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Regulatory guidance and AI transparency: lessons learned from the drug safety industry

Bruno Ohana, June 2022

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We are a startup from Dublin, Ireland uniting deep expertise in pharmacovigilance and AI to deliver faster and safer processes for the industry, discover novel safety insights and help keep patients safe.

ADAPT

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

ENTERPRISE IRELAND
where innovation means business

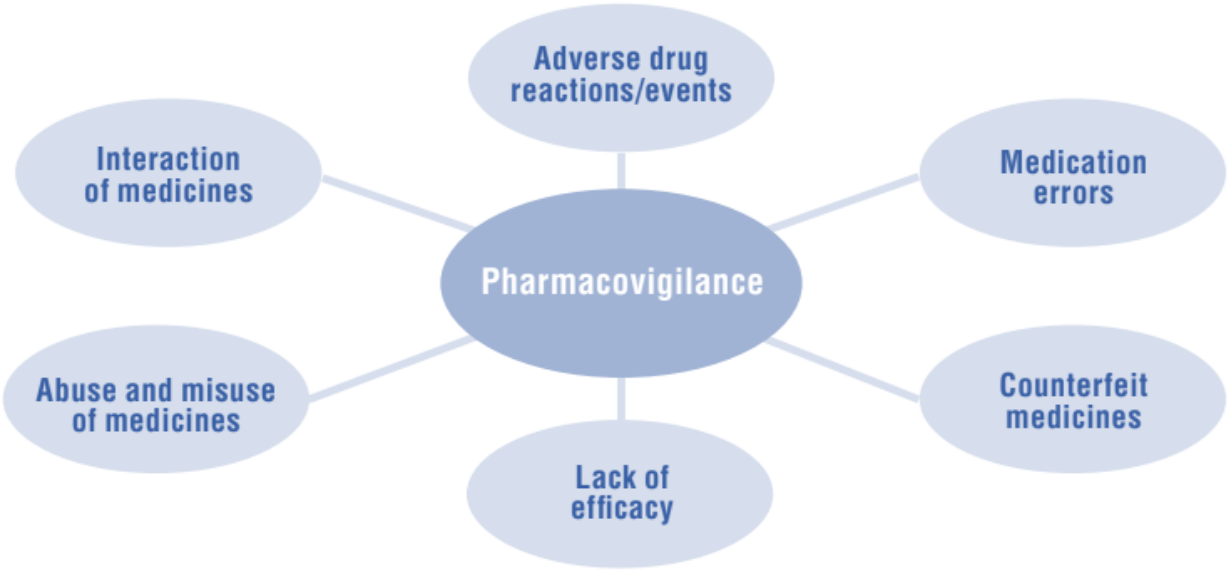
Crossref

Pharmacovigilance and drug safety

"Science and activities relating to the detection, assessment, understanding and prevention of drug adverse effects of any other drug-related problems"

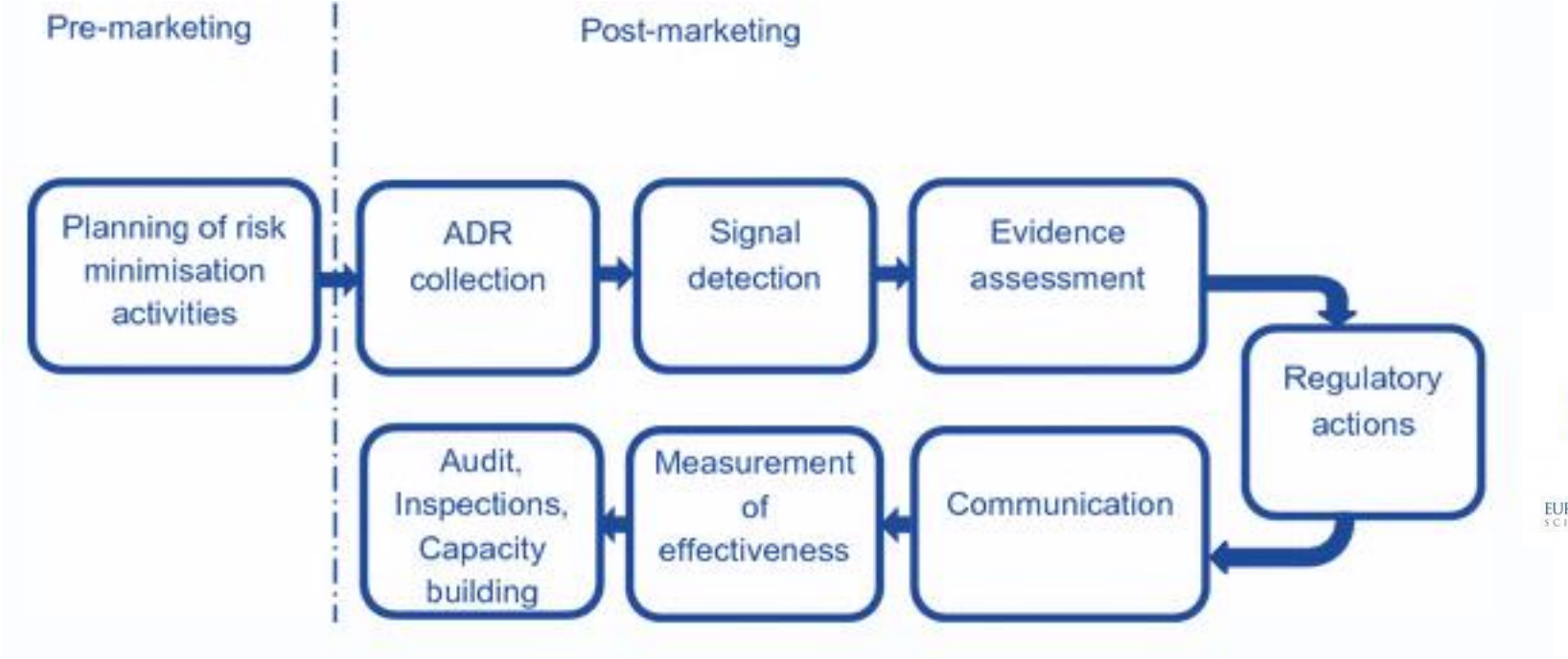
In the EU

- 5% of all hospital admissions
- €79B societal costs
- 197,000 deaths per year



Santoro et al (2017), Promoting and Protecting Public Health: How the EU Pharmacovigilance System Works, Drug Safety v.40

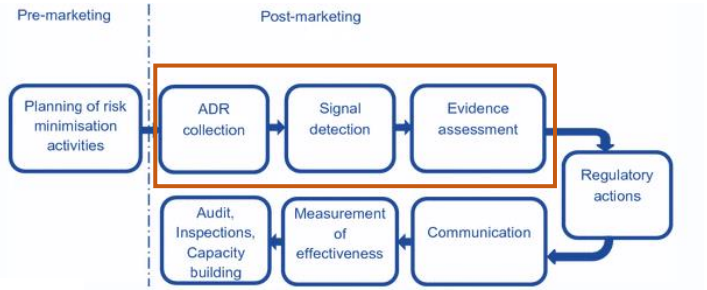
Pharmacovigilance framework

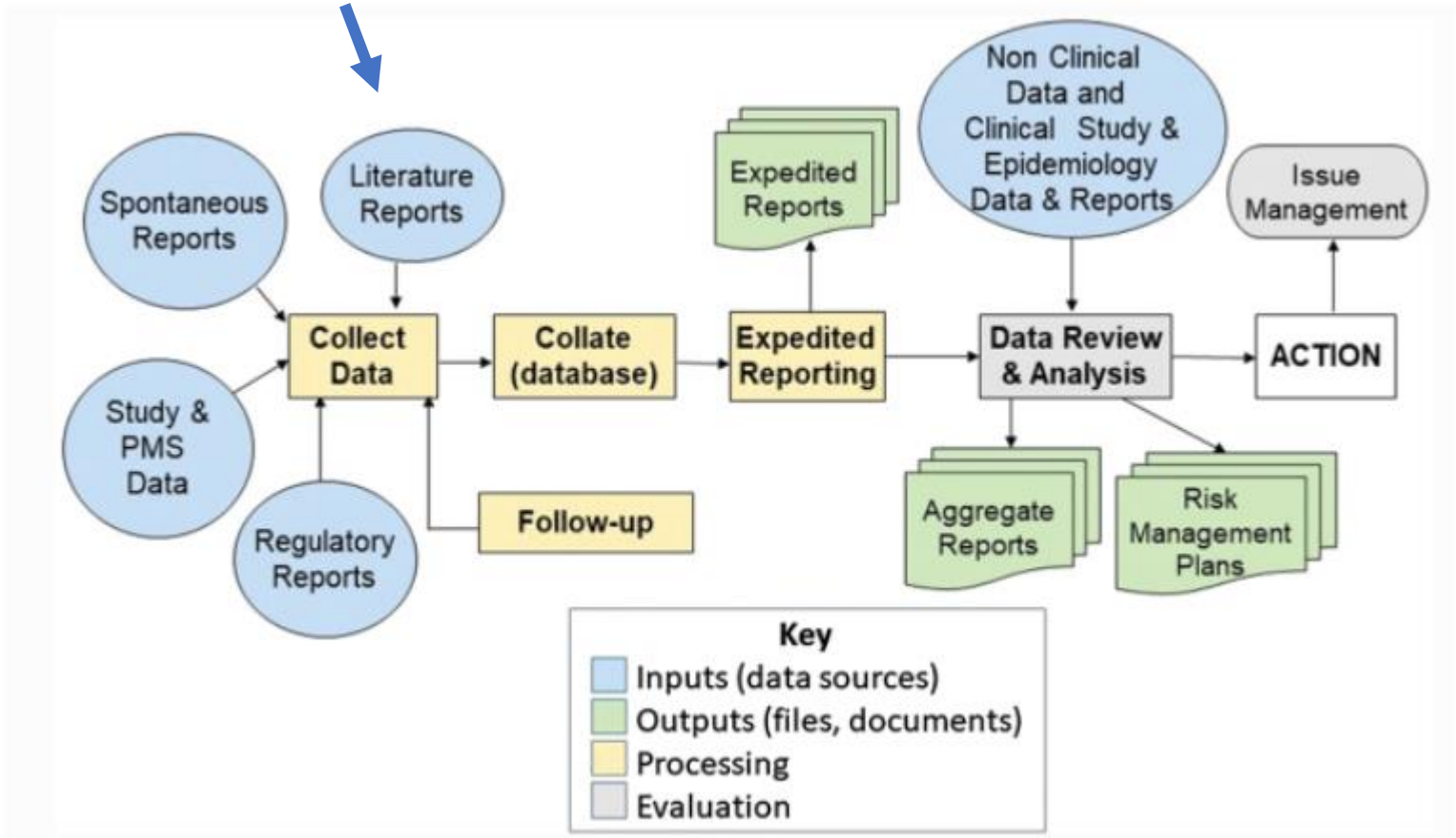


Shared responsibility model with oversight by regulatory agencies worldwide and the WHO

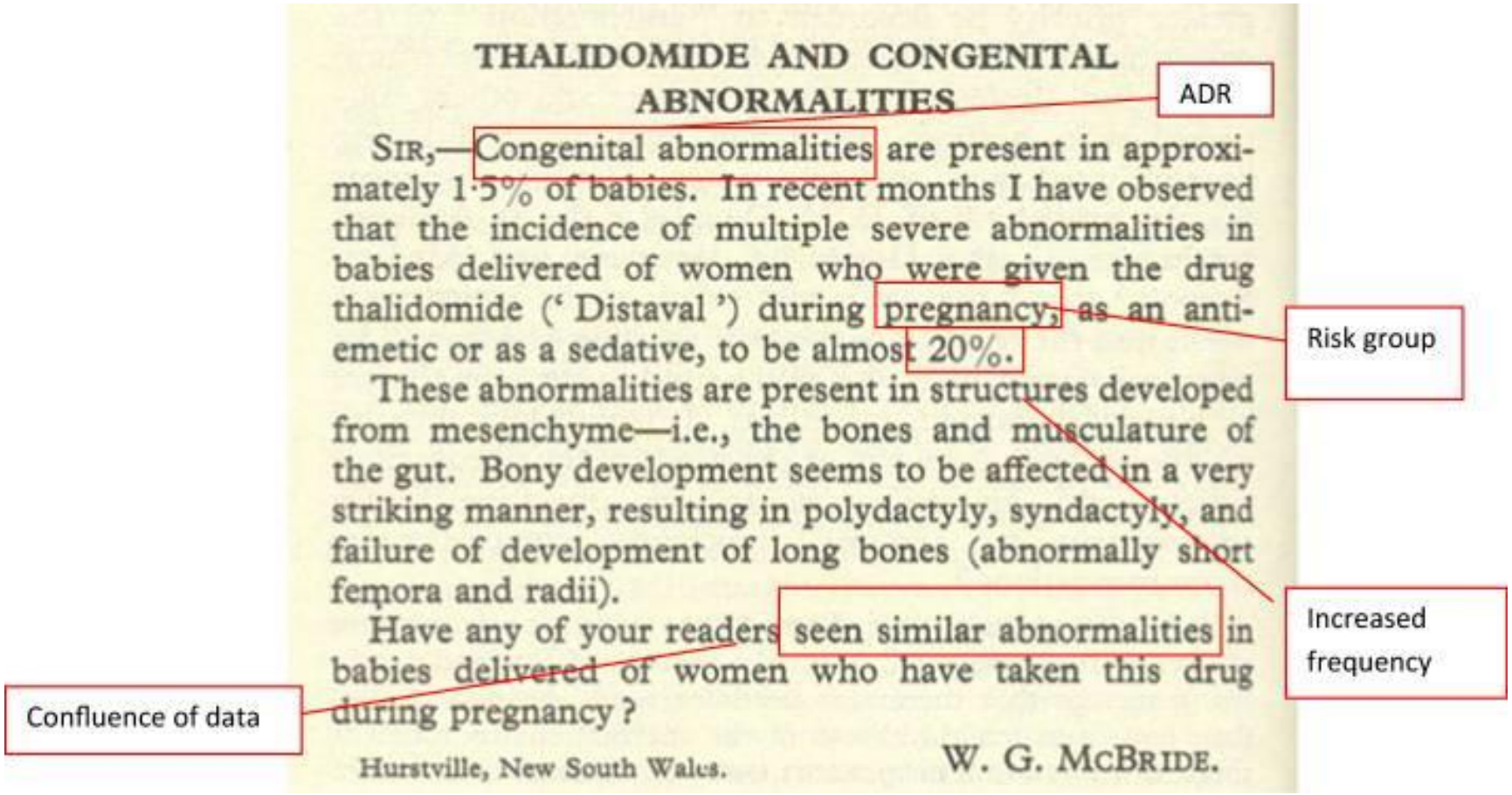
Santoro et al (2017), Promoting and Protecting Public Health: How the EU Pharmacovigilance System Works, Drug Safety v.40

Real world evidence pipeline





Literature monitoring



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

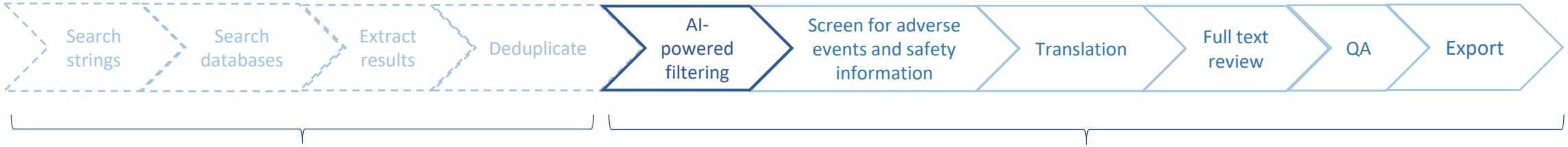
These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

Fornasier et al (2018) A historical overview over Pharmacovigilance, Int. Journal of Clinical Pharmacy v.40

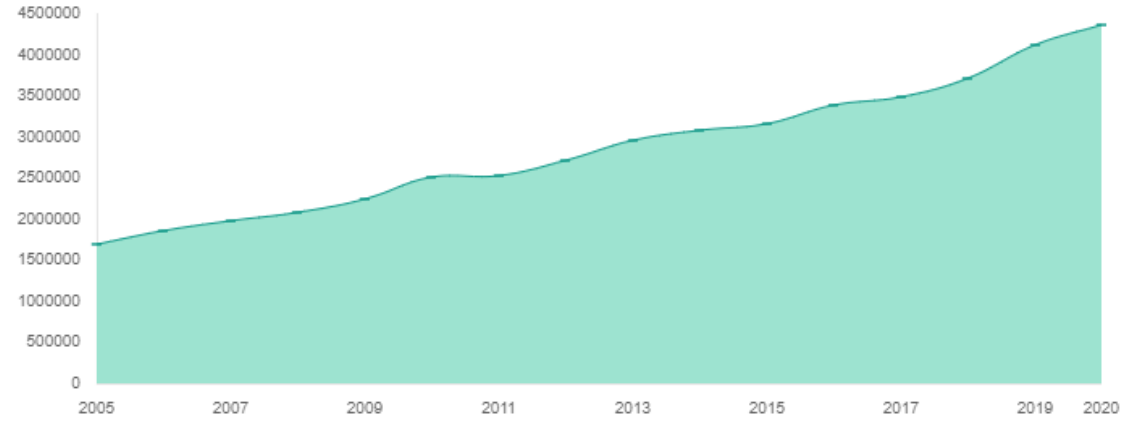
Literature monitoring of adverse events



Automated search on multiple databases with article de-duplication

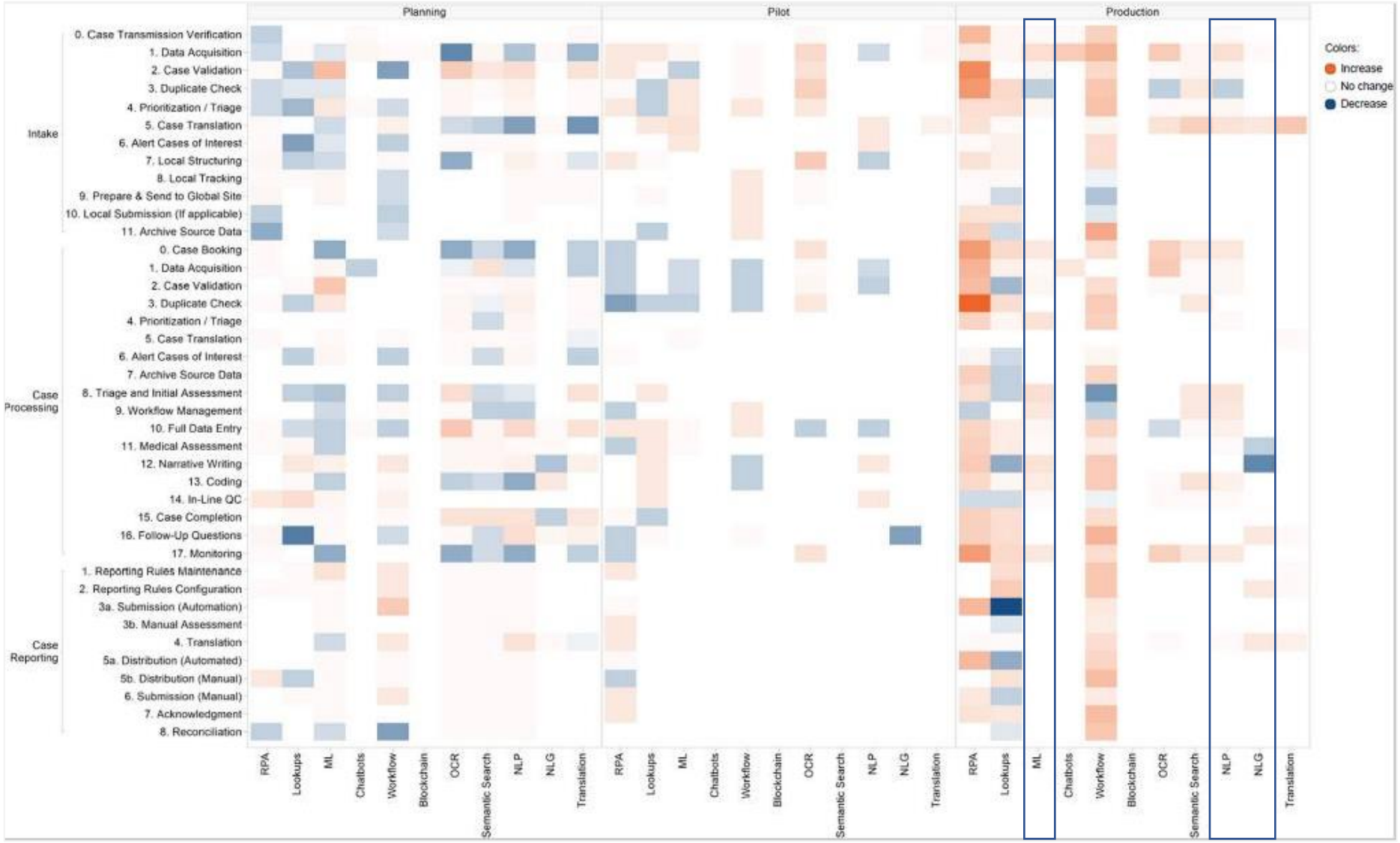
PubMed Crossref Dialnet DOAJ DIRECTORY OF OPEN ACCESS JOURNALS SciELO

AI ranking and filtering of results with integrated workflows to suit Aggregate and Individual Case Safety Reports, Signal and Risk Management



Scientific publication volume - Source: SciLit

AI/ML projects in pharmacovigilance (2022)



Kassekert et al (2022), Industry Perspective on AI/ML in Pharmacovigilance, Drug Safety v. 45

AI in pharmacovigilance: lots of interest but…

“Regulatory and compliance concerns one of the top reasons for not implementing AI”

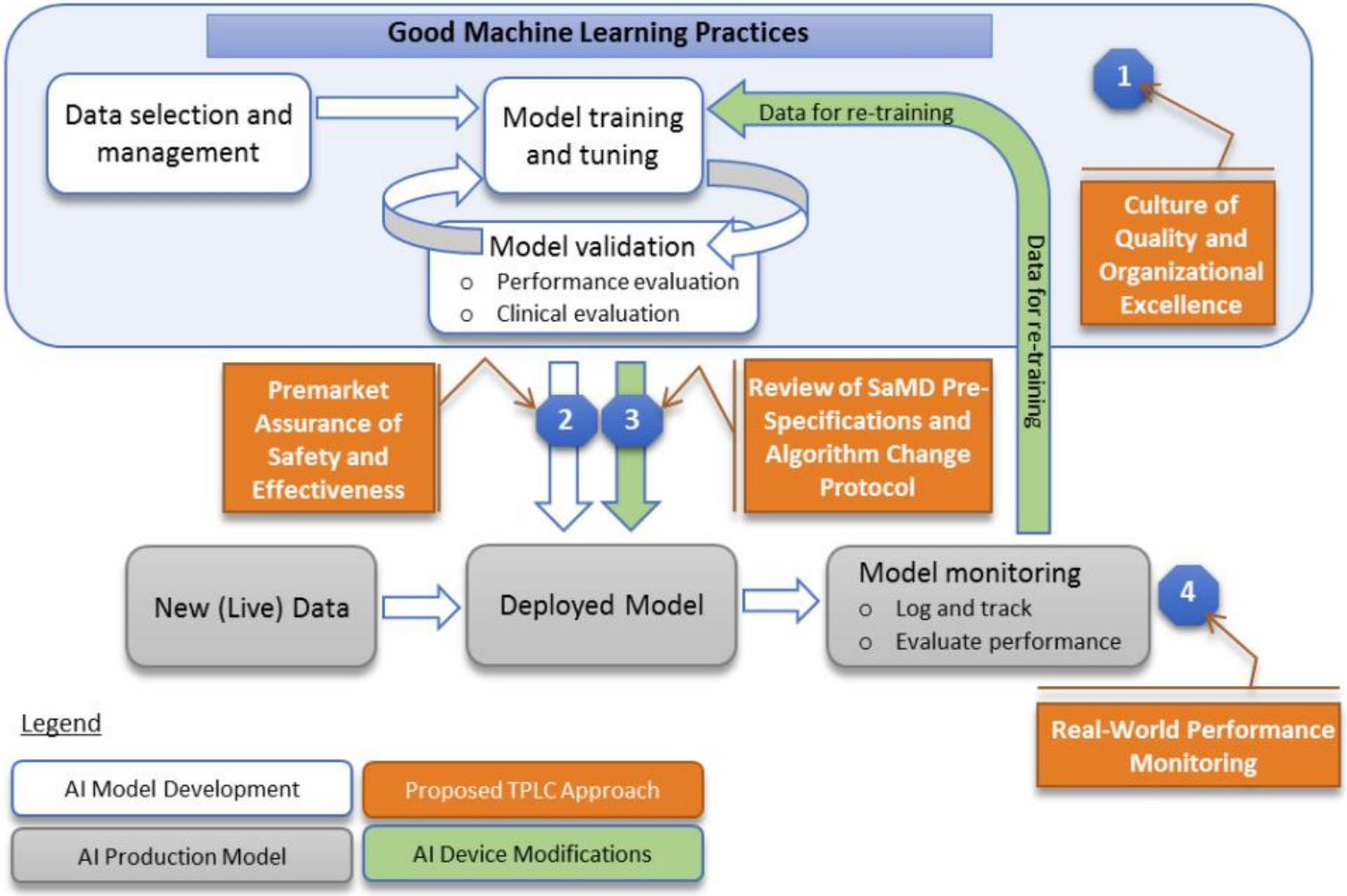
Kassekert et al (2022), Industry Perspective on AI/ML in Pharmacovigilance, Drug Safety v. 45

“Practical experience with stepwise implementation of AI […] will provide important lessons that will inform the necessary policy and regulatory framework to facilitate widespread adoption”

Ball & Dal Pan (2022), Artificial Intelligence for Pharmacovigilance: Ready for Prime Time?, Drug Safety v.45

Regulatory guidance: what does it look like?

FDA AI/ML-Based Software as Medical Device (2019, Revised 2021)



Regulatory guidance: what does it look like?

Good Machine Learning Practice for Medical Device Development:

Guiding Principles

October 2021

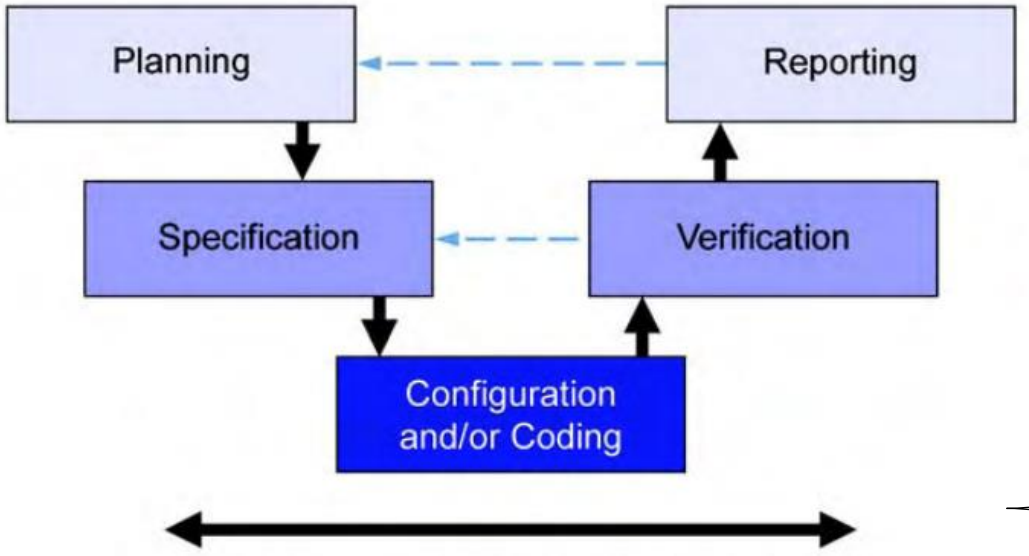
1. **Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle:** In-depth understanding of a model's intended integration into clinical workflow, and the desired benefits and associated patient risks, can help ensure that ML-enabled medical devices are safe and effective and address clinically meaningful needs over the lifecycle of the device.

2. **Good Software Engineering and Security Practices Are Implemented:** Model design is implemented with attention to the "fundamentals": good software engineering practices, data quality assurance, data management, and robust cybersecurity practices. These practices include methodical risk management and design process that can appropriately capture and communicate design, implementation, and risk management decisions and rationale, as well as ensure data authenticity and integrity.

Regulatory guidance: what does it look like?

Validating Intelligent Automation Systems in Pharmacovigilance: Insights from Good Manufacturing Practices [Huysentruyt K, et al, 2021]

Use **ISPE GAMP** as baseline framework → Update with specific considerations for ML



- Risk Management
- Change Management
- Vendor Management
- Training
- Incident Management & correction of errors
- DR

GAMP 5 – A risk-based approach to compliant GxP computerized systems, International Society of Pharmaceutical Engineering (ISPE)

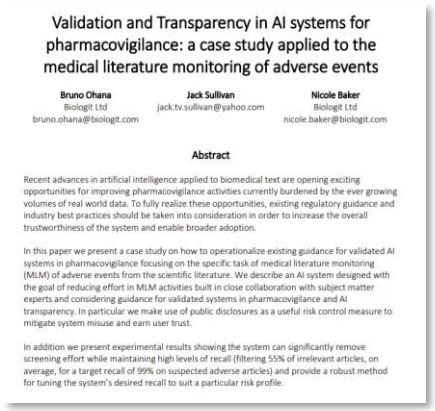
…and yet

“Regulatory guidelines for algorithm development and use in pharmacovigilance should be defined.”

ICMRA Report Aug-21

Making progress: key themes

- Traceability of key decisions & corresponding artifacts
- Total product lifecycle
  - MLOps
  - How things get done in your organization
- Documentation and transparency
- Multi-disciplinary effort



Validation and Transparency in AI systems for pharmacovigilance: a case study applied to the medical literature monitoring of adverse events

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Abstract

Recent advances in artificial intelligence applied to biomedical text are opening exciting opportunities for improving pharmacovigilance activities currently burdened by the ever growing volumes of real world data. To fully realize these opportunities, existing regulatory guidance and industry best practices should be taken into consideration in order to increase the overall trustworthiness of the system and enable broader adoption.

In this paper we present a case study on how to operationalize existing guidance for validated AI systems in pharmacovigilance focusing on the specific task of medical literature monitoring (MLM) of adverse events from the scientific literature. We describe an AI system designed with the goal of reducing effort in MLM activities built in close collaboration with subject matter experts and considering guidance for validated systems in pharmacovigilance and AI transparency. In particular we make use of public disclosures as a useful risk control measure to mitigate system misuse and earn user trust.

In addition we present experimental results showing the system can significantly remove screening effort while maintaining high levels of recall (filtering 55% of irrelevant articles, on average, for a target recall of 99% on suspected adverse articles) and provide a robust method for tuning the system's desired recall to suit a particular risk profile.

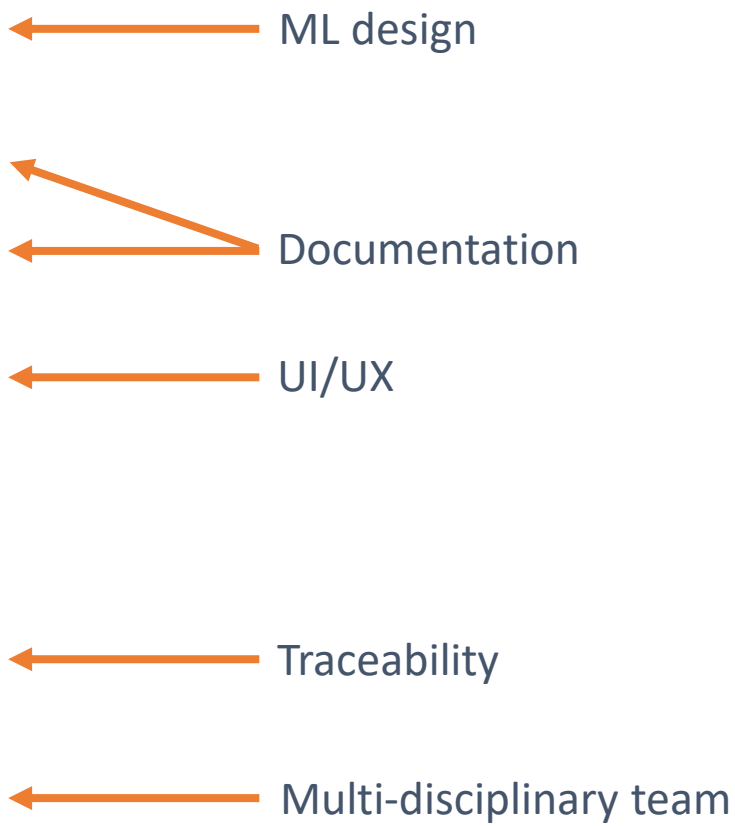
Validation and Transparency in AI for pharmacovigilance: a case study applied to The medical literature monitoring of adverse events.

Upcoming ICPE 2022 (Aug 2022); pre-print: https://arxiv.org/abs/2201.00692

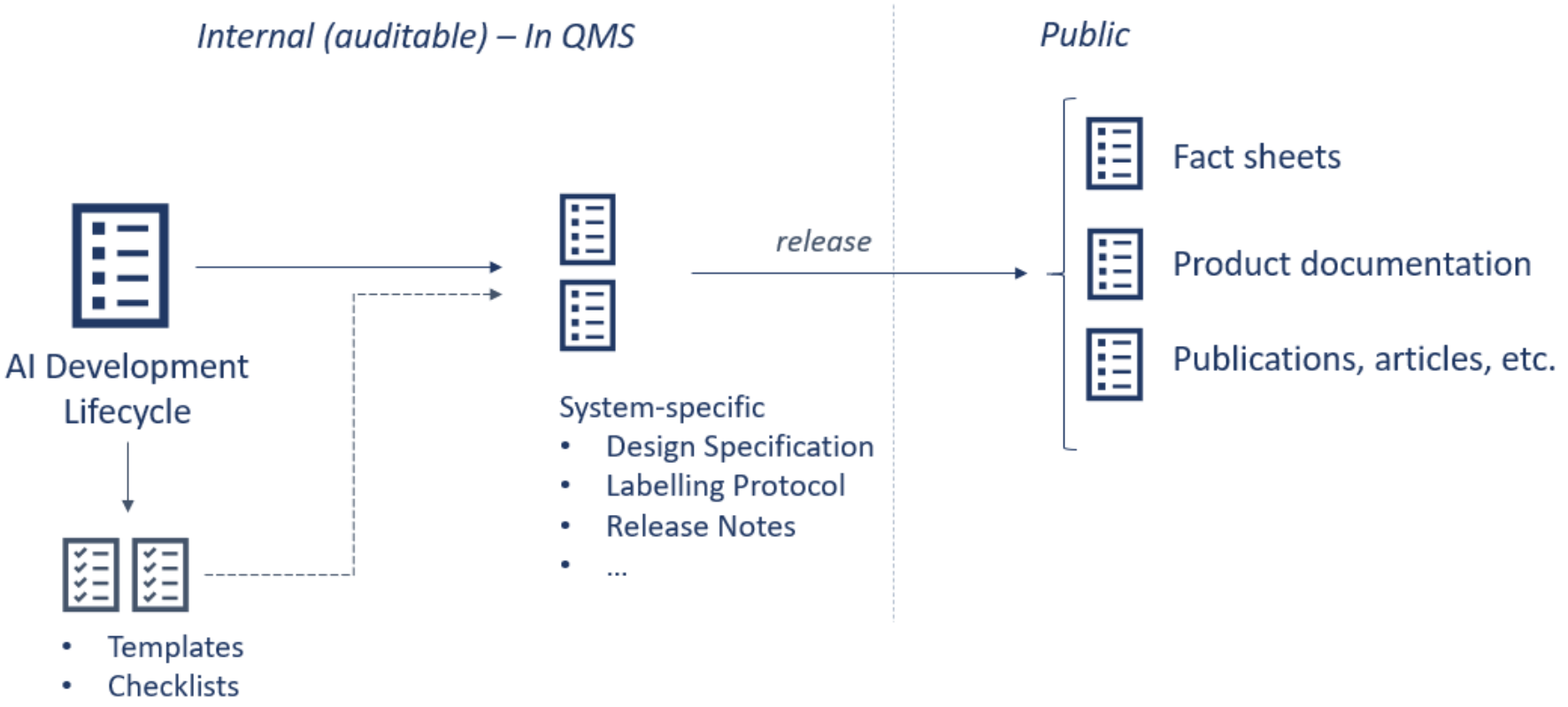
Risk-based approach to ML

Framing and consolidating guidance as risks and controls.

Intended use	The AI system is applied outside of its intended use and operating envelope. [6, 14]	Inference pipeline verifies input within operating envelope (rules stage). Publicly disclose intended use in the system's fact sheet.
Intended use	User over-confidence on predictions from the AI system, performance on data not seen in training is not available. [6, 18]	Publicly disclose performance metrics and justification in system fact sheet. System supports different levels of supervision to facilitate validation and adoption.
Intended use	Full automation derived from model predictions may hide incorrectly predicted documents from users. [6]	System supports diverse levels of supervision and validation, and does not require mandatory full automation. All historical results are auditable irrespective of prediction result.
Data	Inconsistency in labelling training data may lead to poor performance. [6]	Data labelling performed by pharmacovigilance specialists with MLM background; quality checked and monitored for inter-annotator agreement.
Data	Data used in training is not representative for the intended use, or is biased towards certain scenarios, leading to unexpected results. [6]	Training data composition, intended use and domains not covered in the training data are disclosed in the system fact sheet.



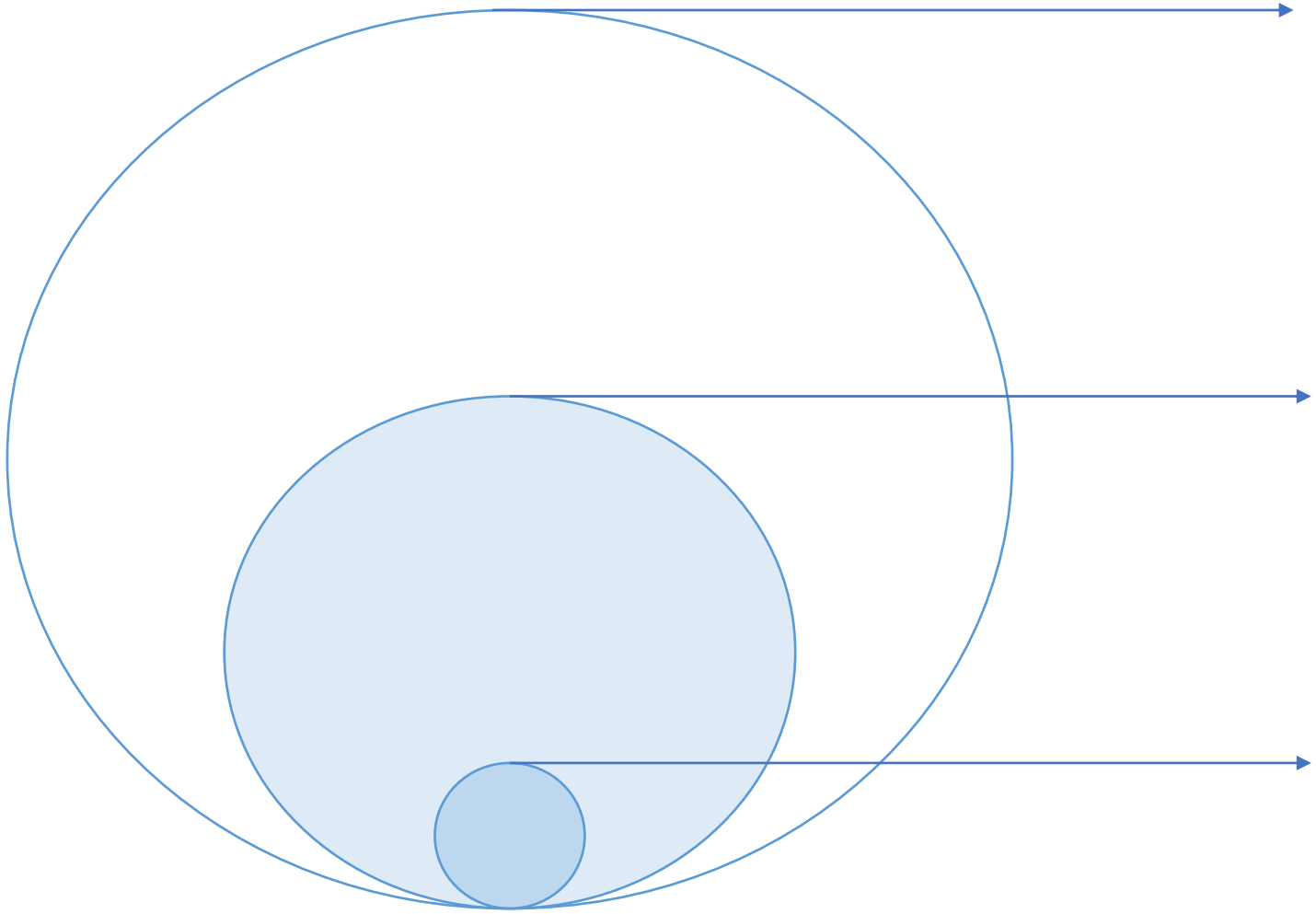
Product lifecycle / Traceability of key decisions



Traceability == Approval mechanisms

- Documents → Confluence + Approval Workflows (our Quality Management System)
- Code/data → git + DVC

ML design – A multi-disciplinary effort



All abstracts matching product

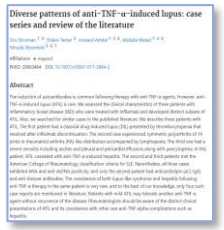
Suspected Adverse Event
Event may be explicit or full description may be in full text.

suspected AE

Identifiable patients
case, report, case series, or studies.

patient | suspected case

ML design – Risk controls



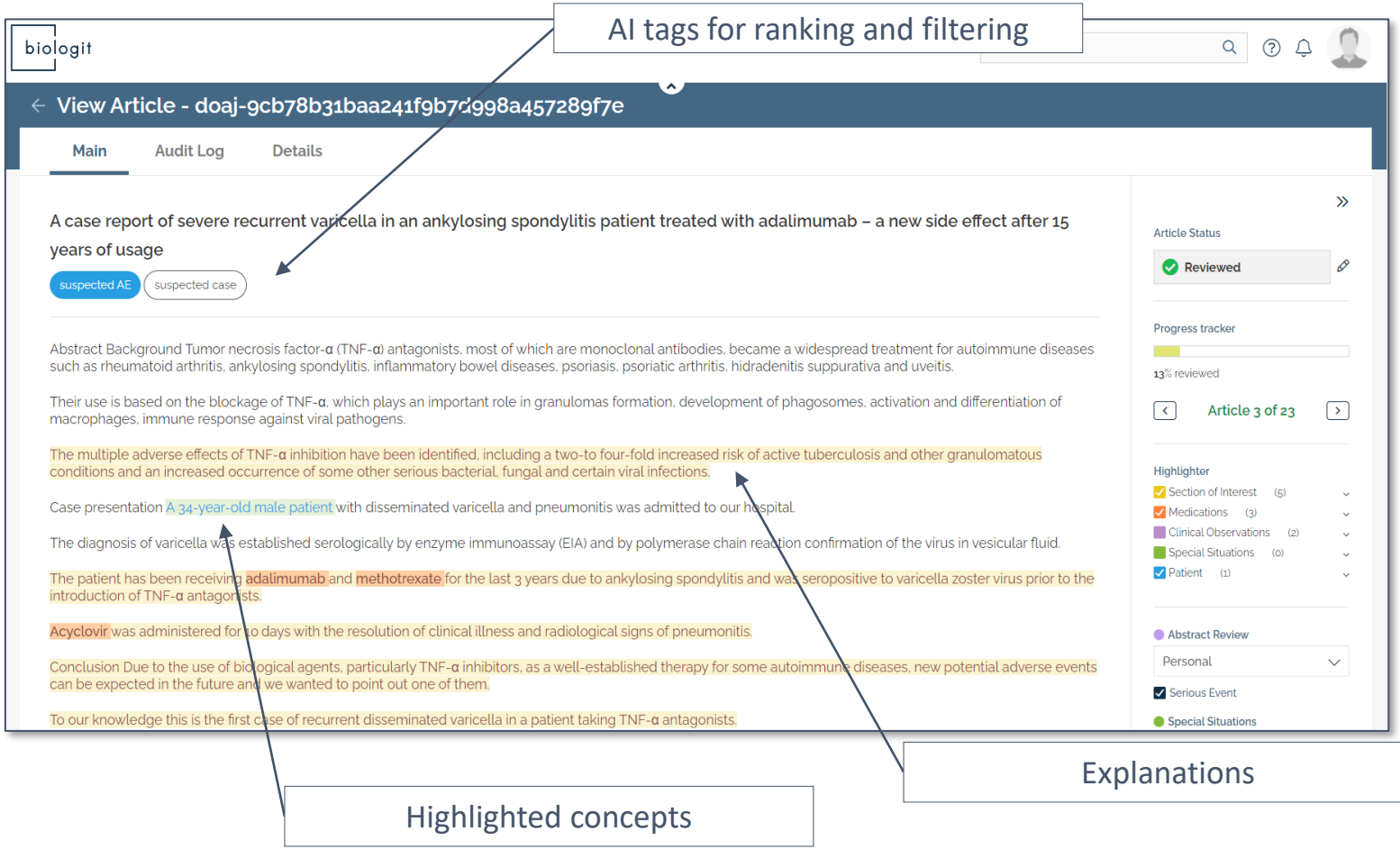
Pre-processing

Model inference

Rule-base

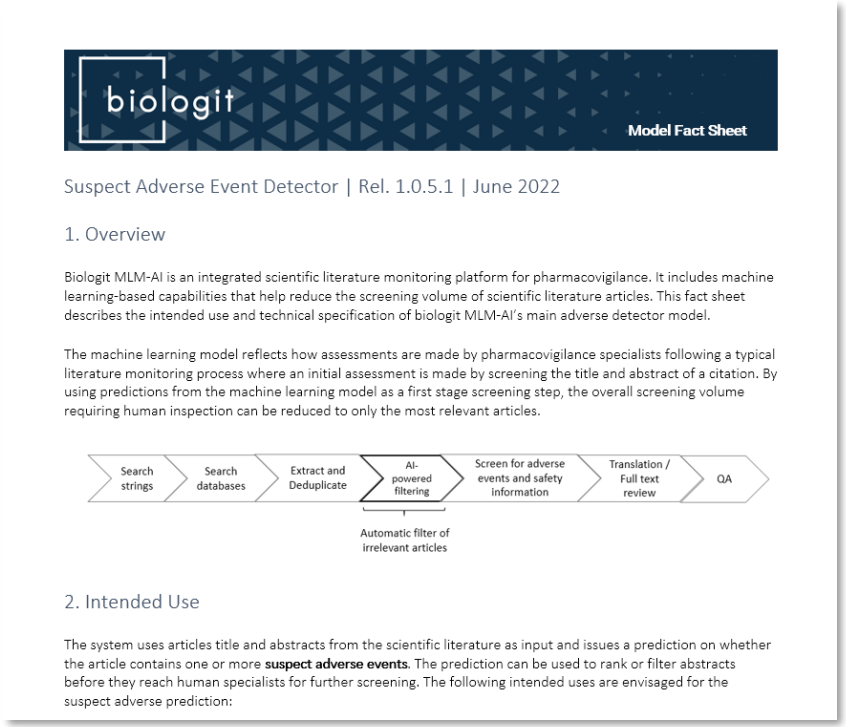
Explanations

Output



Documentation – Model Factsheet

"Where complex models are used it should be possible for someone to describe broadly how the system is working and the principles used for decision making" [Huysentruyt K, et al, 2021]



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Model Fact Sheet

Suspect Adverse Event Detector | Rel. 1.0.5.1 | June 2022

1. Overview

Biologit MLM-AI is an integrated scientific literature monitoring platform for pharmacovigilance. It includes machine learning-based capabilities that help reduce the screening volume of scientific literature articles. This fact sheet describes the intended use and technical specification of biologit MLM-AI's main adverse detector model.

The machine learning model reflects how assessments are made by pharmacovigilance specialists following a typical literature monitoring process where an initial assessment is made by screening the title and abstract of a citation. By using predictions from the machine learning model as a first stage screening step, the overall screening volume requiring human inspection can be reduced to only the most relevant articles.

2. Intended Use

The system uses articles title and abstracts from the scientific literature as input and issues a prediction on whether the article contains one or more **suspect adverse events**. The prediction can be used to rank or filter abstracts before they reach human specialists for further screening. The following intended uses are envisaged for the suspect adverse prediction:

Published with every release:

- Business problem
- Intended use & operating envelope
- Dataset description
- Model description
- Performance metrics

Arnold, Matthew, et al. "FactSheets: Increasing trust in AI services through supplier's declarations of conformity." IBM Journal of Research and Development 63.4/5 (2019): 6-1.

Biologit – Partnership on AI

PARTNERSHIP ON AI

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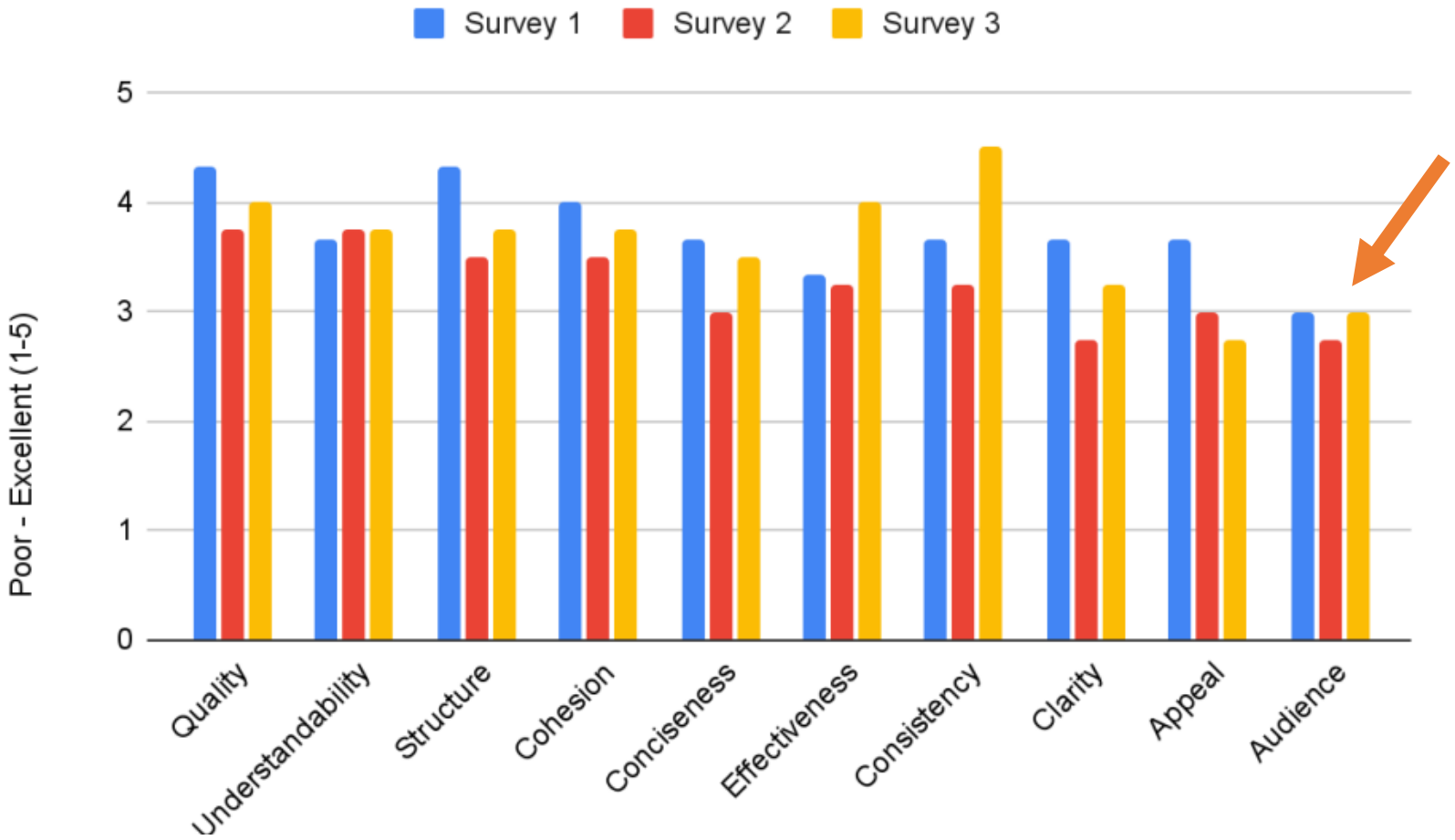
Paper + ML fact sheet, we're done right?? 😇

…nope.



Lessons

Regulatory guidance for AI

- Not a “one and done” effort
- Expected to evolve with ML best practices from ML industry and other high-stakes use cases

Compliance: Its is about the company as much as the product

- Good practices (demonstrably) implemented
- “Culture, processes and methodological rigor”, this is a journey ☺

Documentation practices

- This takes time. Get started soon!

Harvey and Gowda, 2019 “How the FDA Regulates AI”, Academic Radiology

The future

“Qualified Person” for AI ?

- A similar role already exists in pharmacovigilance (the QPPV)
- Personal responsibility over product safety and safety compliance

AI Regulatory Surveillance

- Systematic approach to stay current across all regulatory requirements

What can we learn from Good PV Practices?

- Tried and tested processes for large scale safety surveillance
- Risk management, Correction of errors, Business continuity, Validation…

Thank you!

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