IMPORTANT CLAUSES IN A CLINICAL TRIAL AGREEMENT

by

Nurul Atiqah Abd Rahman[i]

Siti Nuralis Abd Muis [ii]

Siti Nur Hafizah Adnan[iii]

Introduction

An Agreement plays a vital role in any transaction including, Clinical Trial. It must be made in writing and is voluntarily entered into by the parties involved. The Agreement that governs a Clinical Trial is known as Clinical Trial Agreement (CTA). CTA is an essential document that must be negotiated in detail, finalized, and signed before any Clinical Trial/Study can commence at the selected Clinical Trial/Study sites. This article emphasizes some of the necessary provisions or clauses that should be included in the Sponsored Research CTA to address the Clinical Trial/Study, and clear expression of the Parties' rights and obligations under the CTA.

Parties to Clinical Trial Agreement & Related Concerns

CTA is a legally binding document that regulates the relationship between the Pharmaceutical Company as the Sponsor of the Study Drug or the Medical Device, or an organization which initiates the Clinical Trial/Study along with financial support to do so, the Institution as the Clinical Trial/Study Site where its equipment and facility shall be utilized in furtherance of a Clinical Trial/Study and the Principal Investigator (PI) who plays the most prominent role that determines the success of a Study in terms of providing reliable study data and results. In some cases, the Sponsor may authorize or hire a Contract Research Organization (CRO) to enter a CTA with the Institution and the PI. This is usually captured in a separate written agreement between the Sponsor and the CRO of which

the contents are not inconsistent with the CTA entered into by the CRO with the Institution and the PI. In the event, the CRO is contracted, and if the CRO is responsible for the monitoring of the Study and accountable for making payments to the Institution and the PI on behalf of the Sponsor, it must be reflected accordingly in the CTA itself so that the Institution or the PI has a contractual remedy against the CRO in case of any non-payment.[1] One important thing to note when the CRO is signed on behalf of the Sponsor, a Clause on Third-Party Beneficiary Law may be included and the CRO may be signed on behalf of the Sponsor under a Power of Attorney or Letter of Authority and the like, and the Sponsor is now the Third Beneficiary under the CTA under which the Sponsor may sue to enforce obligations under the CTA if the Sponsor is not a Party to the CTA. However, with the presence of the Third-Beneficiary Law clause, it is best practice to either have the Sponsor's indemnity clause in the CTA or in the absence of Sponsor's indemnity clause, there must be a separate written Letter of Indemnification signed by the Sponsor and addressed directly to the Institution and PI so that Institution/PI can claim directly against the Sponsor for any acts or omission. Indemnification is explained in greater detail below. Apart from that, it is also worth noting that the Parties to the CTA in the Malaysian Ministry of Health (MOH) site setting must be local entities. In complying with this requirement, the Foreign Sponsor may authorize its Malaysian entity (if any) or hire a Malaysian CRO to enter the CTA on its behalf.

Description of Clinical Trial/Study

Any Clinical Trial/Study must be identifiable with the Clinical Trial/Study Protocol ID and the Clinical Trial/Study Name. As such, at the beginning of the CTA, it shall provide a brief overview of the Clinical Trial/Study design, which includes, but is not limited to, the Clinical Trial/Study therapeutic area, phase of the study, type of study intervention, and how the data analysis is to be performed. This Clause will generally depend on the Sponsor's preference, and it usually depends

on the nature of the Clinical Trial/Study. Some require a more detailed Study background, such as the objective and outcome desired from the Study Conduct, estimated time where the Study team shall complete the Clinical Trial/Study, and the number of participants to be enrolled. The description of the Clinical Trial/Study is ideally to be limited to one (1) page as the full Study Protocol duly approved by the relevant Ethics Committee shall be incorporated as an attachment in the CTA for ease of reference and guidance.

Clinical Trial Governance

The Clinical Trial Governance clause sets the minimum compliance requirements in respect of the applicable laws and regulations in the country such as policy and procedures laid down by the relevant Ethics Committee or Institutional Review Board, the principles laid down by the 18th World Medical Assembly (The Declaration of Helsinki, 1964), the Malaysia Guidelines for Good Clinical Practice ("MGCP"), the Guidelines for Application to conduct Drug-Related Clinical Trials in Malaysia (Trial Guidelines) and the Guidelines for Good Clinical Practice of the International Conference of Harmonization ("ICH"), the Malaysian Sales of Drugs Act, the Control of Drugs and Cosmetics Regulations, and other regulations, and any amendments to it, and applicable local and foreign laws, rules, regulations and standards governing the performance of clinical investigations, including but not limited to the rules of the FDA and comparable foreign agencies.

Other than the above, compliance with the approved Protocol shall be another essential note to be added under the Clinical Trial Governance Clause. The Protocol is a document that describes how a Clinical Trial shall be conducted in terms of the design, methodology, statistical considerations, and organization of a clinical trial. The Protocol must lay down specific procedures designed by the Sponsor for conducting the

Clinical Trial to ensure the safety of the Clinical Trial Subjects and the integrity of the data collected.[2]

This Clause should also include other regulatory representations and obligations of the Institutions and the PI, including a non-debarment and non-disqualification representation, as well as commitments to report adverse events.

Obligations of Sponsor

Obligations of Sponsor is a pertinent clause in a CTA. CTA shall state the Sponsor's obligations in detail to ensure the Sponsor's accountability. The Sponsor must ensure that each PI shall be qualified by training, i.e., GCP, and should have adequate resources to properly conduct the Study for which the PI is selected. Once the necessary regulatory approval is obtained, the Sponsor's primary obligation is to supply the study drug or medical device (as applicable) in sufficient quantity free of charge to the PI/Institution in a timely manner. In all events, all study drugs or medical devices supplied shall be owned by the Sponsor. Other than the Study Drug or Medical Device, the Sponsor is also responsible for providing some further study-related information and documents, which include, but is not limited to, the Protocol, the up-to-date Investigator Brochure, and the Case Report Form (CRF) or Electronic Case Report Form (e-CRF). The Sponsor’s obligation in monitoring the study conducted shall also be stated in the CTA as monitoring is a crucial activity to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is following the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). The Obligations of Sponsor clause will also revolve around the Sponsor's duty to notify the relevant Ethics Committee or Institutional Review Board of any non-compliance that could impact the Study Subjects' safety and well-being.

Although claims are infrequent, when things go wrong, the impact on human health can be significant; thus, the provision of Clinical Trial Insurance shall also be included as part of the Obligations of Sponsor. It must state that the Sponsor has the Certificate of Clinical Trial Insurance in place, evidencing that the Sponsor has adequate coverage consistent with Clinical Trial industry standards. Insurance is discussed further under the Indemnification heading below.

Clinical Trial/Study Conduct

Clinical Trial/Study Conduct is one of the compulsory clauses in a CTA. This Clause is crucial because it indicates how the Clinical Trial/Study should be conducted where it will be mentioned that the study conducted by the appointed PI and the Study team must comply with the Protocol and any amended Protocol, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice ("ICH GCP"), the principles laid down in the Declaration of the Helsinki, governmental and regulatory authorities' regulations, any conditions imposed by a competent Institutional Review Board/Ethics Committee ("IRB/EC"), applicable Law, and such other guidelines as may be introduced for the safe and proper implementation of the study/trial. Further, this Clause will also highlight that any changes or any amendment of the Protocol must obtain the regulatory bodies' approval. The Clause will generally define the investigational product that belongs to the Sponsor and describes whether the Sponsor may provide or arrange other drug products, if applicable, to be used in the trial following the Protocol. It will also detail the products shall not be used for other purposes and describe the custodian/storage of the products and the right of returning or dispensing the investigational product after the end of the Study. This Clause will also indicate the subject cannot participate in other ancillary Study without the Sponsor's approval. Informed consent shall be obtained from the subjects before enrolling them in the Study, and a separate consent may be needed for future research/ biobanking (if

necessary) and suitable to the Protocol. Under the Clause, it will also describe the scenario if the appointed PI is no longer with the Institution, where usually the Institution will be responsible for notifying Sponsor and CRO, in writing, immediately upon learning that the PI appointed is no longer at the Institution and will use its best efforts to identify a substitute PI acceptable by the Sponsor within a reasonable period and the substitute PI must agree in writing to be bound by all obligations, terms, and conditions of the Agreement.

Study Monitoring

Sponsor, Ethics Committee/Institutional Review Board, and regulatory authorities may monitor, inspect, and audit documents, medical records, licenses, work products, etc., at the respective Institution. Thus, under the Study Monitoring Clause, the relevant parties who should be informed when there is an audit or inspection shall be mentioned; for example, PI shall notify Sponsor via email or by telephone if there is a request for permission to inspect Institution's and/or PI's facilities or research records by the regulatory authority. Cooperation of the Parties is needed during the monitoring, audit, and inspection to ensure that all standard procedures and policies are adhered to. Further, if there are any issues during the monitoring, audit, or inspection and corrective actions are needed, reasonable revisions must be taken.

Obligations of Principal Investigator

Obligations of the PI is one of the crucial Clauses that will be inserted in the CTA where it will be mentioned that the PI shall use his best efforts and lead the team to comply with GCP and the Protocol in conducting the trial. The PI also must not conduct other research that is not required by the Protocol and not conduct other trials that may adversely affect the Protocol. The PI also shall recruit only valid subjects that meet the Clinical Trial/Study criteria and enroll the number of duly qualified subjects according to the Protocol. All subjects must be thoroughly

counseled regarding the Study, and legally valid informed consent must be obtained. Besides that, the PI also shall complete the Case Report Form (CRF) or other relevant documents provided by the Sponsor promptly and accurately. The PI must forward the completed CRF and make available any source documents related to the Study to the Sponsor at periodic monitoring visits or promptly upon request with assistance provided to the Sponsor to resolve any discrepancies, errors, or missing information in the CRF and to assist the Sponsor in conducting audits of original case records, laboratory reports and or raw data sources underlying data recorded in the CRF. Such audits shall be conducted with due regard to patient confidentiality. When performing a blind Study, the PI shall maintain the blinding of the Investigational Product, and the randomization codes shall only be released upon completion of the Study and should a medical emergency occur requiring the PI to break the code for a specific valid subject, the PI agrees to notify the Sponsor immediately. It is also mentioned in the CTA that the PI shall obtain all requisite approvals from the Ethics Committee and regulatory authority on the Protocol, Informed Consent, Study advertisements (if any) and any alteration to, or waiver of, any Valid Subject authorization permitting the disclosure of Valid Subject's confidential information in connection with the Study before the commencement of the Study. The Institution and PI shall inform Sponsor promptly in writing about all changes impacting the Trial Staff and/or facilities.

Insurance/Compensation

In the Malaysian GCP, section 5.8.1 mentions that, "if required by applicable regulatory requirement, the sponsor should provide insurance or should indemnify the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence." Usually, a sponsor must obtain and maintain the Insurance throughout the Study/Trial. Meanwhile, the Institution will need to preserve Insurance as required by local state/federal laws, and if needed,

the Principal Investigator will only maintain his medical professional indemnity insurance. The clinical trial insurance coverage of the Sponsor would cover claims arising from the use of the investigational product or any related procedure in conducting the trial in which the Sponsor must compensate for medical treatment for subjects who have sustained injuries due to participation in the Study/Trial. However, Sponsor's clinical trial insurance does not include the claims arising from the negligence by the Institution or Investigator.

Indemnification by Institution/PI

The indemnification clause is significant as it protects and secures the parties from anticipated liability, harm, damage, or loss. Generally, this Clause indicates that a party agrees to protect the other against any potential damage, injury, or losses that the other party may occur in performing the obligations. Thus, in drafting the indemnification clause in the clinical trial agreement, we will first identify which parties need to be indemnified and ensure that all the rights of the parties involved are protected. Under the indemnification clause, the Sponsor is entitled to indemnify, defend and hold harmless the Principal Investigator/Institution against any loss, liability, or costs incurred in connection with the Study/Trial due to the usage of the Investigational product, and usually, the Agreement provides the circumstances in which the Sponsor will not need to indemnify the Institution, in which the exception is only allowed to the extent that injuries are caused by the Institution's negligence and willful misconduct.

Term and Termination of the Agreement

In general, the term and termination clause stipulates the length of the Agreement and the parties' rights to end the Agreement prior to the end of the term of the Agreement. In the context of the CTA, the PI/Institution and Sponsor shall have the right to terminate the CTA under certain circumstances specified in the termination clause, such as termination for

default. However, early termination by any of the parties shall be notified to the other party effectively.

In the event of premature termination, the pro-rated payment shall be made payable to the Principal Investigator for actual work performed and costs incurred prior to the termination. Besides, the PI shall immediately return to the Sponsor any unused Investigational Product/Medical Device, confidential information, and other proprietary materials provided by the Sponsor once the CTA is terminated.

Governing Law

The Clause is to determine which state law will govern the terms of the Agreement. It is important to protect the interests of the PI/Institution and the study subjects whereby the CTA's governing Law and jurisdiction must be in accordance with the country or territory in which the Principal Investigator practices.

In the Malaysia MOH site setting, the governing Law of the CTA must be Malaysian Law. In reviewing this Clause, we may also consider contractual silence regarding this issue but cannot negotiate any other terms.

Dispute Resolution

Ideally, the parties shall attempt to resolve the dispute through mediation. If mediation fails, then the dispute shall be resolved through arbitration.

In Malaysia, The AIAC Mediation Rules and Malaysian Mediation Act 2012 govern the process of Mediation and Arbitration to aid parties in resolving both international and domestic disputes. The venue shall be conducted at The Asian International Arbitration Centre (Malaysia) ("AIAC"), Kuala Lumpur, Malaysia. Alternatively, if agreeable by the Parties, Parties may also resolve the dispute through litigation in the

Malaysian courts. Mediation is usually cost-saving. Eventually, it is up to the parties' preference.

Payment Terms and Conditions

It is fundamentally important for the financial budget of the Clinical Trial/Study to be negotiated thoroughly. In constructing and negotiating the Clinical Trial/Study budget, the parties must ensure that the payment reflects fair market value for the work performed. In structuring the Sponsor's payment obligation for the Clinical Trial/Study, care should be taken to ensure that the payment structure does not create a financial conflict of interest for the PI or is contrary to any other regulatory laws or requirements.

The payment terms and conditions must also indicate that the Sponsor is responsible for paying any taxes assessed in connection with the transaction. Therefore, the Sponsor needs to adhere to the local taxation system. For example, Malaysia has implemented Sales and Services Tax (SST) effective from 1 September 2018 to replace the previous tax system, Goods and Services Tax (GST).

Other costs, including the costs associated with the study personnel involved (i.e., investigator, nursing staff, study coordinator) and the costs of all services conducted during the Clinical Trial/Study shall be clearly provided for and agreed upon by all parties in the CTA.

It is also important to identify the financial arrangement on the payment for the PI/Institution, such as invoicing details and the requirements/documents needed to disburse the study payment.

Publication

This Clause will determine the Parties holding the rights to publications on new findings or results from that Clinical Trial/Study. In a Clinical Trial/Study, it is common for the Sponsor to grant the Institution/PI the

rights of publication but subject to prior Sponsor's review and approval. Prior to submitting a manuscript or other materials relating to the Clinical Trial/Study to a publisher or organization, the PI shall submit a copy of the manuscripts or materials to the Sponsor for review. The Sponsors should have the right to require the removal of the Sponsor's confidential information to protect their proprietary information and require delayed publication to obtain patent protection.

For a multi-centre trial, the Sponsor can require the results from all trial sites to be included in a single publication. The Sponsor may not permit publications by individual sites until after the release of the multi-centre publication.

Intellectual Property

Generally, the Intellectual Property clause discusses the rights of intellectual property (IP) of the IP Owner. It allows the owner of the patents, trademarks, or copyrighted works to protect their works from any use or implementation without consent. In a clinical trial, there are several matters that are important to be addressed in this Clause. For any intellectual property rights that pre-exist before the effective date of the Agreement, each party will retain its pre-existing IP ownership.

All IP rights to any discovery or invention developed in the study/trial performance shall belong exclusively to the Sponsor. Therefore, it is also essential to include an IP assignment to assign the sole and exclusive ownership to the Sponsor.

Besides that, the Clause shall state that the PI shall retain ownership of any IP they develop during the trial that involves any clinical procedures and related improvements from the trial. For example, during the performance of the Study, if the PI enhances the Sponsor's instrument, the ownership of the IP remains with the PI/Institution.[3]

Confidential Information & Personal Data

The Confidentiality clause addresses the information that will be considered confidential and the obligations to secure and maintain its confidentiality. From the Sponsor's perspective, they need to ensure that any information provided in the performance of the Study will be kept as the Sponsor's confidential information. Meanwhile, the PI/Institution will not accept the confidentiality obligations with unacceptable limitations that will jeopardize their academic interest in promoting research and public welfare.[4]

By addressing the Parties' interests, it is important to ensure that the definition of confidential information must be clearly written in the Agreement and the specific uses of confidential information that are allowed must also be indicated.

There are typical exceptions to the definition of confidential information, which are information that has been made publicly available, information that is in the receiving party's possession prior to receipt from the disclosing party, information independently developed by the receiving party, information lawfully received from the third party, and information disclosed due to any court or administrative ordered for disclosure.

In Malaysia, the use and disclosure of the confidential information such as medical information and personal data of Study Subjects are subject to compliance with applicable national privacy laws and regulations, including the Malaysia Personal Data Protection Act 2010.

Conclusion

It is crystal clear that knowing the important provisions or clauses in a CTA is crucial to avoid unnecessary delay in the negotiation of the CTA between Parties. When any of the Parties breach the term of the CTA, the written Agreement, i.e., the CTA will be used as a reference on what the Parties have agreed on to determine who is really at fault. With the CTA's

clear wordings, Parties can resolve any future dispute or contractual issues quickly and efficiently.

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*[i], [ii] & [iii] Clinical Research Malaysia (Legal & Regulatory Affairs Department).

[Clinical Research Malaysia exists to advance global health solutions for a brighter, more hopeful future for the people by providing speedy and reliable end-to-end clinical research support for quality studies. More information about the organization may be found at https://clinicalresearch.my/].

Endnotes:

[1] Model Clinical Trial Agreement (mCTA) and Clinical Research Organisation Model Clinical Trial Agreement (CRO-mCTA) https://www.myresearchproject.org.uk/Help/Help%20Documents/mCTA-CRO-mCTA-Guidance-March-2020.pdf.

[2] https://hub.ucsf.edu/protocol-development Clinical Trial Protocol Development (Last Revised 10/02/2017).

[3] R. Leibowitz, Katherine. (2005). *The Business of Clinical Trials, Part 1: Negotiating Confidentiality, IP, and Publications. Medical Device and Diagnostic Industry*. Retrieved from https://www.mddionline.com/stub/business-clinical-trials-part-1-negotiating-confidentiality-ip-and-publications.

[4] *Ibid.*