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Harmonization of Busulfan Plasma Exposure Unit (BPEU): A Community-Initiated Consensus Statement

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A B S T R A C T

Busulfan therapeutic drug monitoring (TDM) is often used to achieve target plasma exposures. Variability in busulfan plasma exposure units (BPEU) is a potential source for misinterpretation of publications and protocols and is a barrier to data capture by hematopoietic cell transplantation (HCT) registry databases. We sought to harmonize to a single BPEU for international use. Using Delphi consensus methodology, iterative surveys were sent to an increasing number of relevant clinical stakeholders. In survey 1, 14 stakeholders were asked to identify ideal properties of a BPEU. In survey 2, 52 stakeholders were asked (1) to evaluate BPEU candidates according to ideal BPEU properties established by survey 1 and local position statements for TDM and (2) to identify potential facilitators and barriers to adoption of the harmonized BPEU. The most frequently used BPEU identified, in descending

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order, were area under the curve (AUC) in μM × min, AUC in mg × h/L, concentration at steady state (Css) in ng/mL, AUC in μM × h, and AUC in μg × h/L. All respondents conceptually agreed on the ideal properties of a BPEU and to adopt a harmonized BPEU. Respondents were equally divided between selecting AUC in μM × min versus mg × h/L for harmonization. AUC in mg × h/L was finally selected as the harmonized BPEU, because it satisfied most of the survey-determined ideal properties for the harmonized BPEU and is read easily understood in the clinical practice environment. Furthermore, 10 major professional societies have endorsed AUC in mg × h/L as the harmonized unit for reporting to HCT registry databases and for use in future protocols and publications.

INTRODUCTION

Hematopoietic cell transplantation (HCT) offers curative treatment for malignant and nonmalignant diseases [1]. Recently reported data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show that conditioning regimens for HCT frequently incorporate busulfan, including 58% of allogeneic myeloablative conditioning regimens and 32% of allogeneic reduced-intensity conditioning regimens [2]. For these regimens, busulfan plasma exposure has been associated with important post-transplantation outcomes [3–5]. Although low busulfan plasma exposure (under treatment) is associated with higher rates of graft rejection [6-8] and relapse [9], the converse is associated with increased risk for hepatotoxicity [6,10-14] and nonrelapse mortality [13]. Achieving the optimal plasma exposure improves each of these outcomes [10,15–17].

Currently, multiple busulfan plasma exposure units (BPEU) are used clinically and reported in publications. Lack of BPEU harmonization raises several concerns. First, when clinicians interpret publications or implement a protocol, they must often convert the reported BPEU to the BPEU used by their institution via a complicated and error-prone process. Second, the use of different BPEUs precludes busulfan plasma exposure from being included as a data element in international registries such as that of the CIBMTR. As a result, these large databases cannot be leveraged to answer scientific questions regarding busulfan plasma exposure and HCT outcomes. This is exemplified by the recent experience of the American Society for Blood and Marrow Transplant (ASBMT, now ASTCT) Committee on Practice Guidelines, which was unable to create an evidence-based guideline for busulfan TDM, due in part to heterogeneity in reported BPEUs [5].

The overarching goal of this project was to minimize the risk of busulfan dosing errors and to facilitate the future use of multicenter databases to evaluate the relationship between busulfan plasma exposure and HCT outcome. Given that international harmonization to a single BPEU would likely resolve barriers and create opportunities for the safer and more effective use of busulfan, we sought to achieve international harmonization to a single BPEU. Using Delphi consensus methodology, we administered iterative surveys to relevant stakeholders [18,19]. Herein we present the results of this BPEU harmonization project.

METHODS

Needs Assessment and Formation of Steering Committee

Shortly after the autumn 2016 publication of the ASTCT Practice Guidelines Committee's busulfan considerations [5], 23 busulfan therapeutic drug monitoring (TDM) laboratories and HCT centers worldwide known to perform busulfan TDM were invited to participate in a discussion of solutions to the evidence gaps highlighted in that ASTCT publication. From this group, a Steering Committee (L.L.D., E.M., J.S.M., J.R., and R.F.Y.) was formed. Twenty-eight respondents responded to this invitation and identified a total of 33 concerns. Based on these concerns, the Steering Committee prioritized BPEU harmonization. Before beginning this project, support was obtained from leaders of 7 relevant professional societies (see Acknowledgments).

Delphi Process

This BPEU harmonization project comprised a series of web-based surveys completed by an increasingly larger circle of stakeholders involved in busulfan TDM during HCT. All survey responses were anonymous, and stakeholders were not aware of individual responses. The study was approved by the City of Hope's Institutional Review Board.

Survey Participants

Invited survey participants included HCT physicians who prescribe busulfan and choose the target busulfan plasma exposure, analytic chemists who quantitate busulfan plasma concentrations, and clinical pharmacists and pharmacologists who conduct pharmacokinetic modeling and use those results to personalize busulfan doses. These BPEU stakeholders were organized into 3 groups of increasing diversity of expertise and size (Figure 1, Supplementary Tables 1 and 2): the aforementioned Steering Committee (n = 5), an Expert Panel (n = 9), and a Task Force (n = 38). The Steering Committee included experts in busulfan quantification, pharmacokinetic modeling, and dose individualization. The Expert Panel, formed in August 2017, included Steering Committee members, the physician Chair of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Chemotherapy Dosing Committee, plus HCT physician leaders from around the globe. The Task Force, formed in February 2018, added members recruited via the needs assessment responders and collegial networks of the Steering Committee and Expert Panel.

Purposive sampling to obtain maximum variation in demographics, professional experience, and health care professional roles, as well as snowballing strategies (in which respondents can nominate or extend an invitation to other relevant stakeholders to participate), were used to select respondents.

Surveys

Each survey was developed by 2 coauthors (J.S.M. and C.M.Q.) and reviewed by 2 other members of the Steering Committee (L.L.D. and J.R.) for content and face validity. Surveys are available from J.S.M. on request. Consistent with Delphi methodology [20], Steering Committee and Expert Panel members received a summary of the project's goal and were invited to complete round 1 of survey 1, in which the goal was to identify properties of the ideal BPEU. It included several BPEUs in current use and an initial list of 3 ideal BPEU properties: (1) the relationship between BPEU and busulfan dose unit is clearly understood, (2) BPEU can be clearly understood regardless of the frequency of busulfan administration, and (3) BPEU is used in the available pharmacokinetic software platforms for busulfan TDM. Iterative rounds of survey 1 were developed after analysis of responses to the previous round; new questions could be added based on responses to the previous survey. Revised rounds of survey 1 were sent, together with the aggregated responses of the previous round, until no new information was provided or until consensus was achieved.

For each round, respondents were asked to rate their level of agreement with each statement on a 4-point Likert scale as "not at all important,"

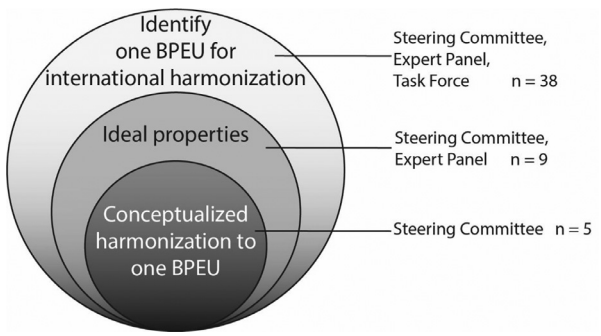

Figure 1. Conceptual schema for identifying a single BPEU for international harmonization.

"slightly important," "moderately important," or "very important." Offering a finite number of response options encouraged respondents to commit to a particular item [20]. To aid clear calculations on agreement and disagreement, a neutral middle point was excluded, to compel respondents to choose a particular option [21]. Consensus was defined a priori as having been achieved when ≥70% of respondents stated that a property was "moderately important" or "very important." Each survey round ended by inviting respondents to provide general free-text feedback.

The goals of survey 2 were to (1) evaluate each BPEU against the properties of the ideal BPEU as established in survey 1, (2) evaluate each BPEU against local position statements for TDM, and (3) identify facilitators and barriers to international harmonization to a single BPEU. Survey 2 participation was broader than survey 1 and included the Steering Committee, Expert Panel and Task Force. Similar to survey 1, iterative rounds of progressively refined surveys were planned until no new information was gathered or consensus was reached regarding the single harmonized BPEU. Consensus was defined a priori as having been reached when ≥70% of respondents ranked a BPEU as "very likely" or "extremely likely" to be adopted for international harmonization. The performance of each candidate BPEU was also evaluated with consensus defined a priori as occurring when ≥70% respondents "agreed" or "strongly agreed" that a BPEU had a property of the ideal BPEU.

This project used Research Electronic Data Capture (REDCap), a secure, HIPPA- and FISMA-compliant web application for building and managing online surveys and databases hosted at City of Hope. Server security and application compliance are jointly managed by administrators in Information Technology Services and Research Informatics. Where feasible, validation rules (eg, logic checks, format restrictions, min/max range) were added to ensure valid and accurate data entry. Users were able to complete surveys on any computer with Internet access or a compatible mobile application [22].

Statistics

There is no universal agreement on the "minimum" or appropriate sample size for a Delphi process. Reliable outcomes have been generated by relatively small Delphi panels in which members are carefully selected based on expertise and background [23]; for example, the chronic graft-versus-host disease (GVHD) Delphi process invited 64 participants) [24]. A priori, for survey 1 we assumed a 100% response rate from the Steering Committee and Expert Panel ($n = 14$). For survey 2, we assumed a 75% response rate from the larger group of stakeholders ($n = 52$) based on the response rate to a recent survey conducted by the International Chronic GVHD Special Interest Group, a voluntary group of investigators interested in chronic GVHD research.

Descriptive statistics of survey responses were used to provide a summary of the group's view on each item, with percentage scores for each statement providing the level of agreement among respondents [21]. SQL exports from the REDCap web-enabled survey data capture system and MS Excel (Microsoft, Redmond, Washington, USA) were used for analysis.

RESULTS

Survey 1: Steering Committee and Expert Panel Identify Properties of an Ideal BPEU

Thirteen of 14 (92%) invited participants responded to the first round of survey 1 (Supplementary Table 3) and identified commonly used BPEUs (Table 1): area under the curve (AUC) in $\mu M \times$ min ($\frac{\text{micromole}}{\text{liter}} \times$ minute) by 54%, AUC in mg × h/L ($\frac{\text{milligram}}{\text{liter}} \times$ hour) by 31%, and concentration at steady state (Css) in ng/mL ($\frac{\text{nanogram}}{\text{milliliLiter}}$) by 15% (Figure 2A). Round 1 identified a new ideal BPEU property that was included in the second round—namely, that an ideal BPEU allows for expression of busulfan exposure as total exposure. Likewise, after round 2, round 3 added that an ideal BPEU avoids the use of decimals ≤.01. Free-text comments from round 3 revealed a position statement of the Australian Royal Academy of Pathologists that is relevant to international BPEU harmonization [25,26]. Therefore, in round 4, participants were asked to describe any additional relevant local position statements; none were identified. Free-text comments from round 4 revealed a fourth BPEU in use, AUC in $\mu M \times$ h ($\frac{\text{micromole}}{\text{liter}} \times$ hour). Survey 1 concluded after round 4 with ≥70% of respondents agreeing on the properties of the ideal BPEU (Figure 2A; Table 2).

Survey 2: Steering Committee, Expert Panel, and Task Force Agree to International Harmonization

In round 1 of survey 2 (Figure 2B), 39 respondents indicated that 4 BPEUs were used globally (Table 1): AUC in $\mu M \times$ min (56%); AUC in mg × h/L (23%), Css in ng/mL (18%), and AUC in μg x h/L (3%). Free-text comments on survey 2, round 1 revealed that a fifth BPEU was in current use: AUC in $\mu g \times$ h/L. The 4 BPEUs identified from survey 1 were evaluated for properties of the ideal BPEU. Consensus was reached that 2 of the AUC units, mg × h/L and $\mu M \times$ min, each met 3 of the 5 ideal properties, whereas AUC in $\mu M \times$ h met only 2 properties, and Css in ng/mL met none of the properties (Supplementary Table 4). No additional local position statements were identified.

In round 2, after iterative reevaluation of the 4 BPEUs, a consensus was reached that AUC in $\mu M \times$ min met 3 of the 5 ideal BPEU properties and AUC in mg × h/L met 2 of the 5 properties, and AUC in $\mu M \times$ h and Css in ng/mL each met only 1 of the 5 properties (Supplementary Table 4). Round 2 was the first to evaluate different BPEUs against the qualities stipulated by the only local position statement identified, the 2010 position statement of the Royal College of Pathologists of Australia. The following question was asked: "We also draw to your attention the 2010 position statement of the Royal College of Pathologists of Australia (Table 4) that states: '. . .it is recommended that mass units be used routinely for reporting results of therapeutic drug concentrations measured by pathology laboratories in Australia and New Zealand. It is also recommended that the litre (liter in American spelling, L) be used as the denominator when expressing the concentration. Examples of these units are mg/L and μg/L. These recommendations relate to drugs which are normally given therapeutically, whether measured for therapeutic drug monitoring purposes or assessment of overdose.'" Thirty-six round 2 respondents were asked which BPEU is in closest agreement with the foregoing position statement; 53% selected AUC in mg × h/L, 33% selected AUC in

Table 1
Survey Responses Regarding BPEU Use in Clinical Practice

	Survey 1, Round 1	Survey 2, Round 1	Survey 2 Round 4
Respondents	Steering Committee and Expert Panel	Steering Committee, Expert Panel, and Task Force	
Number responding	13	39	32*
AUC in $\mu g \times$ h/L†, n (%)	NA	1 (3)	2 (6)
AUC in $\mu M \times$ h†, n (%)	NA	NA	2 (6)
AUC in $\mu M \times$ min, n (%)	7 (54)	22 (56)	17 (53)
AUC in mg × h/L, n (%)	4 (31)	9 (23)	5 (16)
Css in ng/mL, n (%)	2 (15)	7 (18)	5 (16)

This question was asked in survey 1, round 1 (Steering Committee and Expert Panel); survey 2, round 1 (Steering Committee, Expert Panel, and Task Force); and survey 2, round 4 (Steering Committee, Expert Panel, and Task Force). Handwritten responses were counted.

* One respondent purposely stated "other" and typed "micromole × min," which is missing a volume term.

† NA: not asked in survey 1 round 1 or survey 2 round 1. AUC in $\mu g \times$ h/L was handwritten under the "Other" category in survey 2 round 1.

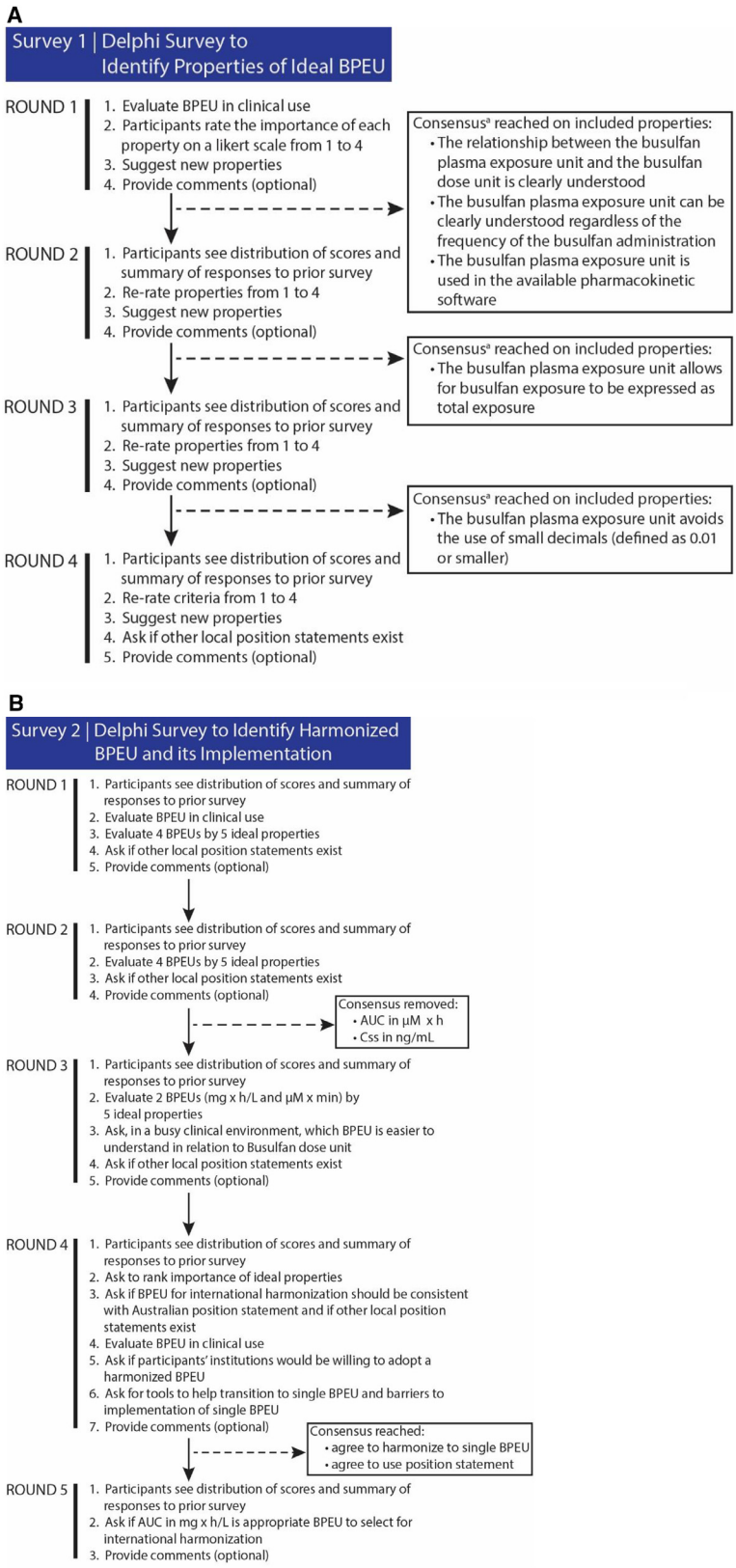

Figure 2. Summaries of survey 1 (A) and survey 2 (B).

Table 2
Rank Order of the Properties of an Ideal BPEU Identified from the Delphi Process of the Survey 1[a,b]

	Property of an Ideal BPEU, n				
Rank	The relationship between the BPEU and the busulfan dose unit (e.g., milligrams) is clear	Allows busulfan exposure to be expressed as total exposure	Is included in the pharmacokinetic software platforms available for busulfan therapeutic drug monitoring	Avoids small decimals (defined as ≤.01)	Is independent of the frequency of busulfan administration
1, Most important	14	7	4	4	3
2	2	11	7	5	7
3	3	9	12	2	6
4	4	5	4	9	10
5, Least important	9	0	5	12	6

[a]Participants were asked to rank the importance of the five ideal properties with 1 being most important: [b]Ranking based on number of respondents reporting the specified format is important or most important. The term "busulfan (plasma) exposure unit" was used in each round of the surveys. 70% of the Expert Panel stated that each of these properties was "moderately important" or "very important" on 2 survey rounds. The rank order of properties of the ideal BPEU was based on results from the broader group survey 2, round 4 that also included the Task Force.

μM × min, 14% chose Css in ng/mL, and none chose AUC in μM × h. Based on the results of the first and second rounds, AUC in μM × min and AUC in mg × h/L remained under consideration as the future harmonized BPEU.

In round 3 of survey 2, respondents were asked to evaluate these 2 BPEUs against the properties of the ideal BPEU. Consensus was reached that each had 3 of the 5 ideal BPEU properties (Table 3). Respondents were also asked which BPEU most agreed with the 2010 position statement of the Royal College of Pathologists of Australia [25,26]. Thirty-three respondents (87%) chose AUC in mg × h/L as being in agreement with the position statement, and 5 respondents (13%) chose AUC in μM × min. An additional question was also asked: "In a busy clinical environment, which BPEU is easier to understand in relation to the busulfan dose unit (e.g., milligrams)?". In response, 22 respondents (63%) chose AUC in mg × h/L and 13 (37%) chose AUC in μM × min.

In round 4 of survey 2, 32 respondents indicated that 5 BPEUs were in use globally (Table 1): AUC in μM × min (53%), AUC in mg × h/L (16%), Css in ng/mL (16%), AUC in μg × h/L (6%), and AUC in μM × h (6%). The respondents were asked to rank the importance of the 5 ideal properties and whether they supported harmonization to a single harmonized BPEU (Table 2). All 32 respondents stated their willingness to harmonize to a single BPEU, and 87% (28 of 32) reported that their respective institution/program would be willing to do so. Consensus was reached that the BPEU chosen for harmonization should be consistent with the 2010 position statement of the Royal College of Pathologists of Australia and easy to understand in relation to the busulfan dose unit (eg, milligrams) in a busy clinical environment (ie, μM × min requires conversion with busulfan's molecular weight, whereas mg × h/L does not) [25].

A final question in round 4 had 32 respondents identify facilitators and barriers to implementation of a harmonized BPEU. An identified facilitator was "step-by-step instructions" in the following formats: web-based app (most preferred), PDF available, smartphone app, video tutorial, and one-on-one personal training (least preferred). Among key barriers to a harmonized BPEU, 78% identified potential lack of familiarity with the chosen BPEU, and 31% identified a lack of perceived benefit of making the change. Other barriers were identified in free-text responses (Supplementary Table 5). In the fifth (final) round iteration, 34 respondents indicated their level of agreement with the statement "AUC in mg × h/L is the appropriate unit of BPEU to select for international harmonization"; 50% selected "strongly agree" or "agree," and 50% chose "strongly disagree" or "disagree."

Choice of BPEU for International Harmonization

Although survey 2 respondents were evenly split in the final round with respect to their choice for the harmonized BPEU, the Steering Committee believed that selection of AUC in mg × h/L as the harmonized BPEU was in closest alignment with the guiding principles and aggregate survey responses. This decision was supported by 10 professional societies (Table 5).

Table 3
Percent of Survey 2 Respondents Who "Agree" or "Strongly Agree" That the BPEU Has the Property Listed

Property of the Ideal BPEU	Round 1		Round 2		Round 3	
	μM × min	mg × h/L	μM × min	mg × h/L	μM × min	mg × h/L
The relationship between BPEU and the busulfan dose unit (e.g., milligrams) is clear.	46%	**82%**	53%	**78%**	50%	**92%**
Allows busulfan exposure to be expressed as cumulative exposure.	**92%**	**90%**	**92%**	**92%**	**89%**	**89%**
Is included in the pharmacokinetic software platforms available for busulfan therapeutic drug monitoring.	**77%**	**74%**	**81%**	69%	**84%**	**76%**
Avoids small decimals (defined as ≤.01.	**100%**	67%	**97%**	56%	**95%**	68%
Is independent of the frequency of busulfan administration.	56%	59%	58%	58%	66%	63%

Values >70% are in bold type.

Table 4
Application of 2010 Position Statement of the Royal College of Pathologists of Australia [25]

Recommendation	Application to BPEUs	Compliance with Recommendation	
		μM × min	mg × h/L
Mass units should be used for reporting therapeutic drug concentrations in Australia and New Zealand.	Busulfan plasma concentrations should be reported in units of ng/mL or μg/L. To avoid conversion to micromolar, only μg × h/L and mg × h/L should be used to report BPEU.	Noncompliant	Compliant
The litre (L) should be used as the denominator when expressing concentration. Examples of these units are mg/L and μg/L.	Busulfan plasma concentrations should be reported in units of μg/L.	Compliant	Compliant
Exceptions relevant to busulfan		Not applicable	Not applicable
Drugs for which there is current uniformity of reporting and supporting information using molar units, notably lithium (mmol/L) and methotrexate (μmol/L)	Table 1 shows that there is no current uniformity of reporting and supporting information using molar units	Not applicable	Not applicable

This position statement was written by a working party from the Australasian Association of Clinical Biochemists, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Royal College of Pathologists of Australasia and Royal Australasian College of Physicians. Thus, the Australian spelling of liter (i.e., litre) is used.

DISCUSSION

Through iterative surveys of international stakeholders in busulfan dose individualization we have (1) found that 5 BPEUs are currently used clinically, (2) reached consensus regarding the properties of the ideal BPEU, and (3) reached consensus regarding willingness to harmonize to a single BPEU. Because the respondents were evenly split regarding the choice of a single BPEU for harmonization, the Steering Committee and ASTCT Practice Guideline Committee made a decision that reflected the consensus reached among stakeholders regarding the most important properties of the ideal BPEU: AUC mg × h/L was selected as the harmonized BPEU. Although we did not meet our threshold for consensus among stakeholders with respect to the selection of the single harmonized BPEU, we believe that the Steering Committee's choice reflects the philosophy expressed by the survey respondents.

Table 5
Professional Societies Supporting AUC in mg × h/L as the single BPEU

Society*	Representative	Date
ACCP Hematology/Oncology Practice and Research Network	Marco Martino	March 2019
ASTCT Executive Committee	Miguel-Angel Perales Navneet Majhail	April 2019
ASTCT Practice Guideline Committee	Paul Carpenter Bipin Savani	February 2019
BMT CTN	Marcelo Pasquini Miguel-Angel Perales	February 2019
Brazil Bone Marrow Transplant Society	Nelson Hamerschlak	January 2019
CIBMTR	Marcelo Pasquini	February 2019
EBMT and EMBT Pharmacy†	Mohamad Mohty Erik van Maarseveen	January 2019
HOPA	Susanne Liewer	June 2019
IATDMCT–Chemotherapy Group	Erik van Maarseveen	January 2019
KSBMT	Hyoung Jin Kang	April 2019
PBMTC	Michael A. Pulsipher	February 2019

ACCP indicates American College of Clinical Pharmacy; ASTCT, American Society for Transplantation and Cellular Therapy; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Marrow Transplantation; HOPA, Hematology/Oncology Pharmacists Association; IATDMCT, International Association of Therapeutic Drug Monitoring and Clinical Toxicology; KSBMT, Korean Society of Blood and Marrow Transplantation; PBMTC, Pediatric Blood & Marrow Transplant Consortium.

* The IATDMCT approved AUC in mg × h/L; the other societies endorsed AUC in mg × h/L.

† The EMBT Pharmacy Committee is responsible for such medication-related decisions; their committee decision is supported by Dr. Mohty, President of the EBMT at the time of the decision.

The Steering Committee and Expert Panel (Figure 1) came to a consensus regarding the ideal properties of a BPEU (Table 3), which focused predominately on ease of use and understanding in the busy clinical setting. Survey 2 respondents reached a consensus that the single BPEU selected for international harmonization should be consistent with the 2010 position statement of the Royal College of Pathologists of Australia [25,26]. This position statement recommended the routine use of mass units for reporting drug concentrations measured by pathology laboratories in Australia and New Zealand, thereby avoiding the need for conversion of concentration time points from mg/mL to μM [27]. Survey 2 respondents also reached consensus that the BPEU should be easy to understand in relation to the busulfan dose unit (eg, milligrams). On this point, the majority (63%) chose AUC in mg × h/L, whereas a minority (37%) chose AUC in μM × min.

When interpreting busulfan pharmacodynamic data, conversion between doses of busulfan (milligrams) and the various BPEUs is difficult. Variations in dose frequency, with busulfan being given every 6, 12, or 24 hours, and total duration of therapy, often ranging from 2 to 4 days, also add complexity. It follows that converting BPEUs is error-prone, but the incidence of near misses resulting from mathematical conversion errors is unknown. Unfortunately, this is not surprising, given that only a few studies to date have explored chemotherapy safety and chemotherapy errors [28–30].

There have been various harmonization efforts within laboratory medicine, including harmonization of cancer biomarkers by pathologists [31]. The University of California Athena Breast Health Network demonstrated variation between expert observers and concluded that technical and interpretive harmonization between expert observers is possible [32]. Another notable example is clinical sequence variant interpretation from the vast amounts of genome-scale sequencing. Supported by the National Institutes of Health, the Clinical Genome Resource (ClinGen) is forming multidisciplinary expert groups to systematically evaluate variants in clinically relevant genes [33]. These examples have established a precedence for multidisciplinary collaboration with the aim of harmonization to improve biomarker testing, documentation, and minimization of interlaboratory variation. Our BPEU

harmonization project is another such effort; here we seek to standardize documentation and facilitate safer and more accurate interpretation of patient results by improving procedures and processes at the laboratory-clinical interface.

We recognize that global BPEU harmonization will require a carefully planned change management strategy to roll out the relevant changes, educate clinicians, and gain acceptance of these processes by all stakeholders [31]. Therefore, we have developed an implementation strategy, which includes the Steering Committee and multiple Expert Panel members working together to develop a plan for educating clinicians. After the final survey, the optimal next steps were discussed and agreed on by the Steering Committee, the ASTCT Practice Guideline Committee, the BMT CTN Chemotherapy Dosing Committee, the Brazilian Bone Marrow Transplant Society, the EBMT Pharmacy Committee, and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology Oncology Scientific Committee. The timeline for implementing AUC in mg × h/L as the harmonized BPEU was developed after a series of verbal and e-mail communications, and 19 months (i.e, January 1, 2021) from the publication of this consensus statement, only AUC in mg × h/L will be used to express plasma busulfan exposure. To facilitate the transition to the BPEU, an updated Technical Appendix and a Microsoft Excel spreadsheet converting between the most common BPEUs are also available [27]. The technical appendix and Excel spreadsheet were reviewed by the Steering Committee, Expert Panel, and pharmacists with leadership positions in the relevant HCT societies. Select members of the Expert Panel are developing a web-based or smartphone-based busulfan calculator to convert between commonly used busulfan concentration units and exposure units. These various processes were designed to maximize acceptance of the harmonized BPEU.

A strength of our study is the use of Delphi methods to create consensus among international stakeholders. The controlled communication of the Delphi process minimizes direct confrontation and allows individual respondents to express independent thought and enables equitable contribution from all respondents. It has been used successfully in many settings, including solid organ transplantation. Specifically, the Standardized Outcomes in Nephrology-Transplantation initiative developed a core outcome set for trials in kidney transplantation based on the shared priorities of all stakeholders [19]. A further strength of this project is the endorsement of AUC in mg × h/L as the harmonized BPEU by leading international organizations (Table 5) and its adoption by journals in this field. Thus, we believe that the validity of our process and the likelihood of stakeholder acceptance are increased.

In conclusion, with international input, we have identified a single BPEU for harmonization: AUC in mg × h/L. This choice is endorsed by 10 professional societies (Table 5). To promote the safe clinical use of busulfan and to facilitate future multicenter research regarding busulfan plasma exposure and HCT outcomes, we strongly suggest that individual centers convert to the harmonized BPEU and that future publications and that research protocols use it exclusively.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826.
2. D'Souza A., Fretham C. Current uses and outcomes of hematopoietic cell transplantation (HCT): CIBMTR summary slides, 2017. Available at: http://www.cibmtr.org. Accessed July 24, 2018.
3. McCune JS, Gibbs JP, Slattery JT. Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin Pharmacokinet*. 2000;39:155–165.
4. McCune JS, Holmberg LA. Busulfan in hematopoietic stem cell transplant setting. *Expert Opin Drug Metab Toxicol*. 2009;5:957–969.
5. Palmer J, McCune JS, Perales MA, et al. Personalizing busulfan-based conditioning: considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. *Biol Blood Marrow Transplant*. 2016;22:1915–1925.
6. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. *Bone Marrow Transplant*. 1995;16:31–42.
7. Bolinger AM, Zangwill AB, Slattery JT, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. *Bone Marrow Transplant*. 2000;25:925–930.
8. McCune JS, Gooley T, Gibbs JP, et al. Busulfan concentration and graft rejection in pediatric patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2002;30:167–173.
9. Slattery JT, Clift RA, Buckner CD, et al. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation. *Blood*. 1997;89:3055–3060.
10. Grochow LB, Jones RJ, Brundrett RB, et al. Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. *Cancer Chemother Pharmacol*. 1989;25:55–61.
11. Dix SP, Wingard JR, Mullins RE, et al. Association of busulfan area under the curve with veno-occlusive disease following BMT. *Bone Marrow Transplant*. 1996;17:225–230.
12. Veal GJ, Nguyen L, Paci A, et al. Busulfan pharmacokinetics following intravenous and oral dosing regimens in children receiving high-dose myeloablative chemotherapy for high-risk neuroblastoma as part of the HR-NBL-1/SIOPEN trial. *Eur J Cancer*. 2012;48:3063–3072.

13. Geddes M, Kangarloo SB, Naveed F, et al. High busulfan exposure is associated with worse outcomes in a daily i.v. busulfan and fludarabine allogeneic transplant regimen. *Biol Blood Marrow Transplant*. 2008;14:220–228.
14. Perkins JB, Kim J, Anasetti C, et al. Maximally tolerated busulfan systemic exposure in combination with fludarabine as conditioning before allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:1099–1107.
15. Bolinger AM, Zangwill AB, Slattery JT, et al. Target dose adjustment of busulfan in pediatric patients undergoing bone marrow transplantation. *Bone Marrow Transplant*. 2001;28:1013–1018.
16. Radich JP, Gooley T, Bensinger W, et al. HLA-matched related hematopoietic cell transplantation for chronic-phase CML using a targeted busulfan and cyclophosphamide preparative regimen. *Blood*. 2003;102:31–35.
17. Deeg HJ, Storer B, Slattery JT, et al. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. *Blood*. 2002;100:1201–1207.
18. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess*. 1998;2:i–iv. 1-88.
19. Tong A, Budde K, Gill J, et al. Standardized outcomes in nephrology-transplantation: a global initiative to develop a core outcome set for trials in kidney transplantation. *Transplant Direct*. 2016;2:e79.
20. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. *Med Teach*. 2005;27:639–643.
21. Goodman CM. The Delphi technique: a critique. *J Adv Nurs*. 1987;12:729–734.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
23. Akins RB, Tolson H, Cole BR. Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. *BMC Med Res Methodol*. 2005;5:37.
24. Inamoto Y, Jagasia M, Wood WA, et al. Investigator feedback about the 2005 NIH diagnostic and scoring criteria for chronic GVHD. *Bone Marrow Transplant*. 2014;49:532–538.
25. Jones GRD, Bryant S, Fullinfaw R, et al. Mass or molar? Recommendations for reporting concentrations of therapeutic drugs. *Med J Aust*. 2013;198:368–369.
26. Position statement. Approval November 2010. Available at http://docplayer.net/38459307-This-document-is-the-result-of-a-recommendation-from-the-aacb-ascept-rcpa-racp-common-units-for-reporting-drug-concentrations-working-party.html. Accessed February 5, 2019.
27. Busulfan pharmacokinetics. Available at https://github.com/busulfanpk/. Accessed April 26, 2019.
28. Goldspiel BR, DeChristoforo R, Daniels CE. A continuous-improvement approach for reducing the number of chemotherapy-related medication errors. *Am J Health Syst Pharm*. 2000;57(suppl 4):S4–S9.
29. Fischer DS, Alfano S, Knobf MT, Donovan C, Beaulieu N. Improving the cancer chemotherapy use process. *J Clin Oncol*. 1996;14:3148–3155.
30. Ranchon F, Salles G, Späth HM, et al. Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs. *BMC Cancer*. 2011;11:478.
31. Tate JR, Johnson R, Barth JH, Panteghini M. Harmonization of laboratory testing: a global activity. *Clin Chim Acta*. 2014;432:1–3.
32. Engelberg JA, Retallack H, Balassanian R, et al. "Score the Core" Web-based pathologist training tool improves the accuracy of breast cancer IHC4 scoring. *Hum Pathol*. 2015;46:1694–1704.
33. Rivera-Muñoz EA, Milko LV, Harrison SM, et al. ClinGen Variant Curation Expert Panel experiences and standardized processes for disease- and gene-level specification of the ACMG/AMP guidelines for sequence variant interpretation. *Hum Mutat*. 2018;39:1614–1622.