		Collecting			❶					
19	**Agreement KKS and Sponsor's Legal representative**	preparation							x	not applicable as covered by Grant Agreement / Consortium Agreement
		Reviewing and release							x	
		Collecting							x	
20	**Contract ECRIN and CRO (English versions)**	Preparation	↱		❶					Contracts based on templates ECRIN ERIC/ECRIN partners
		Reviewing and release	↱		❶	❷				
		Collecting	↱		❶					Delegated from Sponsor to ECRIN
21	If applicable: **Contract DSMB members and Sponsor**	Preparation							x	In case DSMB members receive payment contracting is needed. KKS can provide template.
		Reviewing and release							x	
		Collecting							x	

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22	**Clinical Trial Agreements** First contact to sites and negotiation	❶	❷	❷	❷	❷			Primary contract management via Sponsor. KKS, ECRIN/ECRIN partners / local CRO support in case of country specific questions
	Preparation of templates and collecting of final (signed) contracts (English templates that has been negotiated with the sites will be provided by KKS)	❶	❷ (support only)	❷ support only	❷ only collecting	❷			Sponsor provides templates Sponsor subcontracts German sites only; subcontracting of other sites via NCs KKS: support in German speaking sites ECRIN partners / local CRO: collecting in applicable countries ECRIN supports in case there are special contract templates necessary/available at the site or national request to have bilingual contracts.
	Reviewing and release	❶							
23	**Contract courier (IMP shipment)** Identifying an eligible courier and contracting							X	
24	If applicable: **Contract courier (sample shipment)** If applicable: identifying an eligible courier and contracting (including clarification of export/import licenses)							X	
25	**Contracts:** **a) manufacturing of IMP** **b) IMP logistic/distribution (and import)** **c) Qualified person** **d) recall of IMP** a) manufacturing according to GMP b) IMP-logistic/ tracking: monitor shipment, receipt, expiry dates, stock on site, return (if applicable), destruction. c) monitor IMP quality and recall in case of complaints including possible quality defects							X	
26	If applicable: **other contracts**							X	
27	**Payments**	❶				❷			EU Grant: Horizon 2020 NCs have to pay for insurance, EC fees etc. Case Payment will be hold by sponsor; as soon as visits are documented completely, Sponsor provides NC with case payment, NC will be responsible for transfer of case payment to sites
REGULATORY APPLICATIONS									
Subject insurance									

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28	**Subject insurance (incl. up-dates/ lifetime extension)**	Acquiring national insurance coverage	❶				❶			Each Party performing part of the Clinical Trial shall enter into an insurance policy for patients participating in this Clinical Trial in the respective country in accordance with and if required by applicable laws. Where the Sponsor is required by applicable laws to conclude the insurance policy, the Sponsor shall either delegate its insurance obligation to the respective Party who shall accept such delegation, or the respective Party shall be obliged and authorized to negotiate the contract with the insurance company on behalf of the Sponsor.
		Assistance in meeting national/local requirements for the local insurance coverage		❶	❷ support	❷ support	❶			
		If required: ongoing information of the insurer (e.g. protocol amendments, new ICF etc.; clinical trial end)	❶	❷			❶			
		Charge fees	❶				❶			fees for subject insurance have to be covered by NCs

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National Competent Authorities (NCA) and Ethics Committee (EC) Applications (Initial and Substantial Amendments)									
29	**EudraCT number**	Request		①					Delegated from Sponsor to KKS
30	**NCA application**[1]	Develop master documents relating to submission (e.g. clinical trial application (CTA)...) (English versions) and collect/prepare documents specific to Germany		①					Delegated from Sponsor to KKS
		Collect/prepare documents specific to national submission/ adopt master documents to national requests (other than Germany)	↱		🗗	①	② support		Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO
		Submission and follow-up of submission until approval. Additional submissions/notifications according to local requirements (e.g. yearly status updates (if applicable))	↱	①	🗗	①	② support		Delegated from Sponsor to KKS: central submission via Voluntary Harmonisation Procedure (VHP) and submission in Germany National submissions (Phase 3) of VHP delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
		Continuous information ((non)substantial amendments) based on documents provided by Sponsor	↱	①	🗗	①	② support		see above: KKS: Germany ECRIN partners / local CRO: applicable country
		Notification to local authority ("Landesbehörde") according to German drug law		①					Only applicable in Germany
		Final validation of master CTA	①						
		Translate approval or letters of the NCA into English (if necessary on demand of the sponsor)	↱		🗗	①	② support		Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: Only in cases where the translation is necessary for further decisions of the sponsor, e.g. requested changes of trial protocol, other relevant processes.
		Charge fees	①						all fees for national applications are under the budget of the sponsor and will be invoiced directly to the sponsor's address
		Trial's end notification (regular end or withdrawal)	↱	①	🗗	①	② support		Delegated from Sponsor to KKS: Germany Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: applicable country

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31	**EC application**[1]	Develop master documents relating to submission (e.g. clinical trial application (CTA)...) (English versions)		❶						Delegated from Sponsor to KKS
		Collect/prepare documents specific to national submission/ adopt master documents to national requests	↱		🗗	❶	❷ support			Delegated form Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO
		Collect all CVs or other specific documents	↱	❶	🗗	❶	❷ support			Delegated to KKS: for Germany Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
		Submission and follow-up of submission until approval. Additional submissions/notifications according to local requirements (e.g. yearly status updates (if applicable))	↱	❶	🗗	❶	❷ support			Delegated from Sponsor to KKS: for Germany Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
		Continuous information ((non)substantial amendments) based on documents provided by Sponsor	↱	❶	🗗	❶	❷ support			Delegated from Sponsor to KKS: for Germany Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
		Translate approval or letters of the EC into English (if necessary on demand of the sponsor)	↱		🗗	❶				Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. Only in cases where the translation is necessary for further decisions of the sponsor, e.g. requested changes of trial protocol, other relevant processes
		Final validation of master CTA	❶				❷ support			
		Charge fees	❶				❶			NCs are responsible for country specific payments
		Trial's end notification (regular end or premature termination)	↱	❶	🗗	❶				Delegated from Sponsor to KKS: for Germany Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country

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		Other applications to authorities, Data protection								
32	**Local authority (Germany)[1]**	Notification	↱	❶						Delegated from Sponsor to KKS: Germany
33	**Other Regulatory submission[1]**	If applicable: notifications/submissions according to local law, regulations/guidelines	↱		🗗	❶	❷ support			Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO
34	**Data protection law**	If applicable: notifications/submissions according to local law, regulations/guidelines	↱	❶	🗗	❶	❷ support			Delegated to KKS: Germany Delegated to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
35	**Investigational Medicinal Product (IMP)**	Export authorization: clarify need/provide documentation	❶							
		Import authorization: clarify need/ provide documentation	❶							
36	**Charge Fees**		❶				❶			all fees for national applications are under the budget of the sponsor and will be invoiced directly to the sponsor's address
37	**Forward all relevant regulatory documents (e.g. approvals, notifications) to the sponsor**				🗗	❶	❷ support	❷ support		Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO
		Regulatory requirements due to sample transfer								
38	If applicable: **Sample import authorizations**								X	
39	If applicable: **Sample export authorizations**								X	
40	[1]: also applicable for amendments/ end of trial and NCA/EC/ other authorities requests (e.g. revisions of documents). All documents also applicable to other countries will be developed in English (master template).									

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PROJECT MANAGEMENT										
41	**Sponsor central trial master file (TMF) (in English)**	Design (index)	❶	❶						Delegated partially to KKS: only for assumed tasks/functions. All TMF-sections will be compiled at the end of the trial (see archiving)
		Update	❶	❶			❷ support			Each partner responsible for its own TMF section.
		Print and transfer to sponsor at the end of the trial for archiving		❶						
42	**Country specific trial master file**	Design (index) (in English)	↦	❶	🗗	❶	❷ support			Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. Delegated from Sponsor to KKS. KKS provides Master template/index for TMF; each country modifies according to local requirements.
		Forward country specific index of the TMF to KKS-Heidelberg before implementation	↦		🗗	❶				Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO.
		Update				❶	❷ support			
		Transfer to sponsor at the end of the trial for archiving				❶	❷ support			
43	**Investigator site files (containing English forms/ templates)**	Design and general updates		❶						Subcontracted to KKS: Master ISF for all countries
		Design/adoption to local country specific requests and local updates	↦		🗗	❶	❷ support			Delegated to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: Index in case of local adaptations needs to be sent to KKS-Heidelberg for acknowledgement
		Sent up-dates to sites (based on documents provided by sponsor (documents will be shipped from KKS to CRO))	↦	❶	🗗	❶				Delegated to KKS: for Germany Delegated to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO: for applicable country
44	If applicable: **Pharmacy file (in English)**	Design and general updates (English Master)							X	
		Adoption to local requests							X	
		Sent up-dates to pharmacy (based on documents provided by sponsor (documents will be shipped from KKS to CRO))							X	

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Investigational Medical Product (IMP)										
45	**Financing and manufacturing**	Purchase, manufacturing, packaging, labeling (according to local law (country specific requirements)	❶							
46	**Investigator's Brochure (IB) and up-dates**	Regular IB up-date (yearly); statement to current benefit-risk							x	not applicable (SMPC available)
		Information of all investigators on risks of IMP (results of the pharmacological toxicological investigation), providing the investigator's brochure (incl. up-dates)	❶							If applicable: during investigator meetings
47	**IB notification to EC/NCA**	IB up-dates as (non) substantial amendment (if applicable according to local law/requirements); statement to current benefit-risk (based on documents provided by sponsor)							x	not applicable (SMPC available)
48	**Investigational Medicinal product dossier (IMPD)** (incl. manufacturing authorization/ Certificate of analysis/ Export/Import authorization etc.)) (in English)	Preparation for EC/NCA application, regular up-date and documentation on a master file (incl. manufacturing authorization, certificate of analysis (to document identity, purity, and strength of IMP) etc.)							x	not applicable (SMPC available)
49	**IMP Labels**	Preparation (German and English labels)							x	no labeling necessary
		Provide information on local (country specific) requirements concerning content of labels							x	no labeling necessary
		Reviewing national adapted label and release							x	no labeling necessary
		Translation into national language and release (country specific).							x	no labeling necessary

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50	**Randomization and unblinding**	Preparation of randomization plan		❶						Delegated to KKS
		Organize central randomization	❶	❶						Delegated to KKS
		Monitor randomization activities , file relevant documents		❶						
		Production of a set of individual emergency envelopes (for unblinding) and shipment to participants (e.g. department of pharmcovigilance, manufacturer)							x	not applicable (open label)
		Collection of unopened emergency envelopes during Close-out-visits of the clinical monitor at the end of the trial; documented destruction							x	not applicable (open label)
51	**IMP logistic**	Direct shipment to sites organized by Sponsor	❶							
		Clarify the import conditions to the participating countries (whether an import license is needed or not) and provide import license for application to NCA	❶							
		Describe, organize, monitor and document IMP logistic and management (ordering, shipment, return, destruction)/ traceability on sites	❶	❷		❷				KKS & ECRIN partners/local CROs: monitoring of IMP at sites (according to Monitoring Plan)
		Shipment to sites via courier (if necessary temperature controlled) after release of a site ("green light")	❶							
		Provide sites with necessary equipment (masks, ventiles, portable oxygen equipment)	❶							
		Provide sites with necessary documents and manuals	❶							
		Monitor/ document IMP stock on site and IMP expiry dates	❶	❷		❷				KKS & ECRIN partners/local CROs: monitoring of IMP at sites (according to Monitoring Plan)
		Documented destruction of residual, used IMP (returned from sites) (if not destructed on site).	❶				❶	❶		
		Documented destruction of unused IMP (returned from sites) (if not destructed on site).	❶				❶	❶		
LABORATORY (only clinical trial without sub-studies)										
52	**Proof of qualification**	Collecting/regular up-date of accreditation certificates or other established quality control/external quality assessments or other validation and providing to Sponsor.							x	no accreditation/certification is needed as all lab parameters are routinely assessed, except for BGA (2nd assessment). BGA calibration, however, does not need to be checked.
53	**Normal values**	Provide current normal values of the local laboratory to the Sponsor	↦	❷		❷	❶	❶		Delegated to each trial site (part of site contracts). Collection also acceptable during monitoring-visits (KKS/ ECRIN partners/local CRO)
54	**Normal values/ ranges**	Define ranges for laboratory values for deposition in the clinical database	❶	❷			❷ support			Ranges will be implemented into the data validation plan of the KKS

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PHARMACOVIGILANCE									
55	SAE data base	Set up and regular update		①					
56	SAE management	SAE/SUSAR notification and distribution to KKS					①	①	
		Processing of incoming SAE reports		①					
		Corrective measures in case of violations/incompliances of the participating sites	①						
		SAE second assessment	①						
		Writing SAE narratives	↱	①					
		Reviewing and release of narratives	①						
		Preparation of CIOMS forms in case of SUSARs	↱	①					
		Reviewing and release of CIOMS forms	①						
		Notification of SUSARs (CIOMS) to EC/NCA and all sites (PI) (based on documents provided by Sponsor/KKS)	↱	①	🗗	②			Delegated from Sponsor to KKS. Delegated from Sponsor to ECRIN and subcontracted from ECRIN to ECRIN partners / local CRO for applicable country only if national requirements prevent notification by KKS.
		Further notifications (SAE/SUSAR) acc. to local requirements (based on documents provided by the sponsor/KKS)	↱		🗗	①	② support	② support	Delegated to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. A copy of these notifications must be forwarded to KKS.
		Preparation of Development Safety Update Report (DSUR) (English master version)	↱	①					
		Assistance in meeting local country specific requirements concerning the content of the DSUR (English)	↱		🗗	①	② support		Delegated from Sponsor to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO.
		Review and release of DSUR (final English (local) version(s))	①						
		Notification of (local) DSURs to EC/NCA (based on documents provided by Sponsor/KKS)	↱	①	🗗	②			Delegated to KKS and to ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. KKS will be responsible for notification to all ECs/NCAs if only DSUR is required (without further local documents to be translated). In all other cases: KKS: Germany ECRIN partner / local CRO: applicable country
		Notification of DSUR (English master version) to DSMB	①						If applicable.

		Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
57	**Benefit-Risk assessment**	Continuous monitoring of risks (literature search, IB-up-date, medical monitoring)	1							
		Introducing measures (e.g. early trial termination) in case of direct risks	1							
		Immediate information of the sites, EC/NCA or other institutions on safety concerns that could influence the decision to participate in the trial or the EC/NCA approval	1	2 support		2 support				KKS and ECRIN partners / local CRO: Support in spreading information to sites (based on information provided by the sponsor in addition to the communication pathway the sponsor will use to contact the sites directly)
58	**SAE coding**	According to MedDRA	↱	1						
59	If applicable: **Listings (for DSMB/other committees)**	Preparation of listings (e.g. AE/SAE), safety summaries	↱	1						
		Review, release, shipment of listings	1							

1 executive organ/primary
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🗗	subcontracted

69	If applicable: **Statistical analysis plan (SAP)**
70	**Interim Analysis and report**
71	**Interim report**
72	**Statistical analysis plan (SAP)**
73	**Definition of trial population**
74	**Analysis**
75	**biometrical trial report**

1 executive organ/primary 2 executive organ/secondary (e.g. deputy) ⌐ delegated 🗗 subcontracted	Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
DATA MANAGEMENT delegated from Sponsor to KKS									
60 **Electronic Case Report Form (eCRF); questionnaires (in English)**	Set up		1						
	Reviewing and release	1							
	CRF manual/ user guide/ training environment for user		1						
	Make the eCRF available to all centres		1						
	Provide standardized questionnaires/scales and licenses (if applicable) for official use (for all applicable languages)	1							
	Providing filled eCRF to KKS, archiving of related documents					1	1		
	Design of subject diaries, questionnaires (if applicable)							x	
	Reviewing and release							x	
61 **eCRF account support**	User management		1						
62 **Data management plan**	Design and preparation (incl. updates)		1						
	Reviewing and release	1							
63 **Database (DB)**	Design and preparation/ usability test (incl. updates)		1						
	Data validation plan (DVP) and validation (incl. updates)		1						
	Reviewing and release of DVP (incl. updates)	1							
	Reviewing and release of DB (incl. updates)	1							
	Regular Back up of DB if necessary		1						
64 **Medical data coding (MedDRA)**	Medical history and concomitant diseases							x	
	Adverse events		1						
	Clarification in case of uncertainties concerning the applicable coding	1							
65 **Coding (ATC)**	Concomitant medication							x	
66 **Query and status reports (in English)**	Preparation and dispatch to sites and monitors		1						
	Remind sites in case of outstanding answers to data queries (based on information provided by KKS)		1	🗗	1				Delegated to KKS and ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. KKS: Germany ECRIN partner / local CRO: applicable country, within the defined monitoring tasks
	Answer queries via eCRF					1	1		
67 **other status reports, exports from DB (in English)**	e.g. AE-Listings (for DSMB), subject recruitment (for newsletter), eCRF documentation		1						
68 **Database closure (DBC)**	Reconciliation clinical DB and safety DB		1						KKS: data management and pharmacovigilance
	release DBC	1							
	DBC and export to biometrician		1						
	Data transfer (exported data) to Sponsor and to all sites		1						
	archiving of exported data	1							

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CLINICAL MONITORING delegated to KKS, subcontracted to ECRIN partner / local CRO									
76	**Standard Operating procedures (SOPs) (in German and English)**		❶						
77	**Monitoring manual (English)**	Conception and planning; risk assessment/definition	❶	❶					
		Monitoring manual (applicable to all countries)		❶					
		Review and release	❶						
		Training of external monitors (at least for lead monitor per CRO), including eCRF-training	❶	❶					Delegated to KKS KKS: via monitoring, data management
78	**Prestudy visit**	Visit and report						x	
79	**Initiation visit**	Initial training of sites	❶						Investigator Meeting / Workshops
		Visit and report		❶	🗗	❶			
		Support of initiation visit					❶	❶	
80	**Monitoring visits**	Visit and report		❶	🗗	❶			Delegated to KKS and ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. KKS: Germany ECRIN partner / local CRO: applicable country
		Support of monitoring visit					❶	❶	
81	**Regular contacts to site and sponsor**	Support of sites in case of questions. continuous follow-up of outstanding to do's of the site. Escalating findings to the sponsor in case of relevant or recurrent findings.		❶	🗗	❶			<u>MVR-Review:</u> KKS MV-reports: KKS projectmanager ECRIN partner / local CRO MV-reports: ECRIN partner / local CRO projectmanager, second review by KKS projectmanager according to specific monitoring manual.
82	**Central monitoring**	Using central quality control measurements (if available) to improve trial conduct		❶	🗗	❷			
83	**Close-out visit**	Visit and report		❶	🗗	❶			
		Support of close-out visits					❶	❶	Trial sites have to support all monitoring visits (with regard to scheduling visits, participation in visits, timely response to follow-up letters, etc.).
84	**Trial master file related to monitor**	Regular update; forward to sponsor at the end of the trial		❶	🗗	❶			
85	**Monitoring visit reports (MVR)**	First and second review and release; escalating findings immediately to sponsor (if necessary) according to monitoring manual		❶	🗗	❶			
		Written acknowledgement (signature) of final released version; initiate measurements in case of relevant (e.g. critical/serious) findings	❶						

❶ executive organ/primary ❷ executive organ/secondary (e.g. deputy) ↱ delegated 🗗 subcontracted		Clinical Trial: PROOF **Responsibility Split** V2 02.07.2018	Sponsor	KKS	ECRIN	ECRIN partner/ local CRO	National Coordinator (NC)	Participating sites	NA	Comments
		Substudies (if applicable)[2]								
86	**Trial protocol or addendum to trial protocol**	Description of all procedures concerning the substudies relevant to the clinical trial and the study participants	❶							
87	**Information/Consent Form (ICF)**	Write and release relevant parts of the ICF concerning the substudies	❶							
88	If applicable: **Sample logistic**	Laboratory SOPs and manuals (incl. forms, tracking-logs...).	❶							
		Sample management (shipment etc.)	❶							
		Monitoring	❶							
		Central storage	❶							
		Destruction	❶							
	[2] : submission to NCA/EC/other authorities (as described in line 30/31) is the main responsibility of the sponsor or the leaders of the respective substudies/work packages									
		Data archiving								
89	**Archiving study documents (according to local regulations (e.g. at least 10 years for Germany))**		❶				❶	❶		Sponsor: TMF NCs/Sites: ISF
		Final reporting								
90	**Abbreviated final study report (English)**	Writing, review and release	❶							
		Notification to EC/NCA at the latest one year after the trial is completed (last patient out).	↱	❶	🗗	❶				Delegated to KKS and ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. KKS: Germany CRO: applicable country
		Notification of further information to EC/NCA according to local law/requirements	↱		🗗	❶				
91	**Final study report (English)** (only if additionally necessary)	Writing, review and release	❶							
		Send to EC, NCA	↱	❶	🗗	❶				Delegated to KKS and ECRIN, subcontracted from ECRIN to ECRIN partners / local CRO. KKS: Germany CRO: applicable country
92	**Publications (Results will be published irrespective of findings)**	Writing, review and release	❶				❷ support			
		Support in writing		❶						Delegated to KKS. KKS: Biometrician
		Acknowledgement			❶					The contribution of ECRIN and its national partners will be fairly described in the publications

Appendix 2: Financial Annex (Version n° 2.0, 15/08/2017)

For all required tasks, an overall budget was calculated and agreed between ECRIN and the ECRIN partner as follows:

[redacted]

Table 1: Agreed budget

Tasks	TOTAL COST
[redacted]	

	22 105 €