Artificial intelligence in pharmacovigilance

CIOMS Working Group report Draft, 1 May 2025

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Abbreviations

4	ADR	Adverse Drug Reaction
5	AE	Adverse Event
6	AI	Artificial Intelligence
7	AIA	Algorithmic Impact Assessment
8	AIDA	Artificial Intelligence and Data Act (Canada)
9	ALTAI	Assessment List for Trustworthy Artificial Intelligence
10	ATC	Anatomical Therapeutic Chemical
11	BLEU	Bilingual Evaluation Understudy
12	CDC	Centers for Disease Control and Prevention
13	CIOMS	Council for International Organizations of Medical Sciences
14	CNN	Convolutional Neural Networks
15	CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
16	CSV	Computerized System Validation
17	EEA	European Economic Area
18	EHR	Electronic Health Records
19	EMA	European Medicines Agency
20	ETHER	Event-based Text-mining of Health Electronic Records
21	EU AI Act	European Artificial Intelligence Act
22	EU	European Union
23	FAERS	Food and Drug Administration Adverse Event Reporting System (USA)
24	GAMP 5	Good Automated Manufacturing Practice 5
25	GDPR	General Data Protection Regulation
26	GenAl	Generative Artificial Intelligence
27	GPT	Generative Pre-trained Transformer
28	GSD	Global Safety Database
29	GVP	Good Pharmacovigilance Practices
30	GxP	Good [x] Practices
31	HIC	Human-in-Command
32	HIPAA	Health Insurance Portability and Accountability Act
33	HITL	Human-in-the-Loop
34	HOTL	Human-on-the-Loop
35 36	ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

37	ICSR	Individual Case Safety Report
38	InfoViP	Information Visualization Platform
39	IRB	Institutional Review Board
40	ISIC	International Skin Imaging Collaboration
41	ISPE	International Society for Pharmaceutical Engineering
42	IT	Information Technology
43	KPI	Key Performance Indicator
44	LIME	Local Interpretable Model-Agnostic Explanations
45	LLM	Large Language Models
46	MAH	Marketing Authorisation Holder
47	MedDRA	Medical Dictionary for Regulatory Activities
48	MHRA	Medicines and Healthcare products Regulatory Agency (UK)
49	ML	Machine Learning
50	ML-DSF	Machine Learning-Enabled Device Software Functions
51	NIST	National Institute of Standards and Technology
52	NLP	Natural Language Processing
53	OECD	Organisation for Economic Co-operation and Development
54	ОТС	Over the Counter
55	PASS	Post-Approval Safety Studies
56	PD	Pharmacodynamic
57	PDMP	Prescription Drug Monitoring Program
58	PHI	Protected Health Information
59	РК	Pharmacokinetic
60	PPV	Positive Predictive Value
61	PSMF	Pharmacovigilance System Master File
62	PSUR	Periodic Safety Update Reports
63	PV	Pharmacovigilance
64	QA	Quality Assurance
65	RCT	Randomized controlled trial
66	RMF	Risk Management Framework
67	RPA	Robotics Process Automation
68	RWD	Real-World Data
69	RWE	Real-World Evidence
70	SARAH	Smart Artificial Intelligence Resource Assistant for Health
71	SHAP	Shapley Additive exPlanations
72	SME	Subject Matter Expert

CIOMS Working Group XIV: Abbreviations

73	SmPC	Summary of product characteristics
74	SOP	Standard Operating Procedures
75	US FDA	U.S. Food and Drug Administration
76	UTC	United Therapeutics Corporation
77	WHO	World Health Organization
78	xAI	Explainable Artificial Intelligence

80

Preface

81 The Council for International Organizations of Medical Sciences (CIOMS) has played a pivotal role in

82 the advancement of modern pharmacovigilance (PV) by developing guidelines that address ethical

and scientific aspects of drug development and safety. Notably, CIOMS has published guidance

84 documents that have supported a structured approach for the collection and reporting of adverse

drug reactions (ADRs) in addition to guidance on practical aspects of signal detection in PV, fostering

86 international collaboration and standardization in drug safety monitoring.

87 The thalidomide tragedy of the early 1960s exposed severe deficiencies in global drug safety

88 practices, highlighting the need for comprehensive data collection and international harmonization.

In response, the World Health Organization (WHO) established the Program for International Drug
 Monitoring in 1968, initiating efforts to share individual case reports between countries and

91 harmonize data practices. Building on these foundational efforts, the late 1980s and the 1990s saw

92 pivotal CIOMS reports like the *Monitoring and Assessment of Adverse Drug Effects* (1985) and the

93 International Reporting of Adverse Drug Reactions (1987), both by the CIOMS Working Group I, and

94 the Current Challenges in Pharmacovigilance: Pragmatic Approaches (1999) by the CIOMS Working

95 Group V. Subsequent CIOMS Working Group reports and the establishment of the International

96 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

97 aimed to address the fragmented approaches to drug safety identified decades earlier, providing a 98 framework for standardized adverse event collection and reporting in addition to signal detection

98 framework for standardized adverse event collection and reporting in addition to signal detection
 99 processes.

100 Advancements in technology have transformed PV, with artificial intelligence (AI) playing an

101 increasing role in healthcare. At this juncture, regulatory harmonization and transparency remain

102 critical to leveraging AI effectively, ensuring that data is reliable and that AI systems deliver accurate

and trustworthy results, while ensuring safe and responsible AI use.

As AI continues to evolve and impact biomedical research, its increased integration in and impact on
 PV practice is inevitable. AI's potential for transformative disruption, compels us to engage in critical
 discourse: how do we wish to see AI developed, validated, and deployed within this domain?

Since the CIOMS expert Working Group XIV on AI in PV was established in early 2022, there has been significant progress in the field, marked by the rapid development and widespread availability of generative AI (GenAI). While there is growing interest in exploring GenAI for PV applications, we

110 recognize the need to focus on its appropriate use, which brings specific challenges in highly

111 regulated domains such as PV, and we look to distinguish where possible and beneficial from general

112 issues of AI use. In light of this swiftly evolving context, this report aims to offer a general framework

113 of principles and good practices for developing and using AI in PV. Rather than offering technical

guidance, the aim is to ensure continued relevance as AI capabilities advance. The report focuses on

applications that are specific to PV or issues of particular importance to PV rather than general use

of AI, highlighting issues of high importance or priority to PV, even if they may not have widespread

117 attention or relevance in other contexts.

This report aims to provide guidance to those working in PV, in addition to organisations and
 vendors developing AI solution for the PV domain.

- 120 121 122
- 123

Executive summary

The CIOMS report on artificial intelligence (AI) in pharmacovigilance (PV) tackles a rapidly emerging 125 126 cross-disciplinary field that is at the intersection of PV, computer science, regulation, law, medicine, 127 human rights, psychology and social science. Consequently, just as with medicinal products, it is 128 important to establish the approved indications, posology, side effects, and warnings and 129 precautions for use of AI in PV. This must be clearly defined and understood by many people from 130 diverse backgrounds to propel research and practical implementation in an effective, safe and 131 responsible manner. The diverse pool includes PV professionals, researchers, and decision makers 132 working in PV in the industry, government, academia and software vendors, who are developing AI 133 solutions in the PV space, including signal management and all aspects of Individual Case Safety 134 Report (ICSR) processing. This report provides the requisite terminology and conceptual 135 understanding to actively engage in this space, either by participating in the applied scientific 136 research and public discourse, or by performing evaluations and making decisions at their respective 137 organizations.

- 138 Perhaps more than other Council for International Organizations of Medical Sciences (CIOMS) report
- topics, the potential adverse effects of AI in PV and related points are major elements of our key
- results because rapidly evolving, advanced and often opaque technologies may generate a rush of
- excited promotion and initial over-estimation of utility, observed in so called technology "hype
- 142 cycles", that does not correspond with the practical realities. There is a corresponding safety net of
- 143 core guiding principles for human protection elaborated by multiple organizations, through which AI
- PV must grow. This report provides a set of guiding principles and corresponding organizations that
 have elaborated each one. These principles form the bulk of the report: a risk-based approach,
- huwan oversight, validity and robustness, transparency, data privacy, and governance and
- 147 accountability. Key points to consider for these guiding principles are elaborated throughout the
- 148 report and summarized concisely below.
- Similar to prior CIOMS reports, this one benefits from a consensus position from multiple
 stakeholders, including those based in regulatory agencies, academia, and industry. The Working
 Group (WG) recognized that the field of AI is progressing so rapidly, that a prescriptive document
 would likely be quickly outdated. Instead, the WG decided to focus upon a set of common principles
- that were expected to be useful for years to come for PV professionals. PV is but one of a myriad of
- 154 Al applications that are now transforming many aspects of modern life. As such, this reports benefits
- as well from the increasing interest in AI by national governments, several of which have issued
 legislation and guidances not only on AI in drug development but also more broadly on the general
- 157 use of AI.

158 Risk-based approach. Integrating AI into PV processes needs to take into account the potential 159 inaccuracies and variability of AI algorithms, and corresponding impacts on the safety and well-being 160 of individuals and society. The level of risk, and corresponding intensity of required oversight, will be 161 a function of how high stakes the decision made by the AI is and whether the machine is intended to 162 be used in an unchecked stand-alone mode or with human-machine interaction. A sound risk-based 163 approach, in which the human oversight in the development and deployment of AI is commensurate 164 with these risks, enables organisations to make the most of AI capabilities while ensuring that 165 neither patient safety nor PV stakeholders are adversely affected. The risk-based approach applies to 166 the human oversight modalities, the validity and robustness strategy, the level of transparency, and 167 the efforts to uphold fairness and equity, and data privacy. The risk assessment should consider the 168 Al system itself, the context of use, and the potential impact and likelihood of risks materialising. A 169 risk-based approach should be reviewed at regular intervals and adapted if needed.

Human oversight. Human oversight supports performance optimization of AI in PV and increases
 trustworthiness and accountability. The extent and nature of human oversight for an AI solution

should be risk-based, incorporating quality assurance principles. The human oversight might be

- 173 "human-in-the-loop" meaning that the decision is the end results of a human-machine interaction,
- while in "human-on-the-loop", the machine autonomously makes a decision or otherwise returns a
- result that is checked by a human. Human oversight is necessary to define fit-for-purpose levels of
 performance for the intended task (i.e. validity). It involves predefining acceptable performance
- 177 levels, selecting appropriate data for model development in a realistic setting, an ongoing quality
- assessment process and retraining of the model as needed. Increased use of automation and AI in
- 179 PV will transform traditional roles and competencies, requiring appropriate change management
- 180 and training strategies.

181 **Validity & Robustness.** PV stakeholders must learn to critically appraise proposed AI solutions.

- 182 Performance evaluation must demonstrate acceptable and robust results for intended use under
- 183 realistic conditions. Such an evaluation should be both qualitative and quantitative, and a cross-
- disciplinary exercise and span a diverse range of relevant examples. Evaluations should use a
 sufficient representation of relevant data types to detect biases, promote adequate and
- generalizable performance across the intended deployment domain, assess usability, and identify
- 187 circumstances associated with underperformance. Enrichment strategies to obtain representative
- 188 test sets with high enough prevalence of the outcome may be required. Special care should be taken
- 189 to ensure that performance evaluation results generalize to real-world settings.
- **Transparency.** Declaring when and how AI solutions are used is critical for building trust among
- 191 stakeholders. The nature of AI solutions deployed for core PV tasks should be communicated,
- including model architectures, expected inputs and outputs, and the nature of human-computer
- 193 interaction. To fully characterize an AI solution's effectiveness and limitations, performance
- evaluation results should describe the scope and nature of the test set(s) used including reference
- standards and sampling strategies. Performance metrics should be relevant for the intended tasks,
- compared with relevant benchmarks, and complemented by qualitative review of representative
 examples of correct and incorrect output. Explainability is an important concept relevant to those
- examples of correct and incorrect output. Explainability is an important concept relevant to thosemodels whose internal decision pathways are so intricate and non-linear that they remain
- 199 inscrutable even to technically literate persons so called black boxes of the first kind. Explainable AI
- 200 are a set of techniques that "look under the hood" and return plausible hypothesis about these
- 201 pathways roughly how the black box arrived at its outputs. To be able to do this can be
- advantageous to model building/trouble shooting, building trust, establishing auditability and
- accountability, including providing a basis for a human to challenge an AI result that may be
- adversely impacting them, and regulatory compliance and scientific hypothesis generation.
- 205 However, explainable AI methods have limitations, and they only provide plausible hypothesis, but
- are no guarantee that the AI in fact used the hypothesized decision pathways.
- 207 Data Privacy. The ethical framework to evaluate the use of AI in PV is embedded within the standard 208 principles for research activities involving human subjects. A crucial principle for the use of AI in 209 routine PV is the sanctity of data privacy. With the increasing power of both the hardware and 210 software that power AI, there is a vast potential to build large, linked databases, and the potential 211 inherent in LLMs for patient reidentification. These may pose an ongoing challenge to the traditional 212 safeguards that protect data privacy. In this context, there are multiple opportunities to reveal 213 highly sensitive personal and health information to a broad, cross-disciplinary range of stakeholders 214 throughout the AI development and deployment workflow. Consequently, countries have been 215 enacting legislation and guidances intended to protect these data. PV professionals should recognize 216 that existing procedures used to assure regulatory compliance may need to be reevaluated due to 217 the heightened risks of GenAI to compromise data privacy.
- Fairness & Equity. Supporting fairness and equity, avoiding propagating or amplifying harmful explicit biases underserving certain subpopulations, discrimination and inaccurate results during
- explicit biases underserving certain subpopulations, discrimination and inaccurate results during
 model development and deployment are regulatory and ethical imperatives. Equity may be
- advanced by taking measures to assure that AI in PV returns outputs that are relevant to populations

- 222 anticipated to have exposure to the specific medicinal product being evaluated. Screening,
- identifying and excising explicit or potential bias when possible is key to mitigating risk, determining
- Al applicability and limitations, and defining acceptable performance. Scrutinize training and
- 225 performance evaluation of reference data sets for adequate representation and evaluate
- performance in relevant subgroups when possible. Inadequate reference data is often the cause of inadequate fairness and equity.
- **Governance & Accountability**. Robust governance and clear accountability are crucial for the success of AI initiatives. These principles help ensure that AI systems are used safely, responsibly and ethically, and in compliance of all applicable legal and regulatory mandates while fostering trust and transparency among stakeholders. Clearly defined roles and responsibilities are crucial to enable all stakeholders to understand their accountability and obligations in order to effectively oversee AI systems.
- , 224 As Alteshapler, evelves reverses and economicability from every sublex will need to be adopt
- As AI technology evolves, governance and accountability frameworks will need to be adapted. New
- risks and challenges will emerge, requiring updated principles and practices. Continuous review and
 adaptation are essential for staying ahead of these changes. This includes the adaptation refinement
 of the proposed grid for practical use.

238 Future considerations for development and deployment of artificial intelligence in

- 239 pharmacovigilance. Increasing deployment of AI in PV is expected to prioritize and accommodate
- rapid data collection, assessment and reporting for signal detection in real or quasi real time. This
- 241 may also be accompanied by a relative shift from warm-start to cold-start prediction scenarios (i.e.
- post-approval to early-stage drug development). This could fundamentally change the way we work
 to take advantage of these technological advances, for example, streamlining processes and causing
- changes in the wider healthcare environment and beyond, including patient privacy. We also expect
- to see increasing deployment of AI in PV in the clinic, where it will support primary, secondary and
- tertiary prevention of adverse drug reactions. The extent to which humans remain in or on the loop
- 247 will be determined by the nature of the task (e.g. routinized tasks versus those requiring expert
- clinical and scientific judgement), consistent with the elaborated risk-based approach, but it is
- possible that some AI-based expert systems will eventually develop refined medical and scientificjudgement.
- 251 It is critical that the guiding principles outlined in this report remain as core considerations, but they
- will need to evolve and adapt with advancements and application of AI in PV and medicine in
- 253 general. This is to ensure AI use in PV remains unbiased, transparent, and secure to prevent misuse
- or accidental harm. The appropriate human oversight, including regulatory and ethical safeguards,
- will be as crucial as the technological advancements being applied.

257 Chapter 1: Introduction

258 An artificial intelligence (AI) system is a machine-based system that, for explicit or implicit 259 objectives, infers, from the input it receives, how to generate outputs such as predictions, 260 content, recommendations, or decisions that can influence physical or virtual environments.¹ 261 Different AI systems vary in their levels of autonomy and adaptiveness after deployment. In the 262 context of pharmacovigilance, the use of AI systems and activities is aimed at enhancing drug safety 263 monitoring, patient safety and regulatory compliance. PV is practiced not only at pharmaceutical 264 companies, health authorities, drug monitoring centres and academia, but also in the clinic, and AI is 265 finding applications to PV in all these settings.²

266 An AI solution is designed to address specific objectives within PV. The overall AI solution could be

267 developed with one or many AI systems. An AI system encompasses not only the model itself but

also includes the components necessary for utilization including user interfaces and data processing

269 pipelines. At the core of these systems are AI models. These models utilize parameters to learn

270 relationships within data, enabling the systems to adapt and improve model performance over time.

271 Simpler AI systems, such as statistical methods for signal detection, have been widely utilized in PV

272 for decades.³ However, the past decade(s) have seen drastic improvements in AI capabilities,

273 particularly in image analysis and natural language processing. These advancements have resulted in

a significant increase in their use. In addition, tremendous and continual advances in computing

275 power and model architectures have enabled the development and aggregation of large electronic

- databases with potential for linkage. These have enabled the field of AI to be applied to an increasing
 number of disciplines, including the life sciences.⁴ Within the life sciences, AI is being applied to a
- 278 growing number of areas, such as drug discovery and development, medical imaging and diagnostics,
- genomics, precision medicine, public health, and healthcare delivery.⁵

280 Partly due to advances in AI, the pharmaceutical field is poised for rapid transformation across

281 clinical, regulatory and PV practices, aiming to streamline end-to-end processes to accelerate

282 product development and market delivery. Similarly, there is a growing emphasis focusing on

283 enhancing clinical and post marketing safety and risk management activities to enable proactive

- identification (or even prediction) of safety signals and benefit-risk evaluation. In the clinic, AI is
- being tested or deployed for early diagnosis (and thus secondary and tertiary prevention) of various
- adverse drug reactions. Examples include early detection of hydroxychloroquine retinopathy,⁶

287 digoxin toxicity,⁷ and drug-induced movement disorders in Parkinsons patients.⁸

These advancements leverage massive integrated datasets and inductive logic, enabling AI models to make informed decisions by utilizing accumulated data, rather than relying solely on explicit rules or human intervention. This approach facilitates the development of AI tools that provide new,

improved, or complementary solutions. A critical enabler for AI success within PV will be the ability to

- 292 link and analyze large volumes of heterogeneous data of varying quality from diverse data sources,
- such as electronic health records (EHRs), claims databases, registries, Internet of Things (IoTs), and
- connected devices. The ability to leverage health data can lead to potentially faster development of
- 295 new treatments, improved patient outcomes, and reduced healthcare costs, including the potential
- for unlocking novel, useful, and actionable insights that might not have been identified otherwise.
- 297 Hence, there is an acute need to effectively communicate the key importance of data access to
- 298 support patient safety outcomes.
- Incorporating AI into PV necessitates a thorough assessment of its potential benefits and risks,
 helping stakeholders understand its implications for existing practices. Given the rapid pace of

- change, this document does not prescribe specific uses for AI in PV but rather establishes and
 promotes guiding principles for utilizing AI including ML.
- 303 The start of systematic safety surveillance predated the advent of the internet and widespread
- electronic reporting capabilities. As such, it was a largely manual process that relied upon computing
 for purposes such as summarizing data.

ICSRs are a key component of PV and remain a cornerstone of post-market safety surveillance as
 they provide crucial safety information for an approved pharmaceutical product, which is important
 to mitigate patient harm when assessed within a broader signal management system.

- 309 The processing of ICSRs involves several steps: collection, triage, data entry, quality review, medical
- assessment, a with further transmission to other safety databases (e.g. regulatory authorities). As the
- number of product approvals and the patient exposure grow, so do the number of reported adverse
- events. The increased volume of ICSRs, coupled with stringent safety regulations, create significantchallenges in ICSR processing and compliance.
- 314 Once a signal is detected as a result of individual or aggregate analysis of adverse event reports, it
- 315 needs to be systematically investigated through sequential steps, which include signal triage,
- validation, and, based on scientific assessment, formal evaluation using independent data sets, such
- 317 as hypothesis-testing research studies.⁹ Such investigation must be conducted in an integrated,
- holistic fashion with all available scientific evidence and logic, offering wider opportunities for use of
- 319 Al for data insights (see Figure 1).
- 320 Traditional PV methods for analysis of adverse event reports include:^{10,11}
- Review of individual cases safety reports (ICSRs) or case series in a PV database or in published medical or scientific literature; and
 - Aggregate analyses of case reports using absolute case counts, simple reporting rates, proportions or estimated exposure-adjusted reporting rates.
- 325 While ICSRs are fundamental to PV, other data streams are also considered throughout the PV
- 326 lifecycle. These streams may be directly linked or conceptually related and include pharmacokinetic/
- pharmacodynamic (PK-PD) data, other real-world data (RWD), literature, and information from
 clinical trials.
- 329 Once safety concerns (important identified risks or important potential risks) are identified, it is
- 330 essential to communicate them appropriately to a wide range of stakeholders. This is achieved
- through documents such as aggregate reports, risk management plans, labelling information and
- 332 Dear Healthcare Professional communications (DHCPs).
- 333

323

- 334 [Figure 1]: Traditional signal management process
- 335 Source¹²



- 338 The COVID-19 pandemic has further emphasized the need for advanced methods in PV, as it has led
- to a significant rise in safety reports (see Figures 2 and 3).^{13,14} As public awareness and expectations
- regarding drug safety continue to rise, there is a greater demand for robust PV systems that can
- 341 effectively identify and mitigate potential risks associated with medications.
- 342
- 343

Figure 2: Growth over time of VigiBase, the World Health Organization global database of adverse event reports for medicines and vaccines

Source: VigiBase accessed April 2025.







354 Figure 3: Growth over time of the FDA Adverse Event Reporting System (FAERS) database

355 Source: Constructed using FDA FAERS database.¹⁵

358

359

Nevertheless, the challenges of establishing and maintaining progressively more complex PV systems
 in a globally diverse and evolving regulatory environment are increasing. There is a need to rethink
 traditional PV strategies based on existing pressures on the one hand (e.g. managing increasing

volumes and increasing regulatory complexity), and increasing and data sources on the other.

Technology solutions are already vital for the evolution of PV. While this notion of technology as a transformative enabler spans across all areas of product development, it is evident that applying innovative automation tools and processes to PV is no longer an option but an essential capability.

367 Rapid evolution of artificial intelligence

368 Traditional AI methods (e.g. K-means clustering, decision trees, support vector machines etc.) have

traditionally been tailored for specific tasks, primarily utilizing supervised learning techniques. In

370 contrast, deep neural networks such as BERT¹ have played a significant role in natural language

371 processing, where they are pre-trained on large datasets and subsequently fine-tuned for specific

372 applications delivering predictable outputs.

373 However, the landscape is evolving beyond this framework thanks to emerging technologies like

- 374 Generative AI (GenAI). GenAI models are trained on expansive and varied text corpuses, often
- incorporating phases of human reinforcement learning. These models can perform specific tasks
- 376 using sophisticated prompts, adopting zero-shot or few-shot learning techniques.

CIOMS Working Group XIV: Draft report for Public Consultation 1 May – 6 June 2025

¹ BERT: Bidirectional Encoder Representations from Transformers

377 Scope

378 This document aims to guide those working in PV in addition to organisations developing AI solutions

- 379 for the PV domain, such as medicinal product regulators, medicinal products industry professionals,
- 380 software vendors, international and national PV organizations, researchers, and health care
- 381 professionals.
- 382 This report proposes a broad framework of principles and best practices for integrating and
- implementing AI within PV, not technical guidance. Recognizing the rapid evolution and application
- of AI technology, the CIOMS Working Group XIV developed this document to guide the development
 and integration of AI tools into PV activities.
- 386 Our scope focuses on all aspects, direct and indirect, of the optimal collection, organization, analysis, 387 and communication of ICSRs from any source, including RWD, medical literature, randomized 388 controlled trials, and social media). Additionally, it includes productivity enhancers closely linked to
- 389 PV, such as tools that improve querying of safety databases¹⁶ or capabilities that enable faster, more
- 390 effective, or consistent data entry into a safety database which indirectly contributes to better safety
- 391 surveillance.¹⁷
- 392 The scope deliberately excludes broader healthcare data applications outside the direct purview of
- 393 safety, such as pharmacoepidemiology and other real world evidence study designs and conduct that
- fall outside the realm of ICSRs. Similarly, the general use of AI as a productivity enhancer, if not
- directly connected to PV activities (e.g. for email support), is excluded, as considerations may differ.
- 396 The scope has been intentionally limited to provide a practical guidance organised as principles and
- 397 their applications of AI in PV, rather than detailed guidance to ensure longevity. As AI is progressing
- 398 extremely rapidly, future opportunities and considerations are described in a later chapter.
- 399
- 400

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401

403 Chapter 2: Landscape analysis

404 Use of artificial intelligence in pharmacovigilance to date

AI may directly or indirectly impact all aspects of PV (see Figure 1: Traditional signal management 405 406 process). In this chapter, we discuss solutions that incorporate elements of AI and have been 407 developed or deployed for a variety of tasks across PV, focusing on those that have been 408 implemented specifically for PV or have accounted for attributes or features especially prominent in 409 PV applications. For example, AI solutions for general translation tasks are out of scope, but PV 410 specific translations, e.g. of adverse event reports, are in scope. Further, the landscape analysis 411 reflects the overall scope of the document, which focuses on collection, processing, and analysis of 412 adverse event reports. For this reason, research on AI methods to identify covariates for inclusion in 413 propensity score models for epidemiological studies are out of scope. Rather than seeking to provide an exhaustive enumeration, the aim here is to illustrate the range and variety of current applications. 414 415 Additional examples can be found in recent review articles.¹⁸ The reader is also referred to the many perspectives and commentaries that discuss the use of AI in PV^{19,20,21,22} and the cautionary notes that 416 have been provided.23 417

418 Adverse event reporting and capture

Al solutions have been proposed for a variety of tasks related to natural language processing of social

420 media content to identify references to (personal experiences of) medicine use and adverse events.

421 These tasks include identifying relevant posts,^{24,25} identifying relevant parts of such posts,²⁶

422 normalizing descriptions of adverse events or medicinal products within such posts to standardized

423 terminologies like MedDRA or ATC,²⁷ and classifying the relationship between adverse events and

424 drugs mentioned in the same posts.²⁸ Similarly, screening the scientific literature for adverse events

425 is an investigated AI application.²⁹

426 Individual Case Safety Report Processing

427 An area of ICSR processing where AI solutions have been in routine use by some organizations since

428 at least the 2010's is duplicate detection, which relates to the identification of multiple unlinked

429 records describing the same adverse event in a particular patient.³⁰ Duplicate detection methods

430 based on ML and probabilistic record linkage have been implemented for VigiBase,³¹ FAERS,³² and

431 EudraVigilance.³³ The use of natural language processing to improve duplicate detection by

432 extracting and incorporating information from free text has also been explored.^{34,35} Rule-based

433 methods are more widely used and would be easier to implement but do not perform as well.³⁶

Another area where AI has been used to support ICSR processing is in the encoding of information on adverse events^{37,38} or medicinal products³⁹ in standard terminologies based on verbatim fields and /

436 or free-flowing case narratives. Natural language processing has also been applied to extract relevant

437 information from case narratives and map it to structured fields^{40,41,42,43,44,45} and for ICSR

- 438 translation.⁴⁶ A major challenge is the lack of the data homogeneity⁴⁷ that could be improved by
- adhering to existing common data models and standards that have already demonstrated value in

the PV domain, such as the Observational Medical Outcomes Partnership (OMOP) Common Data

- 441 Model for longitudinal observational health data⁴⁸ and Fast Healthcare Interoperability Resources
- 442 (FHIR), a standard for health care data exchange, published by HL7[®], especially if they are extended
- 443 to support a broader spectrum of PV cases.^{49,50}
- 444 Several organisations who process large numbers of case reports have also automated repetitive,
- labour-intensive tasks using so-called robotic process automation (RPA) technologies.⁵¹ These
- 446 operate on the user interface of other computer systems like humans would.⁵²

447 Other applications of AI solutions during ICSR case processing include methods have been developed

- to help support triage incoming reports for human review,^{53,54} individual case causality assessment,⁵⁵
- 449 and automated redaction of person names in case narratives.⁵⁶

450 Signal detection and analysis

The earliest examples of real-world use of (simple) AI solutions in PV are from the late 1990s. At this 451 452 point, disproportionality analysis, first conceptualized in the 1970s,⁵⁷ began to be implemented as 453 part of triage algorithms to help direct the attention of PV specialists in their analysis of large national and international collections of individual case reports.^{58,59,60,61} Since then, various 454 455 incremental improvements have been introduced and evaluated including automated adjustment for confounding through e.g. regression,^{62,63} or propensity scores,⁶⁴ extensions to drug-drug 456 interactions,^{65,66,67,68,69,70} and other possible risk factors for adverse reactions.^{71,72} Methods to detect 457 adverse events associated with the production process or with substandard or counterfeit medicines 458 have also be explored.^{73,74,75} In addition, there have been efforts to develop predictive models for 459 statistical signal detection that account for other aspects of a case series, such as its geographic 460 spread and the quality and content of individual reports,⁷⁶ the time-to-onset of the reported 461 reactions,⁷⁷ or a combination of e.g. Naranjo scores and the proportions of reports on a drug-adverse 462 event combination coming from healthcare professionals and marketing authorization holders, 463

464 respectively.78

465 Natural language processing has been applied to mine regulatory information,⁷⁹ scientific literature,

466 and clinical notes^{80,81,82,83} for information on already known/unknown and potentially serious adverse

- 467 effects. This may support and streamline decision making, especially during early signal assessment
- and prioritization.
- 469 Some published AI-based signal detection exercises provide tantalizing glimpses of how elegant AI
- 470 solutions may uncover truly novel adverse events.⁸⁴ At the same caution is warranted in that highly
- technical and elegant methods may be associated with overly-optimistic interpretations of, and
- 472 corresponding messaging about, the results, which may disseminate widely.⁸⁵
- 473 Several organizations have developed predictive models for ICSR prioritization to assess causality
- 474 associations between drugs and adverse events⁸⁶ and/or inform a regulatory action.⁸⁷ These can be
- used to prioritize reports for human review during signal assessment and/or case processing.
 Semantic search has been developed for case narratives to support signal detection and
- 477 assessment^{88,89} and there have been efforts to provide machine learning-based decision support for
- signal validation⁹⁰ and to automatically visualize relevant information on case reports to facilitate
- 479 human review during signal assessment.⁹¹ Machine learning has been used to help estimate the
- 480 proportion of patients with a genotype associated with drug toxicity based on the phenotypical
- 481 manifestations reported in ICSRs.⁹²
- 482 Applications of unsupervised learning have been developed to support signal detection and analysis,
- 483 especially seeking to bring together reports describing similar or related adverse events. These
- 484 include network analyses of adverse events (and to a lesser extent drugs)^{93,94,95,96,97} cluster analysis of
- 485 adverse event reports,⁹⁸ and data-driven derivations of semantic representations of adverse events
- 486 and drugs.^{99,100}
- 487 Datasets with information about drug side effects and indications such as DrugBank¹⁰¹ and SIDER,¹⁰²
- 488 as well as those with information on pharmacology and chemical structures such as Bio2RDF,¹⁰³ have
- 489 been leveraged to enhance PV signal detection and analysis, ^{104,105} or derive knowledge graphs that
- 490 can serve as downstream inputs for AI-based predictive signal detection.¹⁰⁶

491 Early applications of generative AI in pharmacovigilance

- 492 Early applications of generative AI in PV have started to be explored. Researchers have applied large
- language models to a variety of PV tasks and reported their experiences. Examples to date include
- use of LLMs to simplify the patient communication from a regulatory authority,¹⁰⁷ summarization for
- ⁴⁹⁵ drug labelling documents,¹⁰⁸ named entity recognition in scientific literature and social media,¹⁰⁹
- 496 search of drug safety documentation,¹¹⁰ Q&A for drug labelling,¹¹¹ PV context-aware generation of
- 497 SQL code¹¹², and drafting follow-up letters to reporters.¹¹³
- 498 However, the landscape is evolving beyond this framework thanks to emerging technologies like
- 499 GenAI. These models, developed from deep neural networks with up to hundreds of billions of
- 500 network parameters provided with vast and opaque large text corpuses, give rise to boundless
- number of multi-modal inputs and outputs (see Figure 4), therefore deciphering useful from
 misleading outputs for the end user can become a challenge. The non-deterministic and 'black box'
- 503 nature of such algorithms as well as the lack of ability to fully understand training can make
- 4 developing and maintaining trust potentially harder as well as the ease of communicating such to
- 505 external parties. As noise and biases may infiltrate the results, leading to potentially unreliable and
- 506 misleading conclusions, necessitating guidance on how these technologies should be used
- 507 appropriately in PV is needed where societal expectations are greater.

508 Figure 4: Multi- modal input models

509 Source: Variation of submitted article to Therapeutic Advances in Drug Safety



510

511 Examples of deployed AI solutions

512 Much of the research and development of AI solutions for PV to date has been experimental, with 513 either no real-world deployment yet or only limited experimental use, for example in the form of 514 pilot studies. However, Error! Reference source not found. presents examples of AI solutions that have been adopted for routine use in PV by various PV organizations and are described in the public 515 516 domain. The deployment of AI solutions by pharmaceutical companies may on the other hand to a large extent be based on software vendor implementations, which are not described in the public 517 518 domain. Table 1: Examples of deployed artificial intelligence solutions in pharmacovigilance 519

- 520 *described in the public domain*
- 521 Source: CIOMS XIV working group 522

Al solution	Pharmacovigilance context / database				
Automated coding of medicinal products	VigiBase ¹¹⁴				
Duplicate detection	FAERS, ¹¹⁵ VigiBase ¹¹⁶				
Automated triages of individual case reports	Swedish Medical Products Agency ¹¹⁷ , pharmaceutical companies ¹¹⁸				
Automated triages for quantitative signal detection	Databases of various regulatory authorities, international organizations, and pharmaceutical companies				

Predictive models for quantitative signal detection	VigiBase, ^{119,120} Netherlands pharmacovigilance centre Lareb ¹²¹				
Adverse event cluster analysis for signal detection and assessment	VigiBase ^{122,123}				
Literature surveillance for safety data	EudraVigilance Netherlands pharmacovigilance centre Lareb ¹²⁴				

523 **Regulatory considerations**

524 Introduction

Since 2017, countries around the world have been developing national AI strategies in order to adapt
 to technological advancements and their impact on society and the economy (OECD).¹²⁵ Countries
 have developed different regulatory frameworks and guiding principles to ensure the ethical use and

528 trustworthiness of AI systems, and legislation of AI are being implemented (i.e. EU AI Act, AIDA, US

529 Algorithmic Accountability Act and Executive Order: Promoting the Use of Trustworthy Artificial

530 Intelligence in the Federal Government) (OECD).¹²⁶ In addition, there have been published reflection

and discussion papers on the use of AI in medicinal products by the EMA and FDA, as well as a draft

532 guidance on AI use to support regulatory decision making for drug products by the FDA.

533

534 *Guiding Principles for AI in Pharmacovigilance*

535 There are numerous published guiding principles for safe and responsible use of AI by governments,

regulatory bodies and international organisations such as the WHO and OECD, that have been

537 reviewed by the CIOMS Working Group XIV. These publications all define guiding principles and

recommend best practices for safe and responsible AI use in regulated fields; however, the majority

of these publications were not developed specifically for PV. Furthermore, it should be

540 acknowledged that some discretion was used to establish the guiding principles by the various

541 organizations, as some of the principles were described in conjunction with other principles.

Nonetheless, these principles can be applied to the field of PV. The table below provides an overall
 comparison of the guiding principles, and a non-exhaustive description of the principles is presented

543 comparison of the 544 in Appendix 2:

546 Table 2: Comparison of CIOMS Working Group XIV guiding principles for artificial

- 547 intelligence across regional and country government institutions, and international
- 548 organizations
- 549 Source: CIOMS Working Group XIV
- 550

	Examples of regional - and country government institutions', and international organisations' principles								
Principle	EU ^{127,128}	Australia ¹²⁹	Canada ¹³⁰	Singapore ¹³¹	UK ¹³²	US ¹³³	PAHO ¹³⁴	WHO ¹³⁵	OECD ¹³⁶
Human Oversight	~	✓	~		~	~	√	~	~
Validity & Robustness	~	✓	~		~		~	~	~
Data Privacy	~	√			\checkmark	\checkmark	~		
Transparency	~	√	✓	√	\checkmark		~	\checkmark	√
Accountability	~	√	~	√	\checkmark	\checkmark	~	\checkmark	√
Societal well- being	~	~		√			~	~	~
Environmental Well-being	~	~						~	~
Fairness & Equity	~	~	✓	~	~	~	✓	~	~
Explainability	~	√		√	\checkmark	\checkmark		\checkmark	√
Safety	~	√	√		\checkmark	\checkmark		\checkmark	√
Governance	1				√			~	

551

552 EMA Reflection Paper on the Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle

553 On September 9, 2024, the European Medicines Agency finalized its Reflection paper on the use of AI 554 in the medicinal product lifecycle.¹³⁷ The reflection paper addresses the use of AI/ML in the safe and 555 effective development, manufacturing and use of medicines.

EMA advocates a risk-based approach for the development, deployment and monitoring of AI and ML tools throughout the system lifecycle. The paper uses the terms 'high patient risk' for systems affecting patient safety and 'high regulatory impact' for cases with a substantial impact on regulatory decision making. It is expected that applicants/marketing authorisation holders (MAHs) and developers of AI and ML systems will perform a regulatory impact and risk analysis. The level of

- scrutiny of the AI and ML systems will be dependent on the assessment of risk level and regulatoryimpact.
- 563 The paper provides technical and regulatory considerations on the use of AI and ML throughout the
- ⁵⁶⁴ lifecycle of medicinal products, from drug discovery and development to post-authorisation settings.
- 565 Specifically for PV, the paper foresees that AI/ML tools can effectively support activities such as
- adverse event report management and signal detection, in line with applicable GVP requirements.
- 567 Applications within PV may allow a more flexible approach to AI/ML modelling and deployment than
- other domains, for example, to improve severity scoring of adverse event reports and signal
- detection. It is, however, the responsibility of the MAH to validate, monitor and document model
- 570 performance and include AI/ML operations in the PV system, to mitigate risks related to all
- algorithms and models used.

- 572 Generally, the applicant or MAH is responsible for ensuring that all elements of the AI and ML
- 573 applications (i.e. algorithms, models, datasets, and data processing pipelines) are fit for purpose and
- 574 comply with GxP standards and current EMA scientific guidelines. Member State data protection
- 575 authorities are responsible for the supervision and monitoring of data protection compliance of
- 576 Al systems. Applicants or MAHs and developers are recommended to engage with EMA on
- 577 experimental technology, especially for AI and ML models that may have a high impact on the
- regulatory decision making.¹³⁸ 578
- 579 The EMA is planning to develop further guidance on the use of AI in the medicines lifecycle, 580 including in PV.¹³⁹
- 581 FDA Discussion Paper on Using artificial Intelligence & Machine Learning in the Development of Drug 582 & Biological Products
- In May 2023, the US FDA published a discussion paper on "Using artificial Intelligence & Machine 583
- Learning in the Development of Drug & Biological Products".¹⁴⁰ The FDA acknowledges the increased 584
- 585 use of AI/ML in the lifecycle of drug development with novel approaches in data mining, analyzing 586
- large multi-omics, PK/PD modeling, real world data, data collection from wearable devices and other
- 587 datasets (e.g. in vitro and in vivo studies, mechanistic studies, and multi-organ chip systems. In the 588
- post-marketing safety surveillance, the FDA sees the potential to: i) automate the processing and 589 prioritization of individual case safety report (ICSR) using AI/ML, due to the increasing volume of
- 590 reports and complexity of data sources; ii) classifying ICSRs on the likelihood of causal relationship
- 591 between the drug and adverse event; iii) determine the seriousness of the outcome of ICSRs; and iv)
- 592 automate aggregate reports for multiple adverse events for a particular product.
- 593 FDA Draft Guidance on Considerations for the Use of Artificial Intelligence to Support Regulatory 594 Decision-Making for Drug and Biological Products
- 595 The FDA published a draft guidance titled "Considerations for the Use of Artificial Intelligence to 596 Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry and 597 Other Interested Parties" in January 2025. It elaborates a risk-based credibility assessment 598 framework for AI. The scope of the document focuses on the support of regulatory decision making 599 pertaining to the safety, effectiveness, or quality for drugs. Out of scope are drug discovery or 600 scenarios in which AI is deployed for operational efficiencies. The draft guidance is not a regulatory 601 mandate, rather the FDA's current thinking and recommendations on AI use. It considers AI broadly, 602 i.e. not limited to specific subsets of AI such as machine learning. There are three major segments of 603 the draft guidance:
- 604 1. Establishing a risk-based credibility assessment framework (see also Chapter on Risk-605 based approach);
- 606 2. Lifecycle credibility maintenance;

- 607 3. Options for sponsors for engaging with the agency to discuss AI model development.
- 608 The risk-based credibility assessment framework has seven steps as below.
 - 1. Define the question to be addressed by an AI model.
- 610 2. Define the "context of use (COU)" defined as "....the specific role and scope of the AI 611 model used to address a question of interest." Importantly this includes whether the questions being answered, and any ensuing classifications or decisions, are based solely 612 on the AI outputs versus the AI being used in conjunction with other information (i.e. 613 614 "model influence"). This is important because it helps define the associated risk in the 615 subsequent step.
- 616 3. Define model risk. This is determined by model influence as defined in COU and decision 617 consequence - i.e. the consequences of an incorrect decision. The risk is highest when

619 major hazard. The required level of oversight throughout the development and 620 production cycle is positively correlated with the risk. 621 4. Develop a plan to establish AI model credibility within the COU. 622 5. Execution of the plan. 623 6. Document the results of the credibility assessment plan and discuss deviations from the 624 plan. 7. Determine the Adequacy of the AI Model for the COU.¹⁴¹ 625 626 FDA Emerging Drug Safety Technology Program (EDSTP) 627 The FDA has established the Emerging Drug Safety Technology Program (EDSTP) in June 2024 to 628 engage with industry stakeholders on AI and other emerging novel technologies used in PV and the lifecycle of the drug product. The three goals of the EDSTP include discussion between industry and 629 FDA, knowledge dissemination of emerging AI/ML models or other emerging novel technologies, and 630 631 to inform potential regulatory or policy development within the context of PV.¹⁴² 632 Guidance on use of Large Language Models 633 Since the release of ChatGPT on November 30, 2022, there has been significant work in exploring 634 how generative AI could be adapted to a variety of tasks (such as text and image generation, coding, brainstorming, and research) for productivity gains. Given the potential use and broad applicability of 635 636 GenAI, regulatory agencies and organizations have developed high level guides and best practices on 637 the safe and responsible use of GenAl by their own staff and broader stakeholder groups, 638 respectively, which aligns with established guiding principles for AI: 639 Guiding principles on the use of large language models in regulatory science and for medicines regulatory activities (EMA¹⁴³); 640 • Guide on the use of generative artificial intelligence (Canada¹⁴⁴); 641 642 • Initial policy considerations for generative artificial intelligence (OECD¹⁴⁵); 643 WHO Ethics and governance of artificial intelligence for health: Guidance on large multi-modal models. (WHO¹⁴⁶). 644 645 Guidelines for safe AI 646 Other related regulatory and international organization (e.g. WHO and OECD) published guidelines for safe AI include: 647 Regulatory considerations on artificial intelligence for health, WHO 2023;¹⁴⁷ 648 Ethics guidelines for trustworthy AI, European Commission 2019;¹⁴⁸ 649 • Recommendation of the Council on Artificial Intelligence, OECD 2019, amended 650 2023;149 651 Good machine learning practice for medical device development: Guiding Principles, 652 653 U.S. Food & Drug Administration FDA, Health Canada, Medicines & Healthcare products Regulatory Agency MHRA 2021.¹⁵⁰ 654 655

the AI model is operating in a stand-alone capacity and incorrect decisions present a

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Principles for integrating and implementing artificial intelligence within pharmacovigilance

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This is a summary of the broad framework of principles for integrating and implementing AI within PV that will be addressed in the following chapters in greater detail.

661 *Risk-based approach*

662 A risk-based approach acknowledges the potential hazards that AI systems can pose and recognises

that different use cases present varying types and levels of risk. This necessitates a risk assessment

that identifies, prioritises, and manages risks that could negatively affect a PV system's behaviour

and results, taking into consideration existing process controls. A risk is characterised by both the

- anticipated impact and the likelihood of negative outcomes.
- 667 This approach also supports procedures to identify and reduce errors and biases in a way that is
- 668 proportionate to their risk. It influences the implementation strategies of AI systems (including
- documentation, compliance, and record-keeping), which should generally be commensurate with the
- 670 identified risk.
- 671 Human oversight
- 672 Human oversight refers to the expected role of humans in the design, implementation, monitoring,
- and analysis of AI systems in PV. It requires a framework to manage performance and to detect and
- 674 mitigate potential issues related to the AI system.
- 675 Validity
- 676 Validity means that a system achieves its intended purpose within acceptable parameters. It requires
- 677 predefining acceptable performance levels, selecting appropriate data for model training and/or
- testing, assessing model performance in a realistic setting, and integrating the system into an
- ongoing quality assessment process.
- 680 Robustness
- 681 Robustness means that a system reliably achieves its intended objectives (while accounting for
- 682 variations in data).
- 683 Transparency
- 684 Transparency regarding AI involves disclosing information between organizations or individuals. This
- 685 includes sharing relevant documentation of the AI system lifecycle (i.e. design, development,
- evaluation, deployment, operation, re-training, maintenance and decommission) to facilitate
- 687 traceability and providing stakeholders with enough information to have a general understanding of
- the AI system, its use, risks, limitations, and impact on their rights.
- 689 Data privacy
- Data privacy refers to the fundamental right of an individual to control how their personal
- 691 information is collected, stored, shared, and used. It is an aspect of the principle of "respect for
- 692 persons" that is foundational to the conduct of biomedical research. Regulations, legislation and
- 693 guidance documents provide measures intended to preserve the confidentiality, anonymity,
- autonomy and control of sensitive and potentially personally identifiable health data in the setting ofPV.
- 696 Fairness & Equity
- 697 Fairness and equity require awareness of and adherence to impartiality, equality, non-discrimination,
- diversity, justice, and lawfulness. The benefits of AI in PV should be equitable across all relevant

- 699 populations and groups. Throughout the AI lifecycle, it is important to avoid and mitigate unfair bias,
- and any discriminatory practices and unjust social wellbeing and environmental impacts.
- 701 Governance
- 702 Governance refers to the human management and oversight used to control and direct the use of AI
- in the PV system. An AI governance framework requires implementation of risk management
- 704 practices and policies to ensure adherence to the AI guiding principles.
- 705 Accountability
- Accountability applies to clearly defined roles, responsibilities and liability for organisations and/or
- individuals deploying, operating and managing AI systems. It requires the adoption of appropriate
- 708 governance measures by relevant stakeholders, including but not limited to regulators, vendors,
- vuers, developers, data providers or pharmaceutical companies involved in setting policy, developing,
- deploying and managing AI systems. This ensures operations remain within expected parameters
- 711 throughout the AI lifecycle while addressing any unforeseen consequences.

712

Chapter 3: Risk-based approach 713

Principle 714

A risk-based approach acknowledges the potential hazards that AI systems can pose and recognises 715 716 that different use cases present varying types and levels of risk. This necessitates a risk assessment 717 that identifies, prioritises, and manages risks that could negatively affect a PV system's behaviour and results, taking into consideration existing process controls. A risk is characterised by both the 718 anticipated impact and the likelihood of negative outcomes.¹⁵¹ 719

720 This approach also supports procedures to identify and reduce errors and biases in a way that is

721 proportionate to their risk. It influences the implementation strategies of AI systems (including

722 documentation, compliance, and record-keeping), which should generally be commensurate with the 723 identified risk.

724 Key messages

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- 725 Integrating AI into PV processes needs to take into account that the performance of both AI • 726 algorithms, and humans, is imperfect.
- 727 The risks potentially associated with the use of AI in PV may affect patient safety, the trust • 728 and engagement of PV users, the efficiency of PV processes as well as compliance with 729 regulatory standards and ethical principles.
- 730 By focusing efforts and resources where they most matter, a sound risk-based approach • 731 enables organisations to make the most of AI capabilities while ensuring that neither patient 732 safety nor PV stakeholders are adversely affected.
- 733 The risk-based approach applies to the human oversight modalities, the validity and • robustness strategy, the level of transparency, and the efforts to uphold fairness and equity, 735 and data privacy.
- 736 The risk assessment should consider the AI system itself, the context of use, and the • 737 potential impact and likelihood of risks materialising.
- 738 Comparative performance to current best practice should also be considered.
- 739 Assessment should be end-to-end with an emphasis on end objective. •
- 740 A risk-based approach should be reviewed at regular intervals and adapted if needed. •

Introduction 741

742 **Regulatory considerations**

743 Regardless of the integration of AI elements, PV systems are expected to comply with existing

regulations and good pharmacovigilance practices (GVP).^{152,153} In accordance with GVP, a wide range 744

745 of PV processes are considered critical for business continuity purposes, including collection and

- 746 handling of ICSRs, signal management, and PSURs.¹⁵⁴
- 747 Regulatory frameworks generally recommend a risk-based approach in the development,
- 748 deployment, monitoring, documentation and regulatory oversight of AI systems, to ensure that
- relevant risks are anticipated, identified and mitigated throughout the system lifecycle.^{155,156,157} The 749
- European Artificial Intelligence Act (EU AI Act)¹⁵⁸ introduces four risk categories for AI systems: low or 750
- minimal risk, limited risk (transparency obligations), high risk, and unacceptable risk (prohibited AI 751
- 752 practices). High-risk AI systems, which include e.g. AI-based medical software/devices or AI systems
- 753 used for staff recruitment, are associated with strict requirements and obligations on providers and
- 754 deployers, including risk-mitigation systems, high quality data sets for training, validation and testing,
- 755 logging of activity, detailed documentation, clear user information, human oversight, and a high level
- 756 of robustness, accuracy, and cybersecurity. While the guiding principles advocated throughout this

- report overlap with the EU AI Act's requirements for high-risk AI systems, determining the applicable
- 758 EU AI Act's risk category of an AI system considered for integration into an organisation's PV process
- vill likely require a careful case-by-case assessment, with legal advice as appropriate. Within the
- 760 medicines' lifecycle, EMA foresees AI systems with 'high patient risk' in use cases where patient
- safety is affected and AI systems with 'high regulatory impact' in use cases where impact on the
- regulatory decision making is substantial.¹⁵⁹ The Artificial Intelligence and Data Act (AIDA) was
- 763 developed to ensure the development of responsible AI in Canada, with a risk-based approach
- aligned with international norms, including the EU AI Act, the OECD AI Principles, and the US National
- ⁷⁶⁵ Institute of Standards and Technology (NIST) Risk Management Framework (RMF).¹⁶⁰
- During development and other stages of an AI solution's lifecycle as relevant, and depending on the
 level of risk to individual patients, public health or the regulatory decision making, applicants and
- developers should consider engaging actively with regulatory authorities and seek suitable scientific
- 769 advice. Where necessary, technical qualification of the AI technology through appropriate channels
- should be sought based on legislative or regulatory requirements applicable to medicinal products,
- 771 medical devices and/or software development.^{161,162} Due to its fast-moving nature, the use of AI
- technology in the medicines' lifecycle including in PV will pose challenges to both regulators,
- required to adapt and keep abreast of this evolving field,¹⁶³ and industry PV stakeholders, required to
- maintain regulatory compliance (see Chapter on <u>Future Vision</u>).

775 Motivation and interplay with other guiding principles

- A sound, risk-based approach will allow organisations to focus their efforts and resources where they
 matter most to maximise their AI capabilities while ensuring that guiding principles are upheld, as
 described earlier.
- 779 Rather than a self-standing principle, a risk-based approach is applicable to the other guiding
- 780 principles presented in this report. Notably, a risk-based approach will inform where, when, how and
- 781 how much human oversight should be implemented within PV processes involving AI in addition to
- 782 other risk mitigation activities and conversely, an AI solution may be 'risk-assessed' assessed taking
- ⁷⁸³ into account the degree and nature of existing human oversight (see Chapter on <u>Human oversight</u>). A
- risk-based approach should be applied to the testing and verification of AI systems (see Chapter on
- 785 <u>Validity & Robustness</u>) and the level of documentation and record-keeping (see Chapter on
- 786 <u>Transparency</u>). A risk-based approach is also relevant to data privacy and fairness and equity. For
- example, AI systems should be assessed for any risks that specific groups may be under-served or
 biased against, and those risks should be appropriately mitigated (see Chapter on Fairness & Equity).

789 **Types of risks**

- This section briefly outlines some of the risks potentially associated with the use of AI solutions in PV.
- 791 Risks to patient safety and public health
- 792 Inadequate use of AI solutions in PV, or their poor performance, may impede the fulfilment of PV
- 793 objectives: detection, assessment, understanding and prevention of adverse effects of drugs or
- vaccines, which may come at the cost of patient safety or public health. Unreliable outputs produced
- ⁷⁹⁵ by an AI system, including but not limited to false negatives or false positives, or unfair bias, could
- negatively impact PV activities with e.g. relevant adverse events not captured, events misclassified
- 797 during case processing, or signals missed. This could result in safety issues not being identified or
- being identified with delay, potentially putting patients at risk. In rare scenarios, the late detection of
- ⁷⁹⁹ new, unexpected safety signals could have a major public health impact ('Black swan' events).¹⁶⁴ An
- 800 initially robust AI tool could also start underperforming over time due to e.g. model drift, or become

- 801 inoperative due to an IT incident or system failure, which would impede the PV activity that the AI
- 802 tool is intended to support.

803 *Risks to user trust and engagement*

804 The lack of transparency and interpretability of certain AI algorithms may hinder trust and 805 acceptance by users, including PV professionals (see Chapter on Transparency). Lack of trust from 806 users may also result from poor previous experience with AI systems of insufficient validity and 807 robustness, leading to mistrust of AI solutions in general. In clinic-based PV settings, a more subtle 808 potential source of mistrust is 'uniqueness neglect', in which patients prefer a human clinician over a 809 more accurate computer due to a belief that machines do not fully accommodate their personal 810 human uniqueness.¹⁶⁵ Other possible sources of mistrust include poor performance for certain subpopulations or failure to protect confidentiality of personal data during the development or 811 812 operation of an AI system. Conversely, some users may put excessive trust in AI systems, leading to 813 automation bias (especially if those have shown robust performance upon validation) and the 814 resulting unconscious bias to accept erroneous outputs. Additionally, integrating AI solutions into 815 existing workflows and systems may pose technical, organisational, and cultural challenges, with a 816 risk of degraded job motivation or satisfaction in the absence of adequate training and change

- 817 management strategies (see Chapter on Human oversight).
- 818 *Risks to efficiency*
- 819 Although the integration of AI in PV processes is generally aimed at increasing efficiency,
- substandard AI solutions may cause more manual work than they save, if for instance, significant
- time is required to understand and verify the AI outputs or bring them up to acceptable standards.
- 822 Uncertainties, such as false positives, in interpretations and actions based on AI outputs might add to
- 823 inefficiencies or suboptimal use of limited resources.
- 824 Legal, ethical and other risks
- Other risks may be related to data privacy, cybersecurity threats, intellectual property, liability, or economic and reputational aspects.
- 827 This chapter mainly focusses on the impact that the use AI tools in PV processes could have on
- patient safety. Potential concerns related to user acceptance and other challenges are further
- discussed in the chapters on <u>Data Privacy</u>, <u>Fairness & Equity</u>, <u>Transparency</u>, <u>Human oversight</u> and
- 830 <u>Governance & Accountability</u>.

831 Risk assessment

832 General considerations

- 833 Organisations planning to deploy AI-based tools to support PV processes are expected to perform a
- thorough risk analysis. This assessment should be performed for each AI system and should form the
- basis for a risk-proportionate approach applied throughout the AI system's lifecycle fromdevelopment to routine use.
- 837 When determining the level of risk related to the implementation of an AI tool within a PV system,
- key considerations include the AI technology itself, the context of use, the likelihood of risks
- 839 materialising and their potential impact.
- 840 *Artificial intelligence technology*
- The level of risk may depend on the type of tool used (e.g. static vs dynamic model), the underlying data quality, the novelty of the technology or the maturity of the system (i.e. lifecycle stage).
- Particular caution should be exercised with the integration of GenAI models within PV processes.
- Compared to simpler or more explainable AI approaches, the non-deterministic nature of GenAI and

- similar AI models, the opacity of training data and the potential for hallucinations, may make the
 detection and mitigation of issues more challenging and require consideration of further guardrails.
- 847 As the AI landscape continues to evolve, so will AI-related risk areas. New risks may emerge while
- others may become less prominent; for instance, the current challenges associated with GenAI/LLMs
- 849 may be solved, making their integration into sensitive PV processes safer.
- 850 *Context of use and degree of influence*
- These broadly refer to the place and importance of the AI solution within the overall PV system,including:
- Whether or not the AI solution is used in a critical PV process or high-risk context (e.g.
 emergency Public Health use, novel substance, clinical trial cases);
 - At which stage within a particular process the AI tool intervenes (e.g. automated triage of relevant cases as a preliminary step to signal review) and whether the tool is assistive or directly supports a PV process;
- The extent of human involvement and oversight in the process (see Chapter on <u>Human</u>
 <u>oversight</u>).
- 860 Impact and likelihood

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- 861 Not all occurrences of system malfunction or suboptimal model performance are as likely, nor will
- they have the same impact. For instance, a duplicate detection tool applied to a very large database
- is not expected to detect 100% of duplicates but missed duplicates will have no or limited
- consequences in terms of patient safety, whereas the late detection of a very serious signal in a
- context of mass patient exposure happens very rarely but may have dramatic public health
 consequences (i.e. black swan event).
-
- 867 Examples of structured approaches
- Risk-based assessment frameworks have been proposed in various domains and may provide
 inspiration to organisations wishing to deploy AI solutions within PV systems. Selected examples are
 briefly described hereafter.
- 871 Credibility assessment framework
- 872 The FDA proposes a stepwise approach to demonstrate the credibility of AI models to produce
- 873 information or data intended to support regulatory decision making regarding the safety,
- effectiveness, or quality of drugs (see also Chapter Landscape analysis).¹⁶⁶ Similar frameworks have
- 875 been proposed for the use of computational models in medical device submissions¹⁶⁷ or drug
- 876 development.¹⁶⁸ The preliminary steps of the credibility assessment, as outlined below, help assess 877 the model risk.
- 878 1. Define the question of interest: This describes the specific question, decision, or concern to be addressed by the AI model. 879 880 2. Define the context of use: this is a description of how the model will be used to address 881 the question of interest, i.e. the specific role and scope of the AI model. 882 3. Assess the AI model risk: this is defined by (i) the contribution of the evidence derived 883 from the AI model relative to other contributing evidence used to inform the question of 884 interest, i.e. model influence; and (ii) the significance of an adverse outcome resulting 885 from an incorrect decision concerning the question of interest, i.e. decision consequence. The ratings for decision consequence and model influence are 886 887 independently determined, but are shaped by the context of use, thus enabling model 888 risk to be case specific. The AI model risk is assessed by subject matter expertise and 889 judgement on the possibility of model output leading to an adverse outcome, rather than

890 891 the intrinsic risk of the model itself. As illustrated in Figure 4, the model risk moves from low to high as decision consequence or model influence increases.

892 Figure 5: Model risk matrix

893 Source: U.S. Food and Drug Administration.¹⁶⁹



894

895 Algorithmic impact assessment

In Canada, the mandatory algorithmic impact assessment (AIA) tool¹⁷⁰ is designed to help

897 departments and agencies better understand and manage the risks associated with automated

decision systems. It is composed of questions in various formats that consider many factors (e.g.

899 system's design, algorithm, decision type, impact, data) within risk and mitigation areas and

900 contribute to a scoring system. The value of each question is weighted based on the level of risk it

901 introduces or mitigates in the automation project. The resulting impact levels (from I: little impact, to

902 IV: very high impact) determine the mitigations required under the Directive on Automated Decision-

903 Making.¹⁷¹

904 Issue detection and risk mitigation

905 Defining when to mitigate requires knowing how to detect issues based on a pre-defined risk-

906 proportionate testing and verification plan which is laid out during the development of the AI system.

907 Testing and verification are essential steps of Computerized System Validation (CSV), which considers

908 different levels based on AI system maturity. The latest version of the Good Automated

909 Manufacturing Practice 5 (GAMP 5) of the International Society for Pharmaceutical Engineering

910 (ISPE), a framework widely adopted by pharmaceutical companies and health authorities, contains an

911 appendix focusing on AI and ML.¹⁷² Testing should be based on pre-defined key performance

912 indicators and acceptance criteria, considering the human performance, and account for the

913 identified risk areas, e.g. low quality data. Issues can be detected using mechanisms such as 'golden

914 questions', i.e. known truths which are checked each time an AI system undergoes a change.

915 After the AI system has been proven fit for purpose and deployed, an ongoing process should be in

- 916 place to monitor its performance and trigger mitigation measures when issues are detected.
- 917 A risk-based approach may be very conservative in the initial stages of deployment with additional
- 918 pre-determined mitigation measures in place, for example, high percentage of human-in-the-loop. As
- 919 confidence in the routine performance increases over time, based on pre-defined indicators and
- 920 examination of sample outputs by human experts, a gradual reduction in the frequency, amount (e.g.
- 921 number of samples) or depth of human controls may be considered.
- 922 When issues or performance deviations are detected, risk-based mitigation measures may include:
- *Human-in-the-loop:* Increased or full human review/quality control, indefinitely or until
 performance levels are back within acceptance criteria, e.g. if a seriousness detection

- 925algorithm fails to detect seriousness criteria in some cases, e.g. false negatives, mitigation926could involve reviewing all cases classified as non-serious until the issue is understood and927addressed;
- 928 Al improvement strategies such as model re-training or hallucination mitigation strategies;¹⁷³
- 929 Articulation of the *level of uncertainty* in AI outputs;
- Approaches to *combat automation bias or complacency*,¹⁷⁴ e.g. mock data simulations or
 injection of simulated false positive outputs for verification/assessment;
- Decommissioning of the tool when mitigation options appear inefficient or costly, in which
 case alternative approaches should be considered.
- Finally, AI components, especially those deployed in critical PV processes, should be included in theorganisation's business continuity plan.
- The above aspects are further developed in the Chapters on <u>Validity & Robustness</u>, <u>Human</u>
 <u>Oversight</u>, and <u>Governance & Accountability</u>.
- The risk-based approach should be reviewed at regular pre-determined intervals to adapt oversight measures based on performance data but also as new technical options for risk mitigation emerge.

940 **Documentation**

- 941 The key components of the AI-related risk management strategy should be documented, including:
- AI system risk assessment;
- 943 Testing plan with key performance indicators and acceptance criteria including any
 944 comparative assessments;
 - Planned mitigation measures including human in-the-loop strategy and criteria for more stringent or reduced quality control, and continual monitoring after deployment;
 - Plans for periodic re-assessment and update of the risk management strategy;
 - Business continuity plan.

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950 Chapter 4: Human oversight

951 Principle

Human oversight refers to the expected role of humans in the design, implementation, monitoring,
and analysis of AI systems in PV. It requires a framework to manage performance and to detect and
mitigate potential issues related to the AI system.

955 *Key messages*

- Human oversight supports the optimisation of the performance of AI systems deployed in PV
 and increases trustworthiness and accountability.
- The extent and nature of human oversight for an AI solution should follow a risk-based
 approach.
 - Quality assurance principles should apply to the conduct of the human oversight of AI systems in PV.
- The increased use of automation and AI to support PV processes will require redefining
 skillsets to integrate AI with human expertise, ensuring robustness and reliability in decision making processes. This will lead to a transformation of traditional roles and competencies
 that requires appropriate change management and training strategies.

966 Introduction

967 Motivation

968 Human oversight is required to minimise the risk that an AI system undermines human autonomy or

- 969 causes other negative or unintended effects.¹⁷⁵ Human agency and oversight are a key requirement
- 970 of trustworthy AI according to several regulatory frameworks, including the Assessment List for
 971 Trustworthy Artificial Intelligence (ALTAI), the EU AI Act, and the Canadian Artificial Intelligence and
- 971 Trustworthy Artificial Intelligence (ALTAI), the EO AFACt, and the Canadian Artificial Intelligence and
 972 Data Act (AIDA), for high-risk systems^{176,177,178} (see also Chapter on Landscape analysis). Although
- 973 human review by itself does not guarantee full accuracy of outputs, human oversight is essential to
- 974 monitor the performance of AI systems and make corrections if needed, thereby increasing
- 975 trustworthiness and accountability for the AI system, especially in some high-risk applications.
- 976 Al systems are often intended to help eliminate manual, labour-intensive or complicated work
- 977 performed by humans, or to enhance human performance when used as intelligence augmentation
- 978 tools. However, due to the complexity and sensitivity of certain PV tasks, and the complex and
- variable nature of PV data, AI components will exhibit increasingly good but imperfect performance.
- 980 This may require more extensive human intervention during the development, evaluation and
- 981 deployment of some AI solutions in PV to monitor and mitigate risks.
- 982 A key challenge and important starting point for defining an AI quality assurance (QA) approach is to
- strike a balance between the efficiency boost that an AI system is intended to provide and the level
- 984 of human intervention that may be required to ensure a high-quality output. In plain words, ideally a
- 985 human expert should not do work that a machine can do well, and a machine should not do poorly
- 986 the work that a human expert can do well.¹⁷⁹
- 987 Human oversight is fundamental to a sound risk-based approach (see Chapter on <u>Risk-based</u>
- approach). The level of monitoring of the performance of AI systems by humans should be
- 989 proportional to the potential impact on patient safety of an undetected mistake or spurious output
- 990 by the AI system.

991 Considerations on human involvement and oversight

992 Multidisciplinary expertise

The successful integration of AI solutions into PV systems requires that multidisciplinary human
expertise is mobilised as appropriate throughout the lifecycle of the tools, from development to
routine use. This multidisciplinary expertise is usually obtained through a close collaboration
between PV professionals, QA staff, data scientists, statisticians, AI/ML engineers, data engineers,
prompt engineers, IT specialists, cybersecurity experts, platform analysts, software engineers, ethics
specialists, legal experts, data protection officers, project managers, senior management, etc. (see
also Chapter on Governance & Accountability).

PV professionals, i.e. staff performing core tasks in ICSR management, signal detection and analytics
or risk management, hold robust 'domain' or 'subject matter' expertise, which is instrumental to
effective integration of AI capabilities into PV processes. As such, PV professionals should be engaged
in the design, development, pre-deployment and testing/piloting of AI solutions to ensure that they
are fit for purpose and widely accepted by the end-users that they - PV professionals - will ultimately
be.

1006 Mechanisms of human oversight

- 1007 Human oversight may serve different objectives and be achieved through governance mechanisms at
- 1008 different stages.¹⁸⁰ There are various possible approaches based on the activity monitored and how
- 1009 much autonomy is granted to an AI system. Depending on the scope, extent and intensity of human
- 1010 intervention, the European Commission's Ethics Guidelines for trustworthy AI describe three main
- 1011 governance mechanisms: human-in-the-loop (HITL), human-on-the-loop (HOTL) and human-in-
- command (HIC). HITL refers to the capability for human intervention in every decision cycle of the AI
 system. HOTL, which foresees a higher autonomy of the AI system, refers to the capability for human
- system. HOTL, which foresees a higher autonomy of the AI system, refers to the capability for human
 intervention during the design of an AI system and monitoring of its operation. HIC refers to the
- intervention during the design of an AI system and monitoring of its operation. HIC refers to thecapability to oversee the overall activity of an AI system, including its broader economic, societal,
- 1016 legal and ethical impact, and the ability to decide when and how to use an AI system. This may
- 1017 include the decision not to use an AI system in a particular situation, to establish levels of human
- discretion during its use, or to ensure the ability to override a decision made by the system.¹⁸¹ The
- 1019 delineations of these three terms may vary according to sources¹⁸² and their practical
- 1020 implementation may differ according to individual organisations and use cases. For example, during
- 1021 the lifecycle of a given AI system in PV, human oversight may be exercised at early stages to help
- 1022define the system's context of use or support the identification or development of reference datasets1023(HOTL) and, when deployed, to perform quality controls of the system (HOTL) or as part of its
- 1024 execution in case of a semi-automated system (HITL).
- As a rule, some level of human oversight is always required and the absence of a human-in/on-theloop in any major or supporting PV process should be substantiated by a risk assessment, with risk mitigation measures in place
- 1027 mitigation measures in place.

1028 Monitoring and interacting with deployed artificial intelligence systems

The level, frequency, means and modalities of human intervention required to monitor and interact
 with AI systems depend on the complexity of the task, the risks associated with suboptimal outputs,
 the type of AI system, and the performance as assessed during validation (see Chapters on <u>Risk-</u>
 <u>based approach</u> and <u>Validity & Robustness</u>). As experience with AI evolves, further clarity, guidance,
 and consistency in assessing these factors are likely to develop. As suggested above, the respective

1034 roles of the human and AI components in a particular process could be seen as a continuum, from an

- 1035 Al tool merely performing preparatory work to support assessment and decision making by a human,
- to a near-fully automated system merely monitored by a human who performs quality controls.
- 1037 Intermediate approaches may also be envisaged where, for instance, an AI solution flags cases it1038 struggles with to a human specialist.
- 1039 The metrics and KPIs used to monitor the performance of deployed AI systems should be pre-defined
- as part of the testing and verification plan (see Chapters on <u>Validity & Robustness</u> and <u>Risk-based</u>
 approach).
- 1042 In situations where the standalone performance of an AI system is suboptimal (e.g. if it cannot match
- the established human performance, or when the associated risks are unacceptably high), one or
 more manual process steps must be considered, with a human fully in control of the final output.
- 1045 Even when a static AI-based system exceeds human performance upon validation, monitoring after
- 1046 development is still recommended to ensure that the performance does not fall below acceptable
- 1047 levels over time (see Chapter on <u>Validity & Robustness</u>). Each time an AI system undergoes
- modifications, human oversight should be directed at the change i.e. change-specific samples shouldbe prioritised.
- 1050 There are different ways the performance of an AI system can be monitored once deployed. In a
- static AI system, one could perform a one-off retrospective analysis by checking a sample or the
- 1052 totality of generated outputs against expected outputs (see Chapter on <u>Validity & Robustness</u>). This
- 1053 may be followed by post hoc corrections and re-training or re-validation of the model. A more
- 1054 dynamic real-time, in-process interaction can also be envisaged where independent human
- assessment is applied to confirm or correct the AI output in a decision-support setting. In such a
- dynamic AI application, the interaction provides an opportunity for immediate feedback to the
 algorithm to continuously learn and adjust if needed. Running an independent model in parallel to
 the main AI system may also be an option in a one-off or continuous manner (AI-assisted human
- 1059 oversight).
- 1060 Caution is required in the monitoring of GenAl/LLM-based systems. Humans-in/on-the-loop should 1061 be aware of the inherent variability of outputs, limited explainability and risk of hallucinations, and 1062 not overly rely on the AI system's results. Processes must be robust, demonstrated to be effective, 1063 and maintain their dependability even in the event of erroneous outputs. Hallucinations, specifically, 1064 may lead to seemingly coherent and convincing outputs that may be deceiving for humans-in/on-1065 the-loop. Regardless of the underlying AI technology, PV professionals should be empowered to 1066 challenge the system's outputs based on their experience and avoid falling for automation bias. On 1067 the other hand, they should be aware of the possibility of confirmation bias and remain open to the 1068 possibility that an AI output, albeit unexpected, is correct. AI solutions with high performance may 1069 also warrant specific monitoring strategies as humans are more prone to miss very rare¹⁸³

1070 Transformation of traditional roles

- 1071 As the PV landscape continues to embrace AI capabilities, a reduced dependency on large workforces 1072 with PV expertise is expected due to the replacement of some of the activities traditionally 1073 performed by PV professionals. Indeed, the increased use of automation and AI within PV processes 1074 will unburden PV professionals from certain repetitive, time-consuming, manual activities. This may 1075 render certain roles obsolete and thereby reduce the size, diversity and experience of the PV 1076 workforce, not unlike the impact on staff observed when organisations offshore activities. This may 1077 create legitimate concerns and anxiety about job displacement and employment prospects in the PV 1078 space, but also around work culture, motivation and fulfilment. Perceived unfairness may also ensue 1079 from the fact that some AI models are trained using historical datasets and documented decisions 1080 based on the work originally performed by PV professionals.
- 1081 On a brighter side, the introduction of AI in PV brings opportunities for growth for PV professionals.
 1082 With fewer menial time-consuming tasks, PV experts will be able to focus on more scientifically

- 1083 complex and intellectually stimulating PV activities. In addition, the business needs associated with AI
- solutions will bring new roles in governance and human oversight. As mentioned earlier, PV
- 1085 professionals will be increasingly involved in the testing, evaluation, implementation, oversight and
- 1086 use of AI models. They will often be best placed to identify those activities in need of automation and
- 1087 suggest AI use cases accordingly. They may have to participate in design and development activities
- 1088 including model training and validation, participate in user acceptance testing, manage the
- 1089 challenges of automating and modifying existing processes, perform monitoring and quality control
- activities, identify and resolve issues related to inconsistent assessments, and interact withautomation experts and vendors.
- 1092 Contributing to the development, use, and maintenance of AI systems will allow PV professionals to
- 1093 evolve with the changing PV landscape, but this will require that they extend their skillsets beyond
- 1094 core PV competencies.¹⁸⁴ These new skills include specific competencies around the use of the new
- systems and the critical evaluation of their outputs, as well as more general literacy around data
- science and AI, including a good understanding of AI capabilities, risks and limitations. Regulatory
- 1097 frameworks such as the EU AI Act impose an obligation on organisations to ensure a sufficient level
- 1098 of AI literacy of staff operating or using deployed AI systems.¹⁸⁵
- 1099 Beyond PV professionals, staff working in QA also need to develop an understanding of the
- 1100 organisation's human oversight strategy in addition to some AI literacy, to ensure that human
- 1101 oversight activities are adequate. Likewise, AI experts involved in the design and development of AI
- 1102 in PV solutions will need to develop an understanding of PV processes and the implications of
- 1103 operating in a regulated environment.
- 1104 Change management and readiness strategies are a key responsibility of organisations, which should
- 1105 put PV staff at the centre of role redefinition and upskilling opportunities. Adequate change
- 1106 management and training plans are a pre-requisite to a seamless, safe and successful integration of
- 1107 Al systems into PV processes, with a wide engagement and adoption by staff and smooth
- 1108 interactions between various roles (see also Chapter on <u>Governance</u>).
- 1109 Training programs should be carefully crafted, documented and evaluated so that their content and
- 1110 format (including materials and methods) meet the learning needs of the target audience (e.g. PV
- 1111 end-users, QA staff, AI experts). Human training in a decision-support context is an approach that
- 1112 may be drawn on to train staff monitoring and interacting with AI systems. It generally refers to
- 1113 programs designed to educate staff to use specific tools and make informed decisions effectively.
- 1114 This involves not only showing staff how to use the software front-end but also explaining the back-
- 1115 end functionalities and helping them build the skillset for critically evaluating the automated output.
- 1116 Training modalities (e.g. classroom-based vs online, live vs asynchronous) should be adapted to the
- 1117 system's complexity, the supported use case or task, and the specific needs of the organisation or the
- 1118 individual.^{186,187,188,189}

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1120 Chapter 5: Validity & Robustness

	• •
1121	Principle
1122 1123 1124 1125	 Validity means that a system achieves its intended purpose within acceptable parameters. It requires predefining acceptable performance levels, selecting appropriate data for model training and/or testing, assessing model performance in a realistic setting, and integrating the system into an ongoing quality assessment process.
1126 1127	 Robustness means that a system reliably achieves its intended objectives (while accounting for variations in data).
1128	Key messages
1129 1130	• PV professionals and decision makers must learn to critically appraise proposed AI solutions whether they acquire them or participate in their development.
1131 1132 1133 1134	 A performance evaluation able to demonstrate acceptable and robust results for the intended use under realistic conditions is crucial. Such an evaluation should cover a wide enough range of relevant examples to interrogate the model's objective and is often based on statistical metrics.
1135 1136 1137 1138	 There should be a focus on looking to ensure sufficient representation of relevant types of data in the test set(s) to detect biases, promote adequate and generalizable performance across the intended deployment domain, assess usability, and identify circumstances where the model may underperform.
1139 1140 1141 1142	 Many PV applications focus on very rare events or patterns (e.g. emerging safety signals, reports of a certain kind – such as related to pregnancy, duplicated reports etc.) and may require enrichment strategies to obtain representative test sets with high enough prevalence of the event of interest. If so, special care should be taken to ensure that performance

1144 Introduction

1143

1145 Ensuring the validity and robustness of AI solutions is central to building trust and achieving the best 1146 possible value for end-users. To invest resources optimally, PV professionals and decision makers 1147 must learn to critically appraise and evaluate proposed AI solutions regardless of whether they 1148 develop them in-house or acquire them from other organizations. This requires familiarity with basic 1149 principles for performance evaluation and some of the common pitfalls that may mislead 1150 expectations on real-world performance in prospective use.

evaluation results generalize to real-world settings.

Al solutions will often be embedded in broader computer systems supporting the PV use case. These should be subjected to general computer system-validation according to standard practices for the organization. In general, this will be considered orthogonal to ensuring the validity and robustness of the core AI solution (and is out of scope for this document). However, some special considerations regarding validation of systems that include dynamic AI models that continually learn from and adapt to incoming data are presented in the Section on Continuous integration and deployment. Our focus

- 1157 will be on key considerations related to establishing the validity and robustness of AI models
- themselves, including their dependency on underlying data for training and deployment and the
- 1159 need for probabilistic / statistical performance evaluation.
- 1160 The nature of PV data may in some instances impact our ability and approach to leveraging AI
- 1161 solutions. AI models depend heavily on the quality of the data they are trained on and the data they
- use for ongoing predictions. PV data suffer from inconsistencies, incomplete entries, and
- 1163 inaccuracies, and may vary substantially depending on the source. For example, the contribution of
- 1164 individual case reports is for the most part voluntary, and reporting practices vary over time,

- between organizations and types of reporters. This may impact the types of adverse events that are
- reported, which information is captured, and how it is encoded. Inconsistencies and inaccuracies can
- 1167 lead to models that are less accurate, and systematic variability can reduce the generalizability of AI
- solutions to adjacent domains and make them more sensitive to data drift. They may also make it
- 1169 more difficult to ensure consistent performance across regions and organizations (see also Chapter 1170 on Fairness & Equity).
- 1171 Generally, the variable quality and consistency of individual case reports and the complex nature of 1172 the studied drug-event relationships may require more extensive human involvement than in other 1173 domains to ensure the validity and robustness of AI solutions for PV (see also the Chapter on Human 1174 oversight). The practice of PV is subject to medicines regulation, and regulatory expectations 1175 regarding validity and robustness may differ from those of the business itself. For example, even if 1176 from a business perspective an organization were prepared to adopt an AI solution whose output 1177 was not fully reproducible in repeated execution using the same input, the organisation would not 1178 consider the acceptability to regulators, as sufficient controls may exist to de-risk the process to 1179 which it is applied.
- 1180 Performance evaluation and testing are crucial considerations in ensuring the validity and robustness
- of AI solutions. While it will usually be more effective to account for these considerations also during
- development and training of AI solutions, to do so might not be feasible or required. For example,
- 1183 LLMs can be capable of zero-shot learning, with solid performance on language tasks for which they
- 1184 have not been specifically trained. What is important even then is to demonstrate adequate
- 1185 performance on the relevant tasks in independent testing with conditions reflecting the intended
- 1186 use.

1187 Specification and design

1188 Use case and deployment domain

1189 The intended use case and deployment domain for AI solutions in PV should be clearly defined, and 1190 the performance evaluation targeted to these, as far as possible. For example, in evaluating methods 1191 for PV signal detection, historical safety signals would typically be a more relevant basis for 1192 performance evaluation than well-known, already labelled adverse drug reactions since their reporting patterns differ in important ways¹⁹⁰ Similarly, if an AI solution for recognizing adverse 1193 1194 events in free text is intended for broad use, its evaluation should include reports related to various 1195 medicinal products and adverse events, from both patients and health professionals, in relevant 1196 languages, etc. Ideally, there should be sufficient representation of relevant types of data in the test 1197 set to detect biases, promote adequate and generalizable performance across the intended 1198 deployment domain, assess usability, and identify circumstances where the model may

1199 underperform.

1200 Multi-disciplinary collaboration

Ensuring the validity and robustness of AI solutions often requires collaboration across disciplines, including not only PV decision makers and practitioners, but also for example, data scientists and AI experts, and individuals with experience in computer systems validation. Diverse perspectives and expertise, in-depth understanding of a model's intended integration into the PV system and defined desired benefits and associated risks can help ensure that deployed AI solutions are effective, and address identified needs over their lifecycle.

- Applications of AI solutions pertaining to the complex relationships between drugs and adverse
 events often require a human-in-the-loop, especially in view of the variable quality and provenance
- 1209 of the underlying PV data. Al outputs in such applications need to be interpreted considering the
- broader clinical context, known pharmacological mechanisms, and possible alternative explanations

1211 which may not be captured in the data at hand and that the AI might not fully account for. Human 1212 intervention ensures that the final output is clinically meaningful and scientifically sound. On the 1213 other hand, more basic tasks such as redaction of personal data or drug and adverse event encoding

1214 may lend themselves to automation with minimal human intervention.

1215 Definition of reference standards

1216 Test sets must be aligned with intended deployment domain and able to demonstrate performance 1217 under realistic conditions. Reference standards relevant to the intended use need to be clearly 1218 defined and kept up to date. In many PV applications, these may be based on human execution of 1219 the task in question. Approaches to mitigate inconsistencies are often required, for example by 1220 having multiple human assessors annotate (parts of) the same data. When legacy human annotations 1221 are used as the reference standard, efforts should be made to clarify the definitions of relevant 1222 categories in the reference standard retrospectively, and to ensure that all included historical 1223 annotations adhere to these standards and are relevant for the intended future use. This may require 1224 the omission of available annotations that were developed following outdated principles or were 1225 based on different types of data. If reference standards are to be developed de novo, an explicit 1226 annotation guideline is recommended. This in turn may require a strengthening and clarification of 1227 existing processes and guidelines for human decision making on the PV task of interest, sometimes 1228 bringing value by harmonizing and making explicit decision processes that may otherwise remain 1229 implicit and variable within an organization. In smaller projects with a limited number of participants, 1230 special care may be required to ensure that annotations of the test set used for performance 1231 evaluation are independent of the development of the AI solution, for example annotations may be 1232 performed preferably by individuals with limited insights and vested interest in a specific AI solution 1233 to avoid conflicts of interest and confirmation bias. Similarly, if testing human-AI teams, the 1234 qualifications of human team member(s) should match those of the intended use case and 1235 deployment domain.

1236 Sometimes, boundaries between reference standard categories are not clear, which yields additional 1237 sources of possible ambiguity. For example, different organizations may have different requirements 1238 on how strong the conviction should be that two individual case reports refer to the same event for 1239 them to be classified as suspected duplicates. This may vary even within an organization depending 1240 on the intended use case, for example one may cast a wider net in highlighting suspected duplicates 1241 if each highlighted pair will be reviewed by a human before action and be more conservative if 1242 suspected duplicates will be automatically removed prior to statistical signal detection. Similar 1243 ambiguities exist in natural language processing tasks seeking to map free text to standard 1244 terminologies such as MedDRA where there may be multiple acceptable terms/codes for a specific 1245 verbatim, and it may be inappropriate to treat terms adjacent to the reference standard annotation 1246 as false positives.

For unsupervised learning like cluster analysis and representation learning, and for applications of
zero-shot learning like text summarization, formal test sets often cannot be obtained and other
approaches to performance evaluation must be considered. In some cases, one may rely on human
subjective review and assessment of an AI solution's output, but then potential biases must be
considered and mitigated. For example, one may present the results of several different AI solutions
to a blinded, domain expert and ask which they prefer. There are also performance evaluation
approaches specifically designed for unsupervised learning like intruder detection analysis.¹⁹¹

A general challenge in PV has been ensuring sustainable and reusable access to reference sets. As AI technologies rapidly advance, the necessity for consistent and frequent testing becomes increasingly important to safeguard against unintended consequences of AI usage. The potential for widespread impact of AI solutions in PV underscores the importance of maintaining up-to-date, accessible

reference standards with clarity on how they were developed and related assumptions.

1259 **Performance evaluation**

Performance evaluation is necessary for critical appraisal of AI solutions. The ability to carry out or
 assess performance evaluations are crucial skills for those who develop AI solutions and for those to
 whom AI solutions are proposed.

1263 Many of the metrics relevant to performance evaluation for AI solutions in PV come from 1264 information retrieval and apply primarily to use cases that can be viewed as binary classification 1265 tasks. In binary classification, we may refer to those instances that we want a method to retrieve as 1266 *positive controls* and those that we do not want it to retrieve as *negative controls*. We use this 1267 terminology throughout the description below (sometimes replacing positive controls by *target* 1268 *events*), acknowledging that other use cases may require different frameworks of evaluation, for 1269 example considering an ordering.

- 1270 Al solutions, like humans, will not always achieve perfect performance on complex tasks. Therefore, 1271 performance is typically assessed statistically for a sample of cases referred to as the test set, 1272 considering measures such as precision (= positive predictive value) and recall (= sensitivity) relative 1273 to the selected reference standard. The balance between precision and recall (and correspondingly 1274 between sensitivity and specificity) should be determined based on the relative costs of different 1275 types of errors (and utilities associated with correct decisions). Composite metrics like the F1 score 1276 (the harmonic mean of precision and recall) provide single-dimensional measures of predictive 1277 accuracy accounting for both precision and recall under some assumptions (for the F1 score that 1278 precision and recall are of equal importance and false positives as costly as false negatives). Test sets 1279 need to be large, diverse, and representative enough to reflect a sufficient portion of the intended 1280 deployment domain and to provide statistically robust estimates of performance. They should
- 1281 include different populations and consider possible scenarios in line with the intended use.²
- 1282 Since the primary interest is the expected performance of an AI solution in prospective use (as part 1283 of an overall system), performance evaluation should be independent of any data directly used 1284 during its development (this is in addition to any cross-validation or other separation of data for 1285 training and validation during development). Various potential sources of dependence between 1286 development and evaluation must be considered and eliminated, the most obvious being the risk 1287 that the same individual data points are considered in both phases. More subtle forms of 1288 dependence, can occur and lead to optimistic performance estimates, for example there may be a 1289 disproportional overlap in scope between the training and test sets compared with the deployment 1290 domain e.g. if training and test sets cover the same subset of drugs and adverse events, which can be
- 1291 referred to as a specific form of data leakage.¹⁹²
- 1292 Selection of machine learning models may also account for indirect performance characteristics such 1293 as an AI model's susceptibility to overfitting, computational cost and robustness to outliers,
- 1294 especially if test sets are not large and diverse enough to be reliably capture their impact during
- 1295 performance evaluation. When comparing different types of methods, any user-driven design
- 1296 decisions should be fixed and finalized before developers first access test sets. This is especially
- 1297 important for more complex methods with numerous analytical choices regarding model
- 1298 architecture, hyper-parameters, and model initialization.¹⁹³ On a related note, complex methods
- 1299 highly dependent on skilful design and deployment by human experts may not readily transfer to
- adjacent application areas without access to the same expertise. In routine deployment one is less
- 1301 concerned about whether one method is theoretically better than another but rather with which one1302 is likely to perform best for a given purpose, irrespective of what design/analytical choices one made.
- is likely to perform best for a given purpose, irrespective of what design/analytical choices one mac

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² For a continually updated inventory, see for example <u>https://oecd.ai/en/catalogue/metrics</u>

1303 Benchmarking

- 1304 Ideally, performance should be compared against relevant benchmark methods, if available. For
- 1305 example, AI-based signal detection methods may be compared against standard disproportionality
- 1306 measures. In the case of more complex benchmark methods, including those based on AI models,
- 1307 special care must be taken to ensure that the benchmark methods have been appropriately
- 1308 instantiated and fine-tuned to the task at hand to serve as a relevant comparator.
- 1309 When public benchmark test sets exist, performance may be evaluated against these, ideally as a
- 1310 complement to performance evaluation targeted to the deployment domain of interest. At present,
- 1311 public benchmarks exist only for some specific applications in PV. They include sets of emerging
- 1312 safety signals, ^{194,195} sets of established adverse drug reactions, ^{196,197,198,199,200} and clinically relevant
- 1313 drug-drug interactions.²⁰¹ However, continual access to benchmark reference sets over time can be a
- 1314 challenge and the degree to which they are maintained and kept up to date varies.
- 1315 To complement overall performance estimates, subgroup analyses can provide useful information on
- 1316 the strengths and weaknesses of the AI solution for different parts of the deployment domains (See
- 1317 also chapter on <u>Fairness & Equity</u>). Along the same lines, sensitivity analyses can help assess the
- 1318 robustness of the AI solution and its evaluation to variations in specification and design.

1319 Special considerations for low-prevalence settings

- 1320 Many PV applications focus on rare patterns and events. For example, in a case retrieval task most
- reports will typically not be relevant for a given topic, such as pregnancy, medication errors, positive
- 1322 rechallenge interventions, or drug-induced liver injury. Similarly, for PV signal detection, most drug-
- event combinations are not true adverse drug reactions, let alone recently detected safety signals.
 Managing and analyzing these rare events effectively requires reliable reference datasets, however,
- existing resources, such as SIDER, are often limited by outdated and static information, underscoring
- 1326 the need for alternative solutions.²⁰² As an even more extreme example, pairs of duplicate reports
- 1327 are vanishingly rare among all possible pairs of reports in large collections of individual case reports –
- 1328 if 10% of the reports in a database of 1 million reports have a (single) duplicate, the chance that a
- 1329 randomly selected pair would be duplicates is only 1 in 10 million.³
- 1330 This low prevalence of positive controls (i.e. class imbalance) limits our ability to achieve accurate
- 1331 performance evaluation and requires special care and consideration. For example, a balance may
- 1332 need to be struck between the quality of each annotation and the resulting size of the test sets (or
- 1333 the cost/time to develop them), for example related to whether double annotations by multiple
- assessors are feasible to increase quality or evaluate consistency. The heterogeneity in skills and
- 1335 preferences among different human reviewers poses a significant challenge to achieving consistent
- quality in annotations. The use of intelligent automation to support decision making can mitigate
 inconsistency and reduce subjective bias in the evaluation process. Moreover, straight random
- 1338 samples of test cases often contain too few positive controls whereas test sets enriched with positive
- 1339 controls can lead to misleading estimates of precision and recall.
- 1340 *Recall* measures how many of the target events are correctly identified (*recalled*) by the AI solution.
- 1341 *Sensitivity* is a synonym. If heuristics are used to increase the proportion of target events in the test
- 1342 set, then recall may be over-estimated since target events which are harder to identify for the AI
- 1343 solution, may less likely be included. This does not mean that rebalancing approaches should
- necessarily be avoided but if they are used, this should be acknowledged and critically assessed.
- 1345 *Precision* is the proportion of target events among all events highlighted by the AI solution. *Positive*
- 1346 *predictive value* (PPV) is a synonym. It is highly dependent on the prevalence of target events in the
- 1347 test set, and if test sets have been enriched with target events, naive test set precision estimates will
- be optimistic. For reliable precision estimates, the prevalence of positive controls in the test sets

- 1349 should match as far as possible that of the intended deployment. For a specific AI solution, this is
- straightforward to obtain by applying the AI solution to a random sample and annotating all
- highlighted instances. However, such test sets are tied to the AI solution in question and will need to
- 1352 be developed again, or at least extended, if the solution is modified.
- Estimates of precision and recall depend on the selected decision threshold, and performance
 evaluation should be targeted at decision thresholds relevant to the intended deployment domain,
- i.e. with a relevant balance between false positives and false negatives.

1356 Beyond summary statistics

1357 Summary statistics as captured by the metrics described in the previous section go only so far in 1358 enabling us to assess and understand the performance of an AI solution. Access to and ability to 1359 inspect representative, concrete examples of an AI solution's classification of individual instances in a 1360 test set is also valuable. Examining false positives and false negatives in an error analysis step can 1361 each give useful insights regarding the strengths and limitations of the AI solution and its evaluation. 1362 For example, if a false negative in de-identification corresponds to a full name preceded by 'Mr', this 1363 may undermine end-users' trust in the solution, even if overall recall is excellent. On the other hand, 1364 if the false negative is 'AF' and it is hard to know from the surrounding text if these are initials or an 1365 abbreviation for atrial fibrillation, then the overall precision metric may be viewed as potentially 1366 conservative. Review of correctly classified instances may in turn give insights regarding an AI 1367 solution's capacity to solve challenging tasks. Does it correctly classify more difficult cases or just the 1368 trivial ones? This may be especially important when there is no baseline comparator, and we may not 1369 understand from overall performance metrics the difficulty of the task at hand. When there is a 1370 baseline comparator method, one may focus on instances that are differentially classified by the two 1371 methods, to better understand the nature of any improved performance of the proposed solution 1372 over the comparator.

1373 Reproducibility

- 1374 Reproducibility for an AI solution requires that it will generate the same output for a given input.
- 1375 Predictive models like support vector machines and decision trees fulfil this requirement. So do
- 1376 certain LLMs and other deep neural networks, once their weights have been fixed at the end of
 1377 training / fine-tuning, even though their model fitting may include stochastic components so that
- 1378 new weights may result if a model is re-trained on the same data.
- GenAl solutions on the other hand include stochastic components also in their execution and will
 typically generate different outputs for the same prompt, without changes to the underlying models.
 The same is true for other methods such as mixture model-based cluster analysis and semantic
 vector representations of adverse events. For such solutions, stability is a key additional performance
 metric, reflecting how similar the results of fully replicated analyses are. While replicability of results
 can sometimes be artificially ensured through seeding the pseudo random number generator, this
 can be non-trivial to do for proprietary models and does not improve the inherent (in)stability of the
- 1386 Al solution, which should be evaluated.
- 1387 Reproducibility, as described here, pertains to an organization that has full access to a specific AI
 1388 model and the relevant reference sets. Full reproducibility by, say, the broader scientific community,
- 1389 in addition requires transparency.

1390 Assessing artificial intelligence solutions with human-in-the-loop

- 1391 Many AI solutions aim for intelligence augmentation, i.e. to support and enhance human decision
- 1392 making. In this context, the relevant focus of performance evaluation would be of the human-AI
- 1393 team. To date, we have limited experience of such studies in PV applications, but at a minimum, they

- 1394 would need to account for the variability in skills and preferences between different human
- 1395 members of the team. Defining a relevant test set may also present new challenges: for example, for
- 1396 signal detection applications, human domain experts could not be blinded to historical safety signals;
- and it may be difficult to obtain a reference standard if the aim is for the human-AI team to *exceed*
- 1398 the quality of classification by unassisted human domain experts.
- 1399 What constitutes acceptable performance may need to account for how the AI solution is integrated
- 1400 with the PV system and whether there is a human in the loop.²⁰³ For example, performance
- 1401 evaluation for an NLP-based system to identify and extract adverse events from source documents
- 1402 might in addition to the overall performance evaluation consider whether errors can be readily
- spotted in the results and whether the end-to-end hybrid process performs better than a fully
 manual approach (for an example see Park et al 2023²⁰⁴).

1405 **Continuous integration and deployment**

- 1406 Deployed models should be monitored in real-world use with a focus on maintained or improved 1407 performance. There may be reasons to revise and update performance criteria in production as the 1408 business understanding of the task is refined or the conditions for the task itself change due to 1409 external factors.
- 1410 For deployed AI solutions that incorporate ML components, there should be appropriate processes
- 1411 and quality controls for periodical re-training to manage risks of performance degradation or
- 1412 negative impact from dataset drift. In some instances, the retraining may consist of incremental fine-
- 1413 tuning within existing model architectures whereas more substantial changes to the deployment
- domain may require changes to the architecture of the AI solution. The latter could result from a
- 1415 change in scope from medicines to vaccines, revisions of the underlying medical terminologies or
- 1416 data structures, updated regulation or conventions and more.
- 1417 Continual performance evaluation can be relevant regardless of whether an AI solution incorporates
 1418 ML components or not. Its frequency should follow the risk-based approach and depending on the
 1419 application, may include data-driven safeguards to identify, for example, substantial data drift or
 1420 performance degradation triggering remedial actions that could include additional evaluation, and
 1421 possible retraining, stopping use of the algorithm and/or introducing quality control measures to
- 1422 maintain confidence in its results. Documentation of activities and acceptance criteria for re-
- 1423 introducing AI solutions under such circumstances may also be required. As an example using
- 1424 mechanisms such as 'ground truths', i.e. known input/output pairs which are checked each time an AI
- 1425 system undergoes a change, or mechanisms to guard against automation bias.
- 1426 One of the potential benefits of ML is the ability to improve performance through iterative 1427 modifications, including by learning from real-world data. To support this approach, the US FDA, 1428 Health Canada, and MHRA described a "Predetermined Change Control Plan" for ML-enabled device 1429 software functions (ML-DSF). Their general principles might conceivably be applied to AI solutions in 1430 PV. A Predetermined Change Control Plan generally includes: 1) a detailed description of the specific, 1431 planned modifications; 2) the associated methodology to develop, validate, and implement those 1432 modifications in a manner that ensures the continued acceptable performance of the algorithm; and 1433 3) an Impact Assessment of the benefits and risks of the planned modifications and risk mitigations. 1434 The detailed description of the planned modification should include changes to the characteristics 1435 and performance of the algorithm resulting from the implementation of the modifications. An 1436 example of a modification might include retraining a ML model. A protocol providing the details of 1437 the data and methods used to develop, evaluate, and implement such a modification should be 1438 created and adhered to. An Impact Assessment of the modification should be carried out and risk 1439 mitigation measures developed to ensure that any identified risks will be controlled. This approach 1440 should be further incorporated into the quality management system governing the PV process being 1441 modified.

- 1442 There should be straightforward means to report issues or anomalies encountered, and these should
- 1443 be addressed promptly. Ideally, the response would include acknowledging receipt of feedback,
- 1444 providing updates on investigations, and implementing necessary changes to the AI system.

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1445 Chapter 6: Transparency

1446 Principle

1447 Transparency regarding AI involves disclosing information between organizations or individuals. This
1448 includes sharing relevant documentation of the AI system lifecycle (i.e. design, development,
1449 evaluation, deployment, operation, re-training, maintenance and decommission) to facilitate
1450 traceability and providing stakeholders with enough information to have a general understanding of
1451 the AI system, its use, risks, limitations, and impact on their rights.

1452 *Key messages*

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- Declaring when and how AI solutions are used for core PV tasks is critical for building trust among domain experts, decision makers, regulatory authorities, and the public.
- The nature of AI solutions deployed for core PV tasks should be described including their
 model architectures, expected inputs and outputs, and the level and type of human computer interaction.
- To give a comprehensive picture of an AI solution's effectiveness and limitations, the presentation of performance evaluation results should describe the scope and nature of the test set(s) used including definitions of their reference standards and sampling strategies.
 Presented performance metrics should be relevant for the intended deployment domain, compared with relevant benchmarks, and complemented by qualitative review of representative examples of correct and incorrect output.
- If possible, a description of the general principles and logic by which an AI model functions and arrives at its outcomes / predictions should be shared, or the lack of such explainability should be acknowledged and its implications discussed.

1467 Introduction

1468 Transparency provides stakeholders with relevant information regarding the nature and use of an AI 1469 solution. It reflects what information is shared with key stakeholders by those who develop or deploy 1470 it. The main purposes of transparency are to build trust, to enable individuals and organizations not 1471 involved in their development to inspect and scrutinize the design and performance of AI solutions, 1472 and to ensure regulatory compliance.

- 1473 As further elaborated on in the chapter on <u>Governance & Accountability</u>, the primary direction of
- 1474 transparency and disclosure of information varies during the phases of the AI solution lifecycle. For
- 1475 example, during the design phase the organization should be transparent toward developers
- 1476 regarding the specification and requirements for an AI solution, whereas the main direction of
- 1477 transparency is the opposite in the pre-deployment phase. During routine use, the most important
- 1478 form of transparency may be from the organization toward end users (and in some cases regulatory
- 1479 authorities).

1480 Disclosing use of artificial intelligence

1481 It is essential to disclose why, when and how AI is being used in different PV tasks. This is to maintain
 1482 trust and accountability among stakeholders, including developers, PV professionals and decision
 1483 makers, regulatory authorities, healthcare professionals, and patients.

1484 Regulatory bodies require disclosure of AI use to assure compliance with applicable laws and

1485 regulations. To this end, software vendors and internal development groups need to be transparent

- toward PV organizations, who in turn need to be transparent toward regulatory authorities. At the
- same time, those individuals who utilize AI solutions to process or analyze PV data must be informed
- about the Al's role in their workflows to help them integrate Al into their processes in an informed

- manner to support its effective application and ensure that they can identify any issues arising fromAl use.
- 1491 PV professionals should also communicate the provenance of data elements and whether AI
- solutions contributed to their capture or development. Human interpretation of PV data may depend
- 1493 on how it was ascertained. For example, signal assessors may lend different weight to a case
- 1494 narrative that was auto generated from structured elements compared with one that documents the
- patients or health professionals' verbatim description of the adverse event. There is also a risk of a
- 1496 vicious circle where AI generated information is used as part of a reference standard in subsequent
- 1497 Al model development, if its provenance is not properly disclosed.

1498 Transparency regarding the artificial intelligence model

- 1499 Ensuring transparency of the AI models used in PV (to the extent possible), is critical to fostering
- 1500 trust, facilitating informed decision making, and ensuring that these models are applied
- 1501 appropriately. Ideally, transparency should be extended to also capture decisions made by PV
- 1502 professionals resulting from the AI model. Model transparency is not only a technical requirement
- 1503 but also an ethical imperative, ensuring that all parties understand the tools they are working with
- 1504 and can make informed decisions based on their outputs. Below are key aspects of an AI model that
- 1505 should be disclosed to stakeholders. The rationale behind the design choices should also be
- 1506 explained, to help ensure that the model is aligned with its intended use and stakeholder needs.

1507 *Table 3: Key aspects of an artificial intelligence model to disclose to stakeholders* 1508 Source: CIOMS Working Group XIV

1509

Intended Use	The intended use of each AI model should be clearly defined and communicated. This includes specifying the PV tasks the model is designed to assist with or perform, such as adverse event recognition in free text, signal detection, or case triage.
Human-Computer Interaction	The level and type of interaction between humans and the AI models should be communicated. This includes specifying whether the AI model is executed autonomously, has a human in-the-loop (and what their required competence would be), or aims to provide decision support to down-stream human specialists.
Model architecture	The type of AI model and its general architecture should be disclosed, such as whether it is rule based, uses linear models, or specific types of neural networks, or combines different ML models in an ensemble, etc. Additionally, relevant details about the model's structure, such as the type and depth of a neural network architecture, should be shared.
Model parameters	At a minimum, key predictors or features that drive the decisions of an AI model should be disclosed, if they are known. If feasible, the full set of model weights and parameters can be shared, to enable external replication and external performance evaluation. See further discussion regarding this, at the end of this section. For AI solutions based on GenAI, any predefined prompts should be specified along with any pre- or post-processing steps.
Explainability	If possible, a description of the general principles and logic by which an AI model functions and arrives at its outcomes / predictions should be shared, or the lack of explainability should be acknowledged and its implications discussed. (<i>See also Section on Explainability</i>).
Training set	Details about the training set(s) based on which ML components have been developed should be disclosed. This would include their size, scope, and creation date, along with reflections on how well they align with the intended deployment domain.

Standard AI Components	If the AI model incorporates public standard components, such as pre-trained ML models, libraries, or frameworks, or datasets, this should be disclosed, including the specific versions used, date of access, and any custom parameter settings.
Acceptable Inputs	The types of inputs that the AI model expects should be specified. This provides insights regarding the basis for the AI model's outputs and ensures that it is only fed data it is designed to handle, thereby maintaining the accuracy and reliability of its outputs.
Type(s) of Output	The types of output generated by the AI model should be described. Examples may be risk scores, classifications, alerts, or free text.
Known Limitations	Any known limitations regarding the nature of the AI model should be communicated, including e.g. features or types of interactions, which it is unable to account for.

1510 To allow other developers and researchers to fully replicate an AI model and possibly even modify it 1511 for further use, an organization might choose to publish its full set of parameters and weights or 1512 even share the source code. This level of openness supports peer review and validation by external 1513 experts, which can enhance trust in the model's reliability and foster innovation. However, it will not 1514 always be feasible due to considerations regarding intellectual property, competitive advantage, or 1515 the sheer complexity of large models. Moreover, for many stakeholders, access to raw code and 1516 parameters of a complex AI model may not enhance their understanding and will need to be 1517 complemented by the other measures for model transparency described above. Understanding the 1518 rationale, assumptions, and subjective decisions made in the implementation can be more important 1519 for gaining meaningful insights into the model's function and effectiveness. For full scientific 1520 reproducibility, developers may also need to share the relevant reference sets, at least those used 1521 for performance evaluation. However, depending on the use case and stakeholders involved this may 1522 conflict with the data privacy principle.

1523 Explainability

- 1524 A specific form of transparency relates to disclosure of the general principles and logic by which an AI
- solution operates and has arrived at a specific output. This may help nurture trust, allow affected
 individuals to understand and influence outcomes, support down-stream human decision making
 and facilitate human oversight and regulatory compliance. In this context, *explainability* and
- 1528 *interpretability* are important concepts, which partly overlap.
- 1529 The set of *Guidelines on the testing of Al-based systems* in the ISO standard for Software testing in
- 1530 Software and systems engineering, characterizes explainability as a *"level of understanding how the*
- 1531 Al-based system ... came up with a given result" and interpretability to a "level of understanding how
- 1532 the underlying (AI) technology works".²⁰⁵
- 1533 Similarly, the AI Risk Management Framework of the US National Institutes of Standards and
- 1534 Technology includes the following statement: "Explainability refers to a representation of the
- mechanisms underlying AI systems' operation, whereas interpretability refers to the meaning of AI systems' output in the context of their designed functional purposes".²⁰⁶
- 1537 The Organisation for Economic Co-operation and Development (OECD) Transparency and 1538 Explainability Principle 1.3 states:²⁰⁷
- "Explainability means enabling people affected by the outcome of an AI system to understand how it
 was arrived at. This entails providing easy-to-understand information to people affected by an AI
 system's outcome that can enable those adversely affected to challenge the outcome, notably to the
 extent practicable the factors and logic that led to an outcome."

- 1543 For the context of this report, we adopt a similar perspective and use *explainability* in a broader
- sense to reflect the degree to which humans can understand the factors and logic that have led to aspecific outcome or that play a role in the general operation of an AI solution.
- 1546 Concrete examples which illustrate the role of explainability in different PV use cases are provided in 1547 the <u>Appendix 4</u>.

1548 Benefits of explainability

- 1549 Explainability can be beneficial because it may:
- Nurture trust in an AI solution, by enabling stakeholders to make sense of and contextualize
 an AI solution's output;
 - Allow individuals affected by an AI solution's output to challenge and influence the outcome;
 - support and speed up human decision-making which builds on or integrates an AI solution output;^{208,209}
- Propose scientific hypotheses for consideration by end users individual or combinations of features such as drugs, diseases, and demographics that are included in the proposed explanation of the findings may provide signals of adverse drug reactions, and adverse drugdisease interactions worthy of evaluation, as well as potential biological mechanisms of adverse drug reactions;²¹⁰
- Enable more complete documentation, audit, and human oversight of AI solutions;
- Contribute to regulatory compliance especially when it is possible to retain and examine the human decision together with the AI output and the explanation upon which the decision was based;
 - Facilitate troubleshooting by revealing issues such as possible biases or likely spurious correlations;^{211,212}
- Contribute towards model assessment and selection by uncovering what is causing different models trained on the same data to perform differently.
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Referring to the definition above, the individuals who could challenge the output of the PV AI system and require explainability are more likely to be stakeholders who are directly involved in the PV process rather than members of the public.²¹³ They may range from the PV and quality assurance staff who are directly interacting with the AI, the developers who are building or maintaining an AI system to the regulators who are inspecting it. Examples on how different stakeholders in the PV process can benefit from explainability are provided in <u>Appendix 4</u>.

1575 Inherent vs post hoc explainability

- AI models of limited complexity may be inherently explainable, allowing the basis for their output to
 be deduced from direct inspection of their model architectures and parameters.²¹⁴ This is also
 referred to as *ante-hoc* explainability. Examples may include simple decision trees, rule-based
 classifiers, and regression models.
- 1580 In contrast, a growing field of research seeks to obtain *post-hoc* explainability (referred to by the
- acronym xAI) for more opaque AI solutions, including deep neural networks with complex
- 1582 architectures and more parameters than a human can survey or comprehend. With such approaches,
- 1583 a separate layer of methods and techniques are applied top of the AI solution²¹⁵ to trace and explain
- 1584 the basis for a specific, already generated output. Some xAI approaches seek to explain the output of
- 1585 complex AI models by estimating relative feature importance and others do so by determining the
- 1586 minimal change in one or more features required to change a given output. There are also xAI
- 1587 methods that provide explainability for a specific output by fitting simpler, inherently interpretable

- models to the local context of a specific output. For examples of specific xAI methods in use at the
 time of writing this report, please see <u>Appendix 4</u>.
- 1590 When an xAI method is used to gain explainability, it must itself comply to the applicable regulatory
- requirements for computerised systems. In other words, the xAI method must be validated and
- 1592 proven to be fit for purpose, and processes must be in place to ensure that it continues to be so.
- 1593 Explanations provided by xAI are an 'approximate understanding of the relationship between the
- data and the predictions' according to Pinheiro et al (2022).²¹⁶ The explanations can be imperfect or incomplete and/or provide only a partial explanation.

1596 Challenges related to explainability

- Stakeholders are advised to critically consider what type of explainability is required for the intended
 use case, for whom, and for what purpose, and whether the system they are considering can provide
 it.²¹⁷
- 1600 The level of explainability of an AI solution's output should not be the sole determining factor for
- 1601 model selection. Some applications (e.g. machine translation) may not require inherent explainability
- and may depend on the capabilities and improved performance offered by more complex AI
- 1603 solutions. In such cases, the negative impact of limited explainability may be mitigated by ensuring
- 1604 high transparency regarding other aspects of the AI solution and its performance, coupled with extra
- 1605 care to achieve validity and robustness and human oversight.²¹⁸ At the same time, it should not be
- 1606 assumed that explainability necessarily leads to lower performance and that a trade-off between the
- 1607 two needs to be made.²¹⁹
- 1608 Similarly, while explainability of an AI solution's output can sometimes help identify issues with
- 1609 validity & robustness or fairness & equity, explainability alone does not prove that the system is fit
- 1610 for purpose, nor does it vouch for the trustworthiness of the system.²²⁰ It attempts to clarify what
- 1611 factors led to a specific output but is not indicative of an AI solution's general performance or of its
- 1612 fairness and equity. For example, even if an inherently explainable AI solution does not include age
- 1613 as one of its explicit features, it could bias against an age group, if this bias is mediated by other
- 1614 features. In fact, explanations may make stakeholders more susceptible to overreliance on model
- 1615 outputs, so called automation bias.²²¹ Also, explainability is no guarantee of transparency an
- 1616 organization may, for example, choose not to disclose the key features and inner logic of an
- 1617 inherently explainable model such as a decision tree.
- 1618 Explainability is not the same for all stakeholders. What is understood by model developers could be 1619 incomprehensible for other stakeholders²²² and cognitive capabilities must be considered to ensure
- 1620 that explanations are comprehensible to humans.²²³ Since humans will need to process and
- 1621 contextualize any explanations provided, they should also be informed about and aware of *their own*
- 1622 possible biases and blind spots which may influence their ability to leverage the explanations.
- 1623 Related to this, it should be noted that, in the worst case, a plausible explanation for an incorrect Al
- 1624 output may increase the likelihood that it is accepted without the appropriate critical review by some
- 1625 end users.

1626 Transparency regarding performance

- 1627 Transparency regarding an AI solution's assessed performance not only communicates how well an
- 1628 AI model operates in practice but also provides stakeholders with insights into the design,
- 1629 implementation, and decision-making processes behind the model. As such, it provides a bridge
- 1630 between theoretical capability and practical utility. Without a clear view of how an AI solution
- 1631 behaves under realistic conditions, stakeholders cannot fully assess its suitability for use or be
- 1632 confident in its robustness and validity. Performance transparency ensures that all stakeholders,
- 1633 from end-users to regulatory authorities, have a clear understanding of an AI solution's strengths,

- 1634 limitations, and expected behaviour in the contexts where it will be deployed. This is particularly
- 1635 important in PV, where AI systems support information processing and decision making, with the aim1636 of safeguarding patient safety and public health.
- 1637 By recording and being able to share detailed performance evaluations with relevant stakeholders,
- 1638 organisations offer clarity on the strengths and limitations of the AI system, as well as the key
- 1639 assumptions made during their design, including quantitative metrics, qualitative examples, and
- 1640 comparisons to benchmarks, and thereby organizations provide the necessary context to build trust
- 1641 and appropriate reliance on AI systems. This transparency allows for informed decision making,
- 1642 ensures that AI systems are used within their intended scope, and helps identify areas where
- adaptations or special measures may be required. Additionally, it supports continuous improvement
- 1644 by highlighting areas where the model may need further refinement or retraining.
- In support of this, there should exist a clear documentation of the data used for performance
 evaluation, including data acquisition, cleaning and transformation, and processes for managing
 missing or erroneous data.
- 1648 Table 4 outlines relevant aspects to disclose to ensure transparency regarding the estimated 1649 performance of an AI solution. For further elaboration, see the Chapter on Validity & Robustness.

1650 Table 4: Relevant aspects to disclose to ensure transparency regarding the estimated 1651 performance of an artificial intelligence solution

1652 Source: CIOMS Working Group XIV

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Scope of evaluation	Describe the nature of the reference sets used for performance evaluation, acknowledging any known deviations from the intended deployment domain (e.g. over- or under-representation of certain drugs, adverse events, patient populations etc.). Relevant information would include the types of data and from where they have been derived.
Sampling	Describe the prevalence of positive and negative controls in the reference set and how this relates to the intended use. If they are different, describe how performance evaluation was adjusted to account for this. Describe any use of data augmentation for performance evaluation.
Reference standard	Disclose the definitions of different categories of classification used in performance evaluation (for example, positive and negative controls in a binary classification task). Share any annotation guidelines used to improve quality and consistency of human annotations in developing the reference standard.
Human input	Describe the qualifications of human assessors contributing to test set development and any use of parallel annotations and evaluations of concordance during this phase. If the AI solution includes a human-in-the-loop during operation, then state the qualifications of those individuals who participated during performance evaluation.
Summary metrics	Present standard performance evaluation metrics when suitable or motivate the use of customized metrics. Place emphasis in this presentation on levels of the decision threshold relevant to the intended use and deployment domain (e.g. with a realistic balance between false positives and false negatives). Complement composite performance metrics with their components (e.g. precision & recall for an F-score).
Benchmarks	Present comparisons against relevant benchmark methods (including human-level performance) and/or standard benchmark reference sets, when available.
Subsets & sensitivity analyses	Present the results of any subset or sensitivity analyses during performance evaluation or acknowledge the lack thereof.
Qualitative review	Provide representative examples of correct classifications and representative examples of incorrect classifications (false positives and false negatives).

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1655 Chapter 7: Data privacy

1656 Principle

Data privacy refers to the fundamental right of an individual to control how their personal
 information is collected, stored, shared, and used. It is an aspect of the principle of "respect for
 persons" that is foundational to the conduct of biomedical research. Regulations, legislation and
 guidance documents provide measures intended to preserve the confidentiality, anonymity,
 autonomy and control of sensitive and potentially personally identifiable health data in the setting of
 PV.

1663 Key messages

1664	•	The ethical framework to evaluate the use of data privacy protected applications of AI in PV
1665		is embedded within the standard principles for research activities involving human subjects.

- The use of certain AI applications in PV requires additional attention to assure data privacy.
- The applications of ethical principles most relevant for the use of AI in routine PV are data privacy, fairness, and equity.
- PV professionals should recognize that existing procedures used to assure regulatory compliance may need to be re-evaluated due to the heightened risks of GenAI to compromise data privacy and for ML to amplify biases.

1672 Introduction

1673 Although data privacy has been recognized as an implicit legal right for well over a century,²²⁴ it was not until the 1970's that this topic began to receive formal international attention. Advances in 1674 1675 computer technology began to facilitate the large-scale collection, organization, and evaluation of 1676 amounts of data that had previously relied upon paperwork. In the absence of any laws regulating 1677 how public bodies could collect, store, or share personal data, the first data privacy law was passed 1678 in 1980.²²⁵ In the US, public concerns about the potential misuse of collected data led to the US Privacy Act (1974),²²⁶ which provided boundaries for the collection, integrity, and use of personal 1679 1680 data. These same issues raised concerns about transfer of large amounts of personal data across borders, which led to the first international guidelines to protect data privacy in the context of 1681 international trade.²²⁷ Similar to this CIOMS Working Group report, the OECD guidelines laid out a set 1682 1683 of core principles; however, its intent was to assist governments, business and consumer 1684 representatives with the objective of supporting data transfer to facilitate commerce while 1685 protecting personal data privacy. Each of these documents were framed as legal responses to 1686 technological threats, and did not explicitly highlight the ethical foundations of data privacy. Over 1687 subsequent decades, the guidelines have influenced most subsequent data protection 1688 regulations/laws, such as the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule 1689 1996 and General Data Protection Regulation (GDPR) 2016, both of which are discussed later in this 1690 chapter. As noted in Appendix 2, considerations to protect data privacy are specifically identified in a 1691 survey of recent major national and international reports on the use of AI, generally and in 1692 pharmaceutical development.

1693 Ethical considerations

1694 While data privacy concerns are widely recognized in the use of AI, at the time of this publication, the 1695 authors are unaware of a standard reference focusing specifically upon the ethical considerations in 1696 the use of AI applied to PV. Many publications that refer to ethics and AI, such as the WHO Guidance, 1697 Ethics and Governance of Artificial Intelligence for Health,²²⁸ emphasize several basic principles that 1698 were first elaborated in the Belmont Report (1979).²²⁹ That report was federally commissioned (USA) 1699 to determine basic ethical principles that are foundational to biomedical and behavioural research

- involving human participants. These principles underlying modern human research protection bear
 upon clinical research as well as certain post-marketing PV activities globally, recognizing that some
 PV activities are not technically considered research.
- 1703 The Belmont Report identified three basic principles that are foundational to interventional and 1704 behavioural research involving human participants: respect for persons; beneficence; and justice.
- 1705 Respect for Persons refers to the obligation for the research subject to enter research knowingly and
- 1706 of their own free will. It also considers that some individuals, such as those who are cognitively
- 1707 impaired, may not be capable of making this decision independently and based on self-
- determination. From a practical perspective, respect for persons is immediately recognized by the use of informed consent documents, which require that research subjects be advised that they are
- use of informed consent documents, which require that research subjects be advised that they are
 being invited to participate in a research study, that they are made aware of the purpose of the
- 1711 study, including its potential risks and benefits, and that the information be transmitted so that it is
- 1712 comprehensible to the participant. Participants must be able to freely choose whether to participate,
- including the option to exit the research project. Participants cannot be unduly influenced or coerced
- 1714 into participation. Informed consent is waived for routine PV activities through statutes recognizing
- 1715 the pre-eminence of societal/public health interest.
- 1716 The principle of Beneficence describes the need for research to be designed to maximize its potential
- benefits while minimizing potential harms. Research in which the harms of participation are known
- to outweigh potential benefits would not be justifiable. This concept also captures the core tenet of
- 1719 the Hippocratic Oath to "do no harm". For those involved in clinical trials, equipoise is a familiar
- 1720 concept, based on the premise that there is genuine uncertainty about which treatment arm in a
- 1721 clinical trial is best with respect to safety and/or efficacy. It captures the concept the research is not
- 1722 frivolous, including that potential risks have been minimized. PV incorporates beneficence into
- 1723 ongoing benefit/risk assessments. It should be acknowledged that there are applications of AI in PV
- that do not contain personal information, and these activities are outside the scope of data privacydiscussed in this chapter.
- 1726 Finally, Justice refers to the ethical obligation to see that research is conducted among those who
- 1727 might benefit and that involvement in research is sensitive to ensuring that certain populations, e.g.
- 1728 prisoners, are not preferentially selected for research out of convenience, and that the burdens and
- 1729 benefits of research should be born equally among those who might benefit.
- 1730 The intent of the Belmont Report was to address considerations in medical research, intended to 1731 advance generalizable knowledge, and draw distinctions with the distinct responsibilities of medical 1732 practice, intended to support individual patient care. The report did not discuss public health 1733 activities, but its key principles are used in public health activities ranging from disease surveillance 1734 to PV. Certain public health activities are mandated by statute, including PV. Drug safety includes 1735 monitoring safety during clinical trials, post-marketing surveillance, and post-approval safety studies 1736 (PASS). Clinical trials are defined as research and are a focus of the Belmont Report. PASS is a form of 1737 real-world evidence, often required as a condition of product licensure (RWE is the focus of CIOMS 1738 Working Group XIII).
- 1739 The ethical implications for the use of AI in PV for approved products that are most pertinent include 1740 data privacy (derived from the principle of Respect for Persons) and fairness and equity (derived 1741 primarily from that of Justice). Respect for persons indicates that every individual has the right to 1742 control information about themselves. In the context of PV, Justice captures the concept of fairness, 1743 meaning that the benefits of PV knowledge should be equitably distributed among those who may 1744 use specific medicinal products, i.e. lack of discrimination. Fairness as applied to PV means that the 1745 activity is conducted in a non-discriminatory manner, ideally so that the methods support the 1746 representativeness of the population being evaluated and equitable to provide insight into the 1747 population that may be exposed to the product. In the context of PV, the principle of Justice is

applied through efforts to assure Fairness and Equity, which is the subject of a separate chapter inthis report.

1750 Data privacy regulations

1751 Many countries have established laws to protect the data privacy rights of the individual. These laws 1752 share the common principle that personal data requires protection, and that this should be 1753 accomplished through mechanisms that mitigate risk to the individual while requiring accountability 1754 of the entity using the data. Two of the most frequently cited are the HIPAA, 1996, used in the United 1755 States, and the GDPR, 2016, which is employed in the European Union. These examples will be used 1756 to illustrate commonalities and differences between data privacy regulations, and their implications

- 1757 for the application of AI to PV.
- 1758 Example: Health Insurance Portability and Accountability Act

1759 As the name suggests, HIPAA (1996) originally focused on health insurance data²³⁰ and was

1760 developed to ensure data privacy as medical information moved from analog to digital. At the same

time, the legislation was intended to advance common administrative standards for health care data.

1762 In short order, the rapid adoption of digital technologies in health care (e.g. electronic health

- 1763 records) and the interest in using electronic data for research and other purposes led to follow on
- 1764 legislation to support the use of electronic health records according to standards that would ensure
- administrative efficiency while protecting patient privacy and security (HIPAA Privacy Rule, 2000;

Security Rule, 2003). The HIPAA Privacy rule defined individually identifiable health information

1767 (Protected Health Information – "PHI") and defined safeguards to protect the privacy of this

- information. HIPAA also delineates Business Associate Agreements, requiring covered entities thathandle PHI to comply with its privacy and security rules.
- 1770 HIPAA emphasizes the confidentiality, integrity and availability of health data, and includes 1771 provisions focused on the "minimum data necessary standard", i.e. limiting data to those necessary 1772 for the specific purpose. It specifies patients' rights to access and amend medical records. To protect 1773 patient confidentiality, HIPAA recognizes types of data that could be used to identify individuals and 1774 specifies 18 unique PHI identifiers. The list underscores the range of common data types that are 1775 largely unrelated to health care and which contain identifiable information that could compromise 1776 patient identity: name(s), geographic subdivisions smaller than a state, dates (except year, e.g. date 1777 of birth), telephone numbers, fax numbers, email addresses, social security numbers, medical record 1778 numbers, health plan beneficiary number, account numbers, certificate/license numbers, vehicle 1779 identifiers, device identifiers, web URLs, internet protocol (IP) addresses, biometric identifiers (e.g. 1780 fingerprints); full face photographs, as well as any other unique identifier that could be used to trace 1781 the identify of an individual. Once these identifiers are stripped from a source record, the record can 1782 be used without restrictions imposed by HIPAA as the record no longer contains PHI.
- Public health often balances societal interest with personal rights. Based on overriding societal needs
 for the safety, effectiveness, and quality of medicinal products licensed for use in the US, routine PV
 activities conducted by license holders are typically exempt from some HIPAA requirements for
- 1786 patient authorization to disclose and use PHI. Medicinal products are governed in the US by Food and
- 1787 Drug Administration (FDA) regulations that require monitoring the quality and safety of FDA-
- regulated products, which is conducted in part through adverse event reporting, product tracking,
 recalls, and post-marketing surveillance. While some PV activities are exempt from HIPAA, data
- privacy protections remain, including: use of the minimum necessary data standard (collecting only
- data essential to fulfil the PV responsibility), de-identification and/or anonymization of data
- (employed where possible); use of technical, administrative, and physical safeguards to prevent
- 1793 unauthorized access, use, and disclosure); and safeguarding by Business Associate Agreements
- 1794 (where vendors or partners are engaged). Within the US, the FDA and Centers for Disease Control
- and Prevention (CDC, Atlanta) have complementary responsibilities to support and advance health.
 Among its responsibilities, the FDA is responsible for "protecting the public health by assuring the

- 1797 safety, efficacy, and security of human (and veterinary drugs), biological products", and medical
- devices. The CDC responsibilities include protecting "America from health, safety and security
- threats, both foreign and in the U.S.", including those associated with domestic and international
- 1800 diseases and chronic or acute diseases. This is accomplished in part by conducting "critical science
- 1801 and providing health information that protects (the US) against expensive and dangerous health
- threats". To fulfil their responsibilities, public health authorities have a somewhat broader remit than
 the private sector and are able to conduct their responsibilities and use PHI without patient
- authorization; however, they implement data privacy safeguards both within their organizations and
- 1805 when collaborating with others.
- 1806 In contrast to public health authorities and the private sector, academic involvement in PV is
- 1807 generally conducted as a research activity (e.g. PASS), and are subject to different oversight,
- 1808 including use of institutional review boards (IRBs, aka ethical review boards) to assure that studies
- 1809 meet appropriate ethical standards, and are conducted with mitigation for data use and privacy, data 1810 use agreements, where applicable with other organizations the use of de-identified and limited data
- 1811 sets, and compliance with both HIPAA and the Common Rule.
- 1812 Example: General Data Protection Regulation
- 1813 The GDPR (Regulation [EU] 2016/679) is a comprehensive set of rules overseeing personal data
- 1814 protection in the European Union and succeeds the earlier Data Protection Directive (Directive
- 1815 95/46/EC), which was issued contemporaneously with HIPPA, at the dawn of the internet age. The
- 1816 scope of the GDPR is much broader than HIPAA as it pertains to the use of personal data affecting all
- 1817 manner of human interaction, including processing by automated means as well, and stems from the
- 1818 1950 European Convention on Human Rights: "Everyone has the right to respect for his private and
- 1819 family life, his home and his correspondence".²³¹
- The GDPR incorporates principles such as lawfulness, fairness, transparency, accuracy and integrity,
 purpose limitation, data minimization, confidentiality, and storage limitation. Compliance is a major
- 1822 feature of the GDPR with organizations such as pharmaceutical companies required to have a Data
- 1823 Protection Officer responsible for overseeing compliance. Penalties for non-compliance are
- 1824 significantly greater than those under HIPAA, with fines up to 4% of global turnover. To offer
- 1825 practical examples, based on the requirements and obligations under the GDPR, four risk-based
- 1826 categories may be differentiated:
- 18271. Prohibited use (e.g. genetic data that might be used for the purpose of drug1828development would require explicit consent from the patient/participant); it is therefore1829prohibited without such consent;
- 18302. Restricted use (e.g. the use of biometric data to identify employees for security purposes1831only, in line with necessity, proportionality and other requirements;
- 18323. Permitted use with safeguards (e.g. use of purchasing history to create targeted1833advertisements would be typically be permissible provided that efforts were made to1834protect customer identity, customers would need to consent and have the opportunity1835to opt-out, and efforts were made to identify and mitigate and risks to customer1836privacy); and
- 18374. General permitted use (e.g. processing customer information for online billing purposes,1838provided that the data are limited to those needed to fulfil the transaction, and that1839security measures are taking to prevent unauthorized access).
- Additionally, several safeguard measures may be used, such as data encryption (preventing access
 without a decryption key), pseudonymisation (replacing identifiable information with pseudonyms to
 mask identity), and use of Data Protection Impact Assessments to identify and mitigate risks in data

- 1843 processing to protect the individual. In contrast to HIPAA, GDPR incorporates a "right to be
- forgotten", permitting individuals to request deletion of their personal data. In the case of special
 categories of personal data, such as health data, explicit consent may be required for data processing
- 1846 under GDPR and, where collected, such consent may be revocable.

Similar to HIPAA, the rules of the GDPR allow for pharmaceutical companies to meet their legal obligations to conduct PV activities, monitor and report adverse events without consent in order to ensure oversight of the safety and effectiveness of medicinal products – provided that certain safeguards are in place. These responsibilities may limit data protection rights normally in place under the GDPR, e.g. the "right to be forgotten". Other safeguards include requirements for data minimization as well as administrative, technical and organizational measures to protect personal data.

- 1854 In fulfilling its responsibilities to assure the safety, effectiveness, and quality of medicinal products
- authorized for use in the European Union, the European Medicines Agency is empowered to assure
 PV oversight in a manner that acknowledges that certain data protection rights, such as the right to
- 1857 be forgotten, may be limited for specific PV activities. The EMA emphasizes the principles of data
- 1858 minimization, purpose limitation, lawfulness, fairness and transparency in its data use. In contrast to
- HIPAA, the GDPR has special provisions for international data transfers, imposing restrictions in
- exporting data collected for EU citizens (regardless of domicile) outside the European Economic Area
- 1861 and applies safeguards to provide an appropriate level of data protection.

Data privacy expectations for PV research conducted by academia in the EU are analogous to those for the US, with IRB oversight and an emphasis upon adherence to principles of data minimization and purpose limitation. Additionally, international collaborations that involve data transfers outside of the EEA require safeguards that typically include contractual language to assure compliance with GDPR rules.

1867 Other data privacy regulations

Although the FDA and EMA data privacy regulations are currently the most widely followed, it should be noted that there are an increasing number of country-specific differences, which pose particular challenges for the use of multinational AI model development using secondary data. Comparison of regulations in place in Germany, China, and Japan illustrate this point.

1872 Table 5: Data privacy regulations for using secondary data in Germany 1872 1872

- 1873 1874
- Source: CIOMS Working Group XIV

Aspect	Germany
Governing Law	General Data Protection Regulation (GDPR) (EU-wide), Federal Data Protection Act (BDSG) (Germany)
Health Data Classification	"Special category data" (Art. 9 GDPR)
Consent Requirements (Research & PV)	Usually required; exceptions for public interest (e.g. PV, RWE)
Secondary Use of Data (e.g. RWE)	Allowed if legal basis exists (public health, scientific research, etc.) with safeguards
De-identification Standards	Pseudonymization encouraged; full anonymization for broader reuse
Cross-border Data Transfer	Allowed to countries with adequacy or with SCCs/BCRs
Pharmacovigilance Exemptions	Explicitly exempt from consent under public health/legal obligation

Regulator Guidance on Biomedical Use	Extensive EMA and national ethics bodies guidance
Oversight Body	German DPAs + European Data Protection Board (EDPB)
Key References	GDPR (Regulation EU 2016/679); EDPB Guidelines 03/2020; EMA Module VI (GVP); BDSG (Germany)

Table 6: Data privacy regulations for using secondary data in ChinaSource: CIOMS Working Group XIV

Aspect	China
Governing Law	Personal Information Protection Law (PIPL)
Health Data Classification	"Sensitive personal information"
Consent Requirements (Research & PV)	Explicit consent generally required; strict interpretation
Secondary Use of Data (e.g. RWE)	Permitted with new consent or proper anonymization
De-identification Standards	Anonymization required to avoid consent; "irreversible" standard
Cross-border Data Transfer	Strict rules: security assessments, contracts, individual consent; limited adequacy
Pharmacovigilance Exemptions	AE reporting permitted but must minimize identifiable data
Regulator Guidance on Biomedical Use	PIPL + draft health data governance rules; evolving
Oversight Body	Cyberspace Administration of China (CAC)
Key References	PIPL (2021); CAC draft regulations on health data; State Council health data measures (2022)

Table 7: Data privacy regulations for using secondary data in JapanSource: CIOMS Working Group XIV

Aspect	Japan
Governing Law	Act on the Protection of Personal Information (APPI)
Health Data Classification	"Special care-required personal information"
Consent Requirements (Research & PV)	Consent generally required, but pseudonymized data may be used for public interest or research
Secondary Use of Data (e.g. RWE)	Allowed with pseudonymization/anonymization and research purpose declaration
De-identification Standards	Recognizes both anonymized and pseudonymized data; latter still regulated
Cross-border Data Transfer	Permitted to "adequate" countries (EU, UK); otherwise, consent or contracts needed

Pharmacovigilance Exemptions	AE reporting allowed without consent under regulatory mandate
Regulator Guidance on Biomedical Use	MHLW guidance on clinical research and PV under APPI
Oversight Body	Personal Information Protection Commission (PPC)
Key References	APPI (2020 amendment); PPC Guidelines; MHLW guidance on GPSP and human research ethics

1875 Practical considerations to support data privacy

As these examples indicate, regulations have been developed to assure appropriate data privacy
within the framework required to conduct routine PV activities. The list of 18 unique identifiers
enumerated by HIPAA highlights the breadth of the types of data that can be used to identify
individuals. In the years following the introduction of HIPAA and the GDPR, there has been
recognition that additional measures may be required to anonymize data.

As a regulated industry, pharmaceutical companies must comply with the data privacy and reporting requirements of all countries in which their products are licensed. As an example, the EMA requires adherence to Good Pharmacovigilance Practices (GVP) and to data protection principles from the GDPR. Ensuring compliance requires attention to evolving country-specific regulations as well as the oversight of vendors that support companies (in some cases conducting certain PV activities for individual companies) as well as business partnerships, e.g. where a combination therapy is codeveloped by more than one company. Regulatory authorities may have different requirements for

- reporting patient information, necessitating some customization and additional oversight to assure
 adherence to local requirements. For example, Australia requires reporting of ethnicity (to support
- fairness/equity), while it is prohibited in France out of concerns of discrimination.
- 1891 To support compliance with global data privacy requirements, contractual arrangements with third
- 1892 parties (e.g. vendors, partners) include privacy-specific provisions and language. In the US,
- 1893 contractual arrangements with vendors/partners require Business Associate Agreements. Under
 1894 GDPR, binding corporate rules (BCRs) may be implemented to enable multinational companies to
- 1895 move personal data within their companies across borders; BCRs are legally binding and require
- 1896 approval from EU authorities. In the EU, an additional layer of oversight is imposed through the
- 1897 required use of in-house data privacy officers for certain businesses such as pharmaceutical
- 1898 companies. Globally, there are a range of potential consequences for data breaches, from
- 1899 requirements for notification to data protection authorities up to and including significant fines and 1900 penalties
- 1901 In the EU, an additional layer of oversight is imposed through the required use of in-house data
- 1902 protection officers for certain businesses such as pharmaceutical companies. In many countries,
- 1903 including in the European Economic Area, there are penalties for data breaches.

1904 Risks to maintaining data privacy as artificial intelligence is employed in pharmacovigilance

1905 One of the promises of AI is that it will permit more efficient processing of large amounts of routine

1906 PV data, e.g. individual case reports. Additionally, large language models (LLMs), whether open or

- 1907 closed, permit nearly instantaneous planned (or unplanned) linking of data sources that would
- 1908 otherwise not have occurred, or have been difficult to accomplish. As discussed below, these risks
- 1909 are substantively greater for open vs closed LLMs. GenAI models are also useful for extrapolation –
- 1910 finding patterns that might otherwise not have been recognized. These attributes raise the question
- 1911 of whether current data privacy tools are sufficient to prevent re-identification of deidentified data.
1912 Adequacy of de-identification measures

In 1990 (six years prior to HIPAA) a US researcher used census data to identify 87% of the US
 population based on three readily available data elements: five-digit mailing (zip) code, gender and
 date of birth, illustrating that few data points were needed to uniquely identify individuals.²³² Though
 mailing codes were subsequently classified as PHI under HIPAA, the point remains that just a few
 generally accessible data points may be needed to compromise data privacy.

A study using data from a children's hospital in Ontario, Canada, demonstrated that the risk of reidentification of individuals based upon de-identified pharmacy data could be minimized, or even eliminated, by reducing the precision of values in selected data elements, such as replacing the admission and discharge dates with the quarter and year of admission. However, the maximum amount of acceptable generalization in the data element values must be determined by formally examining not only the risk of re-identification and breach of patient privacy but also the intended analysis, which may not be conducted without the appropriate level of precision.²³³

- 1925 The EMA and Health Canada now require public sharing of clinical trial reports as part of the drug 1926 approval process. Standards for data anonymization have been issued. Applying these standards,
- 1927 researchers evaluated the risk of re-identification associated with a clinical study report for a
- 1928 nonsteroidal anti-inflammatory drug, grading suspected cases based on the likelihood of accurate
- 1929 matching.²³⁴ The authors found six suspected matches out of 500 reviewed cases and observed that
- 1930 identifying the matches was time-consuming (24.2 hours per case). Matching was best informed by
- social media and death records. Based on the 0.09 probability risk threshold of re-identification
- established by EMA²³⁵ and accepted by Health Canada, the authors concluded that existing
 anonymization guidance was sufficient to provide an adequate level of data protection and advised
- review the mechanisms by which re-identification had occurred. With rapid advances in AI, the time
- required to replicate the reidentification exercise reported in that study (published in 2020) will likely
- 1936 have decreased by the date of this report, and will continue to do so.
- 1937 *Risks of data breaches*

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1942

- 1938 The potential consequences of re-identification of de-identified data are amplified by numerous
 1939 examples of data breaches that have occurred throughout the world. A few examples illustrate the
 1940 breadth of some recent data breaches, along with their potential consequences:
 - A purposeful attack on a US financial firm leading to access of more than 100 million customer accounts and credit card applications;²³⁶
- An apparently politically motivated international attack by a foreign government on a credit reporting agency in the US resulting in the release of names, birth dates, and social security numbers of nearly half the US population, purportedly with the intent of using AI to compromise US government officials;²³⁷
- A purposeful domestic data breach intended to embarrass a political opponent, involving a cyber-attack on an Asian health care plan result in 1.5 million patient records;²³⁸
- An unintentional release of Indian government biometric, and other personal data, in a database containing records of 1.2 billion individuals.²³⁹ In this instance, a criminal group exploited the data breach and offered individual patient records for sale. Approximately 100,000 persons are known to have had their data accessed.
- Each example occurred before the widespread use of generative AI, a technology that has been
 advancing rapidly, and which has the potential to efficiently link publicly available data sources with
 those obtained maliciously, leading to enhanced risk for re-identification and compromising data
 privacy.

1957 Individual responsibility to protect personal data

In addition to processes to ensure data privacy to conform to data privacy regulations, individuals
 play a role in protecting their own data. This responsibility grows in importance with the ever-

1960 increasing number of digital tools (e.g. Smartphones, wearables), apps, and software (e.g. Al-assisted 1961 translation tools, GenAI) that provide opportunities for individuals to disclose personal data that may 1962 not be sufficiently protected. In many instances, there are legal requirements to support an 1963 individual's data privacy (e.g. through the GDPR); however, there remain opportunities for lapses in 1964 data privacy, and these are particularly worrisome in the use of GenAI. Common mechanisms to 1965 advise persons of data use policies may include terms of use (e.g. End User Licensing Agreements – 1966 aka EULA), data privacy notices, and, in some instances, the requirement of explicit consent for use 1967 of personal data. Individuals may share personal data (e.g. names, phone numbers), when submitting 1968 queries without understanding the consequences of disclosing such information. In many instances, 1969 notably those using open GenAI tools, these data may no longer be private. Individuals may also 1970 share context-specific information, such as a recent illness (or as in a noted example, a motor vehicle 1971 accident) that might be used to identify them.²⁴⁰ Users may also unintentionally provide personal identifying information by sharing (e.g. in social media) context-specific data outputted by GenAI. 1972 1973 These data may subsequently be leveraged to identify the individual even if personal data was not 1974 directly entered depending upon the data privacy policies of the respective platform.

1975 Potential risks to data privacy using large language models in pharmacovigilance, and approaches for
 1976 mitigation

1977 In principle, existing data privacy regulations, (or legislation, such as the GDPR), should provide the 1978 basis for protection of data used in AI applications to PV. Model development may require the use of 1979 PV data (such as ICSRs) to data scientists and machine learning engineers for training as well as 1980 execution. All involved parties, which may include both pharmaceutical companies and vendors, may 1981 have access to data that is protected, creating the risk for exposure to larger groups. All parties 1982 should be aware of data privacy requirements. The risk is potentially greater with LLMs, as the 1983 underlying mechanism of these models provides the potential for some re-identification that would 1984 otherwise be unlikely. Those organizations that maintain closed LLMs exercise control of prompts as 1985 well as the data contained in the models; in contrast, open LLM models do not have this safeguard 1986 and run a greater risk of re-identification, due to the LLM capability of drawing from data sources 1987 that may be opaque and not intrinsically within the purview of data privacy regulations (for example, 1988 containing the sort of data described above under Individual responsibility to protect personal data). 1989 Leaks may occur through prompts bypass data privacy considerations or through models that are 1990 trained on personal data. Additionally, as noted above, re-identification can occur even with 1991 presumed de-identified data. PV requires review of potentially identifiable and sensitive information 1992 that includes basic demographics (including birth date) associated with sensitive data elements 1993 including medical or health information (including medicine and vaccine exposure), ethnicity, race, 1994 sexual orientation, genetic information, biometric data, physical characteristics, lifestyle information, 1995 etc., requiring heightened safeguarding measures.

1996 Among the types of challenges posed by GenAI (as well as in some cases ML) for PV are the following.

- Algorithms may be developed within open LLMs, without attentiveness to applicable data
 privacy requirements, thereby posing a potential privacy risk. If these LLMs are then adopted
 for use within closed LLMs, there is the potential risk for disclosure of protected information.
- Within a closed LLM, attention should be paid to different sources that may be added to the LLM for unrelated purposes. If genetic data has been collected (with participant consent) for a study and is added to a LLM for a specific analysis, measures would need to be taken to ensure that it is not used for a different purpose outside of the original consent. The accepted practice is to seek consent for additional uses of those data (as the data would now be part of the LLM).
- Generative AI programs can integrate otherwise discrete data sources such as such as census and vital statistics and public health data, which may be linked to a deidentified health record data set (e.g. in the setting of an active PV activity (e.g. a post-authorization safety study) leading to the possibility of reidentification.

2010 These types of risks are amplified in settings where data privacy regulations are lax or poorly

enforced. LLMs that are smaller and introduced earlier have tended to have more scrutiny for data
 privacy than larger and more recent LLMs (see Figure 6). Reasons may include: 1) lack of public
 availability of newer, larger LLMs; and 2) privacy technologies have struggled to keep up with these
 newer, larger LLMs.

2015 Figure 6: Relationship of timing of large language model introduction, parameter size and

- 2016 attentiveness to data privacy
- 2017 Source: ²⁴¹
- 2018

Parameter size 1.00E+12 + Pal M FALCON + GPT-3.5-turbo + Cohere-xlarge 1.00E+11 = LLaMA-2 + cohere-xlarge Mistral 78 cohere-large = 1.00E+10 TS ... LLaMA-7B GPT2 cohere-medium + Gemini-Nano-2 1.00E+09 clip-vit-large GPT2-Larg Bert-Large GPT2-M GLM-base wav2vec2-large RoBERTa-Base GPT2-base ViT-base 1.00E+08 1.00E+07 Bert-ting 1.00E+06 2017-Sep 2020-Jun 2019-Feb 2021-Oct 2023-Mar 2024-Jul



The horizontal axis represents the time of LLMs release, while the vertical axis represents the size of model parameters. Blue dots signify LLM instances not addressed in the literature pertaining to privacy protection, whereas black dots indicate those that have been examined in such literature. The green backdrop delineates the central cluster zone of LLMs with the potential to facilitate privacy protection.

2025 Conclusions

The right to data privacy resides within the well-established framework of basic ethical principles for human research protection articulated in the Belmont Report. National regulatory authorities have provided requirements intended to protect data privacy, indicating the types of data that can be made available, along with safeguards (such as data minimization, anonymization, de-identification and data encryption) along with potential penalties for non-compliance.

2031 Despite data privacy laws and the increasing sophistication of technical measures employed by 2032 companies entrusted with personal information, attempted and successful data breaches have been 2033 occurring with increasing frequency and often at enormous scale (affecting in some cases >100 2034 million individuals), suggesting both failures in oversight along with technical advances to outwit 2035 cybersecurity measures and break into secure data sources.

- Ever-increasing computational power, larger linked databases, and the introduction of GenAI, are
 occurring in parallel with an increasingly globalized PV landscape involving more numerous and
 complex interdependencies (e.g. business partnerships, international vendors conducting PV
- 2039 activities). The ongoing challenge for PV professionals and regulatory agencies and industry, as well
- as colleagues and academia will be to assure that within this rapidly evolving data science landscape,
- 2041 data privacy measures are monitored and regularly updated to properly protect personal data.
- A potential risk in applying GenAl for PV is patient reidentification, suggesting a need to reconsider the specificity of de-identified data, along with risks associated with open LLMs in which some data sources may be outside the control of the user.
- In addition to following existing data privacy regulations, efforts to mitigate risks to data privacy
 when applying AI to PV may include the following.

- Recognition that the technology is advancing rapidly, requiring ongoing monitoring, e.g. to
 assure that data de-identification measures are adequate.
 - Understanding that open and closed LLMs pose somewhat different challenges to data privacy. Operating closed LLMs in safeguarded environments within institutional firewalls and carefully examining the risks of sharing these models with third parties should be helpful in risk mitigation.
- Audits to evaluate whether only the minimum required personal information is included in reports, that any re-use of data for secondary purposes is consistent with the purposes for which that data was collected and that adequate measures are in place to support compliance with data protection requirements by all entities (e.g. vendors) contributing to PV. Insofar as PV activities may be conducted by a network of collaborating organizations, the organization with the weakest oversight of data privacy may present a risk.
 - Oversight regarding access to LLMs for PV practices to assure that use by trained PV professionals is fit for purpose.

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2061 Chapter 8: Fairness & Equity

2062 Principle

Fairness and equity require awareness of and adherence to impartiality, equality, non-discrimination,
 diversity, justice, and lawfulness. The benefits of AI in PV should be equitable across all relevant
 populations and groups. Throughout the AI lifecycle, it is important to avoid and mitigate unfair bias,
 and any discriminatory practices and unjust social wellbeing and environmental impacts.

2067 Key Messages

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- Consider the development and application of AI impacting fairness and equity, whose lack or imbalance may result in discriminatory harm to subpopulations underserved by an AI solution, explicit biases resulting in negative impact, or impact performance by providing inaccurate results.
- Plan and implement mitigation strategies where possible for areas that bias may be introduced reducing potential underperformance; avoid discriminatory harm to underserved populations.
- Equity may be advanced by taking measures (e.g. assess for representative data sets) to
 assure that AI applications to PV result in outputs (e.g. assessments, aggregated data outputs
 used for product safety assessments, etc.) that are relevant to populations anticipated to
 have exposure to the specific medicinal product being evaluated.
 - Screening and identifying explicit or potential bias when possible is key to implementing mitigation measures to reduce risk, determining AI applicability and limitations, and establishing expected performance acceptance criteria.
- Scrutinize training and performance evaluation reference data sets for adequate
 representation and evaluate performance in relevant subgroups when possible. Inadequate
 reference data is often the cause of inadequate fairness and equity.
- There is limited fairness and equity in ICSRs, with some countries reporting significantly more than others and providing more contextual data available for analysis, such as real-world data (RWD). Consequently, our understanding of routine usage is often limited among underserved populations.

2089 Introduction: general concepts and considerations

In the context of PV, adherence to established laws and regulations such as privacy laws and PV
 regulations must remain intact with the introduction of AI. What has changed is the increasing
 awareness of the need for consideration, governance, and mitigation of potential factors that may
 influence or impact fairness and equity with the use of AI.

Not all fairness and equity concepts, considerations or negative consequences associated with the
use of AI will be uniquely specific to PV. That does not negate the need to address these
considerations. Biases within AI solutions is a general problem which may impact performance, and
not all forms of statistical bias will result in a negative impact on fairness and equity. Within PV, the
focus will be regarding unfair bias introduced through data collection, selection, model development
and human involvement in the design, development and use of AI that could potentially result in
unfairness, discrimination, or inequality.

This chapter will not address the impact of development and use of AI on justice and lawfulness, on individuals' access to essential services, lack of public resources for financing and implementing AI tools and the required ecosystem, and impact on social well-being, because while these are important issues, they are not unique to PV. While not unique to PV, access to AI and the required ecosystem can be a significant barrier for low- and middle-income countries that can result in inequality and underserved populations. Potential workforce implications with introduction of AI in

- 2107 PV will not be addressed here as it is discussed in the Chapter on Human Oversight under the Section
- 2108 on <u>Transformation of traditional roles</u>. In addition, the rapid acceleration in the use of GenAI is
- associated with significantly increased energy demand and environmental consequences, both of
- which are acknowledged as having a broad societal impact, but which are beyond the scope of this
- 2111 report.²⁴²
- 2112 Fairness and equity considerations are challenging and can be influenced by cultural differences,
- 2113 historical inequalities, perceptions, and risk factors may appear subjective. To reduce bias,
- 2114 intentional actions are required throughout the AI lifecycle, from design through implementation,
- and while in production, to reduce discriminatory risk. There are numerous factors that may
- 2116 introduce bias.

2117 Fairness and equity considerations and pharmacovigilance

- 2118 Fairness and equity principles are fundamental in identifying and addressing discriminatory biases
- arising from the use of AI systems. In PV, proactive measures are essential to detect, assess,
- 2120 understand and prevent adverse effects to ensure safe and effective use of medicines. When
- 2121 utilizing AI systems in PV, it is essential to implement proactive strategies to mitigate potential
- 2122 harm caused by high-impact Al systems.
- 2123 Thorough evaluation and ongoing monitoring are required throughout the AI system lifecycle to
- 2124 identify and quantify potential areas of risk and mechanisms through which bias may be introduced
- as a first step to define strategies to mitigate discrimination biases arising from the use of AI systems
- 2126 in PV. Monitoring for biases is required from conception, development, testing, and following
- solution deployment. The frequency of monitoring for bias and appropriate modification needs to be
 defined based on risk assessment, solution results, and potential external factors that may impact
- 2129 model bias and performance.
- 2130 It is crucial to acknowledge the possibility of bias that may lead to unfair practices or unequal
- 2131 treatment of patients when using AI in activities related to detecting, collecting, assessing,
- 2132 monitoring, understanding, and preventing adverse effects or any issues related to medicinal2133 products.
- 2134 The PV professional is responsible for ensuring that the AI solution meets the defined business
- 2135 requirements, supports patient safety activities, and does not introduce bias that may inadvertently
- 2136 place patients at risk, a disadvantaged position or at potential for discrimination, e.g. denied the 2137 potential benefits of a medicinal product, through exclusion based on race, gender, age, or socio-
- 2137 potential benefits of a medicinal product, through exclusion based on race, gender, age, or socio-2138 economic factors. However, we acknowledge that the current system is not perfect; it is essential to
- economic factors. However, we acknowledge that the current system is not perfect; it is essential to
 ensure that AI does not exacerbate existing issues, but instead, contributes to improving fairness and
- equity.

2141 Sources of potential threat to fairness and equity

Inherently, humans are biased and can introduce that bias throughout the AI system lifecycle (e.g.
requirements gathering, model training, monitoring may not detect poor performance, incorrect
results, or missed scenarios). AI experts and developers can have unconscious bias, and potentially if
not identified and addressed, the output can have limitations, be discriminatory and may not be
recognized as biased. Conversely, the output could be accurate, fair, and equitable; however, results
may be rejected by the human with a bias as being poor performance.

2148 Inadequate training and/or testing data set(s)

Bias is primarily introduced in the data used to develop and test AI solutions, which can perpetuate
 bias and discrimination resulting in harm. Incorrect conclusions can occur when there are data

- 2151 limitations such as when it is not a complete dataset or does not represent the population where the
- Al is being applied. The inappropriate or unintended application of Al to populations not represented
- 2153 can occur if data limitations are not transparent or recognized.

2154 Explicit negative bias

- 2155 Some of the main risk to fairness and equity is introduced from explicit biases (e.g. a case
- 2156 prioritization algorithm down-prioritising reports for men because of patterns represented in the 2157 training set).
- 2158 The lack of robustness and availability of data, e.g. health records not digitally available globally, can
- 2159 lead to underserved populations or underperforming models. When data representation is
- 2160 inadequate, the available data does not correspond to the population and consideration is required
- to remediate under-represented groups or lack of available organized data, e.g. regions with less
- 2162 developed PV reporting systems, otherwise scenarios will be biased toward groups represented by 2163 the training data, and since the data does not represent all groups, e.g. ethnicities, results in bias
- against these groups, e.g. minorities.
- 2165 Inadequate data whether as a result of data not being available or organized in a usable format or 2166 structure, lack of data robustness, or inadequate representation of all variables - may result in an 2167 under-performing model, or worse, incorrect conclusions as a result of model limitations not being 2168 recognized, and this may negatively impact patients' health outcomes. Imbalance of data 2169 representation can potentially skew data, amplify imbalances, and it may be difficult to identify and
- assess bias when reviewing an AI solution's output.
- 2171 Historically, there have been examples of bias influencing PV activities because of data limitations 2172 such as known under-reporting or stimulated reporting of adverse events, with inadequate data or 2173 imbalance of data providing artifact that have had negative impacts. Litigation such as class action 2174 lawsuits that are pursuing product liability claims can result in stimulating high volume of reported 2175 adverse events during the process of legal firms identifying potential plaintiffs that could overshadow 2176 unsolicited reports and the imbalance of data could be a threat to fairness and equity considerations 2177 if the data imbalance results in incorrect conclusions with groups that are under-represented as a 2178 result of skewed data. Local prescribing practices' impact on adverse event reporting and data 2179 availability should be considered. These data biases if introduced into an AI solution will potentially
- magnify the negative impact and remain undetected with difficult identification of underlying bias.

2181 Underserved groups

- Under-representation can directly result in underserved population segment(s) and potentially not
 recognize nuances of subpopulations. Population-specific segmentation can be done by
 demographics, disease processes, genetic variability, health practices variability, and cultural
 differences for medical regimens and patient expectations. Such differences can introduce bias with
- a negative impact if data is exclusive to a specific group, if data is exclusionary, or if nuances of a
- 2187 subgroup are not understood, such as a case prioritization algorithm that underperforms in reports
- 2188 from certain countries in Asia, because they were under-represented in a training data set and
- 2189 differed in important ways from other countries represented.
- 2190 During clinical trials, such potential harm may be overlooked if subgroups are under-represented in
- 2191 the study population or receive a lesser level of care, e.g. have limited access to medical
- 2192 professionals or facilities. There may be more focus on preventing false negatives to not miss
- 2193 significant information, e.g. the failure of the PV process to detect potential harm restricted to or
- 2194 over-represented in certain subgroups. In the post-marketing period, deployment of an AI solution
- 2195 working less well in certain patient subpopulations could lead to an inability to detect adverse events
- 2196 from these populations. Conversely, false positives may be of greater concern in duplicate detection

- where a higher rate of reports falsely flagged as suspected duplicates in a specific country could leadto missed or delayed safety signals there.
- Special populations frequently not represented, such as age related (paediatric, geriatric), pregnant
 women, and infrequent or under-reported events such as rare diseases, and events with social
 stigmas need to be considered when assessing bias. In the example of an AI solution implemented to
 support signal detection activities, with limited data from special populations (e.g. pregnancy), the
 negative impact would be magnified with misinterpreted or missed signals.
- Reliance of decision making on data not representative of respective populations (e.g. post-approval risk minimization activities based on data with limited representation of served population) could result in minimization measures not properly addressing safety of patients in the population. If unable to mitigate lack of representation in AI solution, it may require reliance on historical PV approaches and safety measures (e.g. robust monitoring measures for special populations).
- Detailed identification of "groups" that could be disfavoured or low volume events proportionate to
 data set and comprehensive strategies to address data inadequacies can reduce potential bias,
 discrimination, and underserved populations.

2212 Artificial intelligence solution design

- 2213 Algorithms should not perpetuate existing bias or discrimination, and the algorithmic design can lead 2214 to unintended consequences. When AI was used to develop a model to predict what patients would 2215 benefit from proactive intervention in the care of their chronic illness, its results directed more 2216 resources to white patients than black patients, because the data set used for training was based on utilization, not need.²⁴³ Given a healthcare system and a universe of healthcare data that is likely to 2217 2218 carry country-specific biases, any naïve use of AI will reproduce these biases in its predictions. The likelihood of adverse consequences is more likely because of the apparent opacity of AI, hype about 2219 2220 its capabilities, limited understanding of how it works, and unclear pathways to question its 2221 conclusions.
- 2222 Parameters defined by a programmer and how a model processes data could introduce bias or 2223 produce inaccurate results by skewing the result. If a developer selects or designs features for an AI 2224 solution based on their own conscious or unconscious bias, the resulting output could be suboptimal 2225 or even incorrect. In the case of GenAl prompt engineering development, the potential to introduce 2226 bias based on the prompt design, lack of specificity, context, or omission of a required prompt could 2227 result in an output with a negative bias. Individual preferences influence decisions and subsequently 2228 influence data selection and model development. This could occur due to the model developer 2229 having an affinity to subgroups like their own profile (e.g. developer is a young person and may select 2230 data that does not account for paediatric or geriatric populations).
- The development strategy should have a conscious systematic approach to avoid bias and achieve complete and accurate data representation accounting for diverse groups. Documenting how distinct groups are represented in the training and test data may provide insight to limitations, bias, and potential impact supporting implementing mitigation measures. When considering the population of respective groups, confirmation that the data are representative of the global population is needed
- to ensure balance, demographic parity, and appropriate distribution and allocation.
- Al is increasingly employed in the field of medicine to identify patterns and anomalies, such as
- 2238 consistencies, inconsistencies, and outliers in the identification of safety issues and communications.
- 2239 For example, examining sentiment consistency can help flag and mitigate human-induced
- discrepancies. This proactive approach reduces the risk of unfairness and bias, enhancing the
- 2241 reliability and objectivity.244

2242 Risk, impact, and mitigation measures

The consequences of AI on fairness and equity are dependent upon the application of AI within PV, the usability, performance, and the risk of where the AI is being used within the process. When there is discrimination and bias embedded in the AI model through data limitations and/or algorithm development, the negative impact of the resulting biased model is magnified in its application. The model may amplify or skew outcomes resulting in incorrect conclusions, incorrect introduction of an advantage or disadvantage, inequalities, or discrimination of groups or populations.

Evaluating an AI solution pre and post deployment for explicit or potential bias allows for mitigation
 measures to reduce risk. AI solution explainability may highlight explicit bias and understanding the
 profile of training data provides a degree of insight into potential areas where bias may be
 introduced into the solution, determine appropriate use, solution limitations, degree of human
 oversight required, and expected performance. When evaluating for bias, consideration should be
 given to post deployment data annotation processes for future retraining activities and mitigate
 when possible.

Within PV signalling activities, omitted results could cause misrepresentation of a product
 benefit/risk profile and have a detrimental impact, leading to incorrect human conclusions or
 decisions impacting patient safety.

2259 Sensitivity analysis of performance across different subgroups can be important to highlight groups 2260 or populations underserved by an AI solution. A risk-based approach when selecting subgroups to 2261 evaluate performance may be necessary when an exhaustive sensitivity analysis is not feasible and 2262 may be dependent upon data limitations for training and test data for subgroups or populations.

2263	Key mitigation strategies
2264 2265	• Evaluate each AI solution for fairness and equity, outlining the assessment method, results, and any measures taken to mitigate.
2266 2267	 Review training and test data sets thoroughly for completeness and adequate group representation.
2268 2269 2270 2271	• Perform sensitivity analysis when possible, evaluating AI model results for equality by changing subgroups/populations to confirm expected results (e.g. modify gender input and evaluate impact to the output) and highlight potentially underserved populations. This is especially important when an AI solution has a lower level of explainability.
2272 2273	 Review AI solution design, parameters, and feature selection for bias when an AI solution is explainable, and the results are not as expected.
2274 2275 2276 2277	 Ensure training data description is transparent highlighting explicit bias and allow clarity on model limitations to reduce inappropriate application or incorrect conclusions. Determine level of human involvement required in development and monitoring activities providing required input to ensure accurate performance and fair results.
2278 2279 2280 2281 2282 2283	Identification of potential risk areas is challenging but key to preventing bias, discrimination, and suboptimal model performance. Avoidance of data limitations is not always possible and providing visibility of data characteristics allows appropriate application and opportunity to mitigate risk. It is important to understand the model limitations and communicate to the user community and group monitoring AI performance of limitations and potential bias.
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2285 Chapter 9: Governance & Accountability

2286 *Governance - Principle*

Governance refers to the human management and oversight used to control and direct the use of AI
 in the PV system. An AI governance framework requires implementation of risk management
 practices and policies to ensure adherence to the AI guiding principles.

2290 Accountability - Principle

Accountability applies to clearly defined roles, responsibilities and liability for organisations and/or individuals deploying, operating and managing AI systems. It requires the adoption of appropriate governance measures by relevant stakeholders, including but not limited to regulators, vendors, users, developers, data providers or pharmaceutical companies involved in setting policy, developing, deploying and managing AI systems. This ensures operations remain within expected parameters throughout the AI lifecycle while addressing any unforeseen consequences.

2297 Key messages

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- Governance requires a comprehensive approach across all lifecycle stages of an AI solution as well as the processes it impacts and should therefore be established as early as possible.
- Accountability requires clearly defined roles and responsibilities for stakeholders involved in
 Al systems for PV; Al systems themselves cannot be held accountable.
 - Systems and processes, along with service providers and software vendors, need to be qualified.
 - Regular reviews of AI systems and how they adhere to the AI principles are necessary to ensure ongoing regulatory compliance and performance.
- A governance framework grid for an AI system in PV can serve as a structured guide to help
 relevant parties to document e.g. assessments, actions and references processes, such as
 Standard Operating Procedures (SOPs) etc. throughout the lifecycle of the AI system.
- Governance and accountability should be independent of the business' utilization and value
 proposition of the AI system to facilitate unbiased decision making.

2311 Introduction

- 2312 Previous chapters have discussed in detail the importance of taking a risk-based approach, providing
- adequate human oversight, demonstrating validity and robustness, and addressing transparency,
- data privacy, fairness and equity when integrating and implementing AI solutions into the overall PV
- 2315 system. This chapter outlines the guiding principles of governance and accountability in AI-enhanced
- 2316 PV. We will discuss the importance of these two principles, the stages of the AI lifecycle that require
- 2317 specific governance actions, the roles and responsibilities of various stakeholders, regulatory
- 2318 oversight, and the need for ongoing training in the rapidly evolving field of AI technology.
- 2319 Robust governance and clear accountability are crucial for the success of AI initiatives. These
- principles help ensure that AI systems are used responsibly and ethically, are compliant with
 regulations, while fostering trust and transparency among stakeholders. Clearly defined roles and
 responsibilities enable all stakeholders to understand their obligations and effectively oversee AI
 systems.
- As AI technology evolves, governance and accountability frameworks will need to be adapted. New risks and challenges will emerge, requiring updated principles and practices. Continuous review and adaptation are essential for staying ahead of these changes. This includes the refinement of the proposed governance framework grid for practical use.

Governance framework 2328

2329 A governance framework grid (referred to as "grid") for AI solutions in PV (see Table 2) is a structured 2330 guide designed to identify key considerations to address each of the principles throughout the 2331 lifecycle of the AI system, including concept, development, deployment, and monitoring phases of 2332 the AI model developed for PV use.

2333 In addition to serving as a structured guide for planning and overseeing AI solutions, the grid can also 2334 aid in self-assessment. By detailing where each action or process is recommended, the grid helps 2335 ensure that the principles such as transparency, accountability, and a risk-based approach are 2336 consistently adhered to, facilitating the integration of AI into PV systems. Regular reviews of KPIs by a 2337 governance body, aimed at ensuring adherence to the AI guiding principles, can facilitate 2338 identification of gaps and drive improvements in the AI solution. While a governance body with 2339 expertise and focus on AI's use in PV is needed in early phases, integration of the governance process 2340 into the overall PV system oversight mechanisms should be considered when the AI solutions enter 2341 routine use phase. If a risk emerges that warrants significant modification to the AI solution, the AI 2342 focused governance body may need to be re-engaged.

- 2343 Consultation with the grid can occur in multiple ways. A unit within a PV organization may have an 2344 idea for AI-based automation and specify governance requirements upfront when commissioning a 2345 vendor or internal development team. Alternatively, a vendor might present a ready-made AI 2346 solution to a PV organization, which then can be evaluated against the AI guiding principles for 2347 example by applying this grid. Early consideration of governance principles is crucial for the 2348 successful implementation of an AI system. These principles should guide the development or 2349 selection of a vendor solution, deployment, and ongoing management. Early planning should be 2350 focused on identifying potential risks and determining mitigation strategies. Furthermore, it can 2351 stimulate focus on alignment with ethical and regulatory standards of the AI system from the outset, 2352 setting the foundation for a robust and compliant AI system.
- 2353 The grid is composed of five lifecycle phases of the AI solution: an initial requirement specification 2354 phase where business units typically provide input, followed by development, pre-deployment, post-2355 deployment, and routine use. These phases are valid for both initial qualification and iterative 2356 changes of the AI solution. In each phase, the AI guiding principles should be considered, and in the 2357 grid, each principle constitutes a cell for relevant documentation hereof. When the grid is used for a 2358 specific AI solution, each cell is intended to provide information about actions, considerations, or 2359 references to where these actions are documented, such as SOPs, working instructions, or 2360 repositories containing log files, reviewed performance metrics, or names of accountable 2361 persons/review bodies. Illustrations of how each guiding principle is applied throughout the lifecycle 2362 phases can be found below, and examples of how to put this grid into practice can be found in 2363 Appendix 3: Use cases.

2364	Table 8: Governance framework grid
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	Collection of specifications, requirements	Development & change management	Pre-deployment & post-change sign-off	Post-deployment & post-change hyper-care	Routine use	General considerations
Risk-based approach	Risk assessment (theoretical) - AI model - Context of use - Impact & likelihood of risks	Risk mitigation plan	Risk assessment (empirical) Adjustments to risk mitigation plan based on performance evaluation	Intensive or targeted monitoring for risk assessment (empirical), target high risk areas Mitigation if needed	Routine monitoring (e.g. risk for model drift) Mitigation if needed	Review and refine risk- based approach at regular intervals

Human oversight	Multidisciplinar y expertise HOTL (human- on-the-loop; design)	Define HITL (human-in-the- loop; strategy Change management, including staff training plan	Fine-tune HITL strategy Staff training roll- out	Implement HITL strategy Intensive or targeted intervention	Routine HITL activities Adjust and fine- tune(?) HITL strategy as needed	HIC (human-in- command; holistic oversight) HOTL (general monitoring)
Validity & robustness	Specification of use case & deployment domain Specification of reference standard(s) Specification of benchmarks Requirements on reproducibility	Training & validation Development or acquisition of reference standards	Performance evaluation Benchmark comparisons	Performance monitoring	Continuous integration and deployment Periodic performance monitoring	Special considerations for low- prevalence settings Reproducibility Assessing AI solutions with human-in-the- loop
Transparency	[From organization to developer] Model requirements - Intended use - Human- computer interaction - Explainability - Expected outputs Performance evaluation requirements - Scope - Reference standard	[From developer to organization] Model - Architecture - Parameters - Acceptable inputs - Expected outputs - Standard Al components - Training & validation - Known limitations Explainability in support of model development, debugging, and documentation	[From developer to organization] Performance evaluation - Scope - Sampling - Reference standard - Human input - Summary metrics - Benchmarks - Subsets & sensitivity analyses - Qualitative review Explainability in support of assessing Validity & robustness and Fairness & equity	[From developer to organization and from organization to end user] Performance evaluation - Deviations Explainability in support of assessing Validity & robustness and Fairness & equity	[From organization to end user (and regulatory authorities)] Disclosing use of AI Explainability in support of building trust with end users	
Data privacy	Specification of use -Specification of data sources -Identification of data elements that contain identifiers -Jurisdictions / provenance of data Data privacy by design (data minimization)	Training data set selection, algorithm design	Test set (if publishing is intended, e.g. as a public benchmark, need to assure data privacy consistent with local legislation/regula tions/guidance)	Adherence to data privacy considerations in running the models with full / accruing data sets Greater attention to deviations in hypercare	Ongoing processes to identify and rectify data privacy issues in routine use	Data privacy legislation/regul ations vary by country/region, potentially leading to inconsistencies (emerging risks of new prompts)

	-Data protection impact assessment					
Fairness & equity	Context of use -acceptable application	Training data set selection, algorithm design and cognitive bias Avoid -Explicit or potential unfair bias -inadequate data inclusion	Pre-deployment performance evaluation -Reference data sets inadequate (e.g. unavailable, inadequate representation) -Algorithm design - Human/cognitive bias		Routine Monitoring -poor performance related to model shift, inadequate training data (underrepresente d populations, special populations)	Ensure model and training data description is transparent, and limitations highlighted to reduce inappropriate application or incorrect conclusions
Governance & accountability	Consideration on how Al solution fits into existing PV system Key roles (non- exhaustive examples) - PV experts - Al experts	Agreement on KPIs to support implementation Key roles (non- exhaustive examples) - PV experts - Data scientists - AI experts - IT specialists - Ethics specialists	Refinement of KPIs to support implementation, based on performance evaluation Key roles (non- exhaustive examples) - PV experts - Data scientists - AI experts - Senior management	Approval of risk mitigation strategies Key roles (non- exhaustive examples) - PV experts - AI experts - IT specialists - Data protection officers - Cybersecurity experts	Integration into overall PV quality management system including oversight of KPIs Key roles (non- exhaustive examples) - PV experts - AI experts	

2367 Description of each lifecycle phase included in the grid is presented below:

2368 **Collection of specifications, requirements:** This is the initial phase where the stakeholders are 2369 identified and engaged, and the project's objectives, scope and features are defined. The 2370 multidisciplinary team of PV professionals, data scientists, AI/ML engineers, software engineers, IT 2371 specialists, and other domain experts (also refer to the chapter on Human Oversight), is typically 2372 managed by system developers, software vendors, or an internal IT development team. This phase 2373 provides a roadmap for developers and end-users, and lays the foundation for the entire 2374 development process. Like traditional software, as an AI solution evolves, the requirement 2375 specifications may also require iterations, and consequently, the grid may need to be reconsidered 2376 accordingly.

- Development & Change Management: In this phase, the multidisciplinary team focuses on acquiring,
 creating or modifying AI systems, ensuring they are built with the necessary functionality and
 adherence to governance principles. Whether developing an AI system or selecting a vendor solution,
 these principles will apply throughout.
- Pre-Deployment & Post Change "Sign-Off": At this phase, the AI system transitions from the
 development stage to deployment into the PV process. Before implementation, a thorough
 validation and approval process is required to ensure the AI system, or any changes hereof, is ready
 for deployment. Typically, a PV expert becomes accountable for the results produced by the AI
 solution and for adapting the processes in which the solution will be used. Documentation of this
 phase may include risk assessments, review of sufficient adherence to principles, sign-off forms,
 validation reports, and many references to SOPs detailing the sign-off procedure, etc.

- 2388 Post-Deployment & Post Change "Hypercare": Following deployment, this phase is critical for the 2389 immediate monitoring of the AI model's performance or the latest changes' impact. It is a period of 2390 intensive observation to promptly identify and resolve any unanticipated issues, as real-life 2391 application of the AI system in the PV process might surface issues due to various reasons such as 2392 incorrect assumptions, design flaws, unintended bias, in earlier stages. This phase, dominated by 2393 hypercare, differs from traditional software hypercare; for AI solutions, immediate fixes may not be 2394 feasible and other measures such as human intervention or increase in human oversight might be 2395 needed. Documentation is expected and may include incident logs and performance analysis reports 2396 specific to the most recent change while under observation.
- Routine: This phase signifies the full integration of the AI solutions into the PV process. It involves
 ongoing monitoring, maintenance, and documentation to ensure full oversight and allows for the
 identification of trends through the monitoring of pre-defined KPIs. This phase may reference routine
 reports, logs of ongoing actions, and which SOP or working instruction manages this review process,
 reflecting the model's full operational status.
- Of note, discoveries during post-deployment or routine use phases may necessitate the AI solutionbeing sent back to pre-deployment for enhancements.
- The following, non-exhaustive examples illustrate aspects to consider for each guiding principle in relation to the lifecycle phases in the grid:
- 2406 <u>Transparency</u>: In the Development phase, there is a focus on creating comprehensive documentation
- of the development activities including reason for changes and data used in model training. In Pre-
- 2408 Deployment, transparency is further enhanced by adding model performance evaluation, and
- 2409 empirical evidence for fairness and equity. Also, the documentation created should ensure consistent
- 2410 understanding of the intended use among different stakeholders. In routine use, the most important
- transparency is toward the end-users and those responsible for the continual performance evaluation and monitoring.
- 2413 Accountability: Throughout all phases, there is a consistent need to assign and document
- 2414 responsibility, whether it is to IT, vendors, or to PV experts. This ensures clarity about who is
- accountable for the AI model's development, change management, deployment, and performance atany time.
- <u>Risk-based approach and human oversight</u>: This begins with identifying the level of risks associated
 with development of the AI solution. When relevant, it may involve the development of clear
- annotation guidelines for human domain experts to ensure solid method development and
- 2420 performance evaluation. The next step is to propose appropriate mitigation strategies such as
- defining "human-in-the-loop" within an AI solution and other oversight measures up to eventually
- creating risk mitigation requirements in the user interface. It continues with redefining human
- oversight in Pre-Deployment, and further refining these concepts in the Routine phase based on real-
- life observations. This sequential approach highlights the need for evolving risk management as the
- AI model advances through its lifecycle. A risk-based approach in general is recommended for all measures taken to adhere to AI guiding principles.
- 2427 Any changes to the AI system must undergo the same rigorous governance considerations as the
- initial deployment. This ensures that modifications do not compromise the system's integrity or
- 2429 performance. Documentation and validation are essential to maintain transparency and
- accountability. Change management processes should be in place to handle updates and
- modifications effectively and account for a post-deployment phase, that based on "hypercare", willconfirm performance and quality beyond routine monitoring.
- As computer system validation requirements need to be met at the same time, it is advisable to de-
- 2434 couple AI model version control from the rest of the software versioning.

2435 Governance body and accountability assignments

- 2436 To effectively manage the review and agree on actions and risk assessments towards the different 2437 principles, it is advisable to nominate a governance body. This group ideally should be a diverse, 2438 cross-functional team that has sufficient awareness of the end-to-end process and the extent of 2439 automation within it. It should include representatives from all relevant stakeholders and 2440 representation from the software vendor may also be considered. This diversity ensures a broad and 2441 balanced review of the AI solution. The governance body oversees the development, deployment, 2442 and ongoing management of the AI system to ensure that all actions align with guiding principles and 2443 regulatory standards. The governance body also determines accountable persons for the respective 2444 lifecycle phases, which includes sign-off of the documentation prior to deployment of the AI system 2445 into the PV process. Because business cases are often drivers of AI initiatives, the governance body 2446 should also include the respective project managers or sponsors to ensure adequate resourcing of 2447 governance measures during each phase of the lifecycle.
- 2448 Unlike traditional software, the governance body of an AI system should review the adherence to the 2449 Al use guiding principles in defined intervals, and ad-hoc if needed, to ensure the assessments are 2450 still valid. This is due to the rapid evolution of the field and the inherent risks of AI models that 2451 changing inputs, rules or other unforeseen issues may disrupt the solution at varying degrees, some 2452 significantly. The appropriate frequency and scope of reassessment of a deployed AI solution should 2453 be assessed. There should be measures ready to intervene or even disable the AI solution if 2454 necessary. Once the AI solution reaches the routine use phase, governance can be handed off to 2455 process owner to be integrated in the overall PV system monitoring process. Nevertheless, if a risk 2456 emerges that warrants significant modification to the AI solution, the AI focused governance body
 - 2457 may need to be re-engaged. The introduction of version control for the governance framework grid 2458 should also be considered.

2459 Traceability and version control

Traceability and version control are crucial aspects of managing AI solutions, particularly in a regulated field like PV where errors could impact patient safety or public health. They can enable evaluation and reproducibility of earlier versions of an AI solution and are often required for audit purposes (however, see also the discussion of AI solutions with stochastic components in the Chapter on Validity & Robustness). General best practices from existing version control frameworks can offer orientation for the version control of AI models, which should be documented alongside other

- relevant systems involved in the end-to-end process. They should include clear change control processes within both a user acceptance testing environment and the production environment.
- Documentation of an AI model should comprise its entire lifecycle, and may cover the justification,
 initial scoping and conception, development, deployment, validation, and post-deployment. It should
 allow for the retrieval and reproducibility of essential steps and decisions, including justifications and
 reasoning for deviating from pre-specified plans. As in traditional computer system validation,
 experiments conducted in, or before, the development environment are not required to be
- 2473 documented step by step. However, when the outcome of such an experiment or analysis impacts
 2474 how an AI solution is evaluated or deployed, the justification for such decisions should be
 2475 documented. If a decision is based on certain results or insights from the development stage, this
- should be documented.
- 2477 During the development phase, AI models undergo continual experimentation and iterative
 2478 improvement. Transparency between the development team and the PV organization is crucial to
 2479 ensure efficiency and that the solution is fit-for-purpose. Developers may create multiple versions of
 2480 a model, test various features, and experiment with different training sets. In this context, focus
 2481 should be on maintaining clear records of significant milestones such as major changes in model

architecture, the introduction of new datasets, or significant shifts in performance metrics. This
allows developers to track the evolution of the model and understand the implications of key
changes without being overwhelmed by the sheer volume of minor tweaks and experiments.

Once an AI model moves from development to routine use in a production environment, the need
for rigorous traceability and version control increases substantially. Deployed versions of the model
should be documented in detail. In addition to the source code for each version, its underlying model
architecture, training and test sets, and performance evaluation results should also be documented.
From a regulatory perspective, the appropriate place to declare this would be in a document such as
the PV System Master File (PSMF), in the EU.

- 2491 The continual improvement and adaptation of AI models post-deployment should also be
- 2492 documented. It may be triggered by human domain experts or built into the deployment of the AI
- solution itself including pre-specified monitoring of deterioration of performance or model drift.
 Some challenges related to this for Software as Medical Device have been described by FDA [65].
- 2495 When integrating external AI components (such as pre-trained models or libraries), it is important to 2496 document the versions of these components, particularly if they play a critical role in the model's
- 2497 performance. However, it may be sufficient to document these components at the time of significant
- 2498 milestones rather than during every iteration. As an example, for AI-based static systems, previous
- 2499 work proposes a specific documentation approach with proposed considerations for documentation
- 2500 within the different stages of the AI solution lifecycle.

2501 Roles and responsibilities in artificial intelligence-enhanced pharmacovigilance systems

Organizations are accountable for the quality processes associated with their PV system, including
 the oversight of the AI components by the system owner. Oversight activities may be executed by a

- third party under appropriate supervision. Regulations, e.g. EU AI Act, may require organizations to establish specific roles, such as those to promote AI literacy, and facilitate fairness and equity.
- Al systems themselves cannot be held accountable. Human oversight is essential for ensuring the safe and responsible use of Al. Clear roles and responsibilities must be defined for all stakeholders
- 2508 involved in AI initiatives.
- 2509 The roles of PV experts are evolving with the introduction of AI. Already now, AI introduces new
- 2510 tasks, such as overseeing AI systems and interpreting their outputs. PV experts must adapt to these
- 2511 changes and develop new skills and competencies (see chapter on Human Oversight) to fulfil their
- 2512 obligations. This is especially relevant for members of the governance body and persons nominated
- as accountable for a lifecycle phase. The governance framework grid allows stakeholders to assess
 whether certain new activities will become relevant at specific steps, highlighting training needs
- 2515 early.
 - Just like with traditional software providers, the collaboration between vendors of AI solutions and
 PV experts is crucial. This collaboration can facilitate that AI systems meet PV requirements and
 governance principles. Regular audits of vendors and AI systems are essential for maintaining
 compliance and ensuring development standards. Effective collaboration and audits foster
 transparency and accountability. This can ensure AI systems that are reliable, meet regulatory
 - 2521 standards and are inspection ready.
 - Regulatory authorities also play a role in monitoring AI in PV. They oversee that AI systems comply
 with regulatory standards and governance principles through inspections. Regulatory authorities are
 also developing guidance on the use of AI in the drug lifecycle, including PV (see Chapter on
 <u>Landscape analysis</u>). Integration of AI tools into the PV system must include appropriate regulatory
 documentation, such as in the Pharmacovigilance System Master File (PSMF) (see Chapter on
 <u>Transparency</u>).
 - PV inspections are likely to increasingly focus on AI systems, with inspectors reviewing AI-related
 documentation, performance metrics, and governance practices. Inspectors will need adequate

- 2530 competencies to evaluate these systems effectively. This includes technical knowledge of AI and data
- 2531 science. As a result, continuous development and training are needed for inspectors to fulfil their
- 2532 role in new and fast-evolving areas.
- 2533 Balancing innovation with regulatory compliance and adherence to guiding principles is important for
- 2534 the success of AI initiatives. This involves fostering a culture of responsible innovation. These goals
- can be achieved by establishing effective governance processes that include regular reviews of AIsolution KPIs.

2537

Chapter 10: Future considerations for development and deployment of artificial intelligence in pharmacovigilance

2540 The evolution and future of artificial intelligence in pharmacovigilance

2541 The chapter explores the continuing transformative impact of AI on PV from the current application 2542 to a vision of how AI might impact PV in the future. The CIOMS Working Group XIV's discussion in the 2543 earlier chapters of this report is grounded in common principles. Use cases (presented in Appendix 3) 2544 detail various AI systems under evaluation, various stages of deployment and assessment of their 2545 effectiveness within the discipline. To try to predict into the future, it is essential to recognize that 2546 the trajectory of AI is dynamic and highly unpredictable. Indeed, the only truly predictable elements 2547 are that AI will be ubiquitously deployed and is set to revolutionize many aspects, arguably all, of 2548 drug development and medical practice, from bench to bedside – as well as PV. For this reason, this 2549 chapter is grounded on the further developments of AI in PV described in earlier chapters of this 2550 report and anticipates how applications based on the principles might need to evolve as AI use in PV 2551 becomes more prevalent and sophisticated.

2552 The chapter provides considerations for PV stakeholders, including regulators and healthcare 2553 professionals and other industry stakeholders to ensure AI's safe and equitable deployment in PV. 2554 The skillsets needed by PV professionals today will likely differ from those required in the future 2555 necessitating involvement in the design, development, deployment, and routine use of AI in PV. The 2556 examples illustrate the direction and immense potential of AI adoption in PV; however, these 2557 examples are speculative to a certain extent and are not meant to be exhaustive. All is set not only to 2558 potentially revolutionize PV, dissolving traditional boundaries of PV, but also expand its footprint far 2559 more broadly across medical sciences.

2560 The current decade represents a nascent phase for AI adoption in PV, and it is worthwhile 2561 acknowledging that the broad field of AI, particularly GenAI, is currently advancing rapidly. Further 2562 and more extensive deployment of AI may necessitate changes in how we think or approach PV 2563 strategies in the years ahead, driving the discipline of PV beyond its traditional frameworks and 2564 transforming it into self-detecting, real-time monitoring of safety data that aligns with the evolution 2565 of Al-driven medical science; for example, with the ability to rapidly analyse and extract vast 2566 quantities of safety data for case reporting and signal detection purposes. By leveraging this 2567 capability of AI, PV will evolve from a reactive focus on reporting and assessment to a forward-2568 looking approach centred on proactive prediction and prevention and real / near real time learning 2569 systems.

The initial phase of evolution has started to impact PV's core activities including case management and safety surveillance, as it continues to move from reporting and assessment towards prevention, enabled by advancements in AI-enhanced healthcare and into radically new areas of medicine. These technologies have the potential to reduce manual workload and the burden on PV professionals. For example, by accelerating response times for priority events, increased capabilities to sift through large and varied sources of safety data including literature, automatically creating case reports, and performing signal detection.^{245,246,247,248,249}

Transformative role of pharmacovigilance long-term and beyond: from detection to prevention

Advanced AI systems are poised to take PV beyond current boundaries and into automated or
 augmented decision making.²⁵⁰ AI, with capabilities for approximate reasoning, could handle
 ambiguity and partial truth values, for instance, in assessing safety data from social media entries or

from fragmented safety-relevant data across different systems. Such AI systems may enable PV
 professionals to make nuanced decisions in case classification (e.g. assigning causality) or other PV
 situations requiring medical decision making. This would be particularly useful for cases with
 incomplete or conflicting data, where the "gray area" requires sophisticated, context-aware analysis
 and/or medical judgment.^{251,252}

In the future, an expert AI system, designed specifically for PV, may emulate the judgement and 2587 2588 decision-making processes of seasoned professionals or organizations with deep expertise in the 2589 field. These systems may not supplant human experts but augment their capabilities, enabling more 2590 nuanced and efficient decision making. An expert PV AI system would ideally be tailored to 2591 incorporate advanced analytical preciseness specific to therapeutic areas such as oncology, 2592 immunology, vaccines and medical devices as well as very different therapeutic options such as 2593 digital therapies, ensuring they adapt to the complexities of specific therapies, diseases, and patient 2594 populations, within those therapeutic areas, while performing or supporting PV work. While the 2595 development of such systems requires significant investment, their potential to drive the next 2596 generation of targeted PV solutions positions them as a critical innovation in advancing patient 2597 safety.

By mid-century, it is possible that traditional PV will have transitioned from primarily detecting and
processing adverse effects to a frontline technology-driven discipline that is engineering technologies
that can detect, evaluate and share the information with "self" (human or organ: heart, kidney, liver,
lungs etc.).^{253,254,255,256}

This may then allow HCPs and patients to take a more active role in vigilance and prevention by taking corrective actions before adverse symptoms arise. As a discipline, PV leveraging AI is likely to evolve into a function that develops technologies enabled by AI to perform a proactive assessment of anomalies, self-report and self-learn on how to prevent the presence of such anomalies in the future and continue to promote patient wellness and safety. This will include "true" AI-enabled proactive self-regulated vigilance and risk mitigation.

2608 Future development and deployment of AI and the guiding principles

The CIOMS Working Group XIV members made the careful decision to structure the report around 2609 2610 common principles for the use of AI in PV, based in part upon the recognition that this 2611 transformative technology is in a period of exponential growth. A report that was prescriptive and 2612 overly reliant upon current examples would quickly become outdated, especially if AI technologies 2613 from other healthcare domains are leveraged. The authors expect that common principles for the 2614 use of AI in PV will be durable for the foreseeable future. What is less certain is how the guiding 2615 principles may be applied. Although the principles are robust and are expected to endure, it is likely 2616 that they will evolve in parallel with the technical AI advances and their use in detection, prevention 2617 and decision making by the individual human or subject going under medical treatment. The

- 2618 potential implications are discussed for each of the guiding principles below.
- 2619
- 2620 Risk-based approach
- 2621 Chapter 3 discusses risk-based approaches including risk mitigation, and also considers the regulatory2622 framework required.
- The proliferation and advancement of AI may lead to continuous self-learning and potentially autonomous AI systems, with potentially great advancement in PV and benefit to patients and HCPs.

Nevertheless, such systems come with potential concerns and risks. For example, a significant
 concern is the potential for AI to distort our understanding of a medicine's benefit-risk profile in real world settings. Traditionally, these profiles are evaluated through carefully designed frameworks

2628 involving spontaneous reporting systems and planned surveillance studies. However, AI-driven tools

- may inadvertently restrict prescribing practices; for instance, by limiting access to AI-enhanced PV
 systems for high-risk patients or preventing off-label use.
- 2631 Further complicating matters, the adoption and availability of such tools may vary across healthcare
- systems and regions, introducing inconsistencies in data patterns that are challenging to interpret.
- 2633 This fragmented landscape can obscure the true influence that AI systems exert on prescribing
- decisions, making it difficult to assess their actual impact on patient outcomes. In addition, incorrect interpretation and poor utilization of AI is likely to significantly hamper patient safety. The principles
- of human factors and ergonomics (HFE) can assist in simplifying AI design and consecutively optimize human performance ensuring better understanding of AI outcome.²⁵⁷
- 2638 The oversight and risk mitigation of such advanced AI systems demand a dynamic risk assessment
- framework; one that integrates near-real-time monitoring and adaptive evaluation processes.
 Ensuring effective communication of these evolving risks to all stakeholders, including patients
- Ensuring effective communication of these evolving risks to all stakeholders, including patients, will
 be crucial. As part of risk mitigation, healthcare leaders must embrace flexible governance models
- that account for Al's evolving nature, ensuring that transparency, accountability, and equitableaccess remain at the forefront.
- 2644

2645 Human oversight

- 2646 Chapter 4 covers human oversight including the changing and transformation of traditional roles in2647 PV as AI use becomes increasingly embedded and ubiquitous.
- As AI systems become increasingly pervasive and autonomous, the role of human oversight will inevitably shift. While maintaining a "human-in-the-loop" approach will likely remain essential, this may prove insufficient for highly complex or higher-risk applications — including aspects of PV. Conversely, in some scenarios, human oversight may substantially change and become less relevant, as AI systems surpass human capabilities in reviewing data and regulating their own processes ^{258,259,260}
- 2653 processes.^{258,259,260}
- 2654 This evolving landscape will require PV professionals to develop new skillsets and undergo
- 2655 specialized training to effectively oversee AI-driven systems. The focus must extend beyond
- 2656 traditional oversight methods to include competencies in understanding, interpreting, and guiding AI
- 2657 behaviours. By cultivating these skills, PV professionals can ensure that human oversight remains
- 2658 meaningful and effective in safeguarding patient safety and public health.
- 2659

2660 Validity & Robustness

Chapter 5 discusses validity and oversight and considers multi-disciplinary collaborations required as
 well as reference standards and performance evaluation that might be needed to ensure robust and
 valid AI systems.

As AI becomes more embedded and sophisticated, the challenge is to develop appropriate methods and systems that validate and ensure data integrity in tandem with the developments. For example, with the potential for generating vast amounts of data in real time or near real time, there is a need for more appropriate validation methods to avoid the risk of false signals. This may require PV individuals to develop new skill sets or even new specific scientific disciplines. AI use with some advanced technologies would need the creation of new standards and validation methods for the

- 2670 outputs and real-time / near-real-time safety data generated, e.g. neurotechnology such as
- 2671 implantable chips, smart organs, nanotechnology and smart organs.
- 2672

2673 Transparency

2674 Chapter 6 covers transparency and explainability of AI systems and related challenges.

- 2675 As AI becomes increasingly pervasive, our ability to track its deployment and understand its decision-
- 2676 making processes may diminish, posing significant challenges to explainability and transparency. Al
- 2677 systems may mirror complex statistical processes and advance programming or AI-coded programs.
- 2678 Consequently, the necessity, and even practicality, of full transparency may face new challenges.
 2679 Expectations of transparency may need to evolve as trust in AI systems strengthens and meets
- 2679 Expectations of transparency may nee2680 predefined confidence thresholds.
- 2681 Much like Al's role in data analysis, statistics, and signal detection today, tracing Al's precise 2682 influence on downstream decisions may become increasingly difficult. Just as the complexities of 2683 prior distributions in Empirical Bayes Geometric Mean (EBGM) disproportionality models are widely 2684 accepted yet rarely scrutinized, established trust in Al-generated outputs may drive a shift in focus, 2685 with the expectation that errors or miscalculations will still prompt corrective actions to ensure 2686 sound decision making.
- In parallel, as trust in AI solidifies, the emphasis on explainability may similarly evolve. While
 transparency will remain important, its most critical value may emerge during incidents or errors.
 Much like the role of flight data recorders in aviation, explainability may become vital for
 understanding failures and enhancing system improvements rather than serving as a constant
 requirement.
- 2691 requirement.
- This shift may significantly influence PV decision making, emphasizing timely interventions and nearreal-time root cause analysis. Looking ahead, organizations may need to balance the benefits of enhanced-AI performance against the degree of transparency required, carefully weighing improved
- 2695 efficiency with the need for interpretability in high-stakes decisions.
- 2696

2697 Data privacy

- 2698 The right to control one's personal data is durable and has been widely adopted internationally. 2699 What is likely to occur in the coming years is that preserving data privacy will become more 2700 challenging. As noted in Chapter 7, leaks of personal data have been increasing in frequency, with 2701 some at enormous scale.²⁶¹ The increasing use of online platforms for communications and services 2702 has been accompanied (in some countries) by a common lack of understanding into how collected 2703 data are used along with an acquiescence to the risk of data breaches. Breaches have occurred for 2704 reasons ranging from neglect to criminal intent. In the case of health care data, the release of 2705 personal data contrary to individual approval carries risks for emotional well-being, stigmatization, 2706 and discriminatory treatment.
- The pressures to amass and link large health care data sources are compelling, both on account of operational efficiencies (assuring consistencies in clinical care as well as medical care costs) and the advancement of scientific knowledge. At this time, the use of GenAI is in its infancy, and the only certainty is that it will both improve in quality and accelerate in use, as it is applied to many areas of biomedical research and clinical practice, and indeed in our daily lives. The use of open LLMs carries particular risks for the unintended disclosure of personal data, a topic that is likely to receive attention in coming years as the risk becomes clearer.
- 2714 Societies will need to balance the pressures for the commoditization of data to maximize learning 2715 and therefore better outcomes for patients with AI, with protections against unintended disclosure. 2716 One possibility is that data sharing will be automated, but that systems have built-in checks and an 2717 obligation to maximise the demonstrable value of the data for the patients and/or patients' carers. 2718 Security measures to support anonymization might incorporate blockchain or similar technology to 2719 make complete anonymization possible without a patient key to allow all care-relevant data to be 2720 safely shared with complete confidence and assurance that the Individual's data are anonymised. 2721 Without the appropriate regulatory checks and balances, it is also easy to see that these data could 2722 easily be misappropriated or abused.

- 2723 Al's evolution may usher in an era where access to underlying safety data becomes instantaneous,
- 2724 enhancing real-time insights and facilitating seamless data sharing. These advancements could
- significantly improve the timeliness and accuracy of safety assessments. However, an opposing
- scenario is equally plausible, one in which data sharing becomes increasingly restricted due to
- 2727 proprietary concerns, legal complexities, or public mistrust. As awareness grows regarding data's
- value as a commercial asset, particularly in insurance and other industries, heightened caution may
- 2729 further constrain data flow.
- 2730 Balancing these dynamics will be critical. Establishing transparent frameworks that foster trust,
- ensure data integrity, and promote responsible data sharing will be essential to fully realize AI'spotential while safeguarding public confidence.
- 2733

2734 Fairness & Equity

The fairness and equity Chapter 8 considers how and what type of discriminatory biases might be identified, addressed and/or prevented arising from the use of AI systems.

Fairness and equity should mean that patients and health care professionals should have equalaccess to all the new and advanced AI technologies.

- 2739 It is important, as described in the data privacy section above, to ensure that PV with ubiquitous AI
- use is deployed equitably, and that data sharing does not put individuals at risk for e.g. higher costs

associated with more advance monitoring, genetic profiling and/ or personalized risk / remediation,

- e.g. avoiding the risk of discrimination for insurance or treatment purposes.
- 2743 AI should help to ensure equal understanding of safety data and its relevance to all patients,
- irrespective of social circumstances and background, and the understanding of benefits and risks tospecific individuals or subgroups of the population.
- 2746 This presents a unique challenge for vigilance, particularly in identifying rare, unexpected anomalies,
- 2747 the so-called Black Swan incidents.²⁶² While current PV systems are well-equipped to anticipate,
- assess, and manage common safety risks, they must also adapt in detecting these outlier events,
- 2749 particularly where advanced AI systems are deployed.
- 2750

2751 *Governance & Accountability*

- 2752 Chapter 9 of this report covers Governance & Accountability including a governance framework grid2753 for the lifecycle phases of AI solutions in PV.
- The accelerated integration of AI underscores the need for dynamic, risk-based governanceframeworks capable of near-real-time interventions.
- 2756 This is especially true as AI systems become more autonomous and self-determining, for example,
- with automated patient or HCP alerts, which will self-monitor their function and output and take
- 2758 preventative measures based on self-detected alerts. Such advancements raise critical questions:
- how will governance, accountability, and human oversight of PV of these new technologies evolve in
- 2760 tandem with these capabilities?
- 2761 Ideally, regulatory authorities and industry leaders in PV will establish robust oversight mechanisms
- to ensure that AI systems in PV are developed and deployed responsibly. Safeguards must be in place
- to protect against data misuse, uphold privacy standards, and ensure these technologies ultimately
- enhance outcomes for patients.
- 2765 The growing autonomy of AI in PV further emphasizes the need for adaptable regulatory
- 2766 frameworks. Continuous surveillance, proactive auditing, and rigorous inspection protocols will be
- essential to mitigate risks, uphold patient safety, and protect public health. Achieving this will require

a shift toward governance models that are as agile and responsive as the technologies they seek tomanage.

2770 Conclusions to the future considerations for development and deployment of 2771 artificial intelligence in pharmacovigilance

Proliferation and deployment of AI and its integration into PV is set to give a paradigm shift in this
discipline, which is likely to be focused on rapid or real-time data collection, assessment and
reporting; for example, with the ability to analyse and extract vast quantities of safety data for case
reporting and signal detection purposes at a rapid pace. This could fundamentally change the way we
work to take advantage of these technological advances, for example, streamlining processes and
causing changes in the wider healthcare environment and beyond, including patient privacy.

2778 Along with the enormous potential for AI in PV, there are many challenges which warrant future 2779 consideration, particularly around oversight of autonomous AI systems, and how AI may impact data 2780 privacy and ethical frameworks. It is critical that the guiding principles outlined in this report remain 2781 as core considerations, but with the understanding that they will need to evolve and adapt with 2782 advancements and application of AI in PV and medicine in general. This is to ensure AI use in PV 2783 remains unbiased, transparent, and secure to prevent misuse or accidental harm. The appropriate 2784 human oversight, including regulatory and ethical safeguards, will be as crucial as the technological 2785 advancements being applied.

References

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²⁴⁸ Ventola CL. The nanomedicine revolution: part 3: regulatory and safety challenges. P T. 2012 Nov;37(11):631-9. (<u>Abstract</u> accessed 28 April 2025)

²⁴⁹ Ventola CL. Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. P T. 2018 Jun;43(6):340-351. (Abstract accessed 28 April 2025)

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²⁵¹ Eliminating Bias in Al-Assisted Decisions: Chouldechova, A., & Roth, A. (2020). The Frontiers of Fairness in Machine Learning, Communications of the ACM, discusses the ways Al can counteract cognitive biases in human decision-making. (<u>Website</u> accessed 28 April 2025)

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²⁵⁹ Bonabeau, E, Marco D, and Guy T, Swarm Intelligence: From Natural to Artificial Systems (New York, 1999; online edn, Oxford Academic, 12 Nov. 2020), <u>https://doi.org/10.1093/oso/9780195131581.001.0001</u> (Abstract accessed 28 April 2025)
 ²⁶⁰ Imagine you are Living in the Age of Singularity: Karakas, F (2021), Creative Adventures; 75 (Webpage accessed 28 April 2025)

²⁶¹ Cybersecurity Stats: Facts And Figures You Should Know. Forbes. (<u>Webpage</u> accessed 28 April 2025)

²⁶² Kjoersvik O, Bate A. Black Swan Events and Intelligent Automation for Routine Safety Surveillance. Drug Saf. 2022 May;45(5):419-427. doi: 10.1007/s40264-022-01169-0. (<u>Article</u> accessed 28 April 2025)

2786

2787

2788 **APPENDIX 1: Glossary**

This glossary provides definitions specific to terms within the context of Artificial Intelligence use in
 pharmacovigilance. Refer to the International Council for Harmonization of Technical Requirements
 for Pharmaceuticals for Human Use (ICH) compiled by CIOMS in the <u>Glossary of ICH Terms and</u>
 <u>Definitions</u> and all other relevant glossaries available for any additional terms not described within
 this glossary.

2794

2795 Accountability

2796Accountability applies to clearly defined roles, responsibilities and liability for organizations2797and/or individuals deploying, operating and managing artificial intelligence systems. It requires2798the adoption of appropriate governance measures by relevant stakeholders (including but not2799limited to Regulators, Vendors, Users, Developers, Data Providers or Pharmaceutical Company)2800involved in setting policy, developing, deploying, maintaining and managing artificial2801intelligence systems. This ensures operation within expected parameters throughout the2802artificial intelligence lifecycle as well as managing any unforeseen consequences.

- 2803 Proposed by CIOMS Working Group XIV.
- 2804

2805 Adverse event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

- 2812Adopted from: Council for International Organizations of Medical Sciences (CIOMS) Glossary of ICH terms and
definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. (Full text accessed 4 April
2025)28142025)
- 2815

2816 Adverse reaction

2817 A response to a medicinal product that is noxious and unintended, meaning a causal 2818 relationship between the product and the event is at least a reasonable possibility.

2819Adopted from: Council for International Organizations of Medical Sciences (CIOMS) Glossary of ICH terms and2820definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. (Full text accessed 4 April28212025)

2822

2823 Artificial intelligence

- An artificial intelligence (AI) system is a machine-based system that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments.
- 2827Adopted from: OECD (2024), "Explanatory memorandum on the updated OECD definition of an AI system", OECD2828Artificial Intelligence Papers, No. 8, OECD Publishing, Paris, https://doi.org/10.1787/623da898-en.
- 2830 Note: In the context of pharmacovigilance, the use of AI systems and activities is aimed at enhancing drug2831 safety monitoring, patient safety and regulatory compliance.
- 2832

2829

2833	Artific	cial intelligence literacy
2834 2835		Having the essential abilities needed to understand, learn and work in a digital world through Al-driven technologies.
2836 2837 2838		Adopted from: Davy Tsz Kit Ng, Jac Ka Lok Leung, Samuel Kai Wah Chu, Maggie Shen Qiao, Conceptualizing Al literacy: An exploratory review, Computers and Education: Artificial Intelligence, Volume 2, 2021, 100041, ISSN 2666-920X, https://doi.org/10.1016/j.caeai.2021.100041 .
2839		
2840	Augm	ented intelligence / Intelligence augmentation
2841 2842 2843 2844 2845		Augmented intelligence is a conceptualization of artificial intelligence that focuses on artificial intelligence's assistive role. It emphasizes the use of artificial intelligence for enhancing, i.e. augmenting or amplifying human intelligence, rather than replacing it. Inherent in this view is the recognition that artificial intelligence and humans work together in a human-centered partnership, where each one can perform certain tasks better than either could alone.
2846		Combined from:
2847 2848 2849		 Madni AM. Augmented intelligence: A human productivity and performance amplifier in systems engineering and engineered human–machine systems. Systems engineering for the digital age: practitioner perspectives. 2023;Oct8:375-391. (<u>Chapter abstract</u>) <u>https://doi/10.1002/9781394203314.ch17</u>
2850 2851		- World Medical Association (WMA). <i>WMA Statement on augmented intelligence in medical care.</i> 2019. (Webpage accessed 3 April 2025)
2852		
2853	Autor	nation bias or automation complacency
2854 2855 2856 2857 2858 2859 2860		Automation bias and automation complacency are overlapping manifestations of automation- induced phenomena, where human attention plays a central role. Both refer to the human tendency to favour suggestions from automated decision-making systems over non-automated contradictory information even when it is correct. They can involve attentional bias directed toward the automated output, or insufficient attention and monitoring of the automated output, especially in context of multi-tasking where manual tasks compete with the human expert's attention.
2861		Combined from:
2862 2863 2864		 Parasuraman R, Manzey DH. Complacency and bias in human use of automation: An attentional integration. <i>Human factors</i>. 2010Jun;52(3):381-410. (Journal full text) <u>https://doi.org/10.1177/0018720810376055</u>
2865 2866		- Cummings ML. Automation bias in intelligent time critical decision support systems. In Decision making in aviation. 2017;Jul5;289-294. Routledge. (Chapter abstract accessed 4 April 2025)
2867		
2868	Bias	
2869 2870		The tendency of a measurement process to over- or under-estimate the value of a population parameter.
2871 2872 2873 2874 2875 2876 2877		Adopted from: Council for International Organizations of Medical Sciences (CIOMS). Glossary of ICH terms and definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. <u>(Full text accessed 4 April 2025)</u> In AI, bias may be systematic difference in treatment of certain objects, people, or groups in comparison to others [18]. Bias can be introduced into study design, conduct or analysis. Sources of bias include selection bias (of study sample), operational bias, and analyses that do not account for missing data.
2878 2879 2880		Adopted from: International Medical Device Regulators Forum (IMDRF). Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. 2021. (Full text accessed 3 April 2025)

2881 In the context of artificial intelligence, bias can occur when the artificial intelligence data or 2882 algorithms reflect or perpetuate existing social inequalities, leading to discriminatory or unfair 2883 artificial intelligence outputs. 2884 Adopted from: University of Saskatchewan. Generative Artificial Intelligence: Glossary of AI Related Terms. 2885 (Webpage accessed 4 April 2025) 2886 2887 **Black-Box model** 2888 An analytics model that provides results based on received data but the logic used to provide those results cannot be determined or inferred on how it achieved those results. 2889 2890 Proposed by CIOMS Working Group XIV. 2891 2892 **Black Swan event** 2893 Event of extreme impact that, although outside the realm of regular expectations (i.e. 2894 prospectively unpredictable), prompts humans to concoct explanations for its occurrence after 2895 the fact, making it seemingly explainable and predictable (i.e. retrospectively distorted). 2896 Combined from: 2897 - Kjoersvik O, Bate A. Black swan events and intelligent automation for routine safety surveillance. Drug 2898 Safety.2022;May;45(5):419-427. (Journal full text) 2899 - Taleb NN. Black swans and the domains of statistics. The American statistician. 2007;Aug 1;61(3):198-200. (Journal 2900 abstract) https://doi.org/10.1198/000313007X219996 2901 2902 **Business continuity plan** Set of provisions and systems for the prevention of / recovery from events that could severely 2903 2904 impact on an organisation's staff and infrastructure in general or on the structures and 2905 processes for pharmacovigilance in particular, including the urgent exchange of information 2906 within an organisation, amongst organisations sharing pharmacovigilance tasks as well as 2907 between marketing authorisation holders and competent authorities. 2908 Adopted from: Heads of Medicines Agencies (HMA). European Medicines Agency (EMA). Guideline on good 2909 pharmacovigilance practices (GVP): Module I – Pharmacovigilance systems and their quality systems. 2012. (Full 2910 text accessed 3 April 2025) 2911 2912 **Change management** 2913 Change Management describes processes, methods and techniques designed and used to 2914 plan, implement and control changes to organizational structures and/or business processes. Methodologies span around people, process and culture. 2915 2916 Typically Change Management includes following components: Leadership alignment, 2917 Stakeholder engagement, Communication, Training, Impact Assessment, Continuous 2918 improvement. 2919 Adopted from: International Organization for Standardization (ISO). What is change management: a Quick guide. 2920 (Webpage accessed 3 April 2025) 2921 2922 **Class imbalance** 2923 Imbalance between categories in classification tasks. This affects model performance metrics, 2924 e.g. by the fact that a model always predicting the same outcome will be 99% accurate if 99% 2925 of test cases belong to the corresponding class. 2926 Adopted from: European Medicines Agency (EMA). Reflection paper on the use of Artificial Intelligence (AI) in the 2927 medicinal product lifecycle. 2024. (Full text accessed 3 April 2025) 2928

2929	Cluster analysis
2930 2931	An unsupervised machine learning method that groups data elements based on similarities to identify patterns that are not immediately evident.
2932	Proposed by CIOMS Working Group XIV.
2933	
2934	Computerized system validation
2935 2936 2937	Process of establishing and documenting that the specified requirements of a computerized system are fulfilled consistently from design until decommissioning of the system and/or transition to a new system. The approach to validation should focus on a risk assessment that
2938 2939	takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.
2940 2941 2942	Adopted from: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). <i>Integrated Addendum to ICH E6(R1): Guideline for good clinical practice E6(R2)</i> . 2016. (Full text accessed 3 April 2025)
2943	
2944	Confirmation bias
2945 2946	Confirmation bias is the tendency to give greater weight to data that support preliminary assumptive results, while failing to seek or dismissing contradictory evidence.
2947 2948	Adopted from: Elston DM. Confirmation bias in medical decision-making. <i>Journal of the American Academy of Dermatology</i> . 2020;Mar1;82(3):572. (Journal full text) https://doi:10.1016/j.jaad.2019.06.1286
2949	
2950	Cross-validation
2951 2952	Resampling method used to assess the generalisation ability of a machine learning model and prevent overfitting.
2953 2954	Adopted from: D. Cross-Validation. <i>Preprint submitted to Encyclopedia of Bioinformatics and Computational Biology,</i> 2nd edition (Elsevier). 2019;542-545. (Full text accessed 3 April 2025).
2955 2956 2957	Note: This is an alternative to maintaining separate training and validation data sets to provide a more efficient use of data during development.
2958	
2959	Data anonymization
2960 2961 2962	Anonymisation of personal data is the process whereby both direct and indirect personal identifiers are removed, and technical safeguards are used to ensure zero risk of re-identification.
2963 2964 2965	Adopted from: World Health Organization (WHO). <i>Ethics and governance of artificial intelligence for health: Guidance on large multi-modal models</i> . Geneva: World Health Organization. 2024. (<u>Webpage</u> accessed 3 April 2025)
2966	
2967	Data drift
2968	Change in the input data distribution a deployed model receives over time, which can cause
2969 2970	the model's performance to degrade. This occurs when the properties of the underlying data change. Data drift can affect the accuracy and reliability of predictive models.
2971 2972	Adopted from: U.S. Food and Drug Administration. FDA Digital Health and Artificial Intelligence Glossary– Educational Resource. 2024. (<u>Webpage</u> accessed 3 April 2025)
2973	

2974	Data privacy
2975 2976 2977	Data privacy refers to measures taken to protect the fundamental right of individuals to the protection of their personal information. In the setting of PV, these measures emphasize the protection of sensitive and personal data (including health data).
2978 2979	Proposed by CIOMS Working Group XIV.
2980	Decision tree
2981 2982	A model that uses a tree-like structure where data is progressed through various pre-defined tests or attributes to reach a final decision or prediction.
2983	Proposed by CIOMS Working Group XIV.
2984	
2985	Deep learning
2986 2987 2988	A variant of machine learning involving neural networks with multiple layers of processing units known as artificial neurons, or 'perceptrons' (nodes), which together facilitate extraction of higher features of unstructured input data (for example, images, video and text).
2989 2990 2991	Adopted from: Thirunavukkarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in medicine. Nature medicine. 2023;Aug;29(8):1930-1940. (Journal full text) https://doi.org/10.1038/s41591-023- 02448-8
2992 2993	Approach to creating rich hierarchical representations through the training of neural networks with many hidden layers.
2994 2995	Adopted from: European Medicines Agency (EMA). Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle. 2024. (Full text accessed 3 April 2025)
2996	
2997	Explainability
2998 2999	The degree to which humans can understand the factors and logic that have led to a specific outcome or that play a role in the general operation of an AI system.
3000	Proposed by CIOMS Working Group XIV.
3001	
3002	Fairness and equity
3003 3004 3005 3006	Fairness and Equity requires awareness and adherence to the ideas of impartiality, equality, non-discrimination, diversity, justice and lawfulness. Avoidance and mitigation of unfair bias, discriminatory or unjust social wellbeing and environmental impacts and/or outcomes should be considered throughout the whole artificial intelligence lifecycle.
3007 3008	Proposed by CIOMS Working Group XIV.
3009	False negative
3010 3011	The determination of a data point not belonging to a class of interest when the reference or test set states that does belong.
3012	Proposed by CIOMS Working Group XIV.
3013	
3014	False positive
3015 3016	The determination of a data point belonging to a class of interest when the reference or test set states that does not belong.
3017 3018	Proposed by CIOMS Working Group XIV.

3019	Feature
3020 3021	A measurable property or characteristic of the data or engineered through data processing or transformation of the data that is used to train a model.
3022	Proposed by CIOMS Working Group XIV.
3023	Error! Bookmark not defined.
3024	Few-shot learning
3025 3026	AI developed to complete tasks with exposure to only a few initial examples of the task, with accurate generalization to unseen examples.
3027 3028 3029	Adopted from: Thirunavukkarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in medicine. <i>Nature medicine</i> . 2023;Aug;29(8):1930-1940. <u>(Journal full text)</u> <u>https://doi.org/10.1038/s41591-023-02448-8</u>
3030	
3031	Fuzzy logic
3032 3033 3034 3035	An approach to variable processing that allows for multiple possible truth values to be processed through the same variable. Fuzzy logic attempts to solve problems with an open, imprecise spectrum of data and heuristics that makes it possible to obtain an array of accurate conclusions.
3036	Proposed by CIOMS Working Group XIV.
3037	
3038	Generative artificial intelligence
3039 3040	Category of artificial intelligence techniques in which algorithms are trained on data sets that can be used to generate new content, such as text, images or video.
3041	Proposed by CIOMS Working Group XIV.
3042	
3043	Governance
3044 3045 3046	A governance framework requires implementation of risk management practices and policies, responsible use, security, openness, fairness, and ethical practices to ensure adherence to the Artificial Intelligence Guiding Principles in the report of the CIOMS Working Group XIV.
3047	Proposed by CIOMS Working Group XIV.
3048	
3049	Hallucination
3050 3051	In natural language generation tasks, hallucinations are generated content that is either nonsensical or unfaithful to the provided source content.
3052 3053 3054	Adopted from: Huang L, Yu W, Ma W, Zhong W, Feng Z, Wang H, Chen Q, Peng W, Feng X, Qin B, Liu T. A survey on hallucination in large language models: Principles, taxonomy, challenges, and open questions. arXiv preprint arXiv:2311.05232. 2023 Nov 9.
3055	
3056	Human agency
3057 3058	Human agency is the capacity for human beings to make choices out of their own volition and to follow those choices to action.
3059	Proposed by CIOMS Working Group XIV.
3060	
3061	Human-in-command
3062 3063 3064	The capability of a human to oversee the overall activity of an artificial intelligence system, including its broader economic, societal, legal and ethical impact, and the ability to decide if, when, and how to use an artificial intelligence system.

3065 3066	Adopted from: European Commission. <i>Ethics guidelines for trustworthy AI.</i> 2019. (<u>Webpage</u> accessed 3 April 2025)
3067	
3068	Human-in-the-loop
3069	system.
3071 3072	Adopted from: European Commission. <i>Ethics guidelines for trustworthy AI</i> . 2019. (<u>Webpage</u> accessed 3 April 2025)
3073	
3074	Human-on-the-loop
3075 3076	The capability for human intervention during the design of an artificial intelligence system and monitoring of its operation.
3077 3078	Adopted from: European Commission. <i>Ethics guidelines for trustworthy AI</i> . 2019. (Webpage accessed 3 April 2025)
3079	Human oversight
3080 3081 3082	Human oversight refers to the expected role of humans in the design, implementation, monitoring, and analysis of AI in PV. It requires a framework to manage performance and to detect and mitigate potential issues related to the AI system.
3083 3084	Proposed by CIOMS Working Group XIV.
3085	Individual Case Safety Report
3086 3087	A report containing information about a suspected adverse drug reaction related to the administration of one or more medicinal products to a specific patient at a specific time.
3088 3089 3090	Adopted from: Council for International Organizations of Medical Sciences (CIOMS) Glossary of ICH terms and definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. (Full text accessed 4 April 2025)
3091	
3092	Interpretability (See also Explainability)
3093 3094 3095	A description of the general principles and logic by which an Al model functions and arrives at its outcomes / predictions should be shared, or the lack of explainability should be acknowledged and its implications discussed.
3096 3097	Proposed by CIOMS Working Group XIV. Error! Bookmark not defined.
3098	Knowledge graph
3099 3100 3101 3102 3103	A heterogeneous knowledge base consisting of triples (facts) each comprised of object pairs and connecting relationships modelled through graphs and ontologies (a standardized machine readable semantic framework for representing all objects, and their properties and relationships in a domain of knowledge), which extract new insights from existing data sets via their integration.
3104 3105 3106	Adopted from: Manfred Hauben, Mazin Rafi, Knowledge Graphs in Pharmacovigilance: A Step-By-Step Guide, Clinical Therapeutics, Volume 46, Issue 7, 2024, Pages 538-543.
3107	Large language model
3108 3109 3110	A type of artificial intelligence model using deep neural networks to learn the relationships between words in natural language, using large datasets of text to train, these include those with or without decoders.

3111 3112 3113	LLMs can be classified according to their availability and accessibility into two main categories: open-source models (freely accessible to the public) and closed-source models (developed as commercial products and often necessitating licenses or subscriptions for use).
3114 3115 3116	Adopted from: Heads of Medicines Agencies (HMA). European Medicines Agency (EMA). Guiding principles on the use of large language models in regulatory science and for medicines regulatory activities. 2024. (Full text accessed 4 April 2025)
3117	
3118	Local Interpretable Model-Agnostic Explanations (LIME)
3119 3120	A technique that approximates a black box machine learning model with a local, interpretable model to explain each individual prediction.
3121 3122	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle.</i> 2024. (Full text accessed 3 April 2025)
3123	
3124	Machine learning
3125 3126 3127 3128	Computational process of optimising the parameters of a model from data, which is a mathematical construct generating an output based on input data. Machine learning approaches include, for instance, supervised, unsupervised and reinforcement learning, using a variety of methods including deep learning with neural networks.
3129 3130	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle.</i> 2024. (Full text accessed 3 April 2025)
3131	
3132	(AI) Model
3133 3134	Mathematical or computational method with parameters (weights) arranged in an architecture that allows learning of patterns (features) from training data.
3135 3136	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle.</i> 2024. (Full text accessed 3 April 2025)
3137	
3138	Model drift
3139 3140	A process where the model performance changes overtime either in a positive or negative performance outcome.
3141 3142 3143	Adopted from: S. Wang, S. Schlobach, M. Klein, Concept drift and how to identify it J Web Semant: Sci Serv Agents World Wide Web, 9 (2011), <u>10.1016/j.websem.2011.05.003</u>
3144	Natural language processing
3145 3146	Field of artificial intelligence focusing on the interaction between computers and human language.
3147 3148 3149 3150	Adopted from: Thirunavukkarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in medicine. <i>Nature medicine</i> . 2023;Aug;29(8):1930-1940. <u>(Journal full text)</u> https://doi.org/10.1038/s41591-023-02448-8
3151	Negative controls
3152 3153	A real-world data point sampled as not belonging to the class of interest or deliberately created to not trigger a positive response from an artificial intelligence model.
3154	Proposed by CIOMS Working Group XIV.
3155	

3156 **Neural network** 3157 Computing system inspired by biological neural networks, comprising (nodes), edges/weights, 3158 activation functions usually arranged in layers, communicating with one another and performing transformations upon input data. 3159 3160 Adopted from: European Medicines Agency (EMA). Reflection paper on the use of Artificial Intelligence (AI) in the 3161 medicinal product lifecycle. 2024. (Full text accessed 3 April 2025) 3162 3163 Overfitting 3164 Learning details from training data that cannot be generalised to new data. 3165 Adopted from: European Medicines Agency (EMA). Reflection paper on the use of Artificial Intelligence (AI) in the 3166 medicinal product lifecycle. 2024. (Full text accessed 3 April 2025) 3167 3168 Parameter, hyper-parameter 3169 Variable within a machine learning model that is updated — usually automatically — during 3170 training to maximize performance. In deep learning, parameters are the 'weights' or data 3171 transforming functions comprising neural network nodes. 3172 Adopted from: Thirunavukkarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in 3173 medicine. Nature medicine. 2023;Aug;29(8):1930-1940. (Journal full text) https://doi.org/10.1038/s41591-023-3174 02448-8 3175 Hyper-parameters are parameters that are used to configure a model. Unlike model 3176 parameters, they cannot be directly estimated from data learning and must be set before 3177 training a machine learning model. Hyper-parameter tuning is a step often required to build 3178 effective ML models. 3179 Adopted from: Yang L, Shami A. On hyperparameter optimization of machine learning algorithms: Theory and 3180 practice. Neurocomputing. 2020 Nov 20;415:295-316. 3181 3182 **Performance degradation** 3183 When results from an artificial intelligence system either fail or diminish in their ability to 3184 achieve the expected or required results as achieved earlier. 3185 Proposed by CIOMS Working Group XIV. 3186 3187 Personal data 'Personal data' means any information relating to an identified or identifiable natural person 3188 ('data subject'). Information such as a name, an identification number, location data, an online 3189 identifier or to one or more factors specific to the physical, physiological, genetic, mental, 3190 economic, cultural or social identity of that natural person are examples of personal data. 3191 3192 Sensitive (personal) data refers to special categories of personal data. 3193 Adopted from: European Parliament, Council of the European Union. Regulation (EU) 2016/679 of the European 3194 Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of 3195 personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection 3196 Regulation), Art. 4(1). Official Journal of the European Union. 2016; L 119. (Webpage accessed 4 April 2025) 3197 Pharmacovigilance 3198 3199 The science and activities relating to the detection, assessment, understanding and prevention 3200 of adverse effects or any other drug related problem. 3201 Adopted from: CIOMS Cumulative Glossary, with a focus on Pharmacovigilance (Version 2.1). Geneva: Council for International Organizations of Medical Sciences. 2024. (Full text) https://doi.org/10.56759/ocef1297 3202 3203

3204	Pharmacovigilance system
3205 3206 3207	System used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.
3208 3209 3210	Adopted from: Heads of Medicines Agencies (HMA). European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems. 2012. (<u>Full</u> <u>text</u> accessed 3 April 2025)
3211	
3212	Precision
3213 3214 3215	Proportion of retrieved samples which are annotated as positive controls in the reference set, calculated as the ratio between correctly classified positive controls and all samples assigned to that class. Precision is also known as positive predictive value (PPV).
3216 3217 3218 3219	Adopted from: Hicks SA, Strümke I, Thambawita V, Hammou M, Riegler MA, Halvorsen P, Parasa S. On evaluation metrics for medical applications of artificial intelligence. <i>Scientific reports</i> . 2022;Apr8;12(1):5979. (Journal full text) https://doi.org/10.1038/s41598-022-09954-8
3220	Positive controls
3221 3222	A real-world data point sampled as belonging to the class of interest or deliberately created to trigger a positive response from an artificial intelligence model.
3223	Proposed by CIOMS Working Group XIV.
3224	
3225	Predictive models
3226 3227	A machine learning algorithm that analyzes data to identify patterns and trends, allowing it to make predictions about future outcomes or events based on input data.
3228 3229 3230 3231	Adopted from: De Hond AA, Leeuwenberg AM, Hooft L, Kant IM, Nijman SW, van Os HJ, Aardoom JJ, Debray TP, Schuit E, van Smeden M, Reitsma JB. Guidelines and quality criteria for artificial intelligence-based prediction models in healthcare: a scoping review. <i>NPJ digital medicine</i> . 2022;Jan10;5(1):2. (Journal full text) <u>https://doi.org/10.1038/s41746-021-00549-7</u>
3232	
3233	Quality management system
3234 3235 3236 3237	cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.
3238 3239	Adopted from: D. Cross-Validation. <i>Preprint submitted to Encyclopedia of Bioinformatics and Computational Biology,</i> 2nd edition (Elsevier). 2019;542-545. (Full text accessed 3 April 2025).
3240	
3241	Real-world data
3242	Data relating to patient health status and/or the delivery of health care routinely collected
3243 3244	records (EHRs): medical claims and hilling data: data from product and disease registries:
3245	patient-generated data, including from mobile devices and wearables; and data gathered from
3246	other sources that can inform on health status (e.g. genetic and other biomolecular
3247	phenotyping data collected in specific health systems).
3248 3249 3250	Adopted from: Council for International Organizations of Medical Sciences (CIOMS) Glossary of ICH terms and definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. <u>(Full text accessed 4 April 2025)</u>
3251	

3252 Recall 3253 Proportion of positive controls correctly classified as such, calculated as the ratio between 3254 correctly classified positive controls and all positive controls. Also known as sensitivity or true 3255 positive rate (TPR). 3256 Adopted from: Hicks SA, Strümke I, Thambawita V, Hammou M, Riegler MA, Halvorsen P, Parasa S. On evaluation 3257 metrics for medical applications of artificial intelligence. Scientific reports. 2022;Apr8;12(1):5979. (Journal full text)https://doi.org/10.1038/s41598-022-09954-8 3258 3259 3260 Reproducibility 3261 The ability to achieve consistent results when analysis is repeated under the same conditions. 3262 Data and computer codes are used to regenerate the results. 3263 Adopted from: National Academies of Sciences, Engineering, and Medicine; Policy and Global Affairs; Committee on 3264 Science, Engineering, Medicine, and Public Policy; Board on Research Data and Information; Division on Engineering 3265 and Physical Sciences; Committee on Applied and Theoretical Statistics; Board on Mathematical Sciences and 3266 Analytics; Division on Earth and Life Studies; Nuclear and Radiation Studies Board; Division of Behavioral and Social 3267 Sciences and Education; Committee on National Statistics; Board on Behavioral, Cognitive, and Sensory Sciences; 3268 Committee on Reproducibility and Replicability in Science. Reproducibility and Replicability in Science. Washington 3269 (DC): National Academies Press (US); 2019; May7. Chapter 3, Understanding Reproducibility and Replicability. 3270 (Chapter full text accessed 4 April 2025) 3271 3272 **Risk-based approach** 3273 A risk-based approach acknowledges the potential hazards that artificial intelligence systems 3274 can pose and recognises that different use cases present varying types and levels of risk. This 3275 necessitates a risk assessment that identifies, prioritises, and manages potential risks that 3276 could negatively impact a pharmacovigilance system's behaviour and results, taking into 3277 consideration existing process controls. A risk is characterised by both the anticipated impact 3278 and the likelihood of negative outcomes. 3279 This approach also supports procedures to identify and reduce errors and biases in a way that 3280 is proportionate to their risk. It influences the implementation strategies of AI systems 3281 (including documentation, compliance, and record-keeping), which should generally be 3282 commensurate with the identified risk. 3283 Proposed by CIOMS Working Group XIV. 3284 3285 Robustness 3286 A system reliably performs to its intended objectives or requirements accounting for known 3287 variances in data. 3288 Proposed by CIOMS Working Group XIV. 3289 3290 Semantic vector 3291 A mathematical representation of a word, phrase, or document as an identifier, where the 3292 identifier's position in the high-dimensional space captures the meaning or relationship of that 3293 word/phrase, allowing artificial intelligence systems to understand the context and similarity 3294 between different pieces of text based on their meaning. 3295 Adopted from: Cohen T, Widdows D. Empirical distributional semantics: methods and biomedical 3296 applications. Journal of biomedical informatics. 2009;Apr1;42(2):390-405. (Journal full 3297 text) https://doi.org/10.1016/j.jbi.2009.02.002 3298 3299 Sensitivity analysis 3300 An assessment technique used to evaluate how changes in input data or model parameters 3301 affect the output of an artificial intelligence model.
3302 3303	Proposed by CIOMS Working Group XIV.
3304	SHapley Additive exPlanations (SHAP)
3305 3306	Explainable artificial intelligence framework that can provide model-agnostic local explainability for tabular, image, and text datasets.
3307 3308	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle</i> . 2024. (Full text accessed 3 April 2025)
3309	
3310	Note: It is derived from cooperative game theory of payouts to groups of cooperating individuals.
3311	
3312	Signal
3313 3314 3315 3316	Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.
3317 3318 3319 3320 3321	For the purposes of pharmacovigilance a signal is Information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.
3322 3323 3324 3325	Adopted from: Council for International Organizations of Medical Sciences (CIOMS) Glossary of ICH terms and definitions. Geneva: Council for International Organizations of Medical Sciences. 2024. (Full text accessed 4 April 2025)
3326	(Bioartificial) Smart organ technology
3327 3328	A series of enabling techniques that can be used to produce human organs based on bionic principles.
3329 3330	Proposed by CIOMS Working Group XIV.
3331	Supervised learning
3332	Machine learning that makes use of labelled data during training. (ISO/IEC DIS 22989).
3333 3334 3335 3336	Adopted from: International Medical Device Regulators Forum (IMDRF). Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. 2021. (Full text accessed 3 April 2025)
3337	Target levels
3338 3339	A numerical value that serves as a goal or benchmark for artificial intelligence systems to achieve or surpass during their performance evaluation.
3340	Proposed by CIOMS Working Group XIV.
3341	
3342	Test dataset
3343 3344	A subset of the data that is never shown to the machine learning model during training, used to verify what the model has learned. (Modified from ISO/IEC DIS 22989).
3345 3346 3347	Adopted from: International Medical Device Regulators Forum (IMDRF). Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. 2021. (Full text accessed 3 April 2025)
3348 3349 3350	Data used to evaluate the performance of the AI system, before its deployment. It is expected to be similar to production data, and proper evaluation needs test data to be disjointed from any data used during development.

3351 3352	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle</i> . 2024. (Full text accessed 3 April 2025)
3353	
3354	Traceability (AI)
3355 3356	The ability to track and document the data and processes used to create an artificial intelligence model.
3357	Proposed by CIOMS Working Group XIV.
3358	
3359	Training
3360 3361 3362	Process intended to establish or to improve the parameters of a machine learning model, based on a machine learning algorithm, by using training data. (Modified from ISO/IEC DIS 22989).
3363 3364 3365	Adopted from: International Medical Device Regulators Forum (IMDRF). Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. 2021. (<u>Full</u> <u>text</u> accessed 3 April 2025)
3367	Training datacat
3368 3369	Data used specifically in the context of machine learning: it serves as the raw material from which the machine learning algorithm extracts its model to address the given task
3370 3371	Adopted from: European Medicines Agency (EMA). <i>Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle</i> , 2024. (Full text accessed 3 April 2025)
3372	
3373	Transparency
3374	Transparency regarding AI involves disclosing information between organizations or
3375	individuals. This includes sharing relevant documentation of the AI system lifecycle (i.e. design,
3376	development, evaluation, deployment, operation, re-training, maintenance and
3377	decommission) to facilitate traceability and providing stakeholders with enough information to
3378 3379	nave a general understanding of the Al system, its use, risks, limitations, and impact on their rights.
3380	Proposed by CIOMS Working Group XIV.
3381	
3382	Unsupervised learning
3383	Machine learning that makes use of unlabelled data during training. (ISO/IEC DIS 22989)
3384 3385 3386 3387	Adopted from: International Medical Device Regulators Forum (IMDRF). Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. 2021. (Full text accessed 3 April 2025)
3388	Validity
3389	Validity means that a system achieves its intended purpose within acceptable parameters. It
3390	requires predefining acceptable performance levels, selecting appropriate data for model
3391 3392	training and/or testing, assessing model performance in a realistic setting and integrating the system into an ongoing quality assessment process.
3393 3394	Proposed by CIOMS Working Group XIV.
3395	Validation dataset
3396	Data used to tune hyperparameters or to validate some algorithmic choices (rule design, etc.).
3397 3398 3399	Adopted from: International Organization for Standardization (ISO). ISO/IEC DIS 22989. Information technology — Artificial intelligence — Artificial intelligence concepts and terminology. 2022. (<u>Webpage</u> accessed 4 April 2025)

3400 Zero-shot learning

Artificial intelligence developed to complete tasks without exposure to any previous examplesof the task.

3403Adopted from: Thirunavukkarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in3404medicine. Nature medicine. 2023;Aug;29(8):1930-1940. (Journal full text) https://doi.org/10.1038/s41591-023-340502448-8

APPENDIX 2: Comparison table of guiding principles 3407

3408

Table 9: Comparison of CIOMS Working Group XIV guiding principles for artificial intelligence across regional and country government 3409

3410 3411 3412 institutions, and international organizations – Extracted description of principles

Source: CIOMS Working Group XIV

			Examples of regional	- and country gover	nment institutions', a	nd international organi	isations' principles		
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
Human Oversight	Al systems should support human agency and human decision making, as prescribed by the principle of respect for human autonomy.	When an Al system significantly impacts a person, community, group or environment, there should be a timely process to allow people to challenge the use or outcomes of the Al system.	Human Oversight means that high-impact AI systems must be designed and developed in such a way as to enable people managing the operations of the system to exercise meaningful oversight. This includes a level of interpretability appropriate to the context.		AI systems should function in a robust, secure and safe way throughout the AI life cycle, and risks should be continually identified, assessed and managed. Where appropriate, users, impacted third parties and actors in the AI lifecycle should be able to contest an AI decision or outcome that is harmful or creates.	Automated systems"in design and development, pre-development and on-going disparity testing and mitigation, and clear organizational oversight"	Formal processes for human control and review of automated decisions are mandatory.	The principle of autonomy requires that any extension of machine autonomy not undermine human autonomy. In the context of health care, this means that humans should remain in full control of health-care systems and medical decisions. Human oversight may depend on the risks associated with an AI system but should always be meaningful	Mechanisms should be in place, as appropriate, to ensure that if Al systems risk causing undue harm or exhibit undesired behaviour, they can be overridden, repaired, and/or decommissioned safely as needed.

		Examples of regional - and country government institutions', and international organisations' principles								
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²	
								and should thus include effective, transparent monitoring of human values and moral considerations.		
Validity & Robustness	Technical robustness requires that AI systems are developed with a preventative approach to risks and that they behave reliably and as intended while minimising unintentional and unexpected harm as well as preventing it where possible. This should also apply in the event of potential changes in their operating environment or the presence of other agents (human or artificial) that may interact	Al systems should reliably operate in accordance with their intended purpose.	Validity means a high-impact Al system performs consistently with intended objectives. Robustness means a high-impact Al system is stable and resilient in a variety of circumstances.		Consider how the associated actors on the AI supply chain can regularly test or carry out due diligence on the functioning, resilience and security of a system. Provide tools and guidance for undertaking AI- related safety risk assessments and implementing appropriate mitigations.		Al interventions should follow scientific best practice including being reliable, reproducible, fair, honest, and accountable.	All algorithms should be tested rigorously in the settings in which the technology will be used in order to ensure that it meets standards of safety and efficacy. The examination and validation should include the assumptions, operational protocols, data properties and output decisions of the Al technology. There should be robust, independent	Al systems must function in a robust, secure and safe way throughout their lifetimes, and potential risks should be continually assessed and managed.	

		Examples of regional - and country government institutions', and international organisations' principles									
Principle E	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²		
v s r	with the Al system in an adversarial manner.							oversight of such tests and evaluation to ensure that they are conducted safely and effectively.			
Data Privacy F	Principle of prevention of harm is privacy, a fundamental right particularly affected by AI systems. Prevention of harm to privacy also necessitates adequate data governance that covers the quality and integrity of the data used, its relevance in light of the domain in which the AI systems will be deployed, its access protocols and the capability to process data in a manner that	Al systems should respect and uphold privacy rights and data protection, and ensure the security of data.			Encourage AI developers and deployers (within their remit) to mitigate and build resilience to cybersecurity related risks throughout the AI life cycle. Encourage AI developers and deployers to consider and mitigate where possible potential malicious or criminal use of AI products and services.	"Data privacyprotections are included by default, including ensuring that data collection conforms to reasonable expectations and that only data strictly necessary for the specific context is collected".	Privacy, confidentiality, and security of data use must be foundational to every Al development.	Data protection laws are "rights-based approaches" that provide standards for regulating data processing that both protect the rights of individuals and establish obligations for data controllers and processors.			

			Examples of regional	I - and country gover	nment institutions', a	nd international organ	isations' principles		
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
	protects privacy.								
Transparency	transparency which encompasses three elements: 1) traceability, 2) explainability and 3) open communication about the limitations of the AI system.	There should be transparency and responsible disclosure so people can understand when they are being significantly impacted by AI, and can find out when an AI system is engaging with them.	Transparency means providing the public with appropriate information about how high-impact AI systems are being used. The information provided should be sufficient to allow the public to understand the capabilities, limitations, and potential impacts of the systems.	End-users of Al- MD (e.g. medical practitioners, patients) should be informed that they are interacting with an Al-MD.	Encourage AI developers and deployers (within their remit) to implement appropriate transparency and explainability measures.		Transparent approaches must always be used and communicated when developing AI algorithms. Everything must be as open and sharable as possible. Tools and underlying concept of Openness must be a feature and a critical success factor of any AI development.	Al should be intelligible or understandable to developers, users and regulators. Two broad approaches to ensuring intelligibility are improving the transparency and explainability of Al technology.	This principle is about transparency and responsible disclosure around Al systems to ensure that people understand when they are engaging with them and can challenge outcomes.
Accountability	The principle of accountability necessitates that mechanisms be put in place to ensure responsibility for the development, deployment	People responsible for the different phases of the Al system lifecycle should be identifiable and accountable for the	Accountability means that organizations must put in place governance mechanisms needed to ensure compliance with all legal obligations of high-impact Al systems in the context in which they will be used.	While developers should be responsible for the proper design of algorithms used in the AIMD, organisations using AI-MD to deliver care will be responsible for the decision to implement the AI-	See Governance.	"should have access to timely human consideration and remedy by a fallback and escalation process if an automated system fails, it produces an error, or you would like to	See Validity & Robustness.	Although Al technologies perform specific tasks, it is the responsibility of human stakeholders to ensure that they can perform those tasks and that	Organisations and individuals developing, deploying or operating Al systems should be held accountable for their proper functioning.

			Examples of regiona	I - and country gover	nment institutions', a	nd international organi	sations' principles		
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
	and/or use of Al systems.	outcomes of the AI systems, and human oversight of AI systems should be enabled.	This includes the proactive documentation of policies, processes, and measures implemented.	MD and the clinical outcomes arising from the use of AI-MD in ensuring that safe care is delivered. Similar to the implementation of any other MD, the use of AI-MD does not change the liability of the implementing institution or the individual medical professional in their provision of appropriate and safe care.		appeal or contest its impacts on you."		they are used under appropriate conditions. Institutions have not only legal liability but also a duty to assume responsibility for decisions made by the algorithms they use, even if it is not feasible to explain in detail how the algorithms produce their results.	
Societal well-being	the broader society, other sentient beings and the environment should be considered as stakeholders throughout the AI system's life cycle. Ubiquitous exposure to social AI systems in all	Al systems should benefit individuals, society and the environment.		Safeguards in the design, development, and implementation of AI-MD should be put in place to ensure that patients' interests, including their safety and well- being, are protected.			Actions and solutions must be people centred and not be used solely by itself. As one of many technologies to aid public health AI should respect the rights of the individual.	Al technologies should not harm people. They should satisfy regulatory requirements for safety, accuracy and efficacy before deployment, and measures should be in place to ensure quality control	This Principle highlights the potential for trustworthy AI to contribute to overall growth and prosperity for all – individuals, society, and planet – and advance global development objectives.

		Examples of regional - and country gover-ment institutions', and international organisations' principles Australia ²⁶⁵ Canada ²⁶⁶ Singapore ²⁶⁷ UK ²⁶⁸ US ²⁶⁹ PAHO ²⁷⁰ WHO ²⁷¹ OECD ²⁷² our it in n, n, re or omment, rour our our our our er or on of ency, wely ur Image:										
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²			
	areas of our lives (be it in education, work, care or entertainment) may alter our conception of social agency, or negatively impact our social relationships and attachment.							and quality improvement. Thus, funders, developers and users have a continuous duty to measure and monitor the performance of AI algorithms to ensure that AI technologies work as designed and to assess whether they have any detrimental impact on individual patients or groups.				
Environmental well-being	See Societal well-being.	See Societal well-being.						Al systems should be designed to minimize their ecological footprints and increase energy efficiency, so that use of Al is consistent with society's efforts to reduce the impact of human beings on the earth's	See Societal well-being.			

		Australia ²⁶³ Canada ²⁶⁶ Singapore ²⁶⁷ UK ²⁶⁸ US ²⁶⁹ PAHO ²⁷⁰ WHO ²⁷¹ OECD ²⁷² ad Al systems Al systems Fairness and inclusive and and should be inclusive and and should be inclusive and and should be inclusive and infirit in and should be inclusive and and should be inclusive and and should be individuals or result in and should and sporpriate to individuals, ft, es Fairness, and should be inclusive and accessible, and should unfair ont involve or result in discriminatory outcomes. The development and and should be individuals or result in unfair Al systems should not result individuals or or groups. Fairness, and should be design should discriminatory outcomes. Fairness, equilts hal individuals or result in discriminatory outcomes. Al systems and discriminatory outcomes. Al systems and discriminatory outcomes. Al systems and should be design should always form the design should always form the demographic frainress that are appropriate to system' sue, outcomes and the application of relevant law. Fairness, subt be taken to system' sue, outcomes and the application of relevant law. Fairness and discriminatory accessibility for people with disclimines (and and must be grounded in the globall/specifies of human dignity, beneficance, and justic. Al systems should be design should always form the foundation of relevant law.							
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
								environment, ecosystems and climate.	
Fairness & Equity	enable inclusion and diversity throughout the entire AI system's life cycle. AI systems (both for training and operation) may suffer from the inclusion of inadvertent historic bias, incompleteness, and bad governance models.	Al systems should be inclusive and accessible, and should not involve or result in unfair discrimination against individuals, communities or groups.	Fairness and Equity means building high-impact Al systems with an awareness of the potential for discriminatory outcomes. Appropriate actions must be taken to mitigate discriminatory outcomes for individuals and groups.	The development and implementation of AI-MD should not result in discriminatory or unjust clinical impact on patients across different demographic lines (e.g. race, gender, etc.).	Al systems should not undermine the legal rights of individuals or organisations, discriminate unfairly against individuals or create unfair market outcomes. Actors involved in all stages of the Al life cycle should consider descriptions of fairness that are appropriate to a system's use, outcomes and the application of relevant law.	"Algorithmic discrimination protectionsshould include proactive equity assessments as part of the system design, use of representative data and protection against proxies for demographic features, ensuring accessibility for people with disabilities".	Fairness, equality and inclusiveness in impact and design should always form the foundation of any AI initiative for Public Health. Discussions, developments, and implementation must be grounded in the globally-agreed ethical principles of human dignity, beneficence, nonmaleficence and justice.	Inclusiveness requires that AI used in health care is designed to encourage the widest possible appropriate, equitable use and access, irrespective of age, gender, income, ability or other characteristics. AI developers should be aware of the possible biases in their design, implementation and use and the potential harm that biases can cause to individuals and society.	Al systems should be designed in a way that respects the rule of law, human rights, democratic values and diversity, and should include appropriate safeguards to ensure a fair and just society.
Explainability	the ability to explain both the technical processes of the Al system and	See Transparency		The decisions or recommendations from an AI-MD should endeavour to be explainable	See Transparency	"Automated systems should provide explanations that are technically		See Transparency	See Transparency

			Examples of regional	I - and country gover	nment institutions', a	nd international organ	isations' principles		
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
	the reasoning behind the decisions or predictions that the AI system makes.			and reproducible. The level of explainability is dependent on the varying expectations of the end user and the risks of the Al- MD. End-users should be consulted during the development or adoption of the Al-MD to ensure the explainability meets their expectations.		valid, meaningful and useful to you and to any operators or others who need to understand the system, and calibrated to the level of risk based on the context in plain language and assessments of the clarity and quality of the notice and explanations should be made public whenever possible."			
Safety	See Validity & Robustness.	See Validity & Robustness.	Safety means that high-impact AI systems must be proactively assessed to identify harms that could result from use of the system, including through reasonably foreseeable misuse. Measures must be taken to mitigate the risk of harm.		Enable AI deployers (within their remit) and end users to make informed decisions about the safety of AI products and services. Communicate the level of safety related risk in their remit by appropriately identifying, monitoring, communicating	"Automated systemsshould be designed to proactively protect you from harms stemming from unintended, yet foreseeable, uses or impacts".		Preventing harm requires that use of AI technologies does not result in any mental or physical harm.	See Validity & Robustness.

			Examples of regiona	l - and country gover	nment institutions', a	nd international organ	isations' principles		
Principle	EU ^{263,264}	Australia ²⁶⁵	Canada ²⁶⁶	Singapore ²⁶⁷	UK ²⁶⁸	US ²⁶⁹	PAHO ²⁷⁰	WHO ²⁷¹	OECD ²⁷²
					and acting upon risks.				
Governance	See Data Privacy.				Governance measures could be put in place to ensure effective oversight of the supply and use of Al systems, with clear lines of accountability established across the Al life cycle.			Human rights standards, data protection laws and ethical principles are all necessary to guide, regulate and manage the use of AI for health by developers, governments, providers and patients.	

3413

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²⁷² OECD AI Principles overview © 2025 OECD. (<u>Website</u> accessed 27 April 2025)

3414 **APPENDIX 3: Use cases**

3415 Use Case A: Large Language Models data extraction for case processing

- 3416 Source:²⁷³
- 3417 Area of PV: ICSR Processing

3418 A1. Business rational and challenges

As per Good Pharmacovigilance Practices (GVP), pharmaceutical companies must act on potential 3419 3420 adverse reactions to drugs. With significant increases in the number of case reports in recent years, 3421 case intake/processing operations face complex challenges beyond the number of cases, such as 3422 handling very diverse data sources including unstructured texts and scanned documents or managing 3423 sudden peak inflows with a finite workforce. With the complexity of the relevant data points ranging 3424 from simple demographics to more complex lab values, simpler technology approaches like Named 3425 Entity Recognition were unsuccessful in consistently improving case intake/processing operations 3426 under real-world circumstances. The use of Large Language Models (LLMs) in case intake/processing

- 3427 provides potential to advance processes without compromising quality.
- 3428 A2. Solution
- 3429 A pharmaceutical company executed a proof-of-concept study to assess the feasibility as well as the
- 3430 quantitative and qualitative business impact of utilizing LLMs for case intake purposes. Specifically,
- 3431 LLMs were applied for data extraction from source documents for case intake and processing while3432 covering regulatory and compliance aspects.
- 3433 To process the selected source documents and extract pre-defined pieces of information, a 3-step
- semi-automatic processing pipeline was set up. The pipeline consisted of (1) pre-processing steps to
- unify the input for the LLM (OpenAI's GPT-4), (2) a JSON-formatted extraction template that guided
- the LLM in structuring the information as well as providing hints regarding the location of the
- information in the source data, and (3) post-processing steps to match the model output with fields
- 3438 where predefined values were applicable. Original source documents were augmented by references
- 3439 and highlighting of extracted key terms.
- For the assessment of the business impact of using LLMs for case intake, a selection representative cases was identified. A graphical user interface (GUI) was designed for the purpose of comparing the processing performance of (a) the fully manual process vs (b) the manual process augmented by fields pre-filled by the results of the LLM extraction pipeline. Four experienced professionals were randomly assigned to either process version (a) or (b). The processing times were tracked for each source document to derive the overall processing time regarding extraction of the representative set of fields.
- 3447 *A3. Results*
- In this study, two key results were derived from the implementation of LLMs in the case intake andprocessing operations:
- 3450 The first result focused on the performance of the LLM model, measured through the match scores
- of all extracted fields and averaged across cases of a category for the full number of source
- 3452 documents in scope of this study. The statistical evaluation revealed that the model achieved match
- 3453 scores, ranging from 85% to 100% for clinical studies, and 60% to 100% for patient support programs
- 3454 (PSP) cases. For literature cases, while the sample size precludes a robust statistical evaluation,
- 3455 model performance ranges from 67 to 100%, suggesting qualitative results that align with the other3456 types.

- 3457 The high match scores achieved by the model demonstrate its capability to extract accurate and
- relevant information from unstructured sources. This can be translated into tangible efficiency gains 3458 3459 for business operations.
- 3460 The second result highlighted the efficiency gains identified in the business impact assessment. The 3461 implementation of LLM in case intake led to an estimated efficiency gain of 39%, translating to time 3462 savings of approximately 20 minutes per case. Specifically, the study found that the average number 3463 of data points extracted per case was 69.4, with only 2.4 data points requiring manual correction.
- 3464 Implementing LLMs is not just a technical enhancement; it represents a strategic move towards 3465 improving operational efficiency and ensuring high-quality outcomes in PV practices.
- 3466 A4. Compliance with the governance framework

3467 Table 10: Use case A: Alignment with the governance framework (detail)

- 3468 Source: CIOMS Working Group XIV
- 3469

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	A risk-based approach has been followed thoroughly and a 100% QC by human interaction has been applied.	A	A	N/A	N/A	N/A
Human oversight	Implementation of dedicated features to support human oversight, including user-friendly interfaces and references to the source data. The 100% human QC ensures robustness of all extraction outputs.	A	А	N/A	N/A	N/A
Validity and robustness	No continuous learning is applied; rather, the model is used in a locked state. Releases of new versions are quality assured on a sufficiently broad test set to derive.	A	A	N/A	N/A	N/A
Transparency	Model performance has been measured with match score. The correction of the failures can be used as feedback in regular intervals to improve the prompting strategy.	A	A	N/A	N/A	N/A
Data Privacy	The service is established on a private cloud. Access is provided only to project team members. Personally identifiable information is redacted prior to the actual data extraction step.	A	А	N/A	N/A	N/A
Fairness and Equity	Not applicable. The application is not providing any data consolidation or decision support. The 1:1 match of the data extraction is verified by the human QC.	N/A	N/A	N/A	N/A	N/A
Governance & Accountability	The LLM model is using tailored prompting strategy maintained on vendor domain to test the data extraction. The model is provided by Open AI, and is powered by a selection of large language models ("LLMs").	A	A	N/A	N/A	N/A
	The case intake and processing team takes over the accountability and perform the 100% human QC process. The ultimate accountability remains with the pharma company.					

³⁴⁷⁰ 3471

SPEC: Collection of specifications, requirements 3472 DEV: Development and change management

3473 PreD: Pre-deployment & post-change sign-off

3474 PstD: Post-deployment & post-change hyper-care

3475 **RU: Routine Use**

3476

A: Applicable 3477 NA: Not Applicable

Abbreviations

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3479 Use Case B: Case deduplication

- 3480 Source:²⁷⁴
- 3481 Area of PV: ICSR Processing

3482 B1. Business rational and challenges

3483 Adverse event reporting systems (AERS) are essential in PV as they support the identification and 3484 evaluation of safety signals related to the use of medical products. Expert review in safety monitoring 3485 involves several steps, such as data mining and case series analysis, which are significantly affected 3486 by the AERS data quality. A representative example of quality issues is duplication, where more than 3487 one report describes the same patient case and the same adverse event experience for the same 3488 product. Duplicate reports may result in false or missed safety signals and increase the workload for 3489 safety evaluators by misinterpreting the actual number of true adverse events and making a product-3490 event relationship look weaker or stronger.

3491 B2. Solution

3492 A regulatory agency that maintains an AERS for drugs and biologics with >28 million historical reports 3493 and an average of 8,000 new submissions daily sought an efficient solution to deduplicate all 3494 historical and incoming adverse event reports. The regulatory agency collaborated with an academic 3495 partner to address this issue by developing a **deduplication pipeline** relying on modern technologies 3496 (mainly, natural language processing, network analysis, and cloud computing) and utilizing structured 3497 data and free-text narratives. The pipeline executes an initial pass to filter down the pairs of reports 3498 by placing minimum requirements on similarity based on demographic data and other features. 3499 Subsequently, a pairwise streamlined worker implementing a duplicate detection algorithm 3500 performs a probabilistic comparison of all qualifying report pairs and calculates two scores, a 3501 probabilistic weight score and a second component score value, that together rate how similar the 3502 two reports are. In the third step, the pairs exceeding a preselected validated threshold that was 3503 specified in a dedicated analysis are merged into networks (a.k.a. groups) of potentially duplicate 3504 reports and split into tightly linked communities (a.k.a groups) of actual duplicates. Finally, a 3505 reference case selection component identifies the most representative report in each duplicate 3506 group based on several parameters and the remaining reports in the group are flagged as duplicates 3507 and they are excluded from subsequent data mining calculations. An existing decision-support tool 3508 developed to support the case series analysis allows for evaluating the groups of duplicate reports 3509 and verifying the reference case, keeping medical reviewers in the loop.

3510 B3. Results

3511 In an early research study, the **duplicate detection algorithm** was applied to two datasets of post-3512 market reports, one including vaccine product reports and one containing reports for biologics, 3513 identifying 77% of and 13% of known duplicate pairs, respectively, with (nearly) perfect precision in 3514 both cases (95% and 100%, respectively) (https://pubmed.ncbi.nlm.nih.gov/28293864/). This 3515 algorithm was refined in subsequent steps to reach acceptable levels of performance that, in some 3516 cases and based on new evaluations using drug adverse event reports, supported the detection of 3517 duplicate pairs with an F-measure >0.9. The medical reviewers who participated in this new 3518 evaluation round felt confident about the algorithm and expressed their interest in using it, as 3519 discussed in the corresponding publication 3520 (https://www.frontiersin.org/articles/10.3389/fdsfr.2022.918897/full). Subsequently, the medical 3521 reviewers generated a gold standard of 2300 reports with labelled duplicates in a systematic process 3522 to support the validation of the recently built **deduplication pipeline**, which was then compared with 3523 existing deduplication approaches used at the regulatory agency. The deduplication pipeline 3524 outperformed these approaches (results unpublished) and was approved for processing all historical

reports and incoming live data in an ETL process. As of December 20, 2024, the pipeline, installed on

the AWS environment and tightly integrated with the agency's AERS, has screened >30 million 3526 historical reports and continues deduplicating an average of 8,000 new submissions daily. 3527

3528 B4. Compliance with the governance framework

3529 3530 3531 Table 11: Use case B: Alignment with the governance framework (detail) Source: CIOMS Working Group XIV

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	A risk-based approach has been discussed extensively, especially regarding missed or false positive duplicate reports. It has been determined that implementing the pipeline in the decision-support system, with humans- in-command, eliminates any risks for the case series analyses. What remains to be done is acknowledging any risks for data mining calculations and potential noise in signal detection; this part has not yet been fully developed and mostly affects the routine use of deduplication for data mining calculations and not its use in case series analyses that is currently fully implemented.	A	A	A	A	A
Human oversight	Human experts actively provided feedback to the software engineers during the development stage and evaluated the deduplication output to refine and validate the pipeline. Human experts can confirm or modify the reference case selection using an existing decision-support tool while conducting their case series analyses in the routine use setting. On the other hand, data mining calculations incorporate deduplication output without humans being involved.	A	A	A	A	A
Validity & Robustness	The deduplication pipeline has been evaluated and validated to ensure it meets expectations and serves its intended purpose. The effect of deduplicated data on data mining calculations and the discovery of potential safety signals, which is one of the major uses of deduplication output, has not yet been investigated.	A	A	A	A	A
Transparency	Several publications, technical reports, and other documentation describe the pipeline and results of all evaluations conducted with safety reviewers' assistance.	A	A	A	A	A
Data Privacy	Fully complying with the principle as all processing occurs in a secure cloud environment.	А	A	А	A	A
Fairness & Equity	The deduplication pipeline has been evaluated and validated in several rounds and is closely monitored in the post-deployment phase. The pipeline is fully migrated to the production environment to be routinely used at the time of writing this report; it is therefore marked as partially aligned since this process has not been completed yet.	A	A	A	A	A
Governance & Accountability	System administrators have full control and continuously monitor the deduplication pipeline as well as the use of its output in the decision-support tool. A plan has also been developed to incorporate the deduplication output in the data mining calculations.	A	A	A	A	A

Clearly defined roles were specified in the development, pre-deployment, and post-deployment stages, where the Contractor led the pipeline's			
construction and incorporation into the decision- support tool and the existing environment at the			
regulator's site, assisted by the end users and other stakeholders. Roles have not yet been fully assigned in the routing use setting			

Abbreviations

3532 3533 3534 SPEC: Collection of specifications, requirements

DEV: Development and change management

3535 3536 3537 PreD: Pre-deployment & post-change sign-off

PstD: Post-deployment & post-change hyper-care

RU: Routine Use 3538 A: Applicable

3539 NA: Not Applicable

References

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3541 Use Case C: Artificial intelligence translation assistant

- 3542 Source:²⁷⁵
- 3543 Area of PV: ICSR reporting

3544 C1. Business rational and challenges

The pharma company had engaged with a vendor to consolidate and streamline the global case intake and translation process. The vendor had established 2 hubs in Europe and Asia to cover 16 languages across 32 countries replacing a distributed network of multiple local country organizations and local vendors. To further increase productivity, the vendor had been requested to automate the translation process.

3550 *C2. Solution*

3551 While processing foreign language adverse event reports, about half of the effort was required for 3552 accurate translation of source documents from local languages to English, enabling centralized case 3553 management in English and subsequent submission to authorities. The pharma company and the 3554 vendor formed a common project team consisting of experts on ML and PV associates to pilot an AI-3555 powered translation assistant based on commercially available technology. The team had set up a 3556 private cloud environment to store learning data (source texts and human-edited translations) and 3557 developed a user interface to input original text and retrieve and (if necessary) edit the result. The 3558 system automatically stores and analyses any modifications done by the users to enable further 3559 learning iteration and improvement of the first-time quality of the AI translation assistant. A 100% 3560 QC (Quality Control) by a human translator of all the translations was established to always verify the 3561 accuracy of the translation. The solution facilitates continuous learning through the automated 3562 integration of the manual edits into the translation model in defined regular intervals. With each 3563 model update the relevant quality measures (BLEU scores, see below) are re-calculated.

3564 *C3. Results*

3565 The translation's quality was assessed by BLEU scores. BLEU (Bilingual Evaluation Understudy) is a 3566 metric for evaluating machine-translated text. The BLEU score is a number between zero and one 3567 that measures the similarity of the machine-translated text compared to a set of high-quality 3568 reference translations. Within 6 months the AI translation assistant mimicked the quality of a human 3569 translator (i.e. BLEU equal or greater than 0.6).²⁷⁶

- The results of the AI Translation Assistant pilot for the first language (Portuguese) were leading to a
 reduction of translation efforts by ca. 30%. Hence the solution was extended to 5 further languages
 (Chinese, Spanish, French, German, and Dutch). Pharma company and vendor teams are jointly and
 continuously evaluating the BLEU score to monitor the quality of the solution.
- 3574 Improving the AI model is a function of case volume as every revised sample translation provided by 3575 the QC team helps to improve the model. More samples make better models, and better models 3576 finally reduce the effort for the team, allowing them to work through more cases, faster, and with 3577 greater consistency.
- 3577 greater consistency.

3578 Since the initial setup of the AI Assistant for Translation in 2021 the technology has further matured. 3579 The translations obtained by the assistant are generally of high quality and less than 10% corrections 3580 are still necessary by the human translators. An analysis is ongoing to move from 100% human QC to 3581 a sampling approach as a continuous monitoring measure. Depending on the detailed results per 3582 language, the sample size may be adjusted within reasonable borders (up to 100%) to ensure high 3583 quality translations continuously.

C4. Compliance with the governance framework 3585

Table 12: Use case C: Alignment with the governance framework (detail) 3586

3587 3588

Source: CIOMS Working Group XIV

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	A risk-based approach has been followed thoroughly and a 100% QC by human translators has been applied. With further maturing of the system and under close monitoring of the overall quality a reduction of human QC for individual translations should be possible.	A	A	A	A	A
Human oversight	To ensure human oversight a 100% human QC of the translated text by the vendor translators was established from the beginning. The BLEU scores are regularly measured for each language to identify changes in the overall performance.	A	A	A	A	A
Validity and robustness	The system has been implemented following the vendors standard validation approach. The 100% human QC ensures validation of all translation outputs. Any failure of the translation assistant would be immediately detected and corrected.	A	A	A	A	A
Transparency	Transparency of the translation performance is obtained as all translations are tracked by the system as well as any edits by the human translator. These edits are used in regular intervals to improve the model.	A	A	A	A	A
Data Privacy	The service is established on a private cloud. Access is provided only to project team members. Personally identifiable information is redacted prior to the actual translation process. The original source document remains available only for the local team who received the initial information and who may have to follow-up with the initial reporter.	A	A	A	A	A
Fairness and Equity	Not applicable. The application is not providing any data consolidation or decision support. The 1:1 match of the translation is verified by the human QC.	NA	NA	NA	NA	NA
Governance & Accountability	The translation assistant is a standalone tool owned by the vendor. Hence, the regular life-cycle governance is executed by the vendor and available on request to the pharma company. It concerns, e.g. the update of the model based on learning progress. While the responsibility for the execution of the translation lies with the vendor the ultimate accountability remains with the pharma company. Hence, in addition to the 100% human QC process by the vendor, the pharma company is doing a defined sample QC of the overall case intake results, including the translation.	A	A	A	A	A

3589 3590 3591 3592 3593 SPEC: Collection of specifications, requirements DEV: Development and change management

PreD: Pre-deployment & post-change sign-off PstD: Post-deployment & post-change hyper-care

3594 3595 RU: Routine Use

A: Applicable

3596 NA: Not Applicable

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²⁷⁶ Google Cloud. Evaluate AutoML Translation models. Google Cloud. (Webpage accessed 21 March 2025)

Use case D: Large language models for context-aware Structured Query Language

- 3600 Source Article:²⁷⁷
- 3601 Area of PV: Safety analysis
- 3602 D1. Business rational and challenges

3603 Safety scientists are often reliant on technical teams for safety query formulation and extraction of 3604 data from safety databases using SQL, which can introduce delays in assessment. The aim therefore 3605 was to enhance the accuracy of information retrieval from PV databases by employing LLMs to 3606 convert natural language queries (NLQs) into Structured Query Language (SQL) queries, leveraging a 3607 business context document.

3608 *D2. Solution*

3609 A sandboxed version of OpenAI's GPT-4 model was utilized within a retrieval-augmented generation

- 3610 (RAG) framework, enriched with a business context document, to transform NLQs into executable
- 3611 SQL queries. The study was conducted in three phases, varying query complexity, and assessing the
- 3612 LLM's performance both with and without the business context document.
- 3613 *D3. Results*
- 3614 The integration of a business context document markedly improved the LLM's ability to generate
- 3615 accurate SQL queries (i.e. both executable and returning semantically appropriate results), increasing
- 3616 from 8.3% with the database schema alone to 78.3% with the business context document. This
- 3617 enhancement was consistent across low, medium, and high complexity queries.
- 3618 The method is an assistive method to enable non-technical users to perform complex data queries,
- 3619 potentially enhancing timeliness of PV data analysis and reporting.
- 3620 *D4. Compliance with the governance framework*

3621 Table 13: Use case D: Alignment with the governance framework (detail)

- 3622 Source: CIOMS Working Group XIV
- 3623

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	Within this study, the intent is to demonstrate use of natural language to generate SQL queries to retrieve data from a safety database. The risk based approach should consider the feasibility of implementation and controls and processes needed to ensure its appropriate and trusted use.	A	A	N/A	N/A	N/A
Human oversight	Within the PoC human experts have reviewed the relevance of the outputs against a reference standard, within a product setting consideration will need to be given to how human oversight will be provided to ensure robustness of the outputs, including monitoring performance over time and at defined intervals (e.g. change in model version). Human oversight could be applied using a risk-based approach e.g. taking into consideration the intended use of the output.	A	A	N/A	N/A	N/A
Validity & Robustness	The tool has been evaluated against a curated reference standard, beyond the PoC consideration should be given to generalisability in production use.	A	A	N/A	N/A	N/A

Transparency	Whilst there is transparency of the GPT model, the use of RAG and context specific documentation provides transparency of the pipeline and how data is processed to achieve the output.	А	A	N/A	N/A	N/A
Data Privacy	This is an assistive tool not using individual patient data to generate SQL outputs.	N/A	N/A	N/A	N/A	N/A
Fairness & Equity	This is an assistive tool not using individual patient data to generate SQL outputs.	N/A	N/A	N/A	N/A	N/A
Governance & Accountability	During the proof of concept (PoC), the accountability of the methodology remains with the developer. However, if the methodology is integrated into a production setting, accountability would transition to the human subject matter expert.	A	A	N/A	N/A	N/A
	Governance within a PoC ensures that scientific integrity principles are adhered to, while future product use governance should cover how the tool fits into the overall PV system and quality management system (QMS).					

Abbreviations

3625 SPEC: Collection of specifications, requirements

3626 DEV: Development and change management

3627 PreD: Pre-deployment & post-change sign-off

3628 PstD: Post-deployment & post-change hyper-care

3629
3630RU: Routine Use
A: Applicable

3631 NA: Not Applicable

References

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3632

Use Case E: Causality assessment of adverse drug reactions 3633

Source:278 3634

3635 Area of PV: Causality Assessment

E1. Business rational and challenges 3636

3637 Assessing the causal relationship between an adverse event and the patient's exposure to a drug is a 3638 critical part of the PV process. Causality assessment is a time-consuming process requiring manual 3639 review by medical experts who evaluate data in the case with data from external sources (e.g. drug 3640 labels, scientific publications, drug mechanism of action, and disease symptoms). As the volume of 3641 adverse events to be reviewed increases an opportunity exists to create solutions that leverage ML 3642 to support the medical experts by predicting causality assessments.

- 3643 E2. Solution
- 3644 The authors of this paper created a modelling feature set comprising of various data attributes from
- 3645 solicited cases from the pharmaceutical company's safety database relevant to causality assessment
- 3646 of drug-event combinations. This was supplemented by engineered data features comprising
- 3647 external data and data from other internal sources. The resulting training data schema (shown
- 3648 below) was selected as it provides a comprehensive set of features relevant to the causality 3649 assessment process.

3650	Table 14: Use case E: Modeling Data
3651	Source: ²⁷⁹

Source:279 3652

Modeling Data				
Case Level Data		External Sourced Data		
Causality Label	Medical History Exclusions	Disproportionality		
Rechallenge	Drug Exclusions	Anatomical Therapeutic Class & System Organ Class		
Labeledness		Temporal Relationship		
Reporter Causality		Temporal Compatible		

3653 In parallel, a separate decision support tool (CASCADE) was developed and validated through 3654 consultation with experienced drug safety physicians. A decision tree structure was adopted due to 3655 its increased transparency and interpretability when compared to other causality assessment 3656 algorithms. This increased transparency and interpretability allow a clear statement of the rationale 3657 for the assessment to be written (e.g. "The case is deemed causally related as it is (a) Labelled for the 3658 event (b) The event has a plausible temporal relationship, etc.").

3659 The work on the decision tree provided a basis for the subsequent predictive model, informing 3660 contributing factors and the topology of the resulting Bayesian Network model. The authors rationale 3661 for selecting this type of model include: the ability to combine multiple sources of information with 3662 expert knowledge, transparency and interpretability, and their capability to model complex 3663 frameworks with causal dependencies where a lot of uncertainty exists. Model training utilized an 3664 annotated dataset of 50k cases, with a separate test dataset of 20k cases. Both the training and test 3665 dataset represented a broad range of drug classes and event categories. All cases had been 3666 previously assessed by medical experts and were taken from a period where the causality 3667 assessment practices were consistent.

3668 E3. Results

3669 The model demonstrated high performance (sensitivity was 0.900, with Positive Predictive Value of

- 3670 0.778) in predicting the causality assessment of drug–event pairs compared with clinical judgment
- 3671 using global introspection. The authors also explored a learned topology Bayesian Network model

with the same training data. The learned topology model was found to have inferior performance compared to their CASCADE-based model.

3674 *E4. Compliance with the governance framework*

3675 *Table 15: Use case E: Alignment with the governance framework (detail)* 3676 Source: CIOMS Working Group XIV

3677

SPEC DEV PstD Principle Activities PreD RU Risk-based A risk-based approach was used to limit the scope of А А N/A N/A N/A Approach the model to solicited, post-marketing cases as automating the causality of assessment of these cases was determined to have a lower risk/ impact to the PV system. Human Drug safety physicians and SMEs were involved in the А А N/A N/A N/A Oversight data review and model development activities, ensuring the applicability of the model to its intended purpose. As this was a POC/study, there was no discussion about the creation of a quality management framework to support human oversight for future production use. Validity & The use case and deployment domain are described in А А N/A N/A N/A Robustness the paper. The data selection, model training and testing activities used in model development are discussed in detail, as is the approach used for performance assessment. The authors consider areas for investigation that may be used to further demonstrate the model's validity and improve robustness. Transparency The paper provides information about intended use of А A N/A N/A N/A the model and its design, including the decision tree (CASCADE). Data, results, areas for further investigation, and how the model could be applied in a PV system are discussed. Data Privacy In alignment with the principles in this book, the data N/A А А N/A N/A used for the development, training, and validation of the model is from the company's internal postmarketing safety database suggesting it was obtained with the patient's/reporter's consent and in compliance with relevant privacy laws and regulations. Fairness & N/A N/A N/A N/A Based on the article, it is not possible to comment on N/A Equity whether model development aligns with this guiding principle Governance & There is no discussion of governance and N/A N/A N/A N/A N/A Accountability accountability activities, as defined in this guidance, in the paper. The authors do acknowledge the need for models to remain compliant with regulatory frameworks and guidelines. Further, the CASCADE decision tree created is referenced as a causality assessment support tool implying accountability for the final causality assessment decision remains with the drug safety SME.



Abbreviations SPEC: Collection of specifications, requirements

DEV: Development and change management

3681	PreD: Pre-deployment & post-change sign-off
3682	PstD: Post-deployment & post-change hyper-care
3683	RU: Routine Use
3684	A: Applicable
3685	NA: Not Applicable

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3686

Use Case F: Process efficiencies supporting signal detection 3688

- Source Article:²⁸⁰ 3689
- Area of PV: Signal Detection 3690
- 3691 F1. Business rational and challenges

3692 One of the most time- and resource-demanding procedures for dismissing safety signals is the 3693 identification of alternative causes for the reported adverse events (AEs) in ICSRs after signals of 3694 disproportionate reporting have been identified. This includes the screening of co-reported drugs to 3695 identify alternative potential causes for the newly identified drug-event pair.

3696 F2. Solution

3697 This study aimed to develop an AI-based framework to automate (1) the selection of control groups 3698 in disproportionality analyses and (2) the identification of co-reported drugs serving as alternative 3699 causes, to look to dismiss false-positive disproportionality signals.

- 3700 The implementation of automatic selection of controls and dismissal of false positive signals using a 3701 conditional inference tree is summarized in the flowchart below.
- 3702 Figure 8: Flowchart summarizing the implementation of the automatic selection of controls and the 3703 dismissal of false positive signals when using a conditional inference tree Source:281
- 3704



3705 3706

3707 A dual approach combining the Anatomical Therapeutic Chemical (ATC) classification system code 3708 and the approved therapeutic indication in the US Summary of Product Characteristics (SmPC) of 3709 galcanezumab was used for automatizing the selection of controls for disproportionality analysis 3710 when using FAERs. All active ingredients with the same therapeutic target (i.e. CGRP antagonists) as 3711 galcanezumab were identified using the 4th level of the ATC code, or rather the chemical subgroup. 3712 DrugBank was used to identify controls with the same approved therapeutic indication but with 3713 active ingredient outside the chemical subgroup of galcanezumab, aiming to avoid masking due to 3714 drug class effect and confounding by indication.

3715 Disproportionality signals were further analyzed by using conditional inference trees to identify 3716 alternative cause co-reported drugs. The SmPC of disproportionally co-reported drugs was screened 3717 to identify those drugs that listed in the SmPC the AE in disproportionality signal mimicking 3718 procedures performed during signal validation. The disproportionality analysis was conducted again 3719 by removing cases with co-reported drugs for which the AE under investigation was listed in the 3720 SmPC as these cases had alternative causes for the AE.

3721 F3. Results

3722 Al could significantly ease some of the most time-consuming and labour-intensive steps of signal detection and validation. The AI-based approach showed promising results, however, future work is 3723 3724 needed to validate the framework.

3725 F4. Compliance with the governance framework

3726 3727 3728 Table 16: Use case F: Alignment with the governance framework (detail) Source: CIOMS Working Group XIV

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	When developing tools to support signal detection developers should consider the overall impact the tool may have to the PV system within a QMS and consider the need for mitigations that maybe required to support broader deployment.	A	A	N/A	N/A	N/A
Human oversight	Human oversight within the proof-of-concept setting would ensure that the outputs of the conditional inference tree are robust for use in augmenting the quantitative signal detection processes. In a production setting it would include monitoring mechanisms and sampling approaches to ensure ongoing validity.	A	A	N/A	N/A	N/A
Validity & Robustness	The outputs of the conditional inference trees can be subject to existing validation procedures to compare inputs to known outputs.	A	A	N/A	N/A	N/A
Transparency	Transparency would involve clear communication and documentation of the AI system's use in the process of signal detection and validation from ICSRs. Within this proof of concept this includes detailed information about the business case, methodology and training datasets, should the tool move into a production setting further documentation and information relating to how the tool is integrated into the wider PV system and it's QMS would be required.	A	A	N/A	N/A	N/A
Data Privacy	The method uses publicly available information on labelling	N/A	N/A	N/A	N/A	N/A
Fairness & Equity	The method is not using individual patient data.	N/A	N/A	N/A	N/A	N/A
Governance & Accountability	During the proof of concept (PoC), the accountability of the methodology remains with the developer. However, if the methodology is integrated into a production setting, accountability would transition to the human subject matter expert. Governance within a PoC ensures that scientific integrity principles are adhered to, while future product use governance should cover how the tool fits into the overall PV system and quality management system (QMS).	A	A	N/A	N/A	N/A

3729 3730 3731 3732 3733 3734

DEV: Development and change management PreD: Pre-deployment & post-change sign-off

SPEC: Collection of specifications, requirements

PstD: Post-deployment & post-change hyper-care

RU: Routine Use

Abbreviations

3735 A: Applicable

3736 NA: Not Applicable

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²⁸⁰ Al-Azzawi F, Mahmoud I, Haguinet F, Bate A, Sessa M. Developing an Artificial Intelligence-Guided Signal Detection in the Food and Drug Administration Adverse Event Reporting System (FAERS): A Proof-of-Concept Study Using Galcanezumab and Simulated Data. Drug Saf. 2023;Aug;46(8):743-751 (Journal full text) https://doi.org/10.1007/s40264-023-01317-0

²⁸¹ Al-Azzawi F, Mahmoud I, Haguinet F, Bate A, Sessa M. Developing an Artificial Intelligence-Guided Signal Detection in the Food and Drug Administration Adverse Event Reporting System (FAERS): A Proof-of-Concept Study Using Galcanezumab and Simulated Data. Drug Saf. 2023;Aug;46(8):743-751 (Journal full text) https://doi.org/10.1007/s40264-023-01317-0

Use Case G: Generative artificial intelligence for enhanced and intelligently structured outputs from large pharmacovigilance document libraries

- 3739 **Source:** Internal to CIOMS Working Group member organization
- 3740 Area of PV: PV document retrieval
- 3741 G1. Business rational and challenges

Use of AI represents a burgeoning field that has gained significant traction across various industries
 including the pharmaceutical industry. However, due to its relative novelty, concrete business use
 cases remain somewhat scarce, leaving many organizations searching for innovative ways to leverage
 AI technology effectively. LLMs, such as the Generative Pre-trained Transformer (GPT) models, offer
 a potentially valuable resource for businesses seeking historical references and streamlined

- document management solutions, with capabilities to summarize & synthesize large sources of data.
- 3748 G2. Solution
- 3749 Harnesses the power of LLMs to optimize our document filing structure. With hundreds of thousands
- of documents pertaining to patient safety and PV activities, in this use case an AI tool was employed
- to function as a powerful system for searching, extracting and generating information in an effective
- and structured manner specific to the parameters and requirements of the (human) user. By
- automating the process of retrieving relevant information, subject matter experts (SMEs) can
- 3754 redirect their time towards value-added endeavours rather than manual data sifting.

Figure 9: An outline of our initial artificial intelligence architecture

3756 Source: Internal to CIOMS Working Group member organization



3757

The implementation of LLMs not only aids day-to-day tasks but can also enhance efficiency in many
different vigilance activities across all different verticals of vigilance. Currently this tool has the ability
to help support audit and inspection requests, performative AI researcher for PV projects that
require detailed and structured retrieval from safety document libraries, e.g. searching for regulatory
/ safety correspondence.

3763 Development and deployment of a meticulously crafted vector index of relevant company file 3764 structures, allows us to leverage an LLM to easily and efficiently navigate documents, files and data 3765 available within those files. By transitioning to newer models as they release, the organization has 3766 observed improved accuracy and utility in responses, validated through a manual verification of 3767 processes.

Regular feedback sessions are conducted to refine the AI tool's performance and uncover additional
use cases. This iterative approach ensures continual improvement and minimizes errors. Guidelines
were also developed for framing questions to the model effectively, further enhancing the tool's
usability.

- Looking ahead, there are plans to expand this application of GenAI, focusing on areas such as
 summarization of safety literature for example signal detection purposes and summary outputs for
 case reporting. By training additional models on relevant datasets, including Individual Case Safety
- 3775 Reports (ICSR), the organization aims to automate safety summary generation and aggregate
- analysis, trending, any other ad hoc safety questions that can be answered from the data from or
- 3777 within the global safety database (GSD) thereby streamlining decision-making processes.
- 3778 G3. Results
- 3779 The generative AI tool in this use case has demonstrated potential as an AI 'research assistant'
- and enabling PV workers to quickly and efficiently search hundreds and thousands of safety documents
- to provide structured and intelligent outputs. The adoption of AI technology like LLMs could
- 3782 empower organizations using this technology to optimize operational efficiency and prioritize tasks
- that impact product benefit-risk assessments. By leveraging Al-driven document management
- 3784 solutions, subject matter experts can devote more time to critical medical and scientific evaluations,
- ultimately enhancing product safety and efficacy. In addition, the planned expansion of use of LLMs
- in GenAI capabilities to evaluate transactional data and provide scientific analysis and summary has
- 3787 the potential to be a game changer in evaluating product or patient level safety risk in real time, 3788 simply by "asking a question" with well referenced and documented summaries/conclusions.
- 2700 C4 Canadiana it the the second for the content of
- 3789 *G4. Compliance with the governance framework*

During the development and pre-deployment phases, the GenAI project is carefully developed and managed with a limited scope, ensuring full alignment with most guiding principles. As the project transitions into production and its exposure and scope expand, careful consideration will be given to maintaining close alignment with these principles. Therefore, compliance is indicated as closely aligned, laying a foundation of trust in the solution's ability to perform vigilance tasks with adaptive and growth capabilities.

Table 17: Use case G: Alignment with the governance framework (detail) Source: CIOMS Working Group XIV

3798

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	GenAl use is a closed environment used for training and testing during development and pre- development. However, there is communication of potential inaccuracies and pitfalls during these phases. Currently there is no anticipated (patient risk) for post-deployment or routine use. As GenAl achieves more general and expanded risks will be regularly reassessed. Therefore, all phases are considered partially aligned with this guiding principle.	A	A	A	A	A
Human oversight	Fully aligned in development phase. Although there is still human oversight from the user,	A	A	A	A	A

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	there is probably partial alignment during post deployment and routine use as GenAl would not be routinely scrutinized by human oversight and					
Validity & Robustness	Management Validation and testing is extensive during development and pre-deployment and therefore in full alignment with the guiding principle (based on smaller sample set during these stages. Once in post deployment and routine use the data sets are very large and it is not possible to 100% fully test and validate all use cases (therefore in partial alignment). However, if users are noting inaccuracies in information retrieval, feedback will be provided to the human developers of the GenAI to refine and update the system.	A	A	A	A	A
Transparency	In full alignment during development and pre- development. As GenAI system expands in scope and complexity during post-deployment and routine use, further realignment is anticipated. Transparency in relation to the public is not applicable as this is a closed system	A	A	A	A	A
Data Privacy	Fully alignment during all phases. All of data remains internal; therefore, no transfer of information and external vendors/individuals.	A	A	A	A	A
Fairness & Equity	Fully aligned with this guiding principle at all phases. No relevant groups or individuals are being excluded or disadvantaged.	A	A	A	A	A
Governance & Accountability	Accountability from system usage and implementation during development and pre- deployment, e.g. if system is clearly not useful then it will be discontinued / upgraded. Ultimately regulatory accountability resides with subject matter expert / user as they are responsible to review and verify content. Therefore, partial alignment is anticipated from post-deployment onwards	A	A	A	A	A

3799 3800 3801

SPEC: Collection of specifications, requirements

DEV: Development and change management

PreD: Pre-deployment & post-change sign-off

3802 3803 3804 3805 3806 PstD: Post-deployment & post-change hyper-care

RU: Routine Use

A: Applicable

NA: Not Applicable

Use Case H: Artificial intelligence to support diagnosis and prediction of (hydroxy)chloroquine retinopathy

- 3810 Source:^{282,283}
- 3811 Area of PV: Pharmacovigilance in The Clinic
- 3812 H1. Business rational and challenges

3813 PV in the clinic is concerned with the prevention and treatment of adverse drug reactions in 3814 individuals. Prevention may be primary, which can be achieved through identifying potential complex 3815 or non-obvious combinations of patient characteristics that are predictive of adverse drug reactions 3816 to guide optimum medication selection. (i.e. precision medicine) It also encompasses secondary and 3817 tertiary prevention (i.e. early diagnosis of adverse drug reactions, and ensuing interventions) to 3818 mitigate the impacts of ADRs. Examples follow.

3819 Chloroquine and hydroxychloroquine are important drugs in rheumatology. Although relatively well 3820 tolerated compared to some other therapeutic options, retinal toxicity, is a risk which can result in 3821 serious visual impairment if not detected early so that the drug may be discontinued in a timely 3822 manner. Even so, by the time of retinopathy diagnosis there may be irreversible retinal damage. 3823 Conversely, if predictive AI can provide sufficient leading indicators or progression, therapy duration 3824 and attendant therapeutic benefits might be maximized. Historically the gold standard for screening 3825 and detection has been fundus photography and automated perimetry. More recently, multifocal 3826 electroretinography (mfERG) and optical coherence tomography (OCT) have been added to the 3827 diagnostic armamentarium. Each of these are routinely assessed by human readers, ideally retinal 3828 specialists, but subtle changes, including temporal patterns, can be missed, and not all locales have 3829 the necessary instrumentation or available retinal specialists. It would be ideal to augment human 3830 visual assessors to identify early functional changes indicative of retinopathy prior to onset of 3831 irreversibility or better predict progression. AI has shown potential in detecting or predicting various 3832 ocular diseases based on retinal images/fundus photography, such AMD, DR. More AI has been 3833 retrospectively developed and tested to diagnose or predict (hydroxy) chloroquine retinopathy.

3834 H2. Solution

3835 Al has been applied to colour fundus photographs, OCT and multifocal electroretinographic tracings 3836 for diagnosing hydroxychloroquine retinopathy, Fan et al studied hyperspectral imaging (HIS) of 176 3837 fundus photographs from retinopathy positive (25) versus retinopathy negative (66) patients at a 3838 referral clinic using four deep learning models for the detection of retinopathy Kulyabin et al 3839 compared deep learning-based classification of raw mfERGs versus models based on conventional 3840 readout parameters of the mfERG for classification, and for prediction (regression) of visual field 3841 sensitivities from 53 predominantly female patients (35 retinopathy negative, 9 minimal retinopathy, 3842 and 9 manifest retinopathy) monitored with mfERGs and perimetry for period of 0.7-20,9 years. Kalra 3843 et al used random forests for automated diagnosis and prediction of disease progression using 3844 clinical features and features based on spectral domain OCT (SD-OCT) obtained from 388 eyes / 368 3845 patients, a majority being female. Habib et al trained support vector machines (SVM) to identify 3846 hydroxychloroquine retinopathy in 1463 eligible eyes (748 predominantly female patients), of which 3847 95 eyes (48 patients) were eligible for inclusion as controls.

3848 H3. Results

The best performing deep learning models in the study of Fan et al achieved accuracy, precision,
recall, specificity, and F1-scores of ≥0.95., with superior performance using hyperspectral images
versus the original retinal images. Habib et al's SVM returned a specificity of 84.0% with sensitivity of
90.9%. Performance could be calibrated to place a premium on sensitivity for screening or specificity
for diagnosis. Kalra reported a mean AUC of 0.97, a sensitivity 95% and specificity of 91% for
detection, and mean AUC=0,89, recall of 90% ad specificity of 80% for progression prediction.

3855 Kulyabin reported that AI-based models using full mfERG traces had a balanced accuracy of up to 3856 0.795, precision of up to 0.844, recall of up to 0.866, and F1-score of up to 0.771.

3857 H4. Compliance with the governance framework

3858 In considering the alignment of the reviewed studies with the governance framework we note 3859 several points up front. The studies were retrospective and feasibility/pilot studies, without reported 3860 advancement to routine use in the clinic. Because the drugs under study are for autoimmune 3861 disorders, in addition the study populations often being mall, the subjects were predominantly 3862 female, consistent with the treatment indication. The use of eyes as the unit of observation raises 3863 the question of pseudo-replication and its potential impacts of performance estimates, though 3864 confidence intervals were not typically presented. At least one study noted under-representation of Asian in the study sample and the need for further assessment in larger and more diverse 3865 3866 populations. Finally as is often the case in AI applications involving retinal pathology, other ocular 3867 pathologies were excluded, which limits generalizability to more diverse patient populations that 3868 have multiple retinal pathologies (e.g. diabetic retinopathy and drug-induced retinopathy).

3869	Table 18: Use case H: Alignment with the governance framework (detail)
3870	Source: CIOMS Working Group XIV
3871	

Principle	Activities	SPEC	DEV	PreD	PstD	RU
Risk-based approach	Not aligned. Risk assessment and risk mitigation plans not provided in these pilot studies. But placement within a human-in-the-loop framework was explicitly considered in one or more studies	N/A	N/A	N/A	N/A	N/A
Human oversight	Partial alignment. One or more of the publications, which report feasibility/pilot studies in clinical settings, discuss the proper deployment with respect to human oversight, such as HITL. However, change management and staff training plans not discussed. Discussed is the fact that the available human oversight in some locations may be provided by generalists with less experience and expertise that retinal specialists, affording more opportunity for incremental benefits in underserved settings.	A	A	N/A	N/A	N/A
Validity & Robustness	Partial alignment. Reference standards defined. One or more studies note the limitation of the imbalanced data sets used that impair generalizability. Also, in one/more studies patients with other ocular pathology excluded so the two classes were HCQ retinopathy present versus normal retina, which limits generalizability to screening in patients with other coexistent ocular disorders that may affect the retina. Source population (deployment domain) not clearly defined in all studies No discussion of integrating data pre-processing (e.g. cropping retinal images) into routine use). In some studies unit of observation was "eyes" raising questions about pseudo-replication.	A	A	A	N/A	N/A
Transparency	One/more papers report adherence to tenets of the Declaration of Helsinki and obtained Institutional Review Board approval. One or more papers described explanations of results such as heatmaps of feature distributions.	A	A	A	N/A	N/A

Data Privacy	One or more of the referenced studies declared adherence to tenets of the Declaration of Helsinki and obtained Institutional Review Board Approval.	А	А	А	N/A	N/A
Fairness & Equity	One/more of the referenced studies report adherence to tenets of the Declaration of Helsinki and obtaining Institutional Review Board approval. One or more of papers acknowledge that data under-represents specific groups of persons such as Asians, who may display different findings and recommends further assessment with larger data sets with more diverse representations. Further discussion involved scenarios in which retinal specialists may not be available, such as under-resourced or under-represented locales, as also discussed in human oversight above.	A	А	A	N/A	N/A
Governance & Accountability	These studies which occurred in clinical settings were conducted according to the guidelines of the Declaration of Helsinki and approved by the respective Institutional Review Board o	А	N/A	N/A	NA	N/A

Abbreviations

SPEC: Collection of specifications, requirements

3872 3873 3874 DEV: Development and change management 3875

PreD: Pre-deployment & post-change sign-off

PstD: Post-deployment & post-change hyper-care

3877 **RU: Routine Use**

3876

3878 A: Applicable

3879 NA: Not Applicable

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283 Kalra G, Talcott KE, Kaiser S, Ugwuegbu O, Hu M, Srivastava SK, Ehlers JP. Machine learning–based automated detection of hydroxychloroquine toxicity and prediction of future toxicity using higher-order OCT biomarkers. Ophthalmology Retina. 2022;Dec1;6(12):1241-1252. (Journal abstract)https://doi.org/10.1016/j.oret.2022.05.031

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APPENDIX 4: Content related to explainability and to Fairness & Equity

3883

3884 Content related to explainability

3885 *Illustrative examples*

As stated above, diverse stakeholders in PV may require and benefit from explainability. However, the explainability that is required and how it is used, differs depending on the setting, i.e. who is asking and for what, in which task or process and in which system lifecycle stage.²⁸⁴ In the following sections, examples are provided below to illustrate the different scenarios. Finally, the benefits of explainability described in the example are summarised at the end of this section.

- 3891 Examples of explainability in artificial intelligence-supported pharmacovigilance tasks
- Take for example a setting in which a PV officer is reviewing a case that has been selected by the AI
- as a potential signal but does not immediately see why the case was flagged. In such cases, the
 reviewer could benefit from being able to see which text in the case data led the AI to this
 conclusion. An actual example of this is described below.
- 3896 The Information Visualization Platform (InfoViP) developed for the FDA's Center for Drug Evaluation 3897 and Research is an example of explainability supporting the human expert engaged in signal detection and assessment.²⁸⁵ InfoViP uses Natural Language Processing (NLP) and several other 3898 3899 components to process post-market data and visualize information, i.e. explanations, to support 3900 medical reviewers who detect and evaluate potential signals from the millions of adverse event 3901 reports submitted to the FDA's FAERS database. The NLP component, the Event-based Text-mining of 3902 Health Electronic Records (ETHER), coupled with modern frontend techniques, provide visual 3903 information by colour-coded highlighting of relevant text in the case narrative to help reviewers 3904 focus on signal-related information. An informed model further identifies cases containing enough 3905 information to assist reviewers assess the report quality and provides concrete explanations of these 3906 selections. All these functionalities combined with case deduplication and several filtering options 3907 facilitate speedy review by the medical reviewers, an otherwise humanly impossible task across millions of reports.286 3908
- 3909

3910 Figure 10: FDA's Information Visualization Platform user interface illustrates the system

3911 capabilities, focusing on the features that positively contribute to classification for assessability. Source:287

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3915 The example above illustrates a core benefit of explainability described by Albahri et al (2023).²⁸⁸

3916 Explainability can facilitate human experts in making 'sound and reliable' decisions. And ultimately,

3917 when the human decision and the accompanying explanation are retained, this information would

3918 nurture trust of the system owner and quality assurance staff who are tasked with ensuring 3919 compliance as well as the trust of regulators who may wish to inspect why certain cases are selected 3920 or rejected as signals.

3921 Also, it is conceivable that explanations could lead a user to notice a bias or spurious correlation that 3922 is leading to incorrect predictions. Reporting this back to the development team can contribute 3923 towards future improvement. In this way, explainability is useful for ongoing vigilance against bias 3924 risk and performance issues that may appear post-deployment and for continually ensuring the 3925 trustworthiness of the decisions made. As a result, XAI explanations have resulted in increased trust

and the perception of fairness in AI-supported decision making.²⁸⁹ 3926

3927 Examples of pharmacovigilance stakeholders benefitting from explainability

3928 While the likelihood of an individual from the general public requiring explainability in a PV setting is 3929 considered to be small, the possibility of this happening cannot be excluded entirely as the use of AI 3930 becomes more commonplace. Some conceivable scenarios are described below:

- 3931 When a reporter (healthcare professional or patient) directly reports a serious adverse event 3932 and the report is subsequently processed as a non-serious case by an AI triage system, upon 3933 being informed of this, the reporter undergoes a negative experience and may request an 3934 explanation from the MAH. When this scenario takes place in a non-AI setting or an AI-3935 assisted triage setting, the reporter could receive an explanation from the PV officer who has 3936 made the final triage decision. However, when this takes place in a fully-automated AI triage 3937 process, unless some form of explainability is provided, the lack of explainability may impact trust and acceptance of the result by the reporter. 3938
- 3939 When a consumer or a healthcare professional interacts with a medical information chatbot • 3940 used by the MAH to provide drug product information and collect safety data and quality complaints, the individual may question and challenge any information that doesn't make 3941 3942 sense.
- 3943 GenAl could be used in assisting a pharmacist in medication therapy management to prevent 3944 drug interactions. Both the pharmacist and the patient are directly exposed to the Al's
3945 3946 recommendations in this case.²⁹⁰ Here, questions concerning the AI recommendations could be raised by both parties.

3947 Examples of explainability in system development

3948 A developer who is training the AI system benefits from explainability when it reveals which features 3949 are used by the AI to reach a specific prediction or when it reveals a bias in the training data. 3950 Especially in complex systems which lack inherent interpretability and explainability, an XAI tool 3951 could provide explanations that facilitate troubleshooting by revealing what to change or exclude in order to 'flip' the outcome.²⁹¹ Using the XAI explanation, one could discover that needle in the deep 3952 3953 neural network haystack. However, in most cases, tweaking the system architecture of a deep neural 3954 network or specific features will be quite challenging even when XAI points the way. The XAI output 3955 is more likely to identify hidden biases in the training data which can be corrected as illustrated in 3956 the example below.

- 3957 An example presented by Ribeiro et al (2016)²⁹² demonstrates how the XAI explanation provided by 3958 using Local Interpretable Model-Agnostic Explanations LIME could be understood by humans and 3959 reveal the likely cause of incorrect predictions. In this experiment, the model that was trained to 3960 distinguish images of dogs and wolves was first intentionally trained to associate wolves with 3961 snowscapes. In other words, the training data was deliberately biased by excluding images of wolves 3962 in other seasons. This resulted in predictions that included a wolf against a green background 3963 identified as a dog and a husky in a snowscape identified as a wolf. LIME was used to show subjects 3964 which areas of the image were used as features by the AI in its predictions to see if the subjects could 3965 identify the cause of the misidentification. The subjects successfully identified background snow as 3966 the potential feature that led the AI to make the incorrect predictions. Thus, XAI can be used to 3967 explain a prediction made by an inscrutable deep neural network and uncover the underlying issue in 3968 the training data and the resulting spurious correlation that led to the incorrect output.
- 3969 In the context of PV, similar techniques could be used to highlight words in the text which are picked 3970 up by the AI as relevant features. In a real-life but unpublished example in which an AI triage system 3971 was misidentifying some serious cases, developers benefited from seeing which terms in the case 3972 were considered by the AI in its seriousness predictions. In this case, the XAI explanation revealed a 3973 focus on the drug name. Combined with the fact that the missed serious cases concerned Over The 3974 Counter (OTC) drugs, the developers discovered that the AI was basing decisions on the drug name 3975 and a learned spurious assumption that OTC drugs are not likely to cause serious events. Using the 3976 insight gained from explainability, the developers could reject the model in favour of another one, 3977 examine the training data for bias such as the lack of serious OTC cases or when there is no bias, 3978 solve the issue through feature engineering by instructing the AI not to consider the drug name in its 3979 decisions.
- Explainability, therefore, can help developers make informed decisions when assessing AI models by
 uncovering hidden biases as well as features and spurious correlations that are resulting in incorrect
 predictions. Explainability may also reveal the underlying factors that result in performance
 differences between models that are trained on the same training data and aid the developer in
 model selection. In turn, transparent documentation of this process will go a long way towards
 nurturing trust in the system, not only for the developers but also for the system owners, users and
 the regulators.

3987 Examples of explainability in artificial intelligence-systems interacting with health care professionals 3988 and patients

Another hypothetical example can be the case of a healthcare professional (HCP) who is requesting product-specific information via a chatbot provided by a marketing authorisation holder (MAH). Such a chatbot could have multiple objectives ranging from the provision of drug product information to the collection of adverse event and quality defect reports. When the HCP notices that the chatbot response is inadequate, i.e. not considering key medical terms or adverse events, or providing questionable information, the HCP may contact the MAH for an explanation. Explainability, if it isavailable, may help the MAH troubleshoot the system and/or provide information back to the HCP.

3996 While the scenario above is a fictive example, one example of a chatbot that is currently available is 3997 the Smart AI Resource Assistant for Health (SARAH) on the World Health Organization website. This is a prototype chatbot that is intended to provide tips on health topics and not medical advice as 3998 clearly stated on the landing page of SARAH.²⁹³ On one hand, SARAH exemplifies how such an 3999 4000 application could be of service to the public as it is available 24/7 and in eight languages. On the 4001 other hand, incidents of the chatbot providing inaccurate or incorrect information or being unable to 4002 answer some queries have unfortunately been reported in the media and taken up in the OECD AI incidents monitoring database.²⁹⁴ This illustrates how, when a chatbot is deployed, the interacting 4003 patient or healthcare provider or the media may challenge the information that is provided. It is 4004 4005 therefore conceivable that in PV, when a MAH deploys an AI system that interacts directly with the 4006 public, explainability for the public will also be required.

- 4007 Finally, any system that interacts directly with the public in a medical setting warrants extra attention 4008 in that a HCP is likely to notice medically incorrect information, but most consumers and patients 4009 may not be able to do this. Individuals without a medical background will be at risk of accepting and 4010 acting on medically incorrect information. To illustrate this point, in a study of trust and medical 4011 advice provided by ChatGPT, persons without a medical background have been found to trust the 4012 chatbots for lower-risk health topics.²⁹⁵ Without the medical background, a layperson is at increased 4013 risk of harm by not being able to recognize incorrect information. Thus, aside from being able to 4014 provide an explanation to an individual from the public who is challenging the AI output, system 4015 owners must thoroughly consider and mitigate the risks of an AI system that interfaces with the
- 4016 general public. This also touches on the subject of accountability since it is not the chatbot that is 4017 held accountable for any harm that befalls the individual.
- 4018 Example where explainability is not available and not required
- 4019 To illustrate a situation in which explainability is not necessary nor possible, consider first how the 4020 use of publicly available machine translation tools is now commonplace and how the public generally 4021 do not require explanations into how the AI translated the text. Consider also how translations in a 4022 GxP-regulated environment require a quality check regardless of whether the translation was carried 4023 out by a human or a machine. Furthermore, the quality check is normally carried out by an individual 4024 who is proficient in both the source and destination languages. Therefore, not only will the human be 4025 able to spot errors, but also in some cases, understand the underlying reasons for machine 4026 translation errors even without any explanation. An example of a translation issue with a self-evident 4027 root cause is the case of biased gender assignment that occurs when translating a genderless language such as Finnish to English.²⁹⁶ The bilingual human reviewing the translations would easily 4028 4029 notice the gender bias, understand why this has been introduced by the AI and can correct this 4030 accordingly. See also chapters x on human oversight, data privacy and fairness and equity.
- 4031 Example where explainability could be available but is not required
- 4032 In PV, another example of AI use which would not require explainability would be automatic de-4033 identification of case narratives presented by Meldau et al 2024.²⁹⁷ Automatic redaction of case 4034 narratives could ensure data privacy while allowing case narratives sharing which are crucial for 4035 providing more complete information to signal detection assessors. In this case, a system using a 4036 neural network combined with hand-engineered rules was trained to automatically detect names in 4037 case narratives for the purpose of redaction. Using a test set of over 5000 Yellow Card narratives 4038 from the MHRA and over 500 open source annotated and unannotated deidentified patient 4039 discharge summaries from i2b2.org, the system was able to identify 96% of names longer than three 4040 characters and 88% of all names for redaction. The false positive rate was 0.2%. It is not conceivable 4041 that stakeholders would require explanations during routine use of such a system. Even if 4042 stakeholders notice certain names are not being identified, it is conceivable that the reasons could be 4043 self-evident. Taking this system as an example, since it is trained to detect names that consist of

- 4044 three letters or more, it may miss two-letter names which are common in Asia. When such a lapse is 4045 noticed, the developers and stakeholders would not require an explanation in order to take the
- 4046 necessary corrective measures such as re-training using a new dataset or adding new rules.
- 4047 Example of recommended explainability combined with downstream human oversight

Even when there is downstream human quality control and the final decision rests with the human,
explainability remains useful for supporting human decision and nurturing trust in the machine and
in the decision that is made.

- 4051 While the machine translation example above describes one end of the spectrum where
- 4052 explainability is not needed when risks are adequately covered human review, for AI in PV and other
- 4053 GxP environments, it is not conceivable to deploy a system that expects the human to make
 4054 decisions based on AI predictions without any explanation. After all, the human needs to understand
- 4055 why the suggestion presented by the AI is trustworthy. Explainability is therefore essential for making 4056 a well-informed decision. The FDA's InfoVIP system (see above) demonstrates how a medical officer
- 4057 can make an informed decision supported by XAI visualisation of relevant features.
- 4058 Another example from the WHO Collaborating Centre for International Drug Monitoring illustrates 4059 how explanations can be used in reviewing AI case deduplication. In this case, a pair of Norwegian 4060 cases were identified as probable duplicates, while on first glance for the reviewers the duplication 4061 was not obvious. Due to missing outcomes, onset dates and ages that were close but not matching, 4062 and no matches between the registered adverse drug reaction terms, these cases would not have 4063 been identified as duplicates if they were not flagged by the AI. The AI explanation revealed that the 4064 match score was based on six different drug substances which were identical between the cases in 4065 addition to the fact that these six drug substances are commonly not co-reported. The researchers 4066 verified that the cases were indeed duplicates by contacting the Norwegian national centre. The 4067 cases concerned the same incident but were reported by two different physicians from the same hospital, thus accounting for the differences.²⁹⁸ This example illustrates how the explanation could be 4068 essential for the human in order to understand, further investigate the veracity of the prediction and 4069 4070 finally reject or in this case accept the prediction.

4071 Examples of xAI methods

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- 4072 Some xAI methods in use at the time of writing this report include:
- 4073 Local Interpretable Machine-Agnostic Explainability LIME
 - See the example of Ribeiro et al (2016)²⁹⁹ described earlier in this chapter.
- Shapley Additive exPlanations SHAP
- 4076 An example of SHAP explainability in a supervised ML model used to support signal validation is 4077 presented by Imran et al (2024).³⁰⁰
 - Trust scores that indicate the model's uncertainty for the output.³⁰¹
- 4079
 Confidence scores are a metric that is usually available and can be used to flag output that is uncertain for human review.³⁰²
- Visualisation through highlighting of text that was considered by the AI in its prediction and
 saliency maps using a heat map overlay to indicate areas of the input image that are relevant
 for the model's prediction.
- Although assessing and processing images is not a mainstream activity in PV, saliency maps are
 mentioned as another example of XAI to complete the view of the current landscape. See examples
 in Plass et al (2023).³⁰³

In the case of PV where the data is predominantly text based, visual explanations are likely to take
 the form of highlighting relevant text within the case data. See also the FDA InfoViP described above
 as an example of explainability benefits.^{304,305}

4090 Counterfactuals explanations or examples that show what characteristics in the input data
 4091 when changed, would result in different output.³⁰⁶

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Content related to Fairness and Equity 4092

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4094 While not all of the examples provided below are specific to PV, they illustrate the potential

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Impact of inadequate data, bias from underrepresented populations and explicit bias potentially 4097 leading to unfair treatment of specific populations, underserved populations, and potential treatment 4098 inequality.

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4100 Example of inadequate training of AI solutions and/or inadequate data sets that introduced unfair 4101 bias and resulted in inequity.

4102 In the US, prescription opioids are tracked through electronic databases, Prescription Drug 4103 Monitoring Programs (PDMPs). While not a PV specific example, Bamboo Healths NarxCare® is an 4104 example of an AI-powered tool that leverages PDMPs to calculate an opioid risk metric to predict the 4105 likelihood of a potential overdose, and although it is intended to support medical decisions, there 4106 have been observations that patients who are high health care utilizers with complex medical 4107 conditions may be discriminated against and underserved for pain management because of a "high

- 4108 risk score".³⁰⁷ The score is calculated based on limited data available in the PDMP and does not 4109 consider any other factors when calculating the risk score. One factor that influences the score is the
- 4110 number of prescribers. Patients treated at teaching hospitals with multiple healthcare prescribers
- 4111 may have "too many prescribing physicians" and they may be interpreted as seeking treatment from
- 4112 multiple physicians to obtain multiple prescriptions. An April 2021 study in Drug and Alcohol
- 4113 dependence found that "common data driven algorithms" misclassified 20% of patients with cancer
- 4114 who often see multiple specialists as patients seeking multiple physicians in an effort to obtain
- 4115 multiple opioid prescriptions. As noted by the authors, the PDMP data lacks diagnostic information
- 4116 and other critical patient context limiting ability to distinguish misuse from appropriate clinical use.
- 4117 An October 2021 study published in Drug and Alcohol Dependence conducted an independent 4118 validation study found that the NarxCare tool had a 17.2% false positive and 13.4% false negative.³⁰⁸
- 4119 Bias introduced because of data limited to PDMP, interpretation of data, e.g. patients with complex
- 4120 medical conditions, multiple prescribers are perceived as a high risk for abuse, lack of context for
- 4121 patient population, e.g. cancer patients requiring prolonged opioid use, can influence high scores.
- 4122 The threat to fairness and equity for patients within subgroups who have a high score assigned
- 4123 because of bias, potentially may not receive adequate pain management when the high score is
- 4124 considered in isolation.
- 4125 Within PV, the risk to fairness and equity are primarily from explicit biases that may result in negative
- 4126 impact or may result in discriminatory harm to subpopulations underserved by an AI solution. The
- 4127 NarxCare example, while not PV related, demonstrates both explicit bias from inadequate data, lack of context and implicit bias because negative stereotypes associated with "high health care utilizers"
- 4128 4129 were applied.³⁰⁹
- Example of bias applied because of under-represented populations 4130

4131 In Brazil, the assertiveness outcomes of the skin's lesions classification using artificial neural network 4132 in Caucasian patients and Brazilian patients were compared. The skin lesions were classified using 4133 basic architecture of convolutional neural networks (CNN). The ISIC database was used to train the 4134 neural network. This database was applied in about 25 thousand images of skin lesions. These images 4135 have included melanoma, melanocytic nevus, basal cell carcinoma, actinic keratosis, benign 4136

keratosis, dermatofibroma, vascular lesion, and squamous cell carcinoma lesions. The tests

- 4137 performed with ISIC patients had accuracy rates close to 90%. However, the accuracy rate was less
- than 40% when the tests were carried out with Brazilian patients. Thus, there was a great
- discrepancy in the assertiveness of the Artificial Neural Network when applied to Caucasian patients
- and Brazilian patients (Ref. K. Mundim et al).

4141 Example of Explicit negative bias

- 4142 In Appendix 3, "Examples of explainability in system development" included an example describing
- an AI triage system that incorrectly identified serious cases. The AI solution incorrectly learned to
 predict any adverse events associated with an OTC drug of interest as being non-serious because
- serious events were under-represented in the training data. This can also be considered an example
- of explicit negative bias with the inadequate date set resulting in incorrect assessments not
- 4147 recognized because of an explicit bias that it was not likely the OTC products in question would have
- serious adverse events associated with the use of the products. Since populations that may not have
- the same means to seek treatment at a medical facility or access to a healthcare professional may be
- reliant on OTC products, and these groups have a high likelihood of being from minority groups, a
- 4151 systematic misclassification of serious reports for OTC products as being non-serious could be seen
- 4152 as a threat to fairness and equity.

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APPENDIX 5: CIOMS Working Group membership and meetings

- 4156
- 4157 The CIOMS Working Group XIV on *Artificial intelligence in* pharmacovigilance included the following
- 4158 groups of stakeholders: academics, pharmaceutical companies, regulatory authorities, as well as 4159 national and international organisations.
- 4160

Academia					
Name	Company/Organisation	Country			
Altman, Russ	Stanford University	USA			
Botsis, Taxiarchis	Johns Hopkins University School of Medicine	USA			
Dogné, Jean-Michel	University of Namur	Belgium			
Pharmaceutical companie	Pharmaceutical companies				
Name	Company/Organisation	Country			
Amelio, Justyna	AbbVie	UK			
Barrios, Mariane	Merck Sharp & Dohme	Colombia			
Bate, Andrew	GSK	UK			
Bellur, Arvind	CSL Behring	USA			
Berridge, Adrian	Takeda Development Center Americas, Inc	USA			
Carroll, Hua	Biogen	USA			
Cherkas, Yauheniya	Johnson & Johnson	USA			
Comfort, Shaun	Genentech	USA			
Cooper, Selin	AbbVie	UK			
Diniz, Mariane	Bayer	Brazil			
Domalik, Douglas	AstraZeneca	UK			
Franco, Piero Francesco	Pfizer	Italy			
Girod, Julie	Sanofi	USA			
Grabowski, Neal	Sanofi	USA			
Hauben, Manfred	Merck KGaA, Darmstadt, Germany	USA			
Henn, Thomas	United Therapeutics	USA			
Kara, Vijay	GSK	UK			
Kempf, Dieter	Genentech	USA			
Kidos, Kostadinos	Formerly Takeda Development Center Americas, Inc	USA			
Lorenz, Denny	formerly Bayer AG	Germany			

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MacEntee Pileggi, Beth	Johnson & Johnson	USA
Patel, Ravi	United Therapeutics	USA
Reinhard Pietzsch, John	Bayer	Germany
Römming, Hans-Jörg	Merck KGaA, Darmstadt, Germany	Germany
Savage, Elizabeth	Johnson & Johnson	USA
Straus, Walter	Moderna	USA
Whitehead, James	AstraZeneca	UK
Regulatory authorities		
Name	Company/Organisation	Country
Ball, Robert	United States Food and Drug Administration (US FDA)	USA
Buch, Brian	Medicines and Healthcare products Regulatory Agency (MHRA)	UK
Durand, Julie	European Medicines Agency (EMA)	
Egebjerg Juul, Kirsten	Danish Medicines Agency (DKMA)	Denmark
Harrison, Kendal	Medicines and Healthcare products Regulatory Agency (MHRA)	UK
Hirokawa-Voorburg, Satoko	Health and Youth Care Inspectorate (HYCI)	The Netherlands
Horst, Alexander	Swissmedic	Switzerland
Jensen, Morten	Danish Medicines Agency (DKMA)	Denmark
Kikuchi, Yuki	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Kjær, Jesper	Danish Medicines Agency (DKMA)	Denmark
Ling, Benny	Health Canada	Canada
Da Luz Carvalho Soares, Monica	Brazilian Health Regulatory Agency (ANVISA)	Brazil
Maniwa, Harumi	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Matsunuga, Yusuke	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
McAteer, Richard	Health Canada	Canada
Mentzer, Dirk	Paul-Ehrlich-Institut (PEI)	Germany
Messelhäußer, Manuela	Formerly Paul-Ehrlich-Institut (PEI)	Germany
Moreira Cruz, Flávia	Brazilian Health Regulatory Agency (ANVISA)	Brazil
Perez, Nicolas	Swissmedic	Switzerland
Scholz, Irene	Swissmedic	Switzerland
Stammschulte, Thomas	Swissmedic	Switzerland

Tregunno, Phil	Medicines and Healthcare products Regulatory Agency (MHRA)	UK			
National and international organisations					
Name	Company/Organisation	Country			
Mathur, Roli	Indian Council of Medical Research	India			
Meldau, Eva-Lisa	Uppsala Monitoring Centre/World Health Organization	Sweden			
Norén, Niklas	Uppsala Monitoring Centre/World Health Organization	Sweden			
Rosenfeld, Stephen	North Star Review Board	USA			
Yau, Brian	World Health Organization	Switzerland			
CIOMS					
Name	Company/Organisation	Country			
Heaton, Stephen	Individual expert	Germany			
Hill, Sanna	CIOMS	Switzerland			
Le Louët, Hervé	CIOMS	Switzerland			
Rägo, Lembit	CIOMS	Switzerland			
Rannula, Kateriina	CIOMS	Estonia			
Tsintis, Panos	CIOMS	UK			

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The Working Group XIV will have met ten times from 2022 to 2025 at the time of writing and most ofthe meetings at this stage will have been hybrid in nature.

4164

4165	1.	Geneva, Switzerland	18-19 May 2022
4166	2.	Geneva, Switzerland	10-11 October 2022
4167	3.	Virtual meeting	19 January 2023
4168	4.	Virtual meeting	12 April 2023
4169	5.	Zurich, Switzerland	6-7 June 2023
4170	6.	Virtual meeting	8 November 2023
4171	7.	Virtual meeting	11 January 2023
4172	8.	Geneva, Switzerland	7-8 March 2024
4173	9.	Darmstadt, Germany	24-25 September 2024
4174	10.	Geneva, Switzerland	25-26 June 2025 (planned at time of writing)
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4177 APPENDIX 6: Public consultation commentators

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- 4179
- 4180

(to follow)