Enabling RWE Studies in India

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India, with a large population, a variety of communicable and non-communicable diseases, and diversity of healthcare systems, provides immense opportunity for conducting studies in real world evidence (RWE). But this potential is not yet realized because of lack of demand from regulators, payers, insurance companies, and patients, and low level of interest from clinical investigators. This is a brief review of industry's role and challenges in creating an enabling environment for RWE studies.

Nature of Academic Clinical Research

Analysis of Clinical Trials Registry of India shows that academic investigators have registered 1,166 observational clinical studies, 942 prospective and 224 retrospective, since the Registry's 2009 inception. In contrast, industry has registered only 148 observational

studies, 121 prospective and 27 retrospective. Most of these were not systematically planned RWE studies with considerations of design, validity, and quality.

The preponderance of prospective studies suggests a lack of good quality clinical records for retrospective studies. However, the large number of non-industry studies highlights academic clinical investigator interest in conducting observational research studies, and an opportunity for industry to utilize the tremendous potential of such academic studies.

Industry Barriers to RWE Studies

There are several barriers to successful implementation of RWE studies in the pharmaceutical industry.

- **Lack of knowledge and awareness:** Industry product development teams (clinical research, physicians, medical affairs, etc.) who are accustomed to traditional forms of evidence generation such as randomized controlled trials (RCTs) are often not aware of the potential uses of RWE and non-interventional research methodology, and mistrust data collected outside RCTs.
- **Lack of capabilities:** Few personnel involved in product development have experience in planning and conducting observational or non-interventional studies and are usually unable to assess the quality of RWE studies as a result.
- **Lack of appropriate systems:** Most companies do not have special processes for effective execution of observational or alternative trial designs.
- **Nature of data sources:** Real world data are generally less accessible and less precise than data generated by RCTs.

These barriers, although not insurmountable, require industry research and clinical teams to develop competence in planning, conducting, monitoring or auditing, and interpreting RWE studies.

Indian Clinician's Perceptions of RWE Studies

Indian clinicians are busy practitioners who seem to profess little time or inclination for clinical research. Some of them may have experienced clinical research whilst conducting clinical trials for the pharmaceutical industry but are mainly not aware of the concepts and value of RWE and non-interventional clinical research.

For example: A clinician may assume that an RWE study implies using patient data already available from their practice with no need for additional planning or statistical analytical effort. Hence, when that clinician participates in a structured RWE study, they may be concerned about the amount of data collection and documentation effort. The clinician would expect that participation in RWE studies would enhance the evidence base for future practice and improve patient care by providing insight into which treatment works best for whom and under what circumstances. But industry sponsors often focus on reduced oversight and monitoring (and financial support) of RWE studies evaluating the effectiveness of a new drug, compared to RCT Phase 3 trials, which may make the clinician wonder about the quality of a RWE study and its relevance for their

practice. Lack of clinicians' interest and commitment is one of the **main reasons for low recruitment** in prospective registry-based RWE studies.

Harmonizing Academic and Industry RWE Study Objectives

To frame the above discussion in a different way: Clinicians expect RWE studies to generate clinical evidence relevant to their practice and patients. Industry expects RWE studies to provide evidence to support treatment approaches. To a clinician, an industry RWE study targeting collection of effectiveness and safety data in all patients treated with a drug often has the "look and feel" of a post-marketing support study.

Hence, there is a need to harmonize the clinician's and industry's expectations to create innovative RWE studies. Some examples of RWE studies could be:

- COVID-19
  - Natural history and predictive risk factors for prognosis.
  - Effect of standard care on morbidity/mortality.
  - Comparison of survival rate with standard of care between the initial stage versus current stage of pandemic.
  - Comparative effectiveness study of standard care with dexamethasone versus standard care with dexamethasone and remdesivir.
  - Comparison of morbidity/mortality in uncontrolled versus controlled hypertension/diabetes mellitus.
- Other conditions
  - Long-term complications/morbidity of communicable (e.g., drug-resistant TB) and non-communicable (e.g., heart failure) diseases.
  - Health economic outcomes in public versus private hospitals.
  - Repurposing new use for an old drug.
  - Comparative effectiveness studies.
    - Branded versus generic drugs.
    - Biosimilars: Patients who could afford to purchase innovator biologic versus patients who could not afford it and were given free biosimilar.
    - Indian prescribed dose (usually lower than the Western dose) versus recommended dose on package insert.
  - Comparison of major adverse cardiovascular events among new class of anti-diabetics.

These types of topics and studies may attract more Indian clinicians to actively participate in RWE research.

Industry Role in Shaping RWE Study Environment in India

In the absence of a strong regulatory presence, in the setting of a developing country, new clinical research disciplines take time to grow. In India, it took almost a decade – from 1996 to 2005 – for widespread acceptance of Good Clinical Practice (GCP) as the standard of quality clinical research. This was largely due to several enabling efforts by the

pharmaceutical industry, including: 1) supporting physicians and institutes in establishing a clinical research infrastructure; 2) providing clinical research and GCP training; 3) facilitating formation of ethics committees; and 4) initiating global clinical trials. Growth and development of the nascent field of RWE will require similar enabling efforts by the pharmaceutical industry. Industry associations could organize training for physicians and ethics committees on the principles and practices supporting how to use real world data (RWD) to generate RWE. Topics for such training programs would include:

- Definition, concept, and scope of RWE studies.
- Difference between observational and interventional clinical research.
- Protocol design: Hypotheses development, epidemiology designs, pragmatic trials, exposures, outcomes.
- Regulatory and ethical considerations.
- Quality and validity of RWE data and studies.

Pharmaceutical companies could initiate cost-effective short-term studies with real world data to help Indian clinicians gain experience in non-interventional research. There is an opportunity to explore use of artificial intelligence (AI) for medical records in paper format. Natural language processing (NLP) could help in quick extraction of meaning from textual information. Optical character recognition (OCR) would be helpful in electronically converting images of typed, handwritten, or printed text into machine-encoded text.

Such investments in facilitating RWE studies would go a long way in developing a culture of good quality documentation and would simultaneously facilitate adoption of Electronic Health Records (EHRs). Industry's enabling efforts will also help other stakeholders, such as regulators and payers, realize the value of RWE to Indian patients. Future utility of RWE in India rests on these industry efforts to shape an environment conducive to real world research that benefits patients in India.

References available upon request.