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

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

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Declaration of interests

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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, diffuse large B-cell lymphoma, and multiple myeloma. This has resulted in large part from paradigm shifting changes in disease management strategies in these malignancies. Several haematologic malignancies are now experienced by patients as chronic illnesses. 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 this new landscape of haematologic malignancies. This international collaborative effort aims to improve toxicity assessment in haematologic malignancies and addresses changes to the current process of AE assessment, incorporating patient reported outcomes, issues in stem cell transplantation, toxicities in survivorship, regulatory approval challenges, toxicity reporting in the real world, and financial burden of contemporary therapies, all of which present new challenges in the current treatment era world-wide.

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Introduction: Haematologic Malignancies and Their Therapies Have Changed

The haematologic malignancies have been the model for radiation therapy, chemotherapy, immunotherapy, immunomodulators, adoptive t-cell, oncolytic virus, interferons, cytokines, cancer vaccines, and chimeric antigen receptor T cell therapies (**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 dramatically 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 relative to the normal population in some haematologic malignancies diseases. Along with this shift, the patient 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 haematologic malignancies (**Figure 1**.) In Hodgkin lymphoma (HL), limited stage disease was previously managed with high dose radiation therapy (RT) and advanced disease with combination chemotherapy and RT.(1, 2) The late term toxicity of these treatment approaches – including secondary malignancies, heart disease, and pulmonary disease – resulted in more treatment–related deaths from complications of survival than deaths from disease. HL is now managed with de-escalation approaches where possible with either three cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in positron emission tomography (PET) negative patients or 2 cycles of ABVD followed by 20 Gy radiation therapy.(3, 4) The addition of rituximab to chemotherapy, immunochemotherapy, improved overall survival in diffuse large B-cell lymphoma(5-7) and advanced stage follicular lymphoma,(8, 9) and introduced short and later term toxicities of monoclonal antibody therapy, such as infusion reactions and polyoma virus reactivation(10).

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Indolent forms of lymphoproliferative disorders such as 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(11) or even first-line therapy.(12) 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(13) and venetoclax(14) – 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, either with maintenance intravenous therapy with monoclonal antibodies (rituximab or obinutuzumab(15, 16)), or with chronic oral therapy. Idelalisib is FDA-approved in the US for relapsed FL(17), ibrutinib for Waldenström's macroglobulinemia(18), and a host of other oral agents are in active development internationally using this chronic-oral-therapy approach.

In multiple myeloma, the median survival prior to 1997 was 2.5 years which had improved to 4 years by 2008 with the increased use of high dose therapy and the addition of thalidomide, bortezomib, and lenalidomide along with improved supportive care measures.(19) In 2013, the USA Food and Drug Administration approved pomalidomide and carfilzomib. In 2015, four additional drugs were approved in the US: panobinostat, ixazomib, elotuzumab, and daratumumab. The standard of care is now triplet therapy with the advent of new therapies (**Table 3**).(20-22) Venetoclax has now been reported as a promising targeted therapy for relapsed/refractory t(11;14) multiple myeloma.(23)

Perhaps no diseases better exemplifies this paradigm shift than chronic myelogenous leukaemia (CML). In 1983, the mainstays of treatment in chronic myelogenous leukaemia were

busulfan and hydroxyurea followed by recombinant interferon alfa in combination with cytosine arabinoside, and allogeneic stem cell transplantation.(24) CML is now treated almost exclusively with oral tyrosine kinases targeting BCR-ABL. The approved agents of this class, initially imatinib, has now been expanded to include dasatinib, nilotinib, bosutinib, radotinib and ponatinib and these continuously administered agents have resulted in life expectancy that approximates that of the age-matched normal population.(25) 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. Adherence and the achievement of MMR are the only independent predictors for outcome.(26) 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) To further complicate the issue of toxicity, AEs may also occur when patients withdraw from the tyrosine kinase inhibitors.(27)

Treatment of myeloid malignancies beyond CML has also evolved substantially. Lenalidomide improved the outcomes of patients with myelodysplastic syndromes (MDS) and the cytogenetic abnormality del(5q), resulting in transfusion independence and improved quality of life.(28) Patients with higher risk MDS, who historically lacked effective treatment options, can now be maintained, at times for years with hypomethylating agents, allowing some patients to live with MDS as a chronic illness.(29) In the acute leukaemias, targeted therapies are being explored for use in addition to conventional cytotoxic rather in its place, with the notable exception of acute

promyelocytic leukaemia (APL) where targeted therapy with all-trans retinoic acid (ATRA) and arsenic trioxide are capable of curing a high proportion of patients without the use of any cytotoxic chemotherapy. In acute myeloid leukaemia (AML) after approximately four decades, the US FDA for the first time approved three drugs in 2017: midostaurin, a FLT3 inhibitor for FLT3 mutated AML(30), enasidenib, an IDH2 inhibitor for relapsed/refractory IDH2 mutant AML(31), and CPX-351, a liposomal formulation of daunorubicin and cytarabine which demonstrated a survival benefit and better tolerability in secondary AML(32).

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(33), checkpoint blockade inhibitors such as pembrolizumab and nivolumab in HL(34, 35), and the advent of CAR-T cells(36), approved in 2017 in the US for the treatment of relapsed lymphoma, have also brought a dramatic shift in therapy of some diseases, as well as new risk and new categories of AEs.

The result of paradigm shifts 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. Changing side effects of therapy, psychosocial impact on the patient and treatment adherence are increasingly relevant. Financial burdens of these treatments include not only drug costs, but also physician outpatient visits and hospitalizations. Patients and healthcare providers often find themselves poorly equipped to manage these complex challenges.

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 the modern era of haematologic malignancies.

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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. The new therapies that have changed the face of 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 issues and solutions in how we capture and analyse toxicity data on clinical trials, including how optimizing AE assessment may influence the drug development process. The 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)(37), recently published in its fifth version, is one such system.(38) 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. In 1982, the Cancer Therapy

Evaluation Program (CTEP), National Cancer Institute (NCI) developed its first version of the Common Toxicity Criteria (CTC). The CTC was used in adverse drug experience reporting, study AE summaries, Investigational New Drug (IND) reports to the FDA, and publications. The original version of the CTC included 49 AE terms grouped in 18 categories, each with criteria for grading the severity of the AE. In 1998, the CTC v2.0, with 24 Categories and over 250 AEs, was published. Appendixes containing the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Scheme and the BMT Complex/Multi-Component Event Scheme were added. The NCI CTC v2.0 became the worldwide standard dictionary for reporting acute AEs in cancer clinical trials. 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. In CTCAE version 4.0, standards included AE terms that correspond to MedDRA Lowest Level Terms (LLTs) that are organized in MedDRA System Organ Class (SOC) groupings, with a severity grading scale. Finally, version 5.0 of the CTCAE will be published in 2017 and includes the addition of new AE terms and revision of existing grading scales. CTCAE version 5.0 has 837 terms, updated grading information, and a more comprehensive index.

In addition to standardizing the terminology, it is useful to define adverse effects in relation to timing of drug exposure. **Table 4** provides definitions for acute, chronic, cumulative and late effects. Acute effects describe AEs that develop within a short, defined timeframe; they can be transient, reversible or persistent. 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. In contrast, cumulative AEs develop and increase with repeated exposures to drug. Finally, 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 may manifest over an extended timeframe.

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 describing AE data. Current methods of AE analysis fall short in describing toxicities of modern therapies for haematologic malignancies. Typically, when AE data are presented in a clinical trial report, they are 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 and effective way to rapidly assess safety by displaying the 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. 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 represents a more user friendly visual output of AE data than a conventional maximum grade table. Figure 1 illustrates both the advantages of following toxicity over time and the limitations in collecting data on chronic toxicity

in early phase I and II trials. Although early in the courses of therapy there is an apparent decrease in severe toxicity, assessment in later courses is limited because of patient attrition from the trial.

Other types of tools, such as the Toxicity over Time (ToxT) package, produce analytic and graphical outputs that include a depiction of the time profile of AES as well as assessment of the burden of chronic low grade AEs.(39) 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 diarrhea (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 1B from the NCI Web Reporting System and Figure 3 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.

Chronic low-grade toxicities can limit the long-term delivery of therapy; a highly effective approach to the evaluation of most of these AEs is the use of Patient Reported Outcomes (PROs) described in greater detail in Subsection II. 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 for haematology patients. 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. The phase 1 dose escalation study is commonly used for the determination of the dose, schedule and sequence of new drugs in oncology and other disciplines. 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. During the phase 1 study the safety of a drug is often evaluated during the fixed time interval of one cycle. 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(40) (see below and Subsection II for further discussion on tolerability). Molecularly-targeted and immune-oncology 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(41).

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 immune-oncology 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(42, 43). 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 mTPI design(44) that uses all AEs data prior to dose escalation or de-escalation. It may require further modification as it also evaluates DLT in only the first cycle of treatment but could be changed to include a total of two or three cycles prior to selection of the recommended dose and schedule. 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.(41) 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 diarrhea, 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(45). 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 is well tolerated and results in overall response rates of over 80% in the relapsed and refractory setting(34), severe life threatening complications were not seen until patients underwent allogeneic haematopoietic cell transplantation.(46) 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(10) after rituximab therapy in HIV-negative patients, hepatitis B reactivation with rituximab(47), delayed neutropenia with rituximab(48), and an association of ibrutinib with aspergillosis(49) and arrhythmias(50) in haematologic cancers. 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 VI and VII.

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 immune-oncology 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.

Based on the regulatory experience of the last few years, very rare adverse events which were initially unexpected have become common and expected, as with hypophysitis from PD-L1 inhibition. Furthermore, 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 seen with imatinib in chronic myelogenous leukaemia, e.g. cardiac toxicity, abnormal bone and mineral metabolism, hypothyroidism, etc, would not necessarily be observed in studies with exclusively short-term endpoints.(51) 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.

The need to rapidly capture and transfer AE data also illustrates the need for long-term clinical benefit endpoints in later-phase trials. 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.(52) Late phase trials should be designed to assess the true clinical impact as reflected by PRO measures of symptoms or function, in addition to survival. Shorter term endpoints may have regulatory importance in safety assessment, but assessment of longer-term benefit should not be de-emphasized and has a role in tolerability evaluation

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(53) 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.(54)

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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 VI. 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.(55) 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 puritis, maculopapular rash, thyroiditis, pneumonitis, diarrhea, 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.(56) 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) (57) 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(57) 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.(58)

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 patients who are not the perfect clinical trial candidates, with comorbidities that were either not included on previous trials or that were explicitly excluded, and 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, analysis and rethinking of early and late phase clinical trial designs **(Table 5)**. The ascertainment and reporting of AEs would also be enhanced by inclusion of patient-reported outcomes as discussed in the next subsection.

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

Advances in the understanding of tumour biology, immunology and genetics have led to drug and biologic products that can produce deep and durable anti-tumor effects and improved survival in patients with haematologic malignancies.(59) The welcome advances in outcomes with newer therapies are not without costs. 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 assess, analyse and interpret cancer product safety and tolerability as discussed in the preceding subsection.(60) 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.(61)

Some haematologic malignancies are now chronic conditions, which creates a challenge and opportunity to assess the toxicities of prolonged, continuous therapies as part of usual daily life, as opposed to short-course cytotoxic therapy intended to cure. 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.

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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.(62) 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.(63) 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.(64) 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)(65), Functional Assessment of Chronic Illness Therapy (FACIT)(66), and the EuroQOL 5D (EQ-5D)(67) 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.(68) 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.(68, 69) 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 6**). 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.(70) 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.(71, 72) Inconsistencies in the incorporation and analysis of HRQL in these trials, however, makes interpretation of these findings and cross-trial comparisons challenging.(71)

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.(73) 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.(73) 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.(74)

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**).(75, 76)

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.(62) 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, diarrhea 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.(77-80) Targeted therapies often are associated with a spectrum of non-specific AEs that may not be frequent or severe, but alter patient HRQL.(81) 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.(82-84) This difference in clinician and patient responses provides some of the distinction to illustrate the differences between safety and tolerability.(85) 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.

Increasingly, the nature of treatment for haematologic malignancies is resulting in chronic administration of oral medications. 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 1**). 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.(86, 87)

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) (88, 89), standard PRO analytic methods (SISAQOL)(86), and standard PRO protocol elements (SPIRIT-PRO)(21).

Statistical analysis approaches for PRO data are well established(90) 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.(91) Reasons for missed reports should be captured during data collection and reported in manuscripts(92) 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.

Clinician-based AE data are commonly reported using summary measures where the maximum grade during treatment of each AE is computed per patient and then summarized across patients using frequencies and percentages. Subsets of AEs may also be summarized (e.g., only AEs which are at last possibly related to treatment). Alternative approaches include longitudinal modeling or competing risk methodology.

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(93) 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.(94)

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.(95)

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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. (80)

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.(96, 97) 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.(98)

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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.(99-101)

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.

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

Capturing and Evaluating Toxicities Post-Hematopoietic Cell Transplantation

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 can induce a myriad of toxicities and HCT therefore represents a unique situation in toxicity assessment in haematologic malignancies. This subsection will review special issues pertaining to AE assessment in HCT including multiple complex toxicities, graft versus host disease in allogeneic transplantation, AEs related to HCT specific polymedication, infectious AEs, and select longer term AEs post-HCT including sexual dysfunction, infertility, secondary cancers, and neurocognitive impairment.

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. Regimen-related Toxicities have been graded by the Bearman Scale(102) or the National Cancer Institute Common terminology Criteria for Adverse Events (CTCAE) version 4.0.(37)

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 (103) and IBMTR(104) grading systems are in use to document the severity of acute GVHD and, despite some limitations, are commonly employed. In contrast, consensus on the diagnosis, staging and response criteria for chronic GVHD has been challenging. Based on data from the Chronic GVHD Consortium, the 2014 NIH Consensus Conference has proposed a scoring system for chronic GVHD from an assessment of eight organs from which the NIH Global Severity Score is derived.(105)

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. The barrier comes not only from the frequency of the events but also the 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. Additionally, attribution is often difficult and sometimes impossible in the setting of multiple competing risks. The frequency of AEs and their "expectedness" also makes under-reporting an issue, 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(106). 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. The amount of data regarding concomitant drugs is limited to what is considered essential. 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. Briefly, at each monthly interim analysis, the total time on study is plotted against the total number of patients experiencing the toxicity of interest, (e.g., veno-occlusive disease or graft failure) patients experiencing death)(107). 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.(107, 108) 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 many toxicities that can aid in estimating expected rates and understanding HCT toxicity better. In the United States, reporting outcomes of allogeneic HCT recipients to a national registry managed by the CIBMTR has been mandatory since 2006. 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.(109) 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 established, 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).

The US FDA and most other international competent health authorities have grappled with the challenges of identifying drug-related toxicity in the context of numerous comorbidities and transplant/regimen related toxicity. The defibrotide approval in the US and Europe for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction after HCT highlights many of these challenges. Approval was based on Day +100 survival after transplantation across four clinical studies. A CIBMTR registry study and the published literature were used as benchmarks for historical control survival rates to assess the clinical benefit of defibrotide. For severe VOD, a randomized study compared with placebo would have lacked equipoise and posed an ethical challenge. The FDA review team assessed the benefit-risk to be favorable because the safety profile appeared reasonable "when assessed in the context of the treatment of a life-threatening disease with no approved therapy options; however, the safety assessment is limited by the lack of complete controlled safety data."(110)

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.

Drug interactions

In addition to being subject to unique and multiple toxicities, 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.(111) 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(112, 113). However, dose adjustments required when the agents are used concomitantly are highly variable, ranging from 25-90%, due to differences in competitive and non-competitive inhibition (9,10). CYP-mediated interactions can also be responsible for toxicity with use of otherwise relatively benign agents, such as non-absorbable oral steroids.(114) Genetic polymorphisms further complicate potential CYP interactions and the frequencies and types are highly variable among different ethnic groups.(111, 112) The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines on dose adjustments according to CYP polymorphism status for select drugs, such as tacrolimus. It is recommended to check CYP polymorphism status in patients receiving medications that have pharmacogenomic guidance available, although the impact on metabolism is known for very few drugs. Nonetheless, 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%)(115). 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. Agents most highly associated with QTc prolongation include: fluoroquinolones, azole antifungals, antiemetics (5-HT_3 antagonists, dopamine receptor antagonists, atypical antipsychotics), and tyrosine kinase inhibitors. Myelosuppression frequently occurs with immunosuppressants (mycophenolate mofetil), antivirals (ganciclovir/valganciclovir, cidofovir), and targeted therapies (ruxolitinib, ibrutinib)(112). 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 complications

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. (116, 117) 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.(118) Of the three grades described, only grade 3 (the highest degree of severity) was associated with survival ($p<0.0001$). 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(119), 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.(120)

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.(121, 122) 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.(123) Since sexual dysfunction frequently develops with or after other complications, the risk of sexual dysfunction AEs can only be interpreted in the perspective of other AEs. 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(124). The use of self-reported validated sexuality questionnaires (patient reported outcomes), such as the 37 item Sexual Function Questionnaire (SFQ), can help to identify and grade sexual dysfunction after transplant (122). Other prospective studies have used other patient-reported outcome forms such as the Derogatis Interview for Sexual Function (DISF-SR) or the Sexual Problems Measure for assessing sexuality after HCT.(125, 126) 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(127, 128) 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%.(129-131) 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 .(132)

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.(133) 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. 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 7**, we summarize many of the issues pertaining to AE assessment in HCT, as well as potential solutions.

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.(134) 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. Most patients with haematologic malignancies receive systemic therapies; fewer patients receive radiotherapy. 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 greatly improved 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. Although the vast majority of cancer survivors are older, haematologic malignancy survivors include many survivors of childhood, adolescent, and young adult malignancies. 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,(135) the modulating effect of age and breast radiation exposure on the risk of second breast cancer,(136) and the devastating impact of

childhood radiation therapy on subsequent muscle and bone maturity. There is also emerging data suggesting potential interaction between the intrinsic genetic make-up of the individual and the impacts of treatment, both in terms of drug metabolism and risk for long-term toxicities.(137)

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,(138) 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.(139, 140) Large-scale population-based cancer registry studies have quantified specific patterns of risk, which vary substantially for survivors of different types of haematologic malignancies. Smaller studies with more intensive data collection have identified certain treatment exposures as important risk factors for selected second 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(141). 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).(139) 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.(142) 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.(143) 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.(144) 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. As with subsequent neoplasms, a substantial amount has been learned from studying the long-term health of HL survivors, who frequently receive both chest radiotherapy and anthracyclines.(145) 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.(146) Because of the potential for larger than additive joint effects of these treatments with other cardiovascular disease risk factors, further research is needed to better quantify the complex milieu of risk factors present in most patients.(147)

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.(148, 149) Employment is frequently affected during cancer treatment, and changes in work roles often persist long into survivorship. There is increasing interest in studying financial toxicity in cancer patients, and studies report that the economic burden of cancer can persist years after diagnosis.(150) 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.(151, 152)

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 three areas of unmet needs: 1) infrastructure, 2) funding, and 3) healthcare delivery (see **Table 8**).

Infrastructure

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.

HCT survivors have been a focus of study because of their heightened risk of non-relapse mortality, well in excess of the general population, long after receiving their definitive therapy (**Figure 9**). As discussed in the prior subsection, outcomes for HCT survivors are reported to CIBMTR. Much of what is known about the risk of secondary malignancies after HCT across specific disease and age cohorts comes from analyses of these data. 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. Subsection VII will further explore the potential expanded role of such registries.

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.(153) 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. However, we must encourage additional cohort studies to provide insight into long-term outcomes of patients with other haematologic malignancies and receiving a broad range of therapies.

EMRs hold great promise for improving reporting of all AEs, including patient reported outcomes.(106) Unfortunately, substantial barriers remain due to differences in EMRs among institutions and the likelihood that survivors will receive care at different institutions during long-term follow-up. Resolving these issues to harnessing disparate EMRs and other "Big Data" repositories are areas of particular opportunity to expand the study of late AEs.

Funding

Limited availability of funding for longitudinal investigations of long-term toxicity in patients with haematologic malignancies is a key barrier to progress. While the last decade has seen some progress in new funding mechanisms from governmental agencies, philanthropic organizations, and insurance companies, resources have preferentially supported retrospective or cross-sectional studies over establishing cohort studies or testing interventions. This problem is accentuated in haematologic malignancy, which in 2011 was found to be the focus of only 3% of NCI-funded survivorship research.(154) This challenge is only exacerbated by more recent budgetary constraints, which have led to a research climate in which survivorship research must compete with basic science and development of novel therapeutics.

Healthcare Delivery for Survivors

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.(155) The most intensive approach, a multidisciplinary survivorship clinic, 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 (Figures 1-2). 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 AE's, amongst these different models. In addition, multispecialty survivorship care clinics are generally limited to academic medical institutions, which can be a barrier to many patients.

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.(156) 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.(157) 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,(158) and education of haematology-oncology physicians in communication skills inherent to the survivorship transition for lymphoma survivors,(159) 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 age, sex, disease characteristics, and treatment exposures. AEs in these patients may include second malignancies, cardiovascular disease, psychosocial issues, and others. Given the heterogeneity of the population of haematologic malignancy survivors, improvements in infrastructure, funding, 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

Toxicity assessment and reporting are important in the regulatory approval of new drugs. International regulatory processes and challenges will be 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 9)**. Each has basic requirements for reporting AEs that cross a certain qualitative or quantitative threshold. In the US, the Code of Federal Regulations (CFR) Section 312.32 dictates that sponsors must immediately report serious, unexpected, and suspected adverse reactions (SUSARs) that occur on a trial conducted under an investigational new drug application (IND).(160) These regulations were amended in 2010 by the final rule, which attempted to improve the utility of safety reports and increase the efficiency of the reporting process, ultimately to enhance protection of patients enrolled on clinical trials.(161) The regulations require periodic review of aggregated safety data to ensure detection of new safety signals or a higher rate of serious suspected adverse reactions.

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. The EVCTM is dedicated to the collection of Individual Case Safety Reports (ICSRs) for SUSARs in accordance with Directive 2001/20/EC

and Regulation (EU) No. 536/2014. Detailed guidance on the collection, verification, and presentation of AE/reaction reports from clinical trials using medicinal products for human use in the EU is available.(162) 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 9** 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 (163). This potentially translates into a situation where the "noise" of unnecessary safety reports 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. Clinical research professionals note inefficiencies in reporting requirements that may lead to "reporter fatigue" and "reporter bias" seen in AE reporting in medical publications in general, and in oncology trials in particular (164, 165). 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 (166). Other measures of tolerability such as drug interruptions and discontinuations or dose reductions, may not be captured, nor are patient reported outcomes (PROs) (167-169), as will be discussed further below. Healthcare utilization (hospitalizations, concomitant medications) administered to treat toxicity could be better documented. Finally, a well-described limitation of pre-market data is that trial populations are often younger or healthier than those with the disease in the general population (170). Gaps in our understanding of a product's safety and tolerability at the time of approval behoove us to enhance post-marketing surveillance to complement other safety and tolerability assessments and better understand the product's use in a real world population, 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 (171, 172). 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 based on mechanism of action as detailed in prior subsections. Adverse drug reactions may be idiosyncratic or related to cumulative toxicity, but in either case the shorter trial duration and follow-up that is 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. This is particularly problematic in haematology-oncology, where differentiating AEs related to the cancer or other comorbidities from those that are potentially drug related is challenging.

To mitigate these uncertainties, regulatory agencies leverage post-marketing pharmacovigilance and clinical studies. FDA has authority to require (post-marketing requirements, PMRs) or request (post-marketing commitments, PMCs) further studies to better characterize safety following the approval of a drug.(173) 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 under the Pharmaceuticals and Medical Devices Act. At the time of finalizing a procedure or in follow-up of a signal evaluation, the EMA's Committee(s) may agree that the applicant/marketing authorization holder (MAH) should provide additional data post-authorization, including additional pharmacovigilance activities.

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 (174-176). 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 based on the International Conference of Harmonisation (ICH) E2B. FDA recently completed a pilot whereby OHOP, in collaboration with the Office of Surveillance and Epidemiology (OSE), 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) (177). 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; these reports are accessible to all Member States in the European Economic Area (EEA) for further analysis. 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 (21st Century Cures Act;(178) EMA Appendix 2 to the Guideline on the evaluation of anticancer medicinal products in man (179)). 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. Collection of PROs should be methodical, addressing the limitations of missing or biased data that hinder application of statistical rigor, yet should not present a burden to patients (118, 180). PRO may assist in capturing low grade, potentially burdensome side effects that are unlikely to be the basis for non-approval of a therapy, but 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.

Incorporating PRO data to better inform the safety and tolerability of a therapy will require improving acquisition and standard submission of datasets. Leveraging the benefits of electronic methods are critical for the practical integration of PRO data into the regulatory review process. Prolonged assessment and careful documentation of supportive care medication use, hospitalizations, and other healthcare utilization can provide additional complementary safety data informing tolerability. Methods to analyse and visualize PRO data and other patient outcomes to inform treatment tolerability are active areas of research addressed in Subsections I and II. 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.(86, 89, 181, 182) Incorporation of PROs, as well as

assessment of the time course and severity of symptomatic AEs to inform tolerability, 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). The approval of crizotinib for a subset of locally advanced or metastatic lung cancer patients included PRO information that added important complementary material to clinician-reported incidence of vision disorders.(183) In response to PRO assessments, patients reported the onset of visual disturbance within the first week, occurred 4-7 days per week, and lasted up to 1 minute with mild or no impact on daily activities. 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.

Additionally, patients or their advocates can inform drug development during the trial design stage. The FDA Patient Liaison Program, through its Patient Representative Program and other initiatives (78), and the Professional Affairs and Stakeholder Engagement (PASE) initiative in the Center for Drug Evaluation and Research (CDER) (107), incorporate opportunities for patient and advocate involvement in the review process.

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 10**). 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 TGA, although there remains an AE reporting requirement; lack of insurance coverage may limit this practice with increasing drug costs (reference financial toxicity subsection) but not entirely. In other countries where approval and coverage are more closely linked, off-label use is more limited. Nonetheless, 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 (184). 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. An "Enhanced Post-Marketing Monitoring and Analytics" (EPMMA) Project is being implemented, 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, via the product manufacturer or directly to FDA MedWatch. 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.(185) These de-identified data can then be queried for analysis of safety signals.(186)

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 the 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 for authorized medicinal products (GVP Module VI) includes special situations such as off-label use. These reports are submitted to EudraVigilance, and thus accessible to all national Competent Authorities (NCA) in the EEA for signal detection and evaluation. As of the 22nd of November 2017, marketing authorisation holders will also obtain access to EudraVigilance, to the extent necessary to comply with pharmacovigilance obligations. This includes the EudraVigilance Data Analysis component, where companies will have access to all reports related to active substances for which they hold a marketing authorisation in the EEA. Additionally, the IMI WEB-RADR project developed a mobile app for patients and healthcare professionals to report suspected adverse reactions to the respective national NCA. This mobile app was trialed in three Member States with plans for further rollout and enhancement for two-way communication to provide feedback related to medicines for which reports were submitted.

Opportunities to leverage various types of real-world data to inform post-marketing safety exist in resources such as Sentinel, ASCO's CancerLinQ(187), 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, FDA's OHOP, together with the US Department of Health and Human Services' (DHHS) Innovation, Design, Entrepreneurship and Action (IDEA) laboratory, launched 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 (185). 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. FDA has presented results from a collaboration with Flatiron Health that analysed whether patients treated with agents that were approved for use with a companion-diagnostic were

tested (188). A collaboration between FDA and CancerLinQ (CancerLinQ is further described in Subsection VI) is underway to allow for the collection of RWE 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 on a non-haematologic malignancy (melanoma) and the various immune and targeted therapies used in its treatment, 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. OHOP/OCE 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 (189). 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 (190-192). 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 (193). FDA uses real-world evidence garnered electronically for regulatory decisions related to safety; data obtained through FAERS has been used to trigger safety labeling changes initiated by the Agency. 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 (194).

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

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regulatory assessment of AEs in haematologic malignancies both pre and post-marketing (see **Table 10**). 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 the goal of robust collection of relevant toxicity data that can be extrapolated to a broad population of patients and used to inform drug development, approval, and treatment decisions.

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

Drug toxicity is established in clinical trials where standardized and detailed AE (AE) data are collected prospectively and provide a solid foundation for the initial benefit-risk characterization of new anticancer drugs. 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? 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.(195) 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.(196) 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.(197, 198) 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.(199-205) Validation studies have shown high quality of data in terms of accuracy and good database coverage for some of the databases.(203, 206) 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.(207) 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.(208) 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.(209) 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.(210)

The value of real-world toxicity data

Despite these limitations, there is significant value to real world toxicity data (**Table 11**) 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.(211) 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.(212-214) 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.(215) 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.(216) 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.(217)

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.(10) 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.(218) 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 11 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 Common Terminology Criteria for Adverse Events (CTCAE), which provides standardized terminology for AE classification and its associated severity. Ideally, real

world data should be collected with similar consistency, but this is not feasible in a routine clinical setting. 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(187). 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.(219) 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.(220)

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.

The patient perspective on toxicity reporting

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.(210, 221) 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.(222) 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 patient reported outcomes (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 summarize and quantify the wealth of 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.(61, 223) **Figure 11** 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. 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.

Subsection VII: Financial Burden of Therapies for Haematologic Malignancies

In this Commission dedicated to AEs faced by patients with haematologic malignancy, it is important to recognize that the adverse effects of a cancer diagnosis and cancer therapy extend beyond the physical and psychological impacts of the disease and treatment. The social and financial effects of cancer, cancer treatment, and supportive care on the patient, family, and other care providers can profoundly influence the lives of patients and families worldwide.(224) "Affordability" and "sustainability" are practical terms with pragmatic meaning at an international level.(225) Although the cost of cancer drugs is numerically highest in the US, which accounts for 46% of the global oncology market, evidence suggests that when compared against the per capital purchasing power, drugs are most unaffordable in middle income nations.(226)

The costs of cancer care also can have broad reaching effects on cancer patients, providers, health care delivery systems, payers, and society. From the perspectives of society and payers, the costs and benefits of cancer therapies have been extensively studied.(227-236) While certain novel therapies have been associated with favorable cost effectiveness profiles across a series of studies such as rituximab(233, 234, 237) other agents such as bevacizumab in colorectal and lung cancer have less favorable profiles.(235, 238, 239) One recent report used a common framework to examine the cost-effectiveness of the addition of bevacizumab to first-line chemotherapy for metastatic colorectal across five countries demonstrating large differences in cost-effectiveness between countries.(240) Similar approaches will be needed to understand the value and financial impacts of drugs for haematologic malignancies from the societal perspectives across multiple international payers. However, even drugs that produce remarkable benefits for patients with haematological malignancies such as ibrutinib and imatinib are associated with substantial financial burden to patients and society.(241, 242) Moreover, as in the case of imatinib, the price

of the medication is continually escalated over time, reducing the value of past cost-effectiveness calculations for making present decisions.(243) Although the financial burden associated with a treatment strategy can be more difficult to assess that treatment toxicity associated AEs, it has substantial impact on patient well-being and existing Emerging tools, such as the recently described affordability index(244), can be applied to quantify this impact.

The rising costs of cancer therapies

The cost of treating cancer continues to rise to unprecedented heights. Studies in both haematologic malignancies and solid tumors have demonstrated both the rising prices of new cancer drugs over time as they enter the marketplace and increases in post-launch prices over time for orally administered anticancer drugs following approval by the FDA in the US. Even in situations where competition exists in the marketplace or older agents become open to generic manufacturing, drug prices have remained high or increased at rates higher than new agents.(242, 245) For example, imatinib has revolutionized the care of patients with chronic myeloid leukaemia (CML), transforming CML from a disease associated with poor outcomes in 2001(246) except with stem cell transplantation to one that is currently managed as a chronic disease with excellent outcome with oral therapies.(247) Surprisingly, although imatinib cost USD $26,000 per year in 2001, its price rose steadily by 10-20% per year until it reached a maximum of USD $146,000 per year before going generic.(248) Other studies identify that inflation-adjusted per patient monthly drug prices increased by 5-12% per year during the period from 2007-2013.(249, 250) Contrast these price increases with real household income in a nation, such as the US, which has remained stagnant for decades.(243) For this reason, some authors conclude that policy makers who wish

to reduce the costs of anticancer drugs must develop approaches that affect prices long after the drug has reach the market as well as immediately following regulatory approval.

One approach to the latter problem has been to estimate a value based price for new a cancer agent prior to FDA approval.(251) An analysis to establish value-based pricing for an agent links the price of a drug to the benefit that it provides. This value-based pricing model will be tested in the US in practice with the roll out of the first in class CAR-T therapy, tisagenlecleucel, which bears a list price of USD $475,000.(252) A partnership with Centers for Medicare & Medicaid Services in the US to allow for payment only when patients respond by the end of the first month(253). Broader applications of approaches to circumvent the financial burdens of new cancer drugs will require establishing value based frameworks for cancer care.(254-257) Other strategies have been proposed to address the dramatic rises in cancer drug prices although these will involve tradeoffs.(258) An application of this approach to diffuse large B-cell lymphoma (DLBCL) examined the potential cost-effectiveness of DLBCL subtype testing and providing targeted therapies for activated B-cell-line (ABC) DLBCL.(259) These authors showed that a subtype-based approach demonstrated a favorable incremental cost-effectiveness ratio when compared with administering standard therapy (R-CHOP) to all patients regardless of subtype. They also explored the range of scenarios varying test type (immunohistochemistry vs. gene expression), test sensitivity and specificity, and therapeutic benefit for a novel approach to provide benefit for ABC patients. Such an approach can help to identify where subtype-based treatment strategies and novel therapies remain cost-effective and can reduce financial burden, thereby informing the design of phase 3 trials that are needed to validate model findings and draw definitive conclusions.

Modern approaches to drug discovery and development have dramatically increased the number of targets for cancer therapies. The advent of these agents presents a challenge in terms of timeline for drug development and healthcare costs. Overcoming the rising cost of cancer drugs may also require new pricing and payment systems and several approaches have been suggested. Recent approach for delivering cost-effective care and determining the costs of drugs and services for cancer care include: bundled payments,(260) indication specific pricing,(261) payment by results,(262) third party buy and bill,(263) pathway adherence,(263) and value based pricing.(264, 265) and inclusive shared savings.(266) In addition, new strategies are needed to support patient selection and allocation for clinical trials, guideline development, and payer coverage determination to identify individuals and populations most like to benefit from a particular therapy. These approaches should address clinical value in addition to statistically significant clinical benefit, and will be necessary to guide delivery of high value interventions to our patients.

The impact of cost of care on the cancer patient

While discussions about the costs of cancer supportive care commonly focus on balancing the potential to save and extend lives against the costs to society or payers, out-of-pocket expenses incurred by patients for accessing care can range widely and can impact patients' financial well-being significantly and are considered by some as an "adverse event" given the resultant impact on a patient and family and worthy of grading on similar scales as any other AE.(267, 268) Out-of-pocket costs include any payments for medical care that involve costs not covered by health insurance. Types of out-of-pocket cancer care costs include: lodging/travel for medical care; deductibles that are paid for medical care before a health insurance plan begins payments; copayments for each healthcare service such as a doctor appointment or prescription; and

coinsurance, which is the percentage of costs an individual pays for a service in concert with the health insurance plan.

Cancer patients undergoing therapy and cancer survivors commonly report higher out-of-pocket spending than people who have not had cancer. Out-of-pocket expenses may be particularly pertinent in circumstances without universal healthcare coverage or for uninsured or poor individuals for whom cancer care is one of several financial burdens. Over one third of patients with multiple myeloma reported taking a variety of steps to help cover medical costs, including pharmaceutical assistance programs, depleted savings accounts, or borrowing from retirement savings.(269) A cross-sectional pilot analysis of financial toxicity in multiple myeloma has found three factors associated with treatment-related financial hardship: younger age, non-married status, and lower annual household income.(270) It has been estimated that 40-85% of cancer patients stop working during initial treatment, with absences ranging from 45 days to nearly six months and cancer survivors may contend with long-term health barriers that limit return to work after treatment. (271) Consequently, because cancer treatment can affect an individual's ability to work and pay household bills, financial hardship from cancer therapy more commonly affects patients who are the primary or only wage earner for the household; individuals with significant debt or limited assets before the cancer diagnosis, and people with inadequate health and disability insurance.

Cancer survivors also may have financial problems many years after they are diagnosed because they may be paying for ongoing management of late effects. Since many more individuals live longer after an initial diagnosis of haematologic cancer and some patients continue chronic oral therapy or intermittent administration of serial therapies at relapse out-of-pocket expenses may become even more significant for cancer survivors and their families who face recurring and

continuing costs over many years. One study examined the economic burden of oral therapies for the treatment of patients with chronic lymphocytic leukaemia (CLL).(241) Although novel oral therapies for CLL such as ibrutinib, idelalisib, lenalidomide, and venetoclax have facilitated treatment administration, reduced toxicity, and improved outcomes particularly for older patients with CLL, their high cost has raised concerns about affordability and the financial burden to patients and society. The authors utilized a simulation model to project the future prevalence and cost burden of CLL in the era of evolving management of CLL with oral targeted therapies from 2011 to 2025 where: chemoimmunotherapy was the standard of care before 2014, oral targeted therapies were administered for patients with del(17p) and relapsed CLL from 2014, and for first-line treatment from 2016 onward. Utilizing disease progression and survival data for each therapy based on published clinical trials the authors projected that the per-patient lifetime cost of CLL treatment would increase from USD $147,000 to $604,000 (310% increase) as oral targeted therapies become the first-line treatment. The corresponding total out-of-pocket cost was projected to increase from USD $9,200 to $57,000 (520% increase). High cost of care associated with oral and other novel therapies now and in the future can have a substantial impact on patients, their caregivers, and patient outcomes.

The impact of financial hardship on patient outcomes

For some patients the high costs of care may lead to refusal of treatment or nonadherence to recommended treatments and poorer clinical outcomes.(272-274) In one recent analysis based on insurance claims data, higher out-of-pocked costs were linked with high rates of oral prescription abandonment and delayed initiation across a variety of different malignancies.(275). At the extreme, financial hardship following a cancer diagnosis has been associated with increased

risk of filing for bankruptcy.(267) One study linked data from a population-based cancer registry from Western Washington that is part of the National Cancer Institute's Surveillance Epidemiology and End Results Program (SEER) and a randomly sampled age-, sex-, and ZIP code–matched population of people without cancer with federal bankruptcy records for the period 1995–2009. This study found that cancer patients had a rate of bankruptcy that was 2.65 times higher than people without cancer.(267) For cancer patients who experience an extreme form of financial toxicity such as bankruptcy, these financial effects can be associated with increased mortality. (276) Thus, at the extremes it is clear that the financial hardships that cancer care can impose can impact patient outcomes.

Measuring the financial impact of cancer care within clinical trials

One of the most challenging aspects of evaluating the financial impact of new cancer interventions is determining the appropriate measures associated with providing care. The large number of possible measures of financial toxicity, have been categorized into 3 broad areas: monetary measures defined by out-of-pocket expenses or the ratio of out-of-pocket expenses to income; objective measures in assessing debt levels, the need to borrow money from family or friends, sell assets, withdraw money from retirement or savings funds, and filing for bankruptcy; and subjective measures on perceptions of cancer-related financial burden. Each approach measures a different aspect of financial hardship. All three measures should be assessed in clinical trials and in observational studies where possible to provide comprehensive assessment of the financial impact of therapies on patients with haematological malignancies.

When monetary measures are used, clarifying the perspective of who is paying for the costs is an important consideration. The United States Panel on Cost-Effectiveness in Medicine

recommends that healthcare costs be determined from a societal perspective and that all costs are included regardless of who incurs them.(277) However, ascertaining costs from a societal perspective remains challenging. While cost-effectiveness analyses provide a methodology for examining the cost of a drug, in the context of the survival benefit, quality of life, cost of drug administration, AEs and duration of therapy, they also provide a standard toolkit for measuring direct and indirect medical costs. For instance, estimating the unit price of each drug, often uses the average wholesale price data.(278) Projections of the costs of managing of AEs can be based on published guidelines for resources to be utilized and the costs of resource utilization are calculated according to the Medicare physician fee schedule were previously described.(279) This methodology can be incorporated into clinical trials or applied retrospectively to completed randomized controlled clinical trials as has been done in the evaluations of rituximab maintenance therapy and radioimmunotherapy for lymphoma.(233, 234, 237) Such approaches assess the financial burden of an intervention in the broader clinical context. These methods should be used to examine the general value of a therapy irrespective of the individual patient factors describe above that affect and are affected by the financial burden of a therapy.

The inclusion of patient questionnaires in clinical trials to measure quality of life or other patient reported outcome measures is increasing. At the individual patient level, adding questionnaires to the evaluation of novel therapies in clinical trials and observational studies that measure out-of-pocket costs should be feasible if the correct balance of pertinence and brevity can be achieved. Future efforts should draw from expertise in pharmacoeconomics, survivorship, and haematological malignancies to tailor existing tools and design questionnaires that objectively measure factors that influence a patient's perception of financial burden such as: debt level, the need to borrow money or sell assets to cover healthcare expenses, filings for bankruptcy, and

subjective measures concerning perceptions of treatment-related financial burden. In addition, questionnaire linking financial burden to patient outcomes are needed. Such tools will enable assessment of the impact costly therapies have on treatment adherence, new form of medication non-compliance such as dose rationing to reduce the cost of refills, treatment toxicity, treatment response, and survival. Ultimately, demonstration of these impacts of financial burden on outcomes may motivate efforts to curb the rising costs of treatments for patients with haematologic malignancies if in actual practice those treatments do not realize their expected benefits because of their financial burden.

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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 illnesses, with new types of acute, chronic, cumulative and late toxicities that also bear potential psychosocial and financial burdens. 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 have proposed immediate- and long- term solutions to these challenges (summarized in Table 12).

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(38) 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(39) 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.

The changing landscape of therapy for haematologic malignancies requires 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(82). 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(69), 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 a numerous acute anticipated 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, funded, 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. Finding strategies to gather survivors' health information from electronic health records or "big data" repositories is a future avenue. Healthcare delivery for survivors beyond surveillance for recurrence also remains a challenge. Although survivorship care plans as a tool have been proposed, implementation into routine practice has not been achieved internationally. 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(176, 280). 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 is real. 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 accurately reported. Regulatory agencies have also recognized the need to incorporate PRO into tolerability determination, and are involving patient organisations in the definition and implementation of pharmacovigilance systems and risk/benefit assessments. 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. Further outcomes research to explore ways in which real world data can inform product labeling is needed.

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(187) 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.

Adverse effects of haematologic malignancies in real world patients extend beyond treatment-related toxicity and include the social and financial effects on the patients and family. The financial burden of cancer therapy has become a major social issue internationally, affecting patients, providers, health care delivery systems, payers and society(225). Oral agents such as ibrutinib, lenalidomide, venetoclax, and other agents are associated with substantial financial burden. Competition and generic manufacturing drug prices have not altered the course of this trend internationally. Novel approaches to cost-effective care include value-based pricing, indication specific pricing and payment by results, among others. Cost-effective frameworks that

address clinical value in the context of cost should be explored, with a goal of ultimately achieving consensus on an approach to establishing value in the context of financial impact of drugs of haematologic malignancies across multiple international payers. The complexities go further with out-of-pocket cancer care costs, including deductibles, transportation, housing, and other issues. These expenses may be associated with refusal of treatment or nonadherence, which can be associated with poor clinical outcomes.(275) At the extreme is financial bankruptcy due to treatment-related costs. Monetary measures, objective measures and subjective measures of the financial impact of new cancer therapies. Each should be assessed in patients treated on haematologic malignancy trials and observational studies to better understand financial burden on our patients.

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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