Is there a need for investigator-initiated research?

Is there a need for investigator-initiated research? This is a rhetorical question. If there is one thing that should have happened along with the entry of global clinical trials (CTs) in India since 1994, it should have been the blossoming of investigator-initiated academic clinical research (CR).

Why am I saying this? As Chair of the Investigator Council of the Indian Society for Clinical Research (ISCR) for the past 4 years, I have interacted with a few investigators. I have asked them why is it that the investigator community has not come forward to fight for the cause of CR and their patients in India, especially when uninformed elements were trying to sabotage good quality, ethical research in India. Their response was that they were only pure implementers in the global trials that came to India.

They were never a part of protocol development meetings. Hence, they never felt as if they owned those studies. While they did praise the industry for building the right quality and ethical research culture in the country and invested a lot in Good Clinical Research Practice (GCRP) workshops and training, helping set up noninstitutional, independent ethics committees, released the speaking book, created the film on informed consent, set up state-of-the-art CT sites, donated expensive equipment such as DEXA machines (as part of an osteoporosis trial) which then could be used to generate ongoing local data; they felt that, in parallel, the industry should have also facilitated investigator-initiated academic CR.

Not necessarily only drug trials, but also there are unmet medical or CR needs of India which may not always be met by the typical global CTs that come to India. For example, novel oral anticoagulants have been launched with a lot of fanfare in India, and there is Indian patient data generation, both premarketing and in the real world. But, all these are happening in the patients with nonvalvular atrial fibrillation (NVAF). What about rheumatic mitral stenosis associated with atrial fibrillation (AF)? This indication is not being pursued because the prevalence of NVAF in the world is higher, but it is an area which is of relevance in India where the incidence of rheumatic fever may be decreasing, but the burden of rheumatic valvular AF is still high.

It is in such settings that companies should come forward in the spirit of competitive collaboration and facilitate multicenter investigator-initiated trials, made in India for India. Of the investigator, by the investigator, and for the investigator, and his or her patients. There could be other areas of unmet medical need such as true epidemiology (community based) data in AF which are also unfortunately lacking in India. This kind of data generation will also help in the formulation of true Indian guidelines, based on local evidence generated with the highest possible standards. From a company's perspective, this "medical" research will also generate data which can be more accurate for business forecasting and estimates as compared to the typical market research that is done and later one realizes it may be flawed as the data are dependent on what randomly selected doctors answer in response to a questionnaire. One of the Central Drugs Standard Control Organization orders which was welcomed by the medical community was the one on academic CR which stipulated that, if the research had no commercial value, and was purely academic, including repurposing of old drugs for new indications, one need not go to the Drugs Controller General of India for approval and the institutional ethics committee would need to approve the same. Having said this, the basic principles of conducting the study as per the principles of GCRP would need to be adhered to, and if something untoward happened during such trials due to proven willful negligence, the investigators may be sued by the patient/relatives, the way it happens in clinical practice. Investigator-Initiated Research (IIR), as the words suggest, needs to be truly so. In other words, it cannot be that the sponsor wishes the trial to be done through an investigator and subtly convinces him/her to initiate such a trial on behalf of the company. It has to be spontaneous, unsolicited, and the funding agency (company, research society, government body, ISCR) needs to have objective criteria, and an independent impartial panel, to define the basis for approval of the research grant. These could be described as follows:

1. Does the study need to be done in the first place? Is there a gap in the medical literature that this trial will plug?
2. Credentials of the researcher. Has s/he done enough original research?
3. Scientific and ethical aspects of the design
4. Budget.

It should not be approved just because the requester is a key opinion leader or because the research will benefit

the sponsor. Having said this, it is also important for the investigator to understand what are his/her responsibilities as an investigator–sponsor. In such cases, while the company funds the trial, all the other responsibilities (e.g., regulatory and/or ethics committee approval as applicable) lie with the investigator who needs to own this responsibility. S/he needs to be trained on Investigator Initiated Studies (IIS) and on how to apply for and succeed in getting a research grant.

Hence, how should an investigator train himself/herself on being able to do investigator-initiated academic CR? During internship, the medical student can go through a course in GCRP which can stand him/her in good stead, particularly if s/he intends to do postgraduation, as the MD or MS examination eligibility criterion necessitates his/her doing a dissertation. What if the private practitioner, noninstitute-affiliated clinician in practice wishes to do research? It would do him/her good to read Dr. AS Nanivadekar's seminal article in the inaugural issue of Perspectives in Clinical Research which is all about how a clinician can do research in practice.[1] Essentially, one needs to have the right mind set and observation skills, based on which s/he might be able to discern a pattern which needs to be tested by first formulating a research hypothesis.[1] S/he needs to be trained in literature search, designing a study, writing a protocol, creating a case report form from the protocol, and database from the case report form. There are software tools for clinical development that are available for free download. S/he needs to have training in statistics and consult a statistician right at the beginning, and not at the end of the study after the results have been accrued. Funding is the key and to be able to get resources the doctor needs to know to whom to apply, namely, industry, research societies, and government bodies such as the Indian Council of Medical Research, Department of Science and Technology, Department of Biotechnology, and Indian Institute of Science.

ARE THERE BARRIERS TO INVESTIGATOR-INITIATED RESEARCH?

Time is a major reason given by most clinicians, followed by a lack of resources including a dedicated team and funding. There are a few companies which do fund IIR and have a standard operating procedure to decide which proposals can be processed, reviewed, and approved. Data from drug-related IIR in a new indication will not be acceptable by a regulatory authority unless the sponsor, who wishes to use these data to apply for a new indication on the product label, has also overseen the study conduct and verified the credibility of the data. This can be assured if the IIR is done in collaboration with the company who sponsors the study. In oncology, this is a routine practice abroad. In India, it has yet to take off in a similar fashion. Repurposing of old drugs (that have lost exclusivity and are no longer patent protected) for new indications is done in some academic research organizations, but then, there are no takers from industry to commercialize the same. In general, IIR has not taken off in India also because it is very rare that a company will fund an IIR unless it is related in some way to the company's portfolio/therapeutic area (TA) of interest and/or if the doctor is not important for the company. Very rarely will IIR of pure academic interest is funded by industry. Also, nowadays, with the spectre of compensation looming over every drug trial, the investigator would also like the grant for the IIR to cover expenses related to possible compensation issues, investigator indemnification, and insurance for the patients.

WHAT ARE THE BENEFITS OF INVESTIGATOR-INITIATED RESEARCH?

Doctors are trained to think about research, and this GCRP bent of mind has a positive rub-off effect on their good clinical practice. Doctors own studies that they have designed rather than being pure implementers of global trials that others have designed. In this context, if a few Indian doctors are eligible to be a part of the global protocol development meetings, it really helps in getting their buy in; plus the Indian scenario and its unique needs can be incorporated. Just as randomized controlled CTs and the real-world clinical studies are complementary, industry-sponsored and investigator-initiated academic CR are complementary. Currently, it is only ISCR which is really at the forefront fighting for patients and CR in India. If research that investigators and academic research organizations want to do also gets facilitated by industry/ISCR, it can go a long way toward building the right culture of good quality CR in India.

When one reads guidelines, there is always a section which informs the reader of those areas where there is no evidence, and hence one cannot have recommendations. This can be another useful way for furthering science by providing research grants to the medical society behind the guideline so that the next time the guideline is released, those areas where previously there was no evidence, now has studies that addressed the unanswered question. Companies can come together, in a spirit of competitive collaboration, to fund pragmatic trials that address a clinically relevant question, namely, which patient substrate responds best to which treatment regimen. For example, would hormone receptor-positive breast cancer patients (estrogen receptor, progesterone receptor, human

epidermal growth factor receptor-2 neu) do better if started on tamoxifen and then an aromatase inhibitor (letrozole, anastrozole) or inactivator (exemestane) were added, or should they be started on combination therapy, or should it be the reverse sequence, and when should fulvestrant be added? Such trials can be facilitated by industry, and companies need not worry about their respective drugs as the question is not whether this drug is better than that drug. The endeavor is to find which patient responds best to which drug/regimen.

No longer will people say that in India there is a lot of data but they do not get documented or presented/published. India's standing in the medical research fraternity will improve and this will have a positive rub-off effect on clinical practice. Who knows, perhaps, the government may decide to allocate a greater percentage of its gross domestic product on health.

India's unique unmet medical needs can be met, with a Make in India for India initiative, thus greatly reducing our health-care burden. It has been estimated by the WHO that India stands to lose $236 billion this decade, only due to four ailments, namely, cancer, diabetes, cardiovascular diseases, and stroke, for which we also have an National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke. It will also help in bridging the trust deficit that sometimes still exists. Being honest, open, and transparent about research also helps people understand whose study is it anyway. This will eventually pave the way for the Indian society to be for CR. That is when ISCR will have truly arrived. It may take much longer than the next 10 years, but it is a goal worth striving for.

I would like to end by quoting Dr. AS Nanivadekar, "… clinical research ought to be inculcated as an attitude during the formative years of every health-care professional so that it could grow into a habit and become second nature throughout his career."[2]

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Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.PICR_13_17

How to cite this article: Suvarna VR. Is there a need for investigator-initiated research?. Perspect Clin Res 2017;8:55-7.