Ethical considerations for real-world evidence studies

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Abstract

Real-world evidence (RWE) studies are conducted on patient's data primarily collected for monitoring of health status of patients. The use of real-world data to generate evidence in academic research or for regulatory submission raises a variety of ethical issues such as privacy, confidentiality, data protection, data de-identification, data sharing, scientific design of study, and informed consent requirements. The investigators–researchers and sponsors should adhere to current standards of ethics whilst planning and conduct of RWE studies. The ethics committees should consider ethical issues specific to RWE studies before approval.

Keywords: Anonymization, confidentiality, data protection, privacy, real-world evidence

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INTRODUCTION

Real-world data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD comes from a variety of sources – Electronic Health Records (EHRs), registry data, claims data, patient-reported outcome data, and data collected from wearables. RWD are usually collected for documentation and monitoring of the health status of patients. However, now, they are increasingly being used to generate evidence in academic research or for regulatory submission. This raises a variety of ethical issues, which are discussed briefly.

PRIVACY AND CONFIDENTIALITY

Privacy is the right of an individual to control or influence the information that can be collected and stored by whom, and to whom that information may be disclosed or shared.[1] European General Data Protection Regulation (GDPR), released in 2018, has brought into focus the obligations of organizations collecting data related to people.[2] GDPR describes the privacy rights of data subject (the person whose data are processed), which include (1) the right to be informed, (2) the right of access, (3) the right to rectification, (4) the right to erasure, (5) the right to restrict processing, (6) the right to data portability, (7) the right to object, and (8) rights in relation to automated decision-making and profiling.[2]

RWD may include a variety of personal and sensitive information about demography, medical conditions, financial situations, and social behaviors.[3] Risk to privacy would increase significantly when different databases such as EHRs, smartphone data, wearables, and insurance are linked together for analysis of RWD.[3]

Confidentiality is the obligation of the academic researchers, and medical institutions, to the participant to safeguard the entrusted information.[1]

ENSURING DATA PROTECTION

The institutions and academic researchers should be aware of the critical importance of the privacy of patients and

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the confidentiality of their data when they participate in industry-sponsored real-world studies (RWSs). They should ensure the protection of patient's privacy when they share patient's data with the industry, other institutions, and other researchers.

The stakeholders-academic researchers, institutions, and pharma industry-planning or involved in RWS should establish measures for technical and organizational security to protect the privacy of data. Academic researchers and institutions should establish processes to safeguard such data and information from unauthorized access, use, disclosure, modification, loss, or theft. They should ensure that data collection, storage, sharing, and analysis follow established data privacy principles.[1-3]

The academic researchers and institutions should establish processes for (1) data sharing, (2) data de-identification, and (3) informed consent requirements when they participate in RWS sponsored by other institutions or pharma industry.

DATA SHARING

The patient's health status data would include personal data and medical information – history, demography, clinical symptoms and signs, diagnosis, and treatment. When such data are shared with the sponsor of RWS - another institution or industry, the academic researchers - the investigator, and institutions should ensure the protection of privacy and confidentiality of the patient data during and subsequent to the transfer of data.

DATA DE-IDENTIFICATION

The medical institution which has a repository for patient data should have a standard operating process for storing such data in de-identified - pseudonymized or anonymized format.

Pseudonymized data are processed personal data that can no longer be attributed to a specific holder without the use of additional information.

Anonymized data are personal data treated in such a way that it is impossible to re-identify or deduce information about a specific individual. Such data fall into the risk category of less than minimal[1] and are outside the purview of GDPR.[2]

INFORMED CONSENT REQUIREMENTS

The purpose of the collection of health data could be:[2]

- Primary purpose: Explicitly stated at the time of data collection such as monitoring of patient's health
- Secondary: Compatible with the primary purpose, but not explicitly stated at the time of data collection/ clinical trial such as research RWS.

The patients are not aware that their medical data collected routinely would be used for real-world research studies and would be shared with other institutions or pharma industry. Hence, informed consent would be a critical consideration for RWS.

For RWS with prospective design – survey, registry, pragmatic trial, informed consent is essential. For registries, consent may have multiple components:[4]

1. Consent to registry creation by the compilation of patient information
2. Consent to the initial research objectives and uses of registry data; and
3. Consent to subsequent use of registry data by the registry developer or others for the same or different research purposes.

For RWS with retrospective design-case–control, cross-sectional study, cohort study – the academic researcher or the investigator should provide justification for rationale for waiver of informed. The ethics committee (EC) can review and approve the waiver in the following situations:[1,4]

- Research involves no more than minimal risk to the study participants
- The waiver will not adversely affect the rights and welfare of the subjects
- Research cannot practically be carried out without the waiver and the waiver is scientifically justified
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format
- Retrospective studies, where the participants are de-identified or cannot be contacted
- Research on anonymized biological samples/data
- Research on data available in the public domain
- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional information after participation.

SCIENTIFIC DESIGN ISSUES

Interpretation and utility of evidence from RWS depend on the validity of the study design.[5] RWS studies using data collected by mobile health technology could restrict such studies to participants who are competent in using smartphones, wearable devices, and apps.[3] This could introduce bias, limit diversity and equity, and impact the

generalizability of the RW study. The EC should review such design issues and approve an RWS only if it relies on valid scientific methods. Checklists based on reporting standards such as Strengthening the Reporting of Observational Studies in Epidemiology recommendations could help in evaluating scientific design.[6]

REGISTRATION OF REAL-WORLD STUDIES IN REGISTRY

Registration of a clinical research study – interventional or observational in public clinical trial registry is essential to ensure transparency, accountability, and accessibility.[1] Registration is also a prerequisite for publication in many medical journals.

ETHICS COMMITTEE REVIEW OF REAL-WORLD STUDIES

RWS, whether prospective or retrospective design study, requires review by EC before approval. The EC should consider all ethical issues (vide supra) with a specific focus on:

- Purpose of the study – academic, commercial
- Risk–benefit assessment
- Scientific design
- Protection of privacy and confidentiality
- Informed consent process – waiver
- Applicable international rules for global registry, e.g., GDPR, Health Insurance Portability and Accountability Act
- Data de-identification-Anonymization
- Collaboration with other local or international institutes – data sharing
- Registration of study in Clinical Trials Registry–India.

CONCLUSIONS

Using RWS to support evidence-based decision-making requires consideration of the diversity of ethical issues. The investigators–researchers and sponsors should have procedures in place to ensure adherence to current standards of ethics whilst planning and conduct of real-world evidence studies.

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Conflicts of interest
There are no conflicts of interest.

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