Converging lines of evidence in adverse event surveillance:

Enhancing drug development by integrating clinical trial and real-world patient data

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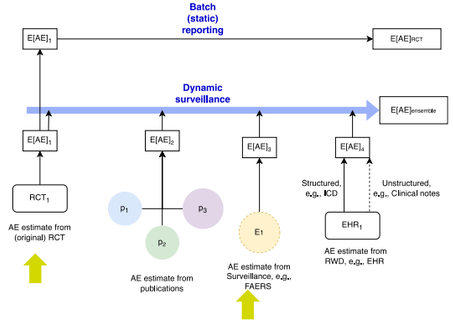
Background

- Can we improve our insight into patient risks in a treatment by leveraging consumer reported data along with clinical trials data ?
  - Viewing adverse events (AEs) in past clinical trials,
  - Viewing AEs reported by patients and providers in real-world
  - Analyzing this dynamic and more current data, thus augmenting product label info
- Following the approval of a pharmaceutical agent based on the outcomes of randomized clinical trials, the drug subsequently becomes the focus of additional investigative studies and post marketing surveillance.
- These studies aim to either validate or refine the therapeutic efficacy initially observed, evaluate the potential risks associated with drug-drug interactions, or explore the feasibility of extending the drug's indications for other medical conditions.
- Frequently, these subsequent studies rely on adverse event data gathered from the initial randomized clinical trials to delineate parameters for patient safety.
- Considerations of both, results from clinical trials as well as results from post marketing real world clinical settings (e.g. the FDA Adverse Event Reporting System(FAERS) provides a complete picture of the safety of a compound to inform patients about risks.

Methods

- Collect AEs data for a drug in market from two data sources among all other potential sources as shown in figure below:
  - From past clinical trials (aact.ctti-clinicaltrials.org) and from FAERS for Adalimumab (Humira).
- Accommodate for differences in data fields and structure of the two sources and analyze, given known caveats of both data sources. Identify common events and differences between both sources. Compare these two sources with product label info. Analyze FAERs data based on patient characteristic fields available in this source.



Results

- The time period for clinical trials AEs is 2000 to 2020, and the time period for FAERS cases is from 2003 to 2023 Q2.
- Among top seven organ system AEs reported in clinical trials, six of them are also among top seven in post-market AE reports, although the order is slightly different between the two sources, see Fig 1.1 and 1.2, and three of these are listed in the product label as well. While others listed in the label can be found in FAERS such as Neoplasms and hepatobiliary, some organ systems that stand out in FAERS are psychiatric, vascular, eye, ear, endocrine, reproductive system and breast disorders, pregnancy and perinatal conditions.
- FAERS also shows that female patients have consistently reported all top adverse events more frequently than male patients, given some gender-unspecified cases. This can be investigated further to determine any gender dependency in reactions to this product.
- Of the seven leading adverse event terms, both FAERS and clinical trials list Arthralgia and Headache. Clinical trials report Nasopharyngitis as the most frequent, while FAERS ranks 'Drug Ineffective'—a measure of efficacy rather than a reaction—as the top adverse event. This calls for a deeper investigation into the drug's effectiveness in the broader patient community. In FAERS, 'Injection Site Pain' is the second most reported, with Arthralgia following closely.
- The FAERS data base does not allow a direct calculation of AE rates as the denominator of all exposed subjects is not known but it provides information on reported events which can be used in the overall assessment of risks for patients. The FAERS AE percentages shown in figure 2.2 are based on the total number of cases reported.
- While majority of AEs in both sources are non-serious as shown in Fig 3.1 and 3.2, the number of serious events reported in FAERS increased from 2013 to 2022, when most of the indications had been approved and exposure could be assumed to be highest. The number of serious AEs in clinical trials was more initially in 2000 and decreased in later trials.

Conclusions

- Reviewing AEs reported in clinical trials alongside AEs from post-marketing surveillance helps to assess patient risks
- It is difficult to infer causality from observational data alone.
- It requires sensitivity to context and care in combining disparate data sources.
- There is scope for applying advanced technologies such as Machine Learning tools to learn more from both data sources to find patterns and clusters by patient characteristics, drug classes, and organ systems.

Clinical Trials

2000 to 2020

Top 7 organ systems (reaction groups)

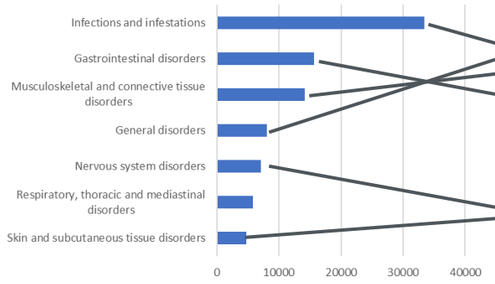


Fig 1.1

FAERS

2003 to 2023 Q2

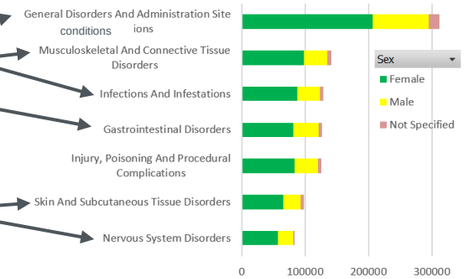


Fig 1.2

Top AEs and Deaths %

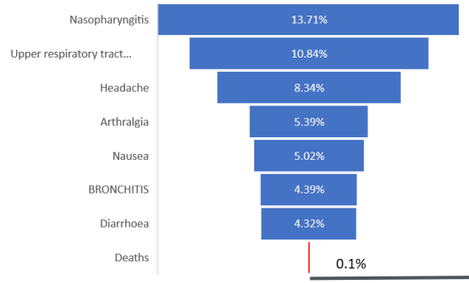


Fig 2.1

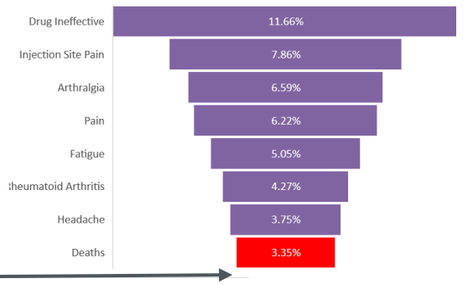


Fig 2.2

Event type by year of trial start date

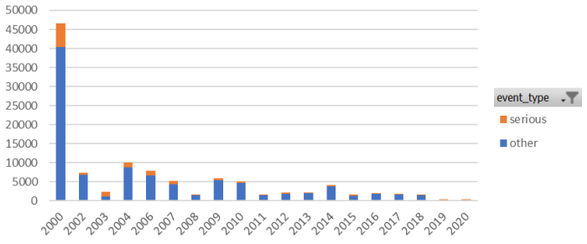


Fig 3.1

Outcome type by reporting year

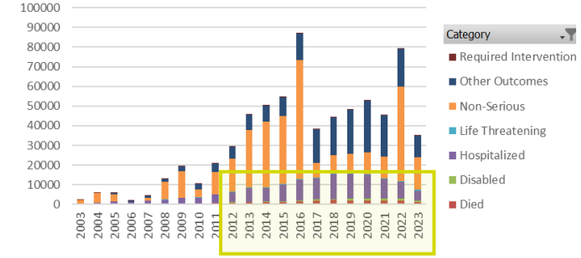


Fig 3.2

REFERENCES

FAERS public dashboard

AACT CTTI clinical trials database