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Beyond Maximum Grade: Modernizing Adverse Event Assessment and Reporting in Haematologic Malignancies

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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, was the Conclusion lead, and edited and reviewed all sections. The Introduction lead author was PM. Co-authors Ja-G, Jo-G, TMH, Ma-M, and MVM participated in the writing and editing of the Introduction. GT, TMH and the Introduction co-authors wrote the Summary. Subsection I lead author was SPI. Co-authors NE, YLK, RL, LMM, SN, JS, CJ and GT participated in the writing and editing of Subsection I. Subsection II lead author was LMM. Co-authors ACD, PGK, CAT, GV and SW participated in the writing and editing of Subsection II. Subsection III lead author was Ar-K. Co-authors FB, MH, AK, Mo-M, JW, and SW participated in the writing and editing of Subsection III. Subsection IV lead author was CAT. Co-authors MH, Ma-M, LM, JFS and FVL participated in the writing and editing of Subsection IV. Subsection V lead author was Av-K. Co-authors ADC, NE, CG, CJ, PGK, SN and KT participated in the writing and editing of Subsection V. Subsection VI lead author was TCEG. TCEG and DV drafted the subsection together. Co-authors SR, FC, DV, SPI and RM reviewed and edited Subsection VI. Subsection VII lead author was CF. Co-authors LN, KBM and VP participated in the writing and editing of Subsection VII. The Conclusion lead authors were FC and TMH. TMH and GT wrote the Conclusions and reviewed the entire commission in detail. FC, Jo-G,YLK, LMM, Ja-G, PS, and JS reviewed the Conclusions as well as the entire Commission in detail. JS reviewed in detail the entire manuscript providing editorial and content feedback. All authors on the Commission reviewed and approved the final version of the Commission.

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Summary

Tremendous progress in treatment and outcomes has been achieved across the spectrum of haematologic malignancies over the last two decades. While cure rates for aggressive

malignancies have risen, nowhere has progress been more impactful than in the management of typically incurable forms of haematologic cancer. Population-based data have demonstrated substantial improvement in five-year survival rates for chronic myelogenous and chronic lymphocytic leukaemia, indolent B-cell lymphomas, and multiple myeloma. This has resulted from substantial changes in disease management strategies in these malignancies. Several haematologic malignancies are now experienced by patients as chronic illnesses treated with chronically administered therapies that bear 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 (AEs) in haematologic malignancies. The issues pertaining to AE assessment examined here are relevant across a spectrum of malignancies and have been, to date, underexplored in the context of hematology. This international collaborative effort aims to improve toxicity assessment in clinical trials in haematologic malignancies by critically examining the current process of AE 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. This Commission identifies a range of priority issues in these areas and defines proposed solutions to challenges of AE assessment in the current treatment landscape of haematologic malignancies world-wide.

Introduction: Haematologic Malignancies and Their Therapies Have Changed

The haematologic malignancies have been the model for chemotherapy, radiotherapy, molecularly-targeted oral agents and an array of immunotherapies (Table 1, Table 2). These modalities are incorporated into different disease types and result in a variety of adverse events (AEs), some well-characterized and others less understood. New treatments have changed the natural history of many of these diseases. The paradigm is now chronic therapy for years or indefinitely with an expectation of normal life expectancy in some haematologic malignancies diseases. Even among haematologic malignancies treated with shorter term conventional cytotoxics with curative intent, there is increasing recognition of late- and long term AEs that plague patients years and decades after treatment. Our understanding of the patient's experience of treatment toxicity has changed substantially.

Lymphoma treatment is one demonstration of changes in paradigms of therapy and the rising use of newer, chronically administered agents in many haematologic malignancies. Figure 1 demonstrates the proliferation of newer molecularly targeted and immune agents used to treat lymphoma, and exemplifies a shift that has been seen across the hematologic malignancies. Indolent forms of lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) have long been approached as chronic illnesses, but the availability of novel therapeutics has led to a shift in disease management strategies. Whereas historically treatment was largely episodic and finite – a set number of cycles of chemotherapy – many patients now receive chronic oral therapy for relapsed disease(1) or even first-line therapy.(2) Ibrutinib, approved by the FDA as first-line therapy of CLL, has a median progression-free survival in excess of three years, and both idelalisib(3) and venetoclax(4) – each approved for relapsed CLL – 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 chronic oral agents. Idelalisib is FDA-approved in the US for relapsed FL(7), ibrutinib for Waldenström's macroglobulinemia(8), and a host of other oral continuously administered drugs are in active development internationally.

Among lymphomas treated with conventional cytotoxic agents in the short term for curative intent, a deeper recognition of late term AEs has led to evolution in treatment paradigms. In Hodgkin lymphoma (HL), limited stage disease was previously managed with high dose radiation therapy (RT) and advanced disease with combination chemotherapy and RT (9, 10). The late toxicity of these treatment approaches – including secondary malignancies, heart disease, and pulmonary complications – resulted in more treatment–related deaths from complications of survival than deaths from disease. HL is now managed with de-escalation approaches with fewer cycles of chemotherapy and less radiotherapy where possible.(11, 12) in non-Hodgkin lymphoma, the addition of rituximab to chemotherapy improved overall survival in diffuse large B-cell lymphoma(13–15) and introduced unexpected later term toxicities of this monoclonal antibody therapy, such polyoma virus reactivation(16).

In multiple myeloma, the median survival prior has improved substantially in the past decade due to the increased use of high dose therapy and the addition of thalidomide, bortezomib, and lenalidomide along with improved supportive care measures.(10, 17) Over the past five years, multiple new drugs including pomalidomide, carfilzomib, panobinostat, ixazomib, elotuzumab, and daratumumab have become available. The current standard of care is triplet therapy with the advent of these new therapies.(18–20) Venetoclax is now a promising targeted therapy for relapsed/refractory t(11;14) multiple myeloma.(21) Facing a multitude of immunomodulators, targeted agents and immunotherapies, the nature of treatment toxicity faced by multiple myeloma patients has changed substantially over the past decade.

Perhaps no haematologic malignancy exemplifies the shift in treatment and the resultant difference in toxicity profiles better than chronic myelogenous leukaemia (CML). CML is now treated almost exclusively with oral tyrosine kinases targeting BCR-ABL. The agents of this class, initially imatinib, have now been expanded to include dasatinib, nilotinib, bosutinib, radotinib and ponatinib. These continuously administered agents have resulted in life expectancy that approximates that of the age-matched normal population.(22) Along with improved survival, these agents introduced a host of novel toxicities and elucidated the importance of compliance with oral therapies. Rates of less than 90% compliance with imatinib are associated with a 28.4% probability of major molecular response (MMR) versus 94.5% if greater than 90%. Less than 80% adherence to imatinib yields a very low likelihood of molecular response.(23) At the same time, only 32.7% of CML patients have shown to be highly adherent to therapy. Specific CML-related side effects had a significant prognostic influence 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.(77)

Treatment of myeloid malignancies beyond CML has also evolved substantially and now includes several chronically administered agents. Lenalidomide has improved the outcomes of patients with myelodysplastic syndromes (MDS) and the cytogenetic abnormality del(5q), resulting in transfusion independence and improved quality of life.(24) Patients with higher risk MDS, who historically lacked effective treatment options, can now be maintained with hypomethylating agents, allowing some patients to live with MDS as a chronic illness.(25) In the acute myeloid leukaemias (AML), oral targeted therapies such as the FLT3 inhibitor midostaurin are being used in addition to conventional cytotoxic induction regimens(26). Enasidenib, an IDH2 inhibitor, is a continuously administered oral monotherapy now available for relapsed or refractory disease.(27)

The landscape of haematologic malignancies has been changed not only by continuously administered targeted therapies but also by advances in immunotherapy and cellular therapies. Bispecific antibodies such as blinatumomab in ALL(28), checkpoint blockade inhibitors such as pembrolizumab and nivolumab in HL(29, 30), and the advent of CAR-T cells(31)for relapsed non-Hodgkin lymphoma, have also brought new risk and new categories of AEs.

The result of treatment changes across haematologic malignancies is that growing numbers of patients are living with the challenge of managing not just their haematologic malignancy, but also managing the chronic therapy for their illnesses in some cases, and new types of toxicities in others. In this Commission, an international expert panel of physicians, clinical investigators, researchers, methodologists, regulators and patient advocates collaborated to identify and begin to address challenges in AE assessment in clinical trials in this modern era of haematologic malignancies. While several sections of this initiative are relevant to malignancies in general and not just hematologic cancers, the aim of this manuscript is to spotlight the relevance of developing a more comprehensive, accurate and patient-focused toxicity assessment in hematology clinical trials both in industry-sponsored trials as well as investigator-initiated studies. This Commission will begin by proposing improvements in the current process of AE evaluation on trials, as well as by emphasizing the inclusion of patient reported outcomes in current hematology trials. Unique issues pertaining to stem cell transplant and late toxicities of survivors of hematologic malignancy will then be explored. Challenges of toxicity assessment in the context of the regulatory approval of new drugs will then be assessed, followed by a discussion on implementation of better toxicity assessment in real world, non-study patients treated in routine clinical practice across the globe. In each section, challenges inherent to toxicity assessment will be described and proposed solutions put forth. In its conclusion, this paper will define actionable targets for improvements in the assessment of AEs in hematology with a goal of defining the path forward.

Subsection I: Current Processes in Adverse Event Assessment: Strengths & Shortcomings

There are numerous challenges and potential solutions to improving AE assessment in haematology, and inherent to these are an understanding of the strengths and shortcomings of our current approach to toxicity assessment. Newer, often chronically administered

therapies used to treat haematologic malignancies bring with them a different range of toxicities, including an increasing number of long-term symptomatic side-effects that challenge our traditional approaches to collect and communicate drug-related AEs. This subsection will address our current processes for defining and analyzing AEs, and then begin to introduce innovations in how we better capture and analyse toxicity data on clinical trials, including how optimizing AE assessment may influence the drug development process. While the majority of this subsection is deliberately tumor agnostic as the challenges and solutions identified here are applicable to a spectrum of cancer clinical trials, this section will conclude with issues pertaining to AE assessment that are unique to haematology.

Current processes for standardization of AE terminology

The initial steps in development of new agents require harmonized systems for patient safety monitoring that can be utilized internationally. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE)(32), recently published in its fifth version, is one such system.(33) Although the NCI CTCAE version 5.0 has international acceptance for establishing severity-based AE grading, other international systems use MedDRA (Medical Dictionary for Regulatory Activities) terminology to describe AEs. 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 (MTD), dose limiting toxicity (DLT), and provide eligibility parameters and guidance for dose modification. The original version published in 1982 of the CTC included 49 AE terms grouped in 18 categories, each with criteria for grading the severity of the AE. CTCAE v3.0 was the first uniform and comprehensive dictionary of AE grading criteria available for use by all modalities used in the treatment of cancer, and included criteria relevant to surgical, radiation and pediatric-based clinical trials. The adoption of MedDRA® terminology by the ICH (International Conference on Harmonization), NCI, industry, and regulatory bodies provided the impetus for NCI to undertake a redesign of CTCAE in 2008 to be harmonized with MedDRA. The most recent version of the CTCAE, published in 2017, has 837 terms, updated grading information, and a comprehensive index.

Improving AE analysis: aggregated safety analysis, graphic readouts and depicting time profile of AEs

Precise, consensus definitions of AEs and their severity are as important as a consensus method of analyzing and presenting AE data. Current methods of AE analysis fall short in describing toxicities of modern therapies for haematologic malignancies. Typically, AE data are presented in a clinical trial report in the form of a summary table of the high-grade toxicity experienced by any patient over the course of the trial. This provides an efficient display present of the safety assessment of a drug, based onthe number and percentage of high grade events. However, these tables provide no information on the trajectory of the AEs, their onset, progression or cumulative effects which may substantially affect tolerability, as will be described further in the subsequent subsection. In addition to standardizing the terminology and grading of effects, it is useful to define adverse effects in relation to timing of drug exposure. Table 3 provides definitions for acute, chronic, cumulative and late effects.

Longitudinal graphs of the prevalence of specific AEs would provide more information about how the AEs arise and whether the effect becomes cumulative, and resolves with supportive care, dose modification or cycle/course of therapy (Figure 2–4). The NCI Web Reporting System is one tool which facilitates graphical outputs of AE information. One such output is shown in Figure 2 which presents more comprehensive visual output of AE data than a conventional maximum grade table. The pie chart (Fig 2, Panel A) illustrates the concept that the specific toxicity frequency is heterogeneous, and the "common" toxicities can be overshadowed by the constellation of "other" that among themselves do not show up except when added together. Figure 2 Panel B, C and D illustrate both the advantages of following toxicity over time and the limitations in collecting data on chronic toxicity in early phase I and II trials. The patients who remain on study tend to be those who do not have toxicity, and because of patient attrition from the trial decreasing the number at risk, the impression is given that the treatment is more tolerable. Graphical displays which include the number at risk are more accurate.

The Toxicity over Time (ToxT) package is another tool capable of producing different analytic and graphical outputs that include the time profile of AES as well as assessment of the burden of chronic low grade AEs.(34) The ToxT performs longitudinal analyses to depict timeframe of AEs in a variety of ways, including bar charts depicting incidence and grade of AEs by cycle, stream plots showing grade AE by cycle, time to event analyses (Figure 3), as well as an area under the curve (Figure 4). An area under the curve approach is particularly relevant to capturing the impact of chronic low grade toxicity. A patient with a continuous low grade toxicity, such as continuous grade 2 diarrhoea (4–6 stools above baseline daily), should be accounted for as their experience is potentially more substantial than a short-lived, isolated grade 3 toxicity. AUC analysis provides this information in numerical and graphical form, and is depictured in both Figure 2B from the NCI Web Reporting System and Figure 4 from the ToxT. Current methods do not sufficiently capture cumulative dose of agents by using AE data from multiple cycles. These approaches have not yet been integrated prospectively into phase 1 designs, but may help identify more tolerable dosing approaches. Other potential approaches to improving toxicity analysis may include pre-programmed algorithms that identify patterns of combined toxicities that portend added risk for severe events or development of syndromes, e.g. cerebrovascular events, haemolytic uremic syndrome, cardiovascular events.

Challenges in dose and schedule determination in early phase haematology trials

Understanding AE definitions and modes of analysis, we will now address AE assessment in drug development. 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 AEs that are used in aggregate to identify the recommended dose and schedule for later phase investigations. Given that many therapeutics in haematological malignancies are now administered over prolonged periods or chronically until disease progression, however, clinical trial designs need to address dose determination and refinement beyond the phase 1 dose escalation. DLT definitions are generally based on single cycle, acute AEs that are of sufficient severity that dosing cannot be continued at the current dose level. When developing non-cytotoxic, continuously or chronically

administered therapies, the relationship between dose-response and toxicity may not be well understood, and evaluating tolerability in such a short window may not be possible(35) (see below and Subsection II for further discussion on tolerability). Molecularly-targeted and immunotherapy drugs may not have doses and schedules determined during the first cycle of therapy, leading to inexact descriptions of DLTs. This hampers establishing the MTD and the recommended phase 2 dose (RP2D) once dose escalation is completed(36).

One way to address this issue is to lengthen the DLT observation window to two or three cycles prior to establishing the recommended phase 2 dose and schedule. Alternatively, expansion cohorts may further characterize safety and tolerability of a treatment which may lead to further dose and schedule refinement. Phase 2 trials evaluating safety, tolerability and activity or efficacy of molecularly-targeted or immunotherapy drugs may inform dose/schedule refinement. Improving the design of these trials to efficiently determine the dose and schedule to move forward is critically important.

The current short observation window for DLT in phase 1 clinical trials does not permit evaluation of lower grade, chronic toxicities which often leading to dose modification or delay in later cycles and impact tolerability, thus compromising effective dose delivery and in some instances efficacy, altering the benefit-risk assessment of therapy over time. The impact of these low-grade toxicities on quality of life in patients with advanced disease may become intolerable with chronic administration, and are often missed in the standard phase 1 trial DLT evaluation window(37, 38). Inclusion late or delayed AEs to determine RP2D is not standardized. Further study of DLTs that occur outside of AE narrowly-specified time frame is required.

One adaptive design that may assist in the evaluation of chronic low grade AEs is the modified toxicity probability interval design (mTPI) (39) that uses all AEs data prior to dose escalation or de-escalation. Its advantage is each AE regardless of grade is used for dose selection rather than only the AEs in one cycle of therapy using 3–6 patients. The larger sample size increases the confidence that the RP2D determination will establish a safe, tolerable dose and schedule of a new drug that is clinically relevant particularly when AEs occur outside of the DLT window. However, a qualitative judgment analysis of the impact of chronic low grade AEs may be needed to evaluate the impact of therapy.

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

Given that the occurrence of chronic, cumulative and late effects are inherent to many modern therapies for haematologic cancers, longer-term follow-up of patients in both early and later phase trials may be needed to capture the relevant AE profile. One example of the need for novel trial designs and longer DLT observation windows came from the analysis of 54 phase I trials of molecularly targeted agents.(36) Almost a quarter of the patients treated (n=599) who developed grade 3 or higher AEs, had their DLT observed after their first cycle of treatment. Of the 2084 patients reviewed in this analysis, grade 2 AEs such as diarrhoea, fatigue and neutropenia, were observed at the highest frequency in treatment cycles 3 to 6, and not during cycle 1. Another example came from a pooled analysis of 576 patients receiving nivolumab for advanced melanoma(40). AEs of any grade occurred any time between 5 weeks for skin toxicities to 15 weeks for renal toxicities for median time to onset.

A greater challenge is capturing the contribution of toxicity attributable to a novel agent that occurs late in the overall therapeutic course. In classical Hodgkin lymphoma, where PD-1 blockade results in overall response rates of over 80% in the relapsed and refractory setting(29), some severe life threatening complications were not seen until patients underwent allogeneic haematopoietic cell transplantation.(41) This type of data relied 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 leukoencephalopathy(16) after rituximab therapy in HIV-negative patients, hepatitis B reactivation with rituximab(42), delayed neutropenia with rituximab(43), and an association of ibrutinib with aspergillosis(44) and arrhythmias(45) in haematologic cancers. Given the potential chronicity of therapy - in CML for example - longer follow-up may become particularly important as AEs may occur long after the mandatory monitoring period has ended. Furthermore, their pattern may be different at re-starting after a deliberate period off-therapy as compared to initial therapy. For example, late toxicity of imatinib, e.g. cardiac toxicity, abnormal bone and mineral metabolism, hypothyroidism, etc, would not necessarily be observed in studies with exclusively short-term endpoints.(46) A greater expectation of the unexpected, which may occur either acutely or quite delayed, requires mandatory, longer term surveillance if safety data are to be captured comprehensively, particularly as some treated haematologic malignancies now become chronic conditions. There is no formal mechanism for this type of activity, but it is nevertheless of critical importance. Post-marketing surveillance for adverse events is further explored in Subsections V and VI.

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 AE profile, has created regulatory challenges. Perhaps the most compelling examples are the seamless phase 1, 2, 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. IRBs were challenged to assure patient safety as rapidly disseminating safety information without the added safeguard of a data safety monitoring committee proved challenging due to rapid accrual. These were not insurmountable problems, although they did raise ethical concerns. The risk of not identifying the optimal RP2D always exists when compiling non-aggregated data.

Furthermore, the desire for quick-answer short-conduct trials may short-circuit the ability to define important longer-term toxicity. The mandatory solution for evaluation of longer-term toxicity is long term follow up of patients participating on late phase clinical trials. Late occurring toxic effects can adversely affect survival, and this impact can only be detected with adequate follow up. For example, in early stage classical Hodgkin lymphoma, when radiotherapy is used compared to standard ABVD alone, PFS is improved with the addition of radiotherapy, but OS may ultimately be compromised, likely due to late effects of RT.(47) Shorter term endpoints may have regulatory importance in safety assessment, but assessment of longer-term benefit should not be de-emphasized

Data informing late term toxicity may also come from other sources such as post hoc analyses with social media and patient advocacy playing an important role. Examples of this include thromboembolic disease with the use of lenalidomide(48) and concerns regarding toxicity of steroids in multiple myeloma. Patient advocates in the Eastern Cooperative Oncology Group in the US identified high-dose steroids as a concern, leading to a randomized phase III trial proving low-dose steroids with lenalidomide improved survival in multiple myeloma and a subsequent regulatory approval in the US.(49)

For the AE profile knowledge base of new medicines to evolve, real-time multi-directional 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 may no longer be the best method of transfer of AE knowledge for the 21st century, as will be addressed in Subsection V. How AE data are presented can, and should, be much improved, striving for real-time monitoring followed by accurate interpretive reporting.

Complexities of AE assessment unique to haematologic cancers

The definition of AEs and challenges inherent in AE analysis given the time profile of toxicities of existing and novel agents are common between haematologic cancers and solid tumours. However, distinct differences specific to haematological cancers which pose challenges to some AE assessment exist and warrant noting. For example, consider bone marrow involvement by tumour, a far more common situation in haematologic malignancies than solid tumors. The gray area between bone marrow toxicity and the desired therapeutic effect complicates AE reporting and 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 AEs brought on by disease or treatment. Navigating around and through these expected events may in some cases be the only avenue for potential cure of the underlying cancer. The grade 3 and 4 haematologic AEs that commonly occur with acute leukaemias and aggressive lymphomas are not indicative of a therapy that is not effective or safe.

Another example where interpretation of clinical and laboratory findings is particularly challenging in haematologic malignancies and has the potential to mislead drug development was observed during the development of ibrutinib for the treatment of CLL. Immediate post treatment leukocytosis could be interpreted as either a toxicity of the agent or as disease progression, when in fact, it represented the therapeutic effect of ibrutinib.(50) Therefore, defining DLT-qualifying toxicities is challenging in these cases. Treatment of haematological diseases with haematopoietic cell transplantation also requires specific attention to AE reporting that differs from most solid tumour settings and this will be addressed in Subsection IV. Collection of the events is necessary, but the appropriate reporting of the AE events must be made in the context of the disease under treatment.

BOX: New contexts of AE evaluation in haematologic malignancies: immune-related AEs

Advances in immunotherapy, both with checkpoint blockade, bi-specific antibodies and CAR-T cells, has been met with significant practice changing approaches in some

haematologic malignancies, but also introduces great complexity to AE assessment. The recent FDA approval of CAR-T cell therapy in the United States, and the proliferation of these therapies in clinical trials for patients with relapsed haematologic malignancies across many developed countries brings along a myriad of immune-related AEs (irAEs) which are not well captured by current systems of adverse event assessment. These immunotherapy-related adverse events have brought new challenges to reporting, dose modifications, and subsequent patient management.

With regards to checkpoint blockade inhibition, the array of immune-related AEs (irAEs) continues to grow, and with the chronicity of this therapy in many cases, these AEs arise at unpredictable times and their duration in some cases can often be prolonged. Because of the efficacy of these drugs, reporting of AEs has been suboptimal, both because of investigator and patient bias towards not wanting to stop an effective therapy. Unique toxicities with check-point inhibitors include pruritus, maculopapular rash, thyroiditis, pneumonitis, diarrhoea, colitis, hepatitis, arthritis, myositis, nephritis, pericarditis, haematologic toxicities, and neurologic toxicities. At what grade level these and other agents must be discontinued and in what circumstances to retreat are not necessarily clear. The majority of clinically significant irAEs occur early in therapy and are reversible with either the discontinuation of the drug and/or the administration of steroids or other immune suppression and these for the most part are reported. However, some occur late in therapy, some have been 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 irAEs that are underreported and clinically underappreciated. In addition, the definition and recognition of an irAE is often the result of a best clinical judgement which involves subjective consideration of a differential diagnosis, and it is rarely biopsy proven (ie in the case of ground glass opacities that could be due to infection or pneumonitis). As the spectrum of these irAEs has become more defined and we have garnered more experience with their management, the recognition and grading of irAEs has become more standardized and management has become more prescribed with many sponsors using predefined case definitions. This alone will certainly improve irAE evaluation and reporting with these new agents. Formally standardizing irAEs and case definitions in terms of type and grading across all studies will help further in this regard.(51) In addition, incorporating patient reporting of AEs in addition to physician reporting in to clinical trials and post-commercialization will deepen our appreciation for how these irAEs affect a patient on a potentially chronic or long term therapy, as will be discussed in Subsection II.

CAR T cell therapy, on the other hand, poses a potentially opposite problem. In this case the therapy is acute, not chronic, and has a defined and relatively limited array of toxicity largely falling into two distinct categories – cytokine release syndrome (CRS) (52) and neurotoxicity. Regarding CRS, the pathophysiology is fairly well understood and effective therapies exist so thankfully this is largely a time-limited and reversible risk. Regarding neurotoxicity, the pathophysiology is not clearly defined and how to best manage these patients is also unclear. As with CRS, the vast majority of cases are time-limited and reversible but rare cases of protracted neurotoxicity and/or death have been reported. The standardization of a CRS and neurotoxicity classification and grading system by Lee et al(52) that is used across most studies has helped to better characterize these AEs, although

the grading, especially for neurotoxicity, remains somewhat subjective with room for improvement, and not all studies use the same grading system (UPenn and Novartis have a separate grading system, whereas most other use the Lee criteria). The FDA is testing the feasibility of keeping a safety database that cross-references safety information across multiple different INDs for CAR T cell products that is aimed to promote dissemination of new safety information both within the FDA and to study sponsors. Such shared community data would be important and similarly helpful for checkpoint inhibitors in addition to CAR T cell therapy. However, unlike with checkpoint inhibitor therapy, the AE reporting following CAR T cell therapy is fairly accurate but is potentially overemphasized given the high intensity but time limited risk of this therapy on the one hand, and the high clinical impact and efficacy on the other.(53)

With both therapies, however, post-market approval AE reporting becomes incredibly important and is likely to fall short. As these drugs and therapies are given to real world patients with comorbidities that were either not included on previous trials or that were explicitly excluded, or following therapies that had not been previously explored, the risk of these AEs may change dramatically, as will be addressed in Subsection VII. Better tools and strategies for post-marketing AE evaluation and reporting are required to best understand from a risk-benefit ratio who should be receiving these therapies off trial.

Ultimately, vast changes in treatment paradigms for haematologic malignancies should spur changes in our current systems of AE assessment and rethinking of early and late phase clinical trial designs for the assessment of not only acute toxicity but also chronic, cumulate and late AEs (Table 3, Table 4). The ascertainment and reporting of AEs would also be enhanced by inclusion of patient-reported outcomes as discussed in the next subsection.

Subsection II: Incorporation of Patient-Reported Outcomes in AE Evaluation

The welcome advances in outcomes with newer therapies for haematologic malignancies are not without costs. There are challenges inherent to assessing the toxicities of prolonged, continuous therapies as part of usual daily life, as opposed to short-course cytotoxic therapy that have for prior decades been the mainstay of treatment for many haematologic cancers. The acceptable toxicities between these two different scenarios are likely different, and our understanding can be enhanced with the use of longitudinal patient reported outcome (PRO) data. This subsection will focus on the role of PROs in enhancing our understanding of toxicity in haematologic malignancies.

Safety profiles of anti-cancer 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 AEs may lead to dose modifications, elective patient discontinuation or poor adherence to long-term treatment plans, and can significantly 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 as discussed in the preceding subsection.(54) In addition to standard routine clinical visits and clinician reporting of AEs,

incorporating the patient in the assessment of cancer therapies is of great interest both in the clinical trial and clinical care settings.(55)

Patient Reported Outcomes, Health-related Quality of Life and PRO-CTCAE

Patient-reported outcomes (PRO) are assessments based on a report that comes directly from a patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.(56) 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 may be assessed by various methods. For example, the clinical outcome of physical function can be measured by a PRO, a clinician-reported outcome assessment (e.g. Karnofsky Performance Scale), or a performance outcome assessment (e.g., 6-minute 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 (HRQL) is a clinical outcome that is assessed using a PRO measure. The outcome of HRQL is a multidimensional construct defined as the subjective perception of the impact of health (including disease and treatment) on physical, psychological and social functioning and well-being.(57) Typically, HRQL assessments in clinical trials are used to evaluate the effects of cancer and its treatment in aggregate on the patient's perception of well-being, as 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.(58) However, PRO assessments of generic HRQL measures or disease modules may not always incorporate the symptoms of interest for the diversity of novel therapies being investigated. Developers of commonly used PRO measures of HRQL, such as European Organisation for Research and Treatment of Cancer (EORTC) (59), Functional Assessment of Chronic Illness Therapy (FACIT)(60), and the EuroQOL 5D (EQ-5D)(61) 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 currently in development for haematologic malignancies. For instance, rash and ocular side effects may not be assessed in older generic tools. In addition, existing HRQL tools are often designed without assessing the burden and incentive of patients to provide meaningful data, further decreasing the validity of current HRQL approaches. Involving patient organisations in the development and validation of such tools may drive acceptability and data validity.

Increasingly, efforts have been made to overcome this lack of flexibility by incorporating additional ad-hoc questions on symptoms or side-effects to capture additional AEs of the new treatments. Both EORTC and FACIT organizations have publicly accessible item libraries of questions which 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 may still include those which are not typically expected to occur (e.g. peripheral neuropathy in a trial with drugs that do not have that specific toxicity previously recognised).

While HRQL and its functional domains (e.g. physical, cognitive, emotional) can be affected by the toxicity of a therapy, increasingly there is interest in specifically assessing symptomatic treatment-related side effects using PRO measures to complement clinical understanding of safety and tolerability. The U.S. NCI recently developed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Event (PRO-CTCAE™) specifically for self-reporting of symptomatic AEs, mapping to the well-established CTCAE system for clinician reports. This item library for patients contains 124 PRO questions reflecting 78 symptomatic AEs, which is derived from and designed to be used alongside standard clinical reported CTCAE assessments.(62) PRO-CTCAE is flexible such that applicable AEs can be selected for administration depending on the expected side effects of the given clinical trial. PRO-CTCAE has demonstrated positive psychometric properties including construct validity, reliability and responsiveness.(62, 63) With PRO-CTCAE, patients score separately the different aspects of a symptomatic AE, such as the presence, frequency, severity and/or activity interference associated with each term. Thus, PRO-CTCAE *scores* do not correspond to clinician CTCAE *grades.* This difference permits the analysis of patient-reported interference separate from severity, which may lead to insights for tolerability.

Patient Reported Outcomes in Existing Haematologic Malignancies Trials

Many clinical trials in patients with haematologic malignancies have not typically incorporated HRQL or other PRO assessments. Data from NCI-sponsored clinical trials from 2004 through 2016 show that less than 10% of the clinical trials with leukaemia, lymphoma and myeloma patients have included PRO or HRQL endpoints (Table 5). The myeloma phase 3 trials were more likely to have HRQL endpoints than any other trials.

Multiple myeloma is a chronic malignancy characterized by significant symptoms related to disease burden (e.g., bony pain, fatigue) and treatment toxicity (e.g., neuropathy). In recent years, many new agents have been approved that have increased the survival in this 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 impact of treatment on HRQL.(64) Two systematic reviews showed the inclusion of HRQL assessments in myeloma clinical trials to be limited but increasing, and the analysis of HRQL assessments showed significant symptomatic improvement during first-line therapy. (65, 66) Inconsistencies in the incorporation and analysis of HRQL in these trials, however, makes interpretation of these findings and cross-trial comparisons challenging.(65)

In addition to measurement of 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 study comparing rituximab maintenance and re-treatment strategy in patients with low-grade NHL.(67) The trial reported similar illness-related anxiety, overall anxiety, and HRQL between the groups. Investigators concluded that relapse may not be not associated with increased anxiety as

previously thought, and the retreatment strategy resulted in similar patient outcomes while utilizing fewer resources.(67) The international phase 3 trial of watch-and-wait versus rituximab induction versus rituximab maintenance included HRQL at 7 months as a primary endpoint. The patients on the rituximab arms had improved progression-free survival and time to chemotherapy or radiation therapy. The patients on maintenance therapy had improved mental adjustment to cancer scores compared to those on watchful waiting, although no difference in overall QOL, anxiety, depression, or distress as measured by Impact of Events-Scale.(68)

HRQL and other more defined PRO measures of patients 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 multi-dimensional construct for HRQL may not provide the specificity to understand what symptomatic toxicities may be driving the tolerability of a specific regimen.

Safety and Tolerability

Safety and tolerability are critical, but capture different aspects of a regimen's effect on patients. Safety is intended to reflect the medical assessment of an AE that occurred to a patient based on the clinician's judgement about information such as medical history, physical examination, laboratory and imaging findings. Tolerability reflects the extent to which overt AEs impact the patient's willingness and ability to continue the treatment regimen (see Figure 5 and Figure 6).(69, 70)

As discussed in the prior subsection, the primary method for assessing and reporting safety is clinician-graded AEs based on the CTCAE that are reported in tables of the worst grade events.(56) These tables quickly and effectively communicate safety according to the numbers of patients who experienced the worst severity of toxicity at any point in time. However, they do not provide specific information on when the AEs developed, resolved, or improved with supportive interventions which are clinically relevant issues with the long-term, chronic, orally administrated agents (or regimens). These aspects may be highly relevant to tolerability, even if they do not specifically impact safety. Novel graphical or analytic approaches such as those presented in the prior subsection are necessary to incorporate the time profile of AEs of several novel agents.

"Low grade" AEs are not often the focus of safety assessments and may not be recorded on case report forms in many cancer trials. Whereas a low-grade change in potassium may not be important to patients, low grade *symptomatic* AEs, such as nausea, diarrhoea or neuropathy, can be burdensome to patients, particularly when persistent, chronic or cumulative. Low-grade symptomatic AEs have resulted in patient non-adherence to therapy.(71–74) Targeted therapies often are associated with a spectrum of non-specific AEs that may not be frequent or severe, but alter patient HRQL.(75) Studies have demonstrated that clinicians may underestimate the incidence and severity of symptoms, compared to patients' self-reports of similar information generated from PRO measures.(76–78) This difference in clinician and patient responses provides some of the distinction to illustrate the differences between safety and tolerability.(79) A patient may have severe nausea that decreases food intake, but he or she is able to drink fluids and is not dehydrated. This patient would likely

rate his or her nausea as severe; however, the clinician would categorize this nausea as grade 2 by CTCAE. While a short course of treatment with the regimen causing this nausea may be tolerable over a few cycles, it is unlikely to be tolerable over months to years of treatment.

Understanding tolerability of agents over time, such as by incorporating methods such as AUC evaluation for toxicity as previously discussed, is essential to maximize patient benefit. Definitions of toxicity relative to drug exposure are helpful to clarify the time-related function of AEs relative to drug exposure (Subsection I, Table 3). The inclusion of patient-reported symptomatic AEs through tools like PRO-CTCAE, can provide additional data that is complementary to safety data. PRO strategies should begin with a baseline assessment with longitudinal assessments throughout and at the end of treatment, as well as multiple analytic and visualization techniques.

Incorporation of HRQL 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 at standardizing how PRO measures can be analysed and presented.(80, 81) There is now growing interest in utilizing item libraries, such as the PRO-CTCAE, to provide the needed flexibility to select the relevant emergent symptomatic AEs for the trial context that can inform drug safety and tolerability in addition to measuring HRQL.

Statistical Analysis Opportunities for PRO Data

Standardizing PRO assessment and analysis in cancer trials is critical, and several international collaborative efforts are underway in key areas including identifying core outcome sets (COMET, ICHOM) (82, 83), standard PRO analytic methods (SISAQOL)(80), and standard PRO protocol elements (SPIRIT-PRO)(19).

Statistical analysis approaches for PRO data are well established(84) and may include cross-sectional mean estimation with comparisons at key time points using t-tests or analyses of covariance where the baseline PRO score is included as a covariate; longitudinal mean estimation with comparisons using generalized linear mixed modeling (GLMM) or generalized estimating equations; or summary measure approaches exemplified in the prior section (e.g., area-under-the-curve, 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 minimize its occurrence through thoughtful design and enhanced data collection and monitoring.(85) Reasons for missed reports should be captured during data collection and reported in manuscripts(86) to understand how the missing data might bias results. The best statistical approach in the presence of missing data is a method which uses all available data and is robust to some types of missing data, followed by sensitivity analyses which employ a range of missing data methods (e.g., GLMM), 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 (e.g.,

the Bonferroni method), resampling methods, or global tests (e.g., O'Brien's test). As is the case with CTCAE safety data, multiplicity is not a concern when PRO-based AE data are presented in a descriptive fashion without formal statistical comparisons.

Opportunities exist for developing optimal strategies for the estimation and visualization of PRO-based AE data. PRO-based methods which typically rely on estimating severities (in trial participants in aggregate) may not adequately communicate findings to a clinical audience who is accustomed to standard AE reporting of percentages of patients with each CTCAE grade level. Summary approaches typically applied to CTCAE data may not adequately address missing PRO data issues nor properly account for baseline symptoms. An alternative summary measure approach taking the baseline score into account(87) has been proposed which mirrors how clinicians are trained to identify AEs. If a symptom is present at baseline, then it may be considered an adverse effect if it worsens during treatment. Thus, in the proposed baseline adjustment approach, PRO-based AE scores which are the same as or improved from baseline are converted to a score of zero, and scores which are worse than baseline are analysed without modification. Taking baseline into account holds the potential to improve attribution of an AE to the drug under study; a particularly challenging issue in cancer trials with residual toxicities and cancer related symptoms at baseline. Alternative methods which have yet to be fully explored for PRO-based AE data may include joint modelling of PRO-based AE data with CTCAE data and/or disease status, or multiple imputation approaches which use clinician-based CTCAE data as auxiliary data.

Electronic Collection of Patient-Reported Outcomes

In addition to novel methods for analysis of PRO data discussed above, 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 collection of PROs may be burdensome to patients and staff, particularly in the setting of inadequate resources and infrastructure. The telephone or electronic collection or PROs may ease some of these burdens in that it eliminates the need for printing, dissemination and collection of questionnaires, manual scoring, and entry into a database. Electronic collection of PROs is reliable, valid, and may be preferred by patients.(88)

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 are unable or unwilling to use electronic devices, particularly elderly or frail patients. Yet, a recent Pew Report shows that roughly two-thirds of those over 65 years of age are going online, and more than 40% have smartphones with the rate of adoption rapidly increasing. This is occurring even as many seniors acknowledge the need for additional help.(89)

Cancer patients themselves are interested in PROs. The global patient organisation CML Advocates Network initiated an online survey across 63 countries to better understand the extent and drivers of non-adherence. Over 2500 CML patients completed the web- and paper-based survey which showed that adherence correlated with key factors which could be influenced through improved doctor-patient communication such as management of side

effects and satisfaction with level of information about disease. The survey noted that only 32.7% of CML patients were highly adherent to CML therapy, despite a clear correlation of adherence with therapy outcomes. (74)

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

Clinical trials evaluating integrating patient-reported symptoms into the routine care of cancer patients have suggested that this approach can improve physician-patient communication, result in better symptom control for individual patients, reduce patient distress, and have a positive impact on patients' QOL.(90, 91) A recent study demonstrated that electronic PRO collection of symptoms in patients with advanced malignancy improved HRQL, decreased emergency room visits, and resulted in increased survival with greater benefits reported by those patients with less computer experience.(92)

Ultimately, electronic collection enables the patient to report symptomatic AEs in "real-time" as they develop, allowing early intervention with supportive medications. Further studies of the ease of workflow in clinics, acceptability by patients and providers, generalizability, and compliance will be necessary to understand the impact and implement in both clinical trials and clinical care.(93–95)

Evolving treatment paradigms in many haematologic malignancies and the proliferation of chronically administered agents across many different diseases have generated new challenges in understanding side effects and how they affect our patients. Assessment of tolerability is as integral as safety of the drug as therapy moves beyond a limited window for cytotoxics and to months or years with novel targeted agents and immune therapies. Incorporation of PROs into AE assessment holds great promise to inform our understanding of tolerability going forward.

Subsection III: Special Issues of Toxicity in Haematopoietic Stem Cell Transplant

The prior subsections have addressed the importance of how AEs are defined, collected and analysed, and the rising need for PROs to enhance tolerability assessment. The focus of this subsection is specifically on AEs of hematopoietic cell transplantation (HCT), a potentially curative procedure used to treat life-threatening malignant and non-malignant haematologic disorders. It is a complex therapeutic approach that often involves administration of high doses of cytotoxic and/or immune suppressive agents. These agents induce a myriad of toxicities and HCT therefore represents a unique situation in toxicity assessment in

haematologic malignancies. This subsection will primarily challenges pertaining to AE assessment in HCT in light of its multiple complex toxicities (including graft versus host disease [GVHD] in allogeneic transplantation), and will propose optimization of achieving consensus on which post-HCT AEs should be considered "expected" as a route to tackling this problem. We will subsequently also review AEs related to HCT-specific polymedication, infectious AEs, and select longer term AEs post-HCT, including sexual dysfunction, infertility, secondary cancers, and neurocognitive impairment.

Challenges to evaluating multiple, complex toxicities in HCT recipients

There are few, if any, HCT recipients who do not experience at least one serious AE and the overwhelming majority will experience more than one. Reporting the myriad of expected AEs in the early HCT setting is often cited as a barrier to performing clinical trials of agents in HCT. Attribution is often difficult and sometimes impossible in the setting of multiple competing risks. AEs of HCT include prolonged cytopenias and impaired innate and adaptive immune responses leading to opportunistic infections, organ toxicity, particularly (though not limited) to the lungs, liver kidney and gastrointestinal tract, and therapy-related cancers. Toxicities are related to the conditioning regimen and may be influenced by the inclusion of total body irradiation. Allogeneic HCT involves infusion of genetically disparate grafts with the potential for graft-versus-host disease (GVHD) which can be itself life-threatening and require prolonged immune suppressive therapy contributing to the emergence of opportunistic infections. Acute GVHD arises when donor graft immune cells recognize host tissue as foreign, and injures skin, gut and liver. The Seattle (96) and IBMTR(97) grading systems are in use to document the severity of acute GVHD and, despite some limitations, are commonly employed.

Additionally, the frequency of AEs and their "expectedness" also makes under-reporting an issue in HCT, when guidance is not specific (other than the usual definition of serious AEs) and when surveillance is not standardized. This is not only true for HCT but has been demonstrated in pediatric acute leukaemia where use of automatic reviews of laboratory values through the electronic health record demonstrated under-reporting of several organ toxicities(98). However, it may be even more important for HCT, where the significance of a particular AE in a specific setting or trial can only be ascertained by understanding its frequency in relation to what is expected.

Taking a "realistic" approach, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), a US National Institutes of Health supported trials group, has developed a model where only unexpected grades 3–5 AEs are reported in an expedited case-by-case manner while all expected events are reported on calendar-driven case report forms. Independent Medical Monitors (typically transplant physicians or disease matter experts) provide unbiased reviews of unexpected (or more frequent than usually expected) events. 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 rate is above the expected. If the number falls outside the previously defined acceptable boundary,

the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study.

This lean AE reporting process allows the Network to minimize the data reporting burden for centers, to ensure that all important toxicities are captured and to separate issues of real concern from the background. The approach was effective in the early detection of events that led to closing the umbilical cord blood cohort of an unrelated donor transplant trial for sickle cell disease and exclusion of busulfan-conditioning regimens from a trial evaluating sirolimus for GVHD prophylaxis after treatment of only eight and ten subjects, respectively. (99, 100) This is a far more effective model than the one-by-one AE reports of common HCT-related toxicities.

Fortunately, the field of HCT is characterized 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) that systematically collect data on several toxicities that can aid in estimating expected rates and understanding HCT toxicity better. They perform a similar function and reporting to both is mandatory. The CIBMTR systematically collects data on all recipients through two years following transplantation and attempts to maintain follow-up on patients through their transplant centers for as long as possible, with data on more than 15,000 15-year survivors. The CIBMTR captures key clinical data entered by centers through an electronic data collection system, but is limited in its scope due to funding constraints.(101) 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 AEs. Nevertheless, a particular strength of CIBMTR outcomes data is the reliability of identifying causes of death in the post-HCT period, as demonstrated in Figure 7. These data serve as a guide to the likely SAEs encountered after HCT and avoid centre- and regimen-specific biases reported in the literature from single institutions.

In a similar manner, the EBMT which is a voluntary organization comprising more than 500 transplant centers from around 60 different countries (outside north America) established a comprehensive transplant registry collecting outcomes data. Accreditation as a member centre requires submission of minimal essential data from all consecutive patients to the central registry in which patients may be identified by the diagnosis of underlying disease, type of transplantation, and transplant-related events. The EBMT registry enables detailed analyses of transplant complications and consequences to be undertaken, 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. While the safety and efficacy (“estimate of effect under ideal circumstances”) of a newly approved agent is usually first assessed in trials, post-regulatory appraisal relying on specific and comprehensive data collection from the registries, will likely demonstrate clinical effectiveness and longer-term safety more effectively (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 transplant/ regimen related toxicity. To help address these issues we propose that the haematology

community optimize their strategies and develop consensus on which post-HCT AEs should be considered “expected”, depending on graft source and transplant regimen, and on acceptably streamlined approaches to capture and analyse these 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 play a key role in determining how trials are performed, particularly in the corporate sector. Automated approaches to assessing data routinely captured in the electronic health record could potentially also help ensure complete reporting of AEs.

Polypharmacy and Drug Interactions as AEs in HCT

In addition to being subject its unique and multiple toxicities with little consensus on what is expected, another challenge to toxicity assessment HCT lies in long list of concomitant medications that must be reported in traditional AE reporting systems, since polypharmacy is the rule for patients in the first few months (and sometimes longer) after HCT. HCT recipients receive complex medication regimens comprising cytotoxic agents, immunosuppressants, antimicrobials, supportive and targeted therapies in many different combinations, and consequently the potential for a drug-drug interaction as an AE is high. Most drug-drug interactions in HCT result in alterations in drug concentration, occur most often within the gut and liver and involve cytochrome P-450 (CYP450)-mediated metabolism, inhibition or induction.(102) For example, fluconazole is a moderate inhibitor of CYP3A4 and posaconazole is a strong inhibitor; therefore, both impact metabolism of the CYP3A4 substrates, tacrolimus and sirolimus(103, 104). CYP-mediated interactions can also be responsible for toxicity with use of otherwise relatively benign agents, such as non-absorbable oral steroids.(105) Genetic polymorphisms further complicate potential CYP interactions and the frequencies and types are highly variable among different ethnic groups. (102, 103) Checking for CYP polymorphisms in patients exhibiting 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 as exemplified by increased incidence (10–15%) of thrombotic microangiopathy (TMA) when tacrolimus and sirolimus are used in combination, versus when each is given alone (<5%)(106). Some of the most frequent pharmacodynamic interactions in HCT are QTc prolongation and myelosuppression, common adverse effects of many of the medications used in HCT.. It is therefore important to consider these types of drug interactions when initiating medications and monitor the patient for AEs potentially related to pharmacokinetic or pharmacodynamic alterations.

Infectious AEs in HCT

Infectious complications are common after HCT and prove to be difficult AEs to characterize and report. Different patterns of infection occur at different times and the risk and type of infectious syndrome varies according to time after transplant and severity and type of immune compromise. (107, 108) Infectious complications frequently occur with or after other non-infectious complications, particularly those that compromise host anatomical barriers (eg, oral or gastrointestinal tract mucosa) and events that impede immune

reconstitution. Thus, the risk for infectious AEs can only be interpreted in the context of other toxicity AEs.

Severity of infectious AEs is also difficult to categorize. To date, only one severity grading system in HCT recipients has been subjected to validation with survival.(109) Unfortunately, that scoring system has limitations. Both severity of infection and resource utilization, such as the need for more complicated therapies (intravenous antimicrobial therapy or hospitalization), were used to drive grading. Although satisfactory more than a decade ago, during the past decade, numerous therapies have become oral or are now routinely managed in an outpatient setting. Moreover, the scoring algorithm did not include a number of infectious complications that now occur. To address these limitations, the BMT-CTN developed a severity algorithm to monitor infectious AEs in its clinical trials(110), but to date it has not been validated with survival.

There are frequent ascertainment biases in measuring infectious risk in HCT 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. In contrast, incomplete diagnostic assessment frequently under-estimates other infectious events and unduly relies on empiric antimicrobial therapies. The aggressiveness of diagnostic assessment varies among centers making cross-center comparisons difficult. Moreover, differences in antimicrobial practices can influence the rates and types of infections. Several studies emphasize the need for audits of data reports by experts knowledgeable in the diagnostic criteria.(111)

The above considerations emphasize current challenges for infectious AE assessments. Validation of a modern severity algorithm is a priority. In studies where infectious AEs 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 AE assessment. Additionally, standardization of diagnostic assessment strategies and antimicrobial use is important to reduce inter-center variability.

Sexual dysfunction and infertility

Sexual dysfunction and fertility issues are to be considered among the serious AEs after HCT, as well as in survivors of some haematologic malignancies who did not undergo transplant. Sexual dysfunction in the form of body image problems, lack of desire and impaired physical functioning are frequent early after HCT.(112, 113) Further, it remains a common problem 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.(114) Sexual dysfunction as a post-transplant AE is often under-diagnosed and underreported, in part due to the lack of a specialized team in sexuality at most transplant centres. Only 20–50% of patients have a discussion with their physicians regarding sexual health after HCT(115). The use of self-reported validated sexuality questionnaires,such as the 37 item Sexual Function Questionnaire (SFQ) or other patient-reported outcome forms, can help to identify and grade sexual dysfunction after transplant (113)..(116, 117) However, the use of different questionnaires across studies makes attempts at comparing results between studies problematic. The development and validation of a tool combining patient reported outcomes

and gradation of AEs is a priority to help to better identify the timing and risk factors of post-transplant sexual dysfunction and enable the development of preventative strategies.

Myeloablative therapy (such as high-dose TBI or high-dose busulfan based regimen conditioning regimens) after HCT is often associated with azoospermia and premature ovarian failure(118, 119) There are challenges inherent to the study of fertility rates after HCT, although a few studies investigated the rate of pregnancy in survivors or in survivor partners and reported pregnancy rates of less than 10%.(120–122) 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 prior to treatment as well as family planning during and after cancer has been an important priority raised by patient advocacy organizations.

Although important progress has been made in the field of fertility medicine as less toxic conditioning regimens are increasingly used, prospective data on fertility and pregnancy outcomes in HCT survivors and their partners are needed .(123)

Neurocognitive Impairment

Impairment of neurocognitive function is increasingly recognized as an important adverse effect and can be observed within the first 100 days after HCT but also up to 10 or more years later. It can affect up to 50% of transplant recipients.(124) Functions subject to impairment include memory including verbal recall, multitasking, co-ordination, motor dexterity and speed. Although a Global Deficit Score has been utilized, a consensus standardized scoring system requires confirmation and itemization and may require consideration of the time after HCT: acute events (within 100 days), dysfunction during the medium (2–5 years; and long term (>6 years). A consensus panel to address these issues is encouraged.

Secondary malignancies after HCT

Different categories of secondary malignancies can occur after HCT, including post-transplant lymphoproliferative disorders (PTLD), donor type secondary leukaemia/other malignancy and de novo solid tumors(125). TBI and the chemotherapeutic drugs used prior to HCT as part of the conditioning regimen can induce new secondary malignancies after HCT. This is attributed to the mutagenic risk of irradiation and chemotherapy, the genetic predisposition of the patient to develop cancer, prolonged immunosuppression, and in elderly patients, to age-related risk. Secondary malignancies after HCT are another example of the myriad of HCT toxicities that challenge conventional toxicity reporting. In Table 6, we summarize many of the issues pertaining to AE assessment in HCT, as well as potential solutions and timelines for action.

Subsection IV: Long Term Toxicity: Survivorship in Haematologic Malignancies

Long term toxicities such as neurocognitive impairment and sexual dysfunction affect not only patients who have undergone HCT but survivors of other haematologic malignancies as well. The current subsection will focus on challenges in AE assessment in survivors of haematologic cancers. It is currently estimated that there are 15.5 million individuals living in the US with a history of cancer and this number is expected to increase to 20.3 million by the year 2026.(126) 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 which, with extended time (many years or even decades), develop into clinically manifest adverse effects. These late effects can substantially impact morbidity, mortality, and quality of life and thus are critical considerations when evaluating survivorship in haematologic malignancies.

Heterogeneity of Late Effects in Survivors of Haematologic Malignancies

There is marked heterogeneity among survivors of haematologic malignancy and, therefore, a highly individualised approach is necessary to understand the risk of late effects for each patient. Key determinants of late effects include treatments administered to cure or control the disease, patient-related factors and the underlying disease itself.

Treatments are typically considered the most important contributor to the development of late adverse effects. For highly curable diseases, such as Hodgkin lymphoma (HL), greater emphasis is now placed on selection of initial treatments to maximally avoid late effects. In contrast, for more aggressive diseases or those 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 spectrum of haematologic malignancies such as chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL), indolent lymphoma, and hairy cell leukaemia, that are generally considered to be incurable but can now be associated with patient survival for decades. These entities now require continued focus on treatment of the inevitable relapses of the underlying malignancy combined with considerations of 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 influence toxicities in survivors of haematologic malignancies, either acting jointly with specific treatment exposures or independently of treatment. The can be intrinsic factors (e.g., age at diagnosis, sex, inherited genetic susceptibility) as well as lifestyle and medical history factors (e.g., cigarette smoking, obesity, exercise). Age at diagnosis is the most established patient-related factor that impacts risk for late adverse effects. Long-term toxicities are of particular concern for individuals diagnosed at younger ages due to the potential for increased susceptibility to adverse effects of treatments as well as the decades of survival over which patients may experience effects. Some specific issues of concern for younger survivors include pubertal development status at treatment and risk

of late infertility, the interaction between anthracyclines and age at exposure on subsequent cardiovascular disease,(127) the modulating effect of age and breast radiation exposure on the risk of second breast cancer,(128) and the devastating impact of childhood radiation therapy on subsequent muscle and bone maturity.

Finally, the disease itself may be an important determinant of long-term toxicities, as some haematologic malignancies are intrinsically associated with future disorders. An example is the strong relationship between several lymphoid malignancies and subsequent melanoma and non-melanoma skin cancer,(129) and the increased propensity of long-term survivors of CLL to develop infections.

Late Effects in Survivors of Haematologic Malignancies

While there are many potential late effects in 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 among survivors of haematologic malignancies.(130, 131) Large-scale population-based cancer registry studies have quantified specific patterns of risk, which vary substantially for survivors of different types of haematologic 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.

HL patients, the most studied group of haematologic malignancy survivors, have three- to greater than 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 due to lymphoma itself (Figure 8). This most notably includes cancers of the breast, thyroid, lung, oesophagus, stomach, pancreas, and colon for which a linear dose-response of increasing risk with increasing radiation dose is observed(132). Cytotoxic chemotherapy also contributes to risk of a number of these subsequent cancers, including a substantially elevated risk for myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML).(130) Reductions in radiotherapy doses and volumes of tissue irradiated as well as the shift to less myelosuppressive chemotherapy regimens (e.g., from MOPP to ABVD) to treat HL are expected to result in lower risk for subsequent malignancies, but long-term follow-up of more recently treated patients is needed to confirm this expectation.

Survivors of other haematologic malignancies also have increased risk of developing subsequent malignancies. Chemotherapy-related MDS/AML risks are elevated for survivors of nearly all haematologic malignancies.(133) With the introduction of targeted therapy and the shift toward an era of oral chronic therapy (e.g., lenalidomide), monitoring risks associated with novel approaches to systemic therapy will be critical. Risks for lung cancer and melanoma after CLL/SLL are higher than for survivors of other types of haematologic malignancies, likely due to long-term immune dysfunction.(134) Studies are increasingly evaluating non-treatment risk factors for subsequent neoplasms as well. Substantial advances in genomics in the last decade hold potential promise for future studies to comprehensively evaluate shared genetic contributors to multiple types of malignancy as well as identify

genetic susceptibility to treatment-related neoplasms.(135) Other major cancer risk factors (e.g., cigarette smoking, obesity, and alcohol) also likely contribute to the occurrence of subsequent neoplasms, although these patterns of risk may be similar to those of the general population.

Cardiovascular disease is increasingly recognized as one of the leading causes of morbidity and mortality among survivors of certain haematologic malignancies. A substantial amount has been learned from studying the long-term health of HL survivors, who frequently receive both chest radiotherapy and anthracyclines.(136) Risks vary by the specific type of cardiovascular disease, emphasizing the importance of detailed clinical data. Specifically, increasing dose of radiation to the chest, exposing 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 five years following treatment and persisting for decades. In contrast, anthracycline-containing chemotherapy is associated with congestive heart failure, with risks sometimes becoming evident during treatment and also persisting for decades. Importantly, the true magnitude of risk is likely underestimated in most previous studies, as a substantial number of survivors may have some degree of unrecognized and asymptomatic cardiovascular impairment.(137)

Survivors of haematological malignancies have an increased risk of psychosocial issues compared to the general population, including depression, somatic distress, anxiety, and post-traumatic stress disorder.(138, 139) Employment is frequently affected during cancer treatment, and changes in work roles often persist long into survivorship. The economic burden of cancer can persist years after diagnosis.(140) In addition to the issues experienced by “cured” survivors, many patients with haematological malignancies have chronic malignancies (e.g. CML, follicular lymphoma, etc.), which may create unique anxiety and uncertainty issues. Development of late medical complications of therapy as well as psychosocial issues are associated with lower quality of life.(141, 142)

Call To Action for Survivor Care: Infrastructure, Funding and Healthcare Delivery

Thus, a challenge clearly exists: there is marked heterogeneity in survivors of haematological malignancies and the potential late adverse effects are numerous. To satisfactorily capture AEs in survivors, we identify two areas of unmet needs: 1) infrastructure, and 2) healthcare delivery.

Quantifying risks of long-term toxicity in survivors of haematologic malignancies will require substantial efforts to develop infrastructure for systematic data collection over an extended period of time and across the multiplicity of healthcare 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 as well as 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) is a retrospective

cohort of >30,000 5-year survivors of childhood cancer diagnosed during 1970–1999 from 31 institutions in the US and Canada.(143) Detailed data on disease characteristics and treatments occurring within the first five years following childhood cancer diagnosis are abstracted onto standardized forms at participating institutions. Vital status is updated through periodic linkage with the National Death Index in the US, whereas other detailed information on a wide range of medical conditions is collected through self-report from patient questionnaires. The Lymphoma Epidemiology of Outcomes (LEO) Cohort Study is a prospective cohort study of >12,000 NHL patients diagnosed at seven centers in the US. Similar to CCSS, data are derived both from medical records and patient questionnaires. These cohorts exemplify the tremendous benefits of capturing detailed long-term toxicity data on patients with haematological malignancies, but the resource-intensive nature of this approach is not feasible across 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 AEs. However, we must encourage additional cohort studies and registries to provide insight into long-term outcomes of patients with other haematologic malignancies and receiving a broad range of therapies. Subsection VII will further explore the potential expanded role of registries.

In addition to improving infrastructure for capture of late toxicities, long-term cancer survivors are in need of coordinated care that goes beyond surveillance for recurrence. A risk-stratified approach to care, where healthcare services are based on risk of recurrence and risk of late effects, has been advocated.(144) The most intensive approach, a multidisciplinary survivorship clinic, generally limited to academic medical institutions, is reserved for those at high risk of serious late effects, such as HL patients treated with intensive regimens before 2000 and those who have undergone HCT Those 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, there are few studies that have compared outcomes, specifically identification of AEs, amongst 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 healthcare. 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.(145) Limitations to more broad adoption include: logistical challenges, as preparing an individualized, evidence-based SCP is a time-consuming and currently non-reimbursed activity; and scientific shortcomings, as few high-quality randomised trials evaluating patient-level impact of SCPs have been performed, and many of those that have been conducted have not shown improved outcomes for patients.(146) Despite these barriers, implementation of SCP has become a component in cancer center quality review and accreditation processes. Better integration of SCPs within electronic health records may lead to improved tailoring of survivorship care,(147) and education of haematology-oncology physicians in communication skills inherent to the survivorship transition for

survivors,(148) are two possible approaches to enhance the impact of SCPs on the well-being of survivors of haematologic 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. AEs in these patients may include second malignancies, cardiovascular disease, psychosocial issues, and others. Improvements in infrastructure and healthcare delivery are essential in order to improve understanding of late toxicities and long-term health of these patients.

Subsection V: AEs in Haematologic Malignancies & Regulatory Approval

Traditional AE reporting: 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 AE evaluation in haematologic 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 US Food and Drug Administration (FDA), European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) have traditionally dealt with toxicity assessments prior to drug approval (see Table 7). Each has basic requirements for reporting AEs that cross a certain qualitative or quantitative threshold. In the US, sponsors must immediately report serious, unexpected, and suspected adverse reactions (SUSARs) that occur on a trial conducted under an investigational new drug application (IND).(149) 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.(150)

In the European Union (EU), the clinical trial sponsor is responsible for recording AEs, reporting SUSARs to the national competent authority (directly or through the Eudravigilance Clinical Trials Module; EVCTM) and the Ethics Committee, and annual safety reporting to the national competent authority and the Ethics Committee(151). The PMDA in Japan and TGA in Australia also require that at least unexpected fatal or life-threatening AEs occurring on registrational trials in those countries be reported to each agency. Table 8 outlines the similarities and differences between the safety requirements of each agency.

While international regulation has been successful in fostering the safe development of therapeutics, harmonization and adherence to regulation of international clinical trials must be improved. Minor differences in requirements across 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 in 2015 to the FDA Office of Haematology Oncology Products (OHOP) were considered informative (152). The “noise” of unnecessary safety reports potentially masks the true safety signals this reporting is intended to detect. Submission of these reports introduces inefficiencies that stand in the way 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 recognized. Inefficiencies in reporting requirements may lead to “reporter fatigue” and “reporter bias” seen in AE reporting in medical publications in general, and in hematology and oncology trials in particular (153, 154). Reliability of toxicity rates is further limited in the pre-marketing setting, since 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 AEs, and some categories may not be equally informative with regard to product safety (155). Measures of tolerability such as drug interruptions and discontinuations or dose reductions, may not be captured, nor are patient reported outcomes (PROs) (156–158). Healthcare utilization (hospitalizations, 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 (159). Gaps in our understanding of a product’s safety and tolerability at the time of approval behove 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, as discussed below and in the next subsection.

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/or high-grade AEs, with some weight given to dose interruptions, discontinuations, and reductions. Increasingly, approval is granted on the basis of surrogate endpoints collected earlier in the drug development process (accelerated approval (AA) in the US, conditional marketing authorization (CMA) in the EU, conditional and term-limited approval in Japan etc.), allowing earlier patient access to promising new therapeutic agents (160, 161). Approval based on endpoints occurring well before death results in shorter duration of administration and follow-up than is seen in randomised trials using survival endpoints. Unlike many cytotoxic agents given intermittently and for relatively short durations, toxicities seen with chronically administered targeted agents can vary in onset, duration and character as detailed in prior subsections. Adverse drug reactions may be idiosyncratic or related to cumulative toxicity, and the shorter trial duration and follow-up characteristic of approvals using expedited regulatory pathways limits characterization of the intermediate and long-term safety profile for these agents. Furthermore, the predominance of single-arm trials using expedited pathways challenges accurate attribution of an AE to the therapy. In haematology-oncology, differentiating AEs 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. FDA has authority to require or request further studies to better characterize safety following the approval of a drug.(162) These studies

assess or identify a serious risk(s) related to the use of a drug, but are subject to the same challenges noted above regarding toxicity reporting in clinical trials. TGA also mandates standard and non-standard post-marketing requirements following approval, and PMDA can mandate post-marketing investigations during the re-examination period. At the time of finalizing a procedure or in follow-up of a signal evaluation, the EMA's Committee(s) may indicate that additional data post-authorization, including additional pharmacovigilance activities, should be provided.

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 current manual reporting/submission systems and region-specific variations on 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(163–165). The risk of missing genuine safety signals due to a large volume of irrelevant information is real, and extraneous data should not be submitted.

To improve efficiency of safety report submission, 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 PMDA. FDA recently completed a pilot that evaluated the feasibility of submission of safety reports in the pre-marketing setting as datasets, which can then be processed for analysis. The results provided a technical framework for digitized submission of premarket safety reports based on existing standards used in the post-marketing setting via FDA's Adverse event Reporting System (FAERS) (166). The project is in its second phase of implementation, which aims to build this as 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 SUSARs to Member States as well as the centralized EVCTM. Non-commercial sponsors can use the EudraVigilance web-interface (EVWEB) to electronically create and submit SUSAR reports, and the EudraVigilance system is used to manage and analyse information on suspected adverse reactions in the pre- and post-authorisation phase.

Legislation has been advanced to support incorporation of the patient experience into drug development (167) (168)). One area of great interest to the drug development community is the use of patient-reported outcomes (PRO) to complement clinical AE evaluation. This topic is comprehensively discussed in Subsection II. PRO data can provide important information to add to the overall benefit-risk assessment, particularly in the evaluation of a drug that has similar efficacy to an available therapy, but that may have a more favourable toxicity profile.

FDA and other international regulatory and healthcare policy leaders are collaborating with experts in the healthcare outcomes research field to explore ways in which this data can

assist regulatory review and inform product labeling.(80, 83, 169–171) . Incorporation of PRO data into labeling has begun at a very early stage. PROs are integral in TGA's decision-making process, using the adopted EMA guidelines referenced above. In the US, certain chronically administered products such as those targeting the PD-1/PD-L1/2 pathway include not only tabulated summaries of clinician-reported AEs and their severity, but also the median time to onset of immune-mediated toxicities (nivolumab, pembrolizumab, and avelumab package inserts). As collection and analysis tools are better refined, regulatory agencies agree that incorporation of these data into the review process is critical 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 programs that incorporate opportunities for patient and advocate involvement in the review process.(172, 173)

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. While post-marketing data may benefit from flexibility and larger sources of data in a broader generalized population, these data are less controlled, adding uncertainty outside the rigor of clinical trials (Figure 9). Safety data may be generated from off-label use of approved products by individual practitioners. Off-label prescribing of drugs and biologics is beyond the authority of FDA and not regulated by TGAalthough there remains an AE reporting requirement.. Once a drug has been approved, it is used in a wider population that may be older, sicker, and with different disease and patient characteristics than those enrolled on clinical trials (174). Furthermore, the duration of therapy may be longer than that of the patients on trial.

Collection of data post-marketing can document long-term toxicities and tolerability, including low-grade toxicity over time and is mandated by some regulatory agencies. In Australia, TGA mandates a 3-year period of post-marketing surveillance update reporting, which enhances assessment of cumulative toxicities of chronically administered products. The agency is implementing a project using a number of IT solutions to enhance TGA's ability to identify and manage risk associated with post-market activities, including electronic submission of AE reports.

FAERS in the US is the main venue for submission of post-marketing safety information by healthcare providers, patients and other stakeholders. FAERS is also subject to limitations of reporter fatigue and bias described above 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 healthcare data, such as electronic health records (EHR), insurance claims data and registries, from a diverse group of data partners.(175) These de-identified data can then be queried for analysis of safety signals.(176)

In Japan, the Pharmaceuticals and Medical Devices Act prescribed re-examination period is 10 years for orphan drugs, 8 years for new molecular entity drugs, and 4 or 6 years for the other drug applications. PMDA has constructed a medical information database "MID-NET," where EHR data, claims data from the national health insurance system and hospital

inpatient expense data are stored. Since 2016, Japan has piloted use of this system for safety data, and they plan to implement full-scale utilization 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 (GVP) provide guidance on the reporting of suspected adverse reactions including special situations such as off-label use(177). These reports are submitted to EudraVigilance, and thus accessible for signal detection and evaluation.. Additionally, a mobile apps for patients and healthcare professionals to report suspected adverse reactions are in development(178).

Opportunities to leverage various types of real-world data to inform post-marketing safety exist in resources such as Sentinel, ASCO's CancerLinQ(179), FLATIRON, Optum, OPeN, disease-specific patient registries, patient-generated data platforms (e.g. 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, institutional data bases and others. Large big data consortium projects that are integrating and analysing anonymous patient data from a number of high quality sources may provide important learnings on outcomes in haematological malignancies as well as support decision making of patients, policy makers and clinicians. As described in Subsection VI, the fact that most records exist in text form (unstructured) presents a challenge to ingestion and aggregation of real-world data.

Recognizing this challenge, and that big-data analytics in other fields may be borrowed for these purposes, FDAlaunched the Information Exchange and Data Transformation (INFORMED) initiative. This aims to expand and maintain an infrastructure for haematology-oncology data science and big-data analytics, as well as to support systems thinking in haematology-oncology regulatory science research; specifically, to devise and use solutions that will improve efficiency, reliability, and productivity (175). The initiative includes recruitment of experts in big-data analytics, the 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 of the current limitations to toxicity assessments discussed above. A collaboration between FDA and CancerLinQ (CancerLinQ is further described in Subsection VI) is underway to allow for the collection of real world evidence when drugs are approved for a specific population; this evidence may potentially inform labeling changes or using data obtained from a real-world population. Although the initial focus is melanoma,, similar approaches in haematologic malignancies are certainly relevant.

As familiarity is gained with how these systems work and how they need to be improved, they may at minimum afford increased data capture in the clinical trial setting. FDA envisions the potential for "novel pipelines" of data, including real-world data, to be submitted as part of a marketing application and taken into account during regulatory decision making (180). 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 (181–183). The ultimate ability to collect real-world data in or out of the context of a clinical trial and 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 (184). This evidence may be the only pragmatic approach at this time to answering questions that often remain at the time of drug approval regarding the optimal dosing regimen, long term use, outcomes in subpopulations, and others (185).

The traditional method of AE 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 build on past experience using novel tools and technologies and improve regulatory assessment of AEs in haematologic malignancies both pre and post-marketing (see Table 8). A more efficient process that is less time consuming and expensive 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 assessment in haematologic malignancies as well as solid tumors, with the goal of robust collection of relevant toxicity data that accurately informs drug development, approval, and treatment decisions for patients.

Subsection VI: Toxicity Reporting in Haematologic Malignancies in the Real World Setting

Drug toxicity is established in clinical trials where standardized and detailed AE data are collected prospectively and provide a solid foundation for the initial benefit-risk characterization of new anticancer drugs. Improving toxicity assessment in clinical trials in haematologic malignancies has been the primary focus of this Commission thus far. So why should we care about real-world evidence with incomplete registrations, insufficient follow-up, biased data, caveats of retrospective causality assessments, and little information on drug dosing schedules in this initiative. Subsection V explored some aspects of post-marketing surveillance of AE from a regulatory standpoint. This section expands upon the importance of toxicity data collected outside of clinical trials, explores the potential returns from improvements in AE assessment and reporting in haematology, and identifies opportunities to enhance this valuable resource in the real world setting.

Collection and documentation of toxicity data in routine clinical practice

In routine clinical practice, it is impractical to perform the detailed toxicity assessments required in clinical trials. Effective treatment of a haematologic malignancy generally takes priority over AE assessments outside of clinical trials, particularly when a treatment is used within its approved indication. Occurrence of AEs are documented in health care records if patients disclose their experience and/or the treating healthcare provider interprets symptoms/findings to be consistent with an adverse drug reaction, and relevant enough to merit their documentation. Patients may minimize or omit some AE for fear of treatment modification or termination. Even when aware of serious AEs, health care professionals only report a small fraction to the health care authorities responsible for conducting

pharmacovigilance.(186) Thus, real-world toxicity data is likely more underreported than in clinical trials. Agreement between the perception of a particular AE between patient and clinician is only moderate, again suggesting a bias in AE reporting by clinicians.(187) These factors represent serious limitations to the use of real-world data for toxicity assessment.

Role of databases and registries in AE collection

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/or outcomes research.(188, 189) A few examples of databases are the Surveillance, Epidemiology, and End Results (SEER) Program which covers approximately 28% of the American population, 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 haematologic malignancies.(10, 190–195) Validation studies have shown high quality of data in terms of accuracy and good database coverage for some of the databases.(192, 194) Registries and databases are potentially valuable resources for AE studies in a real-world patient population, although detailed toxicity data are typically not entered prospectively, as this is not the main purpose of these databases.

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 AEs. They can also be used to identify a relevant patient cohort for a prospective analysis, as done in a Norwegian study 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.(196) 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 AE. In countries like 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, a Swedish study showed that patients surviving Hodgkin lymphoma following contemporary treatment had increased healthcare use compared to the general population during the first decade post-diagnosis, reiterating the burden of late toxicities in Hodgkin lymphoma survivors.(197) Again, these analyses are limited to AEs that consistently require hospital contacts.

Relying on retrospective data collection mandates clear, consistent documentation of AEs based on consensus definitions in medical records and insensitivity to interpretational bias. Fatigue, insomnia, neuropathy, and pain are common symptoms among cancer patients with profound negative impact on quality of life, but these subjective toxicities are not reliably assessed in retrospective studies.(198) In these situations, absence of documentation cannot be taken as evidence of absence of the AE. As many patients with haematological malignancies become long-term survivors or take drugs continuously over months to years to control their disease, AEs that are not life threatening but nevertheless have a negative impact on quality of life become increasingly important. Indeed, quality matters as much as

quantity of life to many cancer patients and data collected prospectively from real-world patients may better inform this difficult balance.(199)

The value of real-world toxicity data

Despite these limitations, there is significant value to real world toxicity data (Table 9) as well as evidence collected and reported by patient organisations in their constituency on real-world side effects. First, only a small proportion of cancer patients (<3% in the US) are treated within clinical trials due to restrictive inclusion criteria and limited availability of clinical trials.(200) Patients volunteering for clinical trials are typically younger, have better performance status and fewer comorbidities than unselected real-world patients, even in settings where the majority are enrolled in a clinical trial.(201–203) 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. This limits extrapolation of clinical trial results to real-world patients, particularly in situations of off-label use, and can lead to greater toxicity in clinical practice than initially anticipated from clinical trials.(204) For example, patients with relapsed/refractory Hodgkin lymphoma previously treated with allogeneic stem cell transplantation were excluded from the initial phase I/II trials of immune checkpoint inhibitors.(205) 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.(206)

Second, follow-up in prospective trials often becomes reduced when the study meets its primary endpoint, limiting the detection of uncommon or late AEs. The discovery of fatal progressive multifocal leukoencephalopathy from JC polyoma virus reactivation in rituximab-exposed patients exemplifies the value of real-world data for post-marketing pharmacovigilance.(16) Third, 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 agents will be used in sequence or combination, and real world data may inform whether prior exposure to a particular treatment increases toxicity from the next line of therapy.

Finally, databases can validate signals from other sources with excellent statistical power. For example, Chen et al estimated the incidence of heart failure or cardiomyopathy in 45,537 older women receiving trastuzumab-containing chemotherapy for early breast cancer using the SEER database.(207) In addition to confirming the results of randomized clinical trials in a general population (this study suggested the incidence of cardiac dysfunction may actually be greater in a population of older women), the study evaluated this particular toxicity endpoint within a sample size that would never have been possible in the context of prospective clinical trials. Table 9 summarizes the strengths and limitations of databases for the assessment of toxicity.

Enhancing AE reporting in databases: lessons from clinical trials

The most obvious way of integrating toxicity data into existing databases is to treat AEs 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 categorization of toxicity. AE reporting in clinical trials is typically based on the CTCAE. Ideally, real world data should be collected with similar consistency, but this 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. Therefore, the process of data ascertainment should not need to be as exquisitely detailed as in clinical trials. Also, increasing complexity will increase resource utilization and cost. Because it would be impractical and resource-intensive to capture every single possible AE for every single patient, some databases could choose to limit their focus to certain patient groups and/or toxicity categories. One example is to focus exclusively on potentially curable haematologic malignancies where toxicity could derail the success of curative therapy. Another example is to collect a range of predetermined AEs that are felt to be most relevant for a given group of patients, although this approach risks missing important unexpected toxicities. Finally, many administrative databases capture “sentinel events” (i.e., emergency room visit, hospital admission, discontinuation or change of prescription, death) which are more objective than many of the toxicity outcomes. This may be a more efficient alternative to screen for the most serious toxicity, but ultimately requires going back to individual medical records.

The CancerLinQ, a physician-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(179). It was primarily developed to improve quality of care for patients treated in a routine clinical setting by providing real-time analyses of real-world data directly to the responsible physician to facilitate more well-informed decisions.(208) 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 discussed above.(209)

Another lesson from clinical trials is that toxicity is best assessed prospectively and in real time, when there may be an opportunity to query the clarity of the data, obtain additional information about a particular AE, or perform real-time checks for emerging toxicity signals. While this may be feasible in databases such as CancerLinQ, other resources such as the large national databases/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 frequency and severity of AEs, but each patient has a unique experience of AEs in the context being diagnosed with cancer and expecting a clinical benefit from treatment. Although this experience is difficult to quantify, they need be accounted better for in future studies of real-world patients. As an example, grade 3 neuropathy may be an acceptable tradeoff for a lymphoma patient receiving curative intent treatment, whereas it may not in an elderly myeloma patient with postural instability receiving palliative treatment. Important elements that influence treatment decisions from a patient's perspective are goal of treatment (curative versus palliative), magnitude of clinical benefit, potential toxicities, personality, and socioeconomic factors.(199, 210) In metastatic colorectal and lung cancer, patients' expectations about effects of chemotherapy were studied in 1,193 individuals and the majority of patients had not fully understood that chemotherapy was unlikely to cure their disease.(211) Misconceptions of treatment goals alter the ability to make informed decisions regarding treatment and probably also influence the subjective experience and acceptance of associated toxicities. Thus, to fully understand the severity of toxicities as experienced by the patients and their impact on quality, we need obtain toxicity data from patients 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 based on data gathered from their constituency. (77)

Taking advantage of the patient experience to guide AE management

Real world AE data can also be enhanced by directly involving patients in the toxicity reporting process. The data generated by transferring the actual reporting to patients themselves could provide a better perspective on the aspects of toxicity that patients, rather than healthcare providers, find most relevant. As explored earlier in this article, the implementation of tools that measure PRO is possible today with the broad availability of mobile devices and obtaining such data in a large scale would improve knowledge about real-world toxicity substantially. As technology improves and becomes more widespread, as the aging population becomes more comfortable with technology, there are opportunities to enhance toxicity reporting with tools such as PROs. A consensus PRO system, such as the PRO-CTCAE discussed in Subsection II, that can translate and quantify information entered by the patient into clinically useful information has the potential to better describe real world patients' symptoms, the impact of a particular symptom control intervention, and track progress over time.(55, 212) Figure 10 outlines a process for optimizing databases for future toxicity studies with integration of genomic data and PRO measures.

Ultimately, clinical trials do not describe the entire picture of the toxicities of a particular treatment. As introducted in Subsection V, real-world data on toxicity 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 maximize the clinical and research value of real-world toxicity data, consistency and standardization procedures similar to those used in clinical trials should be applied. Initiatives like CancerLinQ that data mines electronic health care records 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 may better clarify the impact of AEs 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 & Timelines for Improving Toxicity Assessment in Haematologic Malignancies

As a consequence of paradigm shifting changes in disease management approaches in the 21st century, tremendous progress with improved survival and cure rates in haematologic 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 haematologic malignancy, but also managing chronic therapy for their illness, with new types of acute, chronic, cumulative and late toxicities. This Lancet Haematology 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 haematologic malignancies. This initiative has evaluated current standards of toxicity reporting, the need to incorporate patient-reported outcomes, unique issues of toxicity in HCT and in survivors of haematologic 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 tumor types, but should be emphasized in haematologic malignancies to keep pace with the changing nature of therapies for leukemia, lymphoma and myeloma. We have proposed specific immediate- and long- term solutions to the challenges raised in this manuscript (summarized in Table 10).

Current standard and emerging therapies for haematologic malignancies challenge traditional approaches to collecting and communicating drug-related adverse events. International efforts to harmonize systems for patient safety monitoring have been ongoing and need to continue to evolve. The standardization of terminology using consensus definitions such as CTCAE(33) remains essential, but it is now also imperative to define adverse events in relation to timing of the drug exposure and the duration of these adverse events. Current methods of AE 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 irAEs, 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 the Toxicity over Time(34) 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 standardizing requirements for comprehensive, time-dependent toxicity data in publications and drug labels. Additionally, clinical trial design needs to accommodate delayed AEs. Monitoring for dose limiting toxicity should be expanded to two to three cycles prior to

establishing a recommended phase 2 dosing schedule or expansion cohorts should be encouraged to account for delayed AEs in dose determination.

Changing therapies for haematologic malignancies require new methods to assess, analyse and interpret cancer drug safety and tolerability internationally which must incorporate the voice of the patient via the use of PRO. Clinicians typically tend to underestimate the incidence and severity of symptoms compared to patients' self-reports of similar information generated from PRO measures(76). Clinical trials in patients with haematological malignancies do not typically include PRO assessments. Furthermore, historical PRO tools did not have the flexibility to include items that captured differing toxicity profiles seen with the treatments used in a specific haematologic malignancy. Implementing tools to complement clinician-recorded CTCAE grading in haematologic malignancy trials, such as the PRO-CTCAE(63), can enhance the assessment of tolerability. Further progress would include better integration and development of electronic collection of PROs to enable a patient to report AEs in "real time" through smartphones, wearable devices and other technology. Ideally patient organisations would be involved in the development and validation of these tools. Challenges exist not only in how PRO data should optimally be collected but also in how it should be analysed. Lack of consensus as to the best analytic approaches for PRO data makes interpretation of the findings and cross-trial comparisons challenging. Several international collaborative efforts are underway in key areas including identifying 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.

Hematopoietic stem cell transplantation presents unique challenges that are related to multiple "expected" toxicities, GVHD, drug-drug interactions, infectious AEs, and longer term AEs affecting transplant survivors. The frequency of AEs and their expectedness make reporting those that are of relevance an issue in transplantation and other areas of high dose toxic therapeutic interventions. It is essential that the post-HCT AEs be evaluated in the context of consensus definitions on what would constitute an "expected" AE depending upon the graft source, transplant regimen and other factors. Streamlined approaches are needed to capture and analyse these so that unexpected AEs or increases in frequency of expected AEs can be readily detected without causing undue burden of reporting to clinicians and research staff. Automated approaches that harness the electronic health record may be helpful in the future. Given the number of interventions, AEs resulting from drug-drug interactions and infectious diseases are very complex in transplantation, and their severity is difficult to categorize. For infectious AEs, scoring algorithms must include the number of infectious complications that now occur. Late term effects of transplantation on survivors include infertility, and neurocognitive function, among many others, and the understanding of the incidence and character of these delayed effects is currently inadequate. A more uniform strategy to collect prospective data on fertility and pregnancy outcomes, and standardize evaluation and grading of neurocognitive function, as examples, would be important tasks for a consensus panel dedicated to improvements in assessment of long term AEs in HCT.

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

Making toxicity assessment in haematologic malignancies more comprehensive and accurate without adding logistical complexity and burden is a challenge relevant to regulatory bodies across the globe(164, 165). 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 AE 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 recognized 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 fraction of patients with cancer are treated on clinical trials. In addition, 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 organizations and databases therefore plays an important role in improving 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. Optimizing the systematic, objective collection of AE data over multiple time points 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 AEs, certain patient groups, or toxicity categories. Learning systems such as the CancerLinQ(179) offer the opportunity to study toxicity in large groups of patients by culling data from electronic health records. Real world AE 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 physician-reported and PRO toxicity data in a standardized format for patients being treated off study. Consistency in standardization 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 characterization of toxicity in non-study patients with haematologic malignancies, and it could potentially be harnessed to guide AE management and symptom control in the clinic.

The success in outcomes and survival in many haematological malignancies is historically unparalleled and fueled by scientific discovery and implementation. Measures to address the broad facets of toxicity assessment as outlined in Table 12 must be prioritized and further developed to ultimately enhance accurate, comprehensive, patient-centered toxicity reporting and inform the care of patients with haematologic malignancies.

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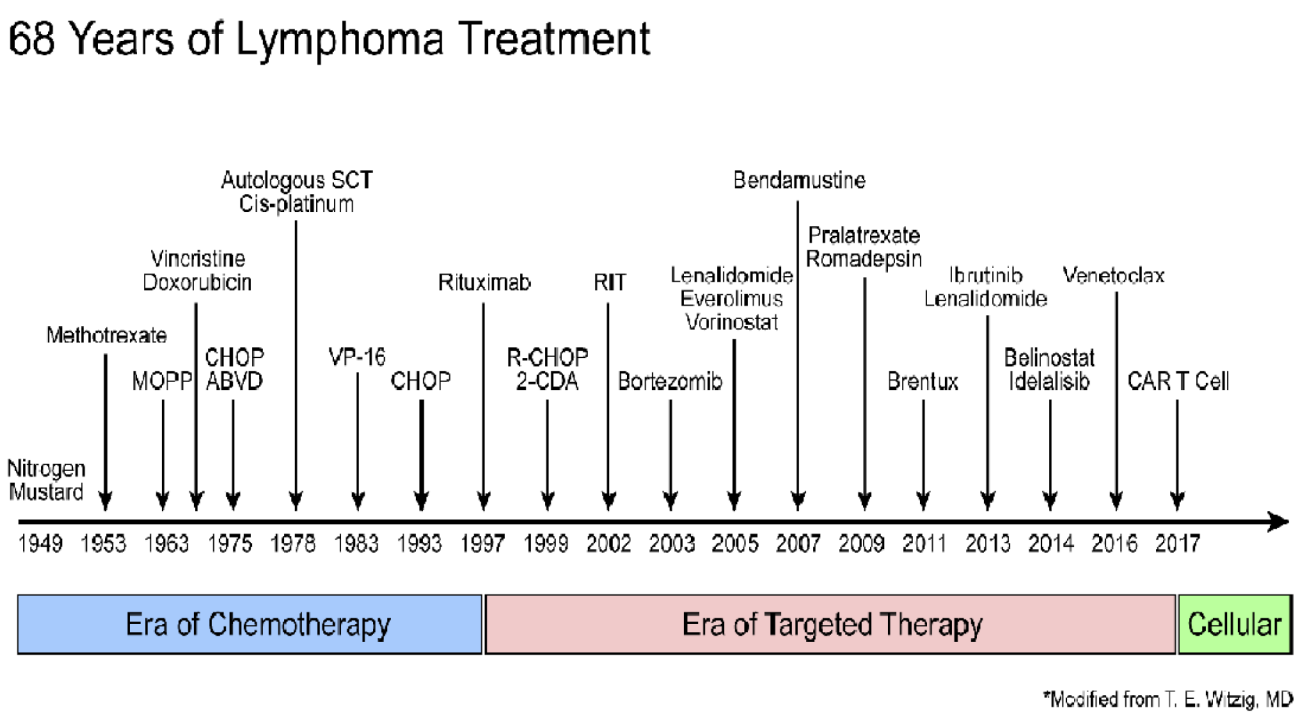


Figure 1.

Evolution of Therapy in Haematologic Malignancies: Lymphoma as an example of shifting treatment strategies

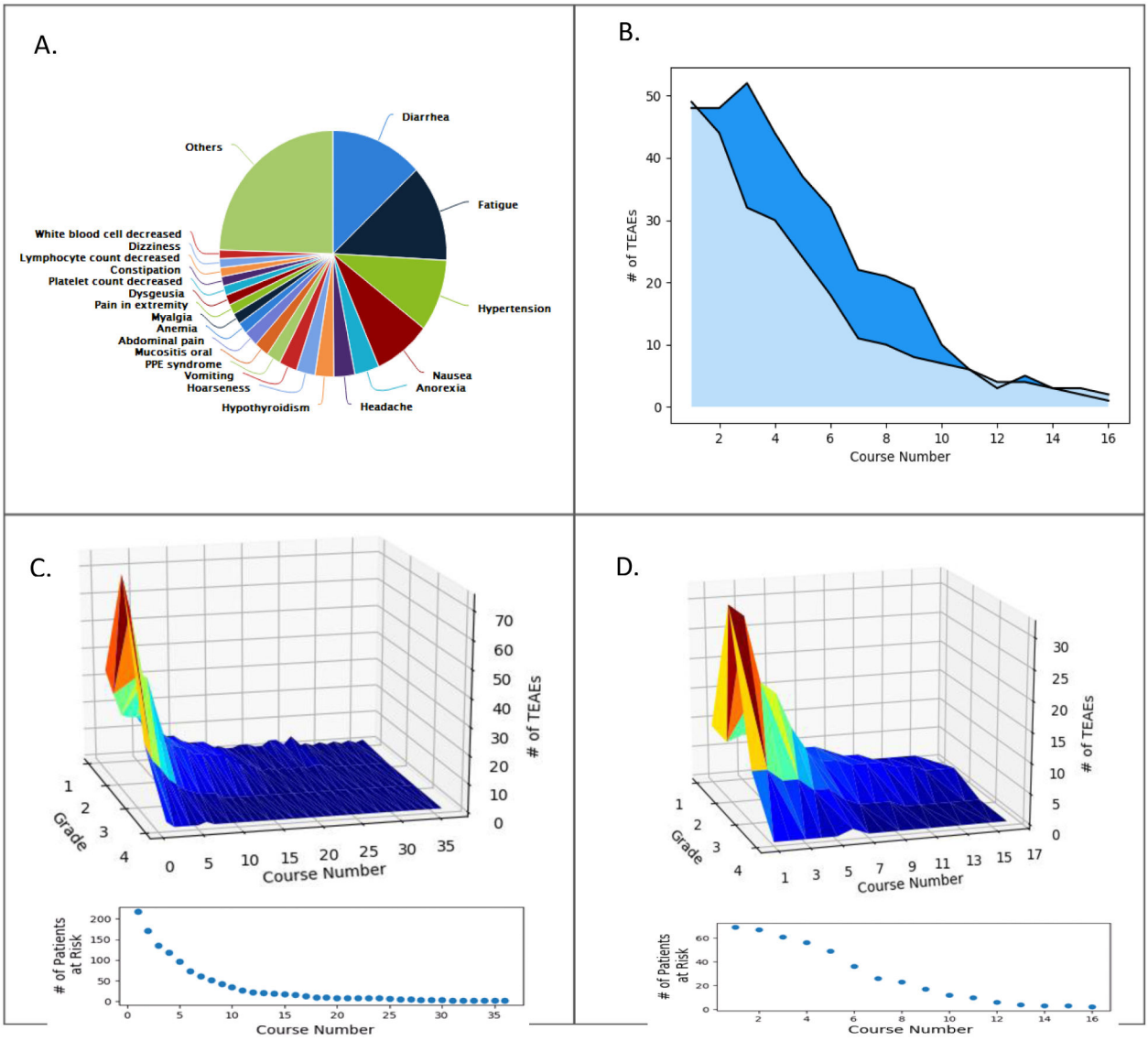


Figure 2. Graphical representations and analysis of AEs by the NCI Web Reporting Tool

Characterization and graphical display of Treatment Emergent Adverse Events (TEAEs) from the NCI Web Reporting System. (A) Pie graph of all TEAEs in patients on a Vascular Endothelial Growth Factor Receptor inhibitor (VEGFR2i) and a DNA Repair inhibitor (DNARi). **(B)** Risk-based monitoring of Diarrhea (dark blue) and Hypertension (light blue) in patients in a clinical trial of a VEGFR2i and a DNARi evaluating AE density by course using an area under the curve approach in a single clinical trial of this combination therapy. **(C)** Hypertension in patients across 5 clinical trials with VEGFR2i evaluated by grade, course number and number of TEAEs using a contour map. Below is graph that depicts the number of patients at risk by course. **(D)** Hypertension TEAEs in patients given a VEGFR2i in a clinical trial evaluated by grade, course number and number of TEAEs using a contour map. Below is a graph that depicts the number of patients at risk by course

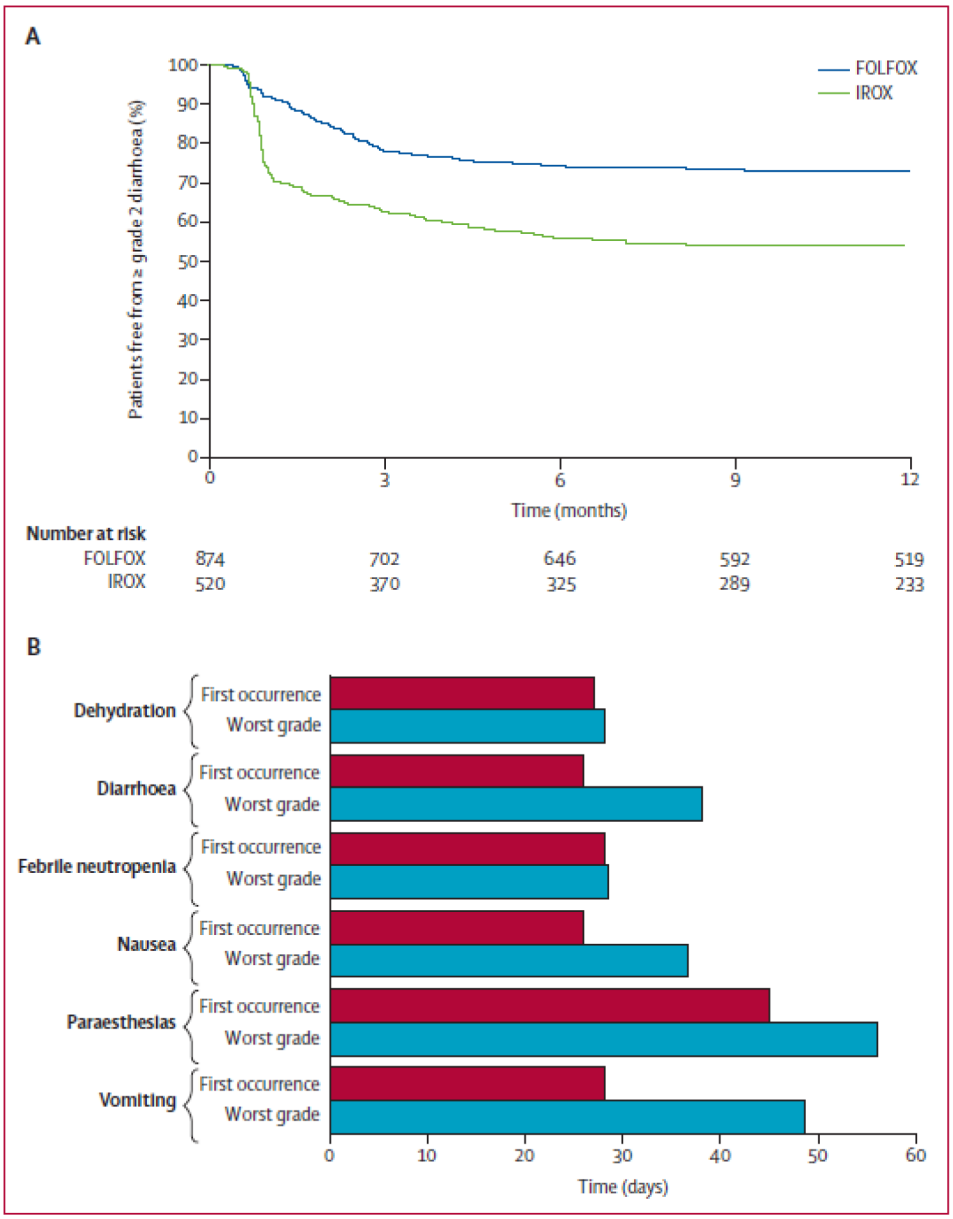


Figure 3. Time to event analyses for adverse events per the Toxicity over Time (ToxT) package

(A) Time to grade 2 or worse diarrhea in patients given FOLFOX and IROX in Alliance/NCCTG N9741 and (B) Median time to first occurrence and worst grade toxic effects in patients on the IROX arm only. Adapted with permission from Thanarajasingam et al, Lancet Oncology 2016; 17: 663–70.

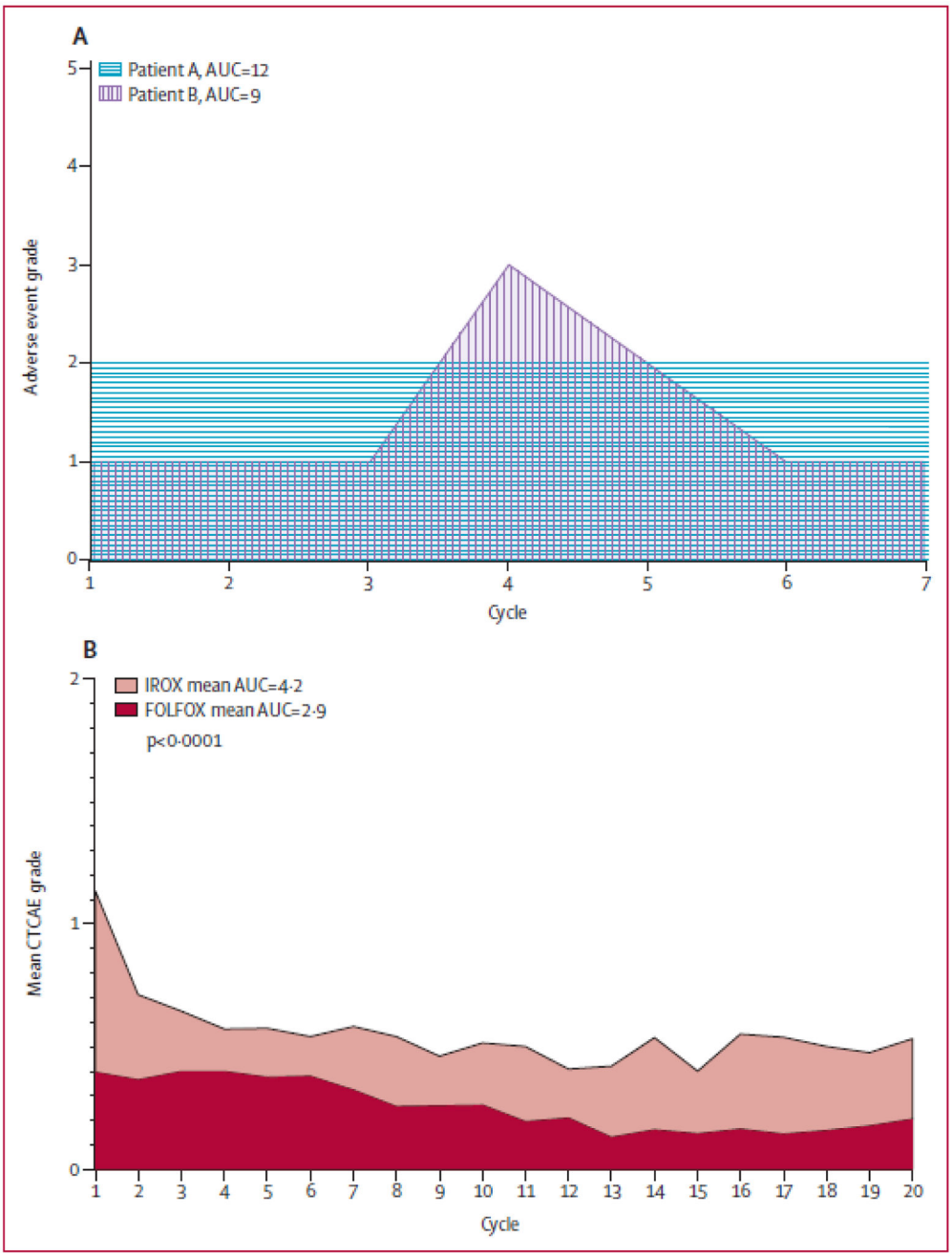


Figure 4. ToxT AUC analysis to compare adverse events over time – conceptual and applied

(A) Conceptual example of AUC analysis with patient B demonstrating continuous grade 2 AE and having a higher AUC than patient A with an isolated grade 3 event. (B) Application of AUC analysis depicting mean diarrhea grade over time in patients given FOLFOX and IROX in clinical trial Alliance/NCCTG N9741. Adapted with permission from Thanarajasingam et al, Lancet Oncology 2016; 17: 663–70.

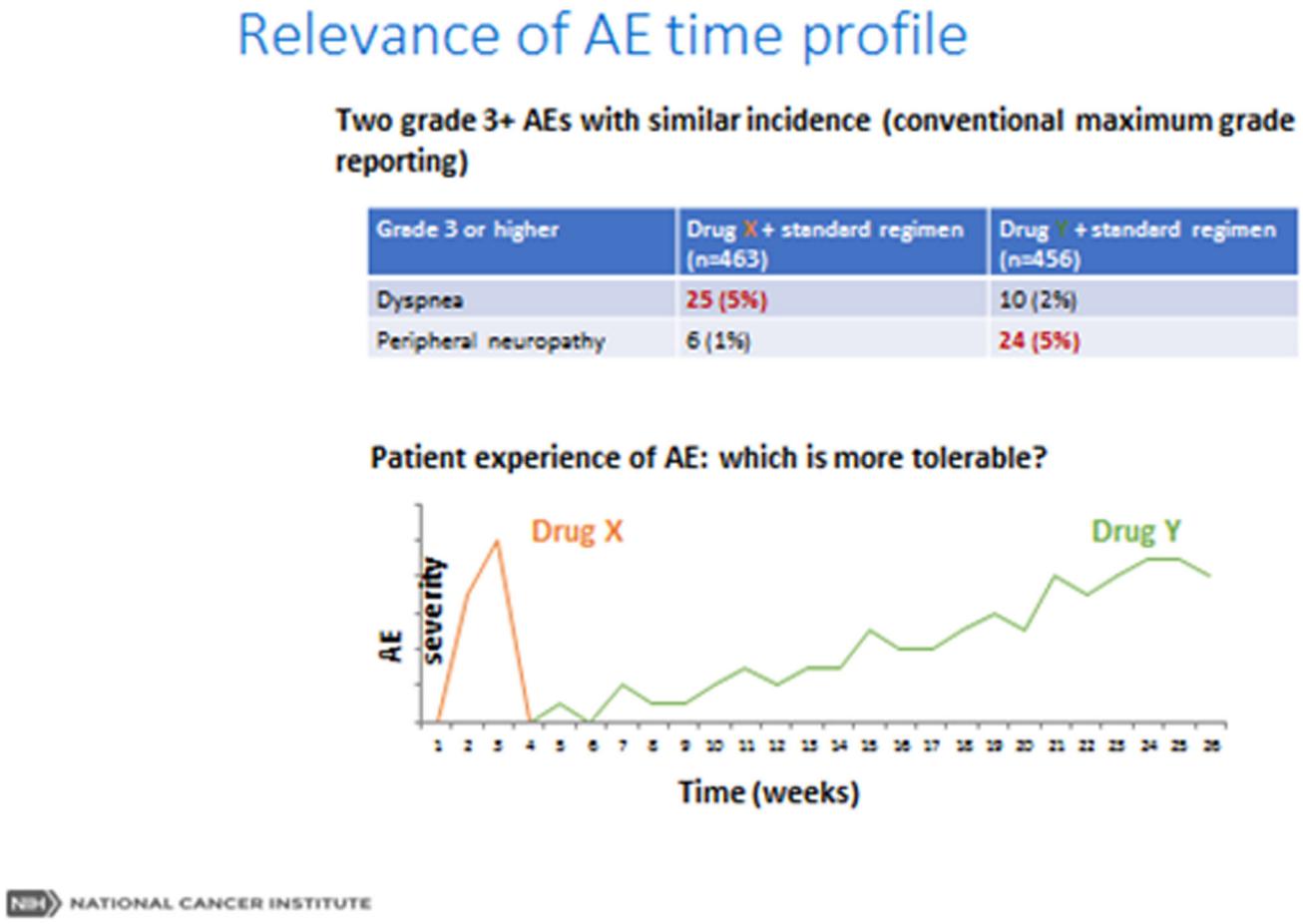


Figure 5.
Relevance of AE Time Profile

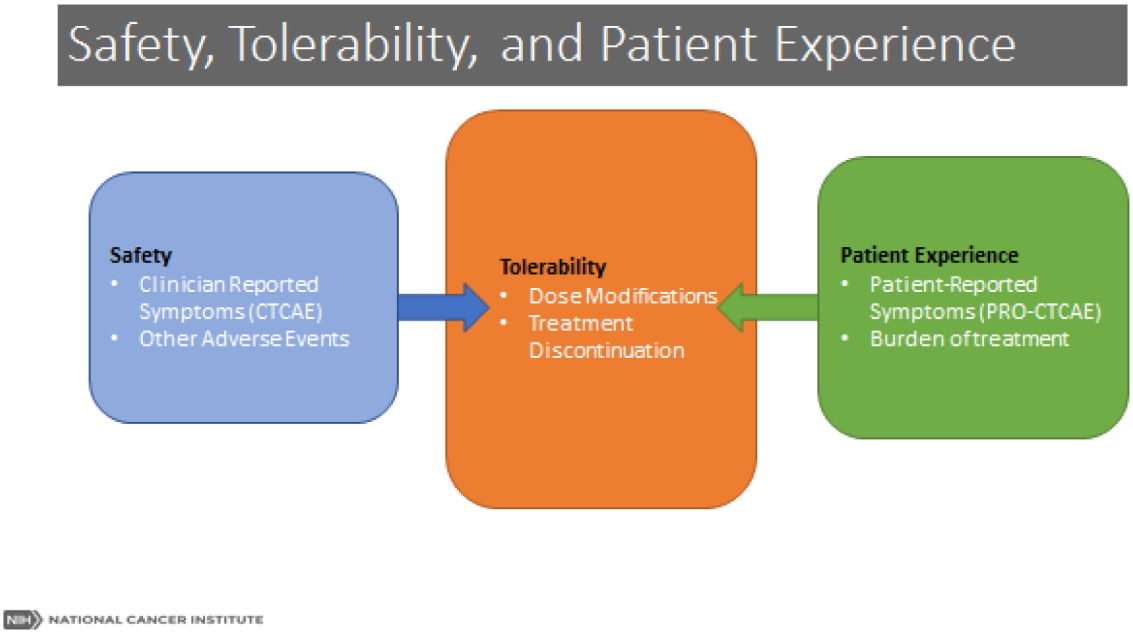
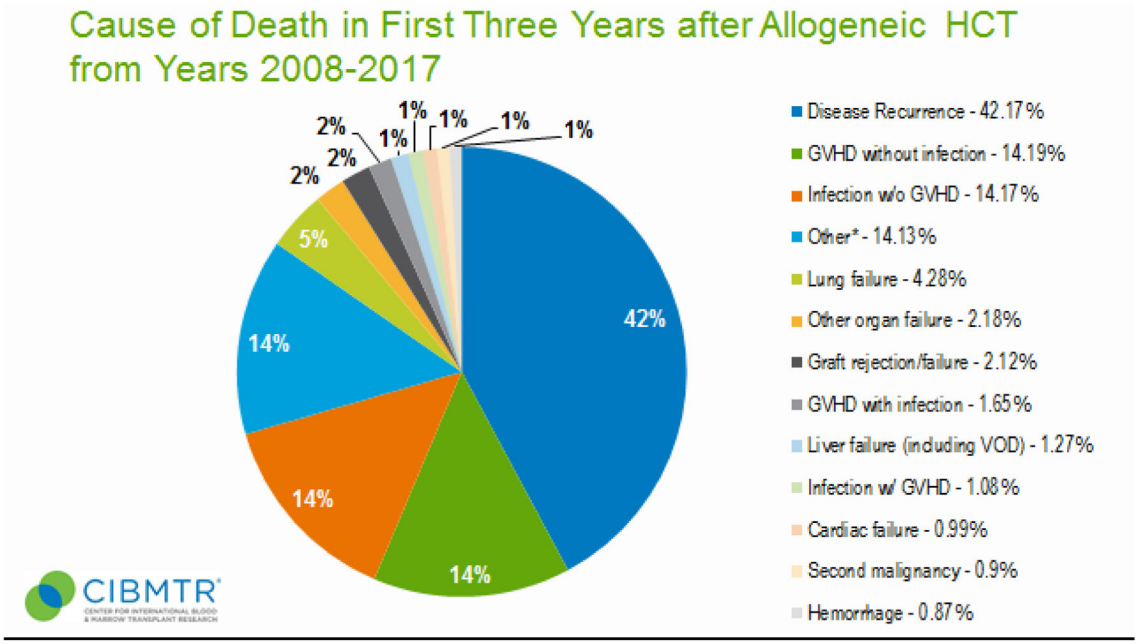


Figure 6.
Safety and the Patient Experience Inform Tolerability.



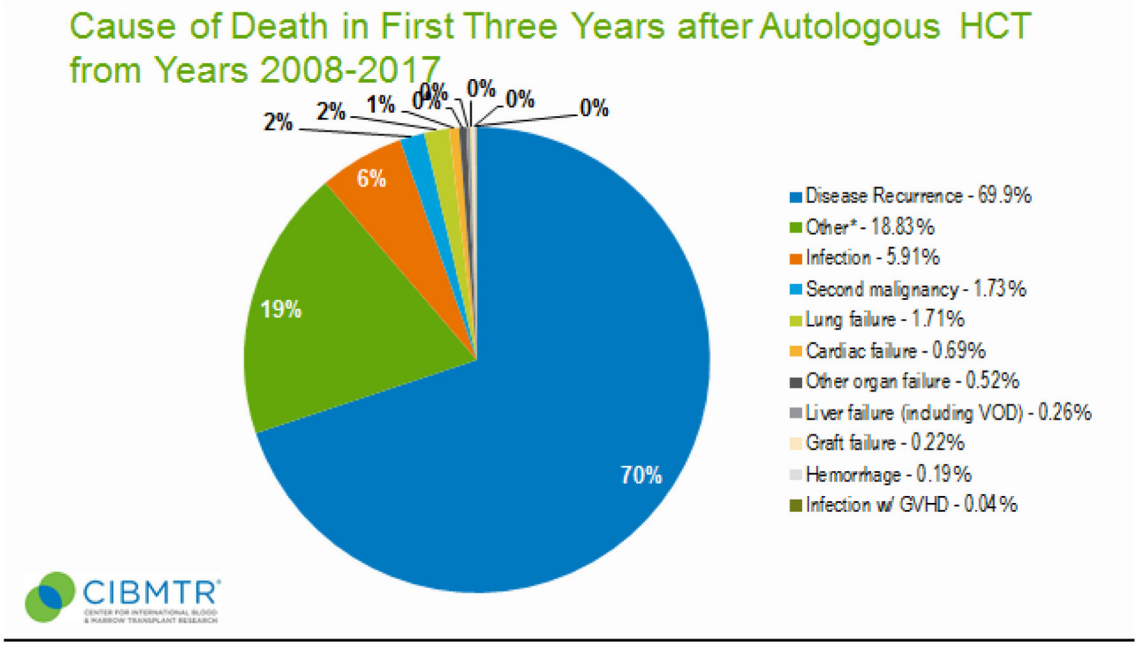


Figure 7A and 7B.
Cause of Death After HCT.

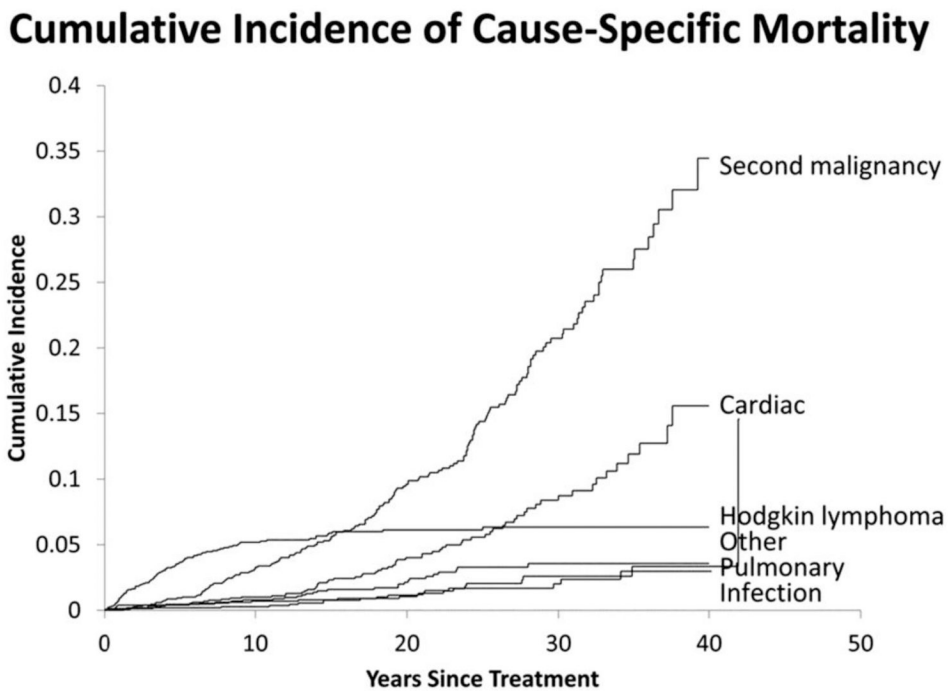


Figure 8.

Cause-specific mortality in adults diagnosed with Hodgkin lymphoma. (Ng Blood 2014 https://doi.org/10.1182/blood-2014-05-579193)

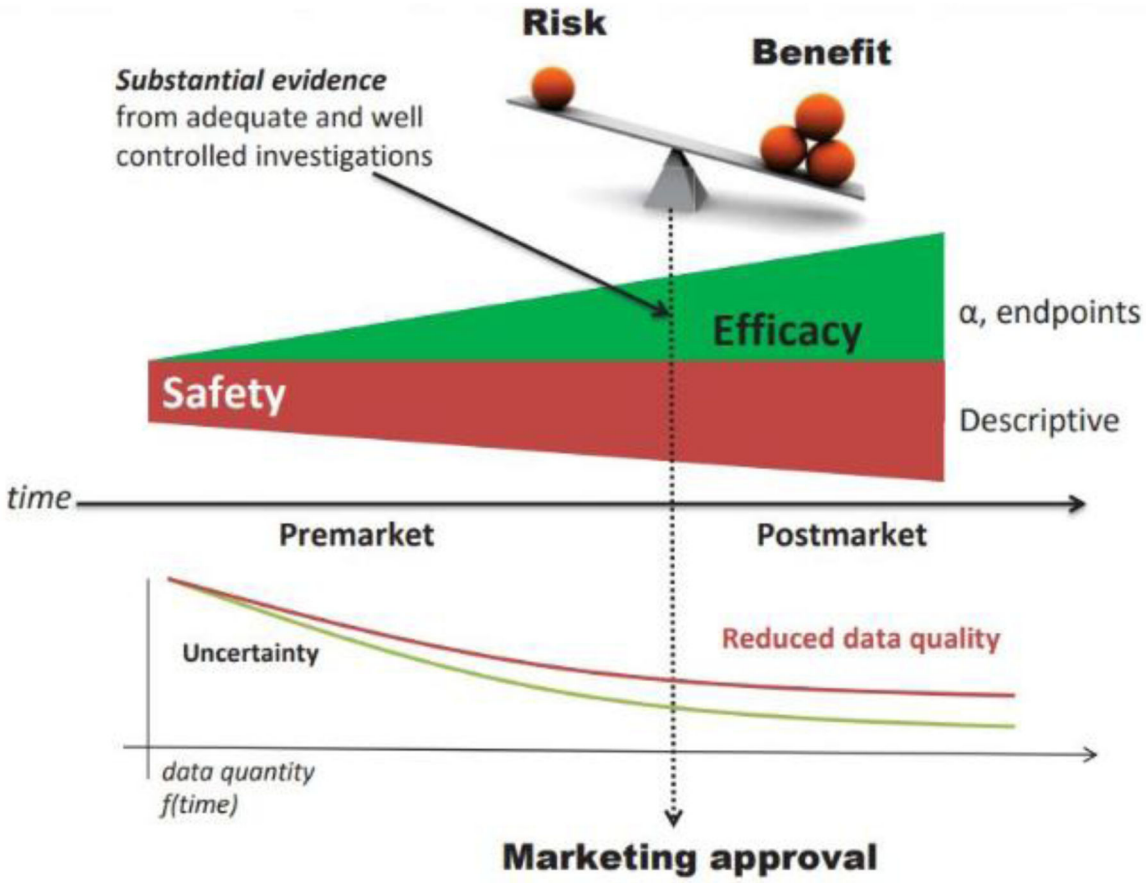


Figure 9. Weighing Safety and Efficacy in New Drugs.

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 us with 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. *Reproduced with permission, Sean Khozin, Case Sudies: Data Collection and Application of RWE, Friends of Cancer Research Blueprint for Breakthrough Forum, June 16, 2016.* https://www.focr.org/sites/default/files/pdf/Blueprint2016%20-%20Panel1.pdf

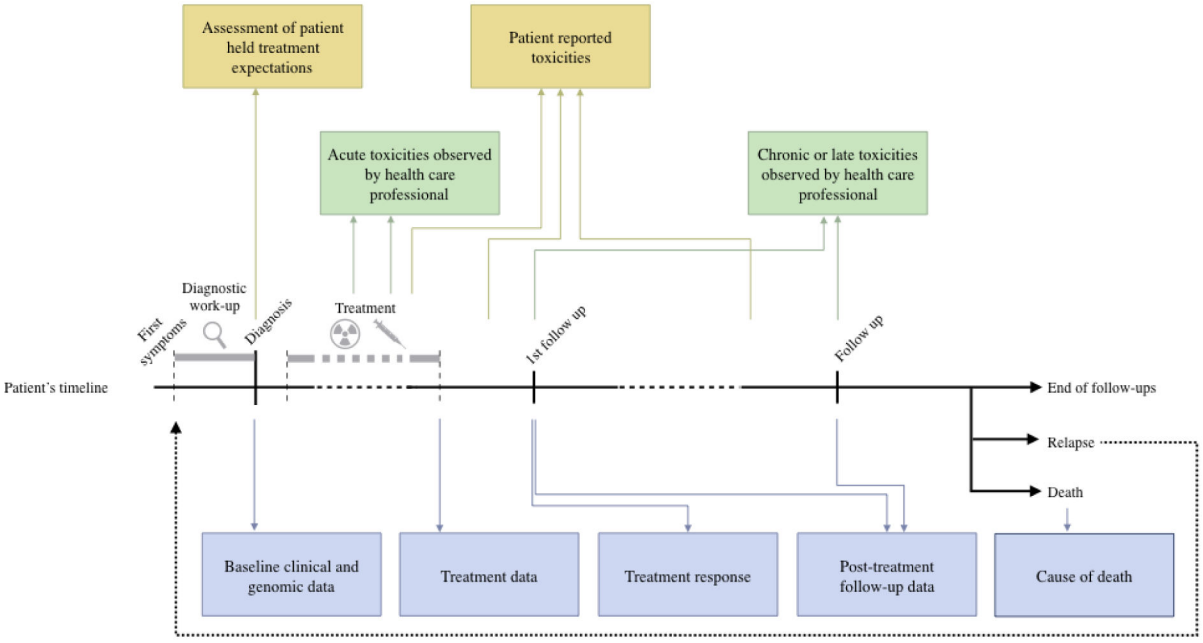


Figure 10: Optimizing Databases for Real World Toxicity Evaluation

Optimizing 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 (yellow boxes)

Table 1.

Immunotherapy in Haematologic Malignancies

Type of Therapy	Type of Agent	Drugs
Mononclonal Antibodies	Anti-CD20 antibodies	rituximab
		rituximab and hyaluronidase
		ofatumumab
		obinutuzumab
	Radiolabeled antibodies	ibritumomab tiuxetin
	Antibody – drug conjugate	brentuximab vedotin
	Bispecific T-cell engager (BiTE) CD19 and CD3 binding domains	bilinatumomab
	Other antibodies	
	CTLA-4 antibody	ipilimumab
	PD-1 antibody	nivolumab, pembrolizumab
	Other antibodies	lirilumab
		atezolizumab
		avelumab
		durvalumab
	Anti-body drug conjugate (anti-CD22 antibody to a calicheamicin-derived cytotoxic moiety	inotuzumab ozogamicin
Immunomodulating drugs		lenalidomide pomalidomide
Chimeric antigen receptor (CAR) T-cell therapy		tisagenlecleucel (CTL019)
		axicabtagene ciloleucel
T-cell therapy (adoptive cell transfer)		
Cellular Therapy	Virus-specific T cells	Epstein Barr Virus (EBV)
		BK virus
		Human Herpes Virus
Nonspecific Immunotherapies	Interferons	interferon alfa-2b
	Cytokines	granulocyte colony stimulating factor (GCSF)
		granulocyte macrophage colony stimulating factor
	Interleukins	interleukin-2
Cancer vaccines		

Table 2.

Molecularly-Targeted Therapies in Haematologic Malignancies

Type of Therapy	Type of Agent	Drugs
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 agents		5-azacytdine decitabine
BCL2 inhibitor		venetoclax
Isocitrate dehydrogenase 2 (IDH2 Inhibitors)		enasidenib
FLT3 Inhibitors		midostaurin sorafenib
mTOR inhibitors	mTOR type 1 inhibitor	everolimus

Table 3.

Definitions of Toxicity Relative to Drug Exposure

Category	Definition
Acute Effects	Acute effects describe AEs that develop within a short, defined timeframe; can be transient or reversible or persistent.
Chronic Effects	Chronic effects are those AEs that 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	Cumulative AEs develop and increase with repeated exposures to drug.
Late Effects	Late effects are AEs that result in subclinical or asymptomatic physiologic changes that do not result in immediate, intermittent, or short-term adverse clinical events, but rather are manifest over an extended timeframe.

Table 4.

Improving AE Analysis and Reporting of Chronic, Cumulative and Late AEs

Improvements in Adverse Event Assessment		
Goal	**Potential approaches to achievement**	**Initial implementation strategy**
Improved analysis of chronic AEs	a. Implementation of longitudinal methods to evaluate chronic, low grade effects over time b. Analysis of chronic AE data in early phase trials for those patients receiving > 6 cycles. c. AUC AE analysis from more than one trial to identify the optimal RP2D d. Evaluation of a subpopulation of patients with chronic effects to identify effect e. Testing of different analytic approaches on existing trial data	Retrospective evaluation of trials in which chronic AEs have been reported: prospective evaluation accomplished over the next 2-5 years
Improved analysis of cumulative AEs	a. Use of data from multiple cycles to explore cumulative effects with dose modifications over time b. Evaluation of cumulative effects of a given agent using AE data from more than one trial c. Inclusion of risk-based AE analysis for effects that are cumulative to account for patient attrition	Retrospective evaluation of trials in which chronic AEs have been reported; prospective evaluation accomplished over the next 2-5 years
Improved analysis of late AEs	a. Require long-term follow up on patients on trials where relevant b. Use of SEER and SEER-Medicare in the USto perform “population” evaluation for late effects; build in the late follow up for late effects in trials c. Inclusion of patient reported outcomes even later on or after a trial	Retrospective analyses could start immediately

Table 5.

Patient-Reported Outcomes (PROs) in NCI Sponsored Hematology Adult Trials*

Disease/Trial Type	Phase I	Phase I/II	Phase II	Phase III	Other	Pilot	Subtotal	Total
Leukaemia Number of Adult Heme Trials with PROs	1	0	2	5	0	0	**8**	
Leukaemia Number of All Adult Heme Trials	49	7	68	11	1	1	**137**	
Lymphoma Number of Adult Heme Trials with PROs	0	1	6	1	--	0	**8**	
Lymphoma Number of All Adult Heme Trials	23	11	63	3	--	1	**101**	
Myeloma Number of Adult Heme Trials with PROs	0	1	2	7	--	0	**10**	
Myeloma Number of All Adult Heme Trials	5	4	13	11	--	2	**35**	
							Total Trials with PROs	**26**
							Total All Trials	**273**

*CTEP treatment trials (all phases) activated between June 30, 2004 and December 31, 2016

Table 6.

Improving AE Assessment in HCT

Priorities for the improvement of AE Assessment in HCT	Proposed Solutions: More Research and Immediate Action	Solutions: Timelines
Improve post-HCT data capture, analysis and evaluation	Engage Haematology and BMT Communities to reach consensus on expected AEs post-HCT	Convene consensus conference of stakeholders for Winter 2018 and provide consensus document 2020
Improve evaluation of drug interactions	Investigate availability of CYP polymorphism status of drugs used post-HCT	Provide report by Summer 2019
Update severity of Infectious Disease Algorithm	Convene Infectious Disease and BMT Stakeholders to develop consensus	Consensus meeting Winter 2018. 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 AEs	Plan consensus conference for Winter 2018 and consensus report, 2020
Neurocognitive studies post-HCT are fragmented	Encourage critical reviews of area	Plan consensus conference on standardization of grading of neurocognitive AEs for Spring 2019

Table 7:

Global Approaches to Adverse Event reporting

	US	EU	Japan	Australia
Form	Centralized Reporting to FDA	Decentralized Reporting to Competent Authority of each member nation or their authorized surrogate	Centralized Reporting to PMDA	Centralized Reporting to TGA
Agency	FDA: Full authority (including withdrawal and approval of products)	EMA: Operates the system on behalf of the European Union (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)
AE Compilation	FAERS (currently only post-approval; pilots of pre-approval safety) Sentinel (post-approval) [a]	Eudravigilance database (pre- 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 7-day: fatal/ life-threatening AEs 15-day: "Alert reports" of serious and unexpected AEs Post-approval 15-day "Alert reports" of serious and unexpected AEs	Pre-approval SUSARs : 7-day: fatal/life-threatening AEs 15-day "Alert reports" of serious and unexpected AEs Post-authorisation ICSRs: 15-day: for serious EEA and non-EEA cases 90-day: for non-serious EEA cases (as of 22 November 2017)	Pre-approval 7-day: unexpected and fatal AEs 15-day: serious and unexpected AEs and expected and fatal AEs Post-authorisation 15-day: serious and unexpected AEs and expected and fatal AEs 15-day or 30-day:serious and expected AEs	Pre-approval 7-day: unexpected and fatal AEs 15-day: serious and unexpected AEs and expected and fatal AEs Post-authorisation 15-day: serious and unexpected AEs and expected and fatal AEs 15-day or 30-day: serious and expected AEs
Periodic AE/ safety updates Submission Frequency Content	Pre-approval: DSUR [b] Post-approval: PADER/PAER DSUR: annually PADER: Quarterly for the first 3 years and	Pre-approval: DSUR Post –approval: PSUR DSUR: annually PSUR: Every 6 months after product authorization; every 6 months for 2 years after marketing; yearly	PBRER based on ICH E2C(R2) 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 NME drugs, and 4 or 6 years for the other drug applications) Analysis, summary table and case list included; individual case safety reports not included	PSUR Every 6 months after product authorization; every 6 months for 2 years after marketing; yearly for following 2 years, and every 3 years thereafter

	US	EU	Japan	Australia
	yearly thereafter Narrative summary of the information in the report and an analysis of the 15-day "Alert reports"	for following 2 years, and every 3 years thereafter (depending on each member nation) Individual case safety reports not included; all AE data submitted directly to Eudravigilance database		

AE, adverse event; AR, Annual Report; DSUR, Development Safety Update report; EMA, European Medicines Agency; EU, European Union; EPMMA , Enhanced Post-Marketing Monitoring and Analytics; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; ICSR, Individual Case Safety Report; JADER, Japanese Adverse Drug Event Report database; MHLW, Ministry of Health, Labour and Welfare; NME, new molecular entity; PADER, periodic adverse drug experience report; PAER:, periodic adverse experience report ; PBRER, periodic benefit risk evaluation report; PMDA, Pharmaceuticals and Medical Devices Agency; PRAC, Pharmacovigilance Risk Assessment Committee; PSUR, periodic safety update report; SUSAR, suspected unexpected serious adverse reaction; US, United States.

[a]The Sentinel database is composed of health outcomes; it might be used to identify outcomes of interest which could be potential AEs, or to establish "background" occurrences of specific medical conditions and/or drug utilization patterns.

[b]IND safety reporting requirements include also submission of aggregate analyses of specific events (21CCFR 312.32©(1)(i)(C). The IND annual report must include a summary of the safety reports submitted during the last year including specific details such as most frequent and most serious AEs, causes of death and dropouts associated with any AE; The DSUR can meet these annual reporting requirements.

Table 8:

Opportunities to advance regulatory assessment of AEs in haematologic malignancies, pre- and post-marketing

Problem	Proposed solution	Timelines
Underreporting and incomplete capture of AEs	Electronic submission of AE reports (all) Simplification of AE reporting (TGA)	TGA: done PMDA: done for commercial submissions only EMA: Ongoing FDA: Ongoing
	Incorporation of RWE into pre- and post-marketing safety (all): EHR, claims data etc.	
	FDA : Sentinel and FAERs INFORMED, partnerships with various platforms PMDA: MID-NET	Ongoing 2017 Full-scale utilization: 2018
	Incorporation of patient voice, including PROs into pre- and post-marketing safety (all)	
	FDA: 21st century cures act : Draft guidances proposed for describing approaches to collection of patient/ caregiver input on burden of disease/therapy, development of holistic sets of impact priorities for patients, measures for analysis of these impacts Incorporation of patient input/data into risk: benefit assessment (clinical reviews) Collaboration with National Cancer Institute and drug development stakeholders to explore the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Involvement in workshops and other scientific working groups to advance PRO measurement tools, trial design and analytic methods	2018-2020 2017 Ongoing Ongoing
	EMA, TGA: Appendix 2 to the Guideline on the evaluation of anticancer medicinal products in man	
Analysis of data obtained from anything other than a clinical trial	INFORMED (FDA) Working groups: RWE, PROs FDA: Contribute to international collaboration to identify core outcome sets and PRO tools for utilization in the post-marketing setting	Ongoing Ongoing

EHR, electronic health record; INFORMED, Information Exchange and Data Transformation initiative; PRO, patient-reported outcome; RWE, real world evidence.

Table 9:

Strengths and weaknesses of databases and registries for adverse event studies

Strengths	Weaknesses
• Real-world patients	• Missing data and non-standardized data acquisition
• Low study costs	• Biased
• Time efficient studies with quick results	• Often sparse information on drug doses
• Large number of patients for analyses	• Not all toxicities are assessable
• Rare/late adverse events can be captured	• Risk of uncontrollable confounding
• Results more likely to apply to all patients	• Patient reported outcomes rarely available

Table 10:

Goals of this Commission: Targets and Timelines for Proposed Long and Short Term Goals in Improving Adverse Event Assessment in Haematologic Malignancies

Issues	Solutions: immediate action (1-5 years)	Solutions: long term (beyond 5 years)
Current Processes in AE Assessment		
Chronic, delayed and cumulative AEs are not well captured, leading to incomplete and potentially inaccurate toxicity assessment	- Design phase I trials with longer DLT evaluation periods and increase use of adaptive designs that span phase I/II - 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 AE data - Standardize and require use of these metrics and displays in publications and drug labels
Patient-Reported Outcomes (PRO) in Haematologic Malignancies		
Patient-reported outcomes are not a standard part of toxicity assessment and therefore tolerability of therapies for haematologic malignancies from the perspective of the patient is not assessed	- Include hypothesis-driven PROs in more haematologic malignancy trials - Increase use of PRO-CTCAE or other tools for capturing patient-reported symptomatic AEs to better inform tolerability of novel and existing drugs for haematologic 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 AE data - Complement clinician graded CTCAE reports with patient-reported symptomatic AE data to improve understanding of tolerability - Standardize these approaches to the analysis of PROs across cancer trials internationally
Toxicities in Haematopoietic Stem Cell Transplant		
Cumbersome reporting of the myriad of expected AEs in the HCT setting is a barrier to performing clinical trials	- Develop consensus on “expected” AEs post HCT based on registry data and develop targeted approaches	- Develop automated approaches that can recognize data routinely captured in the electronic health record as “expected” toxicity data post HCT or highlight provider attention to unexpected, unique and potentially relevant AEs
Long Term Toxicity & Survivorship in Haematologic Malignancies		
The description and management of cumulative and late toxicities in survivors of haematologic malignancy is inconsistent, inadequate or absent	- Develop and support infrastructure to collect data for adult survivors of haematologic malignancies, such as longitudinal patient cohorts - Standardize the use and content of survivorship care plans	- Link PRO, delayed or long term complications of haematologic malignancies, and their baseline treatment in electronic medical records - Increase availability of multidisciplinary survivorship clinics - Sustain funding of survivorship research
Haematologic Malignancies & Regulatory Approval		
Meaningful AEs of therapy for haematologic malignancies are often underreported to regulatory agencies, while reporting of uninformative AEs may obscure true safety signals	- Simplify and make electronic the submission of all AE 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 AE reports to prioritize relevant toxicity data - Incorporate patient experience from trial and non-trial data, including real-world evidence, to inform both the pre-and post-marketing safety evaluation
Toxicity Reporting in Haematologic Malignancies & the Real World Setting		
Toxicities affecting patients with haematologic malignancies in routine clinical practice are difficult to capture and analyse on a large scale	- Optimize 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 information technologists to develop electronic health record systems that reliably capture relevant AEs (both physician reported and PRO) in patients receiving therapy for haematologic malignancies off study in a standardized, manageable format - Utilize systems above to guide AE management and symptom control in patients with haematologic malignancies