Investigator-initiated studies: Challenges and solutions

Mahanjit Konwar, Debdipata Bose, Nithya J. Gogtay, Urmila M. Thatte
Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract
Investigator-initiated studies (IISs) help by generating data on effectiveness and safety of a drug in the real-world setting and attempt to answer questions that clinicians face in their day-to-day practice. These are studies that are initiated and managed by a nonpharmaceutical company researcher/s who could be an individual investigator, an institution or a group of institutions, and a collaborative study group or a cooperative group. They are largely driven by questions that arise beyond the completion of Phase III studies that have not been studied during Phases I–III of drug development. The benefits of doing IISs are often offset by the myriad challenges posed by an IIS. These include finances, regulatory submissions, continuous oversight, training of study personnel, lack of expertise in statistics, data management, and medical writing. Nonetheless, doing an IIS is extremely rewarding for the investigator and has the capacity to contribute to evidence and eventually impact policy. The present article presents both a brief literature review of IISs and a personal narrative of experience gained during the conduct several IISs in the last two decades. Challenges and potential solutions are described.

Keywords: Academic research, clinical trials units, funding

INTRODUCTION
Investigator-initiated studies (IISs) help by generating data on effectiveness and safety of a drug in the real-world setting and attempt to answer questions that clinicians face in their day-to-day practice. Literature abounds in several IISs that have changed the way medicine is practiced. The Anglo-Scandinavian Outcomes Trial (ASCOT)-the Lipid Lowering arm (LLA) of the trial is an example of an IIS, where atorvastatin was shown to have a highly significant reduction in coronary events relative to placebo. The results of ASCOT-LLA changed both British Hypertension Society IV (2004) and European Society of Hypertension guidelines (2003) for management of hypertension. Both these guidelines recommended statin therapy to be used especially in hypertensive men aged over 50 years with a total cholesterol of > 3.5 mmol/L.

Yet, another IIS was a multi-country collaborative study called the pulmonary embolism prevention (PEP) trial. This trial had over 24,000 patients and proved the efficacy of aspirin in the prevention of Venous thromboembolism (VTE) for patients undergoing arthroplasty and for those with a fracture of the hip. The PEP and similar studies led to the American College of Chest Physicians endorsing aspirin (with the highest grade of recommendation) and the American Academy of Orthopedic Surgeons to accepting aspirin as prophylaxis for prevention of VTE in patients undergoing arthroplasty. An IIS in India by D'Cruz et al. comparing elective versus therapeutic neck dissection in...
node-negative oral cancer showed higher rates of overall and disease-free survival with the former. This evidence has now been incorporated into the Spanish Society of Medical Oncology Clinical Guidelines.\(^6\)

This narrative review will discuss the benefits and challenges associated with conducting IISs both based on literature and personal experience. Potential solutions are also presented.

What are investigator-initiated studies?
IISs are clinical studies initiated and managed by a nonpharmaceutical company researcher/s who could be an individual investigator, an institution or a group of institutions, and a collaborative study group or a cooperative group. IISs are also known by several other names that include Investigator-Initiated Trials, Investigator-Sponsored Trials, Noncommercial Trials, Academic Clinical Trials, Physician-Led Studies and Investigator-Driven Clinical Trials, Academic. The term investigator can also be substituted by the term “Academic” or “Physician” and the term “Clinical trial” can be replaced by “Study.”\(^7\) The fundamental premise here is that the responsibility of being both the sponsor and investigator lies with the person who conceives of and conducts the study.

What are the benefits of Investigator-Initiated Studies?
IISs are largely driven by questions that generally arise beyond the completion of Phase III studies that have not been studied during Phases I–III of drug development.\(^8\) For example,

1. A clinician may use an already licensed drug for a different therapeutic indication (use of intravitreal injections of bevacizumab for age-related macular degeneration)\(^9\)
2. Comparison of two different treatment options for a disease (when the two treatment options belong to different pharmaceutical companies (bivalirudin versus heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction))\(^10\)
3. Evaluation of cost-effectiveness of two or more treatment options (endovascular strategy versus open repair for the management of a ruptured abdominal aortic aneurysm).\(^11\) These types of IISs are useful as studies of this nature may not be of interest or commercially viable for the pharmaceutical industry.

Table 1: Benefits of conducting Investigator Initiated Studies

| Benefit                                                                 | Example                                                                 |
|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Data are generated in the real-world setting                           | Applicable to the population where the study is conducted              |
| Assist in developing hospital/state/nation-specific policies            | Generates more safety data and aids in benefit-risk assessment, particularly if pragmatic trials are conducted as IISs |
| Learning tool for site staff to enhance their research skills and helps in team building | Greater generalizability as the studies are conducted in real-world conditions unlike regulatory studies which are conducted in relatively homogenous populations |
| Helps in repurposing of licensed drugs and can convert off-label use to a guideline or policy recommendation | Fewer commercial conflicts of interest |
| Answer research questions that plague physicians in their day-to-day practice | IISs—Investigator-initiated studies |

The benefits of IIS are summarized in Table 1.

Challenges of Investigator-Initiated Studies: A broad perspective
Many clinicians who take part in pharmaceutical industry-sponsored trials often express their dissatisfaction as they are not involved in designing of the study or analysis, interpretation, and ownership of the data. They merely implement these studies. IIS offer clinicians an opportunity to do all of the above. However, initiating, sustaining, and taking an IIS to fruition is not an easy task. Challenges range from finances, regulatory submissions, continuous oversight, training of study personnel, lack of expertise in statistics, data management, and medical writing. While the benefits of doing an IIS are manifold, myriad challenges [Table 2] need to be addressed before embarking on an IIS.

Challenges of investigator-initiated Studies: A personal narrative
The senior authors (UMT and NJG) of this paper have conducted several IISs over the last two decades. A PubMed search of their own published studies. shows that a majority of them are observational (for example, genotyping in patients with epilepsy to individualize drug therapy).\(^12\) Among the interventional studies, most are minimal risk or slightly over minimal risk studies. One interventional study with a high degree of risk was the pharmacokinetics and safety of intravenous colistin in patients critically ill with multi-drug resistant Gram-negative infections.\(^13\) This study was funded in part by a pharmaceutical industry sponsor and required an open dialogue and briefing of the Institutional Ethics Committee (IEC) about the need for a study of this nature and clear, unambiguous presentation of benefit-risk associated with studies of this nature. After this, the IEC approved this study.

An IIS of a similar nature was, however, disallowed by another IEC based on the argument that the funder should compensate for research-related injury including deaths that can occur in critically ill patients. The pharmaceutical industry declined to pay for compensation as they felt that this would tantamount to them being “sponsors” of the study when in fact the study was investigator initiated. They wanted their
Table 2: Challenges associated with doing an Investigator-initiated Study

| Phase of study                  | Challenges                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|
| Pre-protocol development phase  | Inadequate/incomplete literature search while formulating a research question |
|                                 | Failure to hypothesize novel research questions                             |
|                                 | Lack of awareness about recent changes in regulatory guidelines in the country (e.g. compensation for research-related injury, for example) |
|                                 | Inadequate training to address ethical issues in clinical research          |
|                                 | Apathy toward submission to IEC                                             |
|                                 | Inadequate manpower at the study site                                      |
| Protocol development phase      | Lack of skills in various trial aspects such as biostatistics, data management, and manuscript writing |
|                                 | Nonavailability of SOP at the study site                                   |
| Study Phase                     | Inadequate time for the clinicians particularly to engage in long-term research |
|                                 | Lack of laboratory facilities and emergency investigations                  |
|                                 | Inadequate pharmacovigilence facility/training to identify and report ADRs, AEs, or SAEs |
|                                 | Nonavailability of dedicated clinical research coordinator                  |
|                                 | Staff attrition                                                             |
|                                 | Formulating research question without confirming feasibility                |
|                                 | Lack of familiarity with basic research methodology                         |
|                                 | Inadequate/inappropriate sample size calculation                            |
|                                 | Poor framing of budget and conceiving the project without identifying the source of funding |
|                                 | Lack of competency in preparation of multiple documents for submitting project to IEC |
|                                 | Difficulty in preparing a memorandum of understanding/Clinical trial agreement and getting approval, particularly when multiple institutions are involved |
|                                 | Apathy toward registering the study with a clinical trials registry         |
|                                 | Inadequate planning of safety monitoring                                     |
|                                 | Inadequate attention to risk mitigation and strategies therein               |
|                                 | Poor oversight and inadequate team management                               |
|                                 | Not keeping up-to-date with literature in the area for recent developments   |
|                                 | Inadequate training in research methods leading to inadequate implementation of methods like randomization and blinding leading to major biases in conduct of the study |
|                                 | Nonavailability of an internal monitor of the ongoing projects to ensure quality control |
|                                 | Delayed submission of SAEs, AEs, and Protocol Deviations to IEC (lack of monitoring) |
|                                 | Inadequate measure to prevent drop outs, especially when the study involves healthy participants or participants who come from distant areas |
|                                 | Failure to update the registered study in clinical trials registry at periodic intervals |
|                                 | Inadequate archiving facility                                               |
|                                 | Inadequate manpower to handle large data and carry out statistical analysis |
|                                 | Failure to send the study report and summary to the ethics committee to close the project |

Table 2: Contd...

| Phase of study | Challenges |
|----------------|------------|
| Post study     | Failure to close the project with the clinical trials registry             |
|                | Lack of publication policy at the protocol development stage and potential authorship disputes particularly for multicentric studies |
|                | Dispute over data ownership                                               |
|                | Lack of training to write the paper for publication leading to the data remaining unpublished |
|                | Inability to persist with publication when one or more journals reject the paper |

ADRs=Adverse drug reactions, IEC=Institutional Ethics Committee, SOP=Standard operating procedure, AEs=Adverse events, SAEs=Serious adverse events

funding support to be restricted only to provision of drugs for the study. The distinction between a “funder” and a true “sponsor” (one who takes the entire responsibility, that is, the investigator in this case) led to an impasse with the IEC leading to the project being withdrawn by the investigators.

We see at least three prominent challenges that exist with IISs that are interventional in nature and involve a fair bit of risk. The first is that the average investigator will not have the necessary funding and the required expertise in the myriad trial areas (ranging from conceiving of the research question to biostatistics and data management), for example to take the study through to fruition and may have to involve the pharmaceutical industry. Their involvement is more often than not likely to be construed by the IEC as a backdoor entry for the study for the benefit of the pharmaceutical industry to be done under the guise of an IIS. This is very difficult to prove or disprove and can lead to important studies not being done.

Second, the current guideline of the Indian Council of Medical Research (ICMR, 2017) on Biomedical and Health Research involving human participants mandates that compensation should be given for research-related harm including death and the budget for the study should make provisions for this. For IISs the guideline states that the “host institution” is responsible for providing compensation and should have in-built provisions for this. Unless institutions in the country create a corpus for provision of compensation, studies with more than minimal risk simply will not be done. For many institutes in the country including medical colleges, patient care still remains the priority area followed by education and research largely takes a back seat. Until this is addressed, much of the IISs in the country will largely remain observational.

Third, in March 2016, the regulatory authority issued a notification that an academic trial/study with An approved drug formulation no longer needs permission from the
regulator for initiating study with respect to any new indication or new route of administration or new dose or new dosage form as long as the trial is approved by the IEC and data generated is not intended for submission to the regulator.\textsuperscript{[13]} Furthermore, the IEC could submit a request to the regulator and wait for a 30-day period for such studies. In the absence of a reply, the IEC would give its nod for the study. While this is an extremely important step toward promoting IISs in the country, it needs to be strengthened by sufficient training of IECs who need to gain experience and expertise in benefit-risk assessment so that the patients who consent to participate in such studies are protected at all times. In addition, these studies also require the requisite funding to pay for research-related injury, an aspect alluded to earlier.

**Proposed solutions: A personal perspective**

Even though IISs pose many challenges to researchers, most of them can be overcome with robust internal policies and adherence to regulatory requirements. All the challenges discussed earlier should not act as barriers for IISs but rather as useful learning tools for researchers to improve their quality of research. The authors propose a few solutions based on their past experiences after being associated with multiple IISs over the years. These solutions are outlined in Table 3.

**Way forward for investigator-initiated studies**

One way to strengthen and help IISs grow in the country is to establish Clinical Trials Units or Clinical Research Units in academic centers that would help investigators take studies to fruition. These units would have the requisite expertise in all the diverse aspects of clinical trial designing and its execution. These could have intramural funding or funding from Governmental agencies such as the ICMR or the Department of Biotechnology. Support from the pharmaceutical industry could also be sought on a project basis for long-term sustenance of these units (some companies have provision for grants for these studies, information for which are available on their websites). These units could also find individual investigators (counterparts) in other countries for the execution of large-scale multicentric studies. The common ethics approval for multicenter studies mentioned in the recent ICMR Ethics Guidelines (for studies that have low risk) is yet another move that will have far-reaching implications for IISs.\textsuperscript{[14]}

**CONCLUSIONS**

IISs play a vital role in the generation of evidence that can eventually drive policy. A good IIS is one that asks a question that has scientific merit, has robust research methodology, has rigorous ethical and scientific governance, a committed and motivated investigator, institutional support, a funding agency that recognizes the value of the research and a team that backs him/her up. This will pave the way for high-quality research that will eventually drive local/national or even international policy for greater patient good.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.
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