Paper PP02

Effective Adverse Events Management

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ABSTRACT

The International Council for Harmonisation (ICH) introduced the Development Safety Update Report (DSUR) to streamline safety reporting during the development phase of a drug. Adverse events recording and reporting is an important part of a clinical trial that is very time consuming. It is about understanding relationships between adverse events and the drug to ensure the safety of trial participants.

To optimize the management of adverse events, choosing a graph database-based interface is an effective approach. The interface enables the smooth integration of various data sources, intuitive visualization of complex relationships, and flexible querying options. By improving the accuracy and efficiency of adverse event data management, this tool contributes to better decision-making and strengthens patient safety.

This poster will demonstrate how a powerful interface based on a graph database can simplify and enhance the management of adverse events, providing a solid foundation for reports like DSUR.

INTRODUCTION

Reporting serious adverse events (SAEs) to regulatory authorities is a critical and time-intensive aspect of the clinical development of investigational drugs. Understanding the relationships between adverse events and the drug is of highest priority to ensure the safety of trial participants. This process is particularly important during the creation of the Development Safety Update Report (DSUR), a key document submitted to regulatory authorities.

Preparing the DSUR raises questions about how the safety information is gathered, its origins, and how it is utilized during and after the reporting process. Data is often sourced from multiple, disconnected systems, making it difficult to get a comprehensive understanding and to explore further.

Optimizing adverse event management by leveraging a graph database offers a more effective solution than traditional relational databases. An interface that takes advantage of the power a graph database offers, facilitates seamless integration of diverse data sources, intuitive visualization of complex relationships, and flexible querying capabilities. This approach not only simplifies and streamlines adverse event management but also provides a robust foundation for DSUR creation. Moreover, it enables deeper exploration of the data, both before and after the report is generated, fostering improved decision-making and enhanced safety oversight.

COMPONENTS FOR EFFECTIVE VISUALIZATION

Creating a repository that effectively stores and visualizes data requires not only a graph database but also a combination of different useful components:

- Information Model – Defines how the data is modelled.
- Ontology – Provides rules for describing the data in the model.
- Graph Database – Stores the data efficiently.
- Reflective Logic – Facilitates querying and searching within the graph database.
- Interface – Enables visualization and exploration of the data.

These components work together to create a powerful and flexible solution [1].

AN INFORMATION MODEL INCLUDING METADATA

A repository for data should be structured and modeled to enable efficient data search, and by incorporating metadata with the data it gains power. Metadata tells us what we need to know about the data to understand it. Using an information model that is built as a graph with focus on nodes, instead of relationships creates other possibilities than a traditional relational database, such as flexible schema, intuitive visualization, efficient relationship handling and enhanced query performance.

ONTOLOGY

An ontology is holding the rules for the information model and describes the structure of the content. It specifies how nodes of the graph relate to each other, the fields included in each node, the datatypes of the fields, units to be used,

etcetera. The applied ontology also provides a terminology controlling the naming of all the entities. By utilizing the ontology, several benefits are gained, such as, easier data access, simplified exploration, improved sharing, and above all, better understanding.

PROPERTY GRAPH DATABASE VS RELATIONAL DATABASE

A property graph database organizes information in a way like a mind map, where nodes represent data points and edges define the connections between them. In contrast to traditional relational databases, property graph databases internally structure components by assigning properties, categories, and labels to both nodes and relationships. This intuitive structure removes the need for joins commonly required in relational systems and when integrated with a conceptual ontology, it mirrors the way the human brain organizes knowledge. This design also supports smooth incorporation of metadata, making the database less sensitive to changes in structure [2].

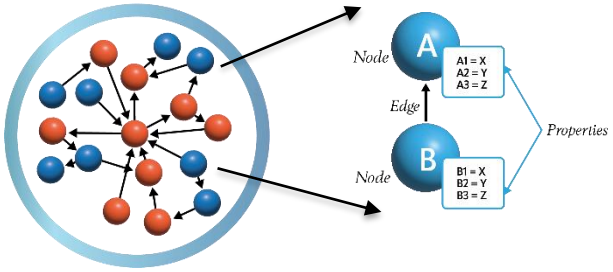

Figure1. Simple representation of two nodes in a labelled and directed property graph.

For the storage of extensive datasets, like those arising from clinical trials, property graph databases outshine other graph database options. This is mainly because of the faster and easier ways to access and query the data. Figure 2 illustrates the differences in structure and relations between a relational database and a property graph database.

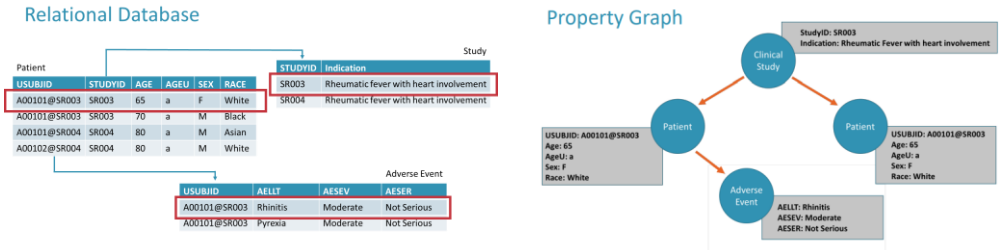

Figure 2. Relational vs property graph database [3].

REFLECTIVE LOGIC

Reflective logic is a novel method developed to enhance the value of graph database queries [4]. It is used to formulate queries with a centricity to find all information that fulfills the query. This means that it makes it possible to explore the data from different perspectives and allows the user to easily create subsets.

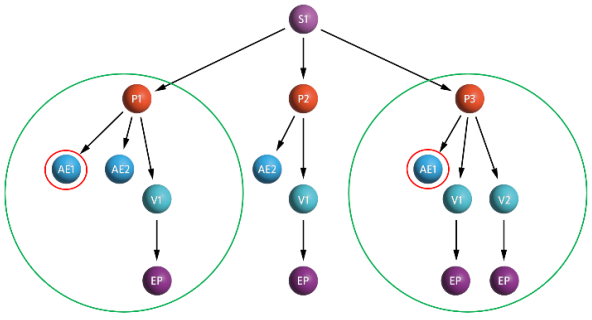

Figure 3. Shows how reflective logic enables patient cohort creation.

INTERFACE FOR A GRAPH DATABASE

A web-based interface for a graph database provides great flexibility in how data can be explored and visualized. By providing users with access to curated and integrated data, the interface supports comprehensive exploration of datasets and facilitates the preparation for regulatory reports. It also improves collaboration and ensures data accessibility for team members.

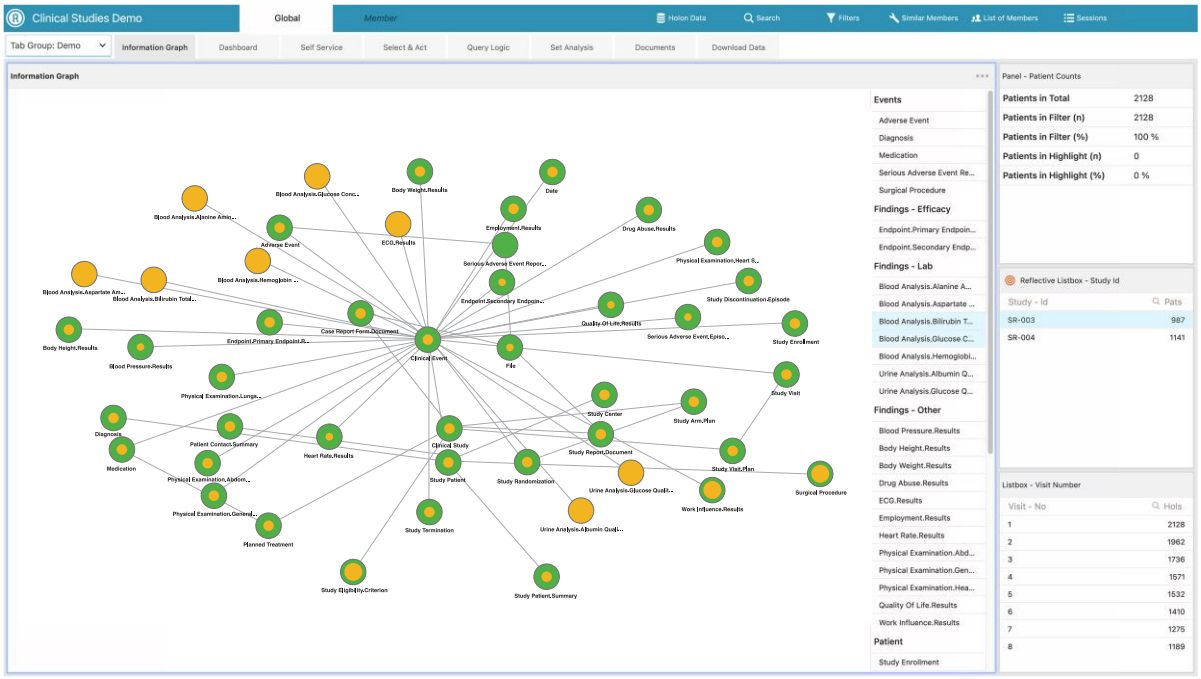

Figure 4: An example of an interface based on a graph database.

DSUR

The Development Safety Update Report (DSUR) is an annual report prepared by a sponsor to update the regulatory authorities about the drug's safety status. It is a yearly summary of SAEs and ADRs (adverse drug reactions) that have been reported during the clinical development of an investigational drug. It integrates safety information from ongoing, completed and terminated clinical trials, preclinical studies, and other sources regardless of indication, population, or formulation. This needs to be done until the drug receives marketing approval, or the clinical development program is determined.

The DSUR creation process is led by the pharmacovigilance/drug safety team, but it is a collaboration of expert teams from different departments. The process often involves integration between safety data and clinical trials data since they often are not available in the same solution.

A DSUR is important since it

- Enhances the understanding of the investigational drug's safety profile.
- Ensures transparency and regulatory compliance.
- Promotes harmonized global reporting for multicenter trials.
- Provides a basis for regulatory decisions and continued clinical development.

APPENDIX 5 LINE LISTING OF SERIOUS ADVERSE REACTIONS

SOC: Immune System Disorders

Trial number [EudraCT #[1]]	Case ID/ Subject #[2]	Country Gender Age	Serious ADR(s)	Outcome[3]	Date of Onset[4] Time to Onset[4]	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
3579DD/013 [2007-001234-56]	2009UK01234 013/012/005	UK F 56y	**Allergic reaction** Rash Oedema Hypotension	Resolved	15-Mar-09 14d	ZB3579	20 mg po tablet	02-Mar-09 - 15-Mar-09 14d	Hospitalised. Diagnosis of drug allergy. Time to onset 2 wks from first dose of ZB3579 and 3d from first dose of amoxicillin (chest infection). Investigator considers the event possibly related to ZB3579 and/or amoxicillin.

SOC: Metabolism and Nutrition

Trial number [EudraCT #[1]]	Case ID/ Subject #[2]	Country Gender Age	Serious ADR(s)	Outcome[3]	Date of Onset[4] Time to Onset[4]	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
3579DD/014 [n/a]	2009US04321 014/010/003	USA F 78y	**Hyponatraemia**	Resolved	26-Feb-09 24d	ZB3579	10 mg po tablet	2-Feb-09– 26-Feb-09 24d	Hospitalised. History of hypercholesterolaemia, hyperuricaemia and diabetes. Multiple concomitant medications. Investigator considers ZB3579 and Altizide/Spironolactone as co-suspect drugs.
etc	etc	etc	etc	etc	etc	etc	etc	etc	etc

Figure 5. It shows a fictional listing of serious adverse events that could be included in DSUR.
https://database.ich.org/sites/default/files/E2F_Example_Commercial_DSUR.pdf

ADVANTAGES OF GRAPH DATABASES FOR DSUR PREPARATION

Using an interface based on a graph database for DSUR, preparation offers significant advantages in managing and analyzing the complex and interconnected data typical in pharmacovigilance. Key benefits include:

- **Efficient Relationship Management**: Handles complex links between patients, trials, drugs, and adverse events.
- **Improved Traceability**: Tracks data origins and connections for better traceability.
- **Integration of Multisource Data**: Combines data from trials, sites, and safety systems seamlessly.
- **Scalability**: Handles large datasets and complex queries more efficiently than relational databases.
- **Data Visualization**: Maps relationships visually for clearer insights.
- **Customization**: Adapts to evolving data structures and requirements.
- **Collaboration**: Centralizes data for team-wide access and streamlined workflows.

This approach not only increases efficiency but also improves data insights and ensures higher-quality reporting during DSUR preparation.

THE MAGIC BOX IS A GOLD MINE

A graph database works like a magic box – once start exploring the data, the desire to dig deeper grows, revealing endless possibilities for discovery. Compared to relational databases, graph databases allow for faster, deeper and more intuitive exploration of interconnected data, especially for use cases involving complex relationships, evolving data structures, and advanced analytics like safety signal detection. Using reflective logic adds even more advantages when searching for complex answers.

By storing data from ongoing and completed studies in a graph database, where queries can be seamlessly run across the entire dataset, it offers significant advantages for the teams. This enables:

- Simplified exploration of complex, multi-dimensional datasets.
- Actionable insights through semantic linking and visualization.
- Accelerated regulatory report preparation with high-quality data summaries.
- Improved collaboration and data sharing among teams.

DIG DEEPER

When preparing a DSUR, it is essential to analyze the relationship between the adverse event and the drug. This may involve comparing various patient groups or examining differences based on the the patient's health status at enrollment. Additionally, it is important to consider the timing of adverse events or adverse drug reactions during the treatment process. Other factors to evaluate include efficacy, patient-reported outcomes, and additional safety parameters, which are often challenging to access within a single solution.

Digging deeper into the data becomes essential when preparing for questions from the authorities.

You may want to:

- Highlight selections.
- Drill down to site or patient level.
- Identify and explore outliers.
- Explore all fields and values.
- Search for similar patient profiles.
- Download data for further processing.

This not only improves the depth of data exploration but also enables users to share findings and collaborate effectively with colleagues. Figure 6 shows examples of some of the features above and how easily subgroups can be created by doing it stepwise.

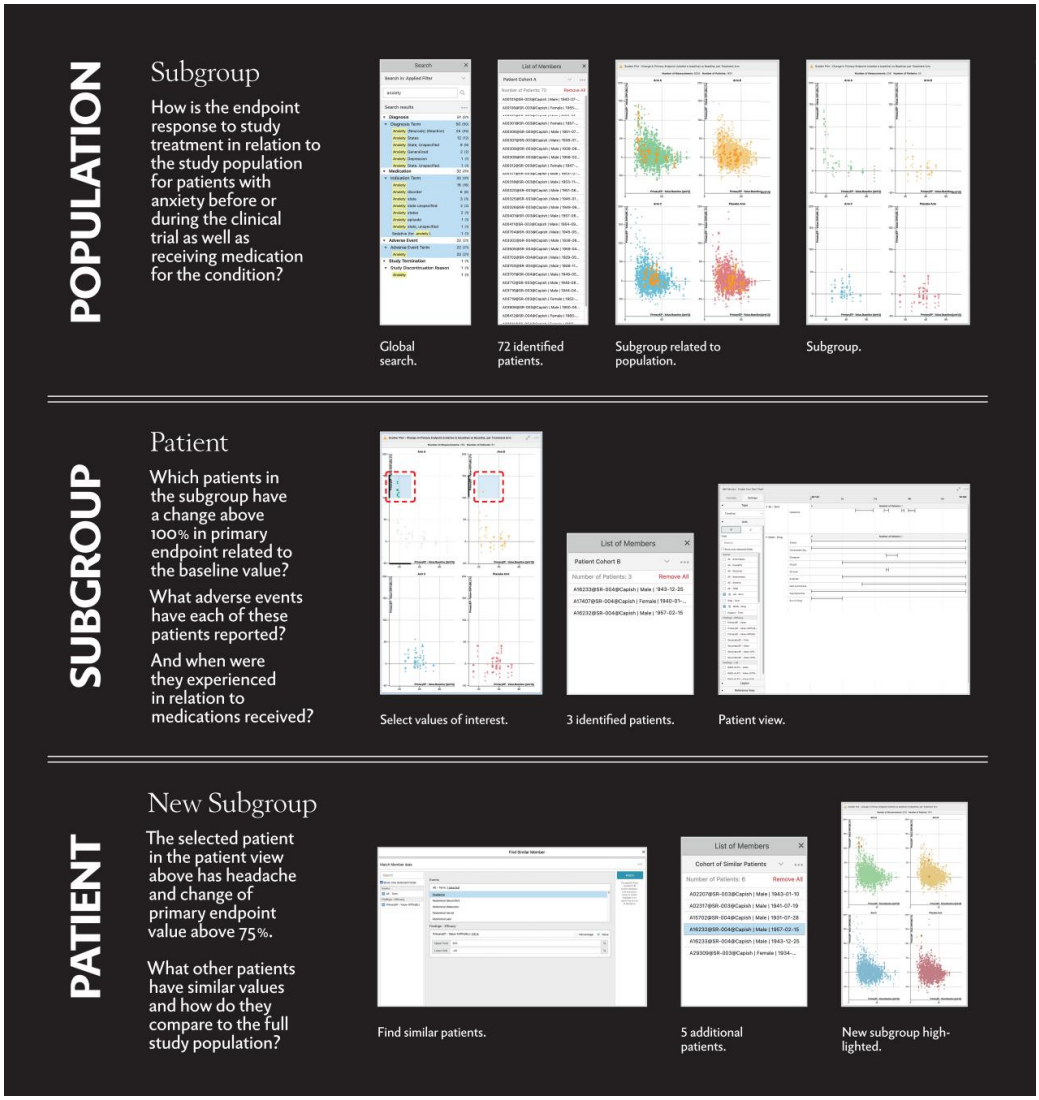

Figure 6: Shows how a flow of questions can dig into the data and gives rise to new questions on different levels [5].

ADVANCED QUERYING

FMQs (FDA Medical Queries) and SMQs (Standardized MedDRA Queries) are different AE groupings serving specific roles in safety monitoring. Working with FMQs/SMQs iteratively throughout a trial will increase the knowledge and understanding of safety issues, contributing to decision-making and protecting patient safety.
Adding more useful data into a graph database is easier and more flexible than in a relational database, allowing for continuous improvement in safety monitoring.

CONCLUSION

A graph database with a powerful interface revolutionizes adverse event management, providing a solid foundation for DSUR preparation and ongoing safety analysis. By empowering users, regardless of team affiliation, to explore data comprehensively, identify important correlations, and share insights, this approach enhances collaboration and efficiency. A graph-based solution is not only an invaluable tool for improving regulatory reporting but also a vital component for advancing clinical development and ensuring patient safety. If the primary goal is simply interacting with the data, a basic graph database will suffice. However, for exploring complex relationships and correlations, more advanced technology is required.

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