Report

Clinical Trials in Iran; Biannual Report of Clinical Trial Committee in Food and Drug Organization, Ministry of Health and Medical Education

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Introduction

The quality and safety of medical products have been of major importance to the Iranian Ministry of Health and Medical Education (MOHME). According to the parliament law of 1985 and its 1988 amendments, MOHME is to establish quality standards for all medicines. The Food and Drug Organization (FDO), within MOHME, has the highest authority over the pharmaceutical sector and, amongst other responsibilities, is in charge of the registration and issuance of market authorization for all medicinal products, including pharmaceuticals.

Prior to 2003, for the registration of new pharmaceutical and medicinal products, FDO relied mainly on clinical document approvals of such products by relevant organizations in other countries, namely the European Medicinal Enterprise Agency (EMEA) in Europe and the Food and Drug Administration (FDA) in the United States. In response to increased capabilities and movement of local pharmaceutical industries toward introducing new products and clinical research institutes for conducting quality medical research, Clinical Trial Committee (CTC) has been established in FDO as the National Regulatory Authority (NRA), in 2003. The main purpose of this attempt has been to assure the quality and safety of medicinal products, not only for those imported into Iran, but also for new products introduced by national manufacturers.

Scope of work and organizational structure of CTC

Not all clinical trials (CTs) conducted in Iran fall into the domain of CTC. CTC deals with those studies in which the purpose of the sponsor or investigator is to obtain approval for the product under investigation to be entered into the Iran Drug List (IDL) and/or obtain authorization for the pharmaceutical market as a part of their registration process. This accounts for a small part of clinical research projects conducted at medical universities and clinical research institutes. It is estimated that from about 8000 medical research projects conducted each year in the country, of which some 4000 projects are reviewed by national and regional Ethics Committees (N/REC), some 30%–50% are CTs.[1] With the establishment of Iranian Registry of Clinical Trials (IRCT) in 2008,[2–3] it has become mandatory to register all CTs in IRCT prior to signing contracts for the conduction of such studies. Therefore, from 860 CTs which have been registered in IRCT[4] over a two year period, about 10% are in the scope of CTC.

CTC operates as an independent secretariat under the Directorate of Pharmaceutical and Narcotic Affairs in FDO and covers CTs of all types of pharmaceutical products, including vaccines, biological, natural and herbal products, as well as chemical and medical related devices. CTC closely works with N/REC and IRCT in the Deputy for Research and Technology and the Control Disease Center (CDC) in the Deputy of Health, both within MOHME. Taking advantage of the integrated systems of health and medical education in Iran, the CTC secretariat has developed a collaborative network and partnerships between relevant sections in MOHME and external researchers from medical universities and pharmaceutical industries. However, the primary interface of CTC in most cases is the sponsor (generally pharmaceutical companies) rather than the principal investigator (PI). Currently, nine members are serving in the CTC which include the secretariat, four representatives from professional offices at FDO, three professionals from medical universities and a representative from NEC.

Responsibilities and work process of the CTC

The CTC secretariat is responsible for managing all administrative issues of CT files that are received. The key functions include: organizing CTC meetings and agendas, communicating with relevant parties involved in conducting CTs, conducting meetings with sponsors and investigators for defining their roles, contribution in developing guidelines and training programs and addressing all correspondence regarding individual applications. Specific activities of the CTC secretariat are as follows:

- Check documentations of CTs based on regulations and Iranian Good Clinical Practice (IR-GCP)
- Review study protocols of CTs
- Issue Clinical Trial Authorization (CTA)
- Conduct inspection of CT sites and documentations
- Review interim and final reports of CTs
- Review reports of CTs of imported products (conducted abroad)
- Review CT protocols for importation of Investigational Medicinal Products (IMP).

Figure 1 is a flowchart of CTC secretariat activities.

WHO GCP and CTC standards

MOHME adopted the World Health Organization (WHO) Good Clinical Practice (GCP) Guidelines[5] in 2003 as the minimum standard for various functions associated with conducting CTs. IR-GCP has been developed based on the WHO GCP and Helsinki Declaration that is further supported by a set of guidelines, list of 26 ethics codes, regulations and a recently approved law in parliament in 2009.[6,7] All of the mentioned documents are available

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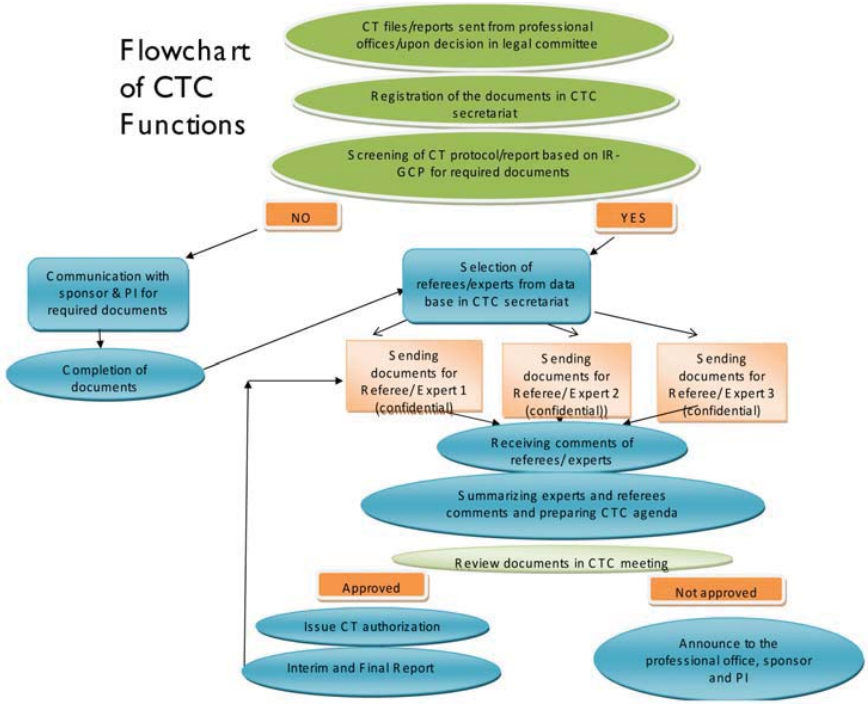

Figure 1. Flowchart of CTC secretariat activities.

online at *www.fdo.behdasht.ir* and *www.hbi.ir* or in person from the CTC secretariat.

According to the IR-GCP, the contents of a CT protocol, in addition to all common issues in a research protocol, should clearly define and demonstrate the following:

- Details of the sponsor, PI and monitor
- Declaration of conflict of interest from either sides, i.e., sponsor and/or study team
- Target population
- Inclusion and exclusion criteria
- Intervention(s)
- Primary and secondary outcomes
- Sample size (detailed assumptions and formula)
- Randomization
- Blinding
- Ethical considerations (see below)
- Data management

The following documents should also accompany the CT protocols upon submission:

- CV of the PI
- Certificate of attendance for the GCP training workshop by the PI or one of the study team members
- IRCT registration number
- Certificate of NEC approval for CTs sponsored by foreign companies/institutions
- Certificate of REC approval for CTs sponsored by local pharmaceutical companies
- Patient consent form
- Insurance/a legal document of sponsor's liability for subjects participating in the study
- Case report form(s) (CRF)
- Other forms and questionnaires used for patient recruitment, random sampling and allocation, adverse drug reactions, evaluation and follow up

Biannual activities of the CTC

Over two consecutive years the CTC secretariat received a total of 113 CT files, of which 55 were from mid-2008 to mid-2009, and the remaining 58 from mid-2009 to mid-2010. Of these, 70%–80% were CT reports, many of which were conducted aboard with the intent to import pharmaceutical products into the country. About 40% of the files over this two year period were protocols for conducting CTs on pharmaceutical products produced and sponsored by the Iranian pharmaceutical industries (Table 1). In addition, a small portion of the applications (5%) intended to import IMP for the conduction of clinical research inside Iran.

The highest frequency of all files received by CTC during these two years belonged to vaccines and biological products (60%), followed by herbal and traditional formulations (25%), and chemical and medical related devices (15%). While the majority of CTs conducted were sponsored by Iranian pharmaceutical companies (80%), a smaller portion was investigator-initiated (28%) and a few were supported by multinational companies. Table 1 demonstrates CT files managed by the CTC during these two years.

Of all studies concluded and reports received by CTC during mid-2008 to mid-2009 60% were approved, 25% deferred to the PI or sponsor for further clarification and 15% were disapproved. From mid-2009 to mid-2010, 66% were approved, 22% were deferred to the PI or sponsor for further clarification and the remaining 12% were disapproved (Table 1). Of protocols reviewed by CTC, CTA were issued for 8% from mid-2008 to mid-2009 and 22% received CTA from mid-2009 to mid-2010. During mid-2008 to mid-2009, 75% of the protocols were deferred fro modifications and in mid-2009 to mid-2010, 78% were deferred.

Table 1. CT files and performance outcome of CTC from mid-2008 to mid-2010.

Type	Year 1, % (*n*)	Year 2, % (*n*)
Protocols	22 (12)	15 (9)
Interim and final reports	73 (40)	83 (48)
Importation of an IMP*	5 (3)	2 (1)
Category		
Vaccines	5 (3)	27 (16)
Biological products other than vaccines	47 (26)	38 (22)
Herbal and natural products	22 (12)	28 (16)
Chemical products and medical devices	25 (14)	7 (4)
Sponsor		
Local industry	53 (6)	70 (6)
Multinational company	14 (2)	9 (1)
Investigator initiated	33 (4)	21 (2)
Others		
Phase III clinical trials	92 (50)	95 (55)
IRCT registered	65 (36)	79 (46)
Performance outcome of CTC Clinical trial reports		
Approved	60 (24)	66 (32)
Deferred for clarification	25 (10)	22 (10)
Disapproved	15 (6)	12 (6)
Protocols		
CT Authorization issued	8 (1)	22 (2)
Deferred for modification	75 (9)	78 (7)
Stopped by sponsor/PI for unknown reason	17 (2)	—

* Investigational medicinal product.

Common findings and challenges

Most applications received by the CTC secretariat lacked the required documents upon submission, which became apparent after the first screening. On average, a time elapse of approximately two months was spent until all required documents were provided by the sponsors or PIs.

One of the major problems in studies reviewed by CTC, particularly the ones designed and conducted in Iran, concerns confusion in the roles of different parties involved in conducting the studies, namely the sponsor, investigational group/institution and the ethics committee that approved the studies, which can cause a potential conflict of interest. This needs to be clarified according to GCP standards in order to improve the quality and credibility of CTs. The CTC secretariat normally conducts a meeting to clarify the roles of each side prior to initiation of a study.

In a number of applications the certificates of the GCP training workshop by the PI or one of his/her study team members, as a required document, were absent. While selected clinical research institutes occasionally conduct GCP workshops, training programs on GCP should be performed in a more organized manner. The CTC secretariat, with contribution from GCP trained researchers, has developed an educational package on IR-GCP and intends to train 450 researchers from clinical research institutes and local pharmaceutical companies.

With respect to the content of CT protocols, there have generally been discussions on the design of CTs, randomization, blinding and more often on assumption of the main clinical outcome/s upon which the sample size of the studies are calculated. Deferring protocols for modifications based on CTC expert recommendations has been another time consuming issue, which, in some instances has taken several months.

While reviewing the interim and final reports, in a number of occasions, it has been noted that the originally approved protocol had substantially been changed with respect to randomization, eligibility criteria and required efficacy tests. The PIs and sponsor must formally inform the CTC secretariat for any major changes to the originally approved protocol and seek CTC approval. During the inspections conducted by CTC, it was noted that there were failures in maintaining adequate and accurate records, and data source documents.

The CTC secretariat at FDO has been approved in 2010 by the WHO for its function on the oversight of CTs of vaccines and biological products as a part of the National Regulatory Authority. CTC is becoming an acceptable partner in research communities in Iran. Inter- and intra-sectoral collaboration and partnership will further improve the conduction of quality clinical research in Iran.

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