



Beyond maximum grade: modernising the assessment and reporting of adverse events in haematological malignancies

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Tremendous progress in treatment and outcomes has been achieved across the whole range of haematological malignancies in the past two decades. Although cure rates for aggressive malignancies have increased, nowhere has progress been more impactful than in the management of typically incurable forms of haematological cancer. Population-based data have shown that 5-year survival for patients with chronic myelogenous and chronic lymphocytic leukaemia, indolent B-cell lymphomas, and multiple myeloma has improved markedly. This improvement is a result of substantial changes in disease management strategies in these malignancies. Several haematological malignancies are now chronic diseases that are treated with continuously administered therapies that have unique side-effects over time. In this Commission, an international panel of clinicians, clinical investigators, methodologists, regulators, and patient advocates representing a broad range of academic and clinical cancer expertise examine adverse events in haematological malignancies. The issues pertaining to assessment of adverse events examined here are relevant to a range of malignancies and have been, to date, underexplored in the context of haematology. The aim of this Commission is to improve toxicity assessment in clinical trials in haematological malignancies by critically examining the current process of adverse event assessment, highlighting the need to incorporate patient-reported outcomes, addressing issues unique to stem-cell transplantation and survivorship, appraising challenges in regulatory approval, and evaluating toxicity in real-world patients. We have identified a range of priority issues in these areas and defined potential solutions to challenges associated with adverse event assessment in the current treatment landscape of haematological malignancies.

Introduction: Haematological malignancies and their therapies have changed

The haematological malignancies have been the model for chemotherapy, radiotherapy, molecularly targeted oral drugs, and an array of immunotherapies (table 1). These treatment modalities are incorporated into different disease types and result in a variety of adverse events—some well characterised, others less well understood. New treatments have changed the natural history of many of these diseases. Chronic or continuous therapy given for years or indefinitely is now the standard for some haematological malignancies. Even for haematological malignancies treated with shorter-term, conventional cytotoxic drugs with curative intent, there is increasing recognition of late-term and long-term adverse events that affect patients for years and decades after treatment. Our understanding of the patient's experience of treatment toxicity has changed substantially.

Lymphoma treatment is an exemplar of changing therapies in haematological malignancies, and the increasing use of new, continuously administered drugs. The proliferation of molecularly targeted drugs and immunotherapy to treat lymphoma shows the treatment shift seen across many haematological malignancies (figure 1). Indolent forms of lymphoproliferative disorders, such as chronic lymphocytic leukaemia and follicular lymphoma, have long been treated as chronic diseases, but the availability of novel therapeutics has shifted disease management strategies. Whereas historically, treatment was largely episodic and finite (ie, a set number

of cycles of chemotherapy), many patients now receive continuous oral therapy for relapsed disease¹ or even first-line therapy.² Patients taking ibrutinib, approved by the US Food and Drug Administration (FDA) as first-line therapy for chronic lymphocytic leukaemia, have a median progression-free survival in excess of 3 years, and both idelalisib³ and venetoclax⁴ (each approved for relapsed chronic lymphocytic leukaemia) share the model of continuous oral therapy, in which treatments are administered until progression or intolerance. Follicular lymphoma is also shifting towards a chronic therapy model, with maintenance intravenous monoclonal antibodies (rituximab or obinutuzumab^{5,6}), or with continuous oral drugs. Idelalisib is FDA-approved in the USA for relapsed follicular lymphoma,⁷ ibrutinib is approved for Waldenström macroglobulinemia,⁸ and a host of other oral, continuously administered drugs are in active development internationally.

Among lymphomas treated with conventional cytotoxic drugs in the short-term for curative intent, a deeper recognition of late-term adverse events has led to an evolution in treatment. In Hodgkin's lymphoma, limited-stage disease was previously managed with high-dose radiation therapy, and advanced disease was treated with a combination of chemotherapy and radiotherapy.^{9,10} The late toxicity of these treatment approaches (eg, secondary malignancies, heart disease, and pulmonary complications) resulted in more treatment-related deaths from complications of survival than deaths from disease. Hodgkin's lymphoma is now managed with de-escalation

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Drugs	
Immunotherapy	
Monoclonal antibodies	
Anti-CD20 antibodies	Rituximab, rituximab and hyaluronidase, ofatumumab, obinutuzumab
Radiolabelled antibodies	Ibritumomab tiuxetan
Antibody-drug conjugate	
Anti-CD30 antibody conjugated to antimitotic monomethyl auristatin E	Brentuximab vedotin
Anti-CD22 antibody conjugated to a calicheamicin-derived cytotoxic moiety	Inotuzumab ozogamicin
Bispecific T-cell engager CD19 and CD3 binding domains	Blinatumomab
CTLA-4 antibody	Ipilimumab
PD-1 antibody	Nivolumab, pembrolizumab
Other antibodies	Lirilumab, atezolizumab, avelumab, durvalumab
Immunomodulating drugs	Lenalidomide, pomalidomide
Chimeric antigen receptor T-cell therapy	Tisagenlecleucel (CTL019), axicabtagene ciloleucel
Cellular therapy	
Virus-specific T cells	Epstein Barr Virus, BK virus, human Herpes virus
Non-specific immunotherapies	
Interferons	Interferon α -2b
Cytokines	Granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor
Interleukins	Interleukin-2
Cancer vaccines	Ongoing development
Molecularly targeted therapy	
B-cell receptor inhibitors	
Bruton's tyrosine kinase inhibitor	Ibrutinib, acalabrutinib
Phosphoinositide 3-kinase inhibitor	Idelalisib, copanlisib
Tyrosine kinase inhibitors	Imatinib, nilotinib, dasatinib, bosutinib, ponatinib
Hypomethylating drugs	5-azacytidine, decitabine
BCL2 inhibitor	Venetoclax
Isocitrate dehydrogenase 2 inhibitors	Enasidenib
FLT3 inhibitors	Midostaurin, sorafenib
mTOR inhibitors	
mTOR type 1 inhibitor	Everolimus

Table 1: Examples of immunotherapy and molecularly targeted therapy now used in the treatment of haematological malignancies

approaches, with fewer cycles of chemotherapy and less radiotherapy than previously, where possible.^{11,12} In non-Hodgkin lymphoma, the addition of rituximab to chemotherapy improved overall survival in patients with diffuse large B-cell lymphoma¹³⁻¹⁵ but introduced unexpected late-term toxicities, such as polyoma virus reactivation.¹⁶

Outcomes for patients with multiple myeloma have improved substantially in the past decade because of the increased use of high-dose therapy and the addition of

thalidomide, bortezomib, and lenalidomide along with improved supportive care measures.^{10,17} Several new drugs have become available in the past 5 years, including pomalidomide, carfilzomib, panobinostat, ixazomib, elotuzumab, and daratumumab. The standard of care is triplet therapy with the advent of these new therapies.¹⁸⁻²⁰ Venetoclax is now a promising targeted therapy for relapsed or refractory t(11;14) multiple myeloma.²¹ Facing a multitude of immunomodulators, targeted drugs, and immunotherapies, the nature of treatment toxicity that patients with multiple myeloma have has changed substantially in the past decade.

Perhaps no haematological malignancy exemplifies the shift in treatment and the resultant difference in toxicity profiles better than chronic myelogenous leukaemia, which is now treated almost exclusively with oral BCR-ABL tyrosine kinase inhibitors. Drugs of this class, initially imatinib, have now been expanded to include dasatinib, nilotinib, bosutinib, radotinib, and ponatinib. These continuously administered drugs have resulted in life expectancy that approximates that of the age-matched normal population.²² Along with improved survival, these drugs introduced a host of novel toxicities and elucidated the importance of adherence with oral therapies. Adherence with imatinib treatment of 90% or less is associated with a 28.5% probability of a major molecular response, whereas the probability is 94% when adherence is more than 90% ($p < 0.001$).²³ Less than 80% adherence to imatinib treatment yielded a very low likelihood of molecular response.²³ Yet only 32.7% of patients with chronic myelogenous leukaemia are highly adherent to therapy. Specific side-effects related to treatment of chronic myelogenous leukaemia had a substantial prognostic effect on the level of intentional non-adherence, and those patients whose side-effects were well managed were more likely to belong to the highly adherent group.^{24,25}

Treatment of myeloid malignancies other than chronic myelogenous leukaemia has also evolved and now includes several continuously administered drugs. Lenalidomide has improved the outcomes of patients with myelodysplastic syndromes and the cytogenetic abnormality del(5q) by giving transfusion independence and improving quality of life.²⁶ Patients with higher-risk myelodysplastic syndromes, who historically lacked effective treatment options, can now take maintenance hypomethylating drugs, allowing some patients to live with the disease as a chronic illness.²⁷ In the acute myeloid leukaemias, oral targeted therapies such as the FLT3 inhibitor midostaurin are being used in addition to conventional cytotoxic induction regimens.²⁸ Enasidenib, an IDH2 inhibitor, is a continuously administered oral monotherapy for relapsed or refractory disease.²⁹

The landscape of haematological malignancies has been changed not only by continuously administered targeted therapies but also by advances in immunotherapy and cellular therapies. Bispecific antibodies such as

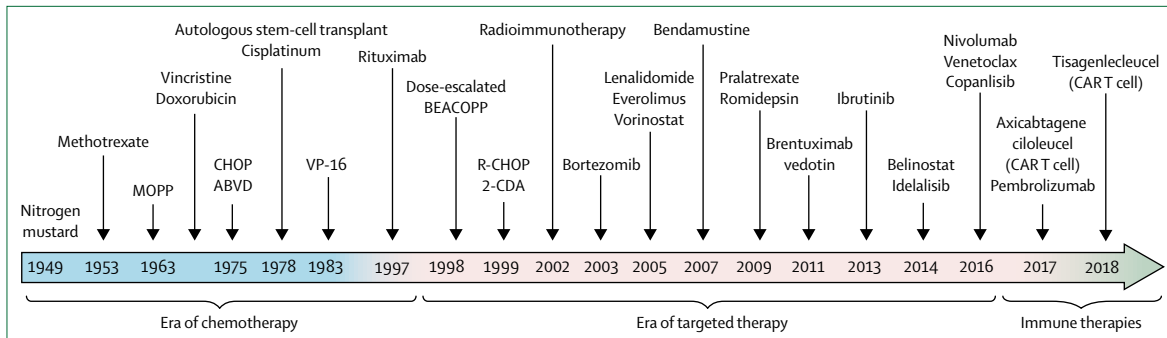


Figure 1: Evolution of therapy in haematological malignancies: lymphoma as an example of shifting treatment strategies

MOPP=mustine, vincristine, procarbazine, and prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. R-CHOP=rituximab plus CHOP. ABVD=adriamycin, bleomycin, vinblastine, dacarbazine. BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone. CAR T cell=chimeric antigen receptor T cell.

blinatumomab for acute lymphocytic leukaemia,³⁰ immune checkpoint inhibitors such as pembrolizumab and nivolumab for Hodgkin's lymphoma,^{31,32} and the advent of chimeric antigen receptors (CAR) T cells³³ for relapsed non-Hodgkin lymphoma, have also brought new risk and new categories of adverse events.

The result of treatment changes across haematological malignancies is that increasing numbers of patients are living with the challenge of managing not just their disease, but also, in some cases, continuous therapies with new, chronic toxic effects. In this Commission, an international expert panel of doctors, clinical investigators, researchers, methodologists, regulators, and patient advocates collaborated to identify and begin to address the challenges of assessing adverse events in clinical trials in this modern era of haematological malignancies. Although several sections of this initiative are relevant to malignancies in general and not just haematological cancers, the aim of this Commission is to highlight the relevance of developing a more comprehensive, accurate, and patient-focused assessment of toxic effects in haematology clinical trials, both in industry-sponsored trials and in investigator-initiated studies. We begin by proposing improvements in the process of adverse event assessment in trials and by emphasising the inclusion of patient-reported outcomes (PROs) in haematology trials. Unique issues pertaining to haemopoietic stem-cell transplantation (HSCT) and late toxic effects in survivors of haematological malignancy will then be explored. Challenges of the assessment in the context of the regulatory approval of new drugs will then be assessed, followed by a discussion on implementation of improved toxicity assessment in real-world, non-study patients treated in routine clinical practice in all parts of the world. In each section, challenges inherent to toxicity assessment will be described and proposed solutions put forth. In the concluding section, we will define actionable targets for improvements in the assessment of adverse events in haematology, with a goal of defining the path forward.

Section 1: Current processes in adverse event assessment: strengths and shortcomings

Numerous challenges and potential solutions to improving assessment of adverse events exist in haematology, and inherent to these are an understanding of the strengths and shortcomings of the approach to toxicity assessment at present. New and often continuously administered therapies for haematological malignancies bring with them a different range of toxicities, including an increasing number of long-term, symptomatic side-effects that challenge the traditional approaches to collecting and communicating drug-related adverse events. In this section we address the existing processes for defining and analysing adverse events and begin to introduce innovations in how to better capture and analyse toxicity data in clinical trials. We also discuss how optimising adverse event assessment could affect the drug development process. Most of this section is deliberately tumour-agnostic, and the challenges and solutions identified here are applicable to a range of cancer clinical trials, but we conclude this section with issues pertaining to adverse event assessment that are unique to haematology.

Processes for standardisation of terminology for adverse events

The initial steps in the development of new drugs require harmonised systems for patient-safety monitoring that can be used internationally. The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is one such system.³⁴ Although the most recent CTCAE (version 5.0) has international acceptance for establishing severity-based adverse event grading, other international systems use Medical Dictionary for Regulatory Activities (MedDRA) terminology to describe adverse events. The purpose of the CTCAE is to provide standards for the description and exchange of safety information of new cancer therapies and treatment modalities in haematology and oncology. It is used to define protocol parameters, such as maximum tolerated dose and dose-limiting toxicity, and

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Panel 1: Definitions of toxicity relative to drug exposure, by drug category

Acute effects

Develop within a short and defined timeframe; can be transient or reversible or persistent.

Chronic effects

Develop over time to be a persistent and unremitting, or intermittent and recurring, series of events, extending past a defined interval such as the first cycle of therapy.

Cumulative effects

Develop and increase with repeated exposures to drug (progressive over time).

Late effects

Result in subclinical or asymptomatic physiological changes that do not result in immediate, intermittent, or short-term adverse clinical events, but rather are manifest over an extended timeframe.

to provide eligibility parameters and guidance for dose modification. The original version of the CTCAE from 1982 included 49 adverse event terms grouped in 18 categories, each with criteria for grading the severity of the adverse event. CTCAE version 3.0 was the first uniform and comprehensive dictionary of adverse event grading criteria for use by all modalities for the treatment of cancer and included criteria relevant to surgical, radiation, and paediatric-based clinical trials. The adoption of MedDRA terminology by the International Conference on Harmonization (ICH), the NCI, industry, and regulatory bodies provided the impetus for the NCI to redesign the CTCAE in 2008 to be harmonised with MedDRA. The most recent version of the CTCAE, from 2017, has 837 terms, updated grading information, and a comprehensive index.

Improving analysis of adverse events: aggregated safety analysis, graphic readouts, and depicting the time profile of adverse events

Precise, consensus definitions of adverse events and their severity are as important as a consensus method of analysing and presenting adverse event data. Existing methods of analysis fall short in describing toxicities of modern therapies for haematological malignancies. Typically, adverse event data are presented in a clinical trial report as a summary table of the high-grade toxicity in any patient during the course of the trial. These tables provide an efficient display of the safety assessment of a drug based on the number and percentage of high-grade events. However, they provide no information on the trajectory of the adverse events, their onset, progression, or cumulative effects, which might substantially affect tolerability.³⁵ In addition to standardising the terminology and grading the effects, it is useful to define adverse effects in relation to timing of drug exposure (panel 1).

Longitudinal graphs of the prevalence of specific adverse events would provide more information about how they arise and whether the effect becomes cumulative or resolves with supportive care, dose modification, or therapy cycle or course. The NCI Web Reporting System, a tool being used in NCI-sponsored early phase clinical trials, facilitates graphical outputs of adverse event information and presents more comprehensive visual output of adverse event data than a conventional maximum grade table (figure 2). A pie chart can be used to illustrate the concept that the specific toxicity frequency is heterogeneous and that common toxicities can be overshadowed by the constellation of other toxicities that among themselves do not show up except when added together. The advantages of following toxicity over time and the limitations in collecting data on chronic toxicity in early-phase trials are illustrated in panels B–D of figure 2. The patients who remain in a study tend to be those who do not have toxicity, and patient attrition from the trial decreasing the number at risk gives the impression that treatment is more tolerable. Graphical displays that include the number at risk are more accurate.

The Toxicity over Time (ToxT) package³⁶ is another tool for producing analytical and graphical outputs that include the time profile of adverse events and an assessment of the burden of chronic, low-grade adverse events. ToxT can be used for longitudinal analyses to depict the timeframe of adverse events in a variety of ways, including bar charts that show incidence and grade of adverse events by cycle, stream plots that show grade of adverse event by cycle, time-to-event analyses (figure 3), and an area-under-the-curve analysis (AUC; figure 4). An AUC approach is particularly relevant to capturing the effect of chronic low-grade toxicity. A patient with a continuous low-grade toxicity, such as continuous grade 2 diarrhoea (four to six stools above baseline daily) should be accounted for because their experience is potentially more substantial than a short-lived, isolated grade 3 toxicity. AUC provides this information in graphical and numerical form (figure 2B; figure 4). Existing methods do not sufficiently capture cumulative dose of drugs by using adverse event data from multiple cycles. These approaches have not yet been integrated prospectively into phase 1 designs but could help identify more tolerable dosing approaches. Other potential approaches to improving toxicity analysis might include preprogrammed algorithms that identify patterns of combined toxicities that portend added risk for severe events or development of syndromes (eg, cerebrovascular events, haemolytic uremic syndrome, cardiovascular events).

Challenges in dose and schedule determination in early-phase haematology trials

Stepwise approaches streamline drug development and lead to the most efficient evaluation of new treatments. Throughout this development process, dose determination is driven by the accumulation of adverse events that are

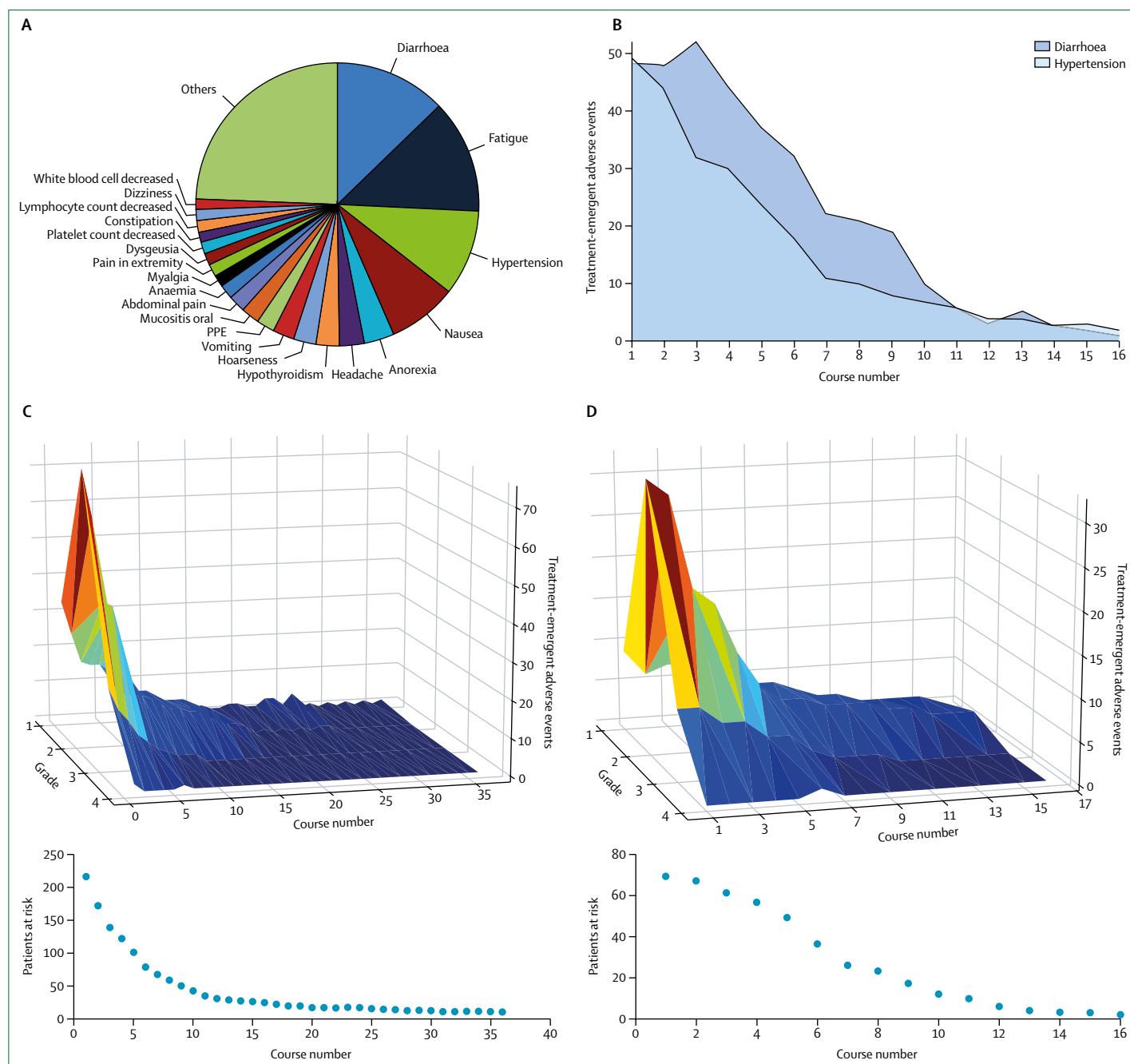


Figure 2: Graphical representations and analysis of adverse events by the National Cancer Institute Web Reporting Tool

(A) Pie chart of all treatment-emergent adverse events in patients treated with a vascular endothelial growth factor receptor inhibitor (VEGFR2i) and a DNA repair inhibitor (DNARi). (B) Risk-based monitoring of diarrhoea and hypertension in patients in a clinical trial of a VEGFR2i and a DNARi to assess the frequency of adverse events by course using an area-under-the-curve-based approach. (C) Hypertension in patients from five clinical trials of VEGFR2i assessed by grade, course number, and number of adverse events using a contour map. Below is graph that depicts the number of patients at risk by course. (D) Hypertension as a treatment-emergent adverse event in patients given VEGFR2i in a clinical trial assessed by grade, course number, and number of adverse events using a contour map. Below is a graph that depicts the number of patients at risk by course. PPE=Palmar-Plantar erythrodysesthesia.

used in aggregate to identify the recommended dose and schedule for later-phase investigations. Given that many therapeutics for haematological malignancies are now administered over prolonged periods, clinical trial designs need to address dose determination and refinement

beyond the phase 1 dose escalation. Definitions of dose-limiting toxicity are generally based on single-cycle, acute adverse events that are of such sufficient severity that dosing cannot be continued at the given dose level. When developing non-cytotoxic, continuously, or chronically

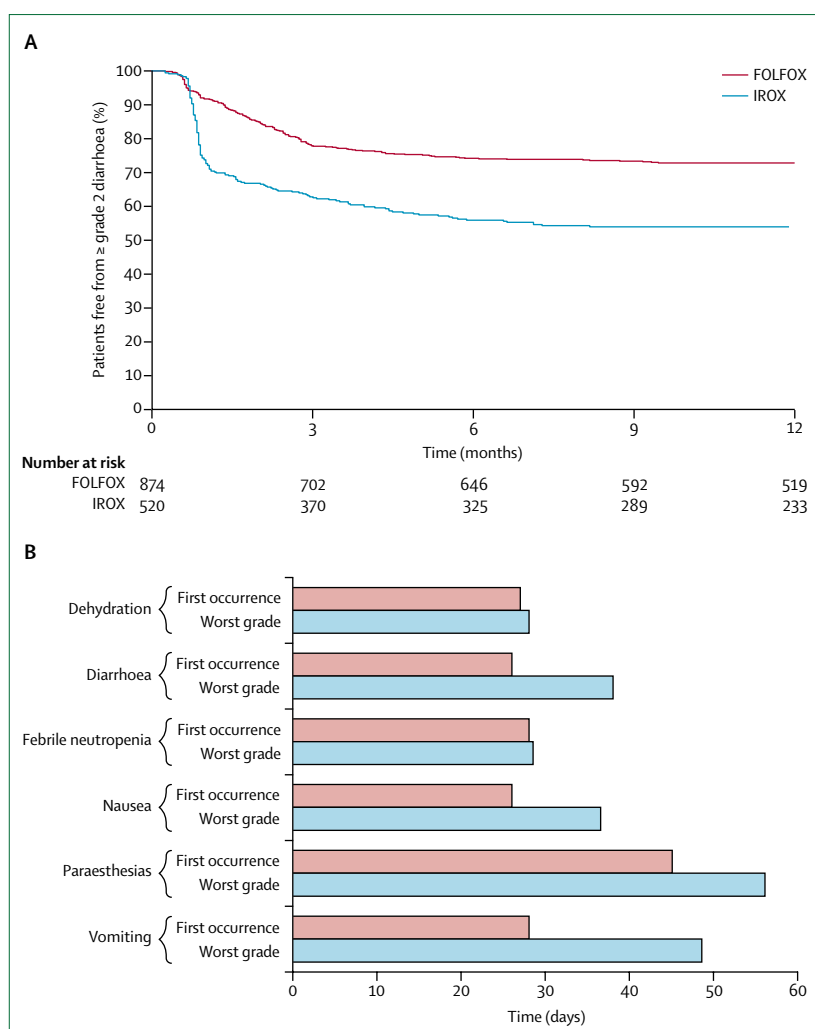


Figure 3: Time-to-event analyses for adverse events using the Toxicity over Time package
(A) Time to grade 2 or worse diarrhoea in patients given FOLFOX and IROX in NCCTG N9741.³⁶ (B) Median time to first occurrence and worst grade toxic effects in patients given IROX in NCCTG N9741.³⁶ The figures capture the time profile of adverse events from these regimens. IROX=irinotecan and oxaliplatin. FOLFOX=leucovorin, fluorouracil, and oxaliplatin.

administered therapies, the relationship between dose-response and toxicity might not be well understood, and assessing tolerability in such a short window might not be possible.³⁷ Molecularly targeted and immunotherapy drugs might not have doses and schedules determined during the first cycle of therapy, leading to inexact descriptions of dose-limiting toxicity. This hampers establishing the maximum tolerated dose and the recommended phase 2 dose once dose escalation is completed.³⁸

One way to address this issue is to lengthen the observation window for the dose-limiting toxicity to two or three cycles before establishing the recommended phase 2 dose and schedule. Alternatively, expansion cohorts could further characterise safety and tolerability of a treatment, which could lead to further dose and schedule refinement. Phase 2 trials evaluating safety, tolerability, activity, or efficacy of molecularly targeted or

immunotherapy drugs could inform dose and schedule refinement. Improving the design of these trials to efficiently determine the dose and schedule is crucial.

At present, the short observation window for determining dose-limiting toxicity in phase 1 clinical trials does not permit the evaluation of lower grade, chronic toxicities that often lead to dose modification or delay in later cycles and affect tolerability. This compromises effective dose delivery and, in some instances, efficacy and alters the benefit-risk assessment of therapy over time. The effect of these low-grade toxicities on quality of life in patients with advanced disease could become intolerable with continuous administration, and the toxicities are often missed in the standard phase 1 trial evaluation window of dose-limiting toxicity.^{39,40} Inclusion of late or delayed adverse events to determine the recommended phase 2 dose is not standardised. Further study of dose-limiting toxicities that occur outside the narrowly specified timeframe for adverse event assessment is required.

One adaptive design that could assist in the evaluation of chronic low-grade adverse events is the modified toxicity probability interval design,⁴¹ which uses all adverse event data gathered before dose escalation or de-escalation. The advantage is that each adverse event is used for dose selection irrespective of grade rather than only the adverse events in one cycle of therapy using three to six patients. The larger sample size increases the confidence that the recommended phase 2 dose will be safe and tolerable and that the schedule of a new drug will be clinically relevant, particularly when adverse events occur outside of the window of detection of the dose-limiting toxicity. However, a qualitative judgment analysis of the effect of chronic low-grade adverse events could be needed to evaluate the effect of therapy.

Challenges to the drug development process posed by chronic, cumulative, and late effects

The occurrence of chronic, cumulative, and late effects are inherent to many modern therapies for haematological malignancies, so longer-term follow-up of patients in both early-phase and later-phase trials might be needed to capture the relevant adverse event profile. One example of the need for novel trial designs and longer observation windows for dose-limiting toxicity comes from the analysis of 54 phase 1 trials of molecularly targeted drugs.³⁸ Almost a quarter of the patients treated (n=599) who developed grade 3 or worse adverse events had their dose-limiting toxicity observed after their first cycle of treatment. Of the 2084 patients reviewed in this analysis, grade 2 adverse events such as diarrhoea, fatigue, and neutropenia were observed at the highest frequency in treatment cycles three to six, and not during cycle 1. Another example comes from a pooled analysis of 576 patients receiving nivolumab for advanced melanoma.⁴² Adverse events of any grade occurred any time between 5 weeks (for skin toxicities) and 15 weeks (for renal toxicities) for median time to onset.

A greater challenge is capturing the contribution of toxicity attributable to a novel drug that occurs late in the overall therapeutic course. In classical Hodgkin's lymphoma, where PD-1 blockade results in more than 80% of patients achieving a partial or complete response in the relapsed and refractory setting,³¹ some severe life-threatening complications were not seen until patients underwent allogeneic HSCT.⁴³ This type of data relies on astute clinicians identifying the occurrence of toxicity in an unusual context or presentation. Other such examples include the identification of the association of progressive multifocal leukoencephalopathy¹⁶ with rituximab therapy in HIV-negative patients, hepatitis B reactivation with rituximab,⁴⁴ delayed neutropenia with rituximab,⁴⁵ and an association of ibrutinib with aspergillosis⁴⁶ and arrhythmias⁴⁷ in patients with haematological malignancies. Because of the potential need for continuous therapy (in chronic myelogenous leukaemia, for example), longer follow-up might become particularly important as adverse events occur long after the mandatory monitoring period has ended. Furthermore, the pattern of adverse events when restarting therapy after a deliberate period off therapy might be different to those that appeared during initial therapy. For example, late toxicity of imatinib (eg, cardiac toxicity, abnormal bone and mineral metabolism, hypothyroidism) would not necessarily be observed in studies with exclusively short-term endpoints.⁴⁸ A greater expectation of unexpected adverse events, which might occur either acutely or quite delayed, requires mandatory, longer-term surveillance if safety data are to be captured comprehensively. No formal mechanism exists for this type of surveillance activity, but it is crucial. Post-marketing surveillance for adverse events is further explored in sections 5 and 6.

The process of learning from one trial to inform the investigators and clinical practice in another trial needs to become increasingly rapid and dynamic, from both regulatory and sound clinical practice perspectives. The rapid roll-out of immunotherapies across tumour types and, concurrently, into regimens of multiple combinations (including other novel therapies), each with a different profile of adverse events, has created regulatory challenges. Perhaps the most compelling examples are the seamless phase 1, phase 2, and phase 3 designs with large expansion cohorts used in some immunotherapy trials. The advantages of this type of design include the ability to rapidly identify areas of disease activity and move quickly to licensing strategies. International review boards have been challenged to assure patient safety because the quick dissemination of rapidly accrued safety information without the added safeguard of a data safety monitoring committee proved difficult. These problems were not insurmountable, but they did raise ethical concerns. The risk of not identifying the optimal recommended phase 2 dose always exists when compiling non-aggregated data.

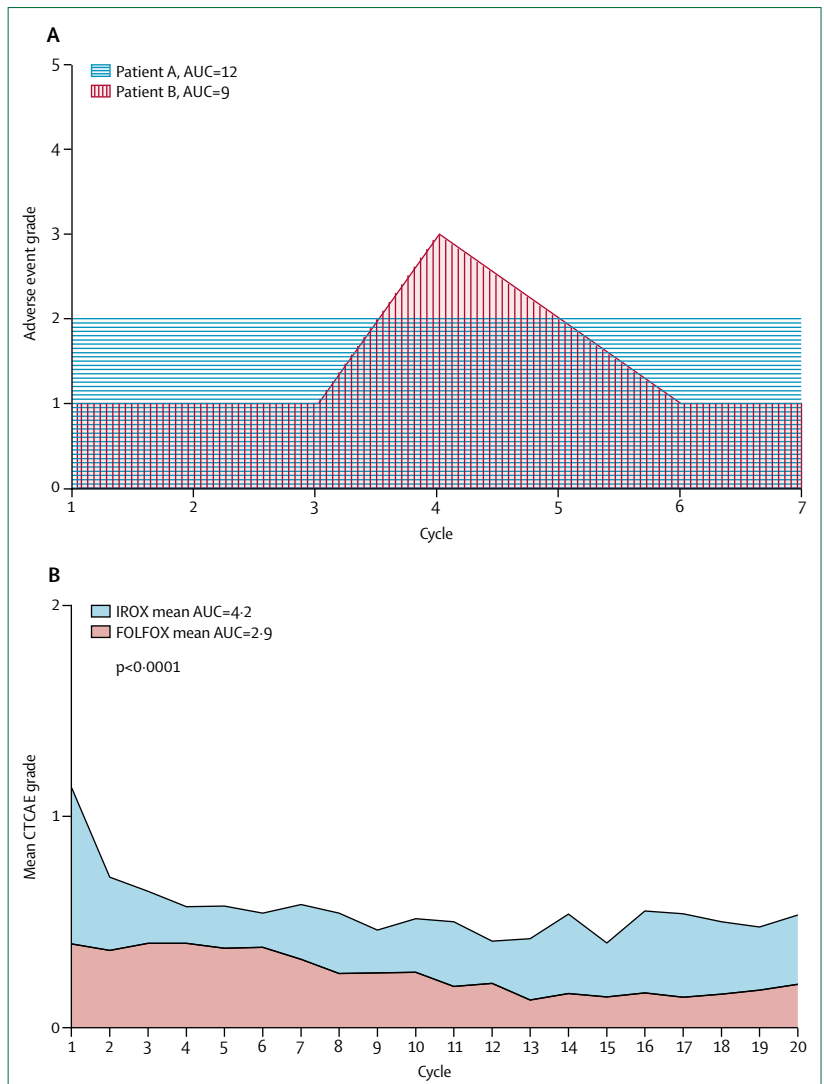


Figure 4: AUC analysis to compare adverse events over time—conceptually and applied

(A) Conceptual example of AUC analysis with patient A, who has a continuous grade 2 adverse event and a higher AUC than patient B, who has an isolated grade 3 event. (B) Application of AUC analysis depicting mean diarrhoea grade over time in patients given FOLFOX and IROX for metastatic colorectal cancer in clinical trial Alliance/NCCTG N9741 (the p value compares the AUC numbers).³⁴ AUC=area under the curve. IROX=irinotecan and oxaliplatin. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. CTCAE=Common Terminology Criteria for Adverse Events.

The desire for quick-answer, short-conduct trials might also impede the ability of investigators to define important longer-term toxicity. This could be addressed by introducing mandatory assessment of longer-term toxicity with long-term follow-up of patients participating in late-phase clinical trials. Late-occurring toxic effects can adversely affect survival, and such effects can only be detected with adequate follow-up. For example, in early-stage classical Hodgkin's lymphoma, the addition of radiotherapy to combination chemotherapy with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) improves progression-free survival compared with ABVD alone, but overall survival might ultimately be compromised, probably because of the late effects of radiotherapy.⁴⁹ Shorter-term

Panel 2: Immune-related adverse events: a new context of adverse event assessment in haematological malignancies

Advances in immunotherapy, including immune checkpoint blocking antibodies, bispecific antibodies, and chimeric antigen receptor (CAR) T cells, have led to substantial practice-changing approaches in some haematological malignancies. They also introduce great complexity to the assessment of adverse events. The recent FDA approval of CAR T-cell therapy in the USA and the proliferation of these therapies in clinical trials for patients with relapsed haematological malignancies in many developed countries bring along a myriad of immune-related adverse events that are not well captured by existing assessment systems. These immunotherapy-related adverse events have brought new challenges to reporting, dose modifications, and subsequent patient management.

With respect to checkpoint blocking antibodies, the array of immune-related adverse events continues to grow, and with the need for continuous therapy in many cases, these adverse events arise at unpredictable times and their duration in some cases can be prolonged. Because of the efficacy of these drugs, the reporting of adverse events has been suboptimal, because of both investigators' and patients' bias toward not wanting to stop an effective therapy. Frequently occurring toxicities with checkpoint inhibitors include pruritus, maculopapular rash, thyroiditis, pneumonitis, diarrhoea, colitis, hepatitis, arthritis, myositis, nephritis, pericarditis, haematological toxicities, and neurologic toxicities. At what grade level these and other drugs must be discontinued, and in which circumstances to retreat, are not necessarily clear. Most clinically relevant immune-related adverse events occur early in therapy and are reversible with either the discontinuation of the drug or the administration of steroids (or other immune suppression), and these are for the most part reported. However, some of these adverse events occur late in therapy, some are recurrent with or without drug rechallenge, some are low-grade but chronic, and some have been fatal. It is these late-occurring, recurrent, or chronic, low-grade, immune-related adverse events that are underreported and clinically underappreciated.

Additionally, the definition and recognition of an immune-related adverse event is often the result of a best clinical judgement, which involves subjective consideration of a differential diagnosis and is rarely biopsy-proven (eg, ground glass opacities could be due to either infection or pneumonitis). As the range of these immune-related adverse events has become more defined and experience with their management has been gained, the recognition and grading of immune-related adverse events has become more standardised, and management has become increasingly prescribed with many sponsors using predefined case definitions. This alone will certainly improve the evaluation and reporting of immune-related adverse events with these new drugs. Formally standardising immune-related adverse

events and case definitions in terms of type and grading across all studies will help further in this respect.⁵³ Furthermore, incorporating both patient-reported and doctor-reported adverse events into clinical trials and after commercialisation will deepen the appreciation for how these immune-related adverse events affect a patient on continuous or long-term therapy.

CAR T-cell therapy, on the other hand, could pose the opposite problem. This therapy is acute, not continuous, and has a defined and relatively limited array of toxic effects largely falling into two distinct categories: cytokine release syndrome⁵⁴ and neurotoxicity. The pathophysiology of cytokine release syndrome is fairly well understood, and the availability of effective therapies renders the risk largely time-limited and reversible. However, the pathophysiology of neurotoxicity is not clearly defined, and how to best manage these patients is also unclear. Rare cases of protracted neurotoxicity or death, or both, have been reported. The standardisation of a classification and grading system for cytokine release syndrome and neurotoxicity by Lee and colleagues,⁵⁴ which is used in most studies, has helped to better characterise these adverse events. Yet the grading, especially for neurotoxicity, remains somewhat subjective and has room for improvement, and not all studies use the same grading system (The University of Pennsylvania has a separate grading system,⁵⁵ whereas most other research groups use the Lee criteria). The FDA is testing the feasibility of keeping a safety database that pools safety information across multiple different investigational new drugs for CAR T-cell products. The purpose of the database is to facilitate assessment of new safety information, and to inform regulatory advice to study sponsors to support the clinical development of their product (or products). Such pooled data might be important and similarly helpful for checkpoint inhibitors and CAR T-cell therapy.⁵⁶ However, unlike with checkpoint-inhibitor therapy, the reporting of adverse events after CAR T-cell therapy is fairly accurate but is potentially overemphasised given the high-intensity but time-limited risk of this therapy on the one hand and the high clinical effect and efficacy on the other.⁵⁷

With both therapies, however, reporting of adverse events after market approval becomes very important and is likely to fall short when these drugs and therapies are given to real-world patients. Such patients might have comorbidities that were either not included or were explicitly excluded in licensing trials, or might have received prior unexplored therapies potentially substantially changing adverse event risk and profile. Improved tools and strategies for post-marketing assessment and reporting of adverse events are necessary to fully understand the risk-benefit ratio and who should be receiving these therapies after the completion of a trial.

endpoints might have regulatory importance in safety assessment, but assessment of longer-term benefit should not be de-emphasised.

Data informing late-term toxicity could also come from other sources such as post-hoc analyses, with social media and patient advocacy playing an important

part. Examples include thromboembolic disease with the use of lenalidomide⁵⁰ and concerns with toxicity of steroids in patients with multiple myeloma.⁵¹ Patient advocates in the Eastern Cooperative Oncology Group in the USA identified high-dose steroids as a concern, leading to a randomised phase 3 trial⁵¹ in which low-dose steroids with lenalidomide was found to improve survival in patients with multiple myeloma and a subsequent regulatory approval in the USA.

For the knowledge base of adverse event profiles to evolve for new medicines, real-time multidirectional information transfer between regulators, clinicians, and clinical investigators is required. For it to be impactful and to better protect patients in ongoing trials and the clinical setting, the information must be made available and must be accurate. The printed product label might no longer be the best method of transferring knowledge about adverse events in the 21st century. How data are presented can and should be much improved, and the goal should be real-time monitoring followed by accurate interpretive reporting.

Complexities of assessing adverse events that are unique to haematological malignancies

The definition of adverse events and challenges inherent in the analysis of adverse events, given the time profile of toxicities of existing and novel drugs, are common between haematological malignancies and solid tumours. However, specific features of haematological malignancies pose challenges to the assessment of some adverse events and warrant noting. For example, consider bone marrow involvement by tumours, a far more common situation in haematological malignancies than in solid tumours. The grey area between bone marrow toxicity and the desired therapeutic effect complicates the reporting of adverse events and the interpretation of the aggregate data. The complex, supportive management of patients with marrow-infiltrative disease must be balanced with treatment to avoid infections, bleeding complications, and other unavoidable adverse events brought on by disease or treatment. Navigating through these expected events might in some cases be the only avenue for potential cure of the underlying cancer. The grade 3 and 4 haematological adverse events that commonly occur with acute leukaemias and aggressive lymphomas are not indicative of a therapy that is not effective or safe.

Another example of how interpretation of clinical and laboratory findings can be particularly challenging in haematological malignancies and have the potential to mislead drug development was seen during the development of ibrutinib for chronic lymphocytic leukaemia. Immediate post-treatment leukocytosis could be interpreted as either a toxicity of the drug or as disease progression, when, in fact, it was the therapeutic effect of ibrutinib.⁵² Defining toxicities that qualify as dose-limiting toxicities is therefore challenging in these cases. Treatment

Potential approaches to achievement		Initial implementation strategy
Improved analysis of chronic adverse events	- Implementation of longitudinal methods to assess chronic, low grade effects over time - Analysis of chronic adverse event data in early phase trials for those patients receiving more than six cycles - Area-under-the-curve analysis of adverse events from more than one trial to identify the optimal recommended phase 2 dose - Assessment of a subpopulation of patients with chronic effects to identify effect - Testing of different analytic approaches on existing trial data	Retrospective assessment of trials in which chronic adverse events have been reported: prospective assessment accomplished in the next 2–5 years
Improved analysis of cumulative adverse events	- Use of data from multiple cycles to explore cumulative effects with dose modifications over time - Assessment of cumulative effects of a given agent using adverse event data from more than one trial - Inclusion of risk-based adverse event analysis for effects that are cumulative to account for patient attrition	- Retrospective assessment of trials in which chronic adverse events have been reported - Prospective assessment accomplished in the next 2–5 years
Improved analysis of late adverse events	- Necessitate long-term follow up on patients on trials where relevant - Use of SEER and SEER-Medicare databases in the USA to do population assessment for late effects - Build in the late follow-up for late effects in trials - Inclusion of patient reported outcomes even later on or after a trial	Retrospective analyses could start immediately

Table 2: Improving analysis and reporting of chronic, cumulative, and late adverse events

of haematological diseases with HSCT also requires specific attention to the reporting of adverse events that differ from most solid tumour settings, and this will be addressed in section 4. Data collection of the adverse events is necessary, but the appropriate reporting must be made in the context of the disease under treatment.

The advent of immune therapies to treat a variety of haematological malignancies has also spurred challenges in adverse event assessment. Immune-related adverse events from checkpoint inhibitor therapy and CAR T-cell therapy, among others, are addressed in panel 2.

Ultimately, vast changes in treatment paradigms for haematological malignancies should spur changes in existing systems of adverse event assessment and a rethinking of early-phase and late-phase clinical trial designs, not only for acute toxicity but also for chronic, cumulative, and late adverse events (table 2). The ascertainment and reporting of adverse events would also be enhanced by inclusion of PROs.

Section 2: Incorporation of PROs in the assessment of adverse events

The welcome advances in outcomes with newer therapies for haematological malignancies are not without costs. There are challenges inherent to assessing the toxicities of prolonged, continuous therapies as part of daily life, as opposed to short-course cytotoxic therapy that have been the mainstay of treatment for many haematological malignancies for decades. The acceptable toxicities between these two different scenarios are probably different, and our understanding can be enhanced with the use of longitudinal PRO data. In this section, we

focus on the use of PROs to enhance the understanding of toxicity in haematological malignancies.

Safety profiles of anticancer drugs are moving from a characteristic group of acute toxicities that recover between intermittent dosing, to potentially prolonged symptomatic side-effects that are heterogeneous in type and kinetics. These symptomatic adverse events might lead to dose modifications, elective patient discontinuation, or poor adherence to long-term treatment plans. They might also profoundly compromise a patient's quality of life. The changing safety profile of cancer drugs has led to a call to rethink old practices and consider new methods to evaluate cancer product safety and tolerability.³⁵ In addition to standard, routine clinical visits and clinician-reporting of adverse events, incorporating the patient in the assessment of cancer therapies is of great interest both in the clinical trial and clinical care settings.⁵⁸

PROs, health-related quality of life, and PRO-CTCAE

PROs are assessments based on a report that comes directly from a patient about the status of their health without amendment or interpretation of their response by a clinician or anyone else.⁵⁹ The term PRO is often confused with the term health-related quality of life. PRO is a broad term describing an assessment method, whereas health-related quality of life is a specific clinical outcome. In some cases, a clinical outcome might be assessed by various methods. For example, the clinical outcome of physical function can be measured by a PRO, a clinician-reported outcome assessment (eg, Karnofsky Performance Scale), or a performance outcome assessment (eg, 6-min walk). Increasingly, there is also interest in the use of wearable devices to quantify a patient's activity in daily life as a clinical outcome.

Health-related quality of life as a clinical outcome is assessed using a PRO measure. The outcome of health-related quality of life is a multidimensional construct defined as the subjective perception of the effect of health (including disease and treatment) on physical, psychological, and social functioning and wellbeing.⁶⁰ Typically, assessments of health-related quality of life in clinical trials are used to assess the effects of cancer and its treatment in aggregate on the patient's perception of wellbeing. Such assessments provide a supportive outcome to complement the usual primary outcomes of disease control and overall survival.

The use of PROs in clinical trials can help to refine the understanding of patient benefit or harm when there are clear objectives for their inclusion. PRO assessments have provided important complementary information from the patient's perspective on functional outcomes and the trajectory of symptoms over time.⁶¹ However, PRO assessments of generic measures of health-related quality of life or disease modules might not always incorporate the symptoms of interest for the diversity of novel therapies being investigated. Developers of

commonly used PRO measures of health-related quality of life, such as the European Organisation for Research and Treatment of Cancer (EORTC),⁶² Functional Assessment of Chronic Illness Therapy (FACIT),⁶³ and the EuroQOL 5D (EQ-5D)⁶⁴ have developed standard disease modules, which are specific sets of questions assessing symptoms typically seen with the specified disease and side-effect profiles of some common, standard therapies. The questions included in these modules do not vary and do not have the flexibility to adjust to differing toxicity profiles seen with the wide range of drug classes in development for haematological malignancies. For instance, rash and ocular side-effects cannot be assessed with older generic tools. In addition, existing tools to measure health-related quality of life are often designed without assessing the burden and incentive of patients to provide meaningful data, further decreasing the validity of existing approaches to measuring health-related quality of life. Involving patient organisations in the development and validation of such tools could drive acceptability and data validity.

Increasingly, efforts have been made to overcome this lack of flexibility by incorporating additional ad-hoc questions about symptoms or side-effects to capture additional adverse events associated with the new treatments. Both EORTC and FACIT have publicly accessible item libraries of questions that allow physical symptoms to be selected to fit the context of the trial. This is a reasonable approach, but the symptom items in the generic forms might still include adverse events that are not typically expected to occur (eg, peripheral neuropathy in a trial with drugs with which that specific toxicity has not previously been recognised). Typically, health-related quality-of-life outcomes are reported as a summed score of the responses to each item. The addition of ad-hoc items would change the score and make it difficult to interpret the findings.

Although health-related quality of life and its functional domains (eg, physical, cognitive, emotional) can be affected by the toxicity of a therapy, there is increasing interest in specifically assessing symptomatic treatment-related side-effects using PRO measures to complement clinical understanding of safety and tolerability. The NCI recently developed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Event (PRO-CTCAE) specifically for self-reporting of symptomatic adverse events, mapping to the well established CTCAE system for clinician reports. This item library for patients contains 124 PRO questions reflecting 78 symptomatic adverse events, which is derived from and designed to be used alongside standard clinical reported CTCAE assessments.⁶⁵ PRO-CTCAE is flexible, such that applicable adverse events can be selected for administration depending on the expected side-effects of the given clinical trial. PRO-CTCAE has positive psychometric properties, including construct validity, reliability, and responsiveness.^{65,66} With

For PRO-CTCAE see <https://healthcaresdelivery.cancer.gov/pro-ctcae/>

	Phase 1	Phase 1/2	Phase 2	Phase 3	Other	Pilot	Total
Leukaemia trials	1/49 (2%)	0/7	2/68 (29%)	5/11 (50%)	0/1	0/1	8/137 (6%)
Lymphoma trials	0/23	1/11 (9%)	6/63 (10%)	1/3 (33%)	..	0/1	8/101 (8%)
Myeloma trials	0/5	1/4 (25%)	2/13 (15%)	7/11 (64%)	..	0/2	10/35 (29%)

Data are number of trials with PROs/total number of trials (%). CTEP treatment trials (all phases) were activated between June 30, 2004, and Dec 31, 2016. In total, only 26 (10%) of 273 adult haematology clinical trials sponsored by the National Cancer Institute had PROs. CTEP=Cancer Therapy Evaluation Program.

Table 3: Patient-reported outcomes (PROs) in 273 haematology adult trials sponsored by the National Cancer Institute

PRO-CTCAE, patients score the different aspects of a symptomatic adverse event separately, such as the presence, frequency, severity, and activity interference associated with each term. PRO-CTCAE scores therefore do not correspond to clinician CTCAE grades. This difference permits the analysis of patient-reported interference separate from severity, which could lead to insights on tolerability.

PROs in existing haematological malignancies trials

Many clinical trials in patients with haematological malignancies have not typically incorporated health-related quality of life or other PRO assessments. Data from NCI-sponsored clinical trials between 2004 and 2016 show that less than 10% of the clinical trials with leukaemia, lymphoma, and myeloma patients have included PRO endpoints of health-related quality of life outcomes (table 3). Health-related quality of life endpoints were more likely to be assessed in myeloma phase 3 trials than in any other trial type.

Multiple myeloma is a chronic malignancy characterised by clinically significant symptoms related to disease burden (eg, bony pain, fatigue) and treatment toxicity (eg, neuropathy). In recent years, many newly approved drugs have improved outcomes in patients with incurable disease, with a shift from intensive induction therapy to a chronic delivery of therapy. Increasingly, PROs are being incorporated into clinical myeloma trials to assess the effect of treatment on health-related quality of life.⁶⁷ Findings from two systematic reviews^{68,69} showed that inclusion of health-related quality-of-life assessments in myeloma clinical trials is limited but increasing, and the analysis of these assessments showed substantial symptomatic improvement in health-related quality of life during first-line therapy. Inconsistencies in the incorporation and analysis of health-related quality of life in these trials, however, makes interpretation of these findings and cross-trial comparisons challenging.⁶⁸

In addition to measuring a drug's effect, PRO data can inform how patients are affected by their disease course. For example, the Eastern Cooperative Oncology Group (ECOG) incorporated longitudinal measurement PROs in the E4402 study⁷⁰ comparing rituximab maintenance and retreatment strategy in patients with low-grade non-Hodgkin lymphoma. The trial reported similar illness-related anxiety, overall anxiety, and health-related quality

of life between the groups. Investigators concluded that relapse might not be not associated with increased anxiety as previously thought, and the retreatment strategy resulted in similar patient outcomes while using fewer resources.⁷⁰ The international phase 3 trial of watch-and-wait versus rituximab induction versus rituximab maintenance⁷¹ included health-related quality of life at 7 months as a primary endpoint. The rituximab groups had longer progression-free survival and time to chemotherapy or radiotherapy than those in the control (watch-and-wait) group, without difference in overall survival. The patients receiving maintenance therapy had improved mental adjustment to cancer scores compared with those on watchful waiting, although no difference was found in overall quality of life, anxiety, depression, or distress as measured by the Impact of Events-Scale.

Thus, use of health-related quality of life and other more defined PRO measures of patient function in these trials can provide additional information to understand the overall effect of the disease and treatment and brings the patient's perspective into the treatment evaluation. However, the multidimensional construct for health-related quality of life might not provide the specificity to understand what symptomatic toxicities could be driving the tolerability of a specific regimen.

Safety and tolerability

Safety and tolerability are crucial but capture different aspects of a regimen's effect on patients. Safety is intended to reflect the medical assessment of an adverse event based on the clinician's judgement about information such as medical history, physical examination, and laboratory and imaging findings. Tolerability reflects the extent to which overt adverse events affect the patient's willingness and ability to continue the treatment regimen (figure 5; figure 6).^{72,73}

As addressed in section 1, the primary method for assessing and reporting safety is clinician-graded adverse events based on the CTCAE that are reported in tables of the worst-grade events. These tables quickly and effectively communicate safety according to the numbers of patients who had the worst severity of toxicity at any point in time. However, the tables do not provide specific information about when the adverse events developed, resolved, or improved with supportive interventions, which are clinically relevant issues with

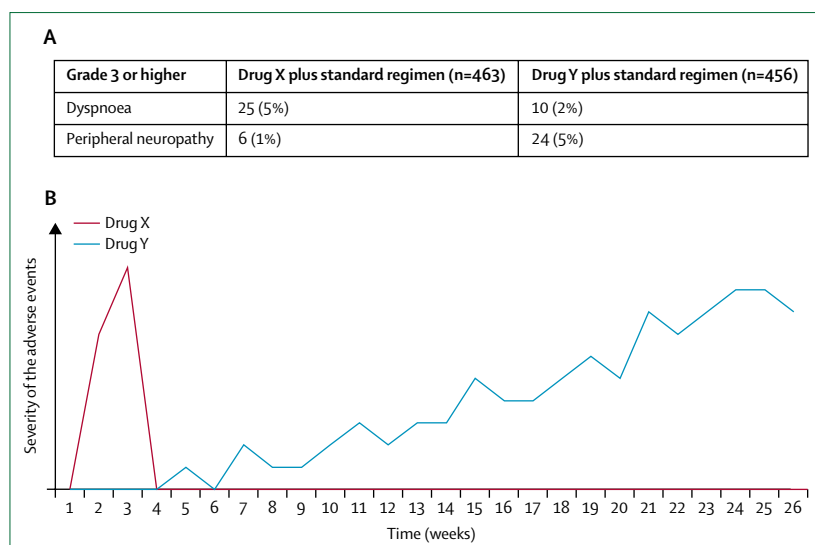


Figure 5: Relevance of a time profile for adverse events
 (A) Two grade 3 or higher adverse events with similar incidence associated with drug X and drug Y (as captured by conventional maximum grade reporting). (B) Conceptual example of a patient's experience of adverse events associated with drug X and drug Y, demonstrating the relevance of time frame of different adverse events. Dyspnoea related to drug X peaks in severity and resolves within a few days, whereas neuropathy related to drug Y worsens steadily over time, having a different implication on tolerability of that regimen for the patient.

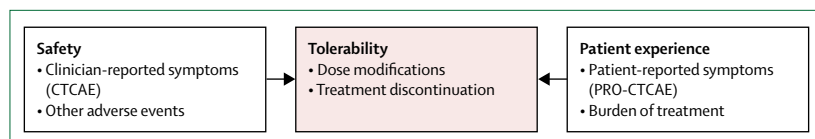


Figure 6: Safety and the patient experience to inform tolerability
 CTCAE=Common Terminology Criteria for Adverse Events. PRO=patient-reported outcome.

the long-term, chronic, orally administrated drugs (or regimens). These aspects might be highly relevant to tolerability, even if they do not specifically affect safety. Novel graphical or analytical approaches (such as those presented in the last section) are necessary to incorporate the time profile of adverse events associated with several novel drugs.

Low-grade adverse events are not often the focus of safety assessments and might not be recorded on case report forms in many cancer trials. Whereas a low-grade change in potassium concentration might not be important to patients, low-grade symptomatic adverse events, such as nausea, diarrhoea, or neuropathy, can be burdensome to patients, particularly when chronic, or cumulative. Low-grade symptomatic adverse events have resulted in patient non-adherence to therapy.^{25,74–76} Targeted therapies are often associated with a spectrum of non-specific adverse events that might not be frequent or severe but alter patient health-related quality of life.⁷⁷ Clinicians might underestimate the incidence and severity of symptoms relative to patients' self-reports of similar information generated from PRO measures.^{78–80} This difference in clinician and patient responses provides some of the distinction to illustrate the

differences between safety and tolerability.⁸¹ A patient might have severe nausea that decreases food intake, but he or she is able to drink fluids and is not dehydrated. This patient would probably rate his or her nausea as severe; however, the clinician would categorise this nausea as grade 2 by CTCAE. Although a short course of treatment with the regimen causing this nausea might be tolerable for a few cycles, the drug is unlikely to be tolerable over months to years of treatment.

Understanding drug tolerability over time, such as by incorporating methods such as AUC evaluation for toxicity, as previously discussed, is essential to maximise patient benefit. Definitions of toxicity relative to drug exposure are helpful to clarify the time-related function of adverse events relative to drug exposure (panel 2). The inclusion of patient-reported symptomatic adverse events with tools such as PRO-CTCAE can provide additional data that is complementary to safety data. PRO strategies should begin with a baseline assessment that includes longitudinal assessments throughout and at the end of treatment as well as multiple analytical and visualisation techniques.

Incorporation of health-related quality of life and other PRO measures to inform the patient experience while exposed to a cancer therapy can add value to our understanding of the effect of a new intervention. Efforts are underway to standardise how PRO measures can be analysed and presented.^{82,83} There is now growing interest in using item libraries such as the PRO-CTCAE to provide the needed flexibility to select the relevant emergent symptomatic adverse events for the trial context that can inform drug safety and tolerability in addition to measuring health-related quality of life.

Statistical analysis opportunities for PRO data

Standardising PRO assessment and analysis in cancer trials is crucial, and several international, collaborative efforts are underway in key areas to identify core outcome sets (eg, ICHOM,⁸⁴ COMET⁸⁵) standardised PRO analytical methods (SISAQOL),⁸³ and standard PRO protocol elements (SPIRIT-PRO).⁸⁶

Although development of a standardised approach to PRO statistical analysis is ongoing by SISAQOL, commonly used statistical analysis approaches to PRO data⁸⁷ include: cross-sectional mean estimation with comparisons at key timepoints using *t* tests or analyses of covariance where the baseline PRO score is included as a covariate; longitudinal mean estimation with comparisons using generalised linear mixed modelling or generalised estimating equations; or summary measure approaches exemplified in the previous section (eg, AUC, responder definitions), with between-arm comparison using an applicable statistical comparison approach.

PRO data analysis should carefully handle missing data and multiplicity. The very best approach to handle missing data is to minimise its occurrence through thoughtful design and enhanced data collection and monitoring.⁸⁸

Reasons for missed reports should be captured during data collection and reported⁸⁹ to understand how the missing data might bias results. The best statistical approach in the presence of missing data is a method that uses all available data and is robust to some types of missing data, followed by sensitivity analyses that employ a range of missing data methods (eg, generalised linear mixed modelling) to assess the robustness of results to various missing data assumptions. Multiplicity is commonly handled using a hierarchy approach where each PRO endpoint is identified as a primary, secondary, or exploratory endpoint. Other methods include alpha adjustment methods (eg, the Bonferroni method), resampling methods, or global tests (eg, O'Brien's test). As is the case with CTCAE safety data, multiplicity is not a concern when PRO-based adverse event data are presented in a descriptive fashion without formal statistical comparisons.

Opportunities exist for developing optimal strategies for the estimation and visualisation of PRO-based adverse event data. PRO-based methods that typically rely on estimating severities (in trial participants in aggregate) might not adequately communicate findings to a clinical audience that is accustomed to standard adverse event reporting of percentages of patients with each CTCAE grade level. Summary approaches typically applied to CTCAE data might not adequately address missing PRO data issues or properly account for baseline symptoms. An alternative summary measure approach taking the baseline score into account⁹⁰ mirrors how clinicians are trained to identify adverse events. If a symptom is present at baseline, then it might be considered an adverse effect if it worsens during treatment. Thus, in the proposed baseline adjustment approach, PRO-based adverse event scores that are the same as or improved from baseline are converted to a score of zero, and scores that are worse than baseline are analysed without modification. Taking baseline into account holds the potential to improve attribution of an adverse event to the drug under study—a particularly challenging issue in cancer trials with residual toxicities and cancer-related symptoms at baseline. Alternative methods that have yet to be fully explored for PRO-based adverse event data might include joint modelling of PRO-based adverse event data with CTCAE data or disease status, or both, or multiple imputation approaches that use clinician-based CTCAE data as auxiliary data.

Electronic collection of PROs

In addition to novel methods for analysis of PRO data, opportunities exist for improving collection of PROs in patients with haematological malignancies, both in the clinical trial setting and the practice setting. The traditional paper-based collection of PROs might be burdensome to patients and staff, particularly in the setting of inadequate resources and infrastructure. The telephone-based or electronic collection of PROs might

ease some of these burdens by eliminating the need for printing, dissemination, and collection of questionnaires, manual scoring, and entry into a database. Electronic collection of PROs is reliable, valid, and might be preferred by patients.⁹¹

Despite the rapid uptake of electronic devices, from smartphones to tablets for entertainment, shopping, and banking, the incorporation of electronic PROs has been relatively slow in non-industry sponsored cancer clinical trials. There is a perception by clinical staff and trial investigators that patients, particularly elderly or frail patients, are unable or unwilling to use electronic devices. Yet findings presented in a recent Pew Report⁹² show that roughly two-thirds of patients older than 65 years use the internet, and more than 40% of this patient group has a smartphone. The rate of adoption is rapidly increasing, even as many senior patients acknowledge the need for additional help.

Patients with cancer are interested in PROs. The global patient organisation CML Advocates Network initiated an online survey in 63 countries to better understand the extent and drivers of non-adherence. More than 2500 patients with chronic myelogenous leukaemia completed the web-based and paper-based survey, the results of which showed that adherence correlated with key factors that could be influenced through improved doctor–patient communication, such as management of side-effects and satisfaction with level of information about the disease. The survey noted that only 32.7% of patients with chronic myelogenous leukaemia were highly adherent to therapy, despite a clear correlation of adherence with therapy outcomes.²⁵

With the widespread use of electronic medical records, it is now feasible to incorporate and display the patient self-reported disease symptoms and adverse events in the medical records. Yet many clinicians are reluctant to embrace electronic methods for collection of patient-reported toxicity for a variety of reasons, including concern about data security, patient privacy and confidentiality, the potential to be overwhelmed with a large electronic workload, and clinical practice burden caused by potential need for clinical provider response to a patient-reported symptom or toxicity. These concerns are not insurmountable, particularly as evidence emerges to support the potential benefits in communication and management of symptoms in the clinical care setting.

Clinical trials to assess the integration of patient-reported symptoms into routine care of patients with cancer have suggested that this approach can improve doctor–patient communication, result in better symptom control for individual patients, reduce patient distress, and have a positive effect on patients' quality of life.^{93,94} Electronic PRO collection of symptoms in patients with advanced malignancy has been found to improve health-related quality of life, decrease emergency room visits, and increase survival, with greatest benefits reported by patients with the least computer experience.⁹⁵

Ultimately, electronic data collection enables the patient to report symptomatic adverse events in real time as they develop, which in turn allows early intervention with supportive medications. Further studies of the ease of workflow in clinics, acceptability by patients and providers, generalisability, and compliance will be necessary to understand the effect and implementation in both clinical trials and clinical care.^{96–98}

Evolving treatment in many haematological malignancies and the proliferation of chronically administered drugs in many different diseases have generated new challenges in understanding side-effects and how they affect patients. As therapy moves beyond a limited treatment window (for cytotoxics) to months or years with novel targeted drugs and immune therapies, tolerability will be just as integral as safety to the assessment of the drug. Incorporation of PROs into the assessment of adverse events holds great promise to inform our understanding of tolerability going forward.

Section 3: Special issues of toxicity from HSCT

In the preceding sections we have addressed the importance of how adverse events are defined, collected, and analysed and the rising need for PROs to enhance tolerability assessment. The focus of this subsection is adverse events of HSCT, a potentially curative procedure used to treat life-threatening malignant and non-malignant haematological disorders. HSCT is a complex therapeutic approach that often involves administration of high doses of cytotoxic or immune suppressive drugs, or both. These drugs induce a myriad of toxicities, and HSCT is therefore a unique situation in toxicity assessment in haematological malignancies. In this section we primarily discuss the challenges pertaining to the assessment of adverse events in HSCT in light of its multiple complex toxicities (including graft-versus-host disease in allogeneic HSCT), and we will propose how best to achieve consensus on which post-HSCT adverse events should be considered expected as a route to tackling this problem. We will subsequently also review adverse events related to HSCT-specific polymedication, infectious adverse events, and selected longer-term adverse events that arise after HSCT.

Challenges to assessing multiple complex toxicities in recipients of HSCT

Most HSCT recipients have at least one serious adverse event, and the overwhelming majority of patients will have more than one adverse event. Reporting the vast array of expected adverse events in the early HSCT setting is often cited as a barrier to clinical trials of drugs in HSCT. Attribution is difficult and sometimes impossible in the setting of multiple competing risks. Adverse events associated with HSCT include prolonged cytopenias and impaired innate and adaptive immune responses, leading to opportunistic infections, organ toxicity (particularly, although not limited, to the lungs, liver, kidney, and

gastrointestinal tract), and therapy-related cancers. Toxicities are related to the conditioning regimen and can be affected by the inclusion of total body irradiation. Allogeneic HSCT involves infusion of genetically disparate grafts, with the potential for graft-versus-host disease, which can be life-threatening and necessitate prolonged immune suppressive therapy, contributing to the emergence of opportunistic infections. Acute graft-versus-host disease arises when donor graft immune cells recognise host tissue as foreign and injures the skin, gut, and liver. The Seattle⁹⁹ and the International Bone Marrow Transplant Registry (IBMTR)¹⁰⁰ grading systems are used to document the severity of acute graft-versus-host disease, despite some limitations.

The frequency of adverse events and the extent to which they are expected also makes under-reporting an issue in HSCT when guidance is not specific (other than the usual definition of serious adverse events) and when surveillance is not standardised. This is not only true for HSCT—in paediatric acute leukaemia, under-reporting of several organ toxicities has been found in automatic reviews of laboratory values through the electronic health record.¹⁰¹ However, under-reporting might be even more important for HSCT, where the importance of a particular adverse event in a specific setting or trial can only be ascertained by understanding its frequency in relation to what is expected.

Taking a so-called realistic approach, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), an American trials group supported by the National Institutes of Health (NIH), has developed a model where only unexpected grade 3–5 adverse events are reported in an expedited case-by-case manner, whereas all expected events are reported on calendar-driven case report forms. Independent medical monitors (typically transplant doctors or disease-matter experts) provide unbiased reviews of unexpected events or events that happen more frequently than expected. Additionally, estimations of expected rates of key toxicities that might be of particular concern, because of the drugs or strategies being tested, are defined in the protocol and monitored specifically with a sequential probability ratio test (SPRT), which allows the medical monitor and data and safety monitoring board to know when the observed adverse event occurs more often than expected. If the frequency falls outside the previously defined acceptable boundary, the SPRT rejects the null hypothesis and concludes that more events happen within the observed study time than predicted.

This so-called lean reporting process allows the BMT CTN to minimise the data reporting burden for centres, to ensure that all important toxicities are captured, and separate issues of real concern from background data. The approach was effective in the early detection of events that led to the closure of a trial of umbilical cord blood transplant from an unrelated donor for sickle cell disease, and the exclusion of busulfan-conditioning

regimens from a trial of sirolimus prophylaxis for graft-versus-host disease after treatment of only eight and ten patients, respectively.^{102,103} This model is a far more effective than the one-by-one adverse event reports of common HSCT-related toxicities.

Fortunately, the field of HSCT is characterised by the existence of large national and international outcomes registries such as the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT), which systematically collect data on several toxicities that can aid in estimating expected rates and improving understanding of HSCT toxicity. These registries have similar functions, and bone-marrow transplant centres report to them. The CIBMTR systematically collects data on all recipients for 2 years after transplantation and attempts to maintain follow-up on patients through their transplant centres for as long as possible. Data are now available for more than 15 000 15-year survivors. The CIBMTR captures key clinical data entered by centres through an electronic data collection system but is limited in its scope because of funding constraints.¹⁰⁴ Limitations to the large-scale registry include patient loss to follow-up, burden of data submission, and limited data on the patient perspective on quality of life and adverse events. Nevertheless, a particular strength of CIBMTR outcomes data is the reliability of identifying causes of death in the post-HSCT period (figure 7). These data serve as a guide to the likely serious adverse events encountered after HSCT and prevent biases that are specific to centres and drug regimens that are seen in the scientific literature.

In a similar manner, the EBMT is a voluntary organisation of more than 500 transplant centres in 60 different countries (outside North America) that established a comprehensive transplant registry to collect outcomes data. Accreditation as a member centre requires submission of minimal essential data from all consecutive patients to the central registry, and patients can be identified by the diagnosis of underlying disease, type of transplantation, and transplant-related events. The EBMT registry enables detailed analyses of transplant-related complications and consequences, giving a real-life picture from many parts of the world. The EBMT and CIBMTR registries represent an unparalleled opportunity to refine the identification process of transplant-related toxicities. Although the safety and efficacy (ie, the estimate of effect under ideal circumstances) of a newly approved drug is usually first assessed in trials, post-regulatory appraisal relying on specific and comprehensive data collection from the registries will probably reveal clinical effectiveness and longer-term safety more efficiently (ie, the real-world effect).

Most international regulatory health authorities have grappled with the challenges of identifying drug-related toxicity in the context of numerous comorbidities and toxicity related to transplant or drug regimen. To help address these issues, we propose that the haematology

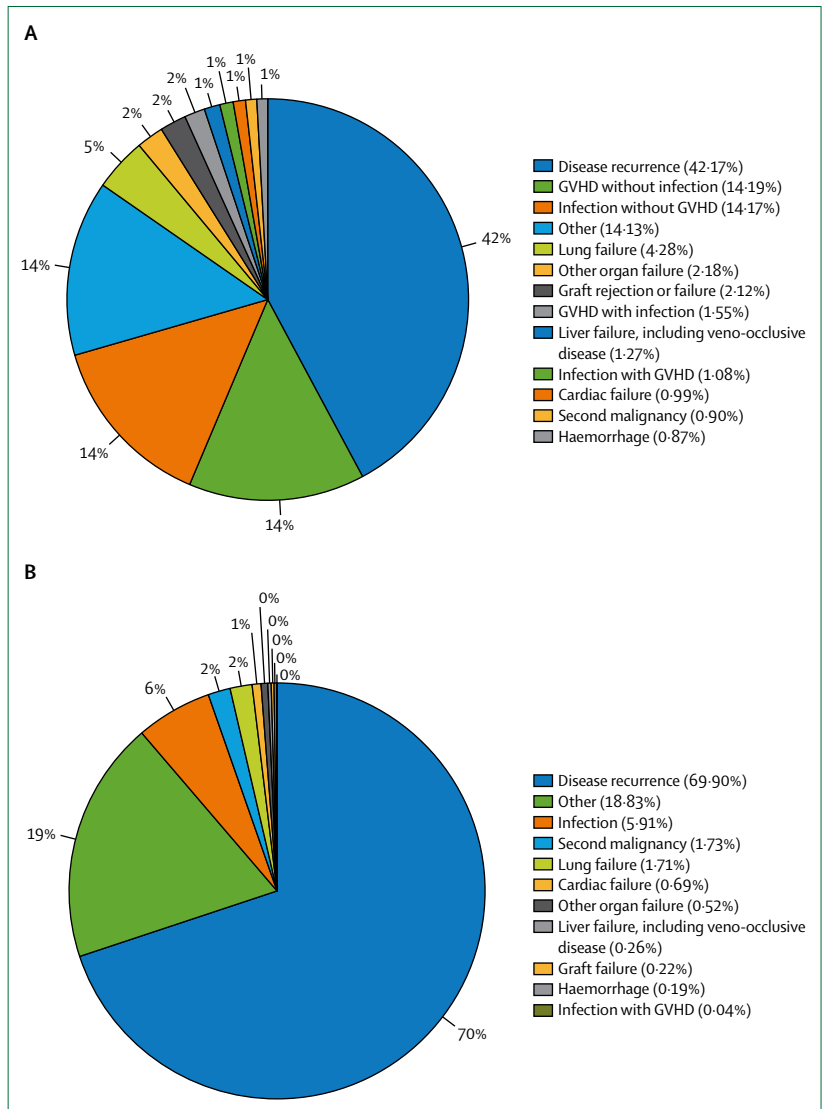


Figure 7: Cause of death after haemopoietic stem-cell transplant (HSCT) from the Center for International Blood and Marrow Transplant Research, an example of valuable data from registries that catalogue toxicity and outcomes after HSCT

(A) Cause of death in first 3 years after allogeneic HSCT from 2008 to 2017. (B) Cause of death in first 3 years after autologous HSCT from 2008 to 2017. GVHD=graft-versus-host disease.

community optimise their strategies and develop consensus on which post-HSCT adverse events should be expected, depending on graft source and transplant regimen, and on acceptably streamlined approaches to capture and analyse these adverse events so that unexpected increases in frequency can be detected without causing undue reporting burden to clinicians and research staff. Such a system should be evaluated and, we hope, advocated by regulatory authorities who have a key role in determining how trials are done, particularly in the corporate sector. Automated approaches to assessing data that are routinely captured in the electronic health record could potentially also help ensure complete reporting of adverse events.

Polypharmacy and drug interactions as adverse events

In addition to its multiple toxicities with little consensus on what is expected, another challenge to toxicity assessment in HSCT lies in long list of concomitant medications that must be reported in traditional adverse event reporting systems. Polypharmacy is the rule for patients in the first few months (and sometimes longer) after HSCT. HSCT recipients receive complex drug regimens including cytotoxic drugs, immunosuppressants, antimicrobials, and supportive and targeted therapies in many different combinations. The risk of a drug–drug interaction as an adverse event is therefore high. Most drug–drug interactions in HSCT alter the concentration of the drug in the body, and they occur most often in the gut and liver and involve cytochrome P-450 (CYP450)-mediated metabolism, inhibition, or induction.¹⁰⁵ For example, fluconazole is a moderate inhibitor of CYP3A4, whereas posaconazole is a strong inhibitor; these drugs therefore both affect metabolism of tacrolimus and sirolimus (both of which are CYP3A4 substrates).^{106,107} Relatively benign drugs such as non-absorbable oral steroids can also trigger CYP-mediated interactions that are toxic.¹⁰⁸ Genetic polymorphisms further complicate potential CYP interactions, and the frequencies and types of interactions are highly variable in different ethnic groups.^{105,106} Checking for CYP polymorphisms in patients who show signs of unusual drug metabolism without other identifiable causes is important.

Pharmacodynamic interactions due to the physiological activity or effects of a drug are also important. For example, the incidence of thrombotic microangiopathy is higher when tacrolimus and sirolimus are used in combination (10–15%) than when each drug is given alone (<5%).¹⁰⁹ Some of the most frequent pharmacodynamic interactions in HSCT are QTc prolongation and myelosuppression, common adverse effects of many of the drugs used in HSCT. These types of drug interactions should therefore be considered when initiating medications, and the patient should be monitored for adverse events that are potentially related to pharmacokinetic or pharmacodynamic alterations.

Infectious adverse events

Infectious complications are common after HSCT and are difficult to characterise and report as adverse events. Different patterns of infection happen at different times, and the risk and type of infectious syndrome varies according to time after transplant and to severity and type of immune compromise.^{110,111} Infectious complications often happen with or after other non-infectious complications, particularly those that compromise tissue barrier function in the host (eg, oral or gastrointestinal tract mucosa) and impede immune reconstitution. The risk for infectious adverse events can therefore only be interpreted in the context of other toxicities.

The severity of infectious adverse events is also difficult to categorise. To date, only one severity grading system in

HSCT recipients has been validated with survival,¹¹² but this scoring system has limitations. Both severity of infection and resource use, such as the need for more complicated therapies (intravenous antimicrobial therapy or hospitalisation), were used to drive grading. Although satisfactory more than a decade ago, many therapies have become oral in the past decade or are now routinely managed in an outpatient setting, making the current scoring system no longer suitable. Moreover, the scoring algorithm did not include several infectious complications that now occur. To address these limitations, the BMT CTN developed a severity algorithm to monitor infectious adverse events in its clinical trials,¹¹³ but it has not been validated with survival.

Ascertainment biases in measuring infectious risk are common in HSCT trials. Two common sources of bias are unfamiliarity with infectious disease definitions and lack of complete diagnostic assessment. Lack of familiarity with infection definitions often leads to over-estimates of certain infectious complications. By contrast, incomplete diagnostic assessment frequently leads to underestimation of other infections and relies unduly on empirical antimicrobial therapies (ie, antimicrobial therapies used presumptively, without a clear definition of the source of infection). The aggressiveness of diagnostic assessment varies between centres, making cross-centre comparisons difficult. Moreover, differences in antimicrobial practices can affect the rates and types of infections. Findings from several studies emphasise the need for audits of data reports by experts who are knowledgeable in the diagnostic criteria.¹¹⁴

The above considerations highlight existing challenges in the assessment of infectious adverse events. Validation of a modern severity algorithm is a priority. In studies where infectious adverse events are primary endpoints or important secondary endpoints, specific training of study personnel at study sites and external auditing of data reports are important for accurate assessment of adverse events. Additionally, standardisation of diagnostic assessment strategies and antimicrobial use is important to reduce inter-centre variability.

Sexual dysfunction and infertility

Sexual dysfunction and fertility issues are to be considered among the serious adverse events after HSCT and in survivors of some haematological malignancies who did not undergo transplant. Sexual dysfunction in the form of body image problems, lack of sexual desire, and impaired physical functioning are common soon after HSCT.^{115,116} These common problems can last for up to 10 years after transplant in female survivors, whereas men are more often able to return to baseline sexual function a few years after transplant.¹¹⁷ Sexual dysfunction as a post-transplant adverse event is often underdiagnosed and underreported, in part because of the lack of a specialised team in sexuality at most transplant centres. Only 20–50% of patients have a discussion with their doctors about sexual health after

HSCT.¹¹⁸ The use of self-reported and validated sexuality questionnaires, such as the 37-item Sexual Function Questionnaire or other patient-reported outcome forms, can help to identify and grade sexual dysfunction after transplant.^{116,119,120} However, the use of different questionnaires between studies makes attempts at comparing results problematic. The development and validation of a tool combining PROs and gradation of adverse events is a priority to help to identify the timing and risk factors of post-HSCT sexual dysfunction and enable the development of preventative strategies.

Myeloablative therapy (such as high-dose total-body irradiation or high-dose busulfan-based regimen conditioning regimens) after HSCT is often associated with azoospermia and premature ovarian failure.^{121,122} There challenges are inherent to the study of fertility after HSCT, although the rate of pregnancy in survivors or in survivor partners has been assessed in a few studies and found to be less than 10%.^{123–125} Potential biases in these studies include lack of systematic paternity testing in female partners of male patients and the likelihood that successful rather than unsuccessful pregnancies are reported. Implementing consultative mechanisms for fertility preservation before treatment and family planning during and after cancer has been an important priority raised by patient advocacy organisations.

Although important progress has been made in fertility medicine as less toxic conditioning regimens are increasingly used, prospective data on fertility and pregnancy outcomes in HSCT survivors and their partners are needed.¹²⁶

Neurocognitive impairment

Impairment of neurocognitive function is increasingly recognised as an important adverse effect and can be seen within the first 100 days after HSCT and up to 10 years later or more. Up to 50% of transplant recipients can be affected by neurocognitive impairment.¹²⁷ Functions subject to impairment include memory, verbal recall, multitasking, coordination, motor dexterity, and speed. Although a global deficit score has been used, a consensus standardised scoring system requires confirmation and itemisation and might have to factor in the time after HSCT (ie, acute events within 100 days vs dysfunction during the medium term [2–5 years] and long term [>6 years]). A consensus panel to address these issues is encouraged.

Secondary malignancies after HSCT

Different categories of secondary malignancies that can occur after HSCT include post-transplant lymphoproliferative disorders, donor-type secondary leukaemia (or other malignancy), and de-novo solid tumours.¹²⁸ Total-body irradiation and the chemotherapeutic drugs used before HSCT as part of the conditioning regimen can induce new secondary malignancies after HSCT. This is attributed to the mutagenic risk of irradiation and

	Proposed solutions: more research and immediate action	Timelines
Improve post-HSCT data capture, analysis, and evaluation	Engage haematology and bone-marrow transplant communities to reach consensus on expected adverse events post-HSCT	Convene consensus conference of stakeholders for early 2019 and provide consensus document in 2020
Improve assessment of drug interactions	Investigate availability of CYP polymorphism status of drugs used post-HSCT	Provide report by mid 2019
Update severity of infectious disease algorithm	Convene infectious disease and bone-marrow transplant stakeholders to develop consensus	Consensus meeting in early 2019; draft consensus document available 2020
Enhance data capture and grading of sexual dysfunction and infertility	Convene consensus conference on combined tool to report outcomes and grading of adverse events	Plan consensus conference for late 2018, and consensus report in 2020
Improve neurocognitive studies post-HSCT	Encourage critical reviews of area	Plan consensus conference on standardisation of grading of neurocognitive adverse events for 2020

Table 4: Improving assessment of adverse events in haemopoietic stem-cell transplantation (HSCT), by priority area

chemotherapy, the genetic predisposition of the patient to develop cancer, prolonged immunosuppression, and to age-related risk (in elderly patients). Secondary malignancies after HSCT are another example of the myriad of toxicities that challenge conventional toxicity reporting. The many issues pertaining to assessment of adverse events in HSCT, as well as potential solutions and timelines for action, are summarised in table 4.

Section 4: Survivorship and long-term toxicity in haematological malignancies

Long-term toxicities such as neurocognitive impairment and sexual dysfunction affect not only patients who have undergone HSCT but survivors of other haematological malignancies. In this section, we focus on challenges in the assessment of adverse events in survivors of haematological cancers. 15·5 million individuals in the USA have a history of cancer, and this number is expected to increase to 20·3 million by 2026.¹²⁹ Long-term toxicity, or late adverse effects, in cancer survivors result from subclinical or asymptomatic physiologic changes that do not cause immediate, intermittent, or short-term clinical events but that, with extended time (many years or even decades), develop into clinically manifest adverse effects. These late effects can substantially affect morbidity, mortality, and quality of life and thus are crucial considerations when assessing survivorship in haematological malignancies.

Heterogeneity of late effects in survivors of haematological malignancies

The marked heterogeneity among survivors of haematological malignancy necessitates a highly individualised approach to understanding the risk of late effects. Key determinants of late effects include treatments administered to cure or control the disease, patient-related factors, and the underlying disease.

Treatments are typically considered the most important contributor to the development of late adverse effects. For highly curable diseases such as Hodgkin's lymphoma, greater emphasis is now placed on selecting initial treatments to maximally avoid late effects. For more aggressive diseases or diseases with greater risk of relapse, higher intensity treatment with a curative goal in the near-term is usually considered more important than the long-term potential for adverse effects. A new challenge is the long-term management of a range of haematological malignancies such as chronic myelogenous leukaemia, chronic lymphocytic leukaemia, indolent lymphoma, and hairy cell leukaemia, which are generally considered incurable but can now be associated with patient survival for decades. These diseases now require continued focus on treating the inevitable relapses of the underlying malignancy and potential late effects. These challenges are further confounded by the relatively recent application of new therapeutic classes of targeted drugs, for which data on potential late effects are only beginning to emerge.

Patient-related factors also affect toxicities in survivors of haematological malignancies, either acting jointly with specific treatment exposures or independently of treatment. These can be intrinsic factors (eg, age at diagnosis, sex, inherited genetic susceptibility) or lifestyle and medical history factors (eg, cigarette smoking, obesity, exercise). Age at diagnosis is the most established patient-related factor that affects risk for late adverse effects. Long-term toxicities are of particular concern for individuals diagnosed at young age because of the potential for increased susceptibility to adverse effects of treatments and the decades of survival during which patients might experience effects. Some specific issues of concern for young survivors include pubertal development status at treatment and risk of late infertility, the interaction between anthracyclines and age at exposure on subsequent cardiovascular disease,¹³⁰ the modulating effect of age and breast radiation exposure on the risk of second breast cancer,¹³¹ and the devastating effect of childhood radiation therapy on subsequent muscle and bone maturity.

The disease itself can be an important determinant of long-term toxicities, as some haematological malignancies are intrinsically associated with future disorders. Examples include the strong relationship between several lymphoid malignancies and subsequent melanoma and non-melanoma skin cancer¹³² and the increased propensity of long-term survivors of chronic lymphocytic leukaemia to develop infections.

Late effects in survivors of haematological malignancies

Many potential late effects can affect survivors of haematological malignancies. We will discuss three broad categories: second malignancies, cardiovascular disease, and psychosocial impairments.

The development of second malignancies is a major contributor to morbidity and mortality in survivors of

haematological malignancies.^{133,134} Large-scale, population-based cancer registry studies have quantified specific patterns of risk, which vary substantially for survivors of different types of haematological malignancies. However, substantial additional research is needed to discover key risk factors, which can then inform long-term follow-up guidelines to screen for second malignancies.

Patients with Hodgkin's lymphoma, the most studied group of haematological malignancy survivors, are at least three-fold to five-fold increased risk of developing subsequent malignancies in or near the radiotherapy field. Indeed, the risk of death from second primary malignancy exceeds that of death from the lymphoma itself.¹³⁵ For cancers of the breast, thyroid, lung, oesophagus, stomach, pancreas, and colon, the risk of death follows a linear dose-response where risk increases with increasing radiation dose.¹³⁶ Some classes of cytotoxic chemotherapy also increase the risk of subsequent cancers, including myelodysplastic syndrome and acute myeloid leukaemia.¹³³ Reductions in radiotherapy doses and volumes of tissue irradiated as well as the shift to less marrow-damaging chemotherapy regimens (eg, from mustine, vincristine, procarbazine, and prednisone [MOPP] to ABVD) to treat Hodgkin's lymphoma are expected to reduce the risk for subsequent malignancies, but long-term follow-up of patients that have been treated recently is needed to confirm this expectation.

Survivors of other haematological malignancies are also at increased risk of developing subsequent malignancies. Risks of chemotherapy-related myelodysplastic syndrome and acute myeloid leukaemia are increased for survivors of nearly all haematological malignancies.¹³⁷ With the introduction of targeted therapy and the shift toward an era of oral chronic therapy, monitoring risks associated with novel approaches to systemic therapy will be pivotal. Risks for lung cancer and melanoma after chronic lymphocytic leukaemia or small lymphocytic lymphoma are higher than for survivors of other types of haematological malignancies, probably because of long-term immune dysfunction.¹³⁸ Non-treatment risk factors for subsequent neoplasms are also being evaluated. Substantial advances in genomics in the past decade hold potential promise for future studies to comprehensively evaluate shared genetic contributors to several types of malignancies and to identify genetic susceptibility to treatment-related neoplasms.¹³⁹ Other major cancer risk factors (eg, cigarette smoking, obesity, and alcohol) also probably contribute to the occurrence of subsequent neoplasms, although these patterns of risk might be similar to those of the general population.

Cardiovascular disease is increasingly recognised as one of the leading causes of morbidity and mortality among survivors of certain haematological malignancies. A substantial amount has been learned from studying the long-term health of survivors of Hodgkin's lymphoma who often receive both chest radiotherapy and anthracyclines.¹⁴⁰ Risks vary by the specific type of cardiovascular

disease, emphasising the importance of detailed clinical data. Specifically, increasing dose of radiation to the chest, which exposes the heart to larger radiation doses, is associated with increasing risk of coronary heart disease, valvular heart disease, congestive heart failure, and pericarditis, with risks first evident 5 years after treatment and persisting for decades. By contrast, anthracycline-containing chemotherapy is associated with congestive heart failure, with risks sometimes becoming evident during treatment and persisting for decades. Importantly, the true magnitude of risk is probably underestimated in most previous studies because a substantial number of survivors might have had some degree of unrecognised and asymptomatic cardiovascular impairment.¹⁴¹

Compared with the general population, survivors of haematological malignancies have an increased risk of psychosocial issues, including depression, somatic distress, anxiety, and post-traumatic stress disorder.^{142,143} Employment is often affected during cancer treatment, and changes in work roles often persist long into survivorship. The economic burden of cancer can persist for years after diagnosis.¹⁴⁴ In addition to the issues experienced by cured survivors, many patients with haematological malignancies have chronic malignancies (eg, chronic myelogenous leukaemia, follicular lymphoma), which might create unique anxiety and uncertainty issues. Development of late medical complications of therapy and psychosocial issues are associated with a reduced quality of life.^{145,146}

Call to action for survivor care: infrastructure and health-care delivery

A challenge clearly exists: there is marked heterogeneity in survivors of haematological malignancies, and the potential late adverse effects are numerous. To satisfactorily capture adverse events in survivors, we identify two areas of unmet needs: infrastructure and health-care delivery.

Quantifying risks of long-term toxicity in survivors of haematological malignancies will rely on substantial efforts to develop infrastructure for systematic data collection over an extended period of time and across the multiplicity of health-care settings traversed by the patient. Focused institutional studies with intensive data collection provide detailed insights into long-term toxicities, whereas large-scale linkage studies provide more population-based information on larger groups of patients, albeit with less detail. Several ongoing efforts exemplify the tremendous promise and the challenges in collecting data necessary for long-term follow-up studies using different strategies.

Two ongoing patient cohorts exemplify the more intensive data collection that also includes direct patient contact. The Childhood Cancer Survivor Study (CCSS)¹⁴⁷ is a retrospective cohort of more than 30 000 5-year survivors of childhood cancer diagnosed during 1970–99 from

31 institutions in the USA and Canada. Detailed data on disease characteristics and treatments occurring within the first 5 years after childhood cancer diagnosis are transferred onto standardised forms at participating institutions. Vital status is updated through periodic linkage with the National Death Index in the USA, whereas other detailed information on a wide range of medical conditions is collected through self-report from patient questionnaires. The Lymphoma Epidemiology of Outcomes Cohort Study is a prospective cohort study of more than 12 000 patients with non-Hodgkin lymphoma who were diagnosed at one of seven centres in the USA. Similar to the CCSS, data are derived both from medical records and patient questionnaires. These cohorts provide the tremendous benefit of capturing detailed long-term toxicity data from patients with haematological malignancies in a systematic way, but the resource-intensive nature of this approach is not feasible for all patients. Limitations to the large-scale cohort or registry include patient loss to follow-up, burden of data submission, and limited data on the patient perspective on quality of life and adverse events. However, additional cohort studies and registries must be encouraged to provide insight into long-term outcomes of patients with other haematological malignancies and receiving a broad range of therapies.

In addition to improving infrastructure to document late toxicities, long-term survivors of cancer are in need of coordinated care that goes beyond surveillance for recurrence. A risk-stratified approach to care, where health-care services are based on risk of recurrence and risk of late effects, has been advocated.¹⁴⁸ The most intensive approach is a multidisciplinary survivorship clinic, which is generally limited to academic medical institutions and reserved for patients at high risk of serious late effects such as patients with Hodgkin's lymphoma who were treated with intensive regimens before 2000 and those patients who have undergone HSCT. Patients at low risk of late effects can be followed by their primary care provider. Many survivors fall into the moderate risk category, where shared care between the haematology–oncology team, primary care team, and perhaps survivorship team, is recommended. However, few studies have compared outcomes, specifically identification of adverse events, between these different models.

Given limitations in the present reach of multidisciplinary survivorship clinics, attention has been focused on survivorship care plans (SCPs) as a tool to promote coordinated, high-quality survivorship care. SCPs offer the promise of promoting patients' understanding of their illness, treatment received, risks of late effects, and ability to seek out appropriate surveillance preventive health care. However, despite repeated calls for increased use of SCPs from the Institute of Medicine, broad implementation of SCPs into routine practice has not been achieved.¹⁴⁹ Limitations to more broad adoption include: logistical challenges

because preparing an individualised, evidence-based SCP is time-consuming and non-reimbursed activity; and scientific shortcomings because few high-quality randomised trials have been done to assess patient-level effect of SCPs, and the benefits have not yet been definitely demonstrated in trials.¹⁵⁰ Despite these barriers, implementation of SCPs has become a component in the cancer centre quality review and accreditation processes. Better integration of SCPs within electronic health records could that improve the tailoring of survivorship care,¹⁵¹ and education of haematology–oncology doctors in communication skills inherent to the survivorship transition for survivors,¹⁵² are two possible approaches to enhancing the effect of SCPs on the wellbeing of survivors of haematological malignancy. Ultimately, evidence-based guidelines for optimal long-term follow-up care of patients are needed.

In conclusion, there are a burgeoning number of survivors of haematological malignancies, with heterogeneity in patients, diseases, and treatment. Adverse events in these patients could include second malignancies, cardiovascular disease, and psychosocial issues. Improvements in infrastructure and health-care delivery are essential to improve understanding of late toxicities and long-term health of these patients.

Section 5: Adverse events in haematological malignancies and regulatory approval

Traditional reporting of adverse events: pre-approval

Although broadly applicable across all malignancies, an understanding of international regulatory processes and challenges inherent to the approval of new cancer drugs is vital to improving processes of adverse event evaluation in haematological malignancies and constitutes the focus of this subsection. Although regulatory bodies of different countries differ with regard to nuanced details of the regulatory process, there are many similarities between the way the FDA, European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) have traditionally dealt with toxicity assessments before drug approval (table 5). Each regulatory body has basic requirements for reporting adverse events that cross a certain qualitative or quantitative threshold. In the USA, sponsors must immediately report serious, unexpected, and suspected adverse reactions that occur on a trial that is done under an investigational new drug application.¹⁵³ These regulations were amended in 2010 by the final rule requiring periodic review of aggregated safety data to ensure detection of new safety signals or a higher rate of serious suspected adverse reactions.¹⁵⁴

In the European Union (EU), the clinical trial sponsor is responsible for recording adverse events, reporting serious, unexpected, and suspected adverse reactions to the national competent authority (directly or through the Eudravigilance Clinical Trials Module; EVCTM) and

the ethics committee, and reporting safety data to the national competent authority and the Ethics Committee on an annual basis.¹⁵⁵ The PMDA in Japan and TGA in Australia also require that at least unexpected fatal or life-threatening adverse events occurring on clinical trials in those countries be reported to each agency.

Although international regulation has been successful in fostering the safe development of therapeutics, harmonisation and adherence to regulation of international clinical trials must be improved. Minor differences in requirements between regulatory bodies mean that individual agencies receive data at different times, potentially leading to variation in the risk–benefit assessment at any given time. Moreover, only 14% of the reports submitted to the FDA Office of Haematology Oncology Products in 2015 were considered informative.¹⁵⁶ The so-called noise of unnecessary safety reports potentially masks the true safety signals that this reporting is intended to detect. Submission of these reports introduces inefficiencies that prevent detection of useful toxicity data that can inform further clinical development and regulatory decision making. The time and financial resources required of already burdened investigators, nurses, and clinical research professionals serve as additional motivation to streamline safety reporting.

Limitations in safety reporting in the premarket setting are widely recognised. Inefficiencies in reporting requirements could lead to the reporter fatigue bias in reporting of adverse events that is generally seen in medical publications, and in haematology and oncology trials in particular.^{157,158} The reliability of toxicity data is further limited in the premarketing setting because safety reports are submitted on an individual basis rather than in aggregate. When submitted in aggregate, safety data are analysed as tabulations of severe or grade 3–4 all-causality adverse events, and some categories might not be equally informative about product safety.¹⁵⁹ Measures of tolerability (eg, drug interruptions and discontinuations or dose reductions) and PROs might not be captured.^{160–162} Health-care utilisation (ie, hospitalisations, concomitant medications) administered to treat toxicity could be better documented. Trial populations are often younger or healthier than those with the disease in the general population.¹⁶³ Gaps in our understanding of a product's safety and tolerability at the time of approval behoove us to enhance post-marketing surveillance to complement other safety and tolerability assessments and better understand the product's use in a real-world population.

Safety review of a submitted marketing application

The standard required for approval across regulatory agencies is demonstration of safety and effectiveness. The safety analysis that informs the risk–benefit assessment relies heavily on the use of tabulated rates of severe and high-grade adverse events, with some weight given to dose interruptions, discontinuations,

	USA	EU	Japan	Australia
Form	Centralised; reporting to FDA	Decentralised; reporting to competent authority of each member nation or their authorised surrogate	Centralised; reporting to PMDA	Centralised; reporting to TGA
Agency	FDA: full authority (including withdrawal and approval of products)	EMA: operates the system on behalf of the EU medicines regulatory network; responsible for signal management of centrally authorised medicinal products in collaboration with PRAC assessor	PMDA and MHLW: full authority (including withdrawal and approval of products)	TGA: full authority (including withdrawal and approval of products)
Adverse event compilation	FAERS (currently only post-approval; pilots of pre-approval safety); Sentinel post-approval*	Eudravigilance database pre-authorisation and post-authorisation	JADER/MID-NET post-authorisation	EPMMA post-authorisation
Expedited safety reporting: attribution	Only events suspected to be drug-related	Events suspected to be related to investigational drugs, including events related to placebo	Only events suspected to be drug-related	Only events suspected to be drug-related
Expedited safety reporting timelines				
Pre-approval	Fatal or life-threatening adverse events within 7 days; Alert Reports of serious and unexpected adverse events within 15 days	Fatal or life-threatening SUSARs within 7 days; Alert Reports of serious and unexpected adverse events within 15 days	Unexpected and fatal adverse events within 7 days; serious and unexpected adverse events and expected and fatal adverse events within 15 days	Unexpected and fatal adverse events within 7 days; serious and unexpected adverse events and expected and fatal adverse events within 15 days
Post-authorisation	Alert Reports of serious and unexpected adverse events within 15 days	Individual case safety report within 15 days for serious EEA and non-EEA cases and within 90 days for non-serious EEA cases (as of Nov 22, 2017)	Serious and unexpected adverse events and expected and fatal adverse events within 15 days or 30 days; serious and expected adverse events within 30 days	Serious and unexpected adverse events and expected and fatal adverse events within 15 days; serious and expected adverse events within 15 days or 30 days
Periodic adverse event and safety updates				
Pre-approval	Annual development safety update report†	Annual development safety update report	Annual development safety update report	Periodic safety update report
Post-approval	Periodic adverse drug experience report; periodic adverse experience report	Periodic safety update report	Periodic benefit-risk assessment report	Periodic adverse event and safety updates
Submission frequency	Annual development safety update report; periodic adverse drug experience report or periodic adverse experience report quarterly for the first 3 years and yearly thereafter	Annual development safety update report; periodic safety update report every 6 months after product authorisation, every 6 months for 2 years after marketing, yearly for the following 2 years, and every 3 years thereafter (depending on each member nation)	Annual development safety update report; periodic benefit-risk assessment report every 6 months for 2 years after marketing, yearly for following years during the re-examination period (10 years for orphan drugs, 8 years for new molecular entity drugs, and 4 years or 6 years for the other drug applications)	Every 6 months after product authorisation, every 6 months for 2 years after marketing, yearly for the following 2 years, and every 3 years thereafter
Content	Narrative summary of the information in the report and an analysis of the 15-day Alert Reports	Individual case safety reports not included; all adverse event data submitted directly to EudraVigilance database	Analysis, summary table, and case list included; individual case safety reports not included	..

EU=European Union. FDA=US Food and Drug Administration. EEA=European Economic Area. EMA=European Medicines Agency. EPMMA=enhanced post-marketing monitoring and analytics. FAERS=FDA adverse event reporting system. IND=investigational new drug. JADER=Japanese Adverse Drug Event Report database. MHLW=Ministry of health, labour and welfare. PMDA=Japanese Pharmaceuticals and Medical Devices Agency. PRAC=Pharmacovigilance Risk Assessment Committee. SUSAR=suspected unexpected serious adverse reaction. TGA=Australian Therapeutic Goods Administration. *The Sentinel database is composed of health outcomes; it might be used to identify outcomes of interest which could be potential adverse events or to establish so-called background occurrences of specific medical conditions or drug utilisation patterns, or both. †IND safety reporting requirements include submission of aggregate analyses of specific events (21CFR 312.32©(1)(i)(C)). The IND annual report must include a summary of the safety reports submitted during the past year and must include specific details such as most frequent and most serious adverse events, causes of death, and dropouts associated with any adverse event; the development safety update report can meet these annual reporting requirements.

Table 5: Global approaches to adverse event reporting

and reductions. Increasingly, approval is granted on the basis of surrogate endpoints collected earlier in the drug development process (accelerated approval in the USA, conditional marketing authorisation in the EU, conditional and term-limited approval in Japan, etc), allowing earlier patient access to promising new therapeutic agents.^{164,165} Approval based on endpoints occurring well before death reduces the duration of administration and follow-up compared with randomised trials using survival endpoints. Unlike many cytotoxic drugs given intermittently and for relatively short durations, toxicities seen with chronically administered, targeted drugs can vary in onset,

duration, and character, as previously discussed. Adverse drug reactions could be idiosyncratic or related to cumulative toxicity, and the shorter trial duration and follow-up characteristic of approvals using expedited regulatory pathways limits characterisation of the intermediate and long-term safety profile for these drugs. Furthermore, the predominance of single-arm trials using expedited pathways challenges accurate attribution of an adverse event to the therapy. In haematology–oncology, differentiating adverse events related to the cancer or other comorbidities from those that are potentially drug-related is particularly challenging.

To mitigate these uncertainties, regulatory agencies leverage post-marketing pharmacovigilance and clinical studies. The FDA has the authority to require or request further studies to better characterise safety after the approval of a drug.¹⁶⁶ These studies assess or identify a serious risk (or risks) related to the use of a drug but are subject to the same challenges with respect to toxicity reporting in clinical trials. The TGA also mandates standard and non-standard post-marketing requirements after approval, and the PMDA can mandate post-marketing investigations during the re-examination period. At the time of finalising a procedure or in follow-up of a signal evaluation, the EMA's committee (or committees) might indicate that a risk-management plan with additional pharmacovigilance activities be provided. This includes the ability to impose a legal obligation to conduct a post-authorisation safety study.¹⁶⁷

Efforts to improve safety reporting and review: pre-market setting and submission review

International regulatory bodies have begun to address impediments to efficient and informative safety data capture. Many issues stem from incomplete reporting or uninformative over-reporting. An expanded toolbox of electronic submission, capture, and analysis of toxicities could improve these deficiencies. The existing manual reporting and submission systems and region-specific variations in regulatory requirements for reporting toxicities, coupled with an often-conservative interpretation of the regulatory requirements by sponsors, has led initial efforts to focus on decreasing the number of safety reports submitted.^{168–170} The risk of missing genuine safety signals because of a large volume of irrelevant information is real, and extraneous data should not be submitted.

To improve efficiency of safety report submission, the TGA has implemented a shift from lengthy paper submissions to a single-page online submission. In Japan, safety reports of industry-sponsored registration trials are electronically submitted to the PMDA. The FDA recently did a pilot project to evaluate the feasibility of submitting safety reports (in the premarketing setting) as datasets that could be processed for analysis. The results of the pilot provide a technical framework for digitised submission of premarket safety reports based on existing standards used in the post-marketing setting via FDA's Adverse event Reporting System (FAERS).¹⁷¹ The project is in its second phase of implementation, and the aim is to build a standard agency process for premarket safety submissions. Once the efficiency of submission and collection is addressed, the breadth of information to be captured needs to be outlined. In the EU, sponsors report serious, unexpected, and suspected adverse reactions to member states and to the centralised EVCTM. Non-commercial sponsors can use the EudraVigilance web-interface to electronically create and submit reports of serious, unexpected, and suspected adverse reactions, and the EudraVigilance

system is used to manage and analyse information on suspected adverse reactions before and after authorisation.

Legislation has been advanced to support incorporation of the patient experience into drug development.^{172,173} One area of great interest to the drug development community is the use of PROs to complement clinical assessment of adverse events. As discussed in section 2, PRO data can add to the overall benefit–risk assessment, particularly in the assessment of a drug that has similar efficacy to an available therapy but a more favourable toxicity profile.

The FDA and other international regulatory and health-care policy leaders are collaborating with experts in the health outcomes research field to explore ways in which these data can assist regulatory review and inform product labeling.^{72,82,84,85} Incorporation of PRO data into labelling has begun at a very early stage.¹⁷⁴ PROs are integral in TGA's decision-making process, which uses the adopted EMA guidelines referenced above. In the USA, certain chronically administered drugs, such as those targeting the PD-1, PD-L1, and PD-L2 pathway include not only tabulated summaries of clinician-reported adverse events and their severity but the median time to onset of immune-mediated toxicities (nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab package inserts). As collection and analysis tools become better refined, regulatory agencies agree that incorporation of these data into the review process is crucial to better describe safety and tolerability.

Patients or their advocates can also inform drug development during the trial design stage. The FDA has a variety of programmes that incorporate opportunities for patient and advocate involvement in the review process.^{175,176}

Post-marketing pharmacovigilance: tools for moving forward

The post-marketing setting provides an opportunity to gain important additional information on safety and tolerability of cancer therapies. Although post-marketing data might benefit from flexibility and larger sources of data in a broader generalised population, these data are less controlled, adding uncertainty outside the rigour of clinical trials (figure 8). Safety data can be generated from off-label use of approved products by individual practitioners. Off-label prescribing of drugs and biologics is beyond the authority of the FDA and not regulated by TGA although the requirement to report adverse events remains. Once a drug has been approved, it is used in a wider population that might be older, sicker, and have different disease and patient characteristics than those enrolled in clinical trials.¹⁷⁸ The duration of therapy might also be longer than that of the patients on trial.

Data collected in the post-marketing phase can document long-term toxicities and tolerability, including low-grade toxicity over time, and is mandated by some regulatory

agencies. In Australia, the TGA mandates a 3-year period of post-marketing surveillance update reporting, which enhances assessment of cumulative toxicities of chronically administered products. The TGA is implementing a project using several IT solutions (eg, electronic submission of adverse event reports) to enhance their ability to identify and manage risk associated with post-market activities.

FAERS in the USA is the main venue for submission of post-marketing safety information by health-care providers, patients, and other stakeholders. FAERS is subject to the same limitations of fatigue and bias seen in the pre-approval setting. In May 2008, the FDA also launched the Sentinel Initiative, which allows the agency to access information from large amounts of electronic health-care data (eg, electronic health records, insurance claims data, and registries) from a diverse group of data partners.¹⁷⁹ These de-identified data can then be queried for analysis of safety signals.¹⁸⁰

In Japan, the re-examination period prescribed by the Pharmaceuticals and Medical Devices Act is 10 years for orphan drugs, 8 years for new molecular entity drugs, and 4 years or 6 years for the other drug applications. The PMDA has constructed the MID-NET medical information database where electronic health record data, claims data from the national health insurance systems, and hospital inpatient expense data are stored. Since 2016, Japan has piloted use of this system for safety data, and they implemented full-scale use in 2018. Signals detected through any of these systems can be used to revise the package insert if assessed as necessary.

In the EU, the Good Pharmacovigilance Practices provide guidance on the reporting of suspected adverse reactions, even in special situations such as off-label use.¹⁸¹ These reports are submitted to EudraVigilance and are thus accessible for signal detection and evaluation. Additionally, mobile apps for patients and health-care professionals for reporting suspected adverse reactions are in development.¹⁸²

Opportunities to leverage various types of real-world data to inform post-marketing safety exist in resources such as Sentinel, the American Society of Clinical Oncology's CancerLinQ,¹⁸³ Flatiron, Optum, OPeN, disease-specific patient registries, patient-generated data platforms (eg, Inspire, PatientsLikeMe, others), ORIEN, large big-data consortium projects in haematology like IMI2 HARMONY and other collaborative efforts (GNS Healthcare and the Multiple Myeloma Research Foundation, Biogen Idec, and Columbia University Medical Center), public and private claims databases, and institutional databases. Large big-data consortium projects that are integrating and analysing anonymous patient data from a high quality sources could provide important learnings on outcomes in haematological malignancies and support decision making of patients, policy makers, and clinicians. The fact that most records exist in

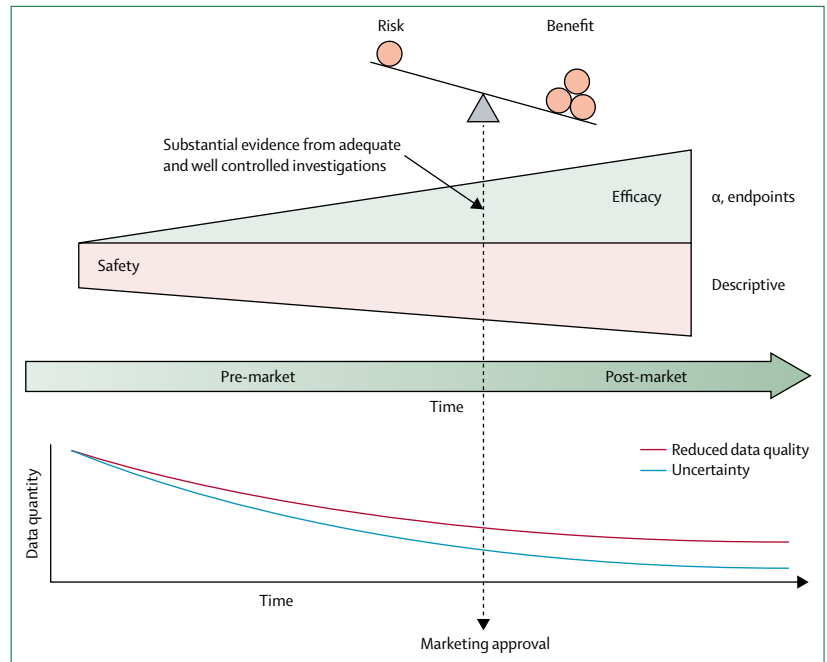


Figure 8: Weighing safety and efficacy in new drugs

Rigorous clinical trials allow for a measure of certainty about the data collected in a selected sample of the general population who will eventually use the therapy. The limited scope of these data at the time of marketing approval necessarily abbreviates the information upon which a regulatory decision must be made. Product regulation does not end at marketing approval, and technology is providing unprecedented opportunities to learn about safety and effectiveness from a greater variety of patients in the post-marketing setting using different data-capture platforms. These data are most often from uncontrolled settings and present a trade-off between large amounts of data in real-world populations on one hand, with challenges in data quality on the other. Adapted from Case Studies: Data Collection and Application of RWE,¹⁷⁷ by permission.

unstructured text form presents a challenge to aggregation and interrogability of real-world data.

Recognising this challenge and that big-data analytics in other research fields can be borrowed for these purposes, the FDA launched the Information Exchange and Data Transformation initiative. The aim of this initiative is to expand and maintain an infrastructure for haematology–oncology data science and big-data analytics to support systems thinking in haematology–oncology regulatory science research, and to devise and use solutions that will improve efficiency, reliability, and productivity.¹⁸⁴ The initiative includes recruitment of experts in big-data analytics, provision of technical infrastructure itself, mentorship, and educational support, and stakeholder engagement. How the data obtained through this initiative will be analysed and interpreted requires much thought and consideration, but the potential to broaden data capture addresses many existing limitations to toxicity assessments. A collaboration between the FDA and CancerLinQ is underway to allow for the collection of real-world evidence when drugs are approved for a specific population; this evidence could inform labelling changes. The initial focus is on patients treated with checkpoint inhibitors, and other approaches in haematological malignancies are certainly relevant.

Panel 3: Opportunities to advance regulatory assessment of adverse events in haematological malignancies, before and after marketing

Underreporting and incomplete capture of adverse events

Electronic submission of adverse event reports (all agencies)

This has been done by the TGA, done for commercial submissions only by PMDA, and is ongoing for the EMA and FDA.

Simplification of adverse event reporting

This has been done by TGA.

Incorporation of real-world evidence into pre-marketing and post-marketing safety (all agencies), using electronic health records, claims data, etc

The FDA uses the Sentinel database, the FDA adverse event reporting system, the Information Exchange and Data Transformation initiative (INFORMED), and partnerships with various platforms. The PMDA uses MID-NET.

Incorporation of patient voice, including PROs into pre-marketing and post-marketing safety (all agencies)

The 21st Century Cures Act requires the FDA to incorporate the patient perspective into drug and device development. Initiatives underway include draft guidances proposed for describing approaches to collection of patient or caregiver input on burden of disease or therapy, development of holistic sets of impact priorities for patients, and measures for analysis of these effects (2018–20); incorporation of patient input and data into risk-benefit assessment (from clinical reviews; 2017); collaboration with the National Cancer Institute and drug development stakeholders to explore the PRO-CTCAE and involvement in workshops and other scientific working groups to advance PRO measurement tools, trial design and analytic methods (ongoing). The EMA and TGA use appendix 2 to the guideline on the evaluation of anticancer medicinal products in humans.^{172,173}

Analysis of data obtained from anything other than a clinical trial

Ongoing efforts of the FDA include the INFORMED initiative, working groups to gather data on real-world evidence and PROs, and contribution to international collaboration to identify core outcome sets and PRO tools for use in the post-market setting.

FDA=US Food and Drug Administration. EMA=European Medicines Agency. PMDA=Japanese Pharmaceuticals and Medical Devices Agency. TGA=Australian Therapeutic Goods Administration. PROs=patient-reported outcomes.

As familiarity is gained with how these systems work and how they need to be improved, they could, at minimum, enable increased data capture in the clinical trial setting. The FDA envisions the potential for novel data pipelines, including real-world data, to be submitted as part of a marketing application and taken into account during regulatory decision making.^{185,186} The ability to harness these capabilities through pragmatic real-world trials would allow for a robust assessment of intervention outcomes in the broader population outside the traditional clinical trial context.^{187–189} The ultimate ability to collect real-world data in or out of the context of a clinical trial and to allow for labelling that better reflects the population to be served, while retaining the rigorous standards for protection of patient safety, is a topic debated in the regulatory community.¹⁹⁰ At this point in time, such evidence might be the only pragmatic approach to answering questions about optimal dosing regimen, long-term use, and outcomes in subpopulations that often remain at the time of drug approval.¹⁹¹

The traditional method of adverse event reporting and analysis has served drug development well for decades but focuses on detection of extreme safety signals such as death and severe morbidity. An opportunity exists to use novel tools and technologies to build on past experience and improve regulatory assessment of adverse events in haematological malignancies, both before and after the marketing phase (panel 3). A more efficient process that is less time consuming and expensive than existing processes will include instruments and analytics that reflect tolerability (using PROs and other clinical outcomes), platforms to integrate all available data from trial participants and real-world patients alike, and analytics to interpret these data. Ultimately, these are fundamental to improving adverse event assessment in haematological malignancies and in solid tumours, with the goal of robust collection of relevant toxicity data that accurately informs drug development, approval, and treatment decisions for patients.

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

Drug toxicity is established in clinical trials where standardised and detailed data about adverse events are collected prospectively and provide a solid foundation for the initial benefit–risk characterisation of new anticancer drugs. Improving toxicity assessment for haematological malignancies in clinical trials has been the primary focus of this Commission thus far. However, real-world evidence is relevant in toxicity assessment as well. In section 5, we explored some aspects of post-marketing surveillance of adverse events from a regulatory standpoint. In this section, we expand on the importance of toxicity data collected outside of clinical trials and identify opportunities to enhance this valuable resource in the real-world setting.

Collection and documentation of toxicity data in routine clinical practice

The detailed toxicity assessments that are required in clinical trials are impractical in routine clinical practice. Effective treatment of a haematological malignancy generally takes priority over adverse event assessments outside of clinical trials, particularly when a treatment is used within its approved indication. Adverse events are documented in health-care records if patients disclose their experience or if the treating health-care provider interprets symptoms and findings as consistent with an adverse drug reaction relevant enough to merit their documentation. Patients might minimise or omit some adverse events for fear of treatment modification or termination. Even when aware of serious adverse events, health-care professionals only report a small fraction of them to the health-care authorities responsible for pharmacovigilance.¹⁹² Real-world toxicity data is therefore likely to be more underreported than in clinical trials.

Agreement between the perception of a particular adverse event between patient and clinician is only moderate, again suggesting a bias in adverse event reporting by clinicians.¹⁹³ These factors are serious limitations to the use of real-world data for toxicity assessment.

Role of databases and registries in collection of adverse event data

Much of what has been learned about toxicity in real-world patients is drawn from several registries and databases that were originally designed to capture data for administrative purposes and outcomes research.^{194,195} A few examples of databases are the Surveillance, Epidemiology, and End Results (SEER) Program (which covers about 28% of the American population), the Mayo Clinic/University of Iowa MER/SPORE hospital-based patient cohort, the regional British Columbia Centre for Lymphoid Cancer database (covering lymphoma patients in the westernmost province of Canada), and national Danish and Swedish registries for several haematological malignancies.^{10,196–201} Some of the databases contain high-quality of data in terms of accuracy and good database coverage.^{198,200} Although registration of detailed toxicity data is not the main purpose of these registries and databases, they are potentially valuable resources for studies of adverse events in real-world patient populations.

At a basic level, databases can be used to identify consecutive patients treated during a given time period, with subsequent back-tracking in medical records for adverse events. Databases can also be used to identify a relevant patient cohort for a prospective analysis, as done in a Norwegian study²⁰² of patients treated with autologous stem-cell transplantation over a period of 20 years. Echocardiography of participating survivors revealed a higher than expected rate of left ventricular systolic dysfunction.²⁰² These approaches add evidence for or against safety signals from other prospective or retrospective reports and provide the denominator of exposed patients needed to estimate the frequency of a particular adverse event. In Denmark and Sweden, unique identification numbers for each individual inhabitant, combined with nationwide patient registries that capture information on hospital contacts, enables nationwide toxicity studies. As an example, data from a Swedish study²⁰³ showed that patients surviving Hodgkin's lymphoma after contemporary treatment had increased health-care use compared with the general population during the first decade after diagnosis, reiterating the burden of late toxicities in survivors of Hodgkin's lymphoma. Again, these analyses are limited to adverse events that consistently require hospital contacts.

Relying on retrospective data collection mandates clear, consistent documentation of adverse events on the basis of consensus definitions in medical records and insensitivity to interpretational bias. Fatigue, insomnia, neuropathy, and pain are common symptoms in cancer patients that have profound negative effects on quality of

Panel 4: Strengths and limitations of databases and registries for adverse event studies

Strengths

- Real-world patients
- Low study costs
- Time efficient studies with quick results
- Large number of patients for analyses
- Rare or late adverse events can be captured
- Results more likely to apply to all patients

Limitations

- Missing data and non-standardised data acquisition
- Biased
- Often sparse information on drug doses
- Not all toxicities are assessable
- Risk of uncontrollable confounding
- Patient reported outcomes rarely available

life, but these subjective toxicities are not reliably assessed in retrospective studies.²⁰⁴ In such situations, absence of documentation cannot be taken as evidence of absence of the adverse event. As many patients with haematological malignancies become long-term survivors or take drugs continuously for months or years to control their disease, adverse events that are not life-threatening but nevertheless have a negative effect on quality of life become increasingly important. Indeed, quality matters as much as quantity of life to many patients with cancer, and data collected prospectively from real-world patients could better inform this difficult balance.²⁰⁵

The value of real-world toxicity data

Despite its limitations, there is substantial value to real-world toxicity data and real-world side effects reported by patients and patient organisations (panel 4). Only a small proportion of patients with cancer (<3% of patients with breast, colorectal, lung, and prostate are enrolled in National Cancer Institute Clinical Trial Cooperative trials in the US) are treated within clinical trials because of restrictive inclusion criteria and limited availability of clinical trials.²⁰⁶ Patients volunteering for clinical trials are typically younger and have better performance status and fewer comorbidities than unselected real-world patients, even in settings where most patients are enrolled in a clinical trial.^{207–209} More importantly, clinical trials protocols often exclude a large proportion of potentially eligible patients on the basis of baseline organ function, comorbidities (including chronic infections), multiple concomitant medications with possible interactions, and certain prior therapies. These conditions limit extrapolation of clinical trial results to real-world patients, particularly in situations of off-label use, and can lead to worse toxicity in clinical practice than initially anticipated from clinical trials.²¹⁰ For example, patients with relapsed or refractory Hodgkin's lymphoma who were previously treated with allogeneic stem-cell transplantation were

excluded from the initial phase 1/2 trials of immune checkpoint inhibitors.²¹¹ Real-world data subsequently described a 30% incidence of acute graft-versus-host disease in patients treated with nivolumab for relapse after allogeneic stem-cell transplant, providing important practice-informing data.²¹²

Follow-up in prospective trials often becomes reduced when the study meets its primary endpoint, limiting the detection of uncommon or late adverse events. The discovery of fatal progressive multifocal leukoencephalopathy from JC polyoma virus reactivation in patients exposed to rituximab exemplifies the value of real-world data for post-marketing pharmacovigilance.¹⁶ The rapidly expanding number of drugs for haematological malignancies, with some patient groups receiving several lines of treatment, underscores the necessity of collecting real-world data that can be used to analyse drug interactions and cumulative toxicities. Many of these drugs will be used in sequence or combination, and real-world data could inform whether prior exposure to a particular treatment increases toxicity from the next line of therapy.

Databases can validate signals from other sources with excellent statistical power. For example, Chen and colleagues²¹³ used the SEER database to estimate the incidence of heart failure or cardiomyopathy in 45 537 elderly women receiving trastuzumab-containing chemotherapy for early breast cancer. In addition to confirming the results of randomised clinical trials in a general population (this study suggested the incidence of cardiac dysfunction might actually be greater in a population of elderly women), this particular toxicity endpoint was evaluated within a sample size that would never have been possible in the context of prospective clinical trials. The strengths and limitations of databases for the assessment of toxicity are summarised in panel 4.

Enhancing reporting of adverse events in databases: lessons from clinical trials

The most obvious way of integrating toxicity data into existing databases and registries is to treat adverse events similarly to other variables already being routinely collected and entered. However, there is more to the process than simply adding new fields for data entry. The main challenge with toxicity is the data itself: many toxicity endpoints are not necessarily objective or easy to measure, introducing subjectivity in the retrospective categorisation of toxicity. Adverse event reporting in clinical trials is typically based on the CTCAE. Ideally, real-world data should be collected with similar consistency, but such consistency is not feasible in a routine clinical setting or in smaller community practices. However, the principles of collecting toxicity data systematically, objectively, and at multiple points over time can certainly be applied to real-world databases.

The main objective of database enhancement is to capture the clinically significant toxicities in a large

population of patients. The process of data ascertainment should therefore not need to be as minutely detailed as in clinical trials. Also, increasing complexity will increase resource utilisation and cost. Capturing every possible adverse event for every patient would be impractical and resource-intensive, so some databases could choose to limit their focus to certain patient groups or toxicity categories. One example is to focus exclusively on potentially curable haematological malignancies where toxicity could derail the success of curative therapy. Another example is to collect a range of predetermined adverse events that are considered most relevant for a given group of patients, although the risk with this approach is missing important and unexpected toxicities. Finally, many administrative databases capture so-called sentinel events (ie, emergency room visit, hospital admission, discontinuation or change of prescription, death), which are more objective than many of the toxicity outcomes. This alternative could be more efficient than screening for the most serious toxicity, but ultimately requires going back to individual medical records.

CancerLinQ, a doctor-led ASCO initiative, is an example of a learning system for oncology that will offer new opportunities to explore real-world toxicities in large groups of patients.¹⁸³ It was primarily developed to improve quality of care for patients treated in a routine clinical setting. Real-time analyses of real-world data were provided directly to the responsible doctor to facilitate more well informed decisions.²¹⁴ By collecting data directly from electronic health-care records, CancerLinQ obviates the need for manual data abstraction, which makes it attractive to clinicians outside academia and ensures fast collection of large amounts of longitudinal data. However, the system relies on data documented in electronic records and therefore shares some of the limitations already discussed.²¹⁵

Another lesson from clinical trials is that toxicity is best assessed prospectively and in real time, when the opportunities to query the clarity of the data, obtain additional information about a particular adverse event, or perform real-time checks for emerging toxicity signals still exist. Although this approach is feasible in databases such as CancerLinQ, other resources such as the large national databases and registries would not be able to accommodate these requirements without substantial investments.

Real-world patients' perspectives on toxicity

Health-care professionals typically collect data to objectively measure the frequency and severity of adverse events, but each patient has a unique experience of adverse events in the context being diagnosed with cancer and expecting a clinical benefit from treatment. Although this experience is difficult to quantify, it must be accounted for better in future studies of real-world patients. As an example, grade 3 neuropathy might be an

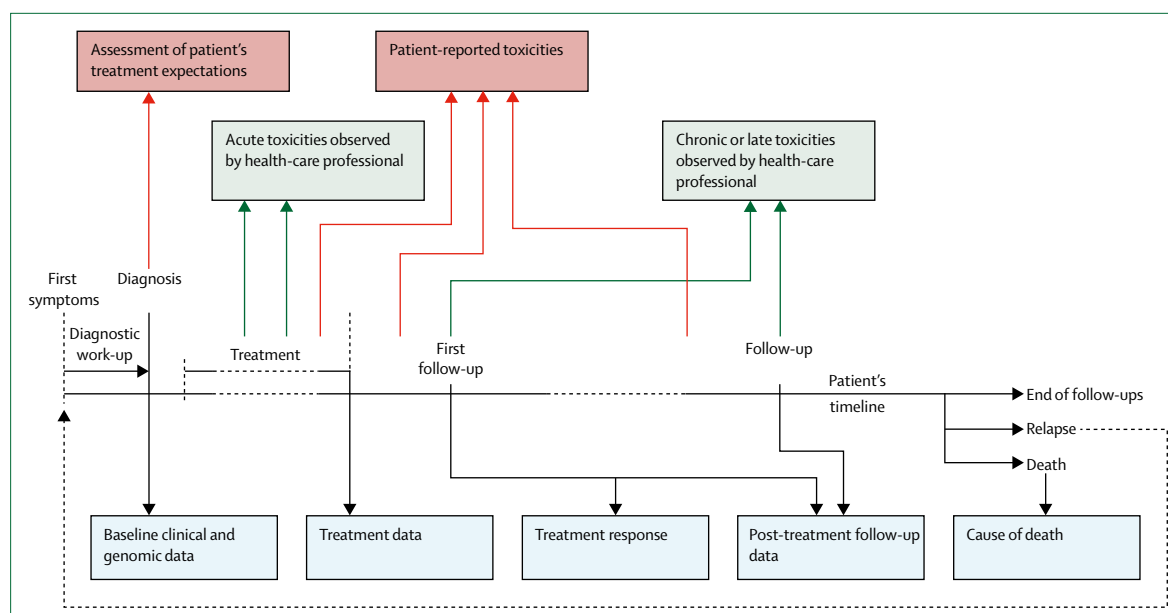


Figure 9: Optimising databases for assessment of real-world toxicity

Optimising databases for future toxicity studies with integration of genomic data and clinical data (blue boxes), real-time toxicity data provided by health-care professionals (green boxes), and patient related outcome measures (red boxes).

acceptable trade-off for a patient with lymphoma receiving curative intent treatment but might not be acceptable to an elderly patient with myeloma who has postural instability and is receiving palliative treatment. Important elements that affect treatment decisions from a patient's perspective are goal of treatment (curative *vs* palliative), magnitude of clinical benefit, potential toxicities, personality, and socioeconomic factors.^{205,216} In metastatic colorectal and lung cancer, patients' expectations about effects of chemotherapy were studied in 1193 individuals,²¹⁷ and most patients had not fully understood that chemotherapy was unlikely to cure their disease. Misconceptions of treatment goals alter the ability to make informed decisions about treatment and probably also affect the subjective experience and acceptance of associated toxicities. To fully understand the severity of toxicities, as experienced by the patients, and their effect on quality of life, toxicity data should be obtained from patients who are fully realistic about the magnitude of clinical benefit from a treatment. Patient organisations are also ideally positioned and increasingly engaged to collect and report real-world evidence on side-effects that is based on data gathered from their constituency.²⁵

Taking advantage of the patient experience to guide management of adverse events

Real-world adverse event data can also be enhanced by directly involving patients in the toxicity reporting process. The data generated by including patients in the actual reporting could provide a better perspective on the aspects of toxicity that patients, rather than health-care

providers, find most relevant. The implementation of tools that measure PRO is possible today with the broad availability of mobile devices, and obtaining such data on a large scale would improve knowledge about real-world toxicity substantially. As technology improves and becomes more widespread and as the ageing population becomes more comfortable with technology, toxicity reporting could be enhanced. A consensus PRO system such as PRO-CTCAE that can translate and quantify information entered by the patient into clinically useful information has the potential to better describe real-world patients' symptoms and the effect of a particular symptom control intervention and to track progress over time.^{58,218} A process for optimising databases for future toxicity studies with integration of genomic data and PRO measures is outlined in figure 9.

Ultimately, clinical trials do not capture the entire picture of toxicities associated with a particular treatment. Real-world data are an important addendum to these data and constitute a resource that has not yet been exploited to its full potential. Many of the existing databases and registries can be harnessed to capture toxicity, but to maximise the clinical and research value of real-world toxicity data, consistency and standardisation procedures similar to those used in clinical trials should be applied. Initiatives like CancerLinQ that mine electronic health-care records for data provide new opportunities for big-data analyses of longitudinal data but cannot stand alone. Incorporation of PROs and integration of genomic and clinical data are initiatives that could clarify the effect of adverse events on the lives of patients. These initiatives will involve a significant

investment that will hopefully pay off with improved patient experiences and outcomes.

A call to action: targets and timelines for improving toxicity assessment in haematological malignancies

As a consequence of substantial changes in disease management approaches in the 21st century, tremendous progress with improved survival and cure rates in haematological malignancies has been achieved. However, new therapies, including chronically administered targeted agents and immunotherapies, among others, present new challenges. Patients are living with the challenge of managing not just their haematological malignancy, but also managing chronic therapy for their illness, with new types of acute, chronic, cumulative and late toxicities. This Commission convened a large, international group of expert authors representing patient advocates, clinicians, clinical researchers, regulators, statisticians and methodologists to address challenges in toxicity reporting in haematological malignancies. This initiative has evaluated current standards of toxicity reporting, the need to incorporate PROs, unique issues of toxicity in HSCT and in survivors of haematological malignancies, regulatory challenges and implementing real world toxicity analysis. We have identified a range of priority issues for improvement in these topic areas, and in this section we define our proposal for improvement and the path moving forward. Many of the proposed solutions are applicable across a broad variety of tumour types, but should be emphasised in haematological malignancies to keep pace with the changing nature of therapies for leukaemia, lymphoma, and myeloma. The challenges identified in this Commission and the specific immediate-term and long-term solutions that constitute this Commission's Call to Action are summarised in table 6.

Current standard and emerging therapies for haematological malignancies challenge traditional approaches to collecting and communicating drug-related adverse events. International efforts to harmonise systems for patient safety monitoring have been ongoing and need to continue to evolve. The standardisation of terminology using consensus definitions such as CTCAE³⁴ remains essential, but defining adverse events in relation to timing of the drug exposure and the duration of these adverse events is now also imperative. Current methods of adverse event analysis focusing solely on maximum grade tables fall short in describing delayed, chronic, or cumulative effects that can limit long-term delivery of therapy. This issue is particularly relevant with the advent of immune therapies and their ensuing immune-related adverse events, which can be delayed, unpredictable, or prolonged. New approaches such as graphical displays from the NCI Web Reporting tool and longitudinal and AUC analyses such as those from ToxT³⁶ have the potential to provide more comprehensive toxicity data in numerical and

graphical form. International stakeholder consensus on the best metrics and representations is important, with the ultimate goal of standardising requirements for comprehensive and time-dependent toxicity data in publications and drug labels. Additionally, clinical trial design needs to accommodate delayed adverse events. Monitoring for dose-limiting toxicity should be expanded to two or three cycles before establishing a recommended phase-2 dosing schedule, or expansion cohorts should be encouraged to account for delayed adverse events in dose determination.

Changing therapies for haematological malignancies require new methods to assess, analyse, and interpret cancer drug safety and tolerability, which must incorporate the voice of the patient through use of PROs. Clinicians tend to underestimate the incidence and severity of symptoms compared with patients' self-reports of similar information generated from PRO measures.⁷⁸ Clinical trials with patients who have haematological malignancies do not typically include PRO assessments. Furthermore, historically, PRO tools did not have the flexibility to include items that captured the differing toxicity profiles seen with the treatments used in a specific haematological malignancy. Implementing tools to complement clinician-recorded CTCAE grading in haematological malignancy trials (eg, PRO-CTCAE⁶⁶), could enhance the assessment of tolerability. Further progress would come with improved integration and development of electronic collection of PROs through smartphones, wearable devices, and other technology that enable a patient to report adverse events in real time. Patient organisations would ideally be involved in the development and validation of these tools. Challenges exist not only in how PRO data should optimally be collected but in how it should be analysed. Lack of consensus as to the best analytical approaches for PRO data makes interpretation of the findings and cross-trial comparisons challenging. Several international collaborative efforts are underway to identify core outcome sets, standard PRO analytic methods, and standard PRO protocol elements. International consensus on the approaches for use and analysis of PROs with clinician-graded adverse events needs to be developed across clinical trials, with input from cooperative groups, patient organisations, regulatory bodies, and agencies.

HSCT presents expected toxicities, graft-versus-host disease, drug-drug interactions, infectious adverse events, and longer-term adverse events affecting transplant survivors. The frequency of adverse events and their expectedness make reporting those that are of relevance an issue in transplantation. It is essential that post-HSCT adverse events be evaluated in the context of consensus definitions of their expectedness, depending on the graft source, transplant regimen, and other factors. Streamlined approaches are needed to capture and analyse these so that unexpected adverse events or increases in frequency of expected adverse events can be readily detected without causing undue burden of

	Concern	Immediate-action solutions (1–5 years)	Long-term solutions (more than 5 years)
Current processes in adverse event assessment (section 1)	Chronic, delayed, and cumulative adverse events are not well captured, leading to incomplete and potentially inaccurate toxicity assessment	- Design phase 1 trials with longer dose-limiting toxicity evaluation periods and increase use of adaptive designs that span phase 1/2 - Continue to develop, disseminate, validate, and apply longitudinal methods for analysis of adverse events	- Establish consensus on the best metrics and representations (tables, graphical representations, etc) of time-dependent adverse event data - Standardise and require use of these metrics and displays in publications and drug labels
Patient-reported outcomes (PROs) in haematological malignancies (section 2)	PROs are not a standard part of toxicity assessment and therefore tolerability of therapies for haematological malignancies from the perspective of the patient is not assessed	- Include hypothesis-driven PROs in more haematological malignancy trials; increase use of PRO-CTCAE or other tools for capturing patient-reported symptomatic adverse events to better inform tolerability of novel and existing drugs for haematological malignancies, particularly those with chronic administration - Explore and facilitate electronic capture of PROs in clinical trials through smartphones, wearable devices, and other technology - Involve patient organisations in development and validation of disease-specific PRO tools	- Identify consensus analytic approaches to convey longitudinal PRO adverse event data - Complement clinician-graded CTCAE reports with patient-reported symptomatic adverse event data to improve understanding of tolerability - Standardise these approaches to the analysis of PROs across cancer trials internationally
Toxicities in HSCT (section 3)	Cumbersome reporting of the myriad of expected adverse events in the HSCT setting is a barrier to performing clinical trials	- Develop consensus on expected adverse events after HSCT based on registry data - Prioritise targeted approaches that focus on unique, potentially relevant adverse events, including unexpected drug interactions and neurocognitive effects	Develop automated approaches that can recognise data routinely captured in the electronic health record as expected toxicity data after HSCT 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 is inconsistent, inadequate, or absent	- Develop and support infrastructure to collect data for adult survivors of haematological malignancies, such as longitudinal patient cohorts - Standardise the use and content of survivorship care plans	- Link PRO, delayed, or long-term complications of haematological malignancies, and their baseline treatment in electronic medical records - Increase availability of multidisciplinary survivorship clinics - Sustain funding of survivorship research
Haematological malignancies and regulatory approval (section 5)	Meaningful adverse events of therapy for haematological malignancies are often underreported to regulatory agencies, while reporting of uninformative adverse events might obscure true safety signals	- Simplify and make electronic the submission of all adverse event reports - Develop better systems for collection and analysis of data obtained from the trial, post-marketing or non-trial setting	- Attain international regulatory consensus on reduction of uninformative adverse event reports to prioritise relevant toxicity data - Incorporate patient experience from trial and non-trial data, including real-world evidence, to inform both the pre-marketing and post-marketing safety evaluation
Toxicity reporting in haematological malignancies and the real-world setting (section 6)	Toxicities affecting patients with haematological malignancies in routine clinical practice are difficult to capture and analyse on a large scale	- Optimise the systematic, objective collection of toxicity data at multiple points over time in real world databases - Explore real-world toxicities in large groups of patients using learning systems and real-time analyses from tools such as CancerLinQ	- Collaborate with informaticists to develop electronic health record systems that reliably capture relevant adverse event (both doctor-reported and PRO) in patients receiving therapy for haematological malignancies off study in a standardised, manageable format - Use systems above to guide adverse event management and symptom control in patients with haematological malignancies

CTCAE=Common Terminology Criteria for Adverse Events. HSCT=haemopoietic stem-cell transplant.

Table 6: Goals of this Commission: summary of targets and timelines for improvements in adverse event assessment in haematological malignancies

reporting to clinicians and research staff. Automated approaches that harness data from electronic health records might be helpful in the future. In view of the number of interventions, adverse events from drug–drug interactions and infectious diseases are very complex in transplantation, and their severity is difficult to categorise. For infectious adverse events, scoring algorithms must include the number of infectious complications that now occur. Late-term effects of transplantation on survivors include sexual dysfunction, infertility, and neurocognitive dysfunction, and the understanding of the incidence and character of these delayed effects is inadequate at present. A uniformed strategy to collect prospective data on fertility and pregnancy outcomes, and a standardised evaluation and grading of neurocognitive function, as examples, would be important tasks for a consensus panel dedicated to improving the assessment of long-term adverse events in HSCT.

Late-term and long-term toxicities affect many survivors of haematological malignancies. Intrinsic factors (age at diagnosis, sex, inherited genetic susceptibilities) and life style factors (smoking, obesity, physical activity, and diet) both affect risks for late toxicity. Secondary malignancies, cardiovascular disease, and psychosocial impairments are major issues that have been reported primarily from national or institutional databases. Standardised, international, longitudinal patient cohorts of adult survivors of haematological malignancies are needed to collect real-life data that cannot come from limited follow-up of most clinical trials. Improved definition of non-relapse mortality is essential. Health-care delivery for survivors beyond surveillance for recurrence also remains a challenge. Evidence-based guidelines for optimal long-term follow-up care of patients with haematological malignancies, ideally within the context of multidisciplinary clinics

dedicated to survivorship and with the involvement of patient support groups, are needed.

Making toxicity assessment in haematological malignancies more comprehensive and accurate without adding logistical complexity and burden is a challenge relevant to regulatory bodies in all parts of the world.^{169,170} Although each country and agency has its own nuanced regulatory process, there are many similarities across bodies such as the FDA, EMA, PMDA, and TGA. Efforts have been made to improve the utility of safety reports and increase the efficiency of reporting process, but there are multiple issues. Unnecessary safety reports, often the result of conservative interpretation of regulatory requirements, are noise that mask true safety signals in the reporting system. The risk of missing genuine safety signals due to a large volume of irrelevant information exists. The time and financial resources required for adverse event reporting are burdensome to patients, investigators, nurses, and clinical research professionals internationally. Meanwhile, relevant information on drug tolerability, such as drug interruptions, discontinuations, or dose reductions are not always reported. Regulatory agencies have also recognised the need to incorporate PRO into tolerability determination, and are involving patient organisations in implementation. The impediments to efficient and informative safety data capture must be discussed at an international level, and an expanded toolbox with simplified, uniform electronic submission is needed. Most regulatory agencies support data collection in the post-marketing setting as an opportunity to gain important additional information on safety and tolerability and revise the package insert of a drug if necessary, but these are subject to reporter fatigue and bias, and their existence is also often unknown to patients. Future directions include pursuing opportunities to leverage a variety of real-world database tools and big-data resources as novel pipelines of data to improve post-marketing toxicity assessment.

Only a small subset of patients with cancer are treated in clinical trials. Additionally, trial populations are often younger or healthier than those with disease in the general population, and follow-up is limited to detect uncommon or late toxicity. The use of real-world data from patients, patient advocacy organisations, and databases is therefore important to improve toxicity assessment. Incomplete registrations, inconsistent terminology and documentation, incomplete follow-up, biased data, and caveats of retrospective causality assessment are all substantial limitations of real-world data. Despite these challenges, harnessing registries and databases to improve toxicity evaluation portends benefit. Optimising the systematic and objective collection of adverse event data over multiple timepoints in real-world databases would facilitate the capture of clinically significant toxicities in large populations of patients. This could be practicably carried out by focusing on a range of predetermined adverse events, certain patient groups, or

toxicity categories. Learning systems such as the CancerLinQ¹⁸³ offer the opportunity to study toxicity in large groups of patients by culling data from electronic health records. Real-world adverse event data is enhanced with the direct involvement of patients and patient organisations in the toxicity reporting process. Ultimately, one goal would be to develop electronic systems that can capture both clinical provider-reported (clinical providers include doctors, nurse practitioners, physician assistants, etc) and PRO toxicity data in a standardised format for patients being treated off study. Consistency in standardisation procedures similar to, but perhaps not as rigorous, as those used in clinical trials should be applied and further developed. This unique data would be valuable for the characterisation of toxicity in non-study patients with haematological malignancies, and it could potentially be harnessed to guide adverse event management and symptom control in the clinic.

The success in outcomes and survival in many haematological malignancies is historically unparalleled and fuelled by scientific discovery and implementation. Measures to address the broad facets of toxicity assessment, as outlined in table 6, must be prioritised and further developed to ultimately enhance accurate, comprehensive, patient-centred toxicity reporting that will meaningfully inform the care of patients with haematological malignancies.

Contributors

GT was the lead author of the Commission and participated in the writing, editing, and review of all sections. TMH was the senior author and participated in the writing of the Introduction, led the writing of the Conclusion, and edited and reviewed all sections. The Introduction lead author was PM (correspondence to philippe.moreau@chu-nantes.fr). Ja-G, Jo-G, TMH, Ma-M, and MVM participated in the writing and editing of the Introduction. GT, TMH, and the authors of the Introduction wrote the Summary. SPI led the writing of section 1 (correspondence to ivyp@ctep.nci.nih.gov). NE, YLK, RL, LMM, SN, JS, CJ, and GT participated in the writing and editing of section 1. LMM led the writing of section 2 (correspondence to minasilo@mail.nih.gov). ACD, PGK, CAT, GV, and SW participated in the writing and editing of section 2. Ar-K led the writing of section 3 (correspondence to armand.keating@uhn.ca). FB, MH, AK, Mo-M, JW, and SW participated in the writing and editing of section 3. CAT led the writing of section 4 (correspondence to thompson.carrie@mayo.edu). MH, Ma-M, LM, JFS, and FVL participated in the writing and editing of section 4. Av-K led the writing of section 5 (correspondence to Aviva.Krauss@fda.hhs.gov). ADC, NE, CG, CJ, PGK, SN, and KT participated in the writing and editing of section 5. TCEG led the writing of section 6 (correspondence to tceg@rn.dk). TCEG and DV drafted section 6, and SR, FC, DV, SPI, and RM reviewed and edited section 6. TMH and GT wrote the conclusions and reviewed the entire commission in detail (correspondence to thanarajasingam.gita@mayo.edu). FC, Jo-G, YLK, LMM, Ja-G, PS, and JS reviewed the conclusions and the entire Commission in detail. JS reviewed in detail the entire manuscript and provided editorial and content feedback. All authors reviewed and approved the final version of the Commission.

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