CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH®

PROTOCOL FOR COLLECTION OF PATIENT REPORTED OUTCOMES (PRO) DATA

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August 2023
Version 3.0

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1 BACKGROUND

1.1 Center for International Blood and Marrow Transplant Research (CIBMTR) Research Database

The CIBMTR is a research affiliation between the National Marrow Donor Program (NMDP) in Minneapolis, Minnesota and the Medical College of Wisconsin (MCW) in Milwaukee, Wisconsin. Established in 2004, the CIBMTR facilitates critical observational and interventional research to advance hematopoietic cell transplantation (HCT) and cellular therapy (hereafter referred together as cellular therapy) worldwide.

The basis of the CIBMTR's observational research program is its Research Database. The CIBMTR has a network of more than 400 centers worldwide that contribute detailed research data on consecutive allogeneic related and unrelated, and autologous cellular therapies. In addition, NMDP centers responsible for managing unrelated donors contribute detailed data on the donation and recovery of unrelated donors. These data are used in observational research studies aimed at improving the safety and effectiveness of cellular therapies for both donors and recipients and understanding the applications for cellular therapies and their associated patient outcomes.

Data from patient and donor healthcare records are submitted to the Research Database by staff at treatment and donor management centers. Data submission to the Research Database as well as data maintenance and protection and access to data by researchers are all activities governed by the CIBMTR multi-institutional research protocol titled *Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries* (NCT01166009, hereafter *CIBMTR Research Database Protocol*).

Recognizing the growing importance of patient reported outcomes (PRO) in assessing and predicting patient and donor outcomes and quality of life after a cellular therapy, the CIBMTR developed this *Protocol for Collection of Patient Reported Outcomes Data* (hereafter *CIBMTR PRO Protocol)* to supplement traditional outcomes, such as survival or disease relapse, in registration and other studies. By centralizing PRO data collection with this protocol, the CIBMTR increases the amount and breadth of outcomes data, without increasing burden on centers.

This protocol, is a CIBMTR single institution protocol that describes the collection of PRO data from patients, caregivers, donors and/or other individuals involved in the cellular therapy process. The protocol is overseen by the NMDP IRB. All PRO data collected through this single institution protocol are entered into the Research Database. Once PRO data enter the Research Database, their maintenance, protection and access by researchers are governed by the multi-institutional *CIBMTR Research Database Protocol.*

1.2 Patient Reported Outcomes (PRO) Research

PROs are defined by the FDA as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." Participant (including patients, donors, caregivers and others) reported outcomes (collectively referred to in this protocol as PRO) are collected from subjects and include quality of life (QOL), biologic and physiologic variables, symptom status, functional status and general health perceptions.

CIBMTR has substantial experience collecting patient reported outcomes centrally and combining these with clinical outcomes data to inform HCT outcomes. In 2018 the CIBMTR launched the Electronic Patient Reported Outcomes (ePRO) system to systematically collect centralized PRO data from a broader group of patients. In addition to collecting PROs, the system is used to electronically obtain and document consent.

2 PRO DATA COLLECTION METHODS

The CIBMTR may utilize multiple modes to collect PRO data, including electronic, pen-and-paper, or phone. Participants can choose the mode of data collection that best suits their needs. Participants can complete surveys in any language relevant to the study.

2.1 Standard PRO Data Collection from Patients

The CIBMTR will collect longitudinal or cross-sectional PRO data from recipients of cellular therapies who are also enrolled in the *CIBMTR Research Database Protocol.* The standard time points for PRO data collection are selected to parallel the time points at which treatment centers submit clinical outcomes data from healthcare records, and to ensure adequate detection of change in patient status. These standard time points are as follows:

- Baseline – at a time prior to treatment
- 30 day (for cellular therapy patients)
- 100 day
- 180 day
- 1 year
- Annually thereafter throughout the patient's life for as long as consent is active.

Additional timepoints may be determined for cross-sectional research, or for PRO collection in specific planned subsets of the patients enrolled.

2.2 Instruments Used for Standard PRO Data Collection

Instruments in the NIH *Patient Reported Outcomes Measurement Information System (PROMIS)* will form the backbone of PRO data collected by the CIBMTR. The PROMIS measures capture patient-reported health status using a set of valid, generic, and adaptable assessment tools. PROMIS consists of many item banks covering specific domains that can be combined to form multi-domain measures of varying length and complexity. Forms and

item banks are available for adults, children, and parent-proxy reporting in multiple languages.

The following list of topics represents examples of the standard PRO data that CIBMTR will collect from cellular therapy recipients. Not every topic will be included in each PRO time point or in questionnaires for all patient groups. The specific instruments used to collect these data may vary due to recipient age or other characteristics or as new versions of the measures become available. The exact measures used for standard PRO data collection may change over time as data collection needs evolve with changes in disease indications for cellular therapies, prognostic factors, amongst other reasons. Researchers and interested parties can view a current list of PRO measures used in standard data collection on the CIBMTR website. PRO questionnaires will take approximately 15-25 minutes to complete at each time point.

- Physical Function
- Fatigue
- Sleep disturbance
- Pain interference
- Anxiety
- Depression
- Cognitive function
- Social function
- Sexual function and satisfaction
- Clinical late effects and health behaviors
- Financial toxicity
- Work and school functioning
- Sociodemographics and social determinants of health

2.3 Additional PRO Data Collection

The CIBMTR may engage in additional PRO data collection beyond the standard set of data described in sections 2.1 and 2.2 of this protocol. Individuals invited to participate in additional PRO data collection activities may include patients, donors, caregivers, family members, healthcare providers, or other individuals who have a relationship to cellular therapy. These additional PRO data collection activities may be cross-sectional or longitudinal but will be linked to a specific study that falls within the scope of this protocol but requires data outside the standard PRO dataset, or from individuals not included in the standard PRO data collection.

Requests for additional PRO data collection may come from CIBMTR or external researchers. Additional PRO data collection may be added to the standard PRO survey for select patient groups or time periods, or may be separate surveys. All additional PRO data will be added to the CIBMTR Research Database, and subsequently accessed for analyses through standard CIBMTR channels as governed by the *CIBMTR Research Database Protocol*. The CIBMTR will submit instruments, consent forms and other patient-facing

materials for additional PRO Data Collection to the NMDP IRB for approval as appropriate.

The *CIBMTR PRO Protocol* team will assess each request to determine how additional PRO data collection will be managed. This includes, but is not limited to, the following examples:

- Adds domains or time points to the standard PRO survey - when the overall length and domain area is within the bounds of standard PRO collection. This would not require any changes to the *CIBMTR PRO Protocol* or existing ICFs.
- Adds an 'ancillary' study to the *CIBMTR PRO Protocol* - when separate survey content (either broader in scope or timing) is added but which will be included in and governed by the *CIBMTR Research Database Protocol*. This would require separate or amended ICFs, but no changes to the *CIBMTR PRO Protocol.*
- Structured as a separate standalone protocol – when the additional PRO data will not (automatically) be available in the *CIBMTR Research Database Protocol*, or the requesting researcher has research aims outside the scope of the *CIBMTR Research Database Protocol.* This will require a separate protocol and ICF and will not be collected under this protocol. Consideration can be given to co-enrollment and/or merging the PRO data into the *CIBMTR Research Database Protocol* after the primary study is complete (with opt-in or opt-out consent to the *CIBMTR PRO Protocol* included on the informed consent forms).

2.4 Safety Mechanisms

PRO data are not monitored in real time as they are registry level data. PRO instruments include a disclaimer to patients that their responses are not monitored and that they should contact their healthcare providers if they are distressed or experiencing acute symptoms or other medical issues.
To minimize distress caused by completing a PRO instrument, patients may skip any question that makes them uncomfortable. This is clearly stated on the consent forms and all PRO instruments.

3 ELIGIBILITY TO PARTICIPATE IN PRO DATA COLLECTION

3.1 Participant Eligibility Criteria

Any person who is scheduled to or has received cellular therapy and consents to the *CIBMTR Research Database Protocol* is eligible to participate in PRO data collection as long as that individual is able to provide consent and complete PRO instruments in the languages available. Participants in standard or additional PRO collection may include but are not limited to cellular therapy patients, caregivers, other family members and donors. Adults without decision-making capacity are eligible to participate when a proxy adult is able to complete PRO instruments. Children are eligible to participate when instruments are validated for their age group, or when a parent proxy is able to complete parent proxy instruments.

Participants may consent to the *CIBMTR PRO Protocol* and complete PRO surveys prior to consenting for the *CIBMTR Research Database Protocol*. However, if they do not subsequently consent to the *CIBMTR Research Database Protocol*, a participant's PRO data cannot be used. If a patient consents to the *CIBMTR PRO Protocol* and later declines consent or is not approached for the *CIBMTR Research Database Protocol*, they will be coded as a Screen Fail for the *CIBMTR PRO Protocol*, the protocol team will cease contacting them for PRO collection, and any already-collected PRO data will treated similarly to all other non-consented data in the CIBMTR Research Database.

3.2 Participant Recruitment

Patients who are scheduling or have received cellular therapy will be recruited through their participation in the *CIBMTR Research Database Protocol.* The consent form for the *CIBMTR Research Database Protocol* includes an option to agree to be contacted for future research.

Participants may also be recruited through other protocols they are participating in, as an optional study on the protocol consent form, or through other avenues such as NMDP/Be The Match patient services.

3.3 Subject Status and Classification

The following subject classifications will be used for this protocol.

Prior to or without *CIBMTR PRO Protocol* consent:

- Recruited: A subject who is being evaluated and actively recruited for study participation.
- Ineligible: A subject who has been evaluated for study participation but does not meet eligibility criteria and is not approached for the *CIBMTR PRO Protocol*.
- Passive Decline: A subject who has been evaluated and actively recruited for study participation but did not sign the ICF after initial contact.
- Unable to Contact (UTC): A subject who has been evaluated and actively recruited for study participation, but were unable to be contacted.
- Declined: A subject who has been evaluated and recruited for study participation, but actively declined participation.

After *CIBMTR PRO Protocol* consent:

- Consented: A subject who signs the Informed Consent Form, meets eligibility criteria but has not yet received a cellular therapy or been presented with the *CIBMTR Research Database Protocol* consent form.
- Screen Failure: A subject who signs the Informed Consent Form, and may have completed PRO surveys, but is not eligible for the protocol, for example due to not signing the *CIBMTR Research Database Protocol* consent form.

- Enrolled: A subject who signs the Informed Consent Form, meets eligibility criteria, and has consented to the *CIBMTR Research Database Protocol*.
- Withdrawn: A subject who was enrolled in the study and subsequently met a criterion for discontinuation from the study or has actively withdrawn from ongoing PRO surveys.
- Deceased: A subject who has enrolled in the study and subsequently passed away.

3.4 Informed Consent

Informed consent for PRO data collection will be obtained by CIBMTR staff who are trained on this protocol. Informed consent may be obtained on paper forms, electronic forms, or verbally over the phone. Informed consent is documented electronically through the ePRO system. If consent is obtained on paper, the original paper form is retained in PRO Protocol study files as a PDF certified copy. CIBMTR is responsible for maintaining documentation of informed consent and, where applicable, the minor assent decision.

Provisions for minor assent include the following:

- The minor may participate in the PRO data collection if the minor and parent or legal guardian agree to the minor's participation. If either the parent or 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.
- Minor patients will be re-consented by the CIBMTR when they reach age of majority.

4 PARTICIPANT WITHDRAWAL

4.1 Withdrawal from PRO Data Collection

At any time, a participant may withdraw from PRO data collection. The participant may make this request by contacting the CIBMTR directly, by requesting the treatment center contact the CIBMTR, or through other methods. A participant's spouse or caregiver, or another proxy, may also withdraw the participant from continued PRO data collection when the participant is ill or otherwise unable to withdraw on their own. Upon withdrawal from PRO data collection, the CIBMTR will cease further contact for PRO collection.

At any time, a participant may request that their previously collected PRO data no longer be made available for research purposes. The participant may make this request directly to the CIBMTR by any method or through his or her corresponding treatment center. PRO data for participants who withdraw from the database will not be available for future

research studies but will be retained in the database if their records were used in prior research studies.

5 DATA PRIVACY AND PATIENT COFIDENTIALITY

5.1 Participant Contact Information

As part of their participation in PRO data collection, participants provide identifying information to CIBMTR, including but not limited to first and last name, mailing and email addresses, and phone numbers, so that they can be directly contacted. These identifying data are stored within the ePRO system in tables with encryption and secured limited access. These data will be accessible by CIBMTR staff members who are responsible for contacting participants for PRO data collection and limited IT staff responsible for maintaining the ePRO system. When identifying data are provided to CIBMTR through a patient's treatment center, these identifying data will remain accessible to the treatment center, including updates to the identifying information. These identifying data are only used for the purpose of contacting participants for PRO data collection and for no other purpose; the identity of participants in this protocol is kept confidential and secure at all times.

5.2 Data Confidentiality and Protection

Participants not already assigned a unique identification number through the CIBMTR Research Database are assigned one when they are invited to PRO data collection. If participants later receive a unique CIBMTR Research Database identification number, it will be applied to their record in the ePRO system. The unique identification number contains no identifying information within it. This number is used to track all information about the participant in the ePRO system and the CIBMTR Research Database.

All PRO data are stored in the CIBMTR Research database. The database is tightly controlled with passwords and logins at multiple levels. Access to the CIBMTR Research Database is limited to those employees who have specific job responsibilities related to the database.

If a patient does not consent, or revokes consent, to the *CIBMTR Research Database Protocol* their PRO data will not be available for future observational research studies of the CIBMTR Research Database. Instead, their PRO data may be used for studies the patient specifically consents to, or for internal process improvement or evaluation analyses within the CIBMTR.

All paper forms containing participant data, including completed surveys and consent forms, are filed in a locked area. Only those employees who have specific job responsibilities related to the files have access to the files.

This *CIBMTR PRO Protocol* is covered by a National Institutes of Health Certificate of Confidentiality (CoC) The CoC protects identifiable research information from forced

disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

All research staff at the CIBMTR whether at MCW or NMDP, maintain 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 Biomedical Research Alliance of New York (BRANY).

Additionally, NMDP and MCW maintain appropriate technical and organizational measures for the adequate protection of the security and privacy of its systems and data. These protections comply with the United States National Institute of Standards and Technology, Security Controls for Federal Information Systems (NIST 800-53), and all other applicable security and data privacy requirements. These safeguards are audited annually by a qualified independent auditor; results are reported to CIBMTR management for timely resolution.

5.3 Sharing Data with Participants

The CIBMTR may provide individual PRO data back to participants, their center or others related to participants' care. The PRO Research Informed Consent Form (ICF) includes an option for participants to agree to or decline receiving their individualized data or sharing with others, who may include but are not limited to their treatment center, their individual medical providers, caregivers, or family. An individual PRO data report may include language drafted by the CIBMTR and NMDP operations that supports interpretation of PRO scores or data and provides recommendations for specific follow-up with the participant's providers.

5.4 Sharing Data with Centers and Researchers

Access to and use of data collected under this *CIBMTR PRO Protocol* for research is governed by and described in the *CIBMTR Research Database Protocol.*

PRO data collected through this protocol is available for center use in the CIBMTR Data Back to Centers (DBtC) portal. Centers will have access to PRO data from individual and groups of patients from their center and who have provided consent to share individual data with their cellular therapy providers.

APPENDIX A. SAMPLE PRO QUESTIONS

The PRO instruments that CIBMTR collects from HCT and other cellular therapy recipients will vary by recipient age and other characteristics and may change as new questionnaire versions become available. When possible, the CIBMTR will collect PROs via Computer Adaptive Test (CAT) in which after an initial question determines an estimated score, a CAT algorithm selects the best subsequent question to ask to refine the score. This process continues until either a score with specified precision is calculated or a maximum number of questions are asked.

Because individual PRO questionnaires will vary by patient, presented here are example questions for adult patients in each domain in the standard PRO data collection.

Physical function

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
Are you able to run errands and shop?	☐	☐	☐	☐	☐

Fatigue

	Not at all	A little bit	Somewhat	Quite a bit	Very much
During the past 7 days…					
I feel fatigued	☐	☐	☐	☐	☐
I have trouble starting things because I am tired	☐	☐	☐	☐	☐
In the past 7 days…					
How run-down did you feel on average?	☐	☐	☐	☐	☐
How fatigued were you on average?	☐	☐	☐	☐	☐

Sleep disturbance

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
My sleep was refreshing	☐	☐	☐	☐	☐
I had a problem with my sleep	☐	☐	☐	☐	☐
I had difficulty falling asleep	☐	☐	☐	☐	☐

Pain interference

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How much did pain interfere with your day to day activities?	☐	☐	☐	☐	☐
How much did pain interfere with work around the home?	☐	☐	☐	☐	☐
How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
How much did pain interfere with your household chores?	☐	☐	☐	☐	☐

Anxiety

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
My worries overwhelmed me	☐	☐	☐	☐	☐
I felt uneasy	☐	☐	☐	☐	☐

Depression

	Never	Rarely	Sometimes	Often	Always

In the past 7 days…					
I felt worthless	☐	☐	☐	☐	☐
I felt helpless	☐	☐	☐	☐	☐
I felt depressed	☐	☐	☐	☐	☐
I felt hopeless	☐	☐	☐	☐	☐

Cognitive function

In the past 7 days…	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Always (Several times a day)
My thinking has been slow	☐	☐	☐	☐	☐
It has seemed like my brain was not working as well as usual	☐	☐	☐	☐	☐
I have had to work harder than usual to keep track of what I was doing	☐	☐	☐	☐	☐
I have had trouble shifting back and forth between different activities that require thinking	☐	☐	☐	☐	☐

Ability to Participate in Social Roles and Activities

	Never	Rarely	Sometimes	Usually	Always
I have trouble doing all of my regular leisure activities with others	☐	☐	☐	☐	☐
I have trouble doing all of the family activities that I want to do	☐	☐	☐	☐	☐
I have trouble doing all of my usual work (including work at home)	☐	☐	☐	☐	☐
I have trouble doing all of the activities with friends that I want to do	☐	☐	☐	☐	☐

Sexual function and satisfaction

In the past 30 days, how interested have you been in sexual activity	Not at all ☐	A little bit ☐	Somewhat ☐	Quite a bit ☐	Very ☐
In the past 30 days, how often have you felt like you wanted to have sexual activity?	Never ☐	Rarely ☐	Sometimes ☐	Often ☐	Always ☐
In the past 30 days, how satisfied have you been with your sex life?	Not at all ☐	A little bit ☐	Somewhat ☐	Quite a bit ☐	Very ☐
In the past 30 days, how much pleasure has your sex life given you?	None ☐	A little bit ☐	Some ☐	Quite a bit ☐	A lot ☐

Financial toxicity

	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	☐	☐	☐	☐	☐
My out-of-pocket medical expenses are more than I thought they would be	☐	☐	☐	☐	☐
I worry about the financial problems I will have in the future as a result of my illness or treatment	☐	☐	☐	☐	☐
I feel I have no choice about the amount of money I spend on care	☐	☐	☐	☐	☐

Work and school functioning

Have you attempted to work/go to school but found that you weren't able to?	Yes ☐	No ☐		
Is your work/school work as important to you now as it was before your diagnosis?	More important ☐	About the same importance ☐	Less important ☐	
Have you changed your goals concerning your work/education as a result of your diagnosis?	My goals haven't changed ☐	My goals have changed slightly ☐	My goals have changed quite a bit ☐	My goals have changed completely ☐

Sociodemographics

In which U.S. state do you currently live?					
What is your marital status?	Single, never married ☐	Married or living with a partner ☐	Separated ☐	Divorced ☐	Widowed ☐
What is the highest grade or level of education you have achieved?	Less than 6th grade ☐	6th - 8th grade ☐	9th - 12th grade (no diploma) ☐	High school graduate or equivalent (GED) ☐	
	Some college, no degree ☐	Vocational or Associate's degree ☐	Bachelor's degree ☐	Higher than Bachelor's degree ☐	