

Contract & Budget Management of Industry-sponsored Clinical Trials in Turkey



In industry-sponsored clinical trials, as the sponsors are for-profit companies, contract negotiations with the trial sites can be difficult and complex. The smooth management of this process mandates understanding the local country processes and considering these from the very beginning of the study management. This paper is intended to contribute to the literature by clarifying the budget preparation and contract management procedures in Turkey. Emphasis has been placed on the specific procedures of different institutions and some key factors in order to achieve the ultimate goal of execution of the planned study deliverables for the industry, as well as for the clinical teams worldwide that are planning or conducting clinical trials in Turkey.

Introduction

Operational aspects of the conduct of sponsored clinical trials consist of a number of steps, such as trial application to independent ethics committees or independent review boards (IECs/IRBs) to get approvals, collection of essential documents, planning and organisation of the study logistics, and managing the budget and contract (clinical trial agreement) process. Among the major challenges in this process are the preparation of the trial budget per country requirements and finalisation of the site contract.

In industry-sponsored clinical trials, as the sponsors are for-profit companies, contract negotiations with the trial sites can be difficult and complex. These agreements are designed to address a large number of issues such as scope of work, budget, payment terms, intellectual property rights, confidentiality, publication rights, indemnification and termination rights^{1,2}. The requirements of each country participating in an international trial have to be considered individually according to each country's healthcare policies, public healthcare system, legal framework ruling the hospitals' financial management and investigator payment procedures, in order to achieve a smooth and complete trial budget and contract management process in the given country.

With its unique geographical location creating a physical, cultural and commercial bridge between East and West, Turkey has been displaying an exponential growth in the number of sponsored clinical trials³. The clinical trial budget preparation and the trial agreement finalisation at Turkish sites is a process that needs to be proactively planned and requires a fully knowledgeable sponsor or contract research organisation (CRO) authorised by the sponsor to manage to activate the Turkish sites and start with subject enrolment within planned timelines.

The main aim of this paper is to contribute to the literature by clarifying the budget preparation and contract management procedures in Turkey. Emphasis has been placed on the specific procedures of different institutions and some key factors to achieve the ultimate goal of execution of the planned study deliverables for the industry, as well as for the clinical teams worldwide that are planning or conducting clinical trials in Turkey.

General Procedure

In all countries, a sponsor develops a high-level draft study budget covering the services to be purchased from the hospital and investigator grant and releases a clinical trial agreement (CTA) template to be negotiated.

During the site identification and qualification process and/or feasibility evaluation of potential clinical sites, the financial procedures at that site are assessed.

In Turkey, a study budget that includes the amounts for the hospital and investigator fees and grants is required for the initial study application. This study budget has to be prepared in a site-specific manner by the sponsor/authorised clinical research organisation (CRO). The final budget needs to be integrated into the research budget form template generated by the Turkish regulatory authority (RA), the Ministry of Health Turkish Medicines and Medical Devices Agency (TMMDA), and is expected to be submitted as part of the initial application binder to the ethics committee (EC) and the RA. Thus, the site-specific budget document is one of the key documents evaluated by the regulatory bodies during the review of the initial study application.

On the other hand, clinical trial agreements (CTAs) do not need to be submitted to or reviewed by the EC or RA in Turkey. The CTA template provided by sponsor is shared with the clinical site institution (hospital) management and the principal investigator (PI). For some sites, there are site-specific CTA templates. The sponsor or site template, or a combination of these two templates as agreed by all parties, can be negotiated. The RA approved budget needs to be incorporated in the CTA.

In Turkey, separate CTAs with the PIs (two-party agreements) are not allowed, thus the CTAs are designed as tripartite (sponsor/CRO, institution, PI) documents. The language of the CTA needs to be bilingual (Turkish – English) as solely English CTAs are not legally valid in Turkey. As per the local legal framework, Turkish language within the CTA prevails over the English⁴.

The clinical study budget and the CTA can be amended during the course of the trial in cases such as protocol amendments or subject number increases requiring budget change. The timelines for budget and the CTA process during the study start-up, execution and close-out at clinical sites are illustrated in Figure 1.

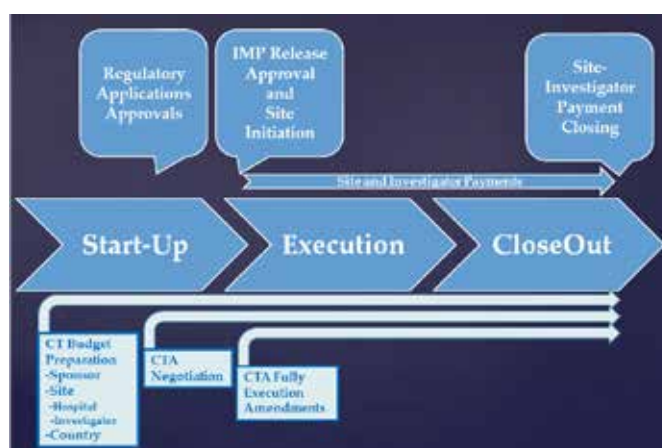


Figure 1: Schematic demonstration of the clinical trial budget preparation and clinical trial agreement process timelines in Turkey.

Clinical Trial Budget Preparation

As per the regulatory process in the country, once the sites are selected and confirmed by the sponsor, one of the participating investigators is selected and allocated as national coordinating investigator (NCI). The initial application is done as a parallel submission to the NCI site's ethics committee (EC) and to the RA. The EC reviews all the sites' information together with the study core documents; the RA reviews the study application as a whole.

The clinical trial budget theoretically has three levels, including study level, institution/investigator level, and subject level. The sponsor provides the country budget to start negotiations with the site. The country budget is split into institution- and investigator-level, as per the institution's requirements.

The study-level budget, which is high-level and compiled at the very beginning of the trial planning, generally includes financial figures for each study visit, including assessment fees and investigator grant together. All of the budget elements need to be carefully determined and implemented in the CT budget. These elements can be lined up as shown in Table 1 as general estimated figures that are received from sponsors, and their customisation aspects as per Turkish sites and for the country.

Investigator-level payments consist of the items other than the procedures listed in the institution budget. These are the assessments directly performed by the investigator at the study site (e.g. ICF collection, questionnaires, data entry) as well as the per-visit investigator fee determined in the budget. Investigator fee payments are made to the institution, and the institution distributes the amount to the investigator after the hospital deductions are made. Additionally, the Turkish Government has introduced new legislative incentives and support mechanisms for research and development activities. In accordance with the 16 February 2016 Amendment Law to the Law Supporting Research and Development Activities (Law No 6676)⁸, the earnings arising from research and development activities in the scope of university-industry cooperation are collected in a separate account, and 85% of the earnings are paid to the investigator with no deduction and exempted from income tax.

However, in order to apply these provisions to the research projects, university management approval upon investigator application is required. Therefore, there is no standard implementation of this amendment in clinical trials. Universities have different approaches and procedures for the application and evaluation of research and development activities.

	Budget Elements	
	General (Estimated)	Customised for Turkey
Study level	Regulatory application fees	EC and RA initial application fees as well as potential substantial and non-substantial amendment submission fees
	Protocol defined protocol procedures fees	The coverage of standard of care cost, if applicable; inclusion as procedures to be performed upon sponsor approval
	Patient expenses to be reimbursed	Subject travel and meals fees per patient and per site – total for patients
	Overhead fees	Calculation of the study-related work for investigators and study teams
	Administrative fees	All institutional administrative fees such as additional submissions, correspondence
Site level	CTA review fees	All sites' CTA review fees and the hospital finance system clinical trial code activation procedures
	Pharmacy fees	All sites' pharmacy facility use fees, if any. In case of no pharmacy use at sites, the unblinded team payment needs to be considered
	Start-up fees	All sites' start-up fees, other than CTA review fee, need to be captured
	Local laboratory fees	All sites' specific hospital laboratory fees and, if required, private laboratory fees
	Assessments' fees	All sites' specific assessments fees
	Site coordinator cost	All sites' externally allocated study coordinators full-time, part-time or per subject visit costs
	Per patient consented fees	All sites' pre-consenting, consenting and re-consenting fees
	Per patient screened fees	All sites' screened patients fees, including the decision of sponsor on screen-failure subjects
	Per patient enrolled/visit performed fees	All sites' protocol defined visits per patient and total for all patients to be enrolled
	Investigator grant	Investigator grant, including the hospital finance departments deduction
Subject Level	Laboratory assessment fees	Any ConMed or Rescue Med stated in protocol to be paid by sponsor for all patients enrolled
	Travel expenses	Hospital local laboratory all assessments, including imaging, and all other procedures that are hospital-specific
	Standard of care not included	Travel of subject, hospital attendance of vulnerable patients, and meals in total per patient and total for all patients
	Protocol-related SAE management costs	Any standard of care cost such as hospitalisation, additional imaging etc., to be included as procedures to be performed upon sponsor approval, as agreed by all parties. If the outcome of these will be evaluated for the study, it should be reimbursed by the sponsor
	Any other costs	Any SAE management-related costs
		Hospital attendance cost for vulnerable subjects

Table 1: General Budget Elements and those of customised budget elements for clinical sites in Turkey.

The items in the institution budget consist of fees for those tests and assessments that are performed using the hospital facilities. These procedures include, but are not limited to, physical examination, local laboratory assessments, imaging services, etc. Assessment fees are non-negotiable and listed in the price tariff of each institution. The price tariffs may vary between sites as listed below:

- Hospital Special Prices (e.g. Kocaeli University, Trakya University, Public and Private Hospitals⁵)
- Social Security Institution Health Implementation Declaration (SUT-Sağlık Uygulama Tebliği)⁶
- Public Health Services Sales Tariff (used by the majority of university hospitals)⁷
- Turkish Medical Association Price Tariff.

Management of the Clinical Trial Contract with the Clinical Sites

The applicable legislations that rule and regulate the management of contracts in clinical trials are summarised in Table 2.

Clinical trial agreements covering the responsibilities of the parties are signed as tripartite agreements between the sponsor/CRO, institution and PI, and have to be bi-lingual (Turkish and English). These agreements need to be signed by the institution unless the institution has a different procedure. Depending on the type of institution and study, there may be further signatories. Once all signatures are completed in a contract, a stamp tax should be paid in accordance with the applicable law. The tax will be calculated depending on the contract content. This requirement has to be discussed with the sponsor at the beginning of the study.

Title of the legislation	Version number and/or date	
Regulation on Clinical Trials of Drug and Biological Products	13 April 2013 with following amendments on 25 June 2014 and 13 Sep 2015 (http://www.titck.gov.tr/Mevzuat/MevzuatGetir?id=2051)	
Ministry of Health Turkish Drug and Medical Device Agency Guidelines on Good Clinical Practices	13 November 2015 (http://www.titck.gov.tr/PortalAdmin/Uploads/UnitPages/Iyi%20Klinik%20Uygulamaları%20Kılavuzu.pdf)	
Social Security Institution Health Implementation Declaration	Official Gazette dated 24 March 2013, numbered 28597 (http://www.resmigazete.gov.tr/eskiler/2013/03/20130324-3.pdf) including any subsequent amendments	
Regulation Concerning the Codes to be Followed in Revolving Fund Entities to be Established	As per article 58 of Higher Education Code numbered 2547 including any subsequent amendments (Official Gazette date: 05 July 1983, Number: 18098) (http://www.mevzuat.gov.tr/Metin.Aspx?MevzuatKod=7.5.10167&sourceXmlSearch=&MevzuatIliski=0)	
Regulation on Advertising Activities of Medicinal Products for Human Use	Official Gazette date: 03 July 2015, Number: 29405 (http://www.resmigazete.gov.tr/eskiler/2015/07/20150703-2.htm)	
Directive on Procedures and Principles for Trials conducted within the scope of Revolving Fund Enterprise by Sponsor request	20 February 2013, number 1488 (http://www.tkhk.gov.tr/828_yonergeler)	
The Implementation Declaration for Treatment Assistance	Official Gazette dated 10 December 2009, numbered 27428 (http://www.resmigazete.gov.tr/eskiler/2009/12/20091210-12.htm)	
Minimum Wage Tariff of Turkish Medical Association	Available upon purchase in Turkish Medical Association.	

Table 2: Applicable local regulations applicable to clinical trials contracts execution

A contract review fee is requested by some sites prior to them accepting to review the CTA. This has to be clarified during the site selection phase. Ege University (Prokom), Istanbul University Clinical Trials Excellence Application and Research Center (IUKAMM), Çukurova University (DAP Unit), and Dokuz Eylül University (DAP Unit) request a contract review fee.

The majority of the sites agree to negotiate and sign the sponsor or CRO contract template. Some of the sites, however, have site-specific contracts/agreements. In such cases, both sponsor/CRO and site-specific contracts have to be executed for full activation of the site, as usually the site-specific contract only covers budgetary items and not necessarily all other items.

The contract template can be a sponsor or CRO template. If a sponsor template will be used in a clinical trial conducted by a CRO, the responsible project team member will review the site contract for relevant terms ensuring consistency with the contract between CRO and sponsor ("sponsor contract"), payment terms and general CRO obligations. If the sponsor prefers to use a CRO template, the current existing contract template is provided by the CRO for sponsor review and facilitates any sponsor-required changes to the template. The final site contract template(s) must be mutually agreed upon between CRO and sponsor before beginning negotiations with the site. A site budget template is also provided along with the parameters.

After completion of the template development step, the project team member who is delegated for contract negotiation needs to generate the contracts incorporating the approved study budget figures in accordance with country and site-specific requirements. Once the negotiation is completed, it can be signed by all parties.

CTA Negotiation and Execution Process

Clinical trial agreement components include, but are not limited to:

- Parties of the contract
- Protocol number and protocol title
- Sponsor and/or CRO details
- Reference to the protocol and applicable local laws
- Obligation of parties, conduct of the trial, terms of termination, confidentiality, indemnity/insurance, trial data, inspections, publications, intellectual property/inventions, equipment retention, if any
- Budget exhibit including EC/RA approved figures, payment terms and payee information
- Tax information including stamp tax payment

Unless a site-specific process is applicable, the following steps are needed for contract/budget negotiations:

1. Budget and contract template is received from the project team
2. Assessment fees of the institution are obtained and budget is split between PI and institution
3. Turkish RA budget form is completed and submitted to EC/MoH as part of the initial submission package
4. Budget and contract template is sent to PI for review and approval
5. Site contract template including the budget table is sent to the institution for review after PI approval
6. Institution approves the template or asks for revisions
7. Any institution revisions are escalated to the project team member and contract is finalised and quality controlled for signature

University Hospitals

Prokom (Ege University):

Ege University has a clinical trials unit that reviews and approves the site budgets and contracts; this is Prokom (Project and Special Services Coordination Center). This site accepts sponsor template contracts, but has a site-specific supplemental agreement template that must also be used.

A submission is made to Prokom for budget and contract review and approval. The submission file is reviewed in the committee meeting held bi-weekly. The submission file includes the following documents: application letter, Ege University budget form, study procedures request form prepared by PI, study stamp, Prokom review fee payment receipt⁹, a copy of EC initial submission file, EC/RA approvals (can be presented afterwards if not obtained at the time of submission to Prokom), contract and supplemental agreement template. The negotiation process is as follows:

- 1 Prokom Submission File is sent for review
- 2 Prokom provides feedback two weeks after the meeting, via e-mail
- 3 Revisions are made and missing documents (including EC/RA approvals) are provided to Prokom
- 4 Contract is executed

Budget presented to Prokom needs to be compliant with the study protocol as the committee reviews the budget versus the protocol. The legal department in Prokom does not approve any reference to other countries' laws and regulations. Although as mentioned previously, submission to Prokom can take place prior to having EC/RA approvals, and Prokom will only proceed with approval for signature after EC and RA approvals are provided. A site-specific supplemental agreement needs to be signed along with the site contract. Stamp tax declaration and payment receipt shall be sent to Prokom after the stamp tax payment is performed.

Istanbul University Clinical Trials Excellence Application and Research Center (IUKAMM):

IUKAMM is the clinical trials unit of the following Istanbul University institutions: Istanbul University Istanbul Medical Faculty, Istanbul University Cerrahpaşa Medical Faculty, Istanbul University Cardiology Institute, Istanbul University Oncology Institute and Istanbul University Pharmacy Faculty. Contract/budget negotiations, contract execution and site payments are performed through IUKAMM. There is an electronic system called Clinical Trial Database, where the contract templates, including the budget, are uploaded for review and approval.

- 1 RA approval is received and contract review fee payment is performed¹⁰
- 2 Contract template is uploaded to IUKAMM's Clinical Trials Database along with RA approval and payment receipt
- 3 IUKAMM reviews and approves the contract template or asks for revisions
- 4 Any institution revisions are escalated to the project team member and contract is finalised/quality controlled for signature
- 5 Contract is executed
- 6 Review process is completed in 3–4 weeks and the status can be tracked through IUKAMM's Clinical Trials Database

Dokuz Eylul University Research Projects With Sponsor (DAP) Unit and Cukurova University:

Dokuz Eylul University and Çukurova University have DAP units reviewing site contracts and organising site payment procedures. Contract review and execution process are as follows:

- 1 Contract template and local agreement template is sent to DAP unit for review
- 2 Any site revisions are escalated to the project team member and contract is finalised/quality controlled for signature
- 3 Site agreement is sent to site for signature along with supporting documents (EC/RA approvals should be in place to start the signature process)
- 4 Contract is executed

The process differs slightly between Çukurova University and Dokuz Eylul University as summarised in Table 3.

	Çukurova University	Dokuz Eylul University
Payment	Contract review fee payment	No contract review fee is requested
Specific DAP agreement template	DAP agreement template is not mandatory	DAP agreement template is mandatory
Contract execution meeting at the site	Monthly meetings	No meeting
Stamp tax payment	Not requested for contract signature process	Requested to be done in order to distribute the original copy of the executed contract
Process	<ul style="list-style-type: none"> The contract is approved by DAP unit Sent for signature with supporting documents as a contract file Contract file is reviewed and approved in monthly meetings Contract is signed a week after the meeting if there are no missing documents in the file 	<ul style="list-style-type: none"> The contract is approved by DAP unit Contract is signed in two weeks Original copy of the executed contract is obtained after stamp tax payment

Table 3: The CTA process differences between Çukurova University and Dokuz Eylul University.

Uludağ University:

There is no specific contract execution meeting at this institution. A copy of the initial EC submission file needs to be sent to Uludag University Medical Faculty EC in addition to EC and RA approvals of the trial for review and signature process of the CTA.

Stamp Tax Payment Procedure for the Fully Executed CTAs

Stamp tax is a consumption tax levied on papers, which are prepared with intent to execute the transactions regarding transfer of goods, services and wealth appearing in the chain extending from production to consumption legally, and paid for each party. Stamp tax is regulated under Stamp Tax Law numbered 488 and dated July 1, 1964 (the "Stamp Tax Law").

The sponsor/CRO is obliged to make the stamp tax payments. Stamp tax declaration is made monthly (declared by the 23rd of the following month). Some of the institutions are requesting proof of the stamp tax payment in order to complete all steps of site activation.

Public (State) Hospitals

Every public hospital is affiliated to a Public Hospitals Union General Secretariat based on their location. Public Hospitals Union General Secretariats are connected to the Public Hospitals Institute located in Ankara. In order to execute a contract in public hospitals, the below described process should be completed in accordance with the Directive on Procedures and Principles for Trials conducted within the scope of a Revolving Fund Enterprise by Sponsor request (Directive number 1488 dated 20 February 2013).

- 1 Study is submitted to Public Hospitals Union (PHU) General Secretariat for pre-approval
- 2 PHU gives pre-approval for the study
- 3 Budget form and pre-approval letters are submitted to Public Hospitals Institute (PHI) for approval
- 4 PHI requests a review fee and determines prices in committee meeting
- 5 Final budget is signed by PHI and sent to sponsor/CRO
- 6 Site agreement, including final budget, is sent to site for signature along with supporting documents
- 7 Contract is executed after RA approval

A pre-approval application file consists of the pre-approval form and protocol synopsis in the local language. Some Hospital Union Secretariats may request additional documents. The application requirements should be confirmed during the application file preparation with the respective Secretariat.

If there are multiple public hospitals in a study, all pre-approvals will need to be collected in order to perform budget submission to PHI.

There is no fixed price tariff for the procedures. The prices are determined in the meeting performed by PHI for the study. The submitted initial budget to PHI is prepared in accordance with the Public Health Services Sales Tariff. PHI either sends a counter-offer after reviewing the budget, or approves the budget without any revisions.

Conclusions and Key Success Factors

Clinical trial budget preparation and the clinical trial agreement finalisation process at Turkish sites is a complex and time-consuming process. There are various contract procedures which change per site in addition to local requirements in Turkey. Planned work, familiarisation with the site-specific procedures and thorough communication with sponsor and project team members play a significant role in finalising the contract execution and managing Turkish sites' activation in a timely manner.

Key success factors include the following:

- There is a study code activation in each hospital/clinical site's finance department. After CTA is signed, this code activation needs to be managed pre-SIV or during the SIV for the site to be ready to enrol a patient. This code activation process varies amongst the sites, e.g. Hacettepe University Medical Faculty requests a site-specific form in addition to EC/RA approval letters, stamp tax payment receipt and fully executed CTA
- Expertise of local legal requirements and site-specific procedures is of key importance
- Good level of knowledge of the study-specific assessments and implementation to local requirements
- Project team member/sponsor should be informed about local requirements and site-specific requirements at the very beginning of the study, so that all steps are followed without any disruption.

The main processes (country- and site-specific) and legal framework ruling and shaping the preparation of the clinical trials budget and CTA procedures have been elaborated in this paper. Having these in mind in combination with real-time experience, we believe these will serve as a useful tool for all stakeholders involved in clinical operations in Turkey.

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