

Beyond Maximum Grade: Key Regulatory Considerations in Adverse Event Reporting

Kyriaki Tzogani¹, Tarek C. El-Galaly^{1,2}, Neil Everest³, Christian Gisselbrecht⁴, Noriko Mitsuiki⁵, Sumimasa Nagai⁶, Rhianna Thompson⁷, Gita Thanarajasingam⁸

Affiliations:

1. The European Medicines Agency, Amsterdam, The Netherlands
2. Departments of Haematology, Molecular Medicine, and Clinical Epidemiology Aarhus, University Hospital and Department of Clinical Medicine, Aarhus University, Denmark
3. Health Resourcing Group, Australian Government Department of Health, Disability and Ageing, Brisbane, Australia
4. Haemato-Oncology Department, Hospital Saint Louis, University Paris Cite, France
5. Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
6. Department of Medical Development, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital, Kyoto, Japan
7. Therapeutic Goods Administration, Australian Department of Health, Disability and Ageing, Canberra, Australia
8. Division of Haematology, Mayo Clinic, Rochester, Minnesota, USA

Conflicts of interest:

KT: None; TCEG: No COI related to this work; NE: None; CG: None; NM: None; SN: Nipro Corporation (grants to institution), Takara Bio, Inc (honoraria); RT: International Society for Cell & Gene Therapy (provided support to institution for representative to travel to and attend meeting); GT: None

Corresponding author: Kyriaki Tzogani, European Medicines Agency, Domenico Scarlattilaan 6 1083 HS Amsterdam, The Netherlands, Phone:0031887817299, kyriaki.tzogani@ema.europa.eu

Key words: haematological malignancies, toxicity, adverse events, regulatory considerations, European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Australian Therapeutic Goods Administration (TGA).

This is the accepted version of the manuscript. The published version is available on the journal website.

Tzogani K, El-Galaly TC, Everest N, Gisselbrecht C, Mitsuiki N, Nagai S, Thompson R, Thanarajasingam G. Beyond maximum grade: key regulatory considerations in adverse event reporting. *Lancet Haematol*. 2026 Sep;13(9):e670-e678. doi: [10.1016/S2352-3026\(26\)00168-7](https://doi.org/10.1016/S2352-3026(26)00168-7). PMID: 42660133.

Search Strategy Box: Search strategy and selection criteria references addressing the key issues and concepts outlined in this Series paper were identified by the international author panel through focused searches in PubMed and Abstract Books of the major haematology conferences. No systematic search or review of the literature was conducted.

Abstract

The therapeutic landscape of haematological malignancies has evolved rapidly with the introduction of targeted therapies, immunotherapies, and cell- and gene-based interventions, leading to improved survival and, in some cases, long-term remission or cure. These advances have exposed limitations in traditional approaches to adverse event (AE) assessment and reporting.

Building on the updated Lancet Haematology Adverse Events Commission, this paper examines how proposed improvements in toxicity reporting can be operationalized and integrated into regulatory decision-making across clinical trials and real-world settings. We focus on key challenges and opportunities related to measuring cumulative and long-term toxicity burden, incorporating patient-reported outcomes, improving AE reporting quality and efficiency in clinical trials, and leveraging real-world data, registries, and emerging technologies such as artificial intelligence and natural language processing.

Regulatory perspectives from international agencies, including the European Medicines Agency, the Japanese Pharmaceuticals and Medical Devices Agency, and the Australian Therapeutic Goods Administration, are discussed.

Introduction

The updated Lancet Haematology Adverse Events Commission on modernizing the assessment and reporting of adverse events (AEs) in haematological malignancies highlighted progress in priority areas for improving toxicity reporting in relation to regulatory approval of new medicines. The initial work focused on challenges in AEs analysis, patient-reported outcomes (PRO) integration, cellular therapy toxicity reporting, and regulatory perspectives.

Building on this, we now discuss how to implement and refine the proposed changes to toxicity reporting and regulatory processes, with a focus on standardizing methodologies and ensuring these advancements are adopted in both clinical trials and real-world settings by regulatory agencies.

The therapeutic landscape for haematological malignancies and other cancers has undergone a remarkable transformation in recent years, driven by the rapid development of targeted therapies, immunomodulatory agents, cellular therapies, and gene-based interventions (1), (2). These innovations have significantly improved patient survival, turning previously terminal conditions into chronic diseases in some cases, and even achieving long-term remission or cure for certain patient populations (3), (4), (5). Alongside these clinical advances, the evaluation of toxicity and tolerability has become increasingly complex.

This paper examines the current key challenges and opportunities in enhancing toxicity reporting, focusing on clinical trials, PROs, real-world data (RWD), longitudinal toxicity monitoring, and

emerging technologies such as artificial intelligence (AI) and machine learning (ML) in the context of international regulatory agencies including European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and Australian Therapeutic Goods Administration (TGA).

- Measuring and evaluating toxicity burden

The toxicity assessment in oncology trials has relied heavily on the common terminology criteria for adverse events (CTCAE), an investigator-reported, organ-based grading system focused on severity at discrete time points. The CTCAE has played a central role in standardizing AE reporting and providing a basis for comparison of different treatment interventions.

However, its limitations have become increasingly clear with a shift away from conventional chemotherapy given for a fixed duration of time towards chronic therapies administered until progression or unacceptable toxicity or, conversely, towards one-time treatments. Examples of the first include Bruton's tyrosine kinase (BTK) inhibitors for chronic lymphocytic leukemia and teclistamab, a bispecific antibody, for relapsed/refractory multiple myeloma (6), (7). Examples of the latter include chimeric antigen receptor T-cell (CAR T-cell) therapy for relapsed/refractory large B-cell lymphoma.

In the European Union (EU), the "guideline on the evaluation of anticancer medicinal products in man" was updated in 2018 to address the evolving landscape of anticancer medicinal products (8). This revision emphasized a new approach to toxicity assessment. For example, the weight of a specific adverse drug reaction (ADR) on the overall benefit-risk balance of a new cancer therapy is not only determined by the crude incidence, but also on how severity changes with time on treatment and whether the ADR can be easily alleviated by dose reduction, short treatment interruption, or supportive care.

In hematological malignancies, as outlined in the recently published Commission paper by Major et al, trials should use longitudinal and time-to-event approaches to refine dose-finding by monitoring toxicities across multiple treatment cycles (9). This is especially important as many treatments show early toxicities (e.g., cytokine release syndrome in CAR T-cell therapies), cumulative or late toxicities (e.g., neutropenia with Venetoclax, cardiovascular effects with tyrosine kinase inhibitors (TKIs), or immune-related AEs (irAEs) with checkpoint inhibitors), or both.

By incorporating data from all treatment cycles, these methods improve the estimation of the maximum tolerated dose (MTD) for long-term therapies and allow for better detection of recurrent toxicities. Examples include adjusting CAR T-cell regimens, personalizing TKI doses in chronic myeloid leukemia, and refining Venetoclax and lenalidomide protocols for safer, more effective outcomes (10), (11), (12), (13). As part of efforts to harmonize international regulation, this guideline has been adopted by other regulatory agencies such as the TGA. Similarly, the guidelines for the clinical evaluation of anti-cancer drugs in Japan were amended in 2021 (14).

Inclusion of pharmacokinetic/pharmacodynamic (PK/PD) modelling for reducing toxicity and improving tolerability of novel cancer therapies should also be considered beyond the short duration phase 1 studies. The PK/PD correlations with tolerability, toxicity, and response may change with longer duration of therapy and not be well reflected by phase 1 results. It is therefore plausible that more adaptive dosing of chronic therapies would be relevant for more of the chronic therapies, changing to lower doses or longer dosing intervals once a remission has been achieved. For example,

for BTKi, one could speculate if lower doses would be equally effective to maintain a remission but more tolerable, rather than primarily changing dosing only in response to observed intolerability.

Furthermore, age is a critical factor in evaluating toxicity and optimizing treatment through PK/PD approaches. Treatment duration and phase (induction or maintenance) can be associated with different toxic effects but also associated with chronic cumulative toxicities. These toxicities need to be explored at the beginning of the development of new agents and reassessed at regular intervals during long-term follow-up.

Beyond regulatory dose-finding considerations, it is essential to go beyond AE reporting systems and explore patient perspectives that account for long-term treatment impacts, as highlighted by Bhatnagar et al's recent AE Commission paper (15). Regulatory agencies have acknowledged that with the chronic targeted therapies and the one-time treatments with gene or cellular therapies, patients may experience low-grade side effects over prolonged periods as they are either continuously on therapy or receive a therapy that induces long-term, maybe permanent, genetic or cellular changes (16), (17).

Therefore, patients treated with those therapies may be prone to chronic toxicities that impact quality of life over longer periods, but how such toxicities influence patients' lives has received less attention and is not optimally captured in current benefit-risk assessments. Regulatory guidance increasingly emphasizes the importance of incorporating PROs and other measures of daily functioning while on therapy to better describe the cumulative toxicity burden of treatment (18), (19).

Some of the new innovative therapies also differ substantially from conventional therapies by being capable of inducing very long remissions, even possibly cure, in patients for whom standard therapies were considered palliative with short-lived responses being the most likely outcome. Regulatory agencies have recognized that this can complicate benefit-risk evaluations, as safety findings must be interpreted in the context of the magnitude and durability of clinical benefit, particularly when long-term or delayed AEs can occur in surviving patients (20), (21).

There are several topics that need further research and prioritization to make regulatory evaluation of new cancer therapies more patient centric. These include:

- Frameworks for weighing chronic toxicities against acute, high-grade toxicities. For example, chronic grade 1-2 nausea for months, as reported by patients, with continuous oral therapies may be worse than multiple short episodes of grade 3 nausea with chemotherapy. It remains unclear how such AEs are weighed against each other consistently across therapies and trials. As a minimum, duration of toxicities is required to estimate total burden.
- Are AE severity assessments good enough to capture the impact on daily functioning, which can be very serious from a patients' perspectives but may not fulfill the conventional regulatory criteria for seriousness? How should these effects be consistently captured across trials and how can this data be included in the benefit-risk assessment in a reproducible way? How do patient backgrounds, cultural and geographical differences influence health outcomes?

- Should tolerability endpoints that include patient-generated data be used to inform regulatory approval and how should patient-generated data be weighed against objective efficacy measures like response rates or PFS as well as more conventional safety measures? Would a therapy that is highly desired by patients due to improved AE profile, but with non-inferior or acceptably inferior efficacy have a clear path to approval in the current regulatory landscape? How would patient preference studies inform such regulatory decisions in future, particularly where there is variability in the safety profile of combinations of targeted therapies for a disease entity?

These considerations are relevant today, where many patients with hematological cancers become long-term survivors and with some patient groups even showing trends toward normalization of residual life expectancies (22), (23). To fully understand these correlations and weigh AEs against clinical benefits of new therapies, more patient involvement is needed. The PROs version of the CTCAE (PRO-CTCAE) was developed specifically to enhance patient-centeredness of AE reporting, an approach explicitly supported by regulatory guidance recognizing the limitations of investigator-reported AEs alone (18). EMA also acknowledges the importance of patient experience data and value when assessing the totality of evidence supporting the regulatory assessment of medicines (24). However, these aspirations still need to be operationalized and implemented consistently in regulatory assessments of new cancer therapies. Patient-friendly AE reporting tools that gather information on severity and interference with daily activities directly from patients are essential in this process. For some patients, the opportunity to report directly to Sponsors may also reduce concerns that reporting AEs could have a negative impact on their cancer treatment. It is already well-described that PRO-CTCAE can identify differences in important toxicities like anorexia, diarrhea, dyspnea, mucositis, nausea, neuropathy, and vomiting between treatment groups, from a patient perspective potentially important differences which are not always captured by investigator-reported AEs (25).

The added value of PROs was also demonstrated in a recent analysis of PROs versus clinician-reported AE in 874 patients from the Phase 3 Polarix study of R-CHOP versus Pola-R-CHP in first-line diffuse large B-cell lymphoma. While there were no meaningful differences between treatment-arms, there were marked differences between clinician-reported AEs and PROs for fatigue and gastrointestinal-symptoms like nausea, vomiting, constipation and diarrhea. For example, PRO data revealed feeling of fatigue in 97% of patients whereas fatigue was only reported for 25% of patients using clinician-reported AEs.

To fully understand and weigh toxicities related to innovative therapies in a more patient-centered way, we need to learn more about patient preferences, including how patients weigh treatments attributes like survival benefits, response rates and toxicity against each other. In other words, how acceptable is an increase in chronic toxicities when treatments only lead to better progression-free survival (PFS) or response rates only in contrast to treatments that lead to better overall survival (OS). Knowledge about survival outcomes may influence acceptability of interference with daily functioning. In Hodgkin lymphoma, a highly curable disease in young patients, a discrete choice experiment showed patients rated survival attributes higher than toxicity attributes (26). In chronic lymphocytic leukaemia (CLL), a chronic disease, there was a patient preference for fixed duration oral treatments with high minimal residual disease (MRD) negativity and high risk of fatigue weighted negatively in decision making (27). From a regulatory perspective, it is increasingly recognized that understanding treatment attributes by conducting

such preference studies is important with a need to integrate patient perspectives systematically into regulatory decisions.

The FDA's patient-focused drug development initiative encourages the use of systematic patient input to inform medical product development and regulatory decision-making, including defining which types of outcomes and treatment characteristics matter most for patient's preferences (28). Additionally, the EMA's reflection paper on patient experience data notes that patient perspectives on benefits, risks, and treatment burden can complement traditional clinical evidence and support regulatory review. Finally, the ICH E22 guideline provides harmonized guidance on designing and using patient preference studies to quantify the relative importance of treatment attributes in regulatory submissions (29).

If patient preference studies were conducted more consistently in different disease settings and for different types of therapies (for example for curative versus palliative or intensive versus non-intensive scenarios) the optimal trade-offs between efficacy and toxicity may be clearer from the perspectives of those who will eventually be potential users of a new therapy. Patient preference studies could examine how unknown effects in terms of efficacy and toxicity impact acceptability for patients when it comes to therapies that are approved based on non-comprehensive data, such as accelerated approvals by FDA or conditional approvals by EMA. With an increasing number of cancer therapy approvals based on single arm studies, understanding how patients would value trade-offs between early access and substantial uncertainties would be highly relevant (30).

However, it is not straightforward, as meaningful response to such questionnaires may require patient to be well educated on the meaning and differences between key outcomes measures such as MRD negativity, PFS and OS and how they may or may not correlate. Interestingly, a study showed that some patients interpret palliative care as potentially curative when it was given with a palliative intent (31). Such misconceptions as well as the complex correlations between surrogate endpoints and patient relevant endpoints may distort AE acceptability from a patients' perspective and underline the importance of providing clear and understandable information to patients about most likely treatment outcomes. Otherwise, it will be difficult for patients to determine if AEs and their impact in daily functioning are acceptable trade-offs for a given therapy.

- Reporting AEs in clinical trials

While regulatory agencies have made progress in adapting to the evolving therapeutic landscape, addressing the persistent gaps in AEs reporting during clinical trials remains a pressing challenge that requires immediate attention. Adequate reporting of AEs is vital to ensure that only safe new medicinal products are approved and reach the patients. After approval, in-depth understanding of AEs is critical for safe use of treatments in the real-world setting and for making informed treatment decisions together with patients. Although regulatory authorities such as EMA, FDA, PMDA, Swissmedic, and Health Canada have been successful in harmonizing clinical trials regulations, the reports submitted to regulatory authorities are not considered as informative in many aspects.

In clinical trials, excessive reporting of minor or irrelevant AEs, known as "noise," can overwhelm researchers and obscure critical safety signals linked to the drug. In addition, unpublished data sources consistently provide significantly more detailed information on AEs compared to published reports. This lack of transparency contributes to "hidden" or "missing" data, which hinders

researchers, clinicians, patients, and regulators from fully understanding the potential harms of interventions (32). An incomplete report of AE attribution and limited information regarding the total frequency of all-grade and grade 3–4 AEs has been reported in literature for clinical trials in oncology (33). Regulators expect attribution to be presented hierarchically starting with all AEs descriptively, followed by analyses of treatment-emergent and treatment-related events. They also highlight the need for the causal relationship between the investigational drug and AEs to be evaluated. From a regulatory standpoint, under-reporting treatment-related AEs can bias the overall benefit-risk assessment at the time of approval, which is why attribution remains an important component of the submission. Incomplete attribution, lack of longitudinal toxicity characterization, and limited incorporation of PROs can influence dose selection, labeling content, risk management plans, and the need for post-authorization safety studies. Insufficient characterization of cumulative or chronic toxicities at the time of approval may complicate long-term benefit-risk assessment, particularly for therapies intended for prolonged or lifelong use. Additionally, switching to a different drug due to intolerance in a real-world setting is important for evaluating long-term treatment tolerability. In general, systematic reporting on how AEs affect patients' quality of life, as well as which toxicities most often lead to dose reductions or treatment discontinuations, are lacking.

Adverse event reporting could be improved by addressing technical challenges that increase complexity and workload. Investigators and data managers currently face the additional hurdle of working across multiple Electronic Data Capture (EDC) systems—or even paper-based systems—to report patient data, including laboratory results, medications, and AEs. These challenges vary depending on the sponsor or Clinical Research Organization (CRO) managing the clinical trial. This lack of harmonization requires them to learn different systems, manage multiple passwords, and, in some cases, resubmit reports due to issues such as illegible handwriting.

This highlights the need for a single, integrated online platform that combines EDC functionality with a safety reporting system deemed acceptable to regulatory agencies. The development of an integrated online platform for EDC and AEs reporting requires collaboration across multiple stakeholders, including companies providing EDC systems, clinical trial sponsors, CROs, regulatory authorities, and healthcare professionals. Key considerations in its development include real-time data integration, security, compliance and usability. Patients, though not directly involved in the technical aspects, play an essential role in reporting AEs and ensuring data accuracy, making their education and engagement crucial for optimizing toxicity reporting in clinical trials.

- Real-world data in pharmacovigilance to inform regulatory agencies

During pre-approval, randomized clinical trials remain the primary source of efficacy and initial safety data, with increasing emphasis on longitudinal toxicity analyses and PROs to inform dose selection and labeling. Following approval, RWD and registries become critical for characterizing long-term safety, and tolerability in patient populations that are not highly selected by narrow inclusion/exclusion criteria typically applied in clinical trials.

Real-world data captures information from routine clinical practice with main sources such as electronic health records and patient registries. Depending on the level of reporting and the granularity of collected data, RWD has the potential to provide real-time and reliable safety information that could be harnessed by regulators in the post-marketing setting.

However, RWD faces challenges in data quality and completeness, as many datasets suffer from missing or inconsistent entries. The observational nature of RWD makes it challenging to evaluate and establish AE causality, necessitating carefully designed non-interventional studies (NIS) to

address potential biases and confounding. In addition, the fragmentation of the data and the lack of integration across systems do not facilitate easy large-scale analyses at this moment. This is problematic, especially in rare disease settings and/or for rare AEs.

A solution to increase utility of RWD in these situations would be to increase international collaboration and data harmonization. The side effect registry immuno-oncology (SERIO) is an example of this, where complex and/or treatment refractory irAEs following immunotherapies are captured from multiple institutions across 13 different countries with the purpose of better characterizing rare serious irAEs and developing best-practice in terms of management (34). In fact, this registry collaborated with the Paul-Ehrlich-Institute, a German federal institute for vaccines and biomedicines, by sharing data and thereby directly or indirectly potentially contributes to regulatory decisions.

Finally, there are privacy concerns related to use of RWD, where patients may not have given consent for secondary use of data for pharmacovigilance purposes. To address these challenges and harness the full potential of RWD, regulatory agencies have begun implementing innovative frameworks and tools.

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has utilized RWD sources to assess post-marketing safety through various pharmacoepidemiological studies and revise package inserts if necessary (35). One of the RWD sources for pharmacovigilance is Medical Information Database NETwork (MID-NET®), a database network system which contains electronic medical records, laboratory test data, claims data, and diagnostic procedure combination data obtained from 31 hospitals throughout Japan (as of December 2024) since 2018. For example, the PMDA conducted a nested case-control study using the MID-NET® database to clarify the association between granulocyte-colony stimulating factor (G-CSF) preparations and thrombocytopenia in patients treated with antineoplastic agents. The use of any G-CSF preparations was compared with the non-use of G-CSF preparation in 733 patients with thrombocytopenia and 5,592 patients without thrombocytopenia. The research showed a significantly increased risk of thrombocytopenia associated with pegfilgrastim. Based on the analysis, the PMDA revised the package insert of pegfilgrastim to inform the increased risk of thrombocytopenia in 2020 (36).

In 2021 the TGA conducted a review into the usage of RWD and PROs in both the pre- and post-marketing settings. The TGA has adopted international guidelines to harmonize data requirements and aligns their approach with comparable regulators where possible. The TGA has also partnered with academia to investigate how the linking of health databases can strengthen their signal detection program. The inclusion of ADR templates in medical record software has also facilitated direct ADR reporting by primary healthcare providers.

In the EU, initiatives such as Data Analysis and Real-World Interrogation Network (DARWIN EU) exemplify efforts to standardize and optimize RWD use in toxicity reporting. DARWIN EU is a federated network of real-world healthcare data to generate real-world evidence (RWE) to support the decision-making of EMA scientific committees and national competent authorities in EU Member States throughout regulatory processes. Following the launch of DARWIN EU, implementation efforts have progressed with an emphasis on expanding the network of data partners and initiating relevant studies. These activities aim to solidify the use of RWD methodologies and integrate the results of RWD analyses into regulatory decision-making processes at the EMA and across the European Medicines Regulatory Network (EMRN) (37). The Heads of Medicines Agencies (HMA)-EMA catalogues

provide a user-friendly environment that promotes information exchange, fosters collaboration and supports compliance with EU pharmacovigilance legislation through the registration of studies subject to regulatory requirements while bringing together diverse data sources -such as electronic health records databases, patient registries, and RWD- to give regulators access to relevant data and enable more thorough and timely assessments of AEs.

DARWIN EU will also be connected to the European Health Data Space (EHDS), an initiative to promote better exchange and access to different types of health data. EHDS, introduced by the European Commission in May 2022, aims to revolutionize healthcare in the EU by empowering citizens with full control over their health data and enhancing its use for research and public health. It ensures that citizens have consistent access to their digital health records across the EU, improving care continuity and decision-making, especially when seeking healthcare abroad. By enabling structured and large-scale access to health data, the EHDS has the potential to facilitate easy and transparent access to electronic health data for public health monitoring, improve healthcare systems efficiency, and ensure patient safety.

Better integration of data and more granular information, especially with data derived from healthcare records rather than from existing administrative registries, will be critical for future post-marketing pharmacovigilance in relation to long-term tolerability and toxicity. Most clinical trials run for a few years, which may have been adequate in the time where limited duration immunochemotherapy was the typical treatment of hematological cancers but may be supplemented by post-registration studies for provisionally registered products.

However, with more chronic therapies or cell therapies, exposure to therapies is much longer and often extends the observation time from pivotal trials. As it is unlikely for feasibility and cost reasons to have trials capturing detailed safety for decades, high-quality, granular RWD will become critical to fill this gap. The broad interest in establishing RWD repositories for patients with cancer in multiple countries is critical to ensure that relevant data are available for analysis. With increasing disparity in access to new therapies, exemplified by CAR-T for various indications, post-marketing pharmacovigilance cannot rely on few countries with a history of well-developed administrative registries. Optimal analyses require relevant, representative data for the treatment context, high levels of granularity, and enough exposed patients (38). This calls for international harmonization efforts, national focus on developing RWD infrastructure, and novel data capture technologies.

Whilst the approach of a single comprehensive international registry to support clinical effectiveness and adverse event outcome reporting and analysis is appealing (that is based on common dataset definitions), national approaches to optimizing registry scope and structure need to be developed and adopted first given there are significant matters of legislative oversight of patient data and privacy, arrangements for data release and impact of confidential funding agreements to be overcome. Any jurisdictional differences in these legislated or contracted arrangements that preclude between product comparisons, and assurance of patient confidentiality need to be addressed to optimize the value of registry data.

- Artificial intelligence / natural language processing

Advanced technologies, such as AI and natural language processing (NLP), can enhance the use of real-world data for regulatory and clinical decision-making by efficiently analyzing PROs on a large scale, and strengthening safety monitoring. Natural language processing has been extensively applied to derive clinical insights from electronic health records (EHRs) (39). Applications of NLP in clinical decision-making include interpreting diagnostic tests and stratifying patients using unstructured EHR. Examples in the literature support the use of NLP to identify the risk of acute care use in oncology patients on chemotherapy, to identify patients undergoing palliative surgical procedures, to efficiently evaluate end-of-life quality indicators, and to extract Eastern Cooperative Oncology Group Performance Status (ECOG PS) from unstructured EHR sources to enhance observational datasets. These applications of NLP have demonstrated accuracy comparable to that of human coders (40), (41), (42).

Utilizing RWD requires innovative tools to analyze large datasets efficiently. AI and machine learning (ML) offer transformative solutions to identify safety signals and improve toxicity reporting in both clinical and real-world settings and have the potential to enable regulatory bodies and pharmaceutical companies to take timely action in addressing safety concerns.

Machine learning models can analyze social media, electronic health records, and other RWE sources to detect signals of potential safety issues. More specifically, AI systems can be used to identify patterns and emerging safety trends that suggest an AE, often before traditional reporting mechanisms would capture them. In post-authorization safety studies, AI can process large-scale data from RWE sources such as EHRs and patient registries. These tools allow for the identification of long-term safety issues, leveraging predictive analytics to recognize potential risks.

For instance, AI has helped improve the detection of irAEs in patients treated with immune checkpoint inhibitors (ICIs) (43). Additional practical examples of such applications include the FDA's Sentinel Initiative, which applies advanced analytics for medical product safety monitoring, and the EMA's exploration of AI tools for regulatory decision-making (44). In March 2024, EMA introduced an AI-enabled knowledge mining tool called scientific explorer for EU regulators (45). The tool enables easy, focused and precise search of regulatory scientific information from network sources to support decision-making and simplify processes. The first release focuses on scientific advice procedures for human medicines and veterinary medicines. As part of a broader Australian government initiative to support the safe and responsible adoption and use of AI technology, the TGA has conducted a review of their legislative framework to clarify and strengthen regulation relating to AI and is exploring the benefits and productivity gains AI may offer the organization (46). The Australian government department of health, disability and ageing has also published the final report from their review of the use of AI in healthcare settings (47).

While AI and ML have shown immense promise in transforming toxicity reporting and signal detection, their implementation is not without challenges. Issues such as data bias, algorithm transparency, and privacy concerns must be addressed to ensure these technologies deliver reliable and equitable insights and that they are suitable for regulatory use. The European medicines regulatory network aims to enable regulatory systems in the EU to use the capabilities of AI while managing the risks. Key risks of AI tools include data quality and bias, where poor or incomplete datasets may produce inaccurate outcomes, whereas traditional manual-based signal identification methods may be comparatively less rapid, comprehensive and more time-consuming than those achieved through the use of AI-based tools thereby impacting patient safety. The lack of transparency and explainability of complex AI models, such as black-box algorithms, raises concerns about trust, reproducibility, and accountability in decision-making. Finally, challenges in regulatory oversight and validation of AI tools highlight the need for clear standards to ensure reliability,

robustness, and ethical use of AI throughout the medicinal product lifecycle, as part of the suite of methods for AE signal identification analysis in pre- and post-marketing settings. Nonetheless, the use of AI in the medicinal product lifecycle may improve the underreporting and timeliness of AEs reporting despite the risks (48).

However, in the absence of an adopted approach, formalizing the integration of AI into routine adverse event reporting processes requires the development of an agreed standardized validation framework to ensure model validation & performance, adequate comparative performance with non-AI based AE reporting, and elimination of bias in the interpretation of AE-related data.

- Multiple registries restructuring

With the transformation of the therapeutic landscape, there is a need to consider the optimal structure and scope of existing and emergent registries that are relevant for informing regulatory decision-making. The principles of single time-point, granular data collection, data storage, access, timeliness of reporting and linkage to other health outcomes datasets support these various registry purposes. Globalized therapy development requires an increased need for academia, study sponsors and regulators to work together to harmonize principles of registry dataset definitions, collection and management across jurisdictions. These factors can be impacted by local manufacture, differences in regional or national legislation, reimbursement arrangements and reporting requirements. The most efficient registry structure is also informed by the costs of establishment, ongoing maintenance of information technology (IT) systems and manpower, and sustainable source(s) of funding.

Accordingly, debate exists between expanding the functions of long-standing registries that are typically condition-specific (in relatively large patient populations) versus the need to comprehensively capture the scope of conditions encompassed by emergent novel therapies that are increasingly individualized. As emergent therapy use expands across broad classes of disease of rare or ultra-rare incidence, and may not be limited to malignancy, there may be little justification to establish additional condition-specific registries, versus those that are therapy class-based, or more broadly established. This is exemplified in the change in scope of the US and Canadian haematopoietic cell transplant registries to now encompass outcomes from cell and gene therapies. Registries with broad scope may support not only regulatory decision-making where longitudinal assessment of performance and safety of provisionally approved therapies is mandated but also provide evidence of outcomes of sequencing therapies in real-world practice that expands beyond clinical trial evidence and identify drivers of use of supportive therapies e.g., immunoglobulin. Similarly, the need to integrate genomic data and health outcomes datasets with therapy use, or impact of prior therapy of conditions that may be expected to transform and impact on post-transformation treatment, can only be assessed if there is sufficiently comprehensive data capture.

The increased linkage of health service utilization and outcomes data and therapy datasets is likely to provide a third option for the future development of a generalizable approach for virtual registries that are not constrained by the disease or therapy-class boundaries above and which can provide a broader source of data to international regulatory agencies. The Australian national strategy for clinical and virtual registries prioritizes disease areas with greatest clinical need, greatest variation in care and outcomes, and financial burden (which includes haematological malignancies), with six principles of: aligning with patient-centered care, improvement to clinical practice and patient outcomes, quality and efficiency of data capture, financial sustainability, transparency and access to data and data linkage & interoperability (49).

The expansion of emergent therapies to solid cancers and non-cancer indications, emergent use of individualized manufacture of products requiring longitudinal data capture, and increased need for registry data to capture clinical safety and effectiveness outcomes that are also relevant for review of risk-share arrangements, plus to compare outcomes across products, drives a need for changes to registry structures. The establishment of optimal & comprehensive registries to perform such diverse functions can only be likely achieved through national policy decisions and funding arrangements.

Conclusions

Advancing toxicity reporting requires collaborative efforts between regulators, industry, and patients with both immediate and long-term priorities. In the near term, efforts should focus on implementing longitudinal toxicity analyses, improving the quality and interpretability of AE reporting in clinical trials, expanding regulatory use of real-world data (RWD), piloting AI/NLP tools for signal detection, and enhancing the scope and interoperability of existing registries.

Long-term solutions focus on fully patient-centered toxicity evaluation, robust global registries, sustainable integration of RWD, and widespread adoption of AI-driven analytics. Together, these strategies enable a lifecycle-based, patient-centered approach to toxicity assessment that better reflects long-term risks and RWD, particularly for rare and ultra-rare conditions (Figure 1).

This review focuses on the regulatory perspectives and adverse event reporting frameworks of the EMA, PMDA, TGA, and FDA; therefore, challenges specific to low- and middle-income countries (LMICs), including resource limitations and differences in pharmacovigilance infrastructure, were not examined in detail and are beyond the scope of the present work ([50](#)).

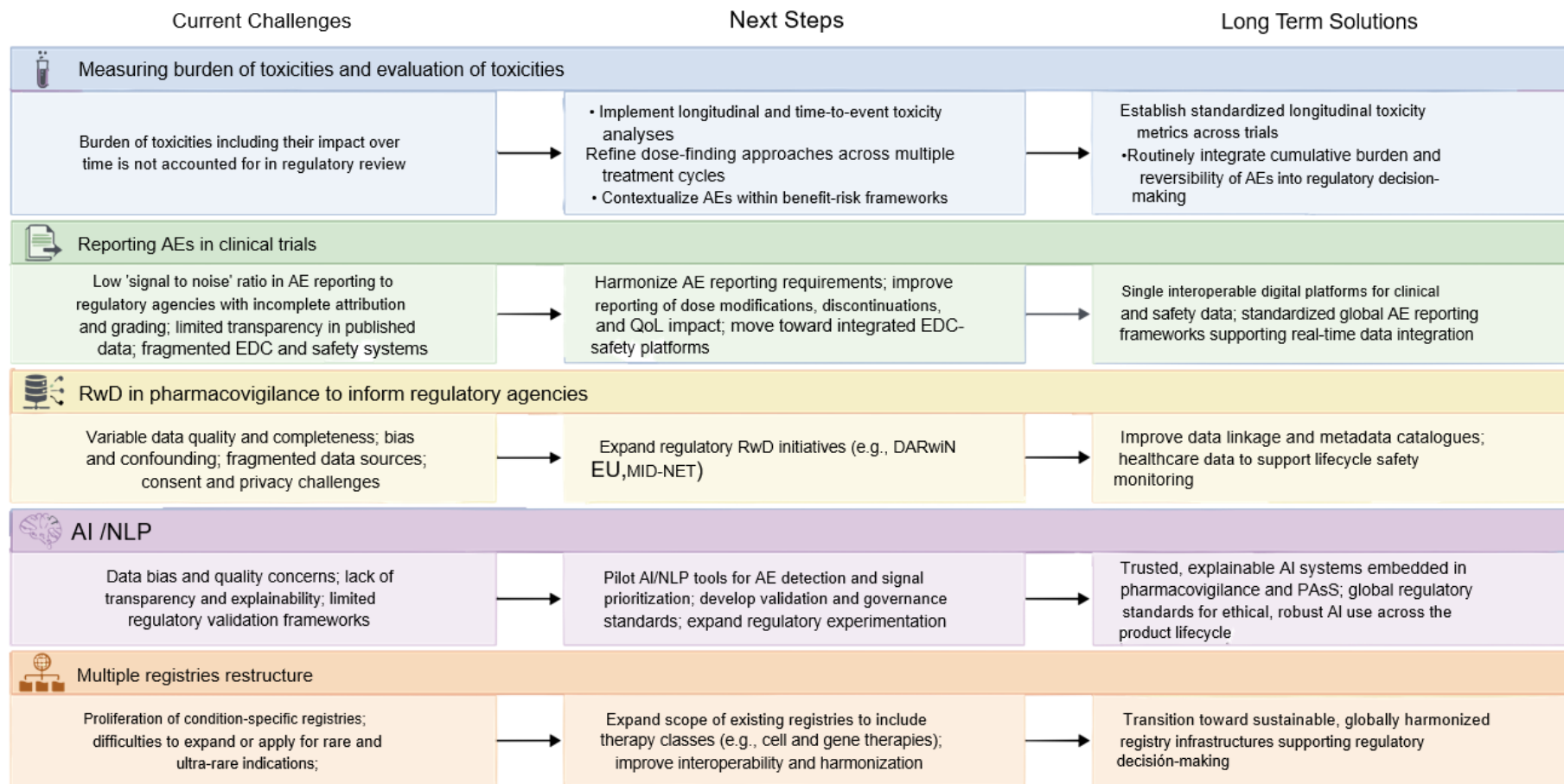
Acknowledgments: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or organisations with which the authors are employed/affiliated.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used (GPT-5.5, OpenAI) in order to improve readability, correct grammar, and shorten selected paragraphs for conciseness and clarity. In addition, Figure Labs Core Engine was used to revert the table into a figure. After using these tools, the authors reviewed and edited the content as needed and tak full responsibility for the content of the published article.

Contributors section : Kyriaki Tzogani, Tarec C. El-Galaly and Gita Thanarajasingam conceived the outline of the manuscript. All authors (Kyriaki Tzogani, Tarec C. El-Galaly, Neil Everest, Christian Gisselbrecht, Noriko Mitsuiki, Sumimasa Nagai, Rhianna Thompson, Gita Thanarajasingam) contributed to the drafting the first version of the manuscript. All authors critically reviewed, edited, and approved the final version of the manuscript.

Figure1. Proposed immediate and long-term solutions to current challenges in adverse event reporting



538 **References**

- 539 1. Sochacka-Ćwikła, A., Mączyński, M., & Regiec, A. (2021). *FDA-Approved Drugs for*
540 *Hematological Malignancies—The Last Decade Review*. *Cancers*, 14(1), 87.
541 DOI:10.3390/cancers14010087.
- 542 2. Hofmarcher, T., Berchet, C., & Dedet, G. (2024). Access to oncology medicines in EU and OECD
543 countries (OECD Health Working Papers No. 170). OECD Publishing.
544 <https://doi.org/10.1787/c263c014-en>.
- 545 3. Ho M, Zanwar S, Paludo J. Chimeric antigen receptor T-cell therapy in hematologic
546 malignancies: Successes, challenges, and opportunities. *Eur J Haematol*. 2024 Feb;112(2):197-
547 210. doi: 10.1111/ejh.14074. Epub 2023 Aug 6. PMID: 37545132.
- 548 4. Li L, et al. Recent advancements in gene therapy for sickle cell disease and β -thalassemia.
549 *Front Hematol*. 2024;3:1468952.
- 550 5. Gaspar AB. Advances in Gene Therapy for Inherited Haemoglobinopathies. *J Clin Med*.
551 2025;18(1):4.
- 552 6. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM,
553 Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG,
554 Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS,
555 Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib Regimens versus
556 Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med*. 2018 Dec
557 27;379(26):2517-2528. doi: 10.1056/NEJMoa1812836. Epub 2018 Dec 1. PMID: 30501481;
558 PMCID: PMC6325637.
- 559 7. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T,
560 Rosinol L, Chari A, Karlin L, Benboubker L, Mateos MV, Bahlis N, Popat R, Besemer B, Martínez-
561 López J, Sidana S, Delforge M, Pei L, Trancucci D, Verona R, Girgis S, Lin SXW, Olyslager Y, Jaffe
562 M, Uhlir C, Stephenson T, Van Rampelbergh R, Banerjee A, Goldberg JD, Kobos R, Krishnan A,
563 Usmani SZ. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med*. 2022 Aug
564 11;387(6):495-505. doi: 10.1056/NEJMoa2203478. Epub 2022 Jun 5. PMID: 35661166; PMCID:
565 PMC10587778.
- 566 8. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf)
567 [medicinal-products-man-revision-5_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf).
- 568 9. Ajay Major, Amylou C Dueck, Gita Thanarajasingam, Beyond maximum grade: advancing the
569 measurement and analysis of adverse events in malignant haematology trials in the modern era,
570 *The Lancet Haematology*, Volume 12, Issue 6, 2025, Pages e451-e462, ISSN 2352-
571 3026, [https://doi.org/10.1016/S2352-3026\(25\)00035-3](https://doi.org/10.1016/S2352-3026(25)00035-3).
- 572 10. Frigault M, Rotte A, Ansari A, Gliner B, Heery C, Shah B. Dose fractionation of CAR-T cells. A
573 systematic review of clinical outcomes. *J Exp Clin Cancer Res*. 2023 Jan 10;42(1):11. doi:
574 10.1186/s13046-022-02540-w. PMID: 36627710; PMCID: PMC9830795.
- 575 11. Zherou He, Xuan Zhou, Ziyu Wen, Zicheng Gao, Hong Chen, Qiang Wang, Hanyin
576 Liang, Dongmei Luo, Xiaoli Liu, Na Xu, Qifa Liu; TKI Dose Optimization Based on Therapeutic Drug
577 Monitoring (TDM) with Encouraging Outcomes and Well-Tolerated for Chronic Myeloid Leukaemia
578 Patients. *Blood* 2023; 142 (Supplement 1): 1807. doi: [https://doi.org/10.1182/blood-2023-](https://doi.org/10.1182/blood-2023-182765)
579 [182765](https://doi.org/10.1182/blood-2023-182765).

580 12. Iurlo A, Cattaneo D, Bucelli C, Breccia M. Dose Optimization of Tyrosine Kinase Inhibitors in
581 Chronic Myeloid Leukemia: A New Therapeutic Challenge. *J Clin Med*. 2021 Feb 1;10(3):515. doi:
582 10.3390/jcm10030515. PMID: 33535564; PMCID: PMC7867069.

583 13. Phillips TJ, Bond D, Takiar R, Kump K, Kandarpa M, Boonstra P, Mayer TL, Nachar V, Wilcox RA,
584 Carty SA, Karimi YH, Nikolovska-Coleska Z, Kaminski MS, Herrera AF, Maddocks K, Popplewell L,
585 Danilov AV. Adding venetoclax to lenalidomide and rituximab is safe and effective in patients with
586 untreated mantle cell lymphoma. *Blood Adv*. 2023 Aug 22;7(16):4518-4527. doi:
587 10.1182/bloodadvances.2023009992. PMID: 37013954; PMCID: PMC10425679.

588 14. Minami H, Kiyota N, Kimbara S, et al. Guidelines for clinical evaluation of anti-cancer
589 drugs. *Cancer Sci*. 2021; 112: 2563–2577. <https://doi.org/10.1111/cas.14967>

590 15. Beyond maximum grade: using patient-generated data to inform tolerability of treatments for
591 haematological malignancies Bhatnagar, Vishal et al. *The Lancet Haematology*, Volume 12, Issue 6,
592 e463 - e469.

593 16. [https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Long-Term-](https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Long-Term-Follow-Up-After-Admin-Human-GT-Products_Jan_2020.pdf)
594 [Follow-Up-After-Admin-Human-GT-Products_Jan_2020.pdf](https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Long-Term-Follow-Up-After-Admin-Human-GT-Products_Jan_2020.pdf)

595 17. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf)
596 [administered-gene-therapy-medicinal-products_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf)

597 18. <https://www.fda.gov/media/149994/download>

598 19. [https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-](https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf)
599 [medicinal-products-man_en.pdf](https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf).

600 20. <https://www.fda.gov/media/188891/download>

601 21. [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-and-](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-and-efficacy-follow-and-risk-management-advanced-therapy-medicinal-products-revision-1_en.pdf)
602 [efficacy-follow-and-risk-management-advanced-therapy-medicinal-products-revision-1_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-and-efficacy-follow-and-risk-management-advanced-therapy-medicinal-products-revision-1_en.pdf)

603 22 Bicer JL, Glimelius I, Eloranta S, Smeland KB, Brown PN, Jakobsen LH, Frederiksen H,
604 Jerkeman M, Fosså A, Andersson TML, Holte H, Bøgstød M, El-Galaly TC, Smedby KE. Relapse Risk
605 and Loss of Lifetime After Modern Combined Modality Treatment of Young Patients With Hodgkin
606 Lymphoma: A Nordic Lymphoma Epidemiology Group Study. *J Clin Oncol*. 2019 Mar 20;37(9):703-
607 713. doi: 10.1200/JCO.18.01652. Epub 2019 Feb 6. PMID: 30726176.

608 23. van der Straten L, Levin MD, Visser O, Posthuma EFM, Doorduyn JK, Kater AP, Dinmohamed
609 AG. Survival continues to increase in chronic lymphocytic leukaemia: a population-based analysis
610 among 20 468 patients diagnosed in the Netherlands between 1989 and 2016. *Br J Haematol*.
611 2020 May;189(3):574-577. doi: 10.1111/bjh.16397. Epub 2020 Jan 20. PMID: 31958141.

612 24. EMA patient experience data reflection paper, draft
613 [https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-patient-](https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-patient-experience-data_en.pdf)
614 [experience-data_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-patient-experience-data_en.pdf)

615 25. Dueck AC, Scher HI, Bennett AV, Mazza GL, Thanarajasingam G, Schwab G, Weitzman AL,
616 Rogak LJ, Basch E. Assessment of Adverse Events From the Patient Perspective in a Phase 3
617 Metastatic Castration-Resistant Prostate Cancer Clinical Trial. *JAMA Oncol*. 2020 Feb
618 1;6(2):e193332. doi: 10.1001/jamaoncol.2019.3332. Epub 2020 Feb 13. PMID: 31556911;
619 PMCID: PMC6764147.

620 26. Khan N, Feliciano J, Müller K, He M, Tao R, Korol E, Dalal M, Rebeira M, Matasar M. Patient
621 preferences for first-line treatment of classical Hodgkin lymphoma: a US survey and discrete

choice experiment. Leuk Lymphoma. 2020 Nov;61(11):2630-2637. doi:
10.1080/10428194.2020.1783443. Epub 2020 Jul 20. PMID: 32684056; PMCID: PMC9175565.

27. Ravelo A, Myers K, Brumble R, Bussberg C, Koffman B, Manzoor BS, Biondo JML, Mansfield C. Patient preferences for chronic lymphocytic leukemia treatments: a discrete-choice experiment. Future Oncol. 2024;20(28):2059-2070. doi: 10.1080/14796694.2024.2348440. Epub 2024 May 22. PMID: 38861284; PMCID: PMC11497998.

28. <https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical>

29. ICH E22 General considerations for patient preference studies - Scientific guideline : <https://www.ema.europa.eu/en/ich-e22-general-considerations-patient-preference-studies-scientific-guideline>

30. <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3554>

31. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, Lennes IT, Dahlin CM, Pirl WF. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. J Clin Oncol. 2011 Jun 10;29(17):2319-26. doi: 10.1200/JCO.2010.32.4459. Epub 2011 May 9. PMID: 21555700.

32. Golder S, Loke YK, Wright K, Norman G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. PLoS Med. 2016 Sep 20;13(9):e1002127. doi: 10.1371/journal.pmed.1002127. PMID: 27649528; PMCID: PMC5029817.

33. Diego Enrico, Federico Waisberg, Jeannette Burton, Pablo Mandó, Matías Chacón, Analysis of adverse events attribution and reporting in cancer clinical trials: A systematic review, Critical Reviews in Oncology/Hematology, Volume 160, 2021, 103296, ISSN 1040-8428, <https://doi.org/10.1016/j.critrevonc.2021.103296>.

34. Kajiyama K, Komamine M, Horiuchi N, Iguchi T, Uyama Y. PMDA Perspective on RWD/RWE Utilization for Regulatory Purposes Including Assessment on the Impacts of Regulatory Actions and Safety Risk of a Drug at Postmarketing Stage. Pharmacoepidemiol Drug Saf. 2024 Sep;33(9):e70007. doi: 10.1002/pds.70007. PMID: 39238427.

35. Carolin Ertl, Theresa Ruf, Dirk Mentzer, Mingzi Kong, Rafaela Kramer, Michael von Bergwelt-Baildon, Marion Subklewe, Dirk Tomsitz, Paolo A. Ascierto, Reinhard Dummer, Helen Gogas, Celeste Lebbé, Georgina V. Long, Grant McArthur, Tomas G. Neilan, Antoni Ribas, Caroline Robert, Dirk Schadendorf, Lisa Zimmer, Thomas Eigentler, Stephan Grabbe, Andrea Forschner, Katharina C. Kähler, Valeria Milani, Claudia Pföhler, Jessica Hassel, Ralf Gutzmer, Carmen Loquai, Bertrand Routy, Andrew J.S. Furness, Christian Blank, Jedd D. Wolchok, Lars E. French, Axel Hauschild, Lucie Heinzerling, The side effect registry immuno-oncology (SERIO) – A tool for systematic analysis of immunotherapy-induced side effects, European Journal of Cancer, Volume 199, 2024, 113505,ISSN 0959-8049, <https://doi.org/10.1016/j.ejca.2023.113505>.

36. Kajiyama K, Ishiguro C, Ando T, Kubota Y, Kinoshita N, Oniyama Y, Iguchi T, Uyama Y. Nested Case-Control Study Utilizing MID-NET® on Thrombocytopenia Associated With Pegfilgrastim in Patients Treated With Antineoplastic Agents. Clin Pharmacol Ther. 2021 Aug;110(2):473-479. doi: 10.1002/cpt.2263. Epub 2021 May 19. PMID: 33866559; PMCID: PMC8359991.

37. Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (EMA).

38. Alex Y. Ge, William B. Feldman, Martin F. Kaiser, Kai Rejeski, Gloria Iacoboni, Gaurav Narula, Jason Yongsheng Chan, Michael J. Dickinson, Aaron S. Kesselheim, Edward R. Scheffer Cliff; Global access to commercial CAR T-cell therapies: a cross-sectional study of health technology assessment across the G20 countries. *Blood* 2026; 147 (14): 1521–1531. doi: <https://doi.org/10.1182/blood.2025030872>

39. Fanconi C, van Buchem M, Hernandez-Boussard T. Natural Language Processing Methods to Identify Oncology Patients at High Risk for Acute Care with Clinical Notes. *AMIA Jt Summits Transl Sci Proc.* 2023 Jun 16;2023:138-147. PMID: 37350895; PMCID: PMC10283145.

40. Sumit Verma, Mike Blecker, Thomas Edwards, Meg Richards, Shreekanth V. Parasuraman, Evan M. Braunstein, Pankit Vachhani; Use of Natural Language Processing to Identify Myeloid/Lymphoid Neoplasm Patients with Fibroblast Growth Factor Receptor 1 Alterations. *Blood* 2024; 144 (Supplement 1): 7900. doi: <https://doi.org/10.1182/blood-2024-199205>

41. Lindvall, Charlotta & Lilley, Elizabeth & Zupanc, Sophia & Chien, Isabel & Udelsman, Brooks & Walling, Anne & Cooper, Zara & Tulskey, James. (2018). Natural Language Processing to Assess End-of-Life Quality Indicators in Cancer Patients Receiving Palliative Surgery. *Journal of Palliative Medicine.* 22. 10.1089/jpm.2018.0326.

42. Cohen, A. B., Rosic, A., Harrison, K., Richey, M., Nemeth, S., Ambwani, G., Miksad, R., Haaland, B., & Jiang, C. (2023). A Natural Language Processing Algorithm to Improve Completeness of ECOG Performance Status in Real-World Data. *Applied Sciences*, 13(10), 6209. <https://doi.org/10.3390/app13106209>

43. Sun VH et al. "Enhancing precision in detecting severe immune-related adverse events: comparative analysis of large language models and ICD codes in patient records" *Journal of Clinical Oncology* DOI: 10.1200/JCO.24.00326

44. <https://www.fda.gov/safety/fdas-sentinel-initiative>.

45. https://www.ema.europa.eu/en/documents/other/scientific-explorer-frequently-asked-questions_en.pdf.

46. Therapeutic Goods Administration, Australian Department of Health, Disability and Ageing (2025), Safe and Responsible Artificial Intelligence in Health Care – Legislation and Regulation Review, Australian Government, <https://www.tga.gov.au/news/news-articles/tga-ai-review-outcomes-report-published>

47. <https://www.health.gov.au/resources/publications/safe-and-responsible-artificial-intelligence-in-health-care-legislation-and-regulation-review-final-report?language=en>

48. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf.

49. National Clinical Quality Registry and Virtual Registry Strategy. Australian Government Department of Health and Aged Care, 2021.

50. Menang O, van Eeuwijk P, Maigetter K, Stergachis A, Burri C. Pharmacovigilance processes in low- and middle-income countries: moving from data collection to data analysis and interpretation. *Ther Adv Drug Saf.* 2025 Jun 11;16:20420986241300006. doi: 10.1177/20420986241300006. PMID: 40510928; PMCID: PMC12159475.

