An application of studying FAERS data to Enhance Drug Safety and Treatment Outcomes in Rare Diseases

Jaber Valinejad
Division of Preclinical Innovations, National Center for Advancing Translational Sciences (NCATS) National Institutes of Health (NIH)
Rockville, USA
Jaber.Valinejad@nih.gov

Yanji Xu
Division of Rare Disease Research Innovations, National Center for Advancing Translational Sciences (NCATS) National Institutes of Health (NIH)
Rockville, USA
yanji.xu@nih.gov

Qian Zhu
Division of Preclinical Innovations, National Center for Advancing Translational Sciences (NCATS) National Institutes of Health (NIH)
Rockville, USA
qian.zhu@nih.gov

Abstract— **Rare diseases affect fewer than 200,000 individuals in the United States, with some being so rare that only a handful of people are impacted. According to the U.S. Food and Drug Administration (FDA), there are 1,268 approved orphan drugs available for treating these conditions. However, potentially beneficial drugs can also have side effects. Some adverse events, while serious, may be rare, making them difficult to identify or quantify in randomized controlled trials. Understanding these events is critical for improving patient safety and treatment outcomes. To better assess these risks, we aimed at summarizing adverse drug events for rare diseases by utilizing FDA Adverse Event Reporting System (FAERS). This study offers a foundation for future research of improving drug safety in rare diseases.**

Keywords—Rare disease, adverse drug event, FAERS, knowledge graph

I. Introduction

According to the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [1], as of August 2024, there have been a total of 29,153,222 adverse event reports submitted. Of these, 16,130,758 reports involved serious reactions (excluding death), while 2,650,057 deaths were linked to drug-related adverse events [2]. Fig. 1 illustrates the trends in the number of deaths, serious adverse drug events, and non-serious events over time, highlighting the ongoing need for safety monitoring.

There are more than 300 million patients worldwide and 95% of over 10, 000 rare diseases lack of treatment [3]. In addition, the safety of orphan drugs was still unknown at the time of approval [4], to ensure the safety and efficacy of orphan drugs and the safe use of drugs by the public, pharmacovigilance studies on drugs for rare diseases are crucial [5].

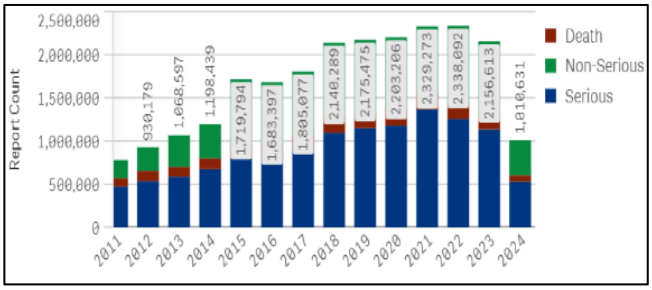

Fig.1. Trends in Deaths, Serious Adverse Drug Events, and Non-Serious Events Over Time [6]

This study systematically collected adverse drug events (ADEs) from FAERS for rare diseases, and presented the ADEs in a knowledge graph named ADE4RD to support pharmacovigilance study in rare diseases.

II. Methods

The FAERS Public Dashboard provides access to four key datasets, namely, Human Drug Adverse Events, Drug Labeling, National Drug Code Directory, Drug Recall Enforcement Reports [2].

In order to capture associations between orphan drugs/designations and rare diseases, we collected orphan drug designations and approvals from FDA[7]. Subsequently we mapped rare diseases obtained from Genetic and Rare Diseases (GARD) Information Center [8] to "Approved Labeled Indication" for FDA approved orphan drugs and "Orphan Designation" for orphan designations based on extract string match. Table 1 presents examples of the mappings.

By analyzing those datasets and aligning with our study goal, we predefined a data model shown in Fig. 2, to semantically representing relationships among those selected concepts. In our data model, we defined ten primary classes depicted as ovals, each containing specific data properties related to drug safety and ADE, which are listed in Table 2. We defined nine object properties as edges representing specific relationships between nodes. Upon the data model, we uploaded the collected to a knowledge graph hosted in a neo4j [9].

TABEL1 - EXAMPLES OF MAPPINGS BETWEEN ORPHAN DESIGNATIONS AND RARE DISEASES

Orphan designation	Mapped rare diseases
Treatment of retinopathy of prematurity	Retinopathy of prematurity (GARD ID: 0005695)
treatment of idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis (GARD ID: 0008609)
treatment of cutaneous variants of porphyria (which includes treatment and prevention of cutaneous manifestations of disease)	Porphyria (GARD ID: 0010353)

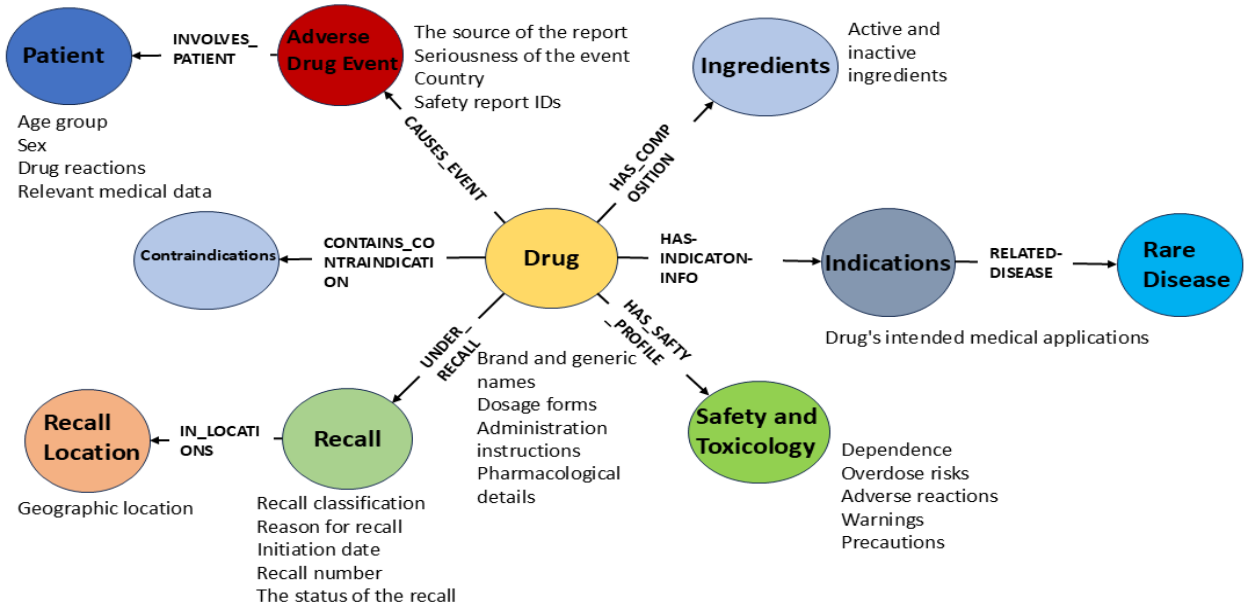

Fig.2. The Data Model of ADE4RD

TABLE 2- FULL LIST OF PRIMARY CLASSES AND THEIR ASSOCIATED DATA PROPERTIES

Primary Classes	Associated Data Properties
Patient	Age group, death date, onset age, sex, weight, reaction
Recall Location	Address 1, address 2, city, country, state
Drug Recall	Reason for recall, recall initiation date, report date, termination date
Adverse Drug Event	Primary source qualification (Physician, Pharmacist, Other Health Professional, Lawyer, Consumer or non-health), primary source country, serious, receive date
Drug	Brand name, dosage and administration, dosage form, dosage forms and strengths, generic name, indications and usage, mechanism of action, product NDC, drug interactions, route
Safety and Toxicology	Adverse reactions, warnings, use in specific populations
Drug Ingerdients	Active ingredient, inactive ingredient, SPL product data elements, active ingredient name, active ingredient strength
Contraindications	Contraindications
Indications	Drug indication, indications and usage, Orphan Designation (FDA Designated and Approved)
Rare disease	GARD name, GARD ID

III. RESULTS

In our knowledge graph, there are 17,833 nodes and 19,617 edges. Table 3 shows the statistical numbers of nodes and edges associated with each class. To demonstrate the use of ADE4RD, we performed two case studies.

Case study 1. To quickly assess the drug safety of orphan drugs in a specific year, we performed a query against the ADE4RD knowledge graph to extract ADEs reported in the year of 2019. There are 6,375 ADEs related to 195 rare diseases. Additionally, there are 509 recalls associated with 334 drugs used to treat rare diseases. Among those ADEs, 3,201 were classified as serious, indicating a significant risk to patient health.

TABEL 3 - THE STATISTICAL NUMBERS OF NODES AND EDGES ASSOCIATED WITH EACH CLASS

Classes	# nodes	# edges
Patient	6,375	6,375
Recall Location	29	508
Drug Recall	509	1,016
Adverse Drug Event	6,375	14,886
Drug	830	12,339
Safety and Toxicology	830	830
Drug Ingerdients	830	830
Contraindications	830	830
Indications	830	1,225
Rare disease	395	395

This serious classification included outcomes such as death, life-threatening conditions, hospitalization (either caused or prolonged), etc. [10]. The numbers illustrate the drug safety remains a big issue for orphan drugs.

Case study 2. To further analyze the impact of specific orphan drugs, we composed Cypher Query 1 to generate the top 10 orphan drugs associated with the highest number of ADEs, shown in Table 4. The results indicated that orphan drugs such as ADALIMUMAB, APREMILAST, METHOTREXATE, and METHOTREXATE SODIUM were associated with the highest number of ADEs. Notably, ADALIMUMAB has been linked to a significant number of ADEs. In addition, ADALIMUMAB is the second drug associated with a high number of fatalities, with 59 deaths reported in safety reports. ADALIMUMAB is commonly prescribed to patients who have not achieved adequate responses from other treatments and have previously undergone at least one systemic therapy [11]. However, its use is associated with an elevated risk of serious infections, which can be fatal. This increased risk is primarily due to ADALIMUMAB's potential to precipitate conditions such as sepsis and tuberculosis, particularly in patients with underlying comorbidities, those concurrently receiving other immunosuppressive therapies, and individuals aged 65 years or older [12]. In addition to infections, ADALIMUMAB has been linked to a range of adverse effects, including allergic reactions, neurological disorders,

TABLE 4-TOP 10 ORPHAN DRUGS ASSOCIATED WITH THE GREATEST NUMBER OF REPORTED ADE

Drug generic names	# Adverse Events	Rare diseases	GARD IDs
ADALIMUMAB	1918	non-infectious anterior uveitis	GARD:0021260
APREMILAST	652	behcet's disease	GARD:0000848
METHOTREXATE, METHOTREXATE SODIUM	407	osteogenic sarcoma	GARD:0007284
PREDNISONE	373	Chronic inflammatory demyelinating polyneuropathy	GARD:0006102
GABAPENTIN	293	Amyotrophic lateral sclerosis	GARD:0005786
ETANERCEPT	278	active polyarticular-course juvenile rheumatoid arthritis	
AFLIBERCEPT	275	Retinopathy of prematurity	GARD:0005695
DUPILUMAB	190	Bullous pemphigoid	GARD:0005972
IBRUTINIB	174	Lymphoma	GARD:0020548
CYCLOPHOSPHAMIDE	159	Systemic sclerosis	GARD:0009748

hematological abnormalities, heart failure, immune-mediated reactions, liver dysfunction, and psoriasis [13].

Cypher Query 1
```
MATCH (n:Event_Information)-[r:HAS_ADVERSE_EFFECT]-(m:Drug)
WITH DISTINCT n, m.openfda_generic_name AS generic_name
WITH generic_name, COUNT(DISTINCT n) AS event_count
RETURN generic_name, event_count
ORDER BY event_count DESC
LIMIT 10
```

IV. DISCUSSION

In this study, we developed a knowledge graph named ADE4RD to capture ADEs and other orphan drug related properties, including contraindications, toxicities. ADE4RD not only allows systematic assessment of drug safety of orphan drugs as being illustrated in the case studies, but also potentially supports drug repurposing applications [14].

FAERS remains a valuable dataset with a comprehensive list of ADEs However, we acknowledged that one significant limitation of FAERS is that it relies on self-reported data, which may contain human errors. These errors can lead to misinterpretations of the safety profiles of orphan drugs. To minimize the impact of those errors for supporting research, we propose two solutions, 1) integrating scientific evidence derived from clinical trials, PubMed literature, 2) explore the use of large language models to validate the data.

V. CONCLUTION

This paper highlights the benefits of using FAERS for accessing ADES for orphan drugs. By developing a data model that maps ADEs to orphan drugs and rare diseases, we provided a foundation for future research aimed at improving drug safety and treatment outcomes. Additionally, the integration of other methodologies, such as large language models and fuzzy matching techniques, will enhance data reliability. Ultimately, our work underscores the importance of ongoing investigation into rare diseases and the need for collaborative efforts to ensure that patients receive safe and effective treatments.

ACKNOWLEDGMENT

This project was partially supported by the intramural programs (ZIA TR000410-05) at NCATS.

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