

Developing Clinical Research Culture in Advancing Medical Research – An Industry Perspective

Manish Narang*

Department of Clinical Research, Abbott Laboratory, New Delhi, India

ABSTRACT

The 20th century witnessed tremendous breakthroughs in medical research by virtue of a plethora of discoveries and advances in fundamental biology and disease management. The 21st century is taking medicine to unprecedented heights. Clinical research sponsored by a flourishing industry shaped our understanding of modern medicine. However, industry funded clinical research cannot answer all medical questions. In this review, we look at the growing impetus on investigator initiated studies, their impact on deeper understanding of real world needs, involvement of pharmaceutical, devices and imaging industry in supporting investigator or institution initiated research and instances of such successful endeavours that has changed the way medicine is practised. We also delve into the changing landscape of clinical research ecosystem in the light of recent advances in technologies like genomics, biologics, companion diagnostics and precision medicine system and the urgent need of creating and supporting a culture of research among individual clinicians, institutions, public and Government bodies in alleviating global disease burden. We recommend structural and functional models of association between the industry and investigator-initiated research in order to overcome the traditional challenges of such research and pave the way for a fruitful and collaborative approach towards inclusive and comprehensive patient centric disease management.

Keywords: Clinical research; Investigator initiated research; Infrastructure; Research culture

INTRODUCTION

In the last hundred years, basic research in general and clinical research in particular have advanced human knowledge about various diseases, their underlying mechanisms, pathophysiology, epidemiology, ways of prevention and cure. The journey has been fascinating. The history of controlled clinical research in modern era dates back to the 1747 Scurvy trial conducted by James Lind. However, the 1943 Patulin trial for common cold, conducted by The UK Medical Research Council (MRC) and the subsequent 1946 Streptomycin trial for Tuberculosis were landmarks in terms of meticulous design, patient enrolment, conduct and data analysis of controlled human studies. Much has evolved since. In this review, we aim to delve on the ecosystem of various types of clinical research; the role of industry in investigator sponsored studies (ISS); responsibilities of various stakeholders; funding, resource allocation, financial management & buy-in from institute and hospital management; forming effective partnerships for ISS and

keys to conducting a successful research.

Research

The term ‘Research’ may be broadly defined as the systematic investigation into and study of materials and sources in order to establish facts and reach new conclusions. According to the American sociologist Earl Robert Babbie, “Research is a systematic inquiry to describe, explain, predict, and control the observed phenomenon. Research involves inductive and deductive methods.” Inductive research methods are used to analyze an observed event, while deductive methods are used to verify the observed event. Inductive approaches are associated with qualitative research and deductive methods are more commonly associated with quantitative research.

Clinical research

In the context of this article, we will focus almost entirely on

Correspondence to: Manish Narang, Department of Clinical Research, Abbott Laboratory, New Delhi, India, E-mail: manish.narang@abbott.com

Received: 04-May-2022, Manuscript No. LDAMR-22-23982; **Editor assigned:** 06-May-2022, PreQC No. LDAMR-22-23982 (PQ); **Reviewed:** 20-May-2022,

QC No. LDAMR-22-23982; **Revised:** 27-May-2022, Manuscript No. LDAMR-22-23982 (R); **Published:** 03-Jun-2022, DOI: 10.12715/2564-8942.22.05.001

Citation: Narang M (2022) Developing Clinical Research Culture in Advancing Medical Research – An Industry Perspective. Adv Med Res. 5:001.

Copyright: © 2022 Narang M. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

clinical research. Clinical research is a component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health. Clinical Research is actually a continuum of studies involving interactions with patients, diagnostic clinical materials or data, or populations in any of the following categories:

(i) disease mechanisms (etiopathogenesis); (ii) bi-directional integrative (translational) research; (iii) clinical knowledge, detection, diagnosis and natural history of disease; (iv) therapeutic interventions including development and clinical trials of drugs, biologics, devices, and instruments; (v) prevention (primary and secondary) and health promotion; (vi) behavioural research; (vii) health services research, including outcomes, and cost-effectiveness; (viii) epidemiology; and (ix) community-based and managed care- based trials.

Good Clinical Practice (GCP)

GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies. It is an international standard guideline and forms the basis for human subject right, safety and welfare as well as quality, reliability and integrity of conduct and data collection in all clinical research. The guidance must be adhered to before, during and after a research study is undertaken.

MATERIAL AND METHODS

Basic science

This encompasses all bench-top research. In today's multi-omics era, basic science is the pillar on which further translational research is built on. Most of these researches are Government funded (for example NIH) and executed through academia.

Industry Initiated Research (IIR)

These are drug or device trials initiated and funded by the industry. An industry initiated clinical research is generally the last and often most expensive leg of the discovery journey, with the objective of obtaining a regulatory approval for marketing registration and market launch.

Investigator Initiated Studies (IIS)

These are studies that are initiated and managed by a non-pharmaceutical 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.

Investigator initiated research-a vital cog in the wheel The need

Often, industry-initiated research is driven by scientific and commercial needs as perceived by the evolving dynamics and trends of the pharmaceutical and device market. While they are the main drivers of advancing patient care, they suffer from inherent drawbacks like restricted research settings, restricted patient population not representative of the real world, commercial interests not truly aligned with specific medical needs like rare diseases and so on. Clinical trials are not exhaustive in nature. They can't be designed to determine all the possible uses for a medication. Similarly, paediatric research is often neglected due to time and money already spent on adult trials, purely due to the burden of prevalence and hence commercial interests. Therefore, there is a definite gap to fulfil.

The namesakes

IIS are also known by several other names that include Investigator Initiated Research, Investigator Initiated Trials, Investigator Sponsored Trials, Non-commercial 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".

The nomenclatures

In the context of IISs, specific nomenclatures are used by FDA. There is a distinction between an "investigator" and a "sponsor". An "investigator" is defined as the individual who conducts the clinical investigation, whereas a "sponsor" is the individual person or entity that takes responsibility for and initiates the clinical study. The "sponsor" in this case is not the "funder". A "sponsor- investigator" is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The obligations of a "sponsor-investigator" include both those of a sponsor and those of an investigator. This means taking responsibility for all aspect of the study, including study design, regulatory approval, initiation, conduct, monitoring, reporting of safety data, analysis and publication of theresults.

Issues addressed

Independent research outside the ambit of industry-initiated projects addresses the following critical aspects of clinical research:

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.

They generate 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.

Some studies of a particular nature may not be of interest or commercially viable for the pharmaceutical industry, but critical to public health.

They complement industry-initiated research and provide complete understanding of the disease and its management.

RESULTS AND DISCUSSION

A clinician-investigator may use an already licensed drug for a different therapeutic indication (off label) as deemed fit by his medical acumen and intellect. A classic example is the use of intravitreal injections of Bevacizumab for age-related macular degeneration. Comparison between two different treatment options available for a disease. For example, Bivalirudin versus Heparin with or without Tirofiban during primary percutaneous coronary intervention in acute myocardial infarction. Evaluation of cost-effectiveness of two or more treatment options. For example, endovascular strategy versus open repair for the management of a ruptured abdominal aortic aneurysm. These are critical research questions answered by IISs which are generally outside the primary ambit of industry sponsored research for obvious resource, time & financial constraints.

Examples of IIS changing the way medicine is practised

The Anglo-Scandinavian Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) is an example of an IIS, where Atorvastatin was

shown to have a highly significant reduction in coronary events when compared to placebo. Both British Hypertension Society IV (2004) and European Society of Hypertension guidelines (2003) changed their guidelines for management of hypertension. Both these guidelines recommended statin therapy to be used especially in hypertensive men aged over 50 years with total cholesterol of ≥ 3.5 mmol/L.

An IIS multi-collaborative study called the pulmonary embolism prevention (PEP) trial 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 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 was later incorporated into the Spanish Society of Medical Oncology Clinical Guidelines.

IIS have also played a critical role in imaging studies. The GOLMePsA study (an investigator-initiated, double-blind, parallel-group, randomised, controlled trial of GOLimumab and Methotrexate versus Methotrexate in early diagnosed psoriatic arthritis using clinical and whole body MRI outcomes) investigated the anticipated benefits of early use of biologic disease-modifying anti-rheumatic drugs leads to sustained response while on Methotrexate monotherapy and better disease control. In addition, rapid optimization of disease management leads to significant improvements in quality of life of affected individuals. Similarly, the EudraCT study involved investigation of changes in disease activity and course of joint destruction by use of 3 tesla whole- bodies MRI, dedicated three tesla MRI, CT of the hand and the soluble biomarkers for rheumatoid arthritis. A subset of the trial threw important insights into tumor necrosis factor-inhibitor (Adalimumab) treatment. [1]

Differences between industry run trial and IIS

A classic example of the differences between these two types of studies can be explained by the SPIRIT III and the TUXEDO trials. The former, initiated by Abbott, showed patients treated with Everolimus-eluting stent experienced significantly improved event-free survival at a 2-year follow-up when compared to Paclitaxel-eluting stent. The latter, an IIS, showed that in patients with diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention, Paclitaxel-eluting stents were not shown to be non-inferior to Everolimus-eluting stents, and they resulted in higher rates of target-vessel failure, myocardial infarction, stent thrombosis, and target-vessel revascularization at 1 year [2]. The features of these two types of clinical research have been elucidated in Table 1.

Table 1: Types of Clinical Research.

Industry Initiated Trials	Investigator Initiated Studies
Regulatory input into drug development	Academic motivation
FDA gives extensive inputs to trial design, especially phase I and phase III	Support product life cycle - Might be part of product development plan
More restrictive	Will not lead to product approval, but can be cited as "supportive"
Comparator agent: approved vs. most current thought	Hypothesis generating
Treatment plan may be a compromise	Publication, presentations
Patient numbers	Less costly than industry conducted trials
Stringent inclusion, exclusion	Wider population and application

Industry initiated clinical trial ecosystem and its challenges

Industry initiated clinical trials are increasingly facing newer and more complex challenges. Some of these challenges have been described below. [3]

Spiralling costs

Difficulty in patient enrolment and retention
Inefficiency in protocol implementation

Ineffectiveness in supporting the development of new medicinal products

Selection and use of right technology

Involvement of huge number of vendors leading to governance issues

Traditional challenges in ISS's

ISS's typically provide more scientific, clinical and intellectual satisfaction to investigator sponsors. In spite of being more rewarding, there are inherent challenges in the way current ISS's are conceived and implemented. In fact, very few ideas ultimately result in research projects.

To further elucidate the practical challenges in improperly guided IIS's, let us look at the some of the incongruences. Inaccuracy was found in the information about sponsors and funders. The information about funding in all resulting publications was also inconsistent between databases of the studies.[4]

Herfarth have published their operational challenges faced during conduct of an IIS named MERIT-UC (Randomized, double blind, prospective trial investigating the efficacy of Methotrexate in induction and maintenance of steroid-free remission in ulcerative colitis) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [5]. The reasons for this termination were overestimation of the number of eligible drug-naive children referred by general paediatricians, personal preferences of investigators for specific antiepileptic drugs and the extensive administrative burden due to additional regulatory guidelines for children. The bottom line is in the current scenario, IIS's suffer from inspirational, financial, operational and regulatory challenges. Industry and Government bodies need to step up to usher in a new era of ISS's.

Research relationship between industry and independent sponsor-investigators

In recent years, the pharmaceutical and medical devices industry is increasingly taking interest in and being receptive to fresh research

ideas originating from the IIS space especially when it comes to generating additional real-world evidence with novel technologies like Imaging, diagnostic tools, implantable devices etc. Industry support is coming in many ways in the form of funding, provision of product and aid in the study design and operational guidance.

Top companies have made conscious financial policies and streamlined process efficiency to support IIS. The industry understands that they can either be facilitators or direct funding sources for innovative research ideas originating directly from the community.

Facilitating Funds: The industry can co-fund or facilitate funding from Government agencies like NIH (National Institute of Health, US), NHS (National Health Services, UK), NHMRC (National Health and Medical Research Council, Australia), Major Research Charities (Cancer Research, UK) and ICMR (Indian Council of Medical Research). However, the process can be cumbersome and needs improvement in efficiency.

Direct Funding: Increasingly, there have been great success stories in industry-clinician partnership in the IIS arena. Proof of concept studies in drug eluting stents for in-stent restenosis and saphenous vein graft; head on comparison studies like PRE-COMBAT, BEST and PREVENT trials as well as use of new technology and treatment studies like FAME and DAPT trials are testimony to industry support for research projects undertaken at academic medical centers are part of the drug or device development process. [6,7]

The future of effective industry-IIS partnership

The Key to Success: Effective future collaborations lie in identifying and pursuing mutually synergistic goals of generating high quality research and data for specific disease states of high importance, which can benefit the industry and clinician community alike. In the order to do that, the vision and roles and responsibilities for both the parties need to be crystallised at the onset.

One key aspect of IIS is to get a buy in from the institute or hospital. There is a lot at stake for them. The most obvious are academic gains like novel research, publications, podium presence and attracting new trials. But the bigger gain is evolution into a center of excellence in spite of being cost neutral [8]. This not only makes the center a preferred partner for research, but also augurs well for regular commercial operations. Since these aspects may not be realized instinctively by hospital management because they are not direct measures of return on investment, it is the responsibility of clinicians to convince the management on the dire need of industry-IIS collaboration aligned with the vision of the management. In fact, 46% of hospital executives don't know if their research programs are profitable, breaking even or even losing money. When utilized successfully, clinical trials offer additional revenue [9,10]. The success measures for buy-in from management

can be estimated and quantified using the matrix provided .

CONCLUSION

IIS's are critical in generating evidence that is outside the scope of industry initiated clinical trials. They can drive policy decisions leading to tremendous advances in medical science and improvement in patient outcomes. In today's era of COVID-19 global pandemic, we are witnessing more and more impactful collaboration between the industry and the clinicians. The key is to forge such collaborations based on mutual trust and respect but fostering the relationship outside the commercial interests of regular operations. It is time to develop a clinical research culture deeply ingrained into the healthcare delivery system. We as drivers of industry and supporters of clinicians must inculcate the mindset of inquiry into observations in practice and have the zeal and craving for answers. The problems are out there in the real world. The answers must come from there.

REFERENCES

1. De-Marco G, Helliwell P, McGonagle D. The GOLMePSA study protocol: an investigator-initiated, double-blind, parallel-group, randomised, controlled trial of GOLimumab and methotrexate versus methotrexate in early diagnosed psoriatic arthritis using clinical and wholebody MRI outcomes. *BMC Musculoskeletal Disord.* 2017;18:303.
2. Stone GW, Midei M, Newman W. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation.* 2009;119:680-686.
3. Institute of Medicine (US). Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (DC): National Academies Press (US). 2010.
4. Madeira C, Santos F, Kubiak C, Demotes J, Monteiro EC. Transparency and accuracy in funding investigator-initiated clinical trials: a systematic search in clinical trials databases. *BMJ Open* 2019;9(5):e023394.
5. Herfarth HH, Jackson S, Schliebe BG. Investigator-Initiated IBD trials in the United States: Facts, obstacles, and answers. *Inflamm Bowel Dis.* 2017;23(1):14-22.
6. Liou k, Jepson N, Cao C, Luo R, Pala S, Ooi, SY. Drug-eluting balloon versus second generation drug eluting stents in the treatment of in-stent restenosis: A systematic review and meta-analysis. *Heart Lung Circ.* 2016;25(12),1184-1194
7. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med.* 2011;364:1718-1727.
8. Heyndrickx GR, Tóth GG. The FAME Trials: Impact on clinical decision making. *Interv Cardiol.* 2016;11:116-119.
9. Suvarna V. Investigator initiated trials (IITs). *Perspect Clin Res.* 2012;3:119-121.
10. Investigator Initiated Trials (IIT). Considerations and Guidance from the Perspective of Clinical Trial Supplies and GMP. 2020.