DOI: 10.46765/2675-374X.2021v2n2p100

ESTABLISHMENT OF THE BRAZILIAN REGISTRY OF HEMATOPOIETIC STEM CELL TRANSPLANTATION, USING THE DATABASE THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH

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Running title: BRAZILIAN REGISTRY OF HSCT

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ABSTRACT

The number of hematopoietic stem cell transplantation (HSCT) in Brazil is growing rapidly. To better understand the outcomes of HSCT in Brazil, strategies have been developed with the Center for International Blood and Marrow Transplant Research (CIBMTR), using its standardized registry structure and data sharing application. The methods adopted to establish the registry were through efforts to increase the Brazilian centers that report to CIBMTR included training courses for HSCT data managers, the officialization of a multicenter HSCT study using the CIBMTR structure and the partnership between Brazilian Society of Bone Marrow Transplantation (SBTMO) and the CIBMTR. Here we describe the history for establishing the HSCT Brazilian database using the CIBMTR back to center data and present the aggregated results since 2016. We found a significant increase in the numbers of active centers reporting to CIBMTR from 11 in 2016 to 21 in 2020 corresponding to higher numbers of transplants reported to the CIBMTR from 574 to 921 in that period. The model used to generate this national database was effective as it leverages existing infrastructure to assess the activity and outcomes of HSCT in Brazil.

Keywords: Hematopoietic Stem Cell Transplantation, CIBMTR, Data manager, Database, Outcomes, Information system and Brazil.

Hematopoietic stem cell transplantation (HSCT) is a treatment that can cure or improve the quality of life of patients with malignant and non-malignant hematologic diseases[1]. HSCT began in Brazil in 1979 with the physicians Ricardo Pasquini and Eurípides Ferreira at the Federal University of Paraná (Universidade Federal do Paraná, UFPR)[2]. Since then, there has been a geometric growth in the number of transplant centers. In addition, the Brazilian volunteer unrelated blood and marrow donor registry (REDOME) has increased substantially, currently being the third largest donor registry, and with the increased popularity of haploidentical HSCT with post-transplant cyclophosphamide (PTCy) strategy, has greatly expanded the donor pool for Brazilian population. In 2010, 1,581 (916 autologous and 665 allogeneic) transplants were reported to the Brazilian Association of Organ Transplantation (ABTO) by 44 groups from 12 Brazilian states[3]. In 2020, the numbers of HSCT was 51% higher, with a total of 3,195 transplants (1,927 autologous and 1,268 allogeneic) reported by 93 groups[4]. However, it would

be extremely important to know quantitative indicators and outcomes after HSCT in Brazil. Although some articles have been published by the GVHD and Others Study Group (Grupo de estudos de doença do enxerto contra o hospedeiro - DECH (GEDECO), a research group within the SBTMO)[5-11], greater scientific production is somewhat hindered by the lack of a consistent database and standardized data collection. Moreover, national benchmarking that would enable analysis-based improvements in the quality of the procedure can be quite challenging without a national registry, not to say hampered.

The establishment of a structure to manage HSCT data is complex, as it requires planning, investment, infrastructure, time, professional training, awareness of transplant teams and support from government entities[12]. Thus, the model proposed by the SBTMO in cooperation with the Center for International Blood and Marrow Transplant Research (CIBMTR) uses the North-American registry infrastructure to allow centers to share the data, which is then processed and returned to the centers. The model here is to aggregate the data from a country and return to a central location to allow an assessment of transplant activity and outcomes in the region. This model has been successful in Canada and Japan. The data is then available in a tool called enhanced Data Back to Centers (eDBtC) which uses QlickView, a Business Intelligence application that extracts the data from the CIBMTR data warehouse in a format that is consumable and analyzable, additionally is includes data visualization tools and data download in different formats. (Figure 1). The importance of this cooperation came from the idea that duplicating the CIBMTR structure would be laborious, costly and redundant, combined with the guidelines of the research regulation in the country (resolution 466/2012)[13], as well as the regulation that ensures the protection of patient's personal data, according to the General Data Protection Law (GDPL 13.709/1018) 14 in force in Brazil.

Many Brazilian centers already had a long standing relationship with the CIBMTR even before this possibility was suggested. Some Brazilian centers, such as the UFPR and the Brazilian National Cancer Institute (Instituto Nacional de Cancer, INCA) had been affiliated to CIBMTR since the 1980's. Other Brazilian centers became members of the CIBMTR after that, with variation over time. Additionally, Brazilian centers with capabilities and certification to perform unrelated donor hematopoietic cell transplant from international donors, were require to report data when performing a transplant with a graft acquisition facilitated by the National Marrow Donor transplant. The CIBMTR is a research affiliation between the Medical College of Wisconsin and the NMDP, and the data for unrelated donor HSCT is done using the CIBMTR systems.

According to the first results of aggregate data from Brazil via CIBMTR[15], in 2008 there were 8 active centers in the registry, with 208 transplants reported to the CIBMTR. From 2008 to 2016, there was a cumulative increase of 28% in the number of active centers (N=11), although there was a large fluctuation from 2010 to 2012. In that period, we had a decrease of 22% in the number of active centers, probably due to the lack of local infrastructure or availability of a professional to perform the data manager position compounded by an increase the amount of data collected in the CIBMTR forms, which required a dedicated professional. As for the number of records, there was a growth of 174% from 2008 to 2016, but from 2010 to 2016 the average was 554 transplants per year, with a fluctuation of less than 10% (Figures 2 and 3).

With the lack of an HSCT data registry that could support the scientific community, public health, medical decision making, and also increase the number of active centers in the CIBMTR registry, a working group of physicians and data managers (DMs), starting in 2016 and in partnership with the CIBMTR and the SBTMO. This was a grass roots initiative to train the trainers, i.e. train data managers that would then serve as reference for other center data managers professionals with the objectives to further establish this profession in Brazil, increase the number of reporting centers, improve the quality of the reported data and to continue data collection to capture long term follow up. (Figure 4)[16].

Between 2016 and 2017, the first free online distance learning (ODL) course was offered in Portuguese and Spanish on filling out the pre and post HSCT Transplant Essential Data (TED) forms of the CIBMTR[17]. This first course joined the data managers from UFPR, Hospital Amaral Carvalho and Hospital Israelita Albert Einstein, which began to perform joint actions to support the establishment of the Brazilian registry. In 2018, the SBTMO board of directors for the 2018 to 2021 triennium established among their priorities of its strategic planning the development of the Brazilian transplant registry and support to DMs. For greater capacity building for DMs, in 2018 the Bone Marrow Association of the State of São Paulo (Associação da Medula Óssea, AMEO) promoted, through a PRONON funding from the Brazilian Ministry of Health, an in-person and online training for data managers with focus on centers of greater complexity and that

are dedicated to allogeneic transplants[18]. This fostered the consolidation of the group of DMs in the country and through SBTMO there was the recognition of the Data Managers Working Group (DMWG) in 2019[19]. The DMWG has promoted activities and fluid and effective communication among the DMs, through monthly meetings on specific HSCT and statistical topics, organization of the DMs meetings at the SBTMO Meeting webinars and group interaction via WhatsApp, with more than 20 interested professionals. Throughout the history of the DMs' scientific production has been awarded as best abstract in the session of the DMs in TCT Meeting in 2017 and 2018, and the Ricardo Pasquini Young Scientist prize at the SBTMO Meeting in 2019 and 2020. Currently there are more than [20] professionals active in the role.

With greater mobilization of the centers to become active in the registry, a multicenter study was proposed to formalize the submission of Brazilian data to the CIBMTR. It was approved in March 2017 by the Institutional Review Board (IRB) of the proposing center representing the SBTMO and by the Central IRB in 2019. The Brazilian Registry of Bone Marrow Transplantation was then formalized with the CIBMTR. Later this year the study was approved by the GEDECO. Currently, this scientific study, which regularizes the sending of data to the CIBMTR, contains 33 participating centers and 24 are waiting for the approval of the Central IRB to make this practice official in the institutions, (N=57).

Reporting the number and type of transplants to the Brazilian National System of Transplants (Sistema Nacional de Transplants, SNT) is mandatory, and this data is compiled by ABTO and made publicly available. No follow-up report is required. Therefore, we found that approximately 30% of the HSCT performed in Brazil in 2020 were reported to the CIBMTR, showing there is room for improvement and a long road until 100%-reporting to the CIBMTR.

As a result of the project, the first report done in the country of 7 participating centers was generated, using Brazilian aggregated data from the CIBMTR through the eDBtC. This study was selected for oral presentation at the Transplantation & Cellular Therapy Meetings in 201920. In 2020 there was the publication of the first article coming out from that study, with the 7 centers cited above, in the Journal of Bone Marrow Transplantation and Cellular Therapy. In 2021, the 1st Brazilian summary slides[21] was made available, which is a contemporary compilation of the transplant activity and general outcomes of HSCT performed in Brazil based on the summary slides annually reported by CIBMTR, with data from 24 institutions participating in the project, covering the period from 2008 to 2020. In recognition, these institutions were certified for being active in the CIBMTR by the National Transplant System (NTS) and SBTMO (figure 5).

Another important step was the formalization of the partnership between the SBTMO and the CIBMTR for our country, through a contract signed in 2019[22] that triggered the creation of the Brazilian dashboard on the CIBMTR portal (figures 5 and 6), with aggregated data from all centers active in the registry. The centers active in the CIBMTR, have access to a tool called eDBtC, which allows the return of data sent to their own transplant center in a standardized way, favoring the analysis of some outcomes. The accessibility to this data is fundamental for health and public administration.

With all the actions described above and some consolidated results of these strategies, an increase of active centers in the CIBMTR was noticed, with an average increased rate of 27%, from 2016 to 2019 and a growth of 88% in the number of Brazilian transplants reported to the CIBMTR. Referring to the last two years, in 2019, 23 centers registered data in the North American data registries with a total N of 1,073 transplants and in 2020, due to COVID-19 pandemic, there was a decrease in active centers to 21 and the number of transplants registered to 931 (Figures 2 and 3). According to the CIBMTR report of April 30, 2021, there are 33 active Brazilian centers in the CIBMTR, 12 in the process of contractual regularization with the CIBMTR, and 10 inactive, with 4 in the process of reactivation to the CIBMTR. It is important to emphasize that the inclusion of data from the centers when they become affiliated is not immediate, because there is an infrastructure preparation in the transplant center, awareness of the medical team on how to record the data in the patient's medical record, and the training of the DM with both the CIBMTR platform and the HSCT area, if this is not the area.

In conclusion, the process of creating an HSCT registry, associated with the affiliation of the CIBMTR was the result of actions of the partnership between the SBTMO, CIBMTR and Brazilian professionals who embraced the cause on behalf of the project. It was possible to obtain feasible data for the analysis of outcome and quantitative indicators in Brazil, which is directly linked to the increase in the number of affiliated centers in the North-American/Brazilian registry. Through the last results that generated the Brazilian summary slides and the direct communication of the SBTMO with the NST, the NTS recognized the CIBMTR, as the HSCT registry of the country, accred-

iting 26 centers affiliated to the CIBMTR, through the issuing of a certificate approving the efforts of the HSCT centers. The efforts from multiple stake holders described here demonstrated that implementation of a Brazilian Transplant Registry is feasible. As the data accumulates there is need to continue promoting this activity to reach close to 100% of centers to have a more representative assessment of transplant activity and results. Additionally, it allows for regional specific research and benchmarking to improve the outcomes of patients and the quality of care for Brazilian patients.

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FIGURE 1: Brazilian Registry Model using the CIBMTR

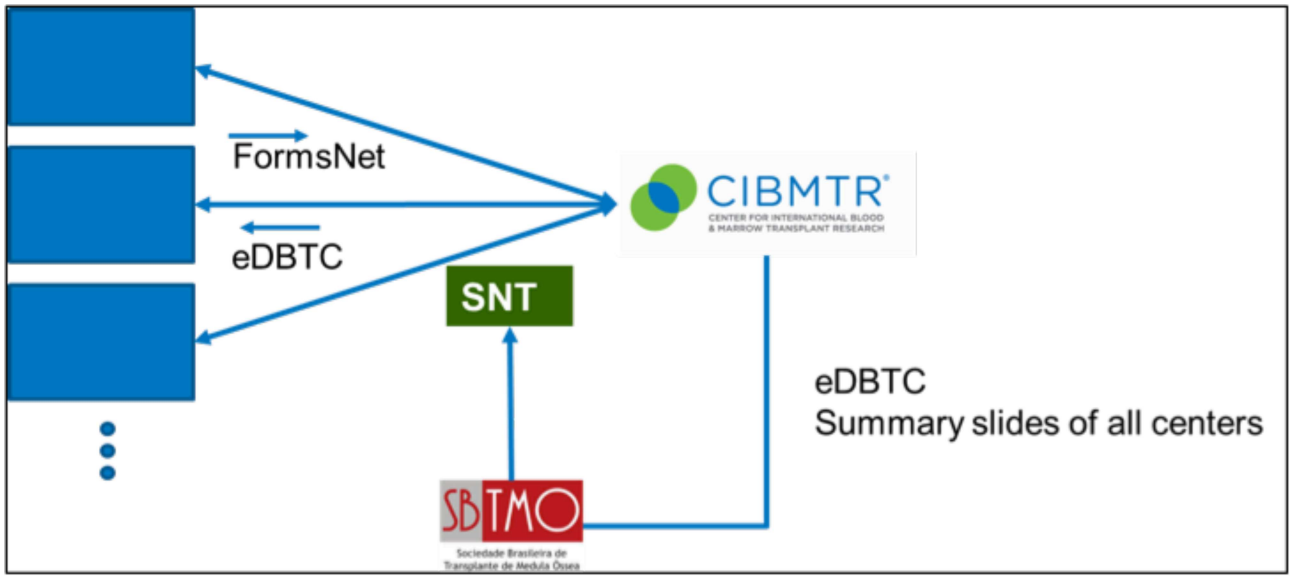


FIGURE 2: Active centers in the CIBMTR registry

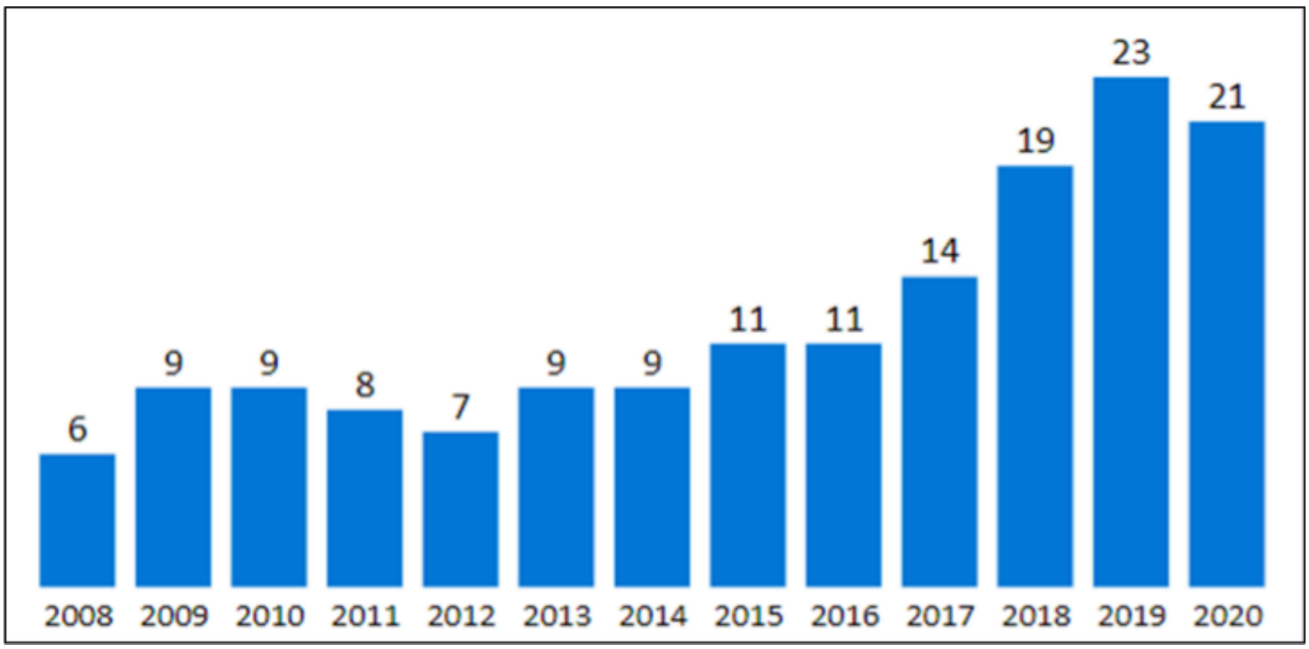


FIGURE 3: Number of transplants registered in the CIBMTR database

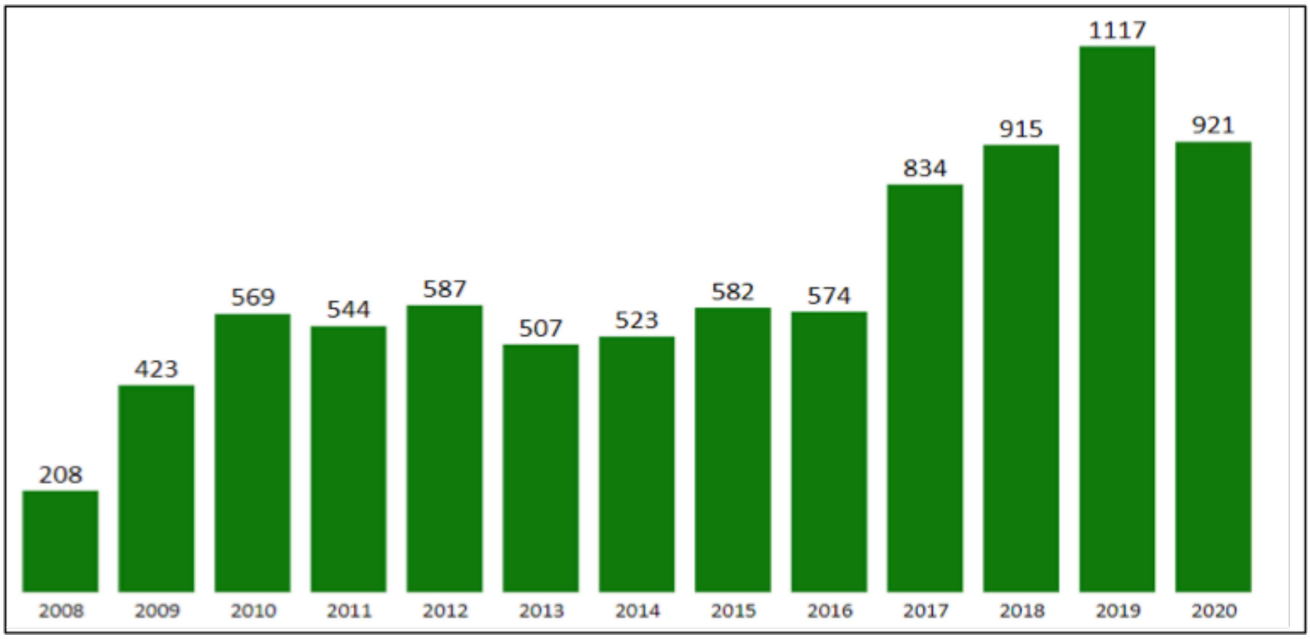


FIGURE 4: Actions timeline

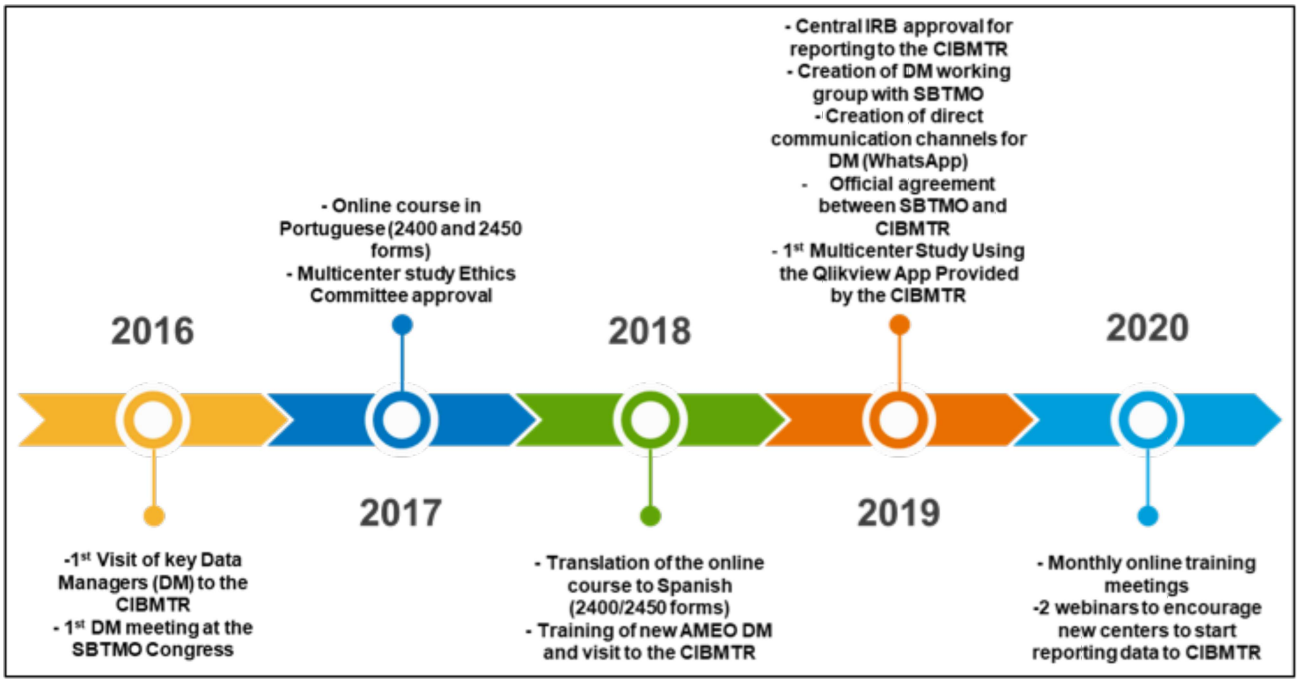
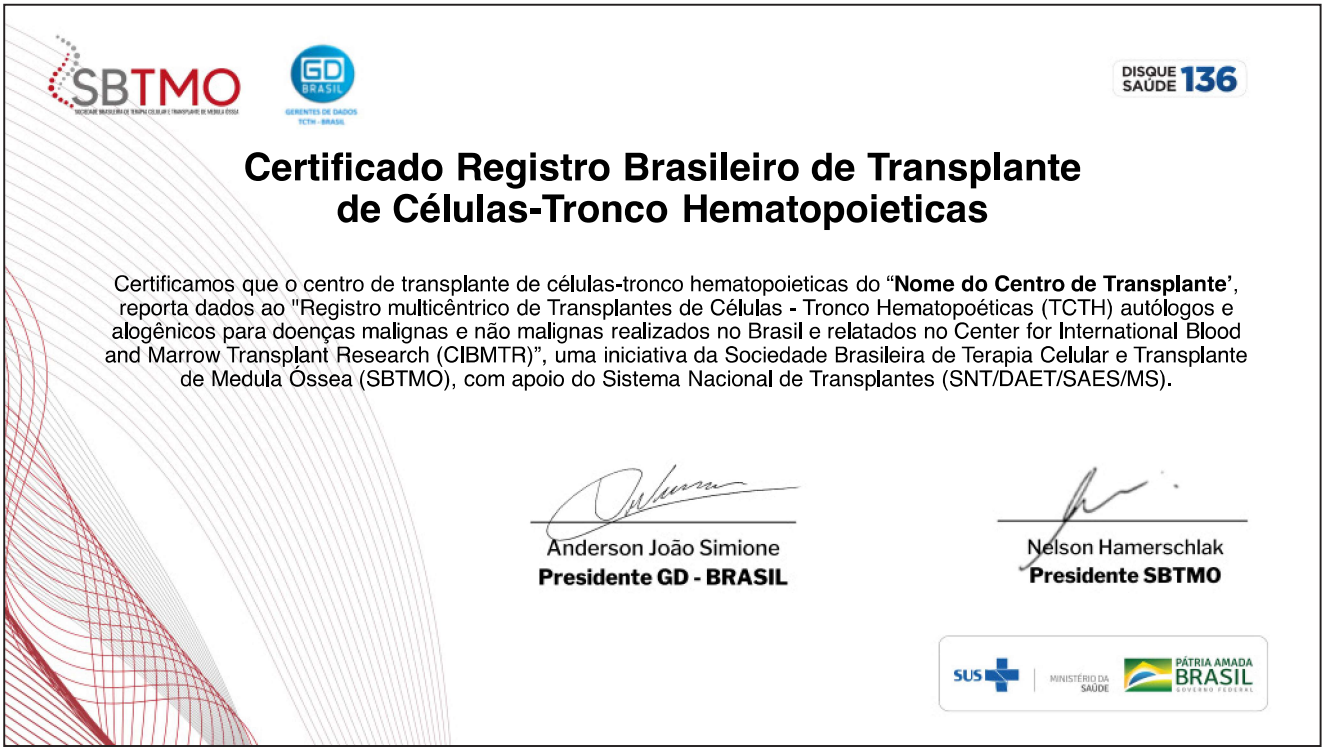


FIGURE 5: Certificate issued by SBTMO and TNS



SBTMO

GD BRASIL

DISQUE SAÚDE 136

Certificado Registro Brasileiro de Transplante de Células-Tronco Hematopoieticas

Certificamos que o centro de transplante de células-tronco hematopoieticas do "**Nome do Centro de Transplante**', reporta dados ao "Registro multicêntrico de Transplantes de Células - Tronco Hematopoéticas (TCTH) autólogos e alogênicos para doenças malignas e não malignas realizados no Brasil e relatados no Center for International Blood and Marrow Transplant Research (CIBMTR)", uma iniciativa da Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea (SBTMO), com apoio do Sistema Nacional de Transplantes (SNT/DAET/SAES/MS).

Anderson João Simione
Presidente GD - BRASIL

Nelson Hamerschlak
Presidente SBTMO

SUS | MINISTÉRIO DA SAÚDE | PÁTRIA AMADA BRASIL GOVERNO FEDERAL

FIGURE 6: Data Back to Centers (DBtC-Consented) - Patient

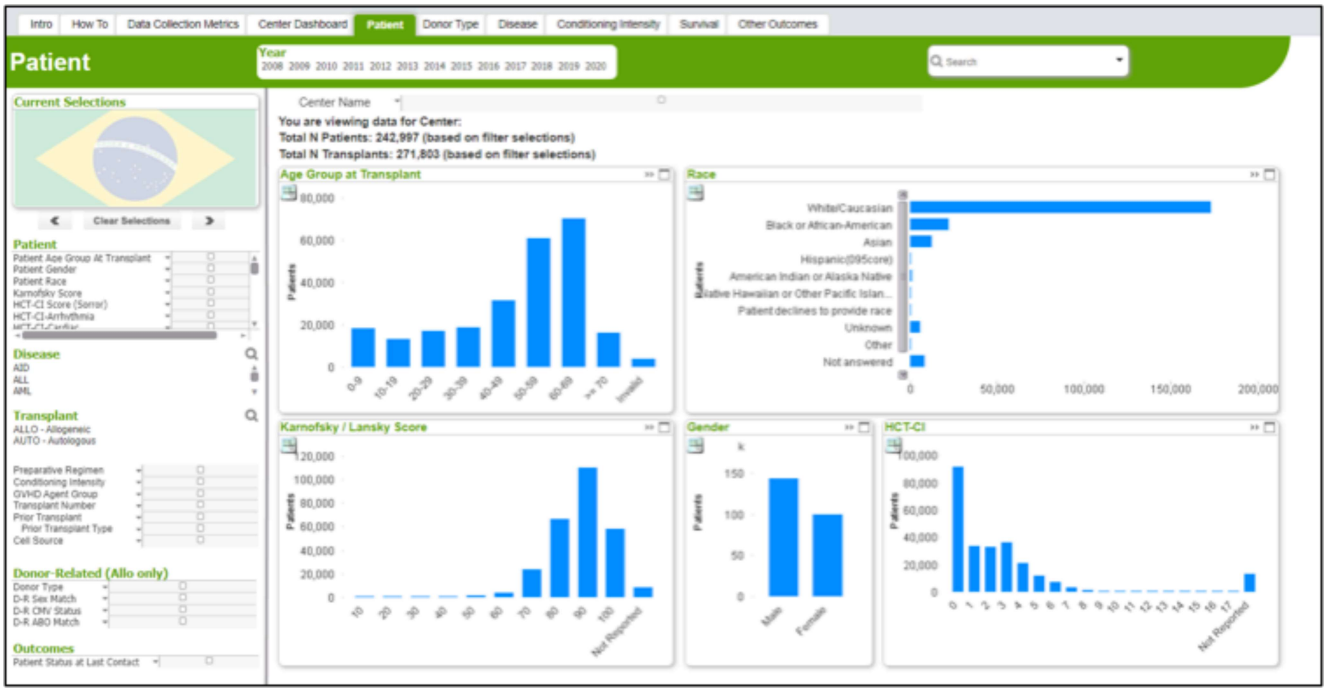


FIGURE 7: Data Back to Center (DBtC-Consented) - Other Outcomes