



Reaching beyond maximum grade: progress and future directions for modernising the assessment and reporting of adverse events in haematological malignancies

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Remarkable improvements in outcomes for many haematological malignancies have been driven primarily by a proliferation of novel therapeutics over the past two decades. Targeted agents, immune and cellular therapies, and combination regimens have adverse event profiles distinct from conventional finite cytotoxic chemotherapies. In 2018, a Commission comprising patient advocates, clinicians, clinical investigators, regulators, biostatisticians, and pharmacists representing a broad range of academic and clinical cancer expertise examined issues of adverse event evaluation in the context of both newer and existing therapies for haematological cancers. The Commission proposed immediate actions and long-term solutions in the current processes in adverse event assessment, patient-reported outcomes in haematological malignancies, toxicities in cellular therapies, long-term toxicity and survivorship in haematological malignancies, issues in regulatory approval from an international perspective, and toxicity reporting in haematological malignancies and the real-world setting. In this follow-up report, the Commission describes progress that has been made in these areas since the initial report.

Introduction: Interim progress since initial publication

Substantial advances and international collaboration in basic science, translational science, and clinical medicine have led to improved disease control and survival outcomes across the spectrum of haematological malignancies over the past several decades. An array of new therapies—many with different mechanisms of action, schedules of administration, and unique toxicities as compared with conventional cytotoxic chemotherapies—are available to treat a variety of haematological cancers. The *Lancet Haematology* Commission on improving adverse event assessment was formed in recognition that in addition to helping patients with blood cancer live longer, helping them live better is a vital complementary goal. There is room for improvement in understanding the true impact of treatment toxicity in patients with haematological malignancies in the current treatment landscape in and outside of clinical trials. Aligning approaches to understanding adverse events with novel therapies, including molecularly targeted agents as well as immune and cellular therapies, and the often prolonged or even indefinite treatment paradigms now prevalent in our field, is a pressing priority. This requires assessing for new and different types of treatment-emergent adverse events, considering their timing and trajectory, and developing common assessment tools to ensure consistency across studies.

This international Commission includes patient advocates, clinicians, clinical investigators, regulators, biostatisticians, pharmacists, and researchers representing a broad range of academic and clinical cancer expertise. The original product of the collaboration,

Beyond Maximum Grade: Modernising the Assessment and Reporting of Adverse Events in Haematological Malignancies, was published in this journal in 2018.¹ The Commission defined six priority areas for improvement and proposed immediate action and long-term solutions in the following areas: (1) current processes in adverse event assessment; (2) incorporation of patient-reported outcomes (PROs) in the assessment of adverse events; (3) toxicities of cellular therapy (now including haematopoietic stem-cell transplantation [HSCT] as well as chimeric antigen receptor [CAR] T-cell therapy); (4) long-term toxicity and survivorship; (5) haematological malignancies and regulatory approval; and (6) toxicity reporting in the real-world setting. Since the publication of the original Commission report, we report on the tangible progress achieved and outline next steps, which require continued broad global stakeholder engagement and collaboration, to further improve toxicity assessment for patients with haematological malignancies over the years to come.

Section 1: Addressing gaps in adverse event assessment

The first section of the Commission described existing processes for defining and grading adverse events, and put forth several new approaches to capture and analyse toxicity data in trials as well as opportunities for improvement in adverse event evaluation during the drug development process. Capture of chronic, delayed, and cumulative adverse events was identified as a gap in adverse event reporting in the context of newer chronically administered therapies used to treat a range of haematological malignancies. Solutions focused on

improving and disseminating novel methods for longitudinal adverse event analysis, as well as innovative design for early phase trials to better characterise toxicity. In the time since publication of the Commission, there has been substantial progress in these areas.

The Toxicity over Time (ToxT) package is a tool that produces analytical and graphical outputs that depict the time profile of adverse events and better displays and quantifies the greater burden of symptomatic adverse events than standard toxicity tables.² This tool reflects the ongoing development and dissemination of longitudinal approaches to toxicity analysis. It has been expanded to include additional longitudinal depictions and incorporation of data from the Patient-Reported Outcomes version of the Common Toxicity Criteria for Adverse Events (PRO-CTCAE).³ Several additional novel analytical approaches to CTCAE data have been developed. For example, the Event Burden Score proposes a single metric for the frequency and severity of multiple adverse events over time, and the Toxicity Index endeavours to account for the burden of multiple cumulative toxicities. These approaches could more accurately reflect patients' experience with specific treatments.^{4,5} Yet, even when investigators use an enhanced adverse event evaluation,⁶ generic incidence and rate-based reports of toxicity prevail in the published literature. The goal to consistently include expanded time-dependent toxicity data remains within reach, and this should also include the addition of granular information on non-progression-related reasons for treatment discontinuation or patients going off study. This approach would more accurately describe treatment-related toxicity.

Challenges remain in the definition of dose-limiting toxicity beyond phase 1 dose escalation studies and in defining optimal approaches to capturing chronic low-grade symptomatic toxicities that might impact treatment tolerability, which clinicians generally under-report in early phase trials.⁷ As oral agents to treat haematological malignancies become increasingly common, improved early phase data on tolerability can be useful to inform selection of optimal dose. Since the previous publication, examples of adaptive phase 1 designs that inform optimal dosing have been implemented in some haematology trials. For example, the MPN-RC 118 trial (NCT03895112) employed a modified toxicity probability interval design coupled with expansion cohorts at two dose levels to further evaluate tolerability and response signals.⁸ Investigators are considering how best to incorporate PRO reporting into early phase trials despite the challenges.⁹ The feasibility of electronic PRO-CTCAE has been reported in a phase 1 trial.¹⁰ Early efforts have coupled PRO pharmacokinetic information to explore the relationship between drug exposure and safety outcomes.^{10,11}

Better characterisation of adverse events reflects the accomplishments of the Commission's short-term goals.

Innovative approaches to longitudinal analysis of toxicity and design of early phase trials have led to incremental progress. There remains a lack of consensus on the optimal analytical strategies for the evaluation of toxicity data. Opportunities exist for implementing standard techniques for longitudinal toxicity analysis. Modernising early phase drug development to include a more comprehensive toxicity evaluation will benefit patients and drug development.

Section 2: Incorporating PROs in adverse event evaluation

While the first section of the Commission addressed shortcomings of conventional toxicity analysis and potential solutions, the second section addressed the importance of including the patient perspective in toxicity assessment via the inclusion of PROs. In the past 3 years, several important activities occurred to raise awareness of the value of PROs in cancer clinical trials. International consensus groups produced best practices for the incorporation of PROs into clinical trial protocols¹² and the analysis of PROs in randomised controlled trials.¹³ Practical considerations were published on how to include patients and patient advocates in the choice and development of patient-reported outcome measures.¹⁴ New insight into the presentation of PRO data helped refine graphical display formats¹⁵ and the US Food and Drug Administration (FDA) piloted an online platform to provide PRO symptom data from specific clinical trials for patients and their health-care providers to use alongside the safety data from the prescribing information (drug label).¹⁶ The Patient-Reported Outcomes Tools: Engaged Users and Stakeholders (PROTEUS) Consortium developed a website to promote tools and resources to optimise the rigorous assessment of PROs in cancer clinical trials and facilitate the use of those outcomes by patients, clinicians, and decisions makers.¹⁷ Furthermore, a multistakeholder working group was convened and proposed a definition of "tolerability" related to treatment on clinical trials that includes ability and desire to receive ongoing therapy from a patient perspective.¹⁸

Efforts are underway to incorporate PRO and wearable device data into current clinical safety and treatment information to form a more holistic understanding of the tolerability of an anticancer treatment in clinical trials (figure 1). The US National Cancer Institute launched a consortium of investigators to analyse both clinician-reported adverse events and patient-reported symptomatic adverse events using the PRO-CTCAE. These investigators are developing approaches and methods for characterising tolerability of cancer treatment by defining the role and analysis of PRO-CTCAE data in determining tolerability,^{19,20} analysing baseline factors which might predict the development of adverse events, and exploring age-related and functional factors which affect treatment discontinuation and hospitalisation.

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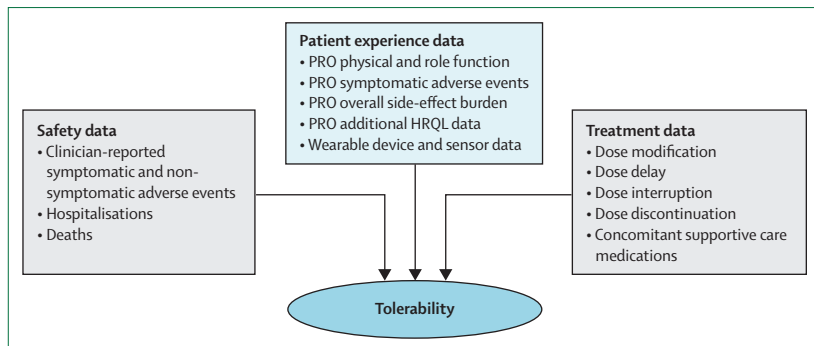


Figure 1: Elements of understanding treatment tolerability

Comprehensive, accurate, and patient-centered evaluation of treatment tolerability involves integration of patient experience data along with safety data and treatment data. HRQL=health-related quality of life. PRO=patient-reported outcome.

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See Online for appendix

The FDA released a draft guidance for industry providing recommendations for collection of a core set of PROs in cancer trials to better characterise symptoms, adverse events, and functional outcomes.²¹ In addition to opportunities for collection within clinical trials, PROs are increasingly incorporated into routine clinical practice. Studies in the clinical care setting have demonstrated patient compliance with electronic reporting, improved symptom control, reduced emergency room visits, and even overall survival benefit in some selected settings.^{22–24} Even with the proliferation of electronic PRO (ePRO) capture, patients might need flexibility in the type of modality for PRO reporting.²⁵ Improved use of ePRO in routine care holds promise to generate a rich stream of structured real-world data that could help advance the goal of a true learning health-care system. Involving patient advocates in the development, selection, and implementation of meaningful PROs for routine care as well as trials will be crucial.

Ultimately, the goal of incorporating PROs into cancer clinical trials and routine practice is to better understand the patient experience of both benefits and harms of anticancer treatments, improve the ability of clinicians to communicate to patients how they might feel and function while on therapy, and discover ways to improve patient outcomes and the treatment experience for patients with haematological malignancies.²⁶

Section 3: Toxicities in cellular therapies: HSCT and CAR T-cell therapy

The preceding sections have covered advances in the assessment of adverse events and incorporation of PROs in haematology and oncology trials. This section will focus more specifically on the challenges of toxicity assessment unique to haematological cellular therapies. Currently available cellular therapies for the treatment of haematological malignancies include HSCT and CAR T-cell therapy as well as donor-derived expanded antiviral T cells. While HSCT has been practiced for over four decades, CAR T-cell therapy is a more recent

therapeutic advance and has expanded in use substantially since the original publication of the Commission.^{27,28} These therapies can lead to long-term remissions and even cure in a proportion of patients, but they are associated with acute, chronic, and late adverse events as described in figure 2. Newer treatments such as natural killer cell therapies are also under clinical investigation²⁹ and might have unique adverse events. There is a need to gain a comprehensive understanding of common and unique adverse events associated with these therapies and to come to a consensus on definitions and severity grading to harmonise data reporting. Additionally, as our understanding of these specific therapies has improved, there is a need to identify expected adverse events as treatment class effects, to reduce the unnecessary burden of data capture and reporting within clinical trials.

Since our last publication, consensus guidelines were developed defining unique acute adverse events associated with CAR T-cell therapy—cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.³⁰ These are now widely incorporated in trial protocols and real-world studies. New data are emerging on other adverse events with CAR T-cell therapy, including risk of bleeding,³¹ which can be driven by a consumptive coagulopathy in some patients, as well as cytopenias, and infections that can continue even months after treatment.^{32,33} Studies describing these effects have used different thresholds to define cytopenias, bleeding complications, and infections. A consensus on definitions of these important adverse events is needed to enable comparison, uniform reporting, and management. For example, uniform guidelines for infectious disease prophylaxis will enable an evidence-based approach to their management. As CAR T-cell therapy is a relatively new therapeutic advance, longer-term adverse events, including delayed neurological or cognitive effects and organ toxicity also need to be evaluated. Late effects, including long-term immunological sequelae, risk of second cancers, and other as yet unknown effects need to be carefully captured. Thorough patient preference studies are required to assess patients' views on difficult trade-offs between clinical effectiveness and toxicity impact of CAR T-cell therapies, particularly in situations where benefit appears less robust. Patients undergoing CAR T-cell therapy require a follow-up of 15 years to allow identification of serious late effects.³⁴ As data emerge, there will be a corresponding requirement for a consensus on these late effects to ensure uniform data capture and analysis. An important tool to allow tracking of long-term outcomes of CAR T-cell therapy is a collaboration between the Center for International Blood and Marrow Transplant Research (CIBMTR) and the various manufacturers of FDA-approved CAR T-cell products to create the Cellular Immunotherapy Data Resource (CIDR).³⁵ Following the model CIBMTR

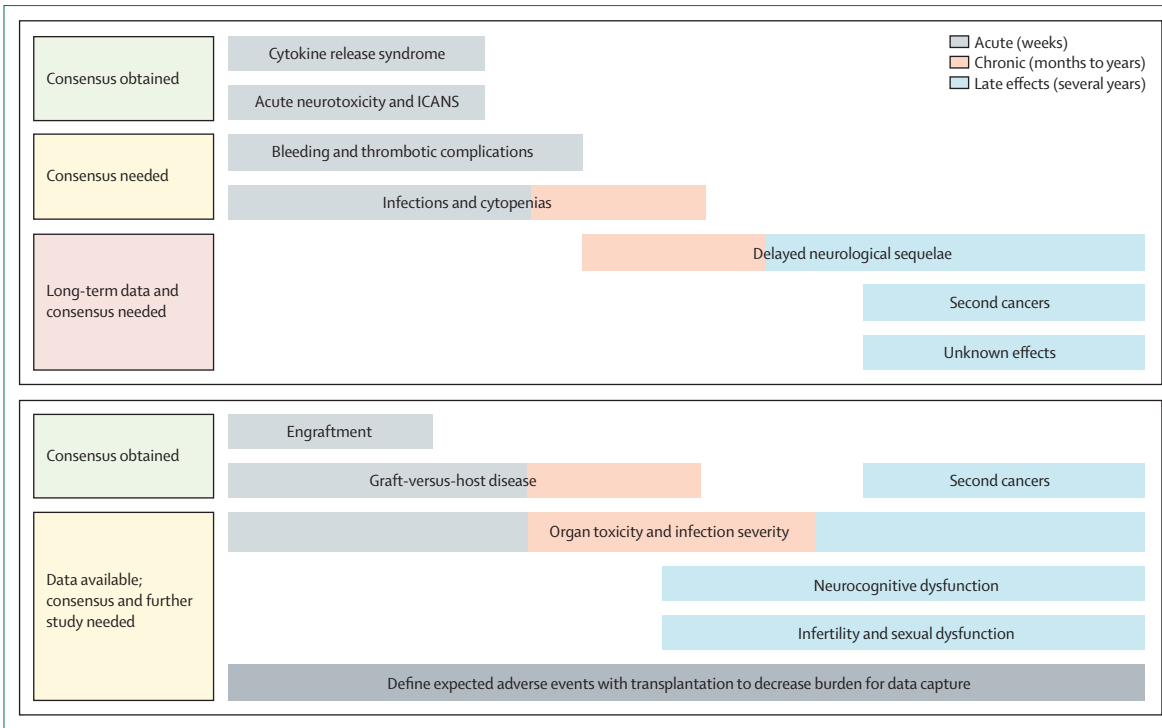


Figure 2: Acute, chronic, and late adverse events following chimeric antigen receptor T-cell therapy and haematopoietic stem-cell transplantation
 Adverse events are categorised by whether reasonable consensus exists on evaluating and documenting these adverse events or whether further study and consensus are needed. ICANS=immune effector cell-associated neurotoxicity syndrome.

established for HSCT, beginning in 1972, longitudinal clinical data on patients receiving CAR T cells is being reported to the CIDR. In addition to providing 15-year real-world safety data to the FDA, the data are being made available for clinical investigations. As of the end of 2020, data from more than 3488 patients had been entered into the database. A similar effort is in progress in Europe by the European Society for Blood and Marrow Transplantation (EBMT).³⁶ These data will be important resources to the scientific community for research.

HSCT is an established field, although novel approaches for graft-versus-host disease prophylaxis as well as cellular graft engineering are emerging with the aim of reducing adverse events and improving therapeutic efficacy.³⁷ Engraftment or immune reconstitution and graft-versus-host disease with current approaches have been well studied and defined.³⁸ Data on major organ adverse events and infections are widely available from different trials, institutional studies, and registries, although consensus on aggregate reporting to identify the overall severity of complications is still needed. As patients can experience multiple adverse events with transplantation, there is a critical need to define expected adverse events, including severity and duration, with each transplantation approach. This will reduce the burden of data capture and toxicity reporting for clinical trials of transplantation strategies and allow identification of unique and newer toxicity signals. In the

long term, the focus should be on developing automated approaches that can recognise data routinely captured in the electronic health record as “expected” toxicity data post-HSCT or CAR T-cell therapy, or highlight provider attention to unexpected, unique, and potentially relevant adverse events.

The effort of defining expected adverse events with transplantation and CAR T-cell therapy will be the main focus of members of this Commission with respect to the next 2–3 years. We plan to convene a consensus panel of clinical experts and informaticians in various fields of transplantation and cellular therapy. Individual patient-level data are available from several large clinical studies and registries of transplantation and cellular therapy and can be interrogated to systematically identify expected adverse events with each regimen and transplant type. For CAR T-cell therapy, developing a consensus on definitions of cytopenias—taking into account duration after CAR T-cell therapy, cell lines involved, need for transfusion or growth factor support, and resulting complications—will be the second focus area of this group. Using these definitions and large databases of real-world data, the goal is to provide guidance on routine capture of adverse events in the medical record, develop electronic modes of sharing these data to minimise reporting burdens, and conduct analyses to identify predisposing factors and prognostic significance for specific adverse events.

Section 4: Long-term toxicity and survivorship in haematological malignancies

The previous section addressed unique toxicities of cellular therapies, including unknowns regarding late effects of newer treatments such as CAR T-cell therapy, underscoring the importance of long-term follow-up for survivors of haematological malignancies. Cumulative and late toxicities in survivors of haematological malignancies such as infertility and second malignancies have been well described in retrospective cohorts, particularly for survivors of Hodgkin lymphoma, following use of conventional therapies such as chemotherapeutic agents and radiotherapy.^{39,40} Nevertheless, the surveillance for, and management of, long-term side-effects of established, as well as of new, targeted biological and cellular therapies in routine clinical practice remains inconsistent, inadequate, or absent for the vast majority of survivors of haematological malignancy.¹

In the original Commission, two areas of unmet needs were highlighted, and, encouragingly, some progress was seen in both high priority areas: (1) infrastructure to identify late complications of haematological malignancies and their treatments, and (2) health-care delivery to survivors. Given the inherent limitations of clinical trials, including highly selected patient groups and a focus on short-term safety follow-up, the establishment of longer-term post-marketing surveillance or registries is vital for identification of late complications, which can inform risk-benefit assessments for decisions regarding treatment protocols. Previously identified solutions in the short term include the development of infrastructure to collect data for adult survivors of haematological malignancies, such as longitudinal patient cohorts or prospective population-based registries. In several countries, such quality-of-care registries are now established and increasingly used in haematology to evaluate long-term drug safety through linkage between registrations of drug use and patient care to identify adverse events.⁴¹ In HSCT, as addressed in the previous section, the existence of multiple large, international registries that have incorporated PRO assessment have

provided a better picture of the long-term clinical outcomes and quality of life of survivors. In Australia, the government commissioned the National Strategic Action Plan for Blood Cancer.⁴² The plan highlighted efforts to increase data linkage and scope of the separate disease registries for bone marrow transplantation, leukaemia and lymphoma, and other haematological diseases. Specifically, the National Clinical Quality Registry Strategy seeks to improve the value and sustainability of a range of clinical registries. Similar registries in broader populations offer important possibilities for comparison and benchmarking.^{43,44}

In the longer term, systems must be implemented to ensure that potential unexpected long-term adverse events are identified and investigated through medical record data or directly through patient reports (figure 3). Ideally, such systems would also capture a broader range of adverse outcomes, including quality of life and psychosocial issues, employment, and financial burden. In this regard, adolescent and young adult (AYA) cancer survivors (ages 15–39 years) have been identified as especially vulnerable, reporting worse psychosocial functioning than older age groups, and experiencing more financial hardships.⁴⁵ The National Comprehensive Cancer Network recently published clinical practice guidelines of supportive care specifically for AYA cancer patients including aspects on how to improve survivorship care and outcomes in this group,⁴⁶ highlighting an increasingly recognised need for survivorship care to be age-adapted. In addition, the Lymphoma Research Foundation assembled a workshop addressing unique issues of the AYA population.⁴⁷ From a patient perspective, the widespread use of social media and digital information exchange could offer new possibilities for identification of and intervention for survivorship issues, especially for younger patients.

Regarding health-care delivery to survivors of haematological malignancies, survivorship care plans have been recognised as a means to empower survivors and promote adherence to guideline-based survivorship care. However, results of trials striving to evaluate their effectiveness have shown mixed results on health outcomes and PROs, and interpretation is sometimes hampered by low adherence.^{48–50} Thus, more efforts are needed to optimise the design and communication of survivorship care plans to maximise accessibility and adherence and to determine the benefit in routine care.⁵¹ In the wake of the COVID-19 pandemic, broader adoption of digital health care and telemedicine has the potential to improve access to survivorship care plans and tele-survivorship clinics, and thereby hopefully to increase quality and benefit of survivorship care.⁵² Looking ahead, it is reassuring to note that large funding bodies such as the US National Institutes of Health have launched calls for cancer survivorship research, specifically addressing knowledge and prevention of late-emerging morbidity from cancer therapy.⁵³ Additionally, cancer care, treatment,

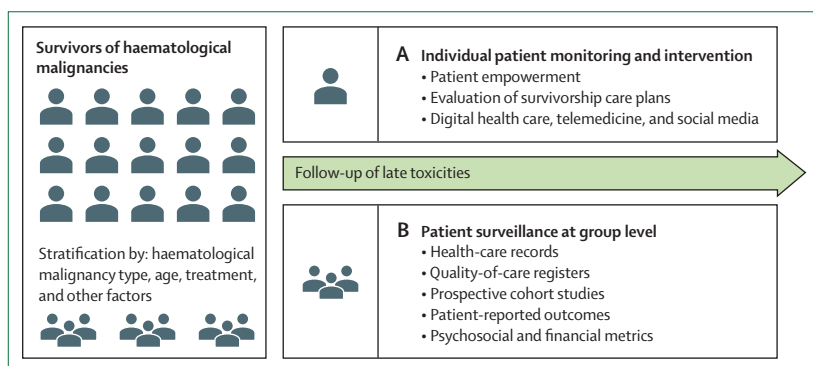


Figure 3: Evaluating late toxicities among patients with haematological malignancies Highlighting the importance of (A) individual patient care and intervention, and (B) methods for quantifying the impact of late toxicity in patients with haematological malignancies.

and quality of life represents one of five big mission areas in the Horizon Europe programme launched in 2021 by the EU.⁵⁴ The European Code of Cancer Practice has also prioritised assessment of long-term effects on survivors and their consequences on survivor care.⁵⁵ Expanded funding and novel, large-scale approaches that leverage digital technology hold tremendous promise for improving survivorship care of patients with haematological malignancies in the years to come.

Section 5: Haematological malignancies and regulatory approval

In addition to covering challenges in adverse event analysis, incorporation of PROs in trials for haematological malignancies, and unique challenges in toxicity reporting in cellular therapies for haematological malignancies, the initial Commission addressed challenges in toxicity reporting from the regulatory perspective. Here, we address progress in the priority areas for improvement in toxicity reporting and regulatory approval.

Simplifying and digitising the submission of all possible adverse event reports were identified as immediate-action priority areas. The present complexity for investigators and patients of the different systems might discourage reporting and result in an underestimate of serious adverse events. In February, 2021, the FDA publicly announced that it is close to accepting investigational new drug safety reports in electronic format for submission to the FDA Adverse Event Reporting System. In preparation, the FDA has issued several guidance documents.^{56–58} In the EU, there are ongoing efforts to simplify the reporting system for adverse events. Specifically, the Clinical Trials Information System (CTIS) will connect with EudraVigilance. This will include an Annual Safety Report repository which will facilitate safety assessments centrally at EU level. It is hoped that the CTIS system will improve transparency of clinical trials and allow more frequent evaluations of ongoing trials. The EudraVigilance system accepts electronic submissions and includes a web-based reporting form for organisations that do not have their own IT systems to create electronic submissions themselves. Learning and face-to-face training on EudraVigilance are available for investigators to encourage its broad use.⁵⁹

Developing better systems for collection and analysis of data obtained from the post-marketing and non-trial setting was a second immediate-action priority area. Towards an effort at modernisation of post-market pharmacovigilance initiatives, the FDA publicly posted a draft of the *Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff*, providing context and a general overview of the agency's approach for timely post-marketing safety analyses of drugs and biological products.⁶⁰ The FDA's Center for Drug Evaluation and Research (CDER) also established the Drug Risk Management Board in January, 2020 as a cross-disciplinary team responsible for addressing,

responding to, and communicating information about major safety issues. In April, 2020, the CDER launched the Newly Identified Safety Signal process to establish a standardised, interdisciplinary approach to systematically identify, evaluate, and resolve both clinical and quality-related safety signals.

In the EU, the Med Safety app is being deployed internationally to boost both the quantity and quality of reporting.⁶¹ The app allows health-care professionals and, if desired, patients to report suspected adverse drug reactions directly to the national centre and receive immediate acknowledgment of the submitted report. As the app uses the International Council for Harmonisation E2B(R2) messaging standard, the individual case safety reports can be transmitted directly to a national database that processes such standard messages.

A long-term priority area identified was to incorporate real-world evidence to inform safety evaluation. The FDA released the Sentinel System Five-Year Strategy 2019–2023,⁶² to expand the Sentinel System's operational foundation, augment the System's safety analysis capabilities and signal detection, and leverage the System to accelerate broader use of real-world data for real-world evidence generation. The European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) set up a joint task force to describe the big data landscape from a regulatory perspective and identify practical steps for the European medicines regulatory network to make best use of big data in support of innovation and public health in the EU. One of the priorities of the HMA–EMA joint big data task force is to deliver a sustainable platform to access and analyse health-care data from across the EU (Data Analysis and Real-World Interrogation Network; DARWIN EU).

Section 6: Toxicity reporting in haematological malignancies and the real-world setting

Many of the previous sections have focused on improving adverse event assessment for research or regulatory purposes; nonetheless, the ultimate aim of this *Lancet Haematology* Commission is to improve the usefulness of adverse event reporting for patients receiving treatment in the real world. This section discusses harnessing real-world data to better understand adverse events occurring in patients treated outside of clinical trials. The interest in use of real-world data in medical research and clinical care has grown substantially since this Commission was launched in 2018, and will continue to grow. Real-world data have been used to establish benchmarks for observations from trials of novel therapies and confirm efficacy of new therapies in a real-world setting. For example, the results of a single-arm trial of tisagenlecleucel (a type of CAR T-cell therapy) for relapsed or refractory lymphoma were interpreted in the context of data on outcomes of similar patients treated with available therapies. Later, the efficacy and safety of tisagenlecleucel in this population was confirmed in an

extensive evaluation of patients treated in the post-marketing setting.^{63,64} More importantly, real-world data have shown the performance of therapies in excluded subgroups including older adults and frail patients.⁶⁴ This emphasises the need for infrastructure outside of clinical trials enabling real-time safety reporting, although it could take up to several years to accumulate sufficient data to detect substantial deviations from trials results.⁶⁵ Due to the number of new drugs in development and the increasingly smaller patient subgroups generated by more refined disease classifications across haematological malignancies, real-world data are expected to play a greater role in future drug development as supplementary data to single-arm trials or trials with short follow-up.⁶⁶ Toxicity assessments using real-world data remain challenging due to the information bias arising from inconsistent recording of adverse events, since adverse events in routine care might be reported less frequently and less quantitatively than on a trial, making it difficult to identify on detailed, retrospective medical record review. Additionally, there might be limited spontaneous adverse event reporting by patients.

For WEB-RADR see
<https://web-radr.eu/>

Several recent initiatives can enhance the use of real-world data for adverse event reporting. The FDA Sentinel System, mentioned in the previous section, will increase its focus on real-world data as part of the current Five-Year Strategy.⁶² This will include a greater use of electronic health records as well as data science technologies with natural language processing to extract unstructured electronic data more efficiently. CancerLinQ, a health technology platform developed and implemented by the American Society of Clinical Oncology (ASCO), collects and analyses cancer care data from electronic health records across the USA. Results are expected to generate large amounts of real-world toxicity data for clinical practice and research. Today's electronic health record ecosystem, with its lack of interoperability and data standardisation, has limited CancerLinQ and similar initiatives in creating informative large data sets for clinical decision support and research. However, the wider adoption of recently developed oncology-specific data standards, such as the Health Level 7 (HL7) Minimal Common Oncology Data Elements (mCODE) standard created by ASCO and other stakeholders, should improve interoperability and mitigate some of these challenges.⁶⁷ Additionally, commercially driven activities partner directly with patients to consolidate their medical records into a single, secure electronic system allowing them to better navigate their health care, while simultaneously facilitating the sharing of de-identified data with researchers.⁶⁸

For CancerLinQ see
<https://www.cancerlinq.org/>

Improving abstraction from electronic health records will not be sufficient to fully leverage the potential of real-world data for adverse event reporting. Many patients are willing to directly report adverse events on a regular basis through standardised tools such as the PRO-CTCAE.³ The EU passed pharmacovigilance legislation in 2012 (Regulation 1027/2012 and Directive 2012/26/EU)

requiring all EU Member States to develop systems to promote direct adverse event reporting from patients, although the structure of these portals might have reduced spontaneous, unsolicited reporting.⁶⁹ To reduce the gap in adverse event reporting by patients, multistakeholder initiatives such as the EU Innovative Medicines Initiative's Recognizing Adverse Drug Reactions (WEB-RADR) have developed mobile apps where patients can report adverse events and receive up-to-date safety information in return. Whether technologies that are based on information from social media produce reliable data comparable to established pharmacovigilance mechanisms remains unclear.⁷⁰

Independent patient network organisations are generating reporting systems to collect data directly from patients. For example, the Acute Leukemia Advocates Network created the Global Quality of Life Survey⁷¹ in which patients directly respond to questions around health-related quality of life and other PROs. Myeloma Patients Europe has set up an Evidence Generation Unit to generate evidence on preferences and needs of patients living with multiple myeloma and amyloidosis. An ePRO platform for Waldenström macroglobulinaemia has collected PRO data on 453 patients with this condition in 19 countries and highlights that ePRO tools are capable of collecting real-world patient-provided data on a rare cancer.⁷² The Workgroup of European Cancer Patient Advocacy Networks has deployed specific training for patient advocates to develop methodological and operational capacity in evidence generation.⁷³ All resources inviting direct patient adverse event data input are subject to responder bias and might not necessarily provide a complete picture of the overall patient adverse event experience, although this caveat is accepted with clinician-reported adverse events. Despite this limitation, registries with direct patient data input are powerful resources for population-based assessments of adverse events and long-term follow-up. Standardisation of data elements, exposure measures, adverse event grading, and data reporting will be necessary for these resources to achieve their full potential.⁷⁴

Although considerable progress in the use of real-world data in clinical research has been made since the first Commission work in 2018, various key challenges remain to be addressed. These include infrastructure for adverse event reporting to electronic health records and registries, more efficient data abstraction, increased focus on patient involvement, and agreement on a common framework for toxicity evaluations in real-world data studies.

Continued forward progress: targets and timelines for ongoing improvement in toxicity assessment across the haematological malignancies

Treatment advances as a result of scientific discovery with several promising new drugs and immune therapies have led to unparalleled improvements in outcomes across the

	Concern	Immediate-action solutions (1–5 years)	Long-term solutions (more than 5 years)
Addressing gaps in adverse event assessment (section 1)	Methods for better describing chronic, delayed, and cumulative adverse events are emerging but uptake remains limited	<ul style="list-style-type: none"> Continued uptake of adaptive designs for early phase trials Consensus on optimal methods for longitudinal adverse event analysis Record more granular information for study discontinuation on haematological malignancy trials (when not progression or death) 	<ul style="list-style-type: none"> Systematic use of consensus-based metrics and graphical representations of adverse events in publications and drug labels
Incorporating PROs in adverse event evaluation (section 2)	PROs are available for assessing symptomatic toxicities and functional outcomes but are heterogeneously deployed with varying levels of rigour in haematological malignancy clinical trials	<ul style="list-style-type: none"> Promote widespread adoption of international standards for incorporation and analysis of PROs into clinical trials^{22,23} Continue efforts to advance rigorous electronic capture of PROs Support longitudinal approaches to analyse symptomatic toxicity and functional data from PRO-CTCAE and other PRO tools to better characterise treatment tolerability Involve patient advocates in the development, selection, and implementation of PRO-CTCAE and PROMs 	<ul style="list-style-type: none"> Identify consensus analytical approaches to convey longitudinal PRO data Continue ongoing efforts to standardise approaches across cancer trials internationally
Toxicities in cellular therapies: HSCT and CAR T-cell therapy (section 3)	Cumbersome reporting of the myriad of expected adverse events in the HSCT and CAR T-cell therapy setting is a barrier to performing clinical trials	<ul style="list-style-type: none"> Develop consensus on “expected” adverse events post-HSCT based on registry and trial data and develop more lean adverse event reporting approaches Develop a consensus on definitions of short-term and long-term cytopenias post-CAR T-cell therapy and resulting complications (infections, bleeding) 	<ul style="list-style-type: none"> Develop automated approaches that can recognise data routinely captured in the electronic health record as “expected” toxicity data post-HSCT or CART-cell therapy, or highlight provider attention to unexpected, unique, and potentially relevant adverse events
Long-term toxicity and survivorship in haematological malignancies (section 4)	The description and management of cumulative and late toxicities in survivors of haematological malignancy remains inconsistent, inadequate, or absent	<ul style="list-style-type: none"> Develop and expand infrastructure to collect data for adult survivors of haematological malignancies, such as longitudinal patient cohorts and registries (eg, Nordic quality of care registries, the LEO cohort, the REALYSA study), considering differences by age and malignancy subtype Identify barriers to the standardised implementation of survivorship care plans and broaden evaluation of outcomes Promote the ongoing growth of funding opportunities for high-quality survivorship research, prioritising the unique and understudied population of AYAs 	<ul style="list-style-type: none"> Link PROs and late complications of haematological malignancies in electronic medical records Increase availability and evaluation of multidisciplinary survivorship clinics harnessing digital health care and telemedicine
Haematological malignancies and regulatory approval (section 5)	Meaningful adverse events might be under-reported and obscured by uninformative reporting	<ul style="list-style-type: none"> Implement and advance electronic adverse event reporting and linkage Continue to optimise systems for collection of quality safety data 	<ul style="list-style-type: none"> Continue efforts to incorporate use of real-world data for regulatory decision making
Toxicity reporting in haematological malignancies in the real-world setting (section 6)	Granular and complete data on toxicities affecting patients with haematological malignancies in routine clinical practice are difficult to capture and characterised by challenges with interoperability and analytical approaches	<ul style="list-style-type: none"> Optimise collection of electronic health record data through initiatives like the FDA Sentinel System and CancerLinQ, including data science initiatives focusing on natural language processing Improve interoperability of electronic health records and utilise data standards such as mCODE that enable aggregation of data across geographies Improve and expand reporting systems for patient self-reporting of adverse events Work towards a common understanding of exposure and toxicity assessments and analytical methodology in real-world data studies Engage patient organisations in real-world evidence generation and practical toxicity self-reporting 	<ul style="list-style-type: none"> Implement learnings from real-world data as decision support tools in clinical care to ensure individual patients are offered treatments with the most optimal efficacy, safety, and tolerability profiles Create large-scale real-world data sets that include clinical and omics data for advanced, multidimensional, and dynamic analytics to identify risk of adverse events before they occur and enable pre-emptive measures

AYAs=adolescents and young adults. CAR=chimeric antigen receptor. FDA=US Food and Drug Administration. HSCT=haematopoietic stem-cell transplantation. mCODE=Minimal Common Oncology Data Elements. PRO=patient-reported outcome. PRO-CTCAE=Patient-Reported Outcomes version of the Common Toxicity Criteria for Adverse Events. PROM=patient-reported outcome measure.

Table: Updated summary of targets and timelines for improvements in adverse event assessment in haematological malignancies

range of haematological malignancies. With newer agents and approaches comes the need to identify ways to capture the variety of different adverse events to understand how best to manage patients through therapy and assure that they can maintain high quality of life during and after treatment. In addition to recognising cumulative and late toxicities of conventional cytotoxic chemotherapy that

survivors of haematological malignancies face, we now also appreciate that newer treatments such as targeted therapies and immune and cellular treatments bear unique, sometimes time-dependent and chronic adverse events. Patients live with the challenge of managing not just their cancer but also the side-effects of long-term therapy for their cancer more than ever before.

Search strategy and selection criteria

This Commission follow-up is an international expert consensus policy paper identifying priorities in improving adverse event evaluation across haematological malignancies. As per the original Commission, a systematic search and formal literature review were not part of this effort. Section lead authors and co-authors were selected to represent subject matter expertise across the haematological malignancies and in toxicity evaluation, and to reflect diverse geography and perspectives. The literature cited in this Commission follow-up was selected by each section lead and their co-authors as the most topically relevant, critical, and current information pertinent to the Commission focus. References received approval from all authors of the paper.

This Commission was assembled as an international group of experts encompassing patient advocates, clinicians, clinical researchers, regulators, statisticians, and methodologists who are focused on addressing challenges in toxicity assessment and reporting in haematological malignancies. In 2018, this group set forth an outline of the priority areas of adverse event analysis, incorporating PROs, toxicities of cellular therapies, toxicities in survivors, challenges in toxicity assessment for regulatory approval, and adverse event evaluation in the real-world setting. In this follow-up, tangible progress has been identified in the proposed immediate-action and the long-term solutions in each of these areas (see appendix pp 3–5 for examples of progress since the original Commission publication). However, in each of these broad domains, there remains work to be done. This paper represents a call to action for leaders of professional bodies in haematology, in international regulatory agencies, and in drug development in both industry and academia—those represented in our authorship and those beyond—to spearhead changes needed to bring toxicity assessment in step with therapeutics for haematological malignancies and most importantly, patients battling these diseases. Improvement in the prospective collection of adverse events by standardising the definitions, capturing patients' own reports, and identifying novel ways to capture adverse events through real-world data, as well as investment in reporting more than just the most severe, acute toxicity, remain essential. The priorities of the Commission and updated roadmap have been redefined and updated for improving toxicity assessment in haematological malignancies in the imminent years to come (see the table). Prioritising and advancing the many facets of toxicity assessment is crucial for comprehensive, accurate, and patient-focused reporting that meaningfully informs the care of patients.

Contributors

GT was the lead author of the Commission and participated in the writing, editing, and review of all sections of this report. TMH was a senior author who edited and reviewed all sections and participated in the writing of the

introduction, conclusion, and summary. LoMM and JFS reviewed in detail the entire manuscript and provided detailed editorial and content feedback on all sections. FC, JaG, JoG, MH, TMH YLK, KM, LoMM, PS, and JFS reviewed the entire manuscript for cohesion. ACD led the writing of section 1 (correspondence to dueck.amylou@mayo.edu). LoMM, RFL, SPI, and GT participated in the writing and editing of section 1. LoMM led the writing of section 2 (correspondence to minasilo@mail.nih.gov). VB, ACD, PGK, and GV participated in the writing and editing of section 2. SS led the writing of section 3 (correspondence to surbhi.sidana@stanford.edu). MH, CJ, AK, M-VM, MM, and JRW participated in the writing and editing of section 3. KES led the writing of section 4 (correspondence to karin.ekstrom.smedby@ki.se). LiMM, MJM, and FvL participated in the writing and editing of section 4. NG led the writing of section 5 (correspondence to nicole.gormley@fda.hhs.gov). RADC, CG, NE, SN, AN, KR, and KT participated in the writing and editing of section 5. TCE-G led the writing of section 6 (correspondence to tarec.galaly@gmail.com). JaG, RSM, PM, LN, and DV reviewed and edited section 6. For full correspondence details of individual section leads, please see the appendix (pp 1–2).

Declaration of interests

CAJ reports personal fees from Kite/Gilead, Novartis, BMS/Celgene, Precision Biosciences, Nkarta, AbbVie, Bluebird Bio, Epizyme, Lonza, and Ipsen, outside the submitted work. DV reports personal fees from AbbVie, AstraZeneca, Kite/Gilead, Kyowa Kirin, Sandoz Canada, Nanostring, Immunovaccine, Roche, Celgene, Seattle Genetics, and Lundbeck/Teva; and research funding (to his institution) from AstraZeneca and Roche, outside the submitted work. GV reports personal fees from Roche, Eisai, Novartis, and Seattle Genetics; and grants from Breast Cancer Now, EORTC, Yorkshire Cancer Research, Pfizer, and IQVIA, outside the submitted work. JaG reports grants from Novartis, Pfizer, Bristol-Myers Squibb, Incyte, Takeda, Servier, UCB, Amgen, Roche, Alnylam, Boehringer-Ingelheim, Biomarin, Daiichi Sankyo, Janssen, Sobi, Gilead, and Bayer, outside the submitted work. JFS reports grants, personal fees, non-financial support, and speakers bureau participation for AbbVie and Roche; personal fees and non-financial support from BMS; personal fees from Genentech, Mei Pharma, Morphosys, Sunesis, and Takeda; and grants and personal fees from Janssen, outside the submitted work. JRW reports personal fees from Merck, Celgene, Cidara, ReViral, Shire, Ansun, Janssen, and Behring, outside the submitted work. KM reports grants from Pfizer, outside the submitted work. LN reports honoraria from ADC Therapeutics, Bayer, and Morphosys; grants and honoraria from BMS/Celgene, Epizyme, Genentech, Gilead/Kite, Novartis, Pfizer, Takeda, and TG Therapeutics; and grants from Caribou Biosciences and IGM Biosciences, outside the submitted work. M-VM reports personal fees from Janssen, BMS-Celgene, Takeda, Amgen, Sanofi, Oncopeptides, Adaptive, GSK, AbbVie, Roche, Seattle Genetics, Pfizer, and Regeneron, outside the submitted work. MH reports grants from U24 CA076518 National Cancer Institute and grants from U24 HL138660 National Heart, Lung and Blood Institute, during the conduct of the study; grants from Amgen, Vor BioPharma, Gamida Cell, Medac, Magenta Therapeutics, Astellas, OncoImmune, and Genentech; and consulting fees from AlloVir, outside the submitted work. MJM reports personal fees from Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacia, Janssen, Seattle Genetics, Immunovaccine Technology, and Takeda; consulting advisory roles for Merck, Juno Therapeutics, Teva, and Daiichi Sankyo; research funding from IGM Biosciences; and a consulting advisory role and research funding from Rocket Medical, outside the submitted work. PM reports personal fees from Janssen, Celgene, BMS, AbbVie, Sanofi, and Amgen, outside the submitted work. PS reports research support from Celgene, Amgen, Janssen, and Takeda; and honoraria and serving on advisory boards for Celgene, Janssen, Amgen, Takeda, BMS, and SkylineDx, outside the submitted work. SS reports grants and consulting fees from BMS, Janssen, and Magenta; grants from Allogene; and consulting fees from Oncopeptides, outside the submitted work. TCE-G reports previous employment at Roche and personal fees from AbbVie, outside the submitted work. All other authors declare no competing interests.

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