

Additional File 4 – Risk Management Tool

INSTRUCTIONS FOR USE

Applicable Cell/Column	Completion Guidelines	Comments
C1	Enter Protocol number/code	Free text allowed. To be completed.
C2	Enter date of initial assessment	Free text allowed. To be completed.
C3	Enter date of last update. It is advisable that prior to change the initial assessment, the tool is duplicated to a new Excel tab [1. Right click under the "RM Tool" tab; 2. Select "Move or Copy"; 3. Select "RM Tool"; 4. Tick option "Make a copy"; 5. Rename the tab, including date of assessment] and the modifications are done in the new tab so no audit trail is possible. Also, it is suggested that cells that suffer any change from the previous assessment are coloured in grey, so collaborators can easily identify the changes.	Free text allowed. To be completed.
Column A	Suggested category of the risk according to its scope. Additional categories can be added to the tool according to the specific sites' needs.	Free text allowed. Categories can be deleted or added as necessary.
Column B	Suggested risk identification. Additional risks can be added to the tool according to the specific sites' needs.	Free text allowed. Risks can be deleted or added as necessary.
Column C	Using a scale of minor, moderate and major, determine the extent of consequences of the identified risk, should it occur, on the trial. A color coding is applied (minor: green, moderate: yellow, major: red).	Choose a pre-defined option from Minor, Moderate or Major.
Column D	Using a scale of rare, possible and almost certain, determine the likelihood of occurrence of the identified risk. A color coding is applied (rare: green; possible: yellow; almost certain: red).	Choose a pre-defined option from Rare, Possible or Almost Certain.
Column E	Overall risk score is automatically calculated by the tool based on the product of impact and probability assessment. The product is categorised as follows: 1-2: low risk; 3-5: moderate risk; 6-9: high risk. A color coding is applied (low: green, moderate: yellow, high: red).	Froze for edition. Automatically calculated.
Column F	Possible causes for the risk identified. The referred topics aim to enhance the multi-disciplinary discussion about the risks which overall score is higher.	Free text allowed.
Column G	A list of mitigations can be found. These can be used as starting points for the discussion on mitigations for the risks identified in categories with highest final scores. If there is a decision to accept or monitor the risk, this can be documented here as well. It is recommended to first complete the risk assessment to have an overall view on the final category scores, so the team can ensure that categories with the highest scores receive priority for targeted monitoring and mitigation. Note that some individual items might still warrant a mitigation to be put in place.	Free text allowed.
Column H	References used to support examples of control and mitigation actions. Additional references can be added as necessary.	Free text allowed.
Column I	Enter the name of the responsible person to implement mitigation plans and monitor the risk.	Free text allowed.
Acronyms		
AE	Adverse Event	
AESI	Adverse Event of Special Interest	
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate	
CRA	clinical Research Associate	
CRC	Clinical Research Coordinator	
CRF	Case Report Form	
CRO	Contract Research Organization	
CRU	Clinical Research Units	
DPO	Data Protection Officer	
EDC	Electronic Data Capture	
EHR	Electronic Health Record System	
FUP	Follow-up	
I/E	Inclusion/Exclusion	
IB	Investigator Brochure	
ICF	Informed Consent Form	
ICH-GCP	Guidelines on Good Clinical Practice	
IP	Investigational Product	
ISF	Investigator Site File	
IxRS	Interactive Response Technology	
PI	Principal Investigator	
PRO	Patient Reported Outcomes	
SAE	Serious Adverse Event	
SIV	Site Initiation Visit	

PROCESS OVERVIEW



RISK MANAGEMENT TOOL

DISCLAIMER: THIS IS NOT A VALIDATED TOOL

PROTOCOL NO.	
DATE OF INITIAL ASSESSMENT	
DATE OF LAST UPDATE	

CATEGORY	IDENTIFIED RISK	PROBABILITY	IMPACT	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Data Collection	Safety reporting fails to meet the required timelines			#N/D	<ol style="list-style-type: none"> 1. Site is aware of an SAE/AESI/Special Situation event during holidays/weekends 2. The agreed method for safety reporting is not available 3. Site does not have all details of AE 4. Seriousness information is missing 5. Investigators delegated to sign the SAE paper reports are not available at the site 	<ol style="list-style-type: none"> a. At the SIV, discuss with the sponsor a reporting method that can be accessed remotely and define the accountable person (and back-up) to report the AE. b. At the SIV, agreed with the sponsor an alternative method to report AE. c. Instruct the team to report AE within the required timelines regardless of the quantity of information available. d. Provide training to investigator regarding classification of any AE in terms of severity, seriousness and causality. 		
Data Collection	No restrict access to the Electronic Health Records System by the sponsor's representatives			#N/D	<ol style="list-style-type: none"> 1. EHRS technical limitations 	<ol style="list-style-type: none"> a. Study who, among the site's team, have access to EHRS and which content is authorised to edit/consult. b. Establish a standardised procedure to certify copies of the EHRS. c. Access if the used EHRS is compliant with ICH-GCP requirements, namely ALCOA principles. 		
Data Collection	Delay in data entry/query resolution			#N/D	<ol style="list-style-type: none"> 1. Limited resources to perform data entry 2. IT connectivity issues at the site 3. Patient records are not completed with all the data required 	<ol style="list-style-type: none"> a. Prioritise the data to be entered in the CRF (safety information or critical visit information first). b. Provide checklists to investigators, indicating all the information that should be recorded in the patient's medical records for a given trial. 		
Data Collection	Delay in EDC signature by PI			#N/D	<ol style="list-style-type: none"> 1. PI did not complete initial training in the EDC platform 2. PI access is expired 3. PI is on holiday and do not have remote access to EDC 4. PI does not remember the e-mail used to log in to the platform 	<ol style="list-style-type: none"> a. When the site is aware that a signature is needed in EDC, FUP with the PI to complete the required training. b. When informed that an EDC signature will be required, confirm that PI has the access activated. c. At SIV, suggest a back-up investigator for EDC signature. 		
Data Collection	AEs not adequately documented in source documents			#N/D	<ol style="list-style-type: none"> 1. Investigator did not document all AE details in the source documents (severity, seriousness, causality, etc.) 2. AE reported by a different medical speciality at the site 3. AE reported by the patient in questionnaires, patient diaries, etc. 	<ol style="list-style-type: none"> a. Provide a checklist with the information that should be reported for each AE to the investigators. 	[1]	
Data Collection	Missing source documents or lack of document specifying the location of source data			#N/D	<ol style="list-style-type: none"> 1. Lab reports not archived in Patient Files 2. Reports from external vendors/clinics not available 	<ol style="list-style-type: none"> a. Agree with the team and sponsor on the location for every source of data. b. Define a responsible person to print and archive source documents (or certified copies) in the Patient File. 		
Essential Documents	New safety information not available for all the required study team members			#N/D	<ol style="list-style-type: none"> 1. There is no accountable person for safety review or the accountable person is not available 2. Safety information is not distributed to all required study members 3. The agreed method for safety review is not available 	<ol style="list-style-type: none"> a. Define an accountable person for safety review and a back-up. b. Agreed on the person and method (by e-mail, shared folder, etc.) to distribute the safety information among the team. c. Contact sponsor to have access to the safety information by an alternative method. 		
Essential Documents	Incomplete/Incorrect site personnel signature log			#N/D	<ol style="list-style-type: none"> 1. Incorrect version of Signature Log used 2. Study staff delegated by PI but not trained 3. Tasks incorrectly delegated (tasks not delegated to any member, tasks delegated to the wrong person, etc.) 	<ol style="list-style-type: none"> a. When CRA informs the site about a new version of the Signature Log, CRC should collect any previous blank versions kept in the ISF and cross them out with a statement indicating that it is obsolete. Also, all empty rows should be crossed out in the current version in use. b. Ensure a new staff member is only delegated after all protocol required training is completed. c. Ensure that all tasks are delegated to at least one person and that every person has at least one assigned task. 		

Essential Documents	ISF is not ready for inspection and relevant documents were either not filed, or filed late, or located outside the ISF structure			#N/D	<ol style="list-style-type: none"> Essential documents not received from the sponsor. Staff signed a document and did not retrieve the original After obtaining, documentation is sent to the sponsor for archiving but it is not archived in the ISF Essential documents are common to several studies and it is just archived in one or few studies' ISFs Essentials documents pending to be signed 	<ol style="list-style-type: none"> When an essential document is received from the sponsor, it should be printed immediately; alternatively, CRC can create a folder where these documents are downloaded and then periodically printed and archived in the ISF. Ask the sponsor for essential documents that cannot be located. Confirm the required process regarding internal courier and instruct staff from other departments to send the original documents accordingly. Finalise documents as they are being completed (for example, crossed out blank fields of Screening Log after the end of recruitment period or training logs once all team is trained in the corresponding document/procedure). Set up a database for common documents across several studies (CVs, GCPs, Lab ranges and accreditation, calibration certificates, etc.) and archive new versions of those document in the ISF as soon as they are released. Train staff in the use of electronic signature through the Citizen Card application freely available; ask sponsor if an electronic signature is acceptable. Review ISF periodically and request the missing documents to the sponsor. 		
Essential Documents	Patient File not completed/completed late			#N/D	<ol style="list-style-type: none"> Lab reports not filled or filled late in the Patient File EHRs is used and certified copies are not printed on time Incomplete PROs or PROs not archived in the Patient File Reports of assessments performed outside the site not received or not archived 	<ol style="list-style-type: none"> At the SIV, agree with the sponsor which documents are expected to be archived in the Patient Files. Using the schedule of assessments provided in the protocol, define in which source document will each required assessment be recorded throughout the study. Use this document to guide which documents are to be printed and archived in the File (if the sponsor does not have such a document to record source documents location, otherwise use the one made available by sponsor). 		
Essential Documents	Relevant correspondence not archived in ISF regularly			#N/D	<ol style="list-style-type: none"> Site is not sure when to consider an e-mail from the sponsor/vendor as "relevant" for archiving Relevant correspondence is received very often as the ongoing communication with the sponsor Relevant communication is done by phone 	<ol style="list-style-type: none"> Request sponsor to indicate in the body of the e-mail if e-mail is required to be archived in the ISF (according to ICH-GCP (R2), other relevant communications other than regarding site visits are required to be archived such as e-mails containing relevant information/instructions/guidance) When a conversation reaches an outcome or conclusion or it is solved, it should be printed immediately; alternatively, CRC can create a folder where these e-mails are downloaded and then periodically printed and archived in the ISF. When the information transmitted by phone or verbally is relevant, safeguard site by requesting the sponsor to send you a written confirmation by e-mail (examples include any approval/guidance/clarification about the protocol and study procedures - approvals of Medical Monitor regarding a patient to continue in the study or to be excluded, etc.). 		
Essential Documents	Delay in CV collection			#N/D	<ol style="list-style-type: none"> Personnel did not have a recent CV Personnel is not available to sign and date the CV on time 	<ol style="list-style-type: none"> Provide the personnel with a simple and short CV template. Set up a CV database and in case any signature/date is needed, send the last CV for personnel to confirm it is current and signature. Ask the sponsor if an electronic signature is acceptable. 		
Essential Documents	Delay in contracts signature by PI or Board of Directors			#N/D	<ol style="list-style-type: none"> PI is not available to sign/date on time Contract takes too long to be sent from the PI's department to the Board of Directors Board of Directors takes a long to sign the contracts Board of Directors does not define clinical research as a strategic priority Board of Directors has limited time 	<ol style="list-style-type: none"> Ask the sponsor if an electronic signature is acceptable. Agree with the Board of Directors upon a common and well-established pathway for contracts negotiation and signature for all clinical trials. Be informed about the upcoming Board's meetings and agreed with them on the timeline to have the contract signed based on these dates. FUP after meetings. Define with Board and sponsor if an electronic signature is acceptable; provide training in the use of electronic signature through the Citizen Card application freely available. Agree with the Board of Directors to delegate a member to sign the contracts on behalf of the President/Board of Directors. 		
Facilities & Supplies	Oversight deficits due to multiple local vendors participating in a trial			#N/D	<ol style="list-style-type: none"> Site is not used to collaborate with the vendors in clinical practice Vendors are not used to participating in clinical research projects PI has limited availability to oversight the vendors' activities 	<ol style="list-style-type: none"> Define a contact person to interact with each contracted vendor on behalf of the PI. Consider having a person responsible for the collaboration so common issues affecting several trials can be addressed with the vendor by only one person. At SIV, consider having at least one person by each vendor present so staff can meet each other and agree on each one's responsibilities. 		
Facilities & Supplies	Delay in assessments performance (for example, imaging examinations)			#N/D	<ol style="list-style-type: none"> Limited resources at the site Long waiting lists 	<ol style="list-style-type: none"> Partner with an external and specialised clinic. 		

Facilities & Supplies	Vendors delays in the transfer of data and query resolution			#N/D	<ol style="list-style-type: none"> 1. Vendor is not aware of their responsibilities with the trial and assume the main site will complete the task 2. Vendor do not follow the agreed communication flow and data is communicated to a different person or not within the required timelines 3. Inappropriate resource allocation at the vendor for timely query resolution 	<ol style="list-style-type: none"> a. Reach the contracted vendor and discuss non-compliance with the signed contract; ask for sponsor help as necessary. b. Ensure the vendor is aware of their responsibilities within the study and reinforce the agreed communication pathway defined. 		
Facilities & Supplies	Lack of communication among participating departments at site			#N/D	<ol style="list-style-type: none"> 1. Departments are not being used to collaborate in clinical practice 2. There is no contact person in the department and information is communicated to several people 	<ol style="list-style-type: none"> a. Define the contact person by each Department involved and share this information among all staff. b. At SIV, consider having at least one person by department present so staff can meet each other and agree on each one's responsibilities. 		
Facilities & Supplies	Miscommunication with central vendors contracted by the sponsor			#N/D	<ol style="list-style-type: none"> 1. Site has no previous experience with the defined central vendor 2. There is no contact person of the central vendor or site is not aware of the defined contact 3. Language barrier 	<ol style="list-style-type: none"> a. Reach sponsor if it is observed that central vendors are non-compliant with the agreed responsibilities and timelines. b. Consider having a template with all central vendors contact person details by study and updated it as long as new contacts details are available. c. In communications with vendors, copy the sponsor's representative, usually monitor, so they can facilitate the communication. 		
Facilities & Supplies	Change in facilities or equipment suitability			#N/D	<ol style="list-style-type: none"> 1. Equipment broken during the trial 2. A specific study assessment started to be performed at a different department/room 	<ol style="list-style-type: none"> a. Inform the sponsor immediately and discuss the possibility of lending equipment for the time equipment will require to be replaced. b. Before the change to the new location, perform feasibility to the new place and inform the sponsor about the new location conditions and expected risks. 		
Facilities & Supplies	Study assessments performed by an external vendor			#N/D	<ol style="list-style-type: none"> 1. Site can not ensure study assessments to be performed within the required timelines 2. Site did not provide the required service 	<ol style="list-style-type: none"> a. Consider have a database with relevant information regarding previous collaboration experiences; and consider preferred partners. b. Detailed the scope of work and responsibilities through a contract. c. Define a person (and a back up) to represent the site in communications; ask the vendor to provide a contact person for administrative and/or technical communication. d. Inform sponsor about the agreed communication flow between site-vendor-sponsor. 		
Investigational Product	Investigational product stock is not adequate			#N/D	<ol style="list-style-type: none"> 1. Site not available to receive IP shipment 2. IP not received at the site in proper conditions (temperature excursion during shipment, compromised /damaged packaging) 3. IP stock not in proper conditions (expired, damaged, etc.) 	<ol style="list-style-type: none"> a. Inform sponsor of the schedule site is available to receive IP (working hours, weekends, planned holidays, etc.). b. Inform sponsor immediately of IP not received in proper conditions (update IxRS as applicable) and request additional IP; put the affected IP in quarantine. c. Confirm the expiration date of IP before dispensing (for example, adding a column to the accountability log to enter the expiration date for each kit at the time of dispensing). 		
Investigational Product	Storage requirements not met for investigational product			#N/D	<ol style="list-style-type: none"> 1. IP not stored at the site as required per protocol/IB (temperature, light and/or humidity requirements) 2. Storage equipment (fridge, freezer, data loggers, etc.) not available/not working 3. Storage information not documented appropriately (temperature records unavailable) 4. Quarantine process not followed to expired/damaged IP 5. IP handled (received, stored) for non-authorized personnel 	<ol style="list-style-type: none"> a. Pharmacy should have facilities that allow for good segregation of IPs and separate from normal pharmacy stock in an area with access restricted to pharmacy staff. b. Set up the required equipment at the site initiation and define back-up equipment. c. Confirm that temperature reading devices are available, including back-up, and working correctly. c. Have a defined label to identify IP in quarantine, clearly segregated from working stock. 	[2]	
Investigational Product	Temperature Excursion not noticed/reported			#N/D	<ol style="list-style-type: none"> 1. Pharmacy staff do not have a standardised process to verify the temperature 2. Datalogger devices are not working properly 3. Alarm is not working 	<ol style="list-style-type: none"> a. Ensure temperature monitoring devices have a valid proof of calibration. b. Ensure the existence of back-up devices. c. Pharmacy should have written procedures in place for the actions to be taken when the storage conditions are outside of the specified range. 	[2]	
Investigational Product	Wrong kit dispensed to a participant			#N/D	<ol style="list-style-type: none"> 1. IxRS is not updated (received, damaged, quarantined IP nor register) 2. Kit assignment was not double-checked before the dispensation 	<ol style="list-style-type: none"> a. Store the investigational product returned by patients separately. b. Update IxRS with the real status of each kit of investigational product. c. Define a process to double-check kit assignment against prescription document; consider involving more than one person in the checking process. 		
Investigational Product	Multiple studies using the same storage place at the site			#N/D	<ol style="list-style-type: none"> 1. Study-specific kits not clearly identified 2. Lack of space to have all investigational products separated 	<ol style="list-style-type: none"> a. Clearly separate the kits and label the different zones with the study identification 		

Staff qualifications & training	PI unavailability			#N/D	1. PI is participating in several studies 2. PI accumulates other roles within the site	a. Have the PI's availability into account during the feasibility and site selection phase and proactively suggest other PI than the one indicated by the sponsor (consider investigators with less clinical research experience and provide the rationale to sponsor). b. Consider having a less experienced investigator accompanying the PI-specific activities closely.		
Staff qualifications & training	A study requires clinical trial naïve investigators			#N/D	1. Studies in the therapeutic area are rare at the site 2. Experienced investigators are responsible for ongoing competitive trials at the site 3. Turnover of experienced colleagues	a. Set up a training session in ICH-GCP and general aspects of clinical research (it can be requested to the sponsor). b. Promote meetings between experience and naïve investigators to share successful experiences and common barriers across their studies.		
Staff qualifications & training	High turnover of study team members			#N/D	1. Natural career progression 2. Lack of research career recognition	a. Inform sponsor as soon as possible about study team members leaving the site both temporarily (for example, due to sick or maternity leave) or permanently (for example, due to retirement or dismissal). b. Ensure that, before leaving, the leaving person handover the tasks and required information to the receiving person who will be in charge of those tasks. c. As possible, as part of succession planning, ensure the site has at least two people delegated for each task to be performed within the study.		
Staff qualifications & training	Staff inadequately trained			#N/D	1. Study personnel not trained on trial-related procedures 2. Training record is not present 3. Training record is incomplete	a. Ensure a study team member is only delegated after the completion of the required training. b. Develop a template to record training provided, including self-training, or request a sponsor's template.		
Study-Specific Procedures	Blinded personnel receive unblinded data			#N/D	1. Staff is not aware of the communication plan to ensure blindness 2. Staff who performed blinded tasks for a study also perform unblinded tasks for another study	a. Review the communication plan with staff at the SIV and regular contacts during the study; ensure unblinded staff is aware of their contact points with sponsor and vendors. b. If staff is participating in more than one study requiring blinding procedures, staff should perform blinded/unblinded roles for all studies they are involved in. c. Review which documents can unblind the patient treatment (lab results, AE information).		
Study-specific Procedures	Handling requirements for study samples not met			#N/D	1. Laboratory kit not available or in proper conditions (expired, damaged, etc.) 2. Samples not collected at the defined timepoint 3. Samples not processed as required per protocol/laboratory manual 4. Storage equipment (fridge, freezer, data loggers, etc.) not available/not working 5. Samples not stored as per requirements (ambient, frozen, etc.) 6. Courier not contacted / not available 7. Shipment not done according to the required conditions (ambient, frozen, etc.) 8. Samples handled (collected, processed, shipped) for non-authorized personnel	a. Delegate a site member (and a back-up) to check the laboratory kits stock and its conditions (expiration date, damage, etc.) and define the frequency for this review. b. Define the process for the expired or damaged kits to be destroyed or stored away from the usable kits and ensure the study team is aware of the procedure defined. c. Delegate a site member (and a back-up) to order laboratory kits in advance. d. Provide the person in charge of the samples' collection with pocket guidance for the study assessments. e. Train the study team to review the laboratory manual before any sample collection; print the relevant laboratory manual pages for each visit and send it to the person responsible for samples processing and storage. f. Delegate a site member (or back-up) to regularly extract temperature records from the fridge/freezer and review them for compliance; Define back-up equipment, and make sure the study team is aware. g. Define the process to contact the courier (who contact the courier, where contacts are available, who update contacts if any change occurs, etc.). h. Confirm the process to request dry ice boxes for shipment.		
Study-specific Procedures	Increased complexity due to multiples sub-studies			#N/D	1. Assessments applied to the participants may differ depending on their authorisation to participate or not in a given sub-study 2. Several ICFs to be signed 3. Requirement for a greater level of organisation to track subjects participating in each sub-study	a. Consider whether multiple informed consent forms need to be administered and provide copies of them along with the main ICF to the investigators who are in charge of presenting the study to participants. b. Confirm the additional assessments that need to be performed by participants who accepted to take part in a sub-study; have a clear track of those patients to avoid perform any assessment to participants that do not consent for it.		
Study-specific Procedures	Network connectivity issues do not allow for ePRO device fully working			#N/D	1. Site's internet does not ensure the full operation of the device 2. Patient has no enough skill to operate the device	a. Confirm if internet connection is adequate for device operation; inform sponsor, ideally during the feasibility phase and, if necessary, request a hotspot to ensure connectivity. b. Confirm if alternative methods can be used to complete the PRO (paper, web-based platform, etc.), for example, in case the device is not working correctly.		

Study-specific Procedures	Study Visits performed out of the required window per protocol			#N/D	<ol style="list-style-type: none"> 1. Method used to calculate visit windows is incorrect 2. Visit scheduled based on the visit window for the wrong subject/study 3. Baseline date for visit window calculation incorrect 4. Re-schedule a subject's visit without re-confirm visit window 5. Bank holidays or study personnel/subjects holiday period 	<ol style="list-style-type: none"> a. Confirm with the sponsor if there is any available tool to calculate the visit windows. b. Avoid the visit window's upper limit to allow visit's re-scheduling if needed (patient or study personnel unavailability, unexpected issue with study equipment, etc.). 		
Subject Recruitment and Retention	The study allows the inclusion of vulnerable population (children, inmates, mentally ill)			#N/D	N/A (not dependent on the site's decision)	<ol style="list-style-type: none"> a. Confirm if there is any specific, informed consent to be signed by these subjects. b. Confirm if a legal representative or witness is required during the informed consent process. c. Confirm if there are any other considerations for special subject populations (different study assessment; dose modifications; etc.). 		
Subject Recruitment and Retention	The study allows the inclusion of women of childbearing potential			#N/D	N/A (not dependent on the site's decision)	<ol style="list-style-type: none"> a. Confirm the I/E criteria and the protocol requirements for women of childbearing potential. b. Discuss with the subject the use of an effective birth control method during the study. c. Discuss with the subject the implications of a pregnancy during the study (study drug discontinuation, study withdrawal, etc.). d. Confirm if there is any specific, informed consent to be signed in case of pregnancy. 		
Subject Recruitment and Retention	High number of consent withdrawals			#N/D	<ol style="list-style-type: none"> 1. Study procedures cause an additional burden on the subjects' routine (more frequent visits, more time on site, etc.) 2. Subjects have to visit several facilities for different procedures (external clinics, different departments within the site, etc.) 3. Study requires a long period of follow-up 	<ol style="list-style-type: none"> a. At the time of consent, review and agree with the subject the assessment flow at each visit and the required time expected. b. Ensure proper appointment booking, so the patient has not to be in crowded waiting rooms. 	[3]	
Subject Recruitment and Retention	Informed Consent / Reconsent process fails to meet regulatory requirements			#N/D	<ol style="list-style-type: none"> 1. Clinical study procedures conducted before discussing and signing ICF 2. ICF not signed/dated by the participant (legal representative, witness) or investigator as required 3. ICF blank fields (investigator contacts, DPO information, etc.) not completed 4. ICF copy not given to the participant 5. Use of an outdated version 6. ICF process not documented in the medical notes 7. ICF process conducted by non-authorized personnel 8. ICF amendment not signed in the next patient visit following new ICF implementation 9. Incomplete ICF signed/dated (for example, not all pages printed due to printer issues) 	<p>Define a step-by-step process to present, discuss and sign the ICF at the site. The defined process should be discussed and agreed upon at the SIV. A suggested process flow to avoid common causes is presented below:</p> <ol style="list-style-type: none"> a. CRC confirms which investigators are trained and delegated to obtain the ICF. b. CRC confirms the applicable version(s) of ICF to be used (confirm whether there are any ICFs other than the main: for genetic purposes, sub-studies, optional procedures, etc.) and provides the investigators with a copy of each document. When a new version is implemented, CRC should collect any previous versions kept by investigators to be destroyed and the copy archived in the ISF should be crossed out with a statement that it is obsolete. c. After the subject's eligibility assessment, the investigator presents the study to the subject and provides the ICF for reading and comprehension. Investigator evaluates if a legal representative/witness is needed. d. CRC further explains to the subject the general aspects of clinical research and the difference from clinical practice and provides a template for the subject to write questions and concerns about the study. e. Subject reads the ICF at the site guided by CRC or at home with family members. f. CRC asks some questions to confirm if the subject understands the study (e.g. what is the purpose of this study?; How long will the study take?; What are the costs of participating in the study?). g. Subject discusses the questions and concerns with the investigator. h. Investigator completes the blank fields of ICF and signs the ICF along with the subjects. i. CRC does a quality check of the signed ICF (applicable version(s), all blank fields completed - contacts; signatures and dates, etc.). If ICF is correct, CRC provides a copy of the signed ICF to the patient. If any error is found, ask the investigator / subject to correct it as per ICH-GCP requirements. j. CRC confirms if any study material is to be provided at the ICF signature time (patient cards, diaries, etc.) and explains its usage. k. The investigator / CRC prints the electronic records and confirms if the ICF process is appropriately documented in the patient medical records. 	[1] , [4] , [5]	

Subject Recruitment and Retention	Recruitment expectations not met			#N/D	<p>1. I/E criteria are very specific.</p> <p>2. Patients diagnosed/treated at a different department not included in the study team.</p> <p>3. Recruitment expectation provided is not realistic.</p>	<p>a. Confirm if the protocol allows for subject rescreening.</p> <p>b. Discuss the patient pathway with the hospital (which medical speciality does the diagnosis; which medical speciality can prescribe the treatment, etc.).</p> <p>c. Liaise with patient representatives and colleagues from different hospitals to let them about the study.</p> <p>d. In the Department meeting, remind that a trial is ongoing and recruiting patients with these eligibility criteria, so the other investigators are aware of them and let them know about the recruitment status.</p>	[6]	
Subject Recruitment and Retention	Delay in the patients' reimbursements			#N/D	<p>1. Sponsors reimbursement timelines.</p>	<p>a. Require sponsors to define timelines for patient's expenses reimbursement at the financial contract and ensure they are being compliant with those timelines.</p> <p>b. Establish a process flow to reimburse patients directly and then having the sponsor reimbursing site.</p>		

General Sources	
Risk Assessment Categorization Tool (RACT)	http://www.transceleratebiopharmainc.com/wp-content/uploads/2020/04/RACT_FINAL_April-2020.xlsx
Risk Indicator Library	https://www.transceleratebiopharmainc.com/wp-content/uploads/2019/02/TransCelerate-RBM-Risk-Indicator-Library_Final-21Feb2019.xlsx
Annual Report of the EMA GCP IWG, 2018	https://www.ema.europa.eu/en/documents/annual-report/annual-report-good-clinical-practice-inspectors-working-group-2018_en.pdf
Inspectional observations from FDA inspections, 2020	https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations