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Next Level Vigilance & Safety:

Insights into the Transformative Potentials of AI & ML

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Executive Summary

Artificial Intelligence ("AI") and Machine Learning ("ML") are creating a buzz in the Pharmacovigilance ("PV") space because of their transformative potential to provide new and interesting insights, by processing big data in a timely, accurate, and cost-efficient manner, and promises to enable product innovations to better protect patients and the world. Yes, this IS a bold assertion, so let's break down this contention in a way that clearly explains how these technologies can be evaluated and leveraged for your operation.

Defining Terms

Artificial Intelligence is a becoming challenging term to pin down because, increasingly, it's applied across an exploding array of new approaches, applications, and products, but I like to think of it as:

> *The ability to train computers to do things that were, or are, being done by humans.*

To demystify this somewhat Orwellian description, let's consider just two applications already in our daily life: cars with lane assist technology, and security measures involving facial recognition. AI is being employed to accelerate data-driven processes affecting our daily lives in ways that were nearly unthinkable (to anyone other than science fiction authors and NASA engineers) even a generation ago.

Defining Terms

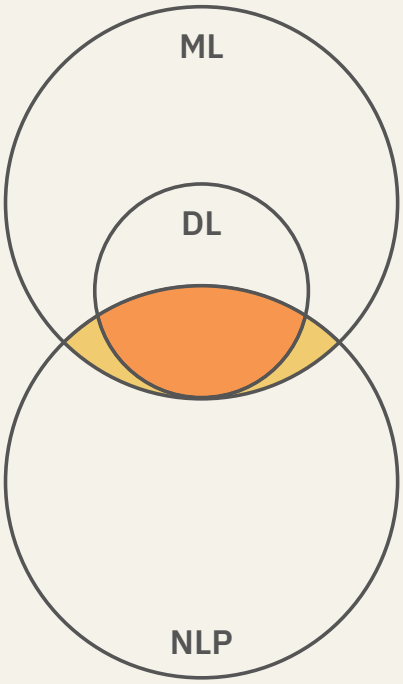
Pharmacovigilance can also benefit from AI—which promises to enhance human health via outcomes of product use—but it will require computers to deliver reliably better results than humans when using the same data. So, with this high of a bar, it makes sense that Artificial intelligence must rely on several subfields to actually facilitate true learning. There are three subfields to know about right now:

- **Machine Learning** ("ML") uses data, algorithms, and processes to mimic how humans learn without being explicitly programmed to do so. As the computer receives more data, it gradually improves its accuracy to predict outcomes. Although we won't cover them in detail here, there are 3 types of ML that are rapidly emerging and developing:
  - Supervised learning
  - Unsupervised learning
  - Reinforcement learning.
- **Deep Learning** ("DL") is a subset of ML that reaches a higher level of sophistication via focusing on pattern recognition in the same way that the human brain does. Speech and facial recognition are two examples of Deep Learning.
- **Natural Language Processing** ("NLP") - is broadly defined as software that automatically manipulates natural language, like human speech and text. Language translation and analysis of unstructured data are two types of applications driven by NLP programs.

These three sub-areas of AI can—and often do—overlap as depicted in **Fig 1**.

Pharmacovigilance can also benefit from AI — which promises to enhance human health via outcomes of product use.

Fig 1.



Defining Terms (contd)

Given the critical nature of computations demanded of AI, and its sub-areas, there is intense focus on monitoring its performance in mission-critical applications. Professionals charged with developing and monitoring AI-supported programs use performance metrics to objectively assess AI processes for quality and consistency.

One popular ***performance metric*** used to evaluate how well ML is performing is the ***F1 score***. The F1 score is a combination of precision and recall.

> **Precision** is the number of True Positives divided by the number of Total Predicted Positives (True Positives + False Positives). Precision can be thought of as a measure of exactness. Therefore, low precision will indicate a large number of False Positives.
>
> **Recall** is the number of True Positives divided by the number of real positive cases (True Positives + False Negatives). Recall can be thought of as a measure of completeness. Therefore, low recall indicates a large number of False Negatives.

The formula for the standard F1 Score is:

$$\frac{2*(\text{Precision}*\text{Recall})}{(\text{Precision}+\text{Recall})}$$

A strong PV system will be able to share or display its "confidence score" on each piece of extracted data, where it is located, and the algorithm(s) or approach(es) it used to obtain the confidence score. In addition, it is highly desirable for your PV system to be able to learn or improve as it receives more data and notifies someone within your organization when a new potential algorithm has been identified.

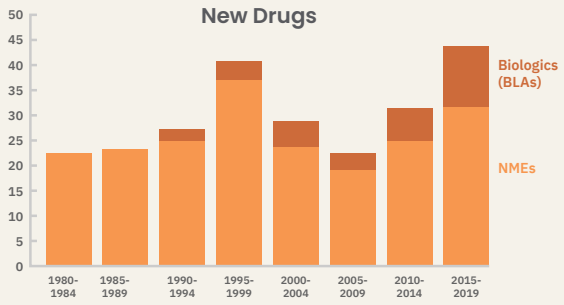
The Confidence Score is typically a number between 0 and 100 that indicates the system's confidence that it has accurately interpreted and parsed the data correctly. The higher the score the greater the system's confidence.

Drivers of Interest in AI

Market factors are compelling product developers and manufacturers to identify and employ novel ways to leverage AI technology as rapidly as possible because:

- Applying elements of Machine Learning to **review and identify suspected adverse reactions appearing in online forums** would reduce the volume of human hours being allocated to a daunting series of tasks. In line with ICH-E2D (GVP Annex IV), marketing authorization holders should regularly screen the internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions.[i]
- Companies involved with producing and marketing Rx products are seeing an increasing volume of unstructured data via digital platforms and electronic media. AI can be applied to **collect, organize, sort, and qualify large volumes of data more rapidly—and reliably—than humans**, which means faster recognition of signals and patterns to trigger reporting and (if necessary) remediation.
- The **increase in the volume of drugs being approved** over the last decade (Fig 2) is generating unprecedented volumes of data. Between 2010 and 2019, 38 new drugs were approved each year, on average. That is about a 60 percent increase compared with the previous decade.[ii]

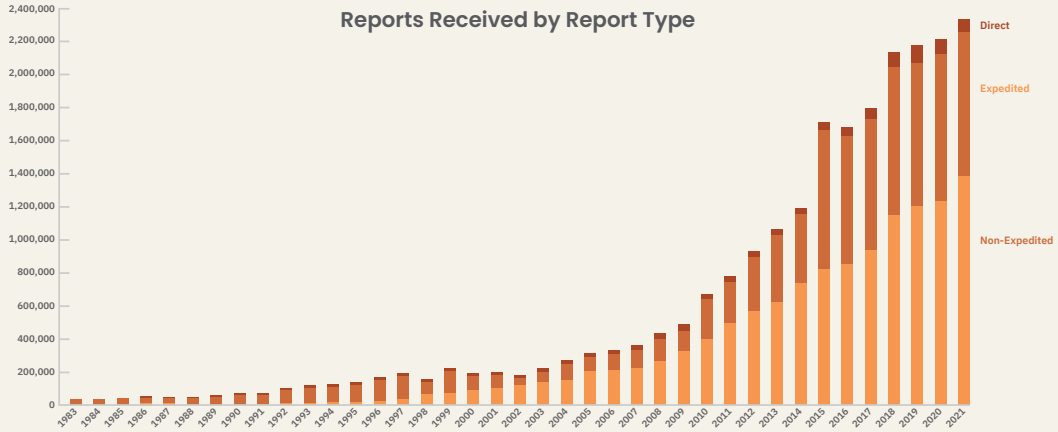
Fig 2. Average Annual Approvals of New Drugs by the FDA



From 2015 to 2019, the FDA approved about twice as many new drugs as it did a decade earlier. Biologic drugs make up a growing share of FDA approvals.

- The volume of Adverse Event cases has increased over the last 10 years driven by an increase in expedited reporting as can be seen in the following Table of FAERS data over the last 10 years as of March 31, 2022 (Fig 3).[iii]
- World population growth has increased the number of people taking medications which, in turn, increases the volume of data for detecting and reporting adverse events.

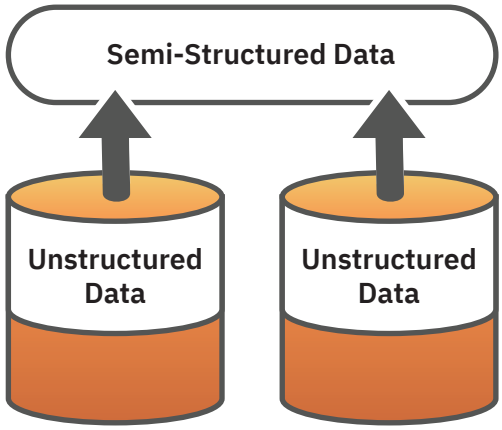
Fig 3. Average Annual Approvals of New Drugs by the FDA



How AI is Answering the Call of Duty in PV

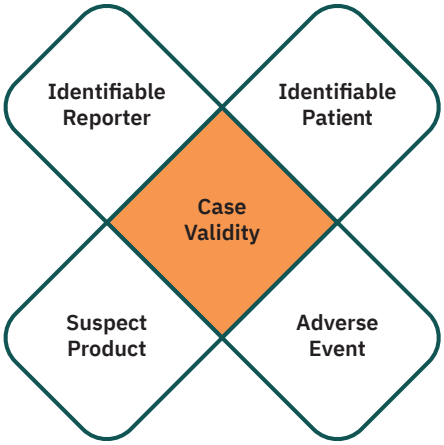
There are many areas where AI offers significant help to reduce errors, gain efficiencies, and better enable employees to focus on key data points. Here are just some of the areas in which companies are employing AI, and related techniques, in the PV process:

- **Case Intake** - The most time-consuming activity in case processing workflow is the intake step. AI technology can parse structured and unstructured data to extract significant amounts of useful case information, along with text-to-speech and OCR for emails, phone calls, faxes, or digital texts. Data extracted via AI has the benefits of improved quality and consistency, especially when processing large volumes of data. While not invariably 100% accurate, AI performance can improve over time with human intervention as it receives growing case volumes.

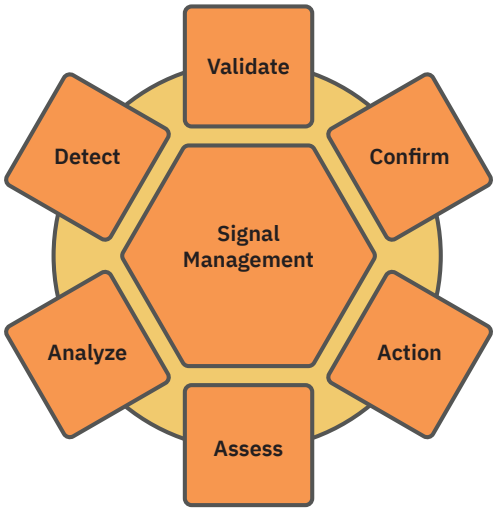


- **Literature Review** – AI can help the literature review by simultaneously reducing time and effort as well as the increasing the volume of findings. NLP, in particular, can be used to review literature abstracts and identify the abstracts that have the greatest probability of containing a valid ICSR (Individual Case Safety Report). A good system will provide end users with higher probability/scoring and bring their attention to the highest ranked articles. Once an article has been identified, the number of patients in an individual article can be identified and data can be extracted for each patient and a corresponding case created. A strong system will be able to display the literature article, identify where the case data was extracted, and attach the article to the created case.

- **Case Validity** – Once data is extracted, ML can help identify the four elements (Identifiable reporter, identifiable patient, adverse event, and suspect product) that characterize a valid case. It is important for a system to be able to produce high confidence in its case validity. Without this high confidence, there is a greater possibility of under--or over-reporting, as well as causing additional effort and reduced confidence among members of the user community.



- **Signal Detection** – Most companies today are using the standard approach with tools, data mining, and reports, to comb through data and identify potential signals. This is a time-intensive reactive process. AI and ML techniques will equip companies to be proactive in their search through large volumes of data in search of potential signals and actively refer them to appropriate teams. Staff will still be required to review the referred cases, and data, to confirm a true signal and whether to move them into their company's Signal Workflow.



A View to Future Use of AI in PV

AI is already having a profound impact on the performance of Pharmacovigilance programs, but we are still scratching the surface of AI's potential role in PV program impact and efficiency. Here's just a sample of the many areas in which AI can be applied:

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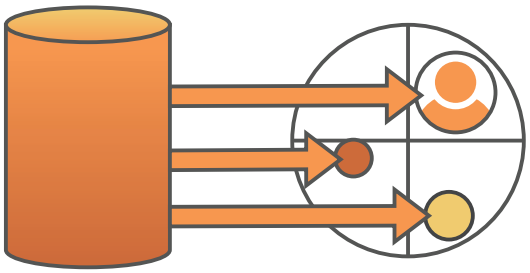
- **Reference Safety Information ("RSI") Evaluate** – Using current AI techniques, your system can read through any of the RSI literature (e.g., Investigative Brochure, Product Insert, Summary of Product Characteristics) to determine and extract the terms that should be used to assess expectedness. As the RSI literature changes, a company can rerun its algorithms and identify changes that need to be applied to its system.
- **Causality Assessment** – Some companies are already evaluating and piloting AI to identify the causality assessment. The problem that companies are seeing is that, in some cases, the F1 score is not high enough, simultaneously increasing manual reviews while decreasing confidence. As algorithms improve, and data increasingly runs through existing algorithms, this will continue to improve.
- **Touchless Workflows** – For certain types of cases with a high enough F1 and confidence score, it is feasible that a user would never have to see the case data. The system would automatically extract the data, process the case and, if required, report it to appropriate agencies. While some companies are piloting this for very specific low-risk non-serious cases. As AI technology improves and PV communities feel more confident with the technology, the volume of cases that would be "Touchless" will increase. This would have one of, if not the biggest, impacts on both the financials and time for processing data.
- **Predictive Patient Risk** – As regulatory agencies and companies receive more data AI can do one of the things it does best: analyze large amounts of data and identify significant patterns. AI could soon enable companies to identify which patients are at greatest risk for an adverse event to a prescribed medicine based on their genetic and biochemical characteristics.



Conclusion

This is an exciting time for professionals working in Pharmacovigilance as industry trends are decidedly in favor of exploring, adopting, and leveraging AI technologies to improve patient safety. There are substantial and measurable rewards for companies willing to take advantage of the functionality in today's leading systems and implement them effectively. While failures in the selection of a PV program, and the design of its implementation, can be frustrating and costly, a well-chosen and expertly implemented system can deliver substantial ROI in terms of timely case processing, enhanced accuracy, and data consistency.

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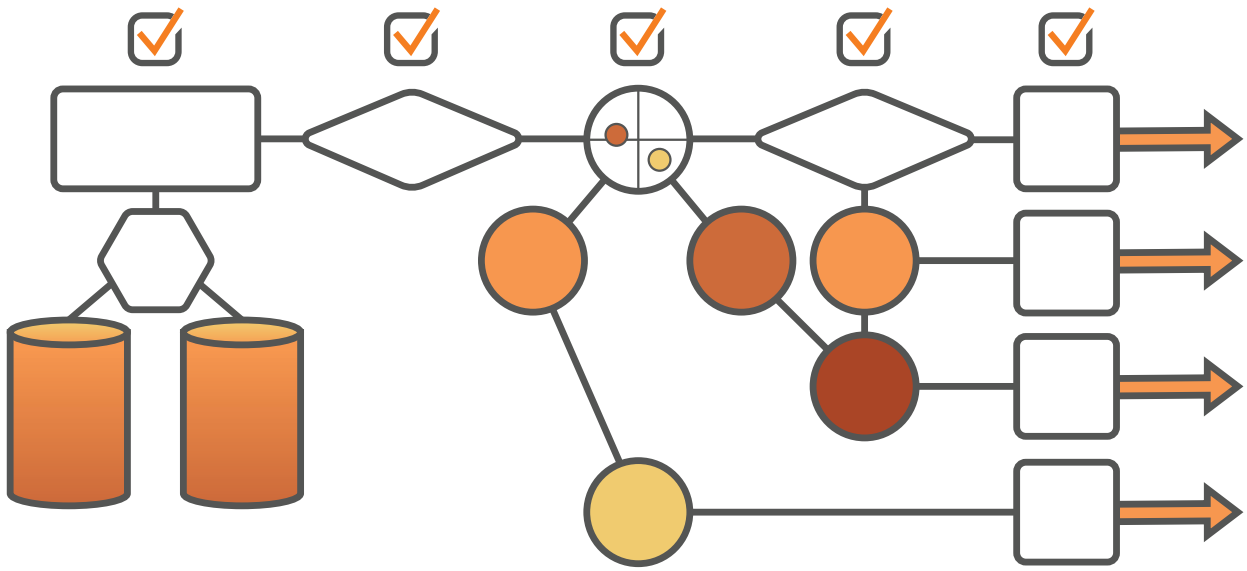
One challenge to the adoption of AI, however, is the limited experience among many company leaders. Today most companies rely on external experts to guide them through the process of selecting and implementing AI technologies. Unfortunately, many of these experts are associated with specific products and technologies which, by necessity, influence both their approaches and capacity for client-centric judgments in choosing and recommending solutions. These vendors' interests, and their products' capabilities, may or may not align completely with their prospective clients' objectives or their operational environment. While this does not necessarily mean that problems will occur in the post-implementation phases, it is likely to necessitate the dedicated focus of client staff to ensure acceptance and/or accommodation throughout the process—which can result in substantial time and reduced productivity.



About Astrix's PV Service

Astrix's Pharmacovigilance Service team is comprised of professionals who have direct expertise with AI systems. Since Astrix does not offer a proprietary PV or AI system and, therefore, is free from any financial incentive to recommend either a proprietary PV or AI system, the team employs a technology-agnostic approach to program selection and AI designs. The absence of a built-in bias toward a specific product enables a true client-centric—versus product-centric—approach assuring clients that all recommendations and reviews are performed with a focus on optimizing their PV system's design, implementation, operation, and outcomes.

References

i. European Medicines Agency, "Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)", 2017, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

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iii. US Food & Drug Administration, "FDA Adverse Event Reporting System (FAERS) Public Dashboard", https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

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