GVHDの有無が治療関連死亡に与える影響の解析 stcrreg vs. stcox

```
stcrreg agvhd24_split2 cgvhd_split2 if rfs_day>100,
compete(event_relapse==1)
```

(Std Err adjusted for 649 clusters in id)

_t	SHR	Robust Std Err	z	P>|z|	[95% Conf	Interval]
agvhd24_split2	1.369613	.2544199	1.69	0.090	.9516523	1.97114
cgvhd_split2	1.243599	.2326844	1.17	0.244	.8618185	1.794506

```
stcox agvhd24_split2 cgvhd_split2 if rfs_day>100
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
agvhd24_split2	1.438011	.2696513	1.94	0.053	.9957434	2.076714
cgvhd_split2	1.12158	.2144507	0.60	0.548	.7710405	1.631487

いずれの方法を用いても、大きくは結果は変わらなかった。

GVHDとGVL effect

そもそもこの解析でGVHDの発症とGVLとの関連が証明できるのだろうか。

再発リスクが高い症例に対しては、免疫抑制剤の早期減量→GVHDの発症→やはり再発、というシナリオも考えられる。

しかし複数の方法を用いて、GVHDの発症と再発リスクの低下が証明できた場合は、比較的強固な相関関係と言えるのかもしれない。

解析目的にあわせて統計手法を選択する必要がある

まとめ

時間とともに変化する因子（GVHDなど）を解析する場合は、ランドマーク解析あるいは時間依存性変数を用いる。

図示の方法は、ランドマーク法、セミランドマーク法、あるいは時間依存性変数を用いた方法がある

GVHDの各グレードが予後に与える影響を解析する場合は、可能であれば、各グレードの発症日を用いて時間依存性変数を作るべきであるが、今のデータでは難しい。

GVHDが再発やTRMに与える影響を解析する場合、どのpopulationを選択べきかは十分に検討すべきである。

急性GVHD、慢性GVHDをそれぞれ時間依存性変数として用いることは可能であるが、交互作用含め十分に検討する必要がある。
また競合因子を考慮した解析も可能であるが、その妥当性は十分検討されるべきである。

いずれにしても複数の方法で検討してそのrobustnessを確認すべきであろう。
また研究目的をしっかり考えて、統計手法を選択すべきである。

◆TRUMP統計セミナー出席者リスト

基礎編		応用編	
名前	ご所属（施設名）	名前	ご所属（施設名）
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◆Stata購入者リスト

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（免疫アレルギー疾患等実用化研究事業　移植医療技術開発研究分野））
委託業務成果報告（業務）

移植後長期生存者のQOLに関する研究

担当責任者　山下 卓也　国立がん研究センター中央病院／造血幹細胞移植科 医長
担当責任者　熱田 由子　日本造血細胞移植データセンター　センター長

研究要旨

本研究は、わが国における造血幹細胞移植後長期生存成人及び小児患者の quality of life（QOL）に関する横断的調査を実施し、移植後 QOL に関連する要因を明らかにすることを目的とする。

2013 年 1 月より、横断的観察研究「本邦の同種造血幹細胞移植後長期生存成人患者における Quality of Life に関する調査研究」及び「本邦の自家及び同種造血幹細胞移植後長期生存小児患者における Quality of Life に関する調査研究」を実施した。両研究ともに、予定を上回る症例数を集積し、登録を終了した。

本研究は、造血幹細胞移植後長期生存患者を対象とした QOL に関するわが国最大の観察研究である。今後、本研究は、この貴重なデータベースを用いた解析を進め、わが国の造血幹細胞移植後患者の QOL の向上に資する研究成果を発信していく。

A．研究目的

わが国における造血幹細胞移植は1970年代に開始され、血液悪性疾患を中心とした各種疾患に対する根治的治療法として確立されてきた。現在では、年間約4,500件（血縁者間移植約1,000件，非血縁者間移植約1,000件，臍帯血移植約1,000件，自家移植約1,500件）の造血幹細胞移植が実施されている。 近年、造血幹細胞移植の治療成績は向上し、移植後2年以上生存する長期生存者を約50-60%と概算すると、毎年約2,500名の移植後長期生存者が増加していることになる。こうした長期生存者の増加により、造血幹細胞移植後患者のquality of life（QOL)やQOLに影響を与える晩期合併症の重要性が認識されている。

欧米からの報告では、移植後患者のQOLは健康対照群に比べて低く、移植片対宿主病（GVHD）の出現や、移植前処置に可憐する晩期合併症の存在に影響されるとされている。しかし、わが国における造血幹細胞移植後患者のQOLに関する報告は少ない。

本研究は、わが国で同種造血幹細胞移植を受けた移植後長期生存成人患者、及び自家または同種造血幹細胞移植を受けた移植後長期生存小児患者のQOLに関する横断的調査を実施し、移植後QOLに関連する要因を明らかにすることを目的とする。特に、移植幹細胞源、ドナー、移植前処置、移植後年数、移植後合併症が移植後長期生存者のQOLに与える影響を明らかにする。また、移植後患者の社会復帰状況とQOLの関係についても検討する。移植後QOLに影響を与える要因を明らかにすることは、今後のわが国の移植後患者のQOLの向上に大いに資するものと考えられる。

B．研究方法

横断的観察研究「本邦の同種造血幹細胞移植後長期生存成人患者における Quality of Life に関する調査研究」（以下「成人研究」）及び「本邦の自家及び同種造血幹細胞移植後長期生存小児患者における Quality of Life に関する調査研究」（以下「小児研究」）（研究代表者：谷口修一，副研究代表者：熱田由子）は，2011 年度からプロトコールを作成し、2012 年度に日本造血細胞移植学会及び主たる研究実施施設での倫理審査を経て、日本造血細胞移植学会主導研究として、2013 年 1 月に研究を開始した。登録予定症例数は、成人研究が 300 例、小児研究が 400 例とした。

対象症例に対して、患者用調査票（小児研究の一部症例においては保護者用調査票）と医師用調査票を用いた調査を並行して実施した。患者用調査票においては、QOL の調査と生活状況についての質問を実施した。医師用調査票においては、対象症例の全身状態や慢性 GVHD の重症度の評価等に関する調査を実施した。

（倫理面への配慮）

これらの観察研究は、ヘルシンキ宣言、疫学研究に関する倫理指針、臨床研究に関する倫理指針等各指針に従って実施した。対象となる患者の人権に十分配慮するとともに、個人情報の厳格な管理を行った。

C．研究結果

成人研究は、48施設において倫理審査の承認を得て2014年4月まで症例登録を実施した。小児研究は、31施設において倫理審査の承認を得て、2014年8月まで症例登録を実施した。

2015年1月31日現在、成人研究においては患者用調査票1,155症例分、医師用調査票1,224症例分、小児研究においては患者用調査票465症例分、医師用調査票549症例分を受領している。

現在、成人研究においては、回収された調査票によって集積したデータを概観して確認する作業を通じて、今後の解析のためのデータ固定を実施している。小児研究においては、引き続き調査票回収作業を継続するとともに、集積したデータの概観及び確認作業の準備を行っている。

D．考察

本研究は、造血幹細胞移植後長期生存患者を対象としたQOLに関するわが国最大の観察研究である。本研究によって集積された情報は、わが国の移植後患者のQOLに関する貴重なデータベースである。このデータベースを用いて、わが国の移植後患者のQOLの実態や、QOLに関連する要因を明らかにすることは、今後のわが国の移植後患者のQOLの向上に大いに資するものと期待される。

成人研究においては、

(1) 移植後長期生存患者におけるQOLの解析
(2) 移植後長期生存患者における社会復帰，収入，婚姻状況の解析
(3) 移植後長期生存患者における慢性GVHDとQOL及び社会復帰との関連に関する解析

の3つの主要テーマの解析を予定している．更に、わが国の造血幹細胞移植に関わる多数の研究者が、本研究のデータベースを有効に活用し、移植後患者のQOLの向上に資する研究成果を発信できるような体制の構築を目指している。

小児研究においては、今後、解析に必要なデータ確認及び固定作業を実施する予定である。

E．結論

本研究は、造血幹細胞移植後長期生存患者を対象としたQOLに関するわが国最大の観察研究である。本研究が予定を大きく上回る症例数の登録を得たことは、造血幹細胞移植に関わる医療者，及び造血幹細胞移植後生存患者や家族にとって、移植後QOLが重要な問題であることを反映した結果であると考えられる。

今後、本研究は、今回集積された情報に基づいて構築された貴重なデータベースを用いた解析を進め、移植後患者のQOLに関する研究を推進する。本研究の成果は、わが国の造血幹細胞移植後患者のQOLの向上に大いに資することが期待される。

F．健康危機情報

該当事項なし

G．研究発表

1. 論文発表

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H．知的財産権の出願・登録状況

該当事項なし

厚生労働科学研究委託費（難治性疾患等実用化研究事業
（免疫アレルギー疾患等実用化研究事業　移植医療技術開発研究分野））
委託業務成果報告（業務）

海外登録機関との連携に関する研究

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担当責任者　鍬塚八千代　名古屋大学医学部附属病院　病院助教

研究要旨
北米の登録機関である Center for International Blood and Marrow Transplant Research (CIBMTR)との国際共同研究（3研究）が実施され、1研究の論文公表、2研究は学会発表までが終了した。複数の造血細胞移植登録データをもつ研究組織間での共同研究を実施する際のガイドラインを策定することを目的として活動したが、ガイドライン案が完成し、国際組織である Worldwide Network of Blood and Marrow Transplantation（WBMT）理事会に提案された。

A．研究目的
2013度までに開始に至った北米の登録機関であるCenter for International Blood and Marrow Transplant Research (CIBMTR)との国際共同研究（3研究）の実施と公表行うこと、複数の造血細胞移植登録データをもつ研究組織間での共同研究を実施する際のガイドラインを策定することを本研究の目的とした。

B．研究方法
CIBMTR の Health Services and International Studies Working Committee (HSIS WC)との共同研究を3研究実施した。日本側のprimary investigatorとしては、担当責任者鍬塚八千代、研究協力者諫田淳也、研究協力者木村文彦が担当した。Worldwide Network of Blood and Marrow Transplantation（WBMT）内に複数の造血細胞移植登録データをもつ研究組織間での共同研究を実施する際のガイドラインを策定することを目的としたTask Forceが設置され、担当責任者熱田由子が CIBMTR の Dr. Marcelo Pasquiniとともにco-chairを担当し、ガイドライン策定を進めた。

（倫理面への配慮）
ガイドライン策定においては、ヘルシンキ宣言に準拠した。

C．研究結果
担当責任者鍬塚八千代が実施した日米の小児・若年成人患者における非血縁者間臍帯血移植は、2014年に論文公表された(Kuwatsuka Y et al. BBMT 2014)。研究協力者諫田淳也が実施した日米の成人 HLA 一致同胞間の骨髄・末梢血幹細胞移植の比較研究は、2015 年 2 月に行われた BMT Tandem Meetings 2015 で口演発表された。研究協力者木村文彦が CIBMTR の Dr. Kumar と実施した再生不良性貧血に対する HLA 一致同胞間の骨髄・末梢血の国際比較研究は、2015 年 2 月に行われた BMT Tandem Meetings 2015 中に実施された HSIS WC 会議において、その進捗状況が報告された。
同 BMT Tandem Meetings 2015 中には WBMT Board Meeting が行われ、担当責任者熱田由子が Dr. Marcel Pasquini と共にガイドライン案（別添資料 x）を提案した。

D．考察
国際共同研究を実施するにおいては、直接会ってのコミュニケーション、時差を超えての電話会議などの積み重ねが極めて重要である。ガイドラインは次年度にリリースされる予定であるが、リリース後、国際共同研究がより活性化されるためには、さらなる活動が必要となると考えられる。

E．結論
北米登録機関CIBMTRと実施した3研究は順調に進んでいる。複数の造血細胞移植登録データをもつ研究組織間での共同研究を実施する際のガイドラインも案の組織内提示にまで至った。

F．健康危険情報
該当なし

G．研究発表
2.　学会発表
1. Junya Kanda, Yachiyo Kuwatsuka, Ruta Brazauskas, Zhen-Huan Hu, Koji Nagafuji, Takahiro Fukuda, Hisashi Sakamaki, Carmen Sales-Bonfim, Jignesh Dalal, Theresa Hahn, Marcelo Pasquini, Yoshiko

Atsuta, Wael Saber, on behalf of the CIBMTR International Studies Working Committee and the JSHCT Source and GVHD working group.Impact of Race on Graft-Versus-Host Disease Rates after HLA-Matched Sibling Bone Marrow or Preipheral Blood Hematopoietic Cell Transplantion:Comparison of North American Caucasian Versus Japanese Populations.BMT Tandem Meeting. Oral Abstracts-Session A. Feb. 2015

H．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

（資料 5） WBMT RESEARCH GUIDELINES

WBMT RESEARCH GUIDELINES
(Proposal for submission to WBMT Board – November 2014)

This document* is developed by the Worldwide Network for Blood and Marrow Transplantation (WBMT) and outlines the guiding principles of research performed directly by this entity through the global survey data or indirectly by fostering collaboration among member societies with the intent of dissemination of information for advancement of the hematopoietic cell transplantation field.

BACKGROUND:

The idea of creating guidelines for research endeavors generated by WBMT Member Societies laterally, or on behalf of the parent organization (WBMT), was first presented during the 2013 annual, in-person Board meeting in Salt Lake City, USA. The Board agreed that guiding principles for the conduct of research by or within the WBMT was an important topic to be explored and formed a Research Activity Task Force to 1) develop a guidelines document on developing, conducting and disseminating results of studies involving data and/or investigators from multiple Member Societies and, 2) to promote collaboration among the WBMT Member Societies/registries through the establishment of a framework for the conduct of research.

During the deliberations of the Research Activity Task Force it was decided to cover this topic of research in two different fronts, first to develop the guiding principles of collection, presentation, dissemination and sharing of the Global Activity Survey data, herein defined as Global Transplant Activity data. Second, the Research Activity Task force would develop guiding principles to provide general guidelines for the conduct of international collaborative research (Appendix D), with the intent to serve as reference for research procedures and for fostering collaboration among member societies.

OVERARCHING WBMT GUIDING PRINCIPLES OF RESEARCH

Overarching Guiding Principle #1

The Worldwide Network for Blood and Marrow Transplantation (WBMT) has the responsibility to collect, store, disseminate information related to global hematopoietic cell transplantation activity. This is done through the annual global activity survey. WBMT will be responsible for safe keeping of this data and oversight of its utilization.

Overarching Guiding Principle #2

The WBMT shall not duplicate or compete with research actively being conducted by its Member Societies and/or registries. Each WBMT Member Society conducts research in its unique manner, independent from the WBMT.

Overarching Guiding Principle #3

The WBMT will foster collaboration through its member societies for the development of collaborative research to address global questions in transplantation, encourage the analysis of regional differences and offer a global perspective on transplantation. Furthermore, this collaborative research shall fulfill the WBMT mission including increase global awareness of the importance of transplantation, improve access to transplant, optimize safety for patients and donors, and improve the quality of all activities associated with hematopoietic cell transplantation

GLOBAL TRANSPLANT ACTIVITY (GTA)

Global Transplant Activity Guiding Principle #1

The WBMT is required to survey transplant activity globally in an annual basis to maintain its Non-Government Organization (NGO) status with the World Health Organization (WHO).

Commentary on GTA Guiding Principle #1

Since the January 2013 award of NGO status by the WHO, there are important and continuing obligations for the WBMT. One such criterion is referred to as "*Global Database on Donation and Transplantation*". WHO, along with the Spanish National Transplant Organization established the Global Observatory on Donation and Transplantation and one of several goals is the development of a global database on donation and transplantation. WBMT has facilitated access to its global survey data for input into this Observatory database since 2006 and remains an ongoing project.

The current process for collecting these Global Activity data is performed by a WBMT paid consultant. All GTA related communication (e.g., requests to centers and registries) is managed by this individual. The data is collected through a survey and represents the number of first transplants performed by a center during a calendar year. Data for a particular year activity is collected from November of the subsequent year through February. For example, submission related to the activity for 2013 will be due starting November 2014 through February 2015. This data will be compiled and released to the WHO and to the public by fall of 2015.

Any transplant center is eligible to provide data to the WBMT through its member society. The only requirement for participation is that each member society has a standing agreement with the WBMT to share transplant activity data. (Appendix A) WBMT will have the autonomy in using this data according to its mission and share with third parties for specific projects (Guiding Principles #2 and #3).

One important exception in the relationship between the WBMT and a member society involves transplant activity data from regions were the regional member society is still in development. In these instances, direct communication from a transplant center and the WBMT is allowed, condition upon having a standing agreement in place. The transplant center is required to include in the survey whether it has an active affiliation (i.e. data reporting) with an outcomes registry (APBMT, CIBMTR or EBMT) or not. Additionally, the regional member society in question needs to be aware of this direct relationship between its transplant center and the WBMT. In case of data being shared from a transplant center directly with the WBMT, the WBMT will share this activity information with the regional member society.

WBMT Global Transplant Activity data reports (Appendix B) capture disease indications (malignant and non-malignant) for allogeneic (related and unrelated) and autologous stem cell transplantation, donor type and stem cell sources. They do not include outcome data. Data are provided to the WBMT by transplant program sites, national societies and/or outcome registries.

The data from an outcomes registry member society (APBMT, CIBMTR and EBMT) that is shared with the WBMT can be utilized by the same member society for other uses without restrictions.

Collection forms are available on the www.wbmt.org website and may be submitted in paper format or electronic mail.

Global Transplant Activity Guiding Principle #2

The WBMT will be responsible for the dissemination of the Global Transplant Activity report .

Commentary on GTA Guiding Principle #2

The responsibilities with the GTA include report annually to the WHO and share the activity with member societies. A summary slide set, updated annually outlying annual and cumulative activity will be uploaded in the WBMT website for public use. Activity reports in form of manuscript for publication are included among the dissemination of global transplant activity and will be done in a minimum schedule of one every other year.

Global Activity Survey Guiding Principle #3

The WBMT has ownership of the GTA data and any use needs to be approved by the WBMT. This includes data requests and proposal for scientific studies that seek to utilize this data for analysis.

Commentary on GTA Guiding Principle #3

The GTA comprises of transplant center level data on volume of transplant activity indications, donor and stem cell sources. These data, in aggregate, demonstrate important information of trends in activities and practices globally. Additional uses of this data are possible by any WBMT member societies. In addition to annual reports of global activities, any individual on behalf of the member societies can request specific information by contacting the WBMT data consultant. If the use is for research purposes, the proponent is required to fill a proposal form (Appendix C) which needs to be approved by his or her Member Society Representative before it can be submitted to the WBMT. This proposal will then be reviewed by the Transplant Center and Recipient Standing Committee before it can be released. For data requests outside the member societies, GTA data can only be released with approval from the WBMT board. In these situations charges may apply.
The data from a member society that is shared with the WBMT can be utilized by the same member society (which also has ownership to its data) without restrictions.

Appendix A
GTA Data Transmission Agreement (DTA)

DATA TRANSMISSION AGREEMENT

This Data Transmission Agreement ("**Agreement**"), effective[*Date*], is entered into by and between the Worldwide Blood and Marrow Transplant Network ("**WBMT**"), a Non-Governmental Organization with the World Health Organization and _____ ("**WBMT Member Society**"), each a "**Party**" and collectively, the "**Parties**".

The purpose of this Agreement is to set forth terms by which the WBMT will facilitate its member societies in data submission related to the Global Transplant Activity ("**GTA**") for public dissemination and research purposes.

Section 1. Data Collection and Records

(a) Type of Data.

i. Global Transplant Activity. The WBMT member society shall submit information related to transplant activity from the transplant centers that are within the region of the member society or has an established relationship with the member society to provide this data. Transplant activity data collected in the Global Activity Survey Form ("**GAS**") includes the volume of first transplants per patients performed at a transplant center in one year with accompanied information related to the indication, graft source and donor type.

(b) Data Collection. The WBMT Member Society shall compile all annual transplant activity data from their participating transplant centers and provide to WBMT with GAS compiled for the specific region as requested by the WBMT within the time frames and in the manner specified by the WBMT. The timeline for submission of the compiled regional GAS is from November to February in reference to the activity of the prior year. The GAS should be submitted directly to the WBMT offices during this specified period.

Section 2. Informed Consent

(a) The GAS does not include any patient specific identifiers. It represent the number of transplant performed at a given transplant centers. The volume per center is not provided to the WBMT, the GAT includes the number of active centers in a particular region and the number of transplants performed annually. Informed consent is not required for collection or submission to WBMT.

Section 3. Term

(a) This Agreement shall commence on its effective date referenced in the first paragraph above and shall continue in force until terminated by either Party at any time, with or without cause, upon thirty (30) days written notice to the other Party. During the thirty (30) day period after such notice is sent, the Parties shall continue to act toward each other in good faith.

Section 5. Miscellaneous

(a) Compliance with Laws and Regulations. The WBMT Member Society shall comply with all applicable statutes and regulations specific to that country, including, but not limited to, those regarding the safeguarding of donor and patient records, privacy regulations and human subjects protection.

(b) Assignment and Subcontracting. The WBMT Member Society may not assign this Agreement or any of their respective rights and responsibilities under this Agreement, without the WBMT's

prior written consent. No responsibilities under this Agreement may be subcontracted without the prior written approval of the Parties.

(c) Amendment. Except as otherwise provided for in this Agreement, this Agreement may not be amended except by written instrument duly signed and delivered by the WBMT and the WBMT Member Society.

(d) Non-Assumption of Liabilities. Neither the WBMT nor the WBMT Member Society shall be liable for any of the prior existing or future obligations, liabilities or debts of the other Party.

(e) Governing Law. This Agreement and all transactions contemplated by this Agreement shall be governed, construed and enforced in accordance with the laws of Switzerland.

(f) Independent Contractors. Nothing in this Agreement is intended to create an employment or agency relationship between the Parties. Neither Party shall be deemed or construed to be an employee or agent of the other.

(g) Notice. Any notice required to be given by this Agreement shall be in writing and sent by: 1) mail, registered or certified, as evidenced by a delivery receipt; 2) with a private delivery service as evidenced by a shipping receipt; or 3) by electronic mail return receipt requested.

(h) Prior Agreement. This Agreement constitutes and contains the entire Agreement between the Parties with respect to the subject matter hereof, including but not limited to the terms and conditions relating to the maintenance and transmission of data, and supersedes any prior oral or written agreements.

(i) Force Majeure. Neither Party shall be considered to have failed in the performance of this Agreement if such failure arises out of causes beyond the control and without the fault or negligence of the Party failing to perform, except that the WBMT Member Society shall not be excused from strict compliance with this Agreement under this clause due to errors, omissions or failures by its independent contractors or lower tier subcontractors.

(j) Successors. This Agreement shall be binding on and will inure to the benefit of the Parties and their respective successors and assigns.

This Agreement is executed by individuals who are duly authorized to enter into the Agreement and legally bind their respective parties to be effective on the date stated in the first paragraph above.

By: WBMT	By: [*WBMT Member Society*]
By: _____	By: _____ Authorized Signature
	_____ (Typed/Printed Name)
Title: Current WBMT President	Title: _____
Date: _____	Date: _____

Appendix B: Sample from the Transplant Activity Survey document (www.wbmt.org)

Country/Hospital:

Contact E mail:
No. Teams reporting:
No. Teams known to transplant but do not report:

WBMT SURVEY ON TRANSPLANT ACTIVITY 20.....

PLEASE REPORT THE NUMBER OF PATIENTS RECEIVING THEIR FIRST TRANSPLANT ONLY FOR THE YEAR 2009/2010/2011/2012
SEPARATELY ON EACH SURVEY SHEET

NUMBER OF PATIENTS RECEIVING FIRST TRANSPLANTS ONLY

	Indication	Allogeneic: Family: HLA - id sibling BM	HLA - id sibling PBSC	HLA - id sibling Cord	non - id* BM	non - id* PBSC	non - id* Cord	twin BM	twin PBSC	Family total	Unrelated BM	Unrelated PBSC	Unrelated Cord	Unrelated total	Autologous BM	Autologous PBSC	Autologous Cord	Total Allo	Total auto	Total Total
Leukemias	**Total Leukemia**																			
	Total AML																			
	AML 1st CR																			
	non 1st CR																			
	Total ALL																			
	ALL 1st CR																			
	non 1st CR																			
	Total CML																			
	CML 1st cP																			
	not 1st cP																			
	Other Leukemia																			
	Total MDS/MPS (incl. combined MDS/MPS)																			
	MDS incl. Sec AL																			
	MPS																			
	CLL incl. PLL																			
LPD	**Total LPD**																			
	Total Plasma Cell Disorder																			
	PCD - Myeloma																			
	PCD - other																			
	Total Lymphoma																			
	HD																			
	NHL																			
	Other LPD																			
Solid tumors	**Total Solid tumors**																			
	Neuroblastoma																			
	Germ cell tumor																			
	Breast Cancer																			
	Ewing																			
	Other solid tumor																			
Non - Malignant disorders	**Total Non-malignant dis.**																			
	Total Bone Marrow Failure																			
	BMF - SAA																			
	BMF - other																			
	Hemoglobinopathy																			
	Primary Immune Deficiency																			
	Inherited Dis of Metabolism																			
	Auto Immune Disease																			
	Other Non Malignant Disease																			
	Other																			
	TOTAL PATIENTS (1st. HSCT)																			

TOTAL NUMBER OF TRANSPLANTS PERFORMED THIS YEAR: includes 1st, 2nd, 3rd. etc.	ALLO:	AUTO:	TOTAL:

EBMT CIC No. / CIBMTR Code / APBMT (if member):.....

Appendix C

GTA Study Form

Global Transplant Activity (GTA) Study Proposal Form

Prepare a brief description of the proposed study as you envision it. This should be no more than three pages, using standard 8½" X 11" paper with 1" margins. Use the outline below and send your description to (H. Baldomero or WBMT site)

I. Study Title

Include the name(s) and institution(s) and WBMT Member Society of the individual(s) proposing the study.

II. Specific Aims

State the primary purpose(s) of the study as concisely and clearly as possible. A reader should have a clear idea of the purpose for which the data will be analyzed.

III. Scientific Justification

Summarize the rationale of the study, citing relevant previous work. This should convey the importance of the intended study.

IV. Study Design (Scientific Plan)

Describe how the specific aims would be addressed using information from the WBMT. It should include the specific statistical methodology planned, with discussion of limitations, if relevant.

Appendix D

COLLABORATIVE INTERNATIONAL RESEARCH IN HEMATOPOIETIC CELL TRANSPLANTATION

- WBMT Reference Document -

General Research Guiding Principle #1

Any collaborative research is required to follow all basic principles for ethical conduct of research in addition of being inclusive to all participating parties, being fair, minimize bias, avoid conflicts of interest and strictly adheres to the WHO guiding principles on cell, tissue and organ transplantation.

Commentary on General Research Guiding Principle #1

International collaborative research is herein defined as biomedical research that includes sharing of data or biologic specimens ("biospecimens") among different organizations or groups that are located in separate countries.
The rules and guiding principles for collaborative research are no different from any biomedical research, as the majority of biomedical research requires some level of collaboration. This guiding principle mostly apply to complex collaborative, involving different organizations situated in different countries that abide to similar but not equal rules and regulations towards the practice of research. This first guiding principle is broad and applies to biomedical research involving human subjects. The ethical principles of conduct of research are derived from the Belmont Report (http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html) and include respect for persons, beneficence and justice. The inclusiveness to all participating parties is an essential component for the conduct of international collaborative research in order to acknowledge all who are involved. This statement would apply when the collaborative parties are large complex organizations or when the number of collaborative parties is large. Fairness applies to all levels of research, development, conduct, interpretation and dissemination. Additionally, this guiding principle is referring to fairness among the collaborative parties. Bias is inherent in research, and minimize bias strengthens research. Finally, conflict of interest at any level, from commercial to self-promotion is deleterious for research as it clouds the conduct and manipulates the message or conclusion of a project.
International collaborative research in hematopoietic cell transplantation is the main responsible for the success of this field. The guiding principles are meant to be a general reference document for the conduct of research and assist investigators to promote the betterment of the practice of transplantation, advance the field by improving access and outcomes of patients and safeguard the health of volunteer donors.

General Research Guiding Principle #2

The process of international collaborative biomedical research requires several steps to ensure its efficiency and fairness at the same time safeguarding the patients' data.

Commentary on General Research Guiding Principle #2

Biomedical research process applied to specific collaborative projects can be stratified into several phases: concept development, project development, data sharing, analysis, results interpretation, dissemination and conclusion. In general these phases can be distinct or combined depending on the project, however consideration of each of these steps are relevant in order to organize the procedures and requirements.
This guiding principle proposes general procedure in each phase of a collaborative project that could be considered.

Concept Development

The inception of a project starts with the concept or idea. The concept often focuses on the hypotheses of interest to be tested in the project. This step can be part of the project development. However, often in the collaborative international research, the concept or proposal is often a necessary step for recruiting collaborators, obtain approval or to better describe a project that is intended. Understanding the availability of data already in existence or procurement of such data can also be considered in the step of the research process.

Project Development

The development of the project requires detail information on the objectives, background, population and requirement of informed consent, data sources and analyses being done. This *a priori* exercise sediment the proposed activities and anticipates all potential pitfalls. The most common procedure in this phase is the development of a protocol that includes all the components of the project. The development of the protocol should be a collaborative effort that ensures that all participating parties are aware of the project details.
Additionally, this phase of the project development needs to address the safeguard of the data, the protection human subjects, funding information, shared responsibilities plan and authorship guidelines, results review process and dissemination plan. Each of these components might not apply to all projects, but if presented upfront might help avoid delays during the life cycle of the project.
The section below outlines each component with proposed format and content.

1. Protocol Document: Describes in detail all the proposed scientific activities to be done with in the project. The protocol document should include the objectives of the project in a succinct and direct language; background that justifies the study and or hypotheses; description of the population of interest and the sources of data; description of the outcomes being tested; detailed of the proposed statistical analysis; relevant references and any additional information that is relevant for the understanding of the project (i.e. demographic table, surveys, etc). If the study involves additional informed consent of recipients, this document would be to be referenced or added to the protocol document.
2. Safeguard of the data: This description could be incorporated in the protocol or in a separate document. However a safeguard plan would requirement agreements between parties if data are being exchanged. The important components for the safeguard plan include description of the data needed in the study, the expected transferring plan, who will be the responsible parties to oversee this exchange or transfer and how the transferred data will be stored, including security details, for how long and the procedures that will take place once the project is completed. In case of data, a description on whether personal health information (PHI, i.e. date of birth, gender, social security or other unique identification number among others) is required for the study and the type of PHI needs to be included. Also, if the project requires data from different databases to be merged, a description of this data merger should include the variables used for the merger, identification of an honest broker in case of datasets with PHI, storage or plans for data destruction once the project is completed.
3. Protection of Human Subjects: any biomedical research that utilizes data requires appropriate informed consent, which authorizes the utilization of data for a particular use or research in general. Ethical committee oversight is a vital component of biomedical research to assure that human subjects are not being harmed. The rules of ethical committee engagement vary in different countries which makes a protection of human subjects document important in collaboration international research. The components of this document should include, the type of data being utilized in the project, whether the patients or individuals who consented for the specific project in question. In case of sharing dataset that include PHI, additional oversight might be required to overview that the process is appropriately set to avoid data breeches or losses. For studies that required additional informed consent, the document should include how the consent procedure will take place.
4. Funding Sources: studies that are done as parted of funded projects may require a document that outlines any restriction that the funding agent might impose on the project. Additionally, the funding plan might require multiple sources which should be outlined accordingly.

5. Shared Responsibilities: It is important to develop a leadership plan that outlines the responsibility of each member of the project and that all members are in agreement with this plan. This document should also include authorship guidelines for any publication that results from this project. The authorship guidelines might be a detailed list of each member of the project and their position in a manuscript or general rules that will be considered to choose authors and their respective position on any manuscript from this project.
6. Results review and Dissemination Plan: some of the components of this section can be included in the protocol document. A detailed plan for how the results will be reviewed and disseminated might be necessary in studies that involve different outcomes databases or research groups. This includes timeline for completion of the analysis, presentation in conferences or meetings and other public dissemination.

Project Analysis

Once the project is developed with documentation and agreements approved, data can be transferred. If the project requires separate informed consent, enrollment of participants may be initiated.

Prior to analyses, verification of the data for errors, outliers and follow up is important to avoid misinterpretation of results. Analyses results when completed should follow the results review and dissemination plan outline above.

Completion of the Project

Once the study is completed, which in some instances might be upon the publication of results or otherwise determined procedures for returning, destroying shared data or left over samples, or indefinitely storage should take place. Additional studies that include any data used in the original project need to be discussed among the original owners of the data before proceeding. This will initiate another project cycle and some of the steps described above may apply.

*This document, once approved by the WBMT Board, will be prominently posted at www.wbmt.org.