National Pharmaceutical Council

AcademyHealth

OBJECTIVE

Improve the credibility and reliability of observational and other real-world evidence studies by promoting the transparency of methods through the following:

- Conducting key informant interviews with NPC members
- Developing a white paper that identifies and describes an initial set of elements associated with high quality and transparent research methods
- Convening a multi-stakeholder panel to review, discuss, and finalize the recommendations provided in the white paper
- Disseminating findings and recommendations to policy-makers

REAL-WORLD EVIDENCE METHODS TRANSPARENCY

Central to the credibility and ultimate acceptance of real-world evidence (RWE) studies is the transparency of research methods. Increasingly, there is a call for broader use of RWE, if it is "transparent, reproducible, disclosed, accurate and valid," yet there is little agreement on how to achieve these elements.

Transparency of methods encompasses a wide range of practices including registering studies as well as making study designs, hypotheses, target populations, measures, statistical analysis plans, and results publicly available. However, unlike clinical trials, RWE studies utilize data developed in the course of health care delivery, such as electronic health records (EHRs), clinical data from laboratories, diagnostic testing, wearable devices, claims data, and pharmacy dispensing data. Thus, with RWE studies, it is not always clear if the study hypotheses have been pre-specified and if the results were subject to selective reporting.

Similar to rationales for registering clinical trials, proponents of registering RWE studies and making protocols publicly available cite ethical obligations along with benefits such as mitigation of publication bias and selective reporting,[1] improvement in reliability, reproducibility, and transparency of evidence,[2,3] and acceleration of knowledge generation.[4] However, others question the value of pre-specified hypotheses and study registration as a means to improve the quality or validity of RWE results[5,6] and the potential to hinder scientific discoveries.[7]

The extent and nature of methods-sharing practices currently followed is unknown. Further, the benefits, resource implications and unintended consequences associated with greater methods transparency for RWE studies are important to understand.

SETTING RECOMMENDATIONS

The National Pharmaceutical Council (NPC) and AcademyHealth collaborated to develop actionable recommendations to promote methods transparency. In particular, we engaged stakeholders through a multi-phase project to develop and prioritize recommendations to improve RWE methods transparency and credibility. Potential benefits, unintended consequences, and resource implications associated with greater transparency were also assessed. Further, incentives needed to encourage research transparency by all researchers, including biopharmaceutical companies, academia, payers, and other research entities, were defined.

RESULTS

PRIMARY LESSONS FROM KEY INFORMANT INTERVIEWS

The key informant interviews (n=14 representing 11 NPC member organizations) were held between September and November 2017. Transparency was generally viewed positively with benefits including improving replicability, reproducibility, and credibility of RWE. Although most interviewees agreed on the need for transparency for hypothesis testing studies and research meant to inform payers or regulatory agencies, they viewed transparency for exploratory studies or data mining efforts to inform internal decision-making as less essential. The discussions also highlighted several challenges and incentives to consider. FDA and payers were viewed as the primary drivers of RWE transparency.

Benefits of Promoting RWE Methods Transparency:

- Replicability, reproducibility, and credibility of RWE
- Improve science of RWE and efficiency of methods and results sharing
- Reduce skepticism of results

Other Implications of Promoting Transparency:

- Proprietary content risk and competition
- Increased administrative processes

Six recommendations were ultimately developed through insights generated from the key informant interviews with NPC member organizations and refined by a multi-stakeholder group. These recommendations serve as a guide to help end-users of RWE to assess whether they can trust and rely on the studies for various health care decision-making. Promoting transparency and operationalizing the recommendations will entail additional administrative processes and human resources and needs to be coupled with considerations of privacy concerns, protection of patient information, and mitigation of misuse of data where applicable.

TABLE 1: RECOMMENDATIONS FOR PROMOTING RESEARCH METHODS TRANSPARENCY

1. The RWE hypothesis statement should be pre-specified and logged in a repository. The origin of the hypothesis should be described.
2. The RWE analysis plan should be pre-specified and logged in a repository. Deviations from the analysis plan should be documented and the rationale for changes should be provided.
3. Steps should be documented to assure that the study data used is feasible using the available data and that the data are, appropriate and of high quality for use given the research question and the hypothesis.
4. Sensitivity analyses should be performed on key definitions and outcomes.
5. Data coding should be made available upon request, along with a natural language description of the coding logic in order to allow other research teams to replicate the study in an appropriate secondary dataset.
6. Access to summary tables of data should be provided.

References:

1. Agha R, Rosin D. The Research Registry – Answering the call to register every research study involving human participants. Annals of Medicine and Surgery. 2015;4(2):
2. Onukwugha E. Improving confidence in observational studies: should statistical analysis plans be made publicly available? PharmacoEconomics. 2013;31(3):177-179.
3. Thomas L, Peterson ED. The value of statistical analysis plans in observational research: Defining high-quality research from the start. JAMA. 2012;308(8):773-774.
4. Loder E, Groves T, MacAuley D. Registration of observational studies. BMJ. 2010;340.
5. Savitz DA. Registration of observational studies does not enhance validity. Clinical pharmacology and therapeutics. 2011;90(5):646-648.
6. Loomis D. Journal requirements to register observational studies: OEM's policy. Occupational and Environmental Medicine. 2011;68(2):83-84.
7. Pearce N. Registration of protocols for observational research is unnecessary and would do more harm than good. Occup and Environmental Medicine. 2011;68(2):86.