CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

STUDY PLAN

PART I OF AN ASSESSMENT OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MEDICARE BENEFICIARIES WITH MYELODYSPLASTIC SYNDROME AND RELATED DISORDERS

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1.0 INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) is the only potentially curative therapy available to patients with myelodysplastic syndromes (MDS). Until recently, however, concerns regarding morbidity and mortality of this intensive procedure limited its application in older patients with MDS. The introduction of reduced intensity conditioning (RIC) regimens greatly expanded the utility of HCT in older and sicker patients by reducing the risk of regimen-related toxicity[1,2]. Although several small studies indicate safety and efficacy of HCT in older patients, [3,4] there are no large prospective studies evaluating outcomes in patients older than 65 years. The aim of this study is to prospectively examine post-HCT outcomes in CMS beneficiaries with MDS to determine whether these outcomes are similar to those in younger patients where the experience with HCT is more extensive and where HCT is an accepted medical therapy.

2.0 HYPOTHESIS:

The outcome of HCT for MDS and related disorders in $\geq$ 65 years of age is similar to outcomes in adults 55-64 years of age.

3.0 SPECIFIC AIMS

3.1. To prospectively determine the following outcomes in Medicare beneficiaries who undergo HCT for MDS and related disorders and compare these outcomes with those of non-Medicare beneficiaries, aged 55-64:

- Early (100-day) mortality
- Acute and chronic graft-versus-host disease (GVHD)
- Relapse and progression
- Disease-free survival
- Progression-free survival
- Overall survival

3.2. To prospectively determine whether there are disease- or patient-related factors that predict outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- World Health Organization (WHO) classification
- International Prognostic Scoring System (IPSS) score
- WHO-based Prognostic Scoring System (WPSS)
- Cytopenias
- Cytogenetics
- Primary versus secondary MDS
- Disease duration and prior therapy
- Recipient age
- Performance score
- Sorror co-morbidity index

3.3. To prospectively evaluate what transplant characteristics are associated with outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- Preparative regimen
- Graft source
- GVHD prophylaxis
- Use of hematopoietic growth factors

3.4. To prospectively evaluate treatment facility characteristics associated with outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- Transplant volume
- Years of operation
- Academic affiliation

This study is Part 1 of a comprehensive evaluation of HCT in Medicare beneficiaries. It will evaluate outcome of allogeneic HCT, with monitoring to ensure that there is not undue early mortality in adults $\geq$ 65 years of age. The intent was to assemble a high quality data set of 240 patients, whose data will be analyzed to provide information pertinent to design of Part II of the study. In addition it would prospectively evaluate the effect of various disease, patient and treatment facility characteristics related to outcome. The study protocol is amended October 30, 2012 to increase the accrual to provide sufficient power to evaluate the effect of these prognostic factors on outcomes of HCT.

4.0 BACKGROUND:

Myelodysplastic syndromes are a group of clonal hematological disorders characterized by progressive cytopenias and leukemic transformation. More than 15,000 patients are diagnosed with MDS each year in the United States, and 80% of those patients are older than 65 years of age. The median age at diagnosis is 70 years in western countries and incidence increases with increasing age. The incidence is 0.22/100,000 in those <49 years, 4.8/100,000 between the ages of 50 and 70 years and 22.8/100,000 in those older than 70 years[5].

MDS is classified using several systems. For many years, MDS subtypes were classified by morphology using the French-American-British FAB) classification; this has now largely been superseded by the WHO classification, which also incorporates cytogenetic abnormalities (5q-). Several prognostic scoring systems are also available. The International Prognostic Scoring System (IPSS) is the most widely accepted. The IPSS uses percentage of blasts, cytogenetic abnormalities and cytopenias to separate patients into 4 different prognostic groups: Low, intermediate-1, intermediate-2 and high risk. Median survivals vary from 0.4 years to 5.7 years for untreated patients with high and low risk disease respectively[6]. More recently, a prognostic system using the WHO classification, transfusion requirement and IPSS cytogenetic risk, the WPSS) is suggested to provide better prognostic

discrimination[7].

Recently the Food and Drug Administration approved three new drugs for therapy of MDS: azacytidine[8], decitabine[9] and lenalidomide[10]. Both azacytidine and decitabine are hypomethylating agents while lenalidomide is a thalidomide analogue. The response rates to those drugs range from 30-70%, however none are curative.

The only available therapy with the potential to cure MDS is HCT and HCT is the treatment of choice for younger patients[11]. Prior to the introduction of RIC regimens, regimen-related morbidity and mortality limited the utility of HCT in older patients and in those with significant co-morbidities. RIC regimens now allow HCT to be offered more safely to those patients but use of HCT in the older population still remains limited. This was evident in a recent study by the CIBMTR where only 10% of patients who underwent RIC HCT were older than 65 years. In that study, age had no significant impact on outcome in multivariate analysis in a cohort of patients between 40 and 70 years.[12] The 100 day mortality rate was about 20% and the 2 year probability of survival was about 40%.

There are multiple reasons that older patients do not undergo transplantation. Older patients may have co-morbidities that compromise their ability to tolerate an intensive therapy like HCT. Some oncologists are reluctant to refer older patients for HCT, even if there are no clinical contraindications, because of perceived worse outcomes in older patients. Some transplant centers have arbitrary upper age limits for HCT candidates. Finally, some third party payers will not cover HCT in older patients until there is transformation to acute leukemia. Until recently, coverage of HCT for MDS by the US Centers for Medicare and Medicaid Services (CMS) depended on local coverage determinations[13]. CMS is the primary health insurer for most US adults 65 years of age or older. Recently, CMS made a National Coverage Determination (NCD) regarding MDS, indicating that data regarding efficacy in a CMS beneficiary population were currently insufficient but that coverage would be provided for patients enrolled in a clinical study appropriately designed to generate data necessary to make a determination about efficacy and effectiveness. This decision acknowledged that “the available evidence suggests that allogeneic HSCT for MDS is reasonable and necessary under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED).”

The aim of this study is to prospectively examine post-HCT outcomes in CMS beneficiaries with MDS to determine whether these outcomes are similar to younger patients where the experience with HCT is more extensive and where HCT is an accepted medical therapy. The study will also evaluate patient, disease and treatment factors which might modify transplant outcomes. The objectives and methods of the study comply with the CMS-specified requirement that a “clinical study seeking Medicare payment … pursuant to Coverage with Evidence Development (CED) must address one or more aspects” of three questions outlined in its Decision Memo (CAG-00415N). The analyses in this Study Plan are for Part 1 of this evaluation and will directly address questions 2 and 3 in that Memo and will

provide data to plan Part 2 of the evaluation, a study directly addressing question 1 in that Memo, which will compare outcomes after HCT to outcomes with non-HCT therapy.

5.0 STUDY POPULATION:

Eligible patients are persons ≥65 years old (or <65 years of age and a CMS beneficiary) with myelodysplastic syndromes and related disorders, including chronic myelomonocyte leukemia (CMML), who are eligible to receive an allogeneic HCT from either an HLA-identical sibling or unrelated donor in a US transplant center and who agree to (sign Informed Consent; Appendix A) submission of comprehensive clinical data on their pre- and post-transplant clinical status and outcomes to the Center for International Blood and Marrow Transplant Research (CIBMTR). Eligibility for HCT will be according to local institutional practices. Patients younger than 65 years of age who are CMS beneficiaries are included but will be analyzed separately. The object is to capture data on the broad range of patients in whom the therapy is used; there is no exclusion for race, gender or prior therapy.

6.0 OUTCOMES:

6.1. Primary outcome

6.1.1. 100 day mortality.

100 day mortality is chosen as the primary outcome because this is a preliminary study designed to provide data necessary to plan a prospective comparative study of transplant and non-transplant therapy. The rationale for use of HCT for MDS in patients ≥65 years old is that outcomes are thought to be similar to those in adults 55-64, where HCT is an accepted therapy, given similar non-age-based eligibility criteria are met[11]. This study will determine, in a large cohort of patient ≥65 years old, whether early mortality is indeed in the range expected and will also provide information on prognostic factors for this outcome.

6.2. Secondary outcomes

6.2.1. Acute GVHD: Occurrence of grade II, III and/or IV skin, gastrointestinal or liver abnormalities fulfilling the IBMTR criteria for acute GVHD.
6.2.2. Chronic GVHD: Occurrence of symptoms in any organ system fulfilling the criteria of chronic GVHD.
6.2.3. Relapse: disease recurrence or persistent disease for patients not in CR at transplant. Those who survive without recurrence or persistent disease are censored at the date of last contact.
6.2.4. Progression: increase in marrow blasts to >20%; patients without progression are censored at time of most recent marrow examination.
6.2.5. Disease-free survival: survival without death or relapse. Those who survive without recurrent or persistent disease are censored at the date of last

contact.
6.2.6. Progression-free survival: survival without increase in marrow blasts to >20%; patients without progression are censored at time of most recent marrow examination.
6.2.7. Overall survival: Surviving patients are censored at the date of last contact.

7.0 DATA COLLECTION:

All data necessary for this study will be collected using the existing mechanisms of the CIBMTR under, operating under the "NMDP and CIBMTR Protocol for a Research Database for Hematopoietic Stem cell Transplantation and marrow Toxic Injuries", version 6.0, (NCT01166009) (Appendix A). The Informed Consent for this protocol is also found in Appendix A. These data collection mechanisms support the reporting required for the Stem Cell Therapeutic Outcomes Database (SCTOD), and the research endeavors of the CIBMTR. Existing data instruments and procedure manuals can be found at www.cibmtr.org/DataManagement. Registration of patients and submission of data will follow standard CIBMTR procedures.

8.0 STUDY DESIGN:

This study initially had a target accrual of 240 patients older than age 65 for the 100 day mortality primary endpoint. Sample sizes were based on an inferiority test of the hypothesis that the 100 day mortality rate in the ≥ 65 year old cohort is higher than 20%, the approximate 100-day mortality rate in a 55-64 year old cohort[12]. The study was designed to have approximately 80% power to detect a 6.5 % or greater increase in 100 day mortality rate in the ≥65 year old cohort. Table 1 below shows the power of the test for various 100 day mortality rates.

Table 1.

True 100 day mortality rates	Power
0.21	10%
0.22	20%
0.23	32%
0.24	46%
0.25	60%
0.26	73%
0.27	83%
0.28	90%
0.29	94%

At each of the four evaluations points, we will prepare descriptive tables of the covariates. Kaplan-Meier estimates of mortality and disease free survival will be

constructed for the entire cohort and by sub-groups defined by the fixed covariates such as IPSS score. Cumulative incidence curves will be constructed to estimate acute GVHD incidence, relapse progression rates. These analyses will be conducted when 60, 120, 180 or 240 patients have at least 100 days of potential follow-up. As they are descriptive in nature, no p-values are computed until the entire cohort has been observed.

When accrual of the first 240 patients is complete and all patients have been followed for at least 100 days, the association between outcomes and the variables listed in Section 3.0 will be examined in either a logistic regression model or a Cox proportional hazards model depending on the outcome of interest. Forward stepwise model selection techniques will be used in this approach. These analyses will include a cohort of patients ages 55-64 years transplanted for MDS and related disorders in the same centers as the CMS beneficiaries included in this analysis.

After accrual is complete, follow-up of this cohort will continue, through standard CIBMTR mechanisms, after completion of these analyses. Evaluation of all secondary endpoints will be repeated when all patients have been followed for a minimum of two years.

Prognostic factors in patients age 65 and older

Another objective of this study is to determine the prognostic value of patient and disease factors upon outcomes of HCT in patients age 65 and older. After evaluating the demographics of the first 180 patients age ≥ 65 accrued to the protocol, several prognostic factors of interest (sections 3.2 and 3.3) are expected to require larger numbers of patients to achieve adequate power to detect meaningful differences in outcomes for patients in this cohort.

Based on an 80% power with an assumption of a 25% 100 day mortality in the most favorable group and a delta as indicated, the number of patients needed for each of the analyses is listed below in Table 2. The anticipated accrual for Part I was based on power calculations for a primary outcome of 100 day survival after HCT in patients 55-64 compared to 65 and older. Based upon the distribution of age (65-69 vs. 70 and over), performance score, HCT Comorbidity index[14], IPSS score, and disease status in the first 180 patients enrolled, we anticipate that 700 patients will be required to complete an analysis of prognostic factors for early outcome in patients 65 and older.

Table 2: Number of patients required to test differences in 100 day mortality with 80% power for specified prognostic factors

Prognostic Factor	Number of Patients based on expected difference		
Age	delta =0.1	delta =0.15	delta =0.2
<70	580	246	130
≥70	183	78	41
Total	763	324	171
HCT-CI (Sorror, et al)			
0-2	294	118	59
≥3	222	89	45
Total	516	207	104
Secondary MDS			
No	649	265	133
Yes	163	67	34
Total	812	332	167
Cytogenetics			
Good/Intermediate	376	152	76
Poor	194	79	40
Estimated Unknown/missing/not done	78	32	16
Total	648	263	132
IPSS			
Low.int-1	311	125	62
Intermediate-2/high	214	87	43
Evaluable patients	525	202	105

The above sample size calculations for prognostic factors are based on the estimated frequencies of these potential risk factors using the data accrued in the first 180 patients and a binary response of alive or dead at 100 days. The final analysis of these factors will be performed in a logistic regression model for 100 day survival or a Cox regression model for other events in the cohort of patients age 65 and older.

The distribution of relevant prognostic factors shown in sections 3.2 and 3.3, and in the power calculations shown in Table 2 will be reviewed after accrual of 500 patients age 65 and over. Adjustments will be made to the final accrual projections at that time.

8.1. Variables to be analyzed for their association with primary and secondary outcomes

8.1.1. Patient related:

- Age: in five year increments (or appropriate cutpoint based on data analysis)
- Gender: male vs. female
- Race: Caucasian vs non-Caucasian
- Karnofsky performance status: <80% vs. ≥80%
- Sorror co-morbidity Index

8.1.2. Disease related:

- WHO Disease classification at diagnosis and just prior to HCT
- FAB classification
- Pretransplant WBC and untransfused platelet count and hemoglobin concentration
- IPSS score immediately prior to transplantation
- WPSS score immediately prior to transplantation
- Cytogenetics
- Primary versus secondary MDS
- Time from diagnosis to transplant: <1 year vs. ≥ 1 year (or more appropriate cutpoint based on data analysis)
- Agents used for prior therapy

8.1.3. Transplant related:

- Conditioning regimen: more versus less intensive; specific regimens to be evaluated if numbers of patients sufficient
- Donor age
- Donor-recipient CMV status: -/- vs. -/+ vs. +/- vs. +/+
- Donor-recipient HLA match: HLA matched sibling vs. 8/8 locus (HLA- A, B, C, DRB1) matched unrelated donor vs. 7/8 locus matched unrelated donor
- Stem cell source: bone marrow vs. peripheral blood
- GVHD prophylaxis: Cyclosporine or Tacrolimus + Methotrexate vs. ex vivo T- cell depletion vs. other
- Donor-recipient gender match: male-male vs. male-female vs. female-male vs. female-female
- Transplant center characteristics: transplant volume, years of operation, academic affiliation

9.0 SCIENTIFIC INTEGRITY AND RELEVANCE TO THE MEDICARE POPULATION

As required in Decision Memo CAG-00415N, this clinical study will adhere to the following standards of scientific integrity and relevance to the Medicare population:

9.1. *The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.*

The principle purpose of the proposed study is to test whether HCT leads to MDS-free survival in a large proportion of patients with acceptable rates of early mortality and GVHD-related morbidity.

9.2. *The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.*

Allogeneic HCT is an accepted therapy for MDS with extensive data in young patients and moderate amounts of data in patients 65 and older. The National Comprehensive Cancer Center Network (NCCN) Guidelines recommend allogeneic HCT at an initial treatment for transplant-eligible patients with IPSS Int2-High Risk disease and as a salvage therapy for other patients who do not respond to non-HCT therapy[11].

9.3. *This research study does not unjustifiably duplicate existing studies*.

There are currently no existing prospective data addressing the outcome of HCT for patients with MDS who are 65 or older. Some data on this population are available but include small numbers and procedures done in an earlier era. As noted in the Decision Memo, CMS feels that there are "*limitations of the evidence base on the use of HSCT for MDS as described in our Analysis section".* The proposed study addresses many of the current data limitations and will not be duplicative of existing studies.

9.4. *The research study design is appropriate to answer the research question being asked in the study.*

The proposed study has 80% power to detect an early mortality rate that is 6.5% higher than the rate that is well-documented in a 55-64 year old patient cohort and includes sufficient numbers of patients to evaluate key prognostic factors in this population. The Methods described in Section 6.0 have been used successfully in hundreds of CIBMTR studies of similar data (see below).

9.5. *The research study is sponsored by an organization or individual capable of executing the proposed study successfully.*

This study will be performed through the CIBMTR, which has performed hundreds of similar analyses over its >30 year history. The CIBMTR is a clinical research program which receives HCT outcomes data from a network of more than 450 transplant centers worldwide. Data are collected and analyzed by the Statistical Center, located at the Medical College of Wisconsin in Milwaukee, WI, and the National Marrow Donor Program located in Minneapolis, MN. The CIBMTR database includes information on about 330,000 transplant recipients and receives information on about 15,000 new transplants annually. CIBMT data and statistical and scientific expertise have resulted in hundreds of peer-reviewed publications (www.cibmtr.org/ReferenceCenter/PubList/index.html).

As of December 2007, all United States transplant centers are required to report data on their related and unrelated donor transplants to the CIBMTR; participation of non-U.S. centers is voluntary. Computerized checks for errors, review of submitted data by physicians and on-site audits of participating centers are used to monitor the quality of the data. The CIBMTR collects data on two levels. All centers register basic data (Pre- Transplant Essential Data) for all patients. Centers provide comprehensive data (Report Forms) for a subset of registered patients. Patients are selected for comprehensive data reporting using a randomization program that weights cases for selection in order to provide adequate numbers of cases for current and future studies and to ensure adequate representation of all transplant types and indications. The selection program is modified as needed to select cases for specific studies such as the one described in this protocol. CIBMTR centers are asked to provide follow-up on all patients for as long as they are able to maintain contact. Completeness rates for one and two year survival data are >95%. These data sets have been used to conduct numerous studies of transplant outcomes, including studies of conditioning regimens. The most recent versions of the CIBMTR study forms can be found at http://www.cibmtr.org/DATA/Data_Mgmt_Forms/index.html.

Additionally, we have assembled a team of HCT and MDS experts to guide development, implementation and completion of this study. Biosketches are included in Appendix B.

All participating centers will be NMDP and/or FACT accredited. See list in Appendix C.

9.6. *The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.*

The data collection and analyses for this protocol will be done in full compliance with the specified Federal regulations. Signing an Informed Consent (Appendix A) for participation is required. The most recent NMDP and transplant center IRB approvals for this protocol are found in Appendix D.

9.7. *All aspects of the research study are conducted according to appropriate standards of scientific integrity (seehttp://www.icmje.org).*

The CIBMTR adheres to all appropriate standard of scientific integrity. An interim monitoring procedure for this study is described in Section 8.0. At the time of each interim analysis, the interim analysis, and summary data on patient demographics, all secondary outcomes and causes of death will be reviewed by the CIBMTR Data Monitoring Board. The primary function of the Monitoring Board is to perform ongoing assessment and monitoring of CIBMTR prospective studies relative to scientific merit/validity, safety and efficacy. The Monitoring Board is comprised of an interdisciplinary membership with expertise in hematopoietic stem cell transplantation, biostatistics, ethics and the conduct of clinical trials.
Key responsibilities of the Monitoring Board are to:

- Offer advice concerning the continued scientific merit and/or validity of each ongoing study.
- Provide continual assessment and monitoring of study participant safety; particularly with respect to the magnitude and impact of any adverse or severe adverse events.
- Provide ongoing assessment and monitoring of all study specific prescribed treatment protocols.
- Review and assess study specific site performance data such as study recruitment and accrual, protocol adherence and data quality.
- Recommend the continuation, amendment or termination of each ongoing study based upon regularly scheduled review of interim data results.
- Ensure study subject confidentiality as well as that of all study data and the conclusions reached as a result of the monitoring process

The Monitoring Board can recommend stopping the study if warranted by their review of the interim data.

9.8. *The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.*

This document serves as the written study plan, which, in combination with the master protocol, A Database Study for Hematopoietic Stem Cell Transplantation and Marrow Injuries, (NCT01166009, Appendix A), addresses, or incorporates by reference, the standards listed.

9.9. *The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.*

The outcomes of this study include measures of efficacy as well as toxicity.

9.10. *The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.*

This study falls under the auspices of NCT01166009 which is registered by the CIBMTR on ClinicalTrials.gov.

9.11. *The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.*

Regardless of the outcomes, the results of this study will be incorporated into a manuscript and submitted to a peer-reviewed journal within 24 months of receipt the 240th patient's 100 day report. Results will likely be made public via an abstract prior to that time, submitted to the American Society of Hematology meetings, the BMT Tandem Meetings or similar appropriate national meeting.

9.12. *The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.*

Our protocol does not limit the inclusion of underrepresented groups. CIBMTR members must report data on *all* HCT recipients at their center regardless of gender, race or age. All patients meeting the broad eligibility criteria (HCT recipient, MDS, CMS beneficiary, informed consent) in Section 5.0 will be included. The association between outcomes and race, gender and age will be explored as indicated in Section 8.1.1.

9.13. *The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.*

This study is expected to include most, if not all, of the CMS beneficiaries who receive HCT for MDS or a related disorder during the period of study, ensuring generalizability. The separation of the beneficiaries into two age groups (64 years and younger vs. 65 years and older) allows for comparison, while the inclusive design ensures applicability to the full population of Medicare beneficiaries.

10.0 TIMELINE

Approval by CMS	**Month 0**
Activation	**Month 1**
Enrollment	**Month 1 – 26**
Interim analysis 3	**Month 22**
Completion of 100-day analyses	**Month 34**
Accrual of all 700 patients	**Month 70**
Completion of follow-up for primary endpoint	**Month 29**
Submission of primary manuscript	**Month 36**
Completion of $\geq$ 2 years of Follow-up in all patients	**Month 94**
Completion of 2-year analyses	**Month 96**

This timeline assumes that about 12 eligible patients per month will be enrolled. Higher or lower rates of HCT for MDS in CMS-eligible patients could substantially affect this timeline.

11.0 REFERENCES:

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12.0 LIST OF APPENDICES

- **A. NMDP AND CIBMTR PROTOCOL FOR A RESEARCH DATABASE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION AND MARROW TOXIC INJURIES and INFORMED CONSENT DOCUMENT**
- **B. BIOSKETCHES FOR STUDY TEAM MEMBERS**
- **C. LIST OF PARTICIPATING CENTERS WITH IRB APPROVAL DATE AND ACCREDITATION STATUS**
- **D. MOST RECENT INSTITUTIONAL REVIEW BOARD APPROVALS**

NATIONAL MARROW DONOR PROGRAM®
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CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH®

PROTOCOL FOR A RESEARCH DATABASE

FOR

HEMATOPOIETIC CELL TRANSPLANTATION, OTHER CELLULAR THERAPIES AND MARROW TOXIC INJURIES

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Table of Contents

1. Background

1.1. National Marrow Donor Program®

The National Marrow Donor Program® (NMDP) was established in 1986 as the result of a Federal contract that was awarded to create and maintain a registry of volunteer hematopoietic cell (HC) donors. Physicians search the NMDP Registry on behalf of patients in need of an HC transplant who have no suitably matching related donor. In 1999 the NMDP added a Cord Blood Registry to provide more donor source options for patients in need of an unrelated HC transplant. Annually, more than 5,000 patients initiate an active donor search through the NMDP, and over 3,000 of these searches result in transplants.

In addition, the Federal contract also recognized that the NMDP could play a critical role in responding to contingency events; primarily radiation and chemical exposures occurring either accidentally or resulting from military or terrorist actions that cause a marrow toxic injury.

1.2. Center for International Blood and Marrow Transplant Research®

The International Bone Marrow Transplant Registry (IBMTR), located within the Department of Medicine of the Medical College of Wisconsin, was established in 1972 to monitor and study outcomes of bone marrow transplants. In 2004 the NMDP and IBMTR established the Center for Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is an affiliation between the NMDP and the Medical College of Wisconsin. The CIBMTR has both a Minneapolis campus located within the NMDP offices and a Milwaukee campus at the Medical College of Wisconsin. The NMDP Research Program is accomplished through the CIBMTR.

The CIBMTR has a network of more than 500 centers worldwide that contribute detailed research data on consecutive allogeneic related and unrelated and autologous hematopoietic cell transplants. In addition, NMDP centers responsible for managing unrelated donors contribute detailed data on the donation and recovery of unrelated donors. In 2011 CIBMTR activities were expanded to include uses of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection.

The CIBMTR Research Database is comprised of databases maintained at the NMDP and the CIBMTR Milwaukee campus.

1.3. Establishment and Purpose of the Research Database

The primary goal of the CIBMTR Research Program is to improve the safety and effectiveness of hematopoietic cell (HC) transplantation for both donors and recipients. The NMDP database was established in 1989 and the IBMTR database was established in 1972. The Research Database contains demographic and clinical data on allogeneic related and unrelated donor and autologous HC transplants. Data are also collected on unrelated donors and their donation experiences. The data

contained in the research databases are observational data. CIBMTR does not determine which therapies are used for patients, but rather collects information regarding therapies as they are applied by transplant centers.

Secondary goals of the CIBMTR Research Program are to understand uses of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection, and to improve treatments and outcomes for those individuals who have been exposed to radiation or other chemicals that are toxic to marrow. In these cases, exposure data, organ injury data, treatment data, and outcomes data are collected.

The NMDP and the CIBMTR are the sole custodians of the data in the Research Database. The NMDP and the CIBMTR are responsible for determining who has access to the data in the Research Database (see Section 6 "Studies Involving Data in the Research Database"). The NMDP and CIBMTR are responsible for determining if and when data will be removed from the database or shared with others.

The primary purpose of the Research Database is to have a comprehensive source of observational data that can be used to study HC transplantation. A secondary purpose of the database is to have a comprehensive source of data to study marrow toxic injuries and the application of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection. Researchers whose study proposals are reviewed and approved in advance by the CIBMTR may use data for studies examining HC transplantation and its effects on recipients and donors, to study marrow toxic injury, or to study regenerative medicine or immune-based therapy, including for malignancy or infection. The following are types of studies in which these data may be included. Studies to determine:

- How well recipients recover from their transplants or cellular therapy;
- How recovery after transplantation or cellular therapy can be improved;
- Long-term outcomes after transplantation or cellular therapy,
- How access to transplantation or cellular therapy for different groups of patients can be improved;
- How well donors recover from collection procedures;
- Success of different treatment models for marrow toxic injury;
- The long-term effects of exposure to radiation or other chemicals;
- The application and success of transplantation in the management of marrow toxic injuries;
- The application and success of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection

Certain studies may require that data in addition to what already exists in the Research Database be collected in order to answer the research question. This protocol makes provisions for additional data collection from existing medical records (see Section 4.4 "Study Specific Data"). Section 6, "Studies Involving Data in the Research Database", describes the process for releasing data to investigators.

2. Eligibility to Participate in the Research Database

2.1. Recipient Eligibility Criteria

Any recipient of an unrelated or related donor or autologous HC transplant (includes cells collected from peripheral blood, bone marrow or cord blood) or any recipient of cellular therapy in a CIBMTR center is eligible to participate in the Research Database. This includes adults with and without decision making capacity, and children.

2.2. Individual with Marrow Toxic Injury Eligibility Criteria

In the event of a radiation exposure accident, the NMDP has a radiation injury treatment network, whose purpose is to collect data to understand the outcomes of patients treated under these circumstances. Any individual who is treated for a marrow toxic injury at a center participating in the NMDP's Radiation Injury Treatment Network (RITN) is eligible to participate in the Research Database. This includes adults with and without decision making capacity, and children. Eligible individuals may have received supportive care only, growth factor support, HC transplant or other appropriate medical treatment for marrow toxic injury. Treatments applied are at the discretion of the care facility, and are not determined by the NMDP or CIBMTR.

2.3. Unrelated Donor Eligibility Criteria

All donors registered on the NMDP Registry who have been requested to donate a product for a recipient are eligible to participate in the Research Database.

2.4. Informed Consent

All U.S. participants will be provided information about participation in the Research Database and must sign an Institutional Review Board (IRB) approved informed consent document indicating their consent to participate in the database. Documentation of assent and of parent or legal guardian permission of minor participants, and consent for adult participants, must be maintained at the center where the participant, or their parent or legal guardian provided consent to participate. To confirm that participants have given consent to participate in the Research Database, the first form submitted on a participant includes confirmation that the participant signed the informed consent document.

Non-U.S. centers contributing data to the Research Database will provide written assurance that the submission of data to the CIBMTR Research Database has on-going oversight by their local Ethics Review Board/Medical Ethics Committee and all national regulations are followed.

2.4.1. Minor Assent

The NMDP Research Database includes pediatric recipients. The procedural risk involved in this protocol meets the definition of minimal risk set forth in

45 CFR 46.102 (i) "*Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."* Participation on this protocol requires submission of medical data from recipients that are available directly from the participant's medical record.

Adequate provisions must be made for soliciting and documenting assent of the children and permission of their parents or legal guardians, as set forth in 45 CFR 46.408.

- The research procedures do not involve more than minimal risk; therefore assent will be sought from all minors 7 to 17 years of age capable of providing assent.
- Age appropriate information will be provided to minors 7 to 11 years of age and minors 12 to 17 years of age.
- Local Institutional Review Boards will be responsible for determining how assent will be documented.
- The research in this protocol is covered by 45 CFR 46.404; therefore the written permission of the parent or legal guardian is required.
- The minor may only participate in the research if the minor and a parent or legal guardian agree to the minor's participation. If either the parent/legal guardian or the minor declines participation in the study, the minor shall not be enrolled in the study. If the minor lacks the capacity to provide assent, parent or legal guardian permission is sufficient.

3. IRB Approval Process for Research Database

All U.S. centers must have an IRB-approved protocol and consent forms prior to submitting data about transplant recipients, transplant donors, or individuals with marrow toxic injury, to the Research Database. The center's designated IRB may not waive informed consent requirements under this protocol. Recipients, individuals with marrow toxic injury and donors must provide informed consent for submission of data to the Research Database.

Local IRB review and approval is necessary except in the case of centers that list the NMDP IRB as a designated IRB on their Federal Wide Assurance (FWA) and have an IRB Authorization Agreement in place with the NMDP that includes the Research Database protocol. This protocol and its associated consent forms are provided to centers. Centers are required to submit this protocol and consent forms to their designated IRBs for review and approval.

International centers must follow their own national regulations and provide assurance to the CIBMTR that national regulations are being followed.

3.1. IRB Approval Process

- The protocol and consent forms may be modified to include the name of the local institution, local institutional contact, and to conform to other similar non-substantive format or content changes required by the center's designated IRB.
- The modified protocol and consent forms must be reviewed and approved by the center's designated IRB.
- Any substantive changes to the protocol or consent forms suggested or stipulated by the local IRB need to be reviewed and approved by the NMDP IRB.
- The IRB approval letter and the IRB-approved protocol and consent forms must be submitted to the IRB Office at the NMDP.
- Centers may begin submitting data for research purposes as soon as the site's Principal Investigator receives notification from NMDP IRB staff acknowledging that an IRB-approved protocol and consent form is in place at the center.
- The above process is followed for each continuing review period. If there is a lapse in IRB approval, the center will not be allowed to submit data for research purposes until IRB-approval has been obtained.
- In cases where the center has designated the NMDP IRB on their center's FWA, and an IRB Authorization Agreement is in place for the Research Database protocol, the center does not need to obtain any additional IRB approval.

4. Collection of Data

4.1. Collection of Recipient Data

Recipient data are collected from pre-existing data within the recipient's medical record chart at the transplant center. Transplant Centers complete the forms at the following time-points.

Time-point	Data Collected
At registration	Name Social Security Number (U.S. participants only) Mother's maiden name City State Country of birth
At the time of transplant	Demographic data such as race and ethnicity, gender, birth date, Median household income (U.S. participants only), Education (U.S. participants only), occupation HLA typing data Pre-transplant disease-specific data such as blood counts, disease status, cytogenetics Co-existing disease at the time of transplant

	Functional status Organ function prior to transplant History of infection exposure prior to transplant Conditioning regimen HSC product manipulation
100 days, six months, one year, two year, post-transplant	Engraftment – neutrophil and platelet recovery Acute and chronic GVHD Chimerism Organ function New malignancy Disease Status Functional status Ability to return to work or school Second transplant Donor leukocyte infusion
Annually starting year three	Acute and chronic GVHD New malignancy Disease Status Functional status Ability to return to work or school Second transplant
At time of death	Primary and contributing cause of death

4.2. Collection of Marrow Toxic Injury Data

Data from individuals with marrow toxic injury are collected from pre-existing data within the individual's medical record chart at the transplant center. Transplant Centers complete the forms at the following time-points.

Time-point	Data Collected
At registration	Name Social Security Number (U.S. participants only) Mother's maiden name City State Country of birth
At the time of initial evaluation	Demographic data such as race and ethnicity, gender, birth date, Pre-existing medical problems Exposure history Blood counts and marrow status Treatment data
At follow-up time points	Response to treatment including: Blood counts

	Laboratory and clinical data pertaining to organ injury New malignancy Functional status Additional treatments Other complications following the marrow toxic injury
At time of death	Primary and contributing cause of death

4.3 Collection of Unrelated Donor Data

Unrelated donor data are collected at the time a donor joins the Registry, when a donor is requested for confirmatory typing to determine if he/she is a match with a potential recipient, during the work-up phase to determine eligibility to donate HC, and post-collection of the HC product. Donor Center staff, and in some cases Transplant Center staff (i.e., confirmatory HLA typing data), complete the forms at the following time-points and submit them to the NMDP. All data submitted are abstracted from the donor's donation record maintained at the Donor Center, the Apheresis Center or marrow Collection Center. All data are collected as part of the standard donation process.

Additionally, donor cells may be tested to determine the number and types of cells, and to test for sterility and other factors important to the transplant. Data collected during these tests may also be used for research purposes.

Time-point	Data Collected
At the time the donor joins the Registry*	HLA typing Race Gender Date of birth
At the time a donor is requested for confirmatory typing*	HLA typing (submitted by transplant center) Infectious disease markers for hepatitis B and C, syphilis, HIV, CMV, HTLV I/II Weight ABO, Rh (D^U) type Allogeneic blood transfusion Number of pregnancies
At the time of the donor work-up for HC donation	Pre-existing medical conditions Infectious disease markers for hepatitis B and C, syphilis, HIV, CMV, HTLV I/II ABO, Rh (D^U) type Serum pregnancy test Screening for hemoglobin S (sickle hemoglobin)
During filgrastim injections (PBSC donors only)	Complete Blood Count Modified Toxicity Criteria
At the time of product collection*	Number and type of cells Sterility

	Other product factors related to transplant
Post HC collection Weekly until recovery One month, six month post collection Annually	Adverse events related to HC collection Ability to return to work, school, and leisure activities Complete Blood Count (at annual follow-up only) Modified Toxicity Criteria Health status

* These data are collected as part of the search and donation process and will only be included in anonymous research studies or studies that are deemed non-human subject research by the criteria included in the October 2008 OHRP Guidance titled *Research Involving Coded Private Information or Biological Specimens*, unless the donor gives consent to participate in the Research Database at the time he/she is requested to donate for a recipient. If consent is given, these data could be used in a linked research study.

4.4 Collection of Study Specific Data

In addition to the standard data collected at specified time points from recipients and donors (see Section 4.1 "Recipient Data", 4.2 "Marrow Toxic Injury Data" and Section 4.3 "Donor Data"), additional participant data may be collected as needed for a specific study. In these cases, any of the required additional data would be data that are available in the participant's medical records. Examples of additional data that may be requested for a specific study are more detailed clinical data at time of diagnosis or more detailed disease status data post-transplant. In no cases would the recipient, individual with a marrow toxic injury or donor be contacted in order to obtain additional data.

5. Collaboration with Other Registries

The CIBMTR has established collaborative relationships with the European Group for Blood and Marrow Transplant (EBMT) and EuroCord.

The EBMT, a non-profit organization based in Maastricht, The Netherlands, was established in 1974 and maintains a research database on outcomes of allogeneic and autologous transplants performed at its member centers. Like the CIBMTR, the EBMT is committed to improving the safety and efficacy of HC transplantation for both donors and recipients. To facilitate international research efforts in HC transplantation, the EBMT routinely provides data on HC transplants reported to the EBMT to the CIBMTR. Data provided by the EBMT does not include any individually identifiable data beyond birth date, location of transplant, treatment, relapse and death dates.

To evaluate cord blood transplants, the EBMT organized EuroCord, a separate European registry of cord blood recipients. The CIBMTR has an agreement with EuroCord to exchange outcomes data. The CIBMTR will provide outcomes data to EuroCord on any U.S. recipient who received a cord blood unit from a non-U.S.

NetCord cord blood bank, and EuroCord will send outcomes data to the CIBMTR on any recipient who received a cord blood unit from a U.S. cord blood bank at a non-U.S. EuroCord participating institution.

CIBMTR will share data with the United States Immunodeficiency Network (USIDNET) for inclusion in the USIDNET database for use in future research as determined by USIDNET. Only data from recipients who are enrolled in both the USIDNET database protocol and the CIBMTR Research Database protocol will be exchanged with USIDNET.

The CIBMTR may also engage in discrete studies with other registries where data from subjects in both registries will be combined for analysis. In these cases subject identifiers will be exchanged with the other registry to ensure that the cases in each registry are properly linked. An example of this type of registry is the End Stage Renal Disease (ESRD) Network. Any study that will use identifiers to match subjects in another registry with subjects in the CIBMTR Research Database will require administrative approval by the NMDP IRB Chair or designated NMDP IRB member.

6. Studies Involving Data in the Research Database

6.1. Who May Request Access to Data

The data in the Research Database are available to researchers both within the CIBMTR network and outside the network. The CIBMTR defines the policies and procedures for release of data.

6.2. How Requests Are Reviewed/Approved

Any legitimate investigator may propose observational research studies to the CIBMTR. Research Database proposals are reviewed and approved by one of the CIBMTR's scientific committees to ensure that the study is scientifically sound. If the study is scientifically sound, the NMDP IRB Chair will perform an administrative review of the study protocol to ensure that it is within the limits defined in the Research Database protocol and is covered by the participant's informed consent document for the Research Database. Studies that fall outside the limits defined the Research Database Protocol will be reviewed by the NMDP IRB. In these cases, additional consent may be required from the participant. Once the study has been approved, the NMDP and the MCW IRB are informed of new studies that are added to the overall research portfolio. A data extract plan is prepared and the data necessary to conduct the study are extracted from the Research Database into a study-specific research dataset. The data extract never includes individually identifiable data beyond treatment center and treatment, relapse and death dates.

In most cases the data analysis for a study is conducted by NMDP and CIBMTR research staff in Milwaukee or Minneapolis. Data from these analyses are shared with investigators, but always as summarized, aggregate data. On the rare occasion

where analysis will occur at an individual investigator's institution, no identifying information is released beyond a randomly generated ID number (distinct from the CIBMTR ID numbers) where CIBMTR maintains the code for the random ID number. At no time is an individual investigator given the names of participants, or the identity of the center where the participant was treated. All relevant dates pertaining to a study are replaced with calculated time interval values.

7. Participant Withdrawal from the Research Database

At any time a participant may request that his or her data no longer be made available for research purposes. The participant may make this request either directly to the NMDP or CIBMTR or through his or her corresponding center.

8. Data Confidentiality

Access to all information in the Research Database is tightly controlled with passwords and logins at multiple levels. Access to the Research Database is limited to those employees who have specific job responsibilities related to the database.

All paper forms containing participant information are filed in a locked area. Only those employees who have specific job responsibilities related to the files have access to the files.

Donors are assigned a donor identification (DID) number when they join the NMDP Registry. The DID contains no identifying information. This DID is used to track all donor information in the Research Database.

Recipients of transplant or hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection, and individuals with marrow toxic injury are assigned a unique identification number when the treatment center registers them with the Research Database. Participant first and last name, social security number (US participants only), mother's maiden name, and city, state and country are collected at the time the unique identification number is assigned to ensure that the participant has not been previously registered by another center. These identifying data are stored in a secure database that is totally separated from the Research Database. These identifying data are never included in data sets for analysis. The unique identification number contains no identifying information within it. This number is used to track all information about the participant in the Research Database.

The identity of participants in the Research Database is kept confidential at all times. Identifying information that is kept in the Research Database for recipients includes transplant date, birth date, and location of transplant. Identifying information that is kept in the research database for individuals with marrow toxic injury includes, exposure date, birth date, location of treatment. Identifying information that is kept in the research database for donors is birth date, donor center, and date and location of HC collection. Data released to investigators

outside the CIBMTR does not include identifying data such as birth date and location of treatment.

All research staff at the CIBMTR and the NMDP maintains up-to-date training in protection of human subjects. This training is received through the Collaborative IRB Training Initiative (CITI) program. This is a web-based training program offered through the University of Miami.

Additionally, systems and applications within the NMDP are certified by the Health Resources Services Administration Office of Information and Technology.

The National Marrow Donor Program® (NMDP) and
Center for International Blood and Marrow Transplant Research® (CIBMTR®)

Research Database for Hematopoietic Cell Transplantation and Cellular Therapies

Adult Allogeneic Recipient Research Consent Form

I. INVITATION AND PURPOSE

The National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR) invite you to take part in a Research Database. The NMDP/CIBMTR does research with medical data from patients who have had a transplant or other cellular therapy and donors who donate bone marrow or peripheral blood stem cells (PBSCs). The goal of this research is to find ways to make bone marrow and PBSC transplants and other cellular therapies work better.

The NMDP/CIBMTR is trying to learn more about what makes bone marrow, PBSC and cord blood transplants and other cellular therapies work well. Although the exact studies for which Research Database data may be used is not known at this time, the following are types of studies in which these data may be included. These are studies to:

- Determine how well recipients recover from their transplant or cellular therapy;
- Determine how recovery after a transplant or cellular therapy can be improved;
- Determine how access to transplant or cellular therapy for different groups of patients can be improved;
- Determine how well donors recover from the collection procedures.

II. RESEARCH DATABASE PROCEDURES

Medical data about your disease and your transplant or cellular therapy will be sent to the NMDP/CIBMTR. Your doctor will send data to the NMDP/CIBMTR before and after your transplant or cellular therapy, and once a year for the rest of your life. If you agree to take part in the Research Database, your data will be used in research studies.

Your transplant-related or cellular therapy-related data may be shared with investigators outside the NMDP/CIBMTR, but no identifying information will given to those investigators. Additionally, all research studies using these data must first be approved by a group of scientists within NMDP/CIBMTR. NMDP will also review the proposed study to make sure the research is consistent with the types of studies described above.

III. POSSIBLE RISKS AND BENEFITS TO PARTICIPATING IN THE RESEARCH DATABASE

Since taking part in this study only involves sending medical data to the NMDP/CIBMTR, there are no physical risks to you if you agree to take part in the study.

There is a small risk that an unauthorized person could find out which data are yours. Your treatment center and the NMDP/CIBMTR have procedures in place to keep your data private. No identifiable information about you will be given to the researchers, nor will it be published or presented at scientific meetings.

You will not be helped by taking part in the Research Database. However, this research may help future patients who need a transplant or cellular therapy.

IV. CONFIDENTIALITY

Your treatment center and the NMDP/CIBMTR will not intentionally tell anyone that you are taking part in the Research Database. The NMDP/CIBMTR has procedures in place so that no one outside the NMDP/CIBMTR will know which data are your data.

The NMDP/CIBMTR or the Food and Drug Administration (FDA) may ask your treatment center if they can look in your medical record. These data reviews are done from time to time to make sure that the data in the Research Database are correct. When you agree to take part in the Research Database, you agree to these reviews, which may include copying parts of your medical record.

A description of this clinical study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. (Identifier: NCT01166009)

V. REIMBURSEMENT AND COSTS

You will not be paid for taking part in the Research Database. It will not cost you anything to take part in the Research Database.

VI. VOLUNTARY PARTICIPATION IN AND WITHDRAWAL FROM THE RESEARCH DATABASE

It is up to you if you want to participate in the Research Database. If you choose not to take part in the Research Database, you will still be able to get healthcare or any other services that you have a right to receive, and you will not lose any benefits which you should receive.

If you decide to take part in the Research Database, you may change your mind at any time in the future. If you do quit, your information will not be included in any future research studies. This will not affect your relationship with your treatment center or the NMDP/CIBMTR.

VII. ALTERNATIVE TO PARTICIPATION

You may choose to not take part in the Research Database. If you choose not to take part in the Research Database you will receive your transplant or cellular therapy as scheduled, but your data will not be included in research studies.

VIII. QUESTIONS OR CONCERNS

If you have questions, concerns, or complaints about the Research Database, please contact *(Treatment Center Physician) (telephone number)* or Dr. Douglas Rizzo, Associate Scientific Director at the CIBMTR. He can be reached at 1-414-805-0700.

If you have questions or concerns about your rights as a research subject or about potential risks and injuries, please contact Roberta King, NMDP IRB Administrator at 1-800/526-7809. If you wish to contact an independent third party not connected with this study about problems, concerns, questions, information, or input, please contact a Patient Services Coordinator with Be the Match® Patient Services at 1-888/999-6743 or patientinfo@nmdp.org. You will be given a copy of this consent form for your records.

IX. RECIPIENT/SUBJECT'S STATEMENT OF CONSENT

I have read this consent form, and I have been given the opportunity to ask questions. I voluntarily agree to take part in the Research Database. My data may be used in research studies as defined in this consent form.

_____ _____

Recipient/Subject Signature *Date*

_____

Print Name of Recipient/Subject

NATIONAL MARROW DONOR PROGRAM®
INSTITUTIONAL REVIEW BOARD

CONSENT FORM APPROVAL DATE:
JULY 30, 2012

Do not sign this form after the
Expiration date of: **July 29, 2013**

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with submitting data to the Research Database have been explained to the above individual and that any questions about this information have been answered.

_____ _____

Counseling Healthcare Professional *Date*

Use of an Interpreter: Complete if the subject is not fluent in English and an interpreter was used to obtain consent.

Print name of interpreter: _____ Date: _____

Signature of interpreter: _____ Date: _____

An oral translation of this document was administered to the subject in _____ (state language) by an individual proficient in English and _____ (state language). See the attached short form addendum for documentation.