BMT CTN Technical Document

Patient-Reported Outcomes Data

1.0 Introduction

Patient-Reported Outcomes (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 document as PRO) are collected from subjects and include quality of life (QOL), biologic and physiologic variables, symptom status, functional and financial status and general health perceptions. PROs have been shown in cancer patients to improve engagement and facilitate patient-physician discussion. In addition, studies have demonstrated that PROs add value in determining HCT outcomes, including survival and QOL, and that QOL post-HCT or post-cellular therapy can be accurately assessed by PROs, and groups at risk for poor QOL can be identified.

BMT CTN has a PRO Working Group whose members are available to help write, review, and approve sections relevant to PROs in all draft protocols, lending expertise in PRO instrument selection, assessment, monitoring and analysis. If an existing protocol team member already fulfills that role (ideally, having joint clinical and PRO expertise) they will be invited to be part of the PRO Working Group and access knowledge and expertise for those areas in which they are not expert. If a protocol team member cannot fulfill this role, a member of the Working Group will be assigned to the protocol and participate on team calls as needed. This protocol team member ensures that appropriate considerations relevant to PROs are addressed in the protocol, informed consent form, analysis plan, and monitoring documents. In addition, they are responsible for tracking the PRO specific accrual and completeness throughout the duration of the study. If issues are identified, they will raise concerns and lead corrective efforts.

BMT CTN has substantial experience collecting PROs centrally and combining these with clinical outcomes data to inform clinical trial 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 contributing data to the registry, and to collect PROs from participants in some BMT CTN clinical trials. In addition to collecting PROs, the system is used to collect and document centralized electronic consent. BMT CTN will continue to utilize the CIBMTR ePRO system to collect PRO data for future clinical studies. After a subject has completed the BMT CTN study period, they will remain in the CIBMTR ePRO system for continued data capture to allow long-term follow-up studies of QOL.

1.1. Data Collection Methods

PRO data are collected in multiple modes, including electronic, pen-and-paper and phone. The BMT CTN protocol team in conjunction with the BMT CTN PRO Working Group will determine the appropriate mode of data collection based on patient needs and feasibility with the specific PRO domains to be collected in each protocol.

Time points: The time points selected for an individual BMT CTN study will be guided by the PRO hypotheses to be answered. It is important to avoid survey fatigue by carefully evaluating any request for additional PROs. Survey fatigue can lead to undue participant burden and poor response rates, compromising the study end points.

Instruments: BMT CTN has agreed that it will use PROMIS measures as the ‘backbone’ of survey instruments for its clinical trials in order to harmonize with CIBMTR data collection and other broader efforts. PROMIS survey may be supplemented by any other appropriate instrument specific to the study and these can be accommodated within the ePRO system.

1.1.1 Standard PRO Data Collection from Patients

The CIBMTR also collects longitudinal or cross-sectional PRO data from a subset of recipients of HCT and other cellular therapies who are also enrolled in the *Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries* (CIBMTR PRO protocol). The time points for PRO data collection parallel the time points at which treatment centers submit clinical outcomes data from healthcare records. These time points are as follows:

- Baseline – within 4 weeks prior to treatment
- 30 day (Cellular therapy patients only)
- 100 day
- 180 day
- 1 year
- Annually thereafter throughout the patient's life for as long as consent is active.

These are standard timepoints with the goal of a minimum schedule of assessments. The needs of a specific study take precedence over routine PRO data collection. Instead of creating trial-specific PROs, a protocol team may choose to co-enroll patients in the CIBMTR PRO Protocol. If a trial's aims require additional PRO topics or timepoints that are not covered by standard PRO data collection, they can be added to the PRO data collection schedule for the study participants but aligning the trial requirements within this schedule will minimize burden to patients and the system. Visit https://www.cibmtr.org/DataManagement/ProtocolConsent/PatientReportedOutcomes/Pages/index.aspx for more information abut the CIBMTR PRO protocol. If the CIBMTR PRO protocol is going to be used, discussion should happen early and involve the CIBMTR PRO data collection team: PRO-surveys@nmdp.org.

Instruments in the NIH *Patient Reported Outcomes Measurement Information System (PROMIS)* will form the backbone of PRO data collected for CIBMTR and BMT CTN studies. 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; and they are available in multiple languages.

- PROMIS Measures
    - Physical Function
    - Fatigue
    - Sleep disturbance
    - Pain interference
    - Anxiety
    - Depression
    - Cognitive functioning
    - Social functioning
    - Sexual health and functioning
- Late effects and health behaviors
- Financial toxicity (COST-FACIT measure)
- Work and school functioning
- Sociodemographics

1.2. Guidelines for Inclusion of PROs in BMT CTN Protocols

When developing a protocol, the following guidelines for including PRO elements are provided for guidance.

a) Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method of obtaining the PRO subsample.

b) Specify the PRO concepts/domain used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time of event) and the principal time point or period of interest.

c) When pediatric subjects are eligible for PRO collection, specify if concepts/domains are available in pediatric self-report or proxy-report versions, and which age groups will use those versions. Specify if subjects will switch from pediatric to adult domains/concepts when they move to different age groups over the course of study.

d) Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.

e) When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.

f) Justify the PRO instruments to be used and describe domains, number of items, recall period, and instruments scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.

g) Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).

h) Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.

i) Specify PRO data collection and management strategies for minimizing avoidable missing data.

j) Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.

k) State PRO analysis methods, including any plans for addressing multiplicity/type 1 (a) error.

l) State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).

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