Investigator initiated trials (IITs)

Why this editorial on IITs? Are such trials truly initiated by investigators? Are these trials initiated by industry? Is there a need for such trials to complement industry initiated trials?

In the recent past, industry has been collaborating with academia to facilitate investigator initiated trials. Ethical research-based companies have written standard operating procedures (SOPs) on IITs.

Clinical investigators may wish to perform clinical trials with or without company drugs within or outside the approved product license or prior to marketing authorization. Companies may consider requests to support such trials pre- and post-first marketing authorization. The company may be willing to support these studies without taking the role of sponsor as defined by the International Conference on Harmonization (ICH)-Good Clinical Practice (GCP).[1] Support from the company may be in the form of drug product, comparator drug, financial resources or all mentioned. Clinical trials proposed upon the initiative of clinical Sponsor-Investigators and without the company taking the role as a sponsor are termed Investigator Initiated Trials.

What is driving the need for IITs? Clinical trials are not, and cannot be, designed to determine all the potential uses for a medication. IITs expand product knowledge, including safety. Physician researchers often identify new ways of using existing treatments, thus improving the health of numerous other patients. And there is always greater weight attached to non-industry sources of data. Even large pivotal randomized clinical trials are done by academic research organizations, e.g., Public Health Research Institute (PHRI) or Duke Clinical Research Institute (DCRI).

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/2229-3485.103591

On the face of it we must have more investigator initiated trials. The usual practice is to design global clinical development programs (with the help of researcher-clinicians) and then place studies in countries where carefully selected investigators execute the study under the oversight of clinical operations. The principal investigator is sometimes reduced to being a pure implementer. At least those clinicians who participate in protocol development meetings get the satisfaction of being a part of cutting edge research and not merely being the executors.

But the evidence from such gold standard prospective, randomized, double blind, controlled clinical trials, while it may help prove the efficacy of the drug and garner marketing authorization approval, may need to be complemented by studies done by doctors in the real world. The former is limited in extrapolation or generalizability and therefore the other RCT or the Real world Clinical Trial needs to be initiated. Of course, IITs can also be done pre-marketing, e.g., in a phase IIIb setting. While companies do conduct such phase IV studies, it is also good if investigators initiate their own research in the post-marketing environment.

In some cases it is part of a company's strategy to expand information around the product and/or therapeutic area. Some IITs are in scope and some are not in scope from the company's perspective. Whether data from IITs, funded by a company, can be used for regulatory submissions to get new indications approved is a matter of debate since these studies are generally not monitored by the company per its SOPs.

There are some important caveats. The trial request must be initiated by the investigator and not by the company. It has to be a spontaneous, unsolicited request. The same needs to be directed to the medical department. The request, in the form of a concept note, is evaluated based on objective criteria such as credentials of the investigator (Curriculum Vitae showing s/he has designed and conducted original research; not black-listed), need for such a study (meets unmet medical need or fills a gap in medical literature), quality of design of the study, and cost-effectiveness (needs to be reasonable enough to fit into the budget).

Whether the company will benefit from the study or whether it involves the product or therapeutic area or whether the investigator is important to the company should not be criteria for approval. Scientific rationale, study design, endpoints, formulation, statistics, budget and availability of local human and financial resources as applicable to oversee and support the study should be the criteria for approval, and compliance with ICH-GCP or local GCP regulations and all laws, rules, guidelines and regulations applicable to the planned IIT, including local, anti-corruption, anti-bribery and anti-kickback laws.

Once a go/no go decision is reached, based on the above criteria, the same is communicated to the investigator. Hence expectations need to be managed upfront. If yes, then a protocol template may be sent to the investigator who is then expected to flesh out the concept note into a full-fledged protocol. The same is again reviewed locally by the medical department, and sent to the regional and global medical team for further inputs into the scientific aspects. Funding of the study is generally done by the local affiliate, though in some cases the global team may also fund.

Once approved/rejected, the same is communicated back to the investigator. If yes, then s/he is expected to be trained on Adverse Event reporting, and other aspects of Good Clinical Research Practice [regulatory authority and ethics committee approval, informed consent, listing the study on Clinical Trials Registry of India (CTRI), etc]. An official agreement is signed between the investigator and company and s/he may receive milestone payments. The investigator is expected to take the study all the way to publication (the researcher is not mandated to share the manuscript with the company) and update CTRI accordingly.

In such studies there is no indemnification of the investigator or insurance of the patient by the company. The company only funds the investigator. All other liability rests with the investigator as outlined in the agreement. The investigator is expected to follow the law of the land (e.g., inclusion of the compensation clause in the informed consent form).

In case a patent or data exclusivity may arise out of data generated from the study, the investigator has the right to decide whether s/he wishes to share the same with the company. Some companies have an agreement with the investigator on co-sharing of patent holder rights. Similarly, the data may be submitted to the regulator in support of a new indication for a product. In such cases it is a different agreement (as with the patent case) and now the company does share liability and may decide to monitor such a study.

Such IITs do serve to add to the body of generalizable evidence and advance medical science. It need not have anything to do with the company or its products or therapeutic area. Of course IITs can also be funded by non-industry, academic bodies or the government. There is always skepticism if industry funds any research though even in industry-sponsored studies, ultimately it is the investigators' study as the data is of their patients, they have full access to the raw data, they review and approve the study report and publication. So whose study is it anyway? One example of a large IIT is the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT).

A good idea would be to simply fund an academic body such as the European Association for Study in Diabetes (EASD) which writes and updates guidelines. If one reads guidelines one does come across areas where research is needed to answer hypotheses. Such research can be funded by industry although it may have nothing to do with their products. Thus one has more of evidence-based medicine and less of opinion- or eminence-based medicine.

Industry (I) could come together with Academia (A) and set up an Institute of Real World Research (R) which can fund such IITs thus also clearing the AIR of misperceptions and increasing transparency. Competitors could collaborate with each other and facilitate practical or pragmatic clinical trials and comparative effectiveness research. It is not that one drug is better than another. The real issue is no longer the choice of the "best" agent, but rather the identification, on a rational basis, of the population of patients who will benefit from a given agent the most.[2]

In practice when a doctor sees every patient s/he is in effect doing a clinical trial.[3,4] It is time to do research in practice and contribute to clinical development and research. It is time to inculcate that mindset of inquiry into observations in practice and have the hunger and thirst of trying to find answers. It is time to make time for truly investigator-initiated trials and not merely industry-initiated trials.

DISCLAIMER

The thoughts are those of the author in his personal capacity and not as the medical director of the company he is currently employed with.

Viraj Suvarna

Medical Director, Boehringer Ingelheim India Private Limited, Mumbai, India

Address for correspondence:
Dr. Viraj Suvarna,
C-35, Rose Blossom, Sitladevi Temple Road,
Mahim, Mumbai – 400 016, India.
E-mail: viraj.suvarna@boehringer-ingelheim.com

REFERENCES

1. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. ICH harmonized tripartite guidelines. Guidelines for GCP E6, 10 Jun 1996.
2. Klastersky J. Antifungal therapy in patients with fever and neutropenia – more rational and less empirical. N Engl J Med 2004;351:1445-7.
3. Chen DT, Miller FG, Rosenstein DL. Clinical Research and the Physician-Patient Relationship. Ann Intern Med 2003;138:669-72.
4. Miller FG, Rosenstein DL. The Therapeutic Orientation to Clinical Trials. N Engl J Med 2003;348:1383-6.

How to cite this article: Suvarna V. Investigator initiated trials (IITs). Perspect Clin Res 2012;3:119-21.