Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

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November 2023	1.0	Initial Version

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Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

Guidance for Industry
Technical Specifications Document[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

1.0 INTRODUCTION

1.1. Purpose

This document provides technical specifications for submitting patient-reported outcome (PRO) data collected in cancer clinical trials to support a marketing application for a medical product in oncology, where a PRO is a type of clinical outcome assessment (COA) used to collect patient experience data.[2] The FDA Patient-Focused Drug Development (PFDD) Glossary defines a PRO as a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else, where a PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response.[3] This technical specifications document supplements FDA's draft guidance for industry *Core Patient-Reported Outcomes in Cancer Clinical Trials* (June 2021)[4] and the PFDD Guidance series.[5]

[1] This guidance has been prepared by the Office of Biostatistics in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at https://www.regulations.gov/docket?D=FDA-2018-D-1216) (see the instructions for submitting comments in the docket).
[2] 21st Century Cures Act section 3001. More information on patient experience data within section 3001 is available at: https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.
[3] More information is available at FDA's PFDD Glossary web page: https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary and at the FDA-NIH BEST web page: https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.patientreported-outcome/.
[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] More information is available at FDA's PFDD Guidance web page: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

1.2. Scope

This document provides specifications for the submission of Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets and specifications for recommended tables and figures. These technical specifications aim to provide general guidelines for (1) standardized dataset content and structure and (2) recommended tables and figures to facilitate FDA review of the marketing application that the submitted data and analysis outputs are intended to support. The SDTM and ADaM specifications outlined in section 3.0 Overview of Dataset Specifications are not prescriptive and do not include an exhaustive list of all datasets, variables, and controlled terminologies to be submitted for FDA review. Further, the recommended tables and figures do not comprise all information needed to support FDA review of a marketing application. The dataset specifications and specifications for tables and figures are pursuant to discussions with FDA and may vary by clinical drug development program and clinical trial therein. These specifications are intended to be applicable to any PRO data used to inform the evaluation of (1) safety and tolerability or (2) clinical benefit in randomized studies (i.e., improvement in disease symptoms) within a cancer clinical trial.

This document does not pertain to submissions needed to support FDA review of the PRO measure itself or the proposed interpretation and use of scores generated by the PRO measure within the context of a specific clinical trial. Agreement on the PRO measure(s) used to collect study data and analyses of the resulting PRO data should be discussed with FDA as early as possible in a medical product development program, for example, prior to trial initiation. Sponsors are strongly encouraged to use the resources described in section 1.3 Relationships to Other Documents and to seek Agency input for confirmation and clarification as needed. Sponsors should consult with the Agency to determine which requested displays defined in section 4.0 Specifications for Tables and Figures apply to the PRO measure used within the marketing application. Lastly, although this guidance focuses on PRO measures, some of these recommendations may be relevant to other COAs (i.e., clinician-reported, observer-reported, and performance outcome measures) in cancer clinical trials.

1.3. Relationship to Other Documents

These technical specifications have been drafted in accordance with the business rules and assumptions outlined in the CDISC SDTM,[6] the SDTM Implementation Guide (SDTMIG),[7] the ADaM[8], and the ADaM Implementation Guide (ADaMIG). As new versions of the models and implementation guides become available, these technical specifications may be updated accordingly to maintain alignment. In addition, the FDA Study Data Technical Conformance Guide (sdTCG)[9] provides general specifications and recommendations for submitting datasets

[6] More information is available at CDISC's SDTM web page: https://cdisc.org/standards/foundational/sdtm.
[7] More information is available at CDISC's SDTMIG web page: https://cdisc.org/standards/foundational/sdtmig.
[8] More information is available at CDISC's ADaM web page: https://cdisc.org/standards/foundational/adam.
[9] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

using the SDTM and ADaM standards. Sponsors should review the FDA Data Standards Catalog[10] to ensure data submissions follow FDA-supported standards.

In addition, sponsors should reference the following:

- Draft guidance for industry *Core Patient-Reported Outcomes in Cancer Clinical Trials* (June 2021)[11]
- FDA PFDD Guidance series[12]
- Guidance for industry *E9(R1) Statistical Principles for Clinical Trials Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021)
- CDISC Controlled Terminology[13]
- CDISC Questionnaires, Ratings and Scales (QRS) Supplements and CDISC QRS Resources, which includes QRS Naming and Business Rules[14]

2.0 RELEVANT ACRONYMS

Abbreviation	Description
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADRG	Analysis Data Reviewer's Guide
AE	Adverse Event
BEST	Biomarkers, EndpointS, and other Tools
BDS	Basic Data Structure
CAT	Computerized Adaptive Testing
CDISC	Clinical Data Interchange Standards Consortium
CDER	Center for Drug Evaluation and Research
COA	Clinical Outcome Assessment
CRF	Case Report Form
cSDRG	Clinical Study Data Reviewer's Guide
CSR	Clinical Study Report
FDA	Food and Drug Administration
INV	Investigator
IRC	Independent Review Committee
NCI EVS	National Cancer Institute Enterprise Vocabulary Services
NIH	National Institutes of Health

[10] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[11] When final, this guidance will represent the FDA's current thinking on this topic.
[12] More information is available at FDA's PFDD Guidance series web page: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.
[13] More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.
[14] More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.

Abbreviation	Description
PFDD	Patient-Focused Drug Development
PRO	Patient-Reported Outcome
QRS	Questionnaires, Ratings and Scales
SAP	Statistical Analysis Plan
sdTCG	Study Data Technical Conformance Guide
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SISAQOL	Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints

3.0 OVERVIEW OF DATASET SPECIFICATIONS

Dataset specifications detail the CDISC datasets that are used to support PRO data tabulation and analyses in cancer clinical trials. Sponsors should implement the CDISC SDTM standard when submitting clinical tabulation data and the CDISC ADaM standard when submitting analysis data. This section supplements existing guidance by providing specifications for submitting PRO data collected in cancer clinical trials but does not cover all data to be submitted for a clinical trial. As documented in the FDA sdTCG,[15] both SDTM and ADaM datasets should be accompanied by informative metadata provided in a compliant data definition file (i.e., Define-XML) and are expected to be accompanied by a Clinical Study Data Reviewer's Guide (cSDRG) and an Analysis Data Reviewer's Guide (ADRG), respectively. Standard CDISC Controlled Terminology[16] developed and maintained by CDISC, and National Cancer Institute Enterprise Vocabulary Services (NCI EVS) should be used where applicable, and codelists may be extensible by adding controlled terminology that is not previously defined. Sponsor-extended codelists and use of alternate (e.g., non-CDISC or sponsor-defined) terminologies should be indicated in the study metadata (e.g., Define-XML file, cSDRG). In addition, software programs used to create ADaM datasets and analyze PRO data should be submitted with the marketing application for FDA review.

3.1 SDTM Specifications

This section details the SDTM specifications for (1) PRO data submitted within the Questionnaires (QS) dataset and (2) the Trial Summary (TS) dataset.

3.1.1 *Questionnaires Dataset*

PRO data should be tabulated using the SDTM QS domain specifications. For select measures, CDISC publishes QRS Supplements[17] that provide guidance on representing named COA measures in the SDTM. CDISC also provides submission values within the controlled terminology related to named COA measures. These resources should be consulted for guidance on a PRO measure, in addition to the guidance provided in the SDTM and SDTMIG.

[15] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[16] More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.
[17] More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.

3.1.1.1 General Considerations

The QS dataset tabulates the PRO data as collected for individual patients at distinct assessment timepoints. The subset of standard QS variables in Table 1 is included to clarify how variables should be completed for PRO measures used in oncology studies to foster consistency and standardization across industry. An example QS dataset is provided in Appendix 5.1.

Table 1. Specifications for a Subset of QS Variables

Variable Name	Variable Label	Type	Comments
QSCAT	Category of Question	Char	The measure name and version number should be provided within QSCAT. Controlled Terminology should be implemented if applicable; if not, QSCAT should be constructed according to CDISC QRS Naming and Business Rules. The most common name that the measure is known by should be used, which can either be the complete name of the measure or an acronym.
QSTESTCD	Question Short Name	Char	A topic variable for QS and short name for the value in QSTEST. Controlled Terminology should be implemented if applicable; if not, construct according to CDISC QRS Naming and Business Rules. QSTESTCD should begin with a short code for the PRO measure followed by the item number (e.g., ABC01). In the case where item numbers are absent, sequential numbers starting with 01 should be used and can be shortened to 1 to accommodate the eight-character limit for values of QSTESTCD.
QSTEST	Question Name	Char	This is the name of the item or, if applicable, the *source data summary score*[18] used to obtain the measurement or finding. QSTEST should start with a short code for the measure followed by a hyphen and a brief description. Controlled Terminology should be implemented if applicable; if not, construct according to CDISC QRS Naming and Business Rules. If QSTEST is > 40 characters in length, put meaningful text in QSTEST and describe the full-text in the study metadata (e.g., the annotated Case Report Form (CRF), the cSDRG, or the Define-XML). For each patient and assessment timepoint where the PRO measure is planned to be administered per the protocol-defined schedule of assessments, a record should be provided for each item or source data summary score within the measure, including records for measures not administered to the patient (See section 3.1.1.2 Handling of Missing PRO Data and section 3.1.1.3 Handling of PRO Data Not Collected due to Skip Logic or Computerized Adaptive Testing).
QSSTAT	Completion Status	Char	This is populated as 'NOT DONE' when an item score (response) or source data summary score is empty/null. QSSTAT is empty/null if a value exists in QSORRES.
QSREASND	Reason Not Performed	Char	This is used in conjunction with QSSTAT when QSSTAT = 'NOT DONE' to describe why an item score or source data summary score is empty/null (See section 3.1.1.2 Handling of Missing PRO Data and section 3.1.1.3 Handling of PRO Data Not Collected due to Skip Logic or Computerized Adaptive Testing).

[18] S*ource data summary scores* are summary scores (e.g., total scores, subscale scores) that are source data (e.g., data reported within a CRF) and are submitted in the QS dataset.

Additional Considerations:

Additional source data captured should be submitted either as additional rows with relevant QSTEST and QSTESTCD values within the QS dataset or within a Supplemental Questionnaires (SUPPQS) dataset. Additional content is dependent on the PRO measure administered, and if needed for analysis, should be copied into the applicable ADaM dataset. Example content captured within SUPPQS for each patient and assessment timepoint includes:

- **Data Collection Mode:** The mode of data collection used in the administration of the PRO measure, if differing from the protocol and/or varying across patients, assessment timepoints, or sites (e.g., clinical trial site, home). Examples of data collection mode may include paper-based administration, handheld electronic device, computer web-based application, or telephone-based administration.

- **Data Collector:** In cases where the measure is not self-administered (i.e., not independently completed by the patient without any assistance), the individual administering the PRO measure to the patient (e.g., caregiver, study staff member) by reading items to the patient and/or recording the patient's responses.

- **Language:** The language in which the measure was administered to the patient.

3.1.1.2 Handling of Missing PRO Data

Understanding the reasons for and prevalence of missing PRO data are critical to support FDA review and regulatory decision-making. Missing PRO data should be represented within the QS dataset with the reason for missingness captured under 'Reason Not Performed' (QSREASND). The QS dataset should include one record per item per PRO measure per patient per assessment timepoint, regardless of whether an item response is missing. When applicable, the QS dataset should also include one row per source data summary score per PRO measure per patient per assessment timepoint, regardless of whether the source data summary score is missing. Table 2 provides scenario-specific recommendations for displaying PRO data that are missing at a planned (i.e., per protocol) assessment timepoint. Appendix 5.1 demonstrates scenarios for representing missing data within the QS dataset. CDISC QRS Supplements[19] provide additional guidance on modeling missing data for named COA measures in SDTM datasets, including the modeling of timing variables.

Table 2. Recommended QS Representation of Missing PRO Data

Scenario	Recommended Representation in QS Dataset
The patient did not respond to an item administered within a PRO measure.	The row for the missing item response should include: • QSSTAT = 'NOT DONE' • QSREASND contains the reason the patient did not respond if known/collected. Otherwise, QSREASND is empty/null.
A source data summary score cannot be calculated per the scoring algorithm based on the available item	The row for the missing source data summary score should include: • QSSTAT = 'NOT DONE'

[19] More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.

Scenario	Recommended Representation in QS Dataset
responses (e.g., due to insufficient item response data).	• QSREASND is populated if known/collected (e.g., QSREASND = 'NOT CALCULABLE'). Otherwise, QSREASND is empty/null.
The patient was not administered the PRO measure either at an onsite visit attended by the patient or at a planned (per protocol) offsite PRO assessment timepoint.	The row for each missing item response and source data summary score within the measure should include: • QSSTAT = 'NOT DONE' • QSREASND contains the reason the measure was not administered if known/collected. Examples include, but are not limited to, patient was physically unable to complete the PRO measure due to adverse event, patient refusal, patient did not provide, study site failed to administer or other site staff error, or technological problems with a PRO administered electronically.
The patient did not attend an onsite visit and the PRO measure is only administered onsite.	The row for each missing item response and source data summary score within the measure should include: • QSSTAT = 'NOT DONE' • QSREASND contains the reason the patient did not attend the visit if known/collected. Examples include, but are not limited to, patient was unable to attend a scheduled trial visit due to hospitalization.

3.1.1.3 Handling of PRO Data Not Collected due to Use of Skip Logic or Computerized Adaptive Testing

Separate from missing data, PRO data may not be collected from the patient due to the use of skip logic or computerized adaptive testing to administer PRO items. When implemented, skip logic may be created based on the response to certain items. When the patient is not administered an item within a PRO measure due to the use of skip logic, the representation in the QS dataset should follow the guidance provided in the sdTCG.

Computerized adaptive testing (CAT) refers to a sequential form of individual testing administered by a computer in which successive items in the measure are selected for administration based primarily on the item's psychometric properties and content in relation to the patient's responses to previous items.[20] When the patient was not administered an item from an item bank (i.e., the total set of items from which a subset is selected for the patient during adaptive testing) for a PRO measure due to the use of CAT, a row for each remaining unadministered item within the item bank should not be included within the QS dataset. Rather, only the administered items for CAT-administered measures should be submitted within the QS dataset.

3.1.2 *Trial Summary Dataset*

Data related to the trial summary should be stored in the TS dataset. Of particular interest to FDA is the frequency with which these technical specifications are used to create and submit

[20] American Educational Research Association, American Psychological Association, National Council on Measurement in Education, 2014, The Standards for Educational and Psychological Testing, Washington (DC): American Educational Research Association Publications.

trial data. Per the FDA sdTCG, sponsors may include the following parameter and associated value in the TS dataset to indicate that these technical specifications were used for the study:

- TSPARAMCD = 'FDATCHSP'
- TSPARAM = 'FDA Tech Spec'
- TSVAL = 'Oncology PROs Technical Specifications Guidance v1.0'

3.2 ADaM Specifications

This section provides specifications for the ADaM dataset containing analysis-ready PRO data (referenced in this document as the 'ADQS' dataset), which are derived from PRO data in the SDTM QS dataset discussed in section 3.1.1 Questionnaires (QS) Dataset in conjunction with other SDTM and ADaM data.

3.2.1 *General Considerations*

The ADQS dataset described in this section follows the ADaM Basic Data Structure (BDS). In addition to variables for treatment assignment, stratification, subgrouping, and other covariates needed for analysis, the ADQS dataset should contain all individual item scores and summary scores (e.g., subscale scores, total scores, other composite or index scores). Table 3 contains specifications for a subset of ADQS variables, some of which are standard variables (included here to clarify how they should be completed for PRO measures used in oncology studies to foster consistency and standardization across industry as well as traceability) and some of which are newly defined. Table 3 does not include all ADQS variables to be submitted, such as timing and treatment variables. An example ADQS dataset is provided in Appendix 5.2.

Table 3. Specifications for a Subset of ADQS Variables

Variable Name	Variable Label	Type	Comments
PARCATy	Parameter Category y	Char	**PARCAT1:** The measure name(s) and version(s) should be provided within PARCAT1 for each item and summary score provided in PARAM to differentiate between PRO measures administered during the study. The measure name may match the value stored in the variable QS.QSCAT from the input SDTM QS dataset. **Additional PARCATy variables:** As demonstrated within section 3.2.3 ADQS Dataset Structure, the recommended number of PARCATy variables and their corresponding values differ based on the PRO measure and the number of summary scores calculated.
PARAM	Parameter	Char	The description of the analysis parameter (e.g., individual item or summary score). The value of PARAM may match the value stored in QS.QSTEST for parameters existing in the input SDTM QS dataset. Individual parameters are needed for each summary score. Documentation for derived parameters should be provided in submitted study metadata (e.g., the Define-XML file and the ADRG).

Variable Name	Variable Label	Type	Comments
PARAMCD	Parameter Code	Char	The short name of the analysis parameter in PARAM. The value of PARAMCD may match the values stored in QS.QSTESTCD for parameters existing in the input SDTM QS dataset.
AVAL / AVALC	Analysis Value / Analysis Value (C)	Num/ Char	The analysis value for each parameter described by PARAM. For parameters existing in the input SDTM QS dataset, quantitative values used for analysis and captured in AVAL may be copied from QS.QSSTRESN, and qualitative values used for analysis and captured in AVALC may be copied from QS.QSSTRESC. In some cases, it is acceptable to populate AVAL for qualitative values. Reference the ADaMIG for details around populating AVAL and AVALC. Study metadata should describe how the analysis value is calculated for derived parameters.
DTYPE	Derivation Type	Char	Analysis value derivation method. DTYPE must be populated with the algorithm or statistical method used when AVAL or AVALC has been imputed or derived differently than the other analysis values within the parameter. Reference the ADaMIG for details around the submission of DTYPE. This document utilizes phantom records (i.e., where DTYPE = 'PHANTOM') to represent missing item scores or summary scores such that each patient has the same number of observations (See section 3.2.2 Handling of Missing PRO Data and Intercurrent Events and the examples within Appendix 5.2). Based on the study attributes, alternate DTYPE values may be used to handle missing data depending on the imputation method(s) implemented. When imputation is performed, imputation rules are included in the study's Statistical Analysis Plan (SAP). Imputation methods are not specified within this document for oncology PROs.
ONTRTFL	On Treatment Record Flag	Char	A character indicator variable to specify whether the observation occurred while the patient was on treatment. This flag is strongly recommended within the ADQS dataset to denote whether the patient was on treatment during administration of the PRO measure at a given assessment timepoint.
ONTRxxFL	On Treatment in Period xx Record Flag	Char	For multi-period studies, a character indicator variable to specify whether the observation occurred while the patient was on treatment for period xx. This flag is strongly recommended within the ADQS dataset when multiple periods exist to denote whether the patient was on treatment during administration of the PRO measure at a given assessment timepoint within period xx.
SCBLFL	Screening Used as Baseline Flag	Char	When applicable to include, an indicator variable to specify when the baseline record (i.e., the record where ABLFL = 'Y') is sourced from a Screening assessment timepoint(s) rather than from a prespecified baseline assessment timepoint. Clear documentation defining the PRO Baseline score should be provided within the study metadata.
PROEXPFL	PRO Expected Flag	Char	An indicator variable to specify whether the PRO parameter (e.g., the individual item or summary score reported within a row) corresponds to a planned (per protocol) PRO assessment timepoint. The type of PRO objective (e.g., clinical benefit vs. safety and tolerability) affects whether PROEXPFL is populated

Variable Name	Variable Label	Type	Comments
			at a given assessment timepoint (e.g., if PRO data are used to evaluate clinical benefit, patients who discontinue from treatment may be expected to take the PRO measure and PROEXPFL = 'Y'.) (See section 4.0 Specifications for Tables and Figures and the examples within Appendix 5.2). If PRO objectives for both (1) clinical benefit and (2) safety and tolerability are present within the same trial, two PRO Expected Flag variables should be submitted within the ADQS dataset (e.g., PROEX1FL and PROEX2FL) with definitions for each variable provided within the study metadata.
PROSCMFL	PRO Score Completed Flag	Char	An indicator variable to specify whether the PRO item score or summary score is populated at a planned (per protocol) PRO assessment timepoint (i.e., where AVAL or AVALC is not empty/null). For example, the indicator value is null for any item within the PRO measure where a response is not provided by the patient.
AREASND	Analysis Reason Not Performed	Char	Describes the reason for missing PRO data. It is recommended that AREASND is populated for records where item score or summary score is missing (i.e., where AVAL or AVALC is empty/null). The value of AREASND should match the value stored in QS.QSREASND when QSREASND is populated in the input SDTM QS dataset. When QS.QSREASND is not populated, AREASND is populated by another source, when available. For example, if the PRO data are used to evaluate clinical benefit, AREASND may be populated for phantom records using DS.DSDECOD or ADSL.DCTREASP for a patient who died or discontinued from treatment, or using DM.ACTARM for patients who were randomized but not treated (See section 3.2.2 Handling of Missing PRO Data and Intercurrent Events and the examples within Appendix 5.2).
Variables in ADQS copied from the ADaM ADSL Dataset or Other Datasets			
FPDDT	First Progressive Disease Date	Num	Date of first progression. Null if no progression occurred for the patient throughout the study. FDA understands that the interpretation of progression outcomes can differ between independent review committees (IRCs) and site investigators (INV). If progression is evaluated by both an IRC and an INV, then two First Progressive Disease Date variables are recommended for submission (e.g., FPDIRCDT = First Progressive Disease as Assessed by IRC Date and FPDINVDT = First Progressive Disease as Assessed by INV Date). The date(s) should align with the study rules outlined in the study protocol and the SAP. The interpretation used for the primary analysis should be clearly defined within the study metadata.
DTHDT	Date of Death	Num	Date of patient's death.
EOSDT	End of Study Date	Num	Date patient ended the study.
EOSSTT	End of Study Status	Char	The patient's status as of the end of study or data cutoff. Examples: COMPLETED, DISCONTINUED, ONGOING.
DCSREAS	Reason for Discontinuation from Study	Char	Reason for a patient's discontinuation from study, if applicable. Null for patients who completed the study.
EOTDT	Date of Treatment Discontinuation	Num	Date the patient discontinued from treatment. May equal EOSDT.

Variable Name	Variable Label	Type	Comments
EOTSTT	End of Treatment Status	Char	The patient's status as of the end of treatment or data cutoff. Examples: COMPLETED, DISCONTINUED, ONGOING.
DCTREAS	Reason for Discontinuation of Treatment	Char	Reason for a patient's discontinuation of treatment, if applicable. This variable represents discontinuation of treatment in the overall study and not discontinuation of treatment within individual treatment periods; reference the ADaMIG for period-specific discontinuation variables.
TRTDURD	Total Treatment Duration (Days)	Num	Total treatment duration as measured in days.
TRxxDURD	Treatment Duration in Period xx (Days)	Num	For multi-period studies, treatment duration for period xx as measured in days.
RANDDT	Date of Randomization	Num	Date of patient's randomization.
RANDFL	Randomized Population Flag	Char	Indicates whether the patient is included in the randomized population.
SAFFL	Safety Population Flag	Char	Indicates whether the patient is included in the safety population.
ITTFL	Intent-To-Treat Population Flag	Char	Indicates whether the patient is included in the intent-to-treat population.
Variables in ADQS copied from input SDTM QS Dataset			
QSSEQ	Sequence Number	Num	Sponsors should include any SDTM variables in the ADQS dataset needed to provide traceability to the source SDTM QS dataset.
VISIT	Visit Name	Char	
VISITNUM	Visit Number	Num	
QSSTAT	Completion Status	Char	Sponsors should include SDTM variables that provide explanations for missing item scores or missing source data summary scores. See Comments for QSSTAT and QSREASND provided in Table 1. Specifications for a Subset of QS Variables.
QSREASND	Reason Not Performed	Char	

3.2.2 *Handling of Missing PRO Data and Intercurrent Events*

As discussed in SDTM section 3.1.1.2 Handling of Missing PRO Data and section 3.1.1.3 Handling of PRO Data Not Collected due to Skip Logic or Computerized Adaptive Testing, understanding the reasons for and prevalence of missing PRO data or PRO data not collected, as well as intercurrent events[21] occurring during the study, are critical to support FDA review and regulatory decision-making. Approaches to represent missing data and intercurrent events within the ADQS dataset are provided in section 3.2.2.1 Approaches to Represent Missing Data and Intercurrent Events and scenarios to represent missing PRO data and intercurrent events within the ADQS dataset are provided in section 3.2.2.2 Scenarios to Represent Missing Data and Intercurrent Events which further depend on the PRO objective (i.e., clinical benefit vs. safety and tolerability). When provided, the reason for missing PRO data should be distributed across all rows for each item score and summary score within the missing PRO measure at each planned (per protocol) PRO assessment timepoint. The example provided in Appendix 5.2 illustrates the

[21] See the guidance for industry *E9(R1) Statistical Principles for Clinical Trials Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021). For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

representation of missing data, and the tables and figures requested by the Agency to analyze missing data are specified within section 4.0 Specifications for Tables and Figures.

3.2.2.1 Approaches to Represent Missing Data and Intercurrent Events

Approaches to represent missing PRO data within the ADQS dataset include:

- Copying records from the SDTM QS dataset, where QS.QSSTAT = 'NOT DONE' and QS.QSREASND is populated with the reason the item(s) and/or summary score(s) are missing, or

- Deriving new phantom records in the ADQS dataset (e.g., where DTYPE = 'PHANTOM').

When QS.QSREASND is populated within the SDTM QS dataset for a record, the value should be copied into the ADQS dataset within QSREASND. ADQS.AREASND should be populated in the ADQS dataset to indicate the reason the item score or summary score was not done when reason is available, including for phantom records. QS.QSSTAT and QS.QSREASND are null for phantom records derived in the ADQS dataset, and phantom records should only be derived when the row representing the missing item score or source data summary score (if applicable) does not exist in the SDTM QS dataset. When phantom records are derived in the ADQS dataset for an entire PRO measure, a row should be derived for each item and summary score within the PRO measure, with the reason populated in ADQS.AREASND (if known) and distributed across all rows.

3.2.2.2 Scenarios to Represent Missing Data and Intercurrent Events

When the PRO objective is to evaluate clinical benefit, rows should be represented in the ADQS dataset for each item score and summary score within the PRO measure for all randomized patients at each planned (per protocol) PRO assessment timepoint, regardless of whether the item score or summary score has a value populated. PRO data may be collected for patients after intercurrent events such as treatment discontinuation due to disease progression or due to adverse event (AE), which is further described within section 4.0 Specifications for Tables and Figures. Intercurrent events include "events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Intercurrent events should be addressed when describing the clinical question of interest to precisely define the treatment effect that is to be estimated."[22] If records are not tabulated in the QS dataset at each PRO assessment timepoint for the patient, including PRO assessment timepoints after an intercurrent event, including a terminal intercurrent event such as death, then these records should be derived as phantom records in the ADQS dataset. Since rows are represented for all randomized patients, records are also derived for patients who were randomized but not treated.

[22] See the guidance for industry *E9(R1) Statistical Principles for Clinical Trials Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

When the PRO objective is to inform the evaluation of safety and tolerability, rows are only represented in the ADQS dataset for each item score and summary score within the PRO measure for patients where the PRO is expected to be completed at the planned (per protocol) PRO assessment timepoints, including rows for patients who are on therapy throughout the study and rows for patients at assessment timepoints prior to treatment discontinuation or death. The number of PRO assessments to be administered after a patient discontinues treatment should be carefully considered and minimized to reduce patient burden. Rationale regarding the number of PRO assessments to be administered should be provided, given that the administration of PRO measures beyond treatment discontinuation can be challenging in cancer clinical trials. Sponsors are strongly encouraged to consult with the Agency to make appropriate determinations. Rows would not be created in the ADQS dataset for assessment timepoints after a patient's death or for any PRO assessment timepoints for randomized but not treated patients. When rows are created in the ADQS dataset for the applicable patients and assessment timepoints when informing the evaluation of safety and tolerability, rows should be created for each item score and summary score within the PRO measure, regardless of whether the item score or summary score has a value populated.

Regardless of PRO objective, if a patient pauses treatment and does not have records included in the QS dataset, these records should be derived as phantom records in the ADQS dataset. In addition, there are certain scenarios regardless of PRO objective where the PRO measure is not administered to a patient, and missing data rows do not need to be created for the patient in the ADQS dataset such as when the PRO measure is not available in the patient's language.

3.2.3 *ADQS Dataset Structure*

Example dataset structures are described below for PRO measures where individual item scores are used to calculate at least one summary score and where item scores are analyzed individually.

3.2.3.1 Dataset Structure for PRO Measures Where Summary Scores are Calculated

The preferred dataset structure for PRO measures where individual item scores are used to calculate summary scores includes the consistent use of parameter category variables (e.g., PARCAT1, PARCAT2) to allow for the easy identification of each measure, score, and item. The scenarios below within Tables 4-7 illustrate how categorical variables are recommended for use based on the complexity of relationships between items, subscales, and higher-level scales within the PRO measure.

As described within Table 3: Specifications for a Subset of ADQS Variables, PARCAT1 reports the PRO measure name and version. PARCAT2 is created within the ADQS dataset for PRO measures where summary scores are calculated to indicate whether PARAM represents an item or a summary score, where the summary score calculated is dependent on the instrument scoring manual. Example terminology values for PARCAT2 include, but are not limited to, 'ITEM', 'SUBSCALE SCORE', 'SCALE SCORE', 'RAW SCORE', 'TOTAL SCORE', 'COMPOSITE SCORE', and 'INDEX SCORE'. The number of additional PARCATy variables within the

ADQS dataset depends on the summary scores to be calculated based on the intended use of the PRO measure as described in the protocol, SAP, and instrument scoring manual.

Scenario 1 within Table 4 represents a simple scenario where items within a two-item measure are used to compute a single total score.

Table 4. ADQS Dataset Structure for Scenario 1

PARCAT1	PARCAT2	PARAM
Measure Name and Version	ITEM	Item 1
Measure Name and Version	ITEM	Item 2
Measure Name and Version	TOTAL SCORE	Total Score

Scenario 2 within Table 5 represents a scenario where multiple scores are calculated, and each scale score is calculated from distinct, mutually exclusive item score(s). PARCAT3 reports the scale to which each item contributes.

Table 5. ADQS Dataset Structure for Scenario 2

PARCAT1	PARCAT2	PARCAT3	PARAM
Measure Name and Version	ITEM	Scale Score 1	Item 1
Measure Name and Version	ITEM	Scale Score 1	Item 2
Measure Name and Version	ITEM	Scale Score 1	Item 3
Measure Name and Version	ITEM	Scale Score 2	Item 4
Measure Name and Version	ITEM	Scale Score 2	Item 5
Measure Name and Version	ITEM	Scale Score 3	Item 6
Measure Name and Version	SCALE SCORE	Scale Score 1	Scale Score 1
Measure Name and Version	SCALE SCORE	Scale Score 2	Scale Score 2
Measure Name and Version	SCALE SCORE	Scale Score 3	Scale Score 3

Scenario 3 within Table 6 represents a scenario where (1) multiple subscale scores are calculated, and each subscale score is calculated from distinct, mutually exclusive item score(s), and (2) multiple scale scores are calculated, and each scale score is calculated from distinct, mutually exclusive subscale score(s). PARCAT3 reports the subscale to which an item contributes, and PARCAT4 reports the scale to which a subscale contributes.

Table 6. ADQS Dataset Structure for Scenario 3

PARCAT1	PARCAT2	PARCAT3	PARCAT4	PARAM
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Item 1
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Item 2
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Item 3
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Item 4
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Item 5
Measure Name and Version	ITEM	Subscale Score 3	Scale Score B	Item 6
Measure Name and Version	SUBSCALE SCORE	Subscale Score 1	Scale Score A	Subscale Score 1
Measure Name and Version	SUBSCALE SCORE	Subscale Score 2	Scale Score A	Subscale Score 2
Measure Name and Version	SUBSCALE SCORE	Subscale Score 3	Scale Score B	Subscale Score 3
Measure Name and Version	SCALE SCORE		Scale Score A	Scale Score A
Measure Name and Version	SCALE SCORE		Scale Score B	Scale Score B

Scenario 4 within Table 7 represents a scenario where (1) multiple subscale scores are calculated, and each subscale is calculated from distinct, mutually exclusive item score(s), and (2) multiple scale scores are calculated. However, in this scenario, a single subscale score can contribute to multiple scale scores. PARCAT3 reports the subscale to which an item contributes and separate categorical variables (i.e., PARCAT4 and PARCAT5) report the individual scale to which a subscale contributes. Similarly, if an item can contribute to multiple subscales, a separate PARCATy is needed for each subscale (not pictured).

Table 7. ADQS Dataset Structure for Scenario 4

PARCAT1	PARCAT2	PARCAT3	PARCAT4	PARCAT5	PARAM
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 1
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 2
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 3
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Scale Score B	Item 4
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Scale Score B	Item 5
Measure Name and Version	ITEM	Subscale Score 3	Scale Score A		Item 6
Measure Name and Version	SUBSCALE SCORE	Subscale Score 1	Scale Score A	Scale Score B	Subscale Score 1
Measure Name and Version	SUBSCALE SCORE	Subscale Score 2	Scale Score A	Scale Score B	Subscale Score 2
Measure Name and Version	SUBSCALE SCORE	Subscale Score 3	Scale Score A		Subscale Score 3
Measure Name and Version	SCALE SCORE		Scale Score A		Scale Score A
Measure Name and Version	SCALE SCORE			Scale Score B	Scale Score B

3.2.3.2 Dataset Structure for PRO Measures Where Summary Scores are Not Calculated

The preferred dataset structure when summary scores are not calculated and item scores are analyzed individually include PRO measures that analyze attributes of symptomatic AEs, where AEs are selected from an item library prior to trial initiation. Scenario 5 within Table 8 represents the consistent use of parameter category variables to allow for the easy identification of the measure, symptoms (e.g., rash, headache), and attributes (e.g., presence, severity, frequency) within an example PRO measure. PARCAT2 reports the stand-alone symptom and PARCAT3 reports the stand-alone attribute. PARAM is a compliant, stand-alone analysis variable. CDISC Controlled Terminology is implemented when available for the PRO measure.

Table 8. ADQS Dataset Structure for Scenario 5

PARCAT1	PARCAT2	PARCAT3	PARAM
Measure Name and Version	Symptom 1	Attribute 1	Symptom 1 Attribute 1
Measure Name and Version	Symptom 2	Attribute 2	Symptom 2 Attribute 2
Measure Name and Version	Symptom 2	Attribute 3	Symptom 2 Attribute 3
Measure Name and Version	Symptom 3	Attribute 1	Symptom 3 Attribute 1

4.0 SPECIFICATIONS FOR TABLES AND FIGURES

In addition to the sponsor's prespecified tables and figures presenting analyses of PRO data, the Agency strongly recommends the following tables and figures based on PRO data be provided within the Clinical Study Report (CSR) to facilitate the evaluation of the PRO measure in cancer clinical trials. Sponsors should also provide an executive summary of clinical interpretation of the most critical PRO results informing risk(s) and benefit(s) within the CSR. Examples of the requested tables and figures are shown in Appendix 5.3 which are partitioned by treatment arm and assessment timepoint. Analysis visits (ADQS.AVISIT) should be assigned from SDTM visits (QS.VISIT) based on windowing rules in the study's SAP. It is possible that not all records are assigned an AVISIT (e.g., records for unscheduled visits), and these records are excluded from the requested tables and figures. In the examples, counts and percentages are provided within the requested tables and percentages are provided within the requested bar charts.

4.1 Patient Disposition

Provide a table and bar chart summarizing cumulative patient disposition. Whether a PRO measure is expected to be completed for a patient differs based on the PRO objective as described in sections 4.1.1 and 4.1.2 (i.e., when PRO data are used to evaluate clinical benefit vs. safety and tolerability).

4.1.1 *Clinical Benefit*

When the PRO objective is clinical benefit, the percentage for each disposition category should be calculated using the randomized population as the fixed denominator. The PRO measure is expected to be completed by the patient for the following:

- Patients who are on therapy.
- Patients who discontinued from treatment due to disease progression, AE, or other reason as specified in the protocol.
- Patients who were randomized but not treated.
- Patients who paused treatment.

When the PRO measure is expected to be completed at a PRO assessment timepoint, the PRO Expected Flag (PROEXPFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables.

Conversely, the PRO measure is not expected to be completed by the patient for the following:

- PRO assessment timepoints after death for patients who died.
- Translation of the PRO measure is not available in the patient's language (affects all PRO assessment timepoints).

When the PRO measure is not expected to be completed at a PRO assessment timepoint, the PRO Expected Flag (PROEXPFL) is null.

An example table and bar chart illustrating the structure and inputs for the table and figure, including the preferred categories, are provided in Appendix 5.3.1. Within the table and figure, the three recommended categories for treatment discontinuation include treatment discontinuation due to disease progression, treatment discontinuation due to AE, and all other reasons for treatment discontinuation. In addition, an Other category within PRO Not Expected groups patients who were not expected to complete the PRO measure at a designated assessment timepoint for reasons other than patient death (e.g., the translation of the PRO measure is not available in the patient's language).

4.1.2 *Safety and Tolerability*

When the PRO objective is safety and tolerability, the percentage for disposition categories should be calculated using the safety population as the fixed denominator. The PRO measure is expected to be completed for patients who are either on therapy or paused treatment at a given PRO assessment timepoint, which are totaled within a PRO Expected column. When the PRO measure is expected to be completed by the patient at a PRO assessment timepoint, the PRO Expected Flag (PROEXPFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables.

Conversely, the PRO measure is not expected to be completed by the patient for reasons including:

- PRO assessment timepoints after death for patients who died.
- Patients who were randomized but not treated (affects all PRO assessment timepoints).
- Translation of the PRO measure is not available in the patient's language (affects all PRO assessment timepoints).

In some cases, PRO assessment timepoints may be less frequent or stop after treatment discontinuation for patients who discontinued from treatment due to disease progression, AE, or other reason. Expectations for when PRO assessments will be collected should be planned in advance with FDA. See Section 3.2.2.2.

When the PRO measure is not expected to be completed at a PRO assessment timepoint, the PRO Expected Flag (PROEXPFL) is null. An example table and bar chart illustrating the structure and inputs, including the preferred categories, are provided in Appendix 5.3.2. Within the table and figure, the three recommended categories for treatment discontinuation include treatment discontinuation due to disease progression, treatment discontinuation due to AE, and all other reasons for treatment discontinuation. In addition, an Other category within PRO Not

Expected groups patients who were not expected to complete the PRO measure at a designated assessment timepoint for reasons other than patient death or treatment discontinuation.

4.2 PRO Data Completeness

Provide a table and data visualization summarizing PRO data completeness.[23] The denominator used to evaluate data completeness differs based on the PRO objective (i.e., when PRO data are used to inform the evaluation of clinical benefit vs. safety and tolerability) as described in sections 4.2.1 and 4.2.2. The numerator (referenced as the 'PRO Completed' column in Table A6 and Table A7) is the number of patients submitting a completed PRO measure at the designated PRO assessment timepoint and does not differ based on PRO objective. Sponsors should defer to the instructions provided within the instrument scoring manual to determine what constitutes a 'complete' PRO measure (i.e., number of items needed for completion to produce a reliable score). When not provided within the instrument scoring manual, sponsors should provide rationale for the number of responses necessary to constitute a complete PRO measure.

Within the tables, counts and percentages of patients who did not complete the PRO measure (referenced as 'Reason for PRO Not Completed' in Table A6 and Table A7) should be calculated with the accompanying reasons for missing observations based on collected data. If reasons are unknown or not collected, a separate column should be provided to report the affected count and percentage. The example tables contain possible reasons for noncompletion and should be modified to represent the reported reasons collected within the clinical trial (See section 3.1.1.2 Handling of Missing PRO Data for example reasons for noncompletion). If both clinical benefit as well as safety and tolerability PRO objectives are specified within a single trial, the sponsor should submit the requested tables and data visualizations for both available data rate and completion rate as described below.

4.2.1 *Available Data Rate (Clinical Benefit)*

When PRO data are used to evaluate clinical benefit, the available data rate should be calculated where the randomized population is used as a fixed denominator. The table and data visualization should be provided based on available data rate (1) at the PRO instrument level and (2) for the concept(s) evaluated by the PRO measure (e.g., single item score or a summary score such as subscale score or total score). When the concept measured is a summary score (e.g., physical functioning), the table and data visualization should be provided for both the summary score and for each individual item score that contributes to the summary score. An example table and bar chart illustrating the structure and inputs are provided in Appendix 5.3.3, with percentages provided for each category within the bar chart. Reasons for treatment discontinuation are included in the table and figure as described in the table footnotes.

4.2.2 *Completion Rate (Safety and Tolerability)*

When PRO data are used to inform the evaluation of safety and tolerability, the completion rate should be calculated where the denominator is the number of patients expected to complete the PRO measure at the designated PRO assessment timepoint as described in section 4.1.2 Patient

[23]More information is available at SISAQOL's web page: https://www.sisaqol-imi.org/.

Disposition for Safety and Tolerability (i.e., where PRO Expected Flag (PROEXPFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables). Thus, the denominator can decrease throughout an oncology trial based on attrition over time. The table and data visualization should be provided at the PRO instrument level based on completion rate. The sponsor should consult with the Agency to determine additional tables and data visualizations to provide for individual items (including patient-reported symptomatic adverse events) and/or summary scores. An example table and bar chart illustrating the structure and inputs are provided in Appendix 5.3.4, with percentages provided for each category within the bar chart. Reasons for treatment discontinuation may be excluded as reasons for PRO noncompletion in the table and figure as described in the table footnotes.

4.3 Distributions

Provide a table and data visualization summarizing the distribution of responses and the distribution of change in responses from baseline. When the PRO measure is used to inform the evaluation of safety and tolerability, the sponsor should consult with the Agency to determine the tables and data visualizations to provide for individual items (including patient-reported symptomatic adverse events) and/or summary scores. When the PRO measure is to evaluate clinical benefit, the table and data visualization should be provided for the concept(s) evaluated by the PRO measure (e.g., single item score, subscale score, total score). When the concept measured is a summary score (e.g., physical functioning), the table and data visualization should be provided for both the summary score and for each individual item score that contributes to the summary score.

Within the table, counts and percentages should be provided for PRO Completed and PRO Not Completed. Additional columns within the table depends on PRO objective; when the PRO objective is safety and tolerability, the count and percentage for PRO Expected should be provided. When the PRO objective is clinical benefit, the count and percentage for the randomized population should be provided. When the PRO objective is safety and tolerability, the denominator used to determine the percentage for PRO Completed and PRO Not Completed is the number of patients expected to complete the PRO measure at the designated PRO assessment timepoint as described in section 4.1.2 Patient Disposition for Safety and Tolerability (i.e., where PRO Expected Flag (PROEXPFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables). When the PRO objective is clinical benefit, the denominator used to determine the percentage for PRO Completed and PRO Not Completed is the randomized population.

When the concept measured has categorical response options with binary or ordinal outcomes, counts and percentages within the table for the response categories or change in response categories should be provided where the denominator used to determine the percentage for each category is PRO Completed (i.e., where PRO Score Completed Flag (PROSCMFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables). When the concept measured has continuous response options, summary statistics should be provided and are calculated based on PRO Completed.

Within the data visualization, counts for PRO Completed and PRO Not Completed should be provided below the figure as shown in the examples within the appendices. In addition, if the PRO objective is safety and tolerability, counts for PRO Expected should be provided; if the PRO objective is clinical benefit, counts for the randomized population should be provided. The type of data visualization provided further depends on the response options for the PRO measure. A bar chart should be provided when the concept measured has categorical response options with binary or ordinal outcomes. When the concept measured has continuous response options, a line graph should be provided. For example, a line graph with descriptive means may be provided when the PRO objective is safety and tolerability objective. The sponsor may consult with the Agency to discuss alternative data visualizations (e.g., density curves, box plots) to provide when continuous data are captured. Within the line graph, standard error bars with jittering should be provided as well as labels to indicate improving/worsening or higher/lower functioning, depending on the concept measured.

4.3.1 *Distribution of Responses*

When the concept measured has categorical response options with a binary or ordinal outcome, the distribution of responses in the table and bar chart should include all possible response options for the item or summary score with the percentage provided for each category within the bar chart. Within Appendix 5.3.5, an example table is provided in Table A8 and a bar chart is provided in Figure A5 for a single item for a safety and tolerability PRO objective.

When the concept measured has continuous response options, the distribution of responses in the table and line graph should represent a summary statistic (e.g., the mean score) over time. An example table is provided in Table A9, and a line graph is provided in Figure A6 for a single item showing descriptive means for a safety and tolerability PRO objective.

4.3.2 *Distribution of Change in Responses from Baseline*

When the concept measured includes categorical response options with a binary or ordinal outcome, the distribution of change in response categories for the table and bar chart should include all possible scenarios (e.g., improving, no change, worsening) based on the number of response categories for the item or summary score with the percentage provided for each change category within the bar chart. Within Appendix 5.3.6, an example table is provided in Table A10 and a bar chart is provided in Figure A7 for a single item for a safety and tolerability PRO objective. Labels for 'No Change or Improving' and 'Worsening' should be provided in the bar chart as shown in the example.

When the concept measured has continuous response options, the distribution of change in responses from baseline in the table and line graph should represent a summary statistic (e.g., mean) change from baseline over time. An example table is provided in Table A11 and a line graph is provided in Figure A8 for a single item showing descriptive mean change from baseline for a safety and tolerability PRO objective.

4.4 Incidence of Healthcare Utilization

Provide a table summarizing the incidence of healthcare utilization, including emergency department visits, hospitalizations, supportive care medications, supportive care procedures, and other relevant interventions depending on the study. Each supportive care medication and supportive care procedure should be represented as a separate column within the table. The denominator used to determine the percentage for each intervention depends on PRO objective. When the PRO objective is safety and tolerability, the denominator is the number of patients expected to complete the PRO measure at the designated PRO assessment timepoint as described in section 4.1.2 Patient Disposition for Safety and Tolerability (i.e., where PRO Expected Flag (PROEXPFL) equals 'Y' as defined in Table 3: Specifications for a Subset of ADQS Variables). When the PRO objective is clinical benefit, the denominator is the randomized population. In addition to columns for healthcare utilization interventions, columns are provided for Randomized Patients and PRO Expected.

An example table illustrating the structure and inputs is provided in Appendix 5.3.7. The table contains example healthcare utilization values for supportive procedures and supportive medications, but the table should be modified to represent the intervention within the study. The sponsor may consult with the Agency to determine the appropriate supportive care medications and supportive care procedures to provide (e.g., growth factors, steroids, and transfusions depend on the cancer type and may not always be relevant).

5.0 APPENDIX

Table A1 represents an example schedule of assessments within the study protocol (not pictured) for Study A, where the patient-reported outcome (PRO) data are used to evaluate clinical benefit. Study A is referenced in the example Questionnaires (QS) dataset in Appendix 5.1 and the example Questionnaires Analysis Dataset (ADQS) in Appendix 5.2. As shown in Table A1, the PRO measure is administered initially onsite at the Screening visit and subsequently onsite on Day 1 of each of three cycles, where Cycle 1 Day 1 represents the Baseline visit. The example PRO measure administered to patients in Study A is a two-item measure, where answers to both items are used to calculate total score according to the instrument scoring manual (not pictured). The total score is not collected as source data and is calculated in the Analysis Data Model (ADaM) ADQS dataset. Note the numeric values provided in QS.QSORRES within Table A2 and ADQS.AVAL within Table A3 are provided for illustrative purposes only.

Table A1. Example Schedule of Assessments

Activity	Visit			
	Screening	Cycles 1 through 3 (Cycle Length = 21 Days)		
		Day 1	Day 8	Day 15
PRO Measure	X	X		

5.1 Example SDTM Questionnaires Dataset

Table A2 shows an example of tabulated data using the QS domain specifications. Where the PRO measure was not completed as expected, Table A2 shows a subset of variables to be submitted within the QS dataset and illustrates how missing PRO assessment timepoints are represented. Scenarios displayed in Table A2 include:

- Patient 1 only responded to one of two items in the PRO measure at the Cycle 1 Day 1 visit.
    - Row 3 shows QSSTAT = ‘NOT DONE’ and null QSREASND since reason for the missing item is not captured within the administered PRO measure.
- Patient 1 attended the onsite Cycle 3 Day 1 visit but refused to take the PRO measure. When the PRO measure is not administered, rows are created for each item.

  - Rows 7 through 8 show null QSORRES, QSSTAT = 'NOT DONE', and QSREASND = 'PATIENT REFUSAL', where 'PATIENT REFUSAL' is captured on the CRF. Given the onsite visit was attended, Date/Time of Finding (QSDTC) is populated.

- Patient 2 was unable to attend the onsite Cycle 1 Day 1 visit due to hospitalization; thus, the PRO measure was not administered. In this scenario, rows are created for each item.

  - Rows 11 through 12 show null QSORRES, QSSTAT = 'NOT DONE', and QSREASND = 'HOSPITALIZATION'. To indicate the onsite visit was not attended by Patient 2, QSDTC is set to null.

- Patient 2 died after the Cycle 1 Day 1 visit. Thus, no visit data are available in the QS dataset for the remaining visits. Since the PRO data are used to evaluate clinical benefit, the remaining visits are omitted from the QS dataset and derived as phantom records in the ADQS dataset shown in Appendix 5.2.

Table A2. Subset of Sample QS Dataset

Row	USUBJID	VISIT	QSCAT	QSTEST	QSTESTCD	QSORRES	QSSTAT	QSREASND	QSDTC
1	A_100_1	SCREENING	Measure Name and Version	I01-Item 1	I01	3			2022-02-01
2	A_100_1	SCREENING	Measure Name and Version	I01-Item 2	I02	5			2022-02-01
3	A_100_1	CYCLE 1 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE		2022-02-22
4	A_100_1	CYCLE 1 DAY 1	Measure Name and Version	I01-Item 2	I02	4			2022-02-22
5	A_100_1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01	2			2022-03-15
6	A_100_1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02	4			2022-03-15
7	A_100_1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE	PATIENT REFUSAL	2022-04-05
8	A_100_1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02		NOT DONE	PATIENT REFUSAL	2022-04-05
9	A_100_2	SCREENING	Measure Name and Version	I01-Item 1	I01	4			2022-03-14
10	A_100_2	SCREENING	Measure Name and Version	I01-Item 2	I02	5			2022-03-14

Row	USUBJID	VISIT	QSCAT	QSTEST	QSTESTCD	QSORRES	QSSTAT	QSREASND	QSDTC
11	A_100_2	CYCLE 1 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE	HOSPITALIZATION	
12	A_100_2	CYCLE 1 DAY 1	Measure Name and Version	I01-Item 2	I02		NOT DONE	HOSPITALIZATION	

5.2 Example ADaM Questionnaires Analysis Dataset

Table A3 shows an example ADQS dataset for the same patients and scenario descriptions as those provided in Appendix 5.1. Note that this table only shows a subset of variables to be submitted in the ADQS dataset; additional variables, such as population flags and treatment variables, are not provided as these depend on individual study needs. In this example, total score is calculated for each patient and analysis visit (i.e., where PARAM = 'Total Score') since scores are not captured within the SDTM QS dataset. Scenarios displayed in Table A3 include:

- Patient 1 only responded to one of two items at the Baseline visit. Thus, per the scoring manual, Total Score is incalculable in the ADQS dataset.
    - Row 6 reports Total Score and shows AREASND = 'NOT CALCULABLE'. QSSTAT and QSREASND are null since records for PARAM = 'Total Score' are created in the ADQS dataset.
    - Rows 4 through 6 report ONTRTFL = 'Y' since the patient was on treatment during the Baseline visit and PROEXPFL = 'Y' since the patient was expected to complete the PRO measure at the Baseline visit. PROSCMFL = 'Y' in Row 5 since only Item 2 had a response provided by the patient.
- Patient 1 attended the Cycle 3 Day 1 visit but refused to take the PRO measure.
    - Row 12 reports Total Score and shows AREASND = 'PATIENT REFUSAL' as reported within QS.QSREASND for the individual items in Rows 10 and 11.
    - Rows 10 through 12 report ONTRTFL = 'Y' since the patient was on treatment and PROEXPFL = 'Y' since the patient was expected to complete the PRO measure at the visit. PROSCMFL is null for all rows since the measure was not completed.
- Patient 2 was unable to attend the Baseline visit due to hospitalization.

- Row 18 reports Total Score and shows AREASND = 'HOSPITALIZATION' as reported within QS.QSREASND for the individual items in Rows 16 and 17.

- Rows 16 through 18 report null ONTRTFL since the patient was not on treatment but PROEXPFL = 'Y' since the patient was still expected to complete the PRO measure at the visit. PROSCMFL is null for all rows since the measure was not completed.

- Patient 2 died after the Baseline visit. Since the PRO data are used to evaluate clinical benefit, phantom records are derived in the ADQS dataset for all items and summary scores for the missing analysis visits at Cycle 2 Day 1 and Cycle 3 Day 1. These missing visits are derived as phantom records in the ADaM dataset with DTYPE = 'PHANTOM' and AREASND = 'DEATH', where, in this example, AREASND is populated from ADSL.DCTREAS. Note that QSSTAT and QSREAND are null. For phantom records, AVISIT is populated to represent the visit number for the missing visit. Given the patient died, ONTRTFL, PROEXPFL, and PROSCMFL are null.

Table A3. (Part 1) Subset of Sample ADQS Dataset

Row	USUBJID	VISIT	AVISIT	PARCAT1	PARAM	PARAMCD	AVAL	QSSTAT
1	A_100_1	SCREENING	SCREENING	Measure Name and Version	I01-Item 1	I01	3	
2	A_100_1	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5	
3	A_100_1	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	8	
4	A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE
5	A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02	4	
6	A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS		
7	A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01	2	
8	A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02	4	
9	A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS	6	
10	A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE
11	A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02		NOT DONE
12	A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	Total Score	TS		
13	A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 1	I01	4	
14	A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5	
15	A_100_2	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	9	
16	A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE

Row	USUBJID	VISIT	AVISIT	PARCAT1	PARAM	PARAMCD	AVAL	QSSTAT
17	A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02		NOT DONE
18	A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS		
19	A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01		
20	A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02		
21	A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS		
22	A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		
23	A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02		
24	A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	Total Score	TS		

Table A3. (Part 2) Subset of Sample ADQS Dataset

Row	QSREASND	DTYPE	AREASND	DCTREAS	PROEXPFL	PROSCMFL	ONTRTFL
1					Y	Y	
2					Y	Y	
3					Y	Y	
4					Y		Y
5					Y	Y	Y
6			NOT CALCULABLE		Y		Y
7					Y	Y	Y
8					Y	Y	Y
9					Y	Y	Y
10	PATIENT REFUSAL		PATIENT REFUSAL		Y		Y
11	PATIENT REFUSAL		PATIENT REFUSAL		Y		Y
12			PATIENT REFUSAL		Y		Y
13					Y	Y	
14					Y	Y	
15					Y	Y	
16	HOSPITALIZATION		HOSPITALIZATION		Y		
17	HOSPITALIZATION		HOSPITALIZATION		Y		
18			HOSPITALIZATION		Y		
19		PHANTOM	DEATH	DEATH			

Row	QSREASND	DTYPE	AREASND	DCTREAS	PROEXPFL	PROSCMFL	ONTRTFL
20		PHANTOM	DEATH	DEATH			
21		PHANTOM	DEATH	DEATH			
22		PHANTOM	DEATH	DEATH			
23		PHANTOM	DEATH	DEATH			
24		PHANTOM	DEATH	DEATH			

5.3 Example Tables and Figures

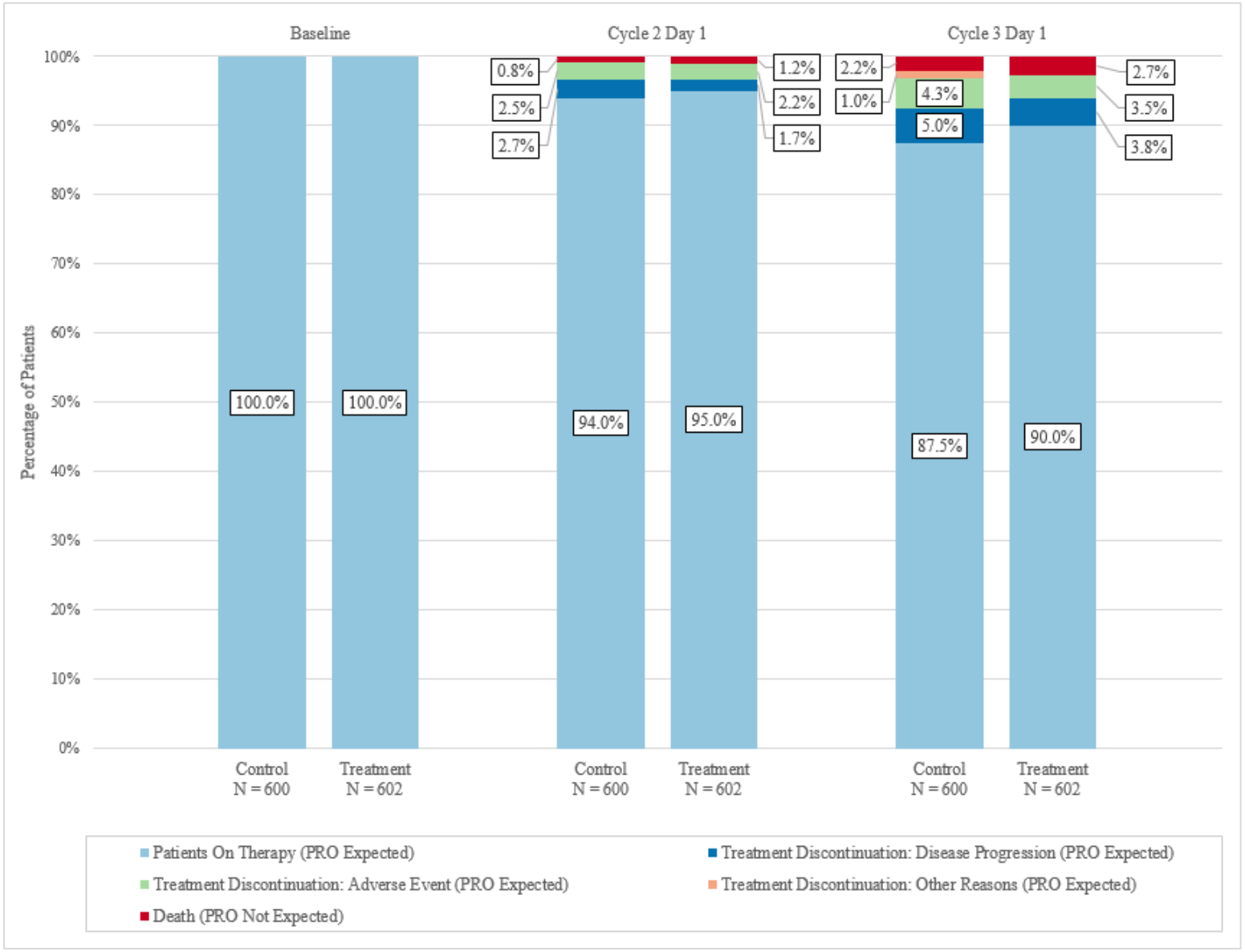
5.3.1 *Patient Disposition when Evaluating Clinical Benefit*

Table A4. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)[1]

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Expected[2]				PRO Not Expected	
			Patients On Therapy, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Treatment Discontinuation: Adverse Event (AE), n (%)	Treatment Discontinuation: Other Reasons, n (%)	Death, n (%)	Other,[3] n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	564 (94.0%)	16 (2.7%)	15 (2.5%)	0 (0.0%)	5 (0.8%)	0 (0.0%)
	Treatment	602	572 (95.0%)	10 (1.7%)	13 (2.2%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Cycle 3 Day 1	Control	600	525 (87.5%)	30 (5.0%)	26 (4.3%)	6 (1.0%)	13 (2.2%)	0 (0.0%)
	Treatment	602	542 (90.0%)	23 (3.8%)	21 (3.5%)	0 (0.0%)	16 (2.7%)	0 (0.0%)

[1] Denominator used to calculate percentages is the number of randomized patients.
[2] When PRO data are used to evaluate clinical benefit, the PRO measure is generally expected to be completed for patients who both did not discontinue treatment and who discontinued treatment for reasons other than death. Columns under PRO Expected includes patients who both completed and did not complete the PRO measure (e.g., the patient did not attend an onsite visit, the patient did not complete the PRO measure at the attended onsite visit or at a prespecified offsite assessment timepoint, the patient partially completed the PRO measure resulting in incalculable summary scores).
[3] The Other column groups patients not expected to complete the PRO measure at a designated assessment timepoint for reasons other than patient death (e.g., the translation of the PRO measure is not available in the patient's language).

Figure A1. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)



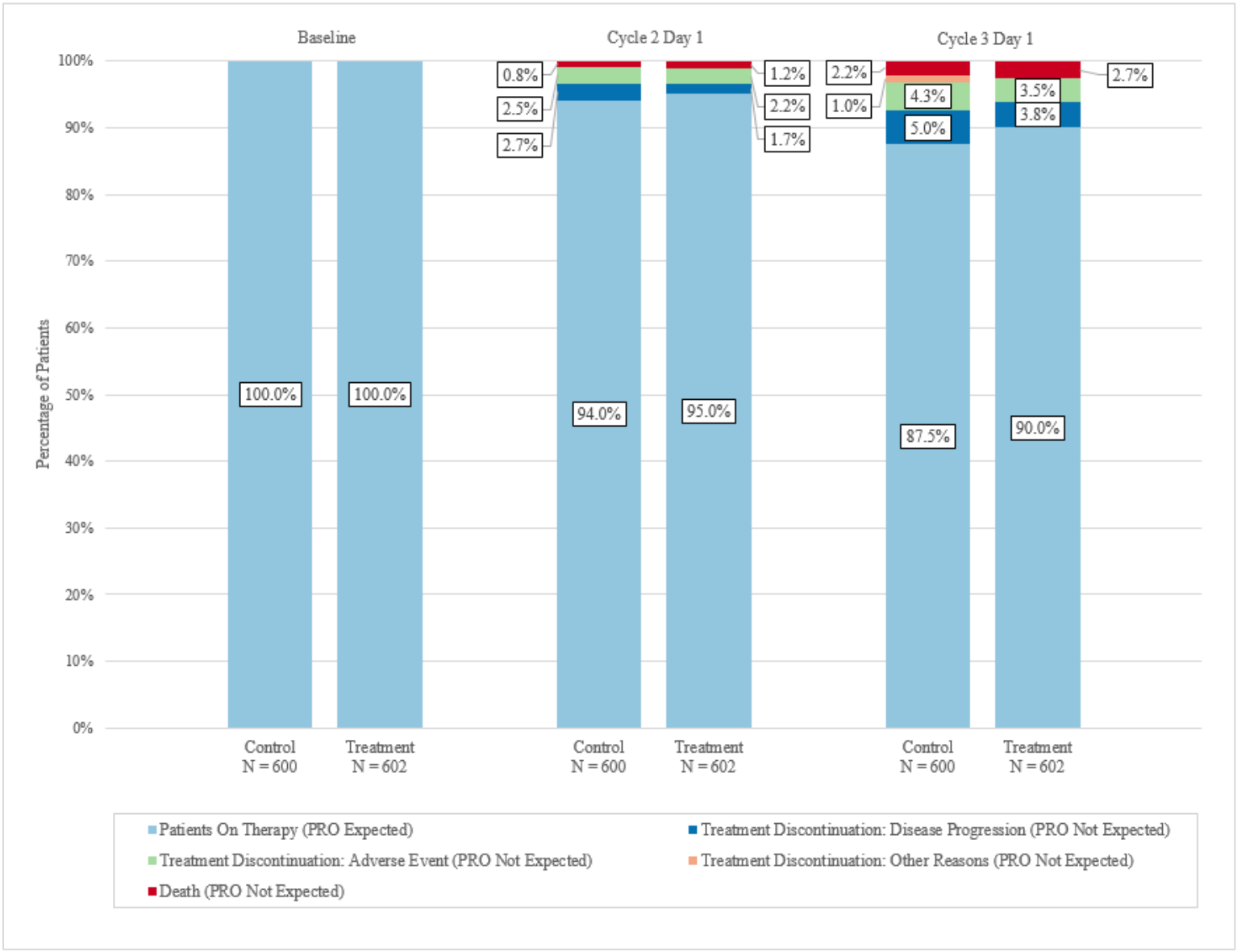
5.3.2 *Patient Disposition when Informing Safety and Tolerability*

Table A5. Patient Disposition when Informing the Evaluation of Safety and Tolerability (Denominator = Safety Population)[4]

Analysis Visit	Treatment Arm	Randomized Population (N)	Safety Population (N)	PRO Expected,[5] n (%)	PRO Not Expected				
					Death, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Treatment Discontinuation: Adverse Event, n (%)	Treatment Discontinuation: Other Reasons, n (%)	Other,[6] n (%)
Baseline	Control	600	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	600	564 (94.0%)	5 (0.8%)	16 (2.7%)	15 (2.5%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602	572 (95.0%)	7 (1.2%)	10 (1.7%)	13 (2.2%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	Control	600	600	525 (87.5%)	13 (2.2%)	30 (5.0%)	26 (4.3%)	6 (1.0%)	0 (0.0%)
	Treatment	602	602	542 (90.0%)	16 (2.7%)	23 (3.8%)	21 (3.5%)	0 (0.0%)	0 (0.0%)

[4] Denominator used to calculate percentages is the number of patients in the safety population.
[5] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. Thus, the PRO Expected column excludes patients who discontinued from treatment. The PRO Expected column is determined where PRO Expected Flag (PROEXPFL) equals 'Y' and includes patients who both completed and did not complete the PRO measure (e.g., the patient did not attend an onsite visit, the patient did not complete the PRO measure at the attended onsite visit or at a prespecified offsite assessment timepoint, the patient partially completed the PRO measure resulting in incalculable summary scores).
[6] The Other column groups patients who were not expected to complete the PRO measure at a designated assessment timepoint for reasons other than treatment discontinuation or patient death (e.g., the translation of the PRO measure is not available in the patient's language).

Figure A2. Patient Disposition when Informing the Evaluation of Safety and Tolerability (Denominator = Safety Population)



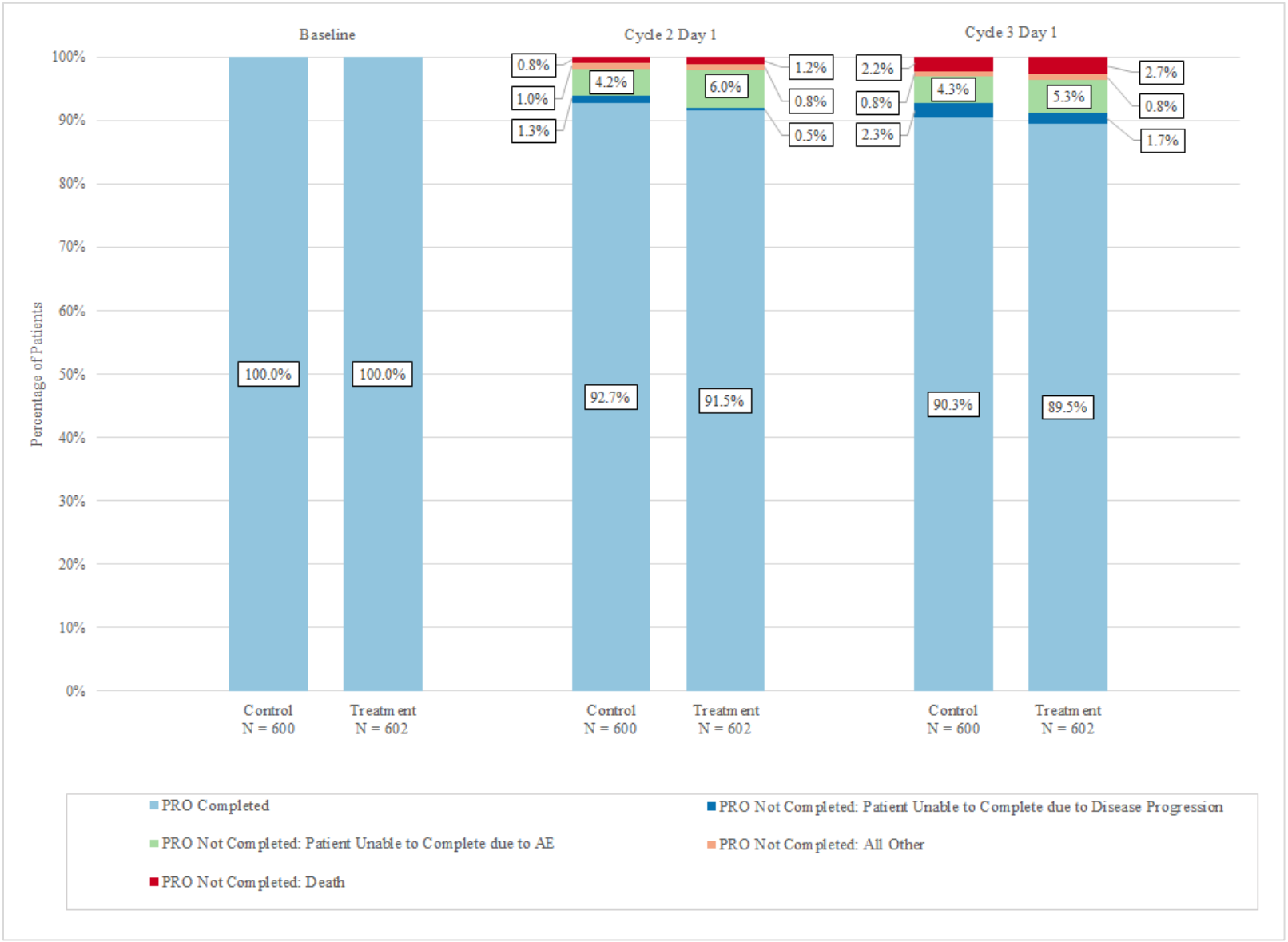
5.3.3 *Available Data Rate for Clinical Benefit*

Table A6. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)[7]

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Completed, n (%)	PRO Not Completed[8] (excluding Death), n (%)	Reason for PRO Not Completed,[9] n (%)					Death, n (%)
					Patient Unable to Complete due to Disease Progression	Patient Unable to Complete due to Adverse Event (AE)	Patient Refusal	Device Failure	Reason Unknown,[10] n (%)	
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	556 (92.7%)	39 (6.5%)	8 (1.3%)	25 (4.2%)	6 (1.0%)	0 (0.0%)	0 (0.0%)	5 (0.8%)
	Treatment	602	551 (91.5%)	44 (7.3%)	3 (0.5%)	36 (6.0%)	5 (0.8%)	0 (0.0%)	0 (0.0%)	7 (1.2%)
Cycle 3 Day 1	Control	600	542 (90.3%)	45 (7.5%)	14 (2.3%)	26 (4.3%)	0 (0.0%)	5 (0.8%)	0 (0.0%)	13 (2.2%)
	Treatment	602	539 (89.5%)	47 (7.8%)	10 (1.7%)	32 (5.3%)	5 (0.8%)	0 (0.0%)	0 (0.0%)	16 (2.7%)

[7] Denominator used to calculate percentages is the number of randomized patients.
[8] The PRO Not Completed column is calculated where PROEXPFL = 'Y' and PROSCMFL is null; thus, death is excluded from the counts and percentages and is provided as a standalone column.
[9] When PRO data are used to evaluate clinical benefit, reasons for PRO Not Completed are based on collected data from QS.QSREASND within the study. All reasons for noncompletion collected during the study should be included. Counts can include patients who were on therapy and who discontinued; thus, counts in Table A6 may be larger than counts in Table A7 given that patients complete the PRO measure after treatment discontinuation when evaluating clinical benefit.
[10] Unknown reasons, if present, should be tabulated within the separate 'Reason Unknown' column.

Figure A3. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)



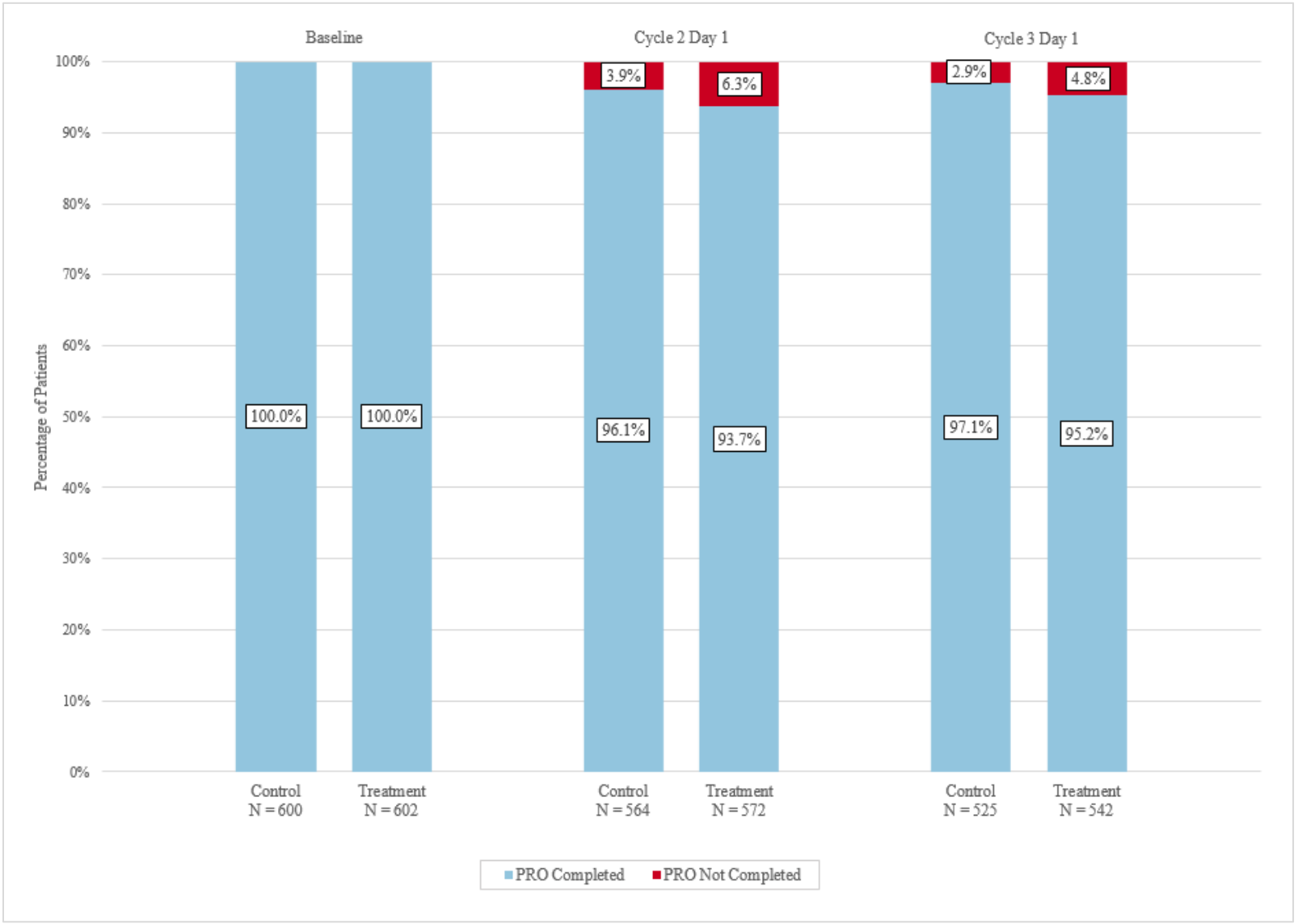
5.3.4 *Completion Rate for Safety and Tolerability*

Table A7. Completion Rate for Safety and Tolerability (Denominator = PRO Expected Population)[11]

Analysis Visit	Treatment Arm	PRO Expected[12] (N)	PRO Completed, n (%)	PRO Not Completed, n (%)	Reason for PRO Not Completed,[13] n (%)			
					Patient Refusal	Patient Unable to Complete due to AE	Device Failure	Reason Unknown,[14] n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	6 (1.1%)	16 (2.8%)	0 (0.0%)	0 (0.0%)
	Treatment	572	536 (93.7%)	36 (6.3%)	5 (0.9%)	31 (5.4%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	0 (0.0%)	10 (1.9%)	5 (1.0%)	0 (0.0%)
	Treatment	542	516 (95.2%)	26 (4.8%)	5 (0.9%)	21 (3.9%)	0 (0.0%)	0 (0.0%)

[11] Denominator used to calculate percentages is PRO Expected.
[12] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.
[13] Reasons for PRO Not Completed are based on collected data within the study and represent reasons the PRO measure was not completed when the patient did not discontinue from treatment. All reasons for noncompletion collected during the study should be included.
[14] Unknown reasons, if present, should be tabulated within the separate 'Reason Unknown' column.

Figure A4. Completion Rate for Safety and Tolerability (Denominator = PRO Expected Population)



5.3.5 *Distribution of Responses*

Table A8. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example)[15]

Analysis Visit	Treatment Arm	PRO Expected[16]	PRO Completed, n (%)	PRO Not Completed, n (%)	Response Categories,[17] n (%)			
					Not at all	A little	Quite a bit	Very much
Baseline	Control	600	600 (100.0%)	0 (0.0%)	332 (55.3%)	220 (36.7%)	31 (5.2%)	17 (2.8%)
	Treatment	602	602 (100.0%)	0 (0.0%)	313 (52.0%)	228 (37.9%)	38 (6.3%)	23 (3.8%)
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	299 (55.2%)	188 (34.7%)	34 (6.3%)	21 (3.9%)
	Treatment	572	536 (93.7%)	36 (6.3%)	268 (50.0%)	199 (37.1%)	41 (7.6%)	28 (5.2%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	225 (44.1%)	189 (37.1%)	63 (12.4%)	33 (6.5%)
	Treatment	542	516 (95.2%)	26 (4.8%)	203 (39.3%)	193 (37.4%)	71 (13.8%)	49 (9.5%)

[15] Denominator used to calculate percentages for PRO Completed and PRO Not Completed is PRO Expected. Denominator used to calculate percentages for each response category is PRO Completed.

[16] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.

[17] The example response categories represent the response options for the item.

Figure A5. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed)

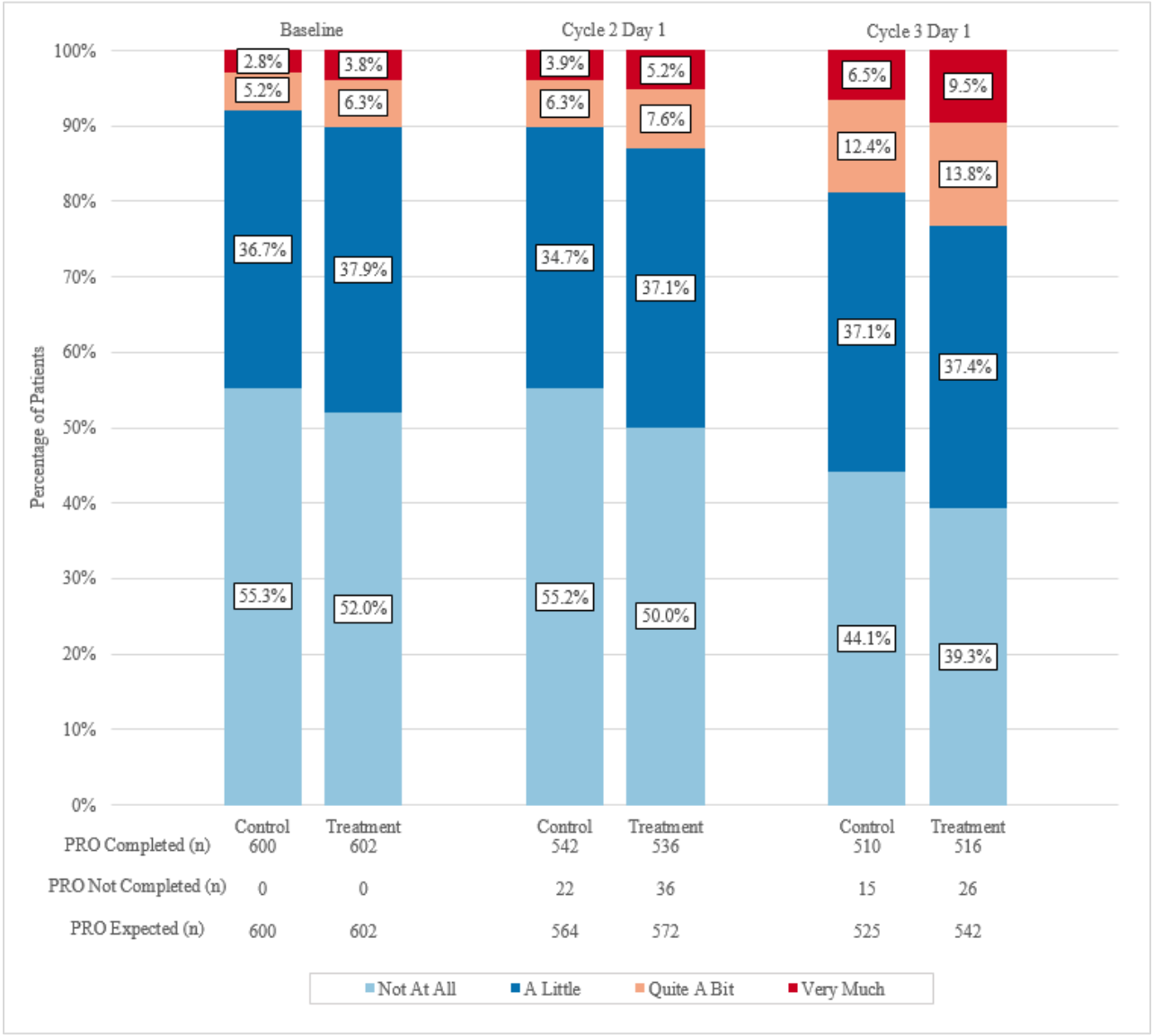


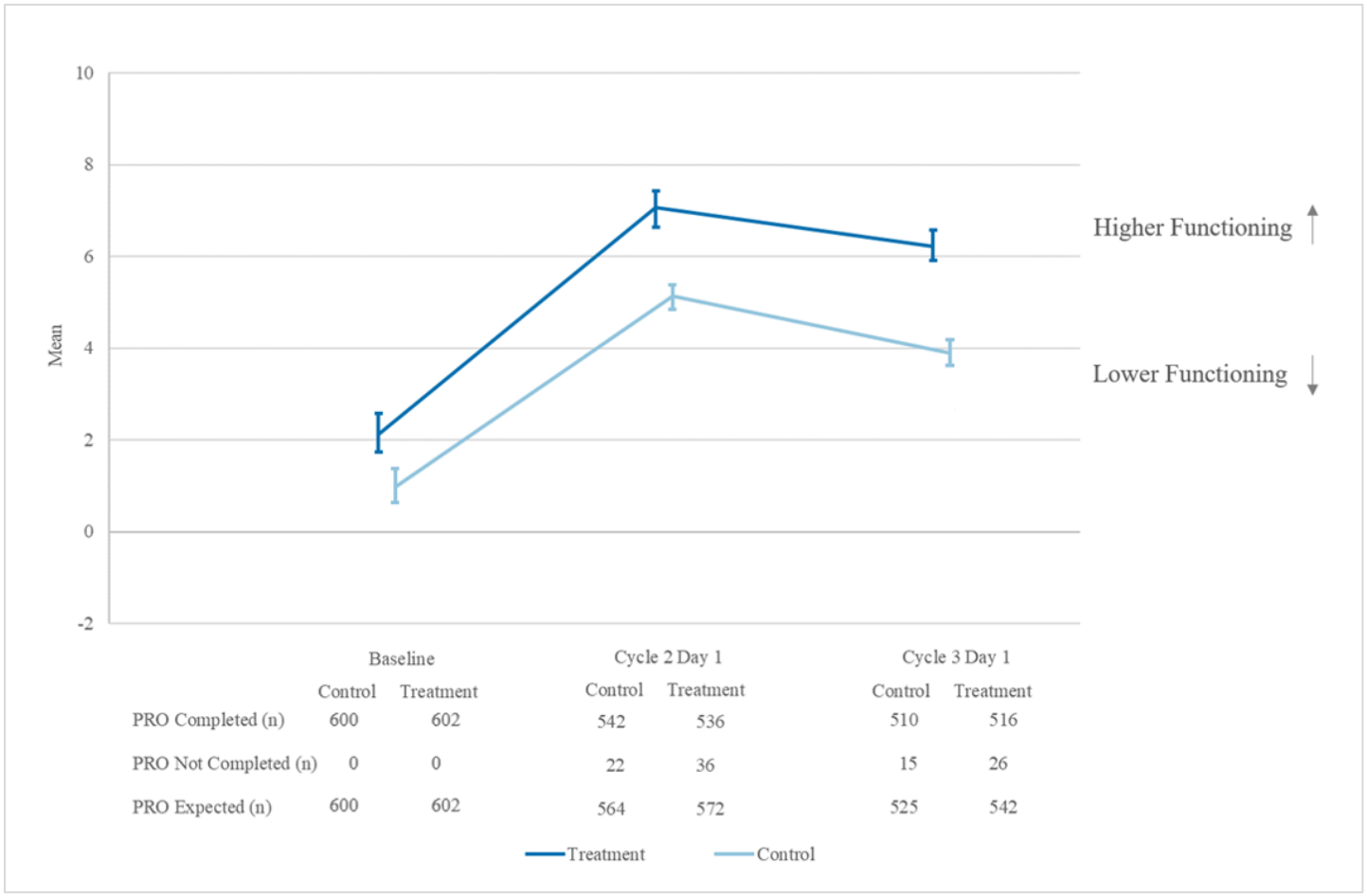
Table A9. Summary Statistics for Item 2 with Continuous Response Options (Safety and Tolerability Example)[18]

Analysis Visit		Control	Treatment
Baseline	PRO Expected[19] (N)	600	602
	PRO Not Completed, n (%)	0 (0.0%)	0 (0.0%)
	PRO Completed, n (%)	600 (100.0%)	602 (100.0%)
	Summary Statistics[20]		
	Mean	2.1	1.0
	Standard Deviation	1.8	0.9
	Standard Error	0.07	0.04
	Median	2.1	1.0
	Minimum	0.0	0.0
	Maximum	4.1	2.0
Cycle 2 Day 1	PRO Expected (N)	564	572
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)
	Summary Statistics		
	Mean	7.1	5.1
	Standard Deviation	4.6	3.7
	Standard Error	0.19	0.15
	Median	7.2	5.1
	Minimum	0.3	0.2
	Maximum	11.8	9.8
Cycle 3 Day 1	PRO Expected (N)	525	542
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)
	Summary Statistics		
	Mean	6.2	3.9
	Standard Deviation	5.2	2.7
	Standard Error	0.23	0.12
	Median	6.6	3.8
	Minimum	0.1	0.0

[18] Denominator used to calculate percentages for PRO Completed and PRO Not Completed is PRO Expected.
[19] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.
[20] Summary Statistics are calculated based on PRO Completed.

	Maximum	11.4	10.0

Figure A6. Descriptive Means for Item 2 with Continuous Response Options (Safety and Tolerability Example for Physical Functioning)[21,22]



[21] The 'Higher Functioning' and 'Lower Functioning' labels are provided as examples for physical functioning. Labels provided within the figure should accurately represent the concept being measured.
[22] Error bars based on a 95% confidence internal for the mean are represented within the line plot.

5.3.6 *Distribution of Change in Responses from Baseline*

Table A10. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example)[23]

Analysis Visit	Treatment Arm	PRO Expected[24]	PRO Completed, n (%)	PRO Not Completed, n (%)	Change in Response Categories,[25] n (%)						
					Improving 1	Improving 2	Improving 3	No Change	Worsening 1	Worsening 2	Worsening 3
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	38 (7.0%)	11 (2.0%)	3 (0.6%)	303 (55.9%)	132 (24.4%)	38 (7.0%)	17 (3.1%)
	Treatment	572	536 (93.7%)	36 (6.3%)	33 (6.2%)	14 (2.6%)	6 (1.1%)	296 (55.2%)	141 (26.3%)	32 (6.0%)	14 (2.6%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	50 (9.8%)	24 (4.7%)	10 (2.0%)	261 (51.2%)	126 (24.7%)	29 (5.7%)	10 (2.0%)
	Treatment	542	516 (95.2%)	26 (4.8%)	44 (8.5%)	28 (5.4%)	11 (2.1%)	261 (50.6%)	123 (23.8%)	39 (7.6%)	10 (1.9%)

[23] Denominator used to calculate percentages for PRO Completed and PRO Not Completed is PRO Expected. Denominator used to calculate percentages for each change in response category is PRO Completed.
[24] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.
[25] The example response categories represent the response options for the item.

Figure A7. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed)

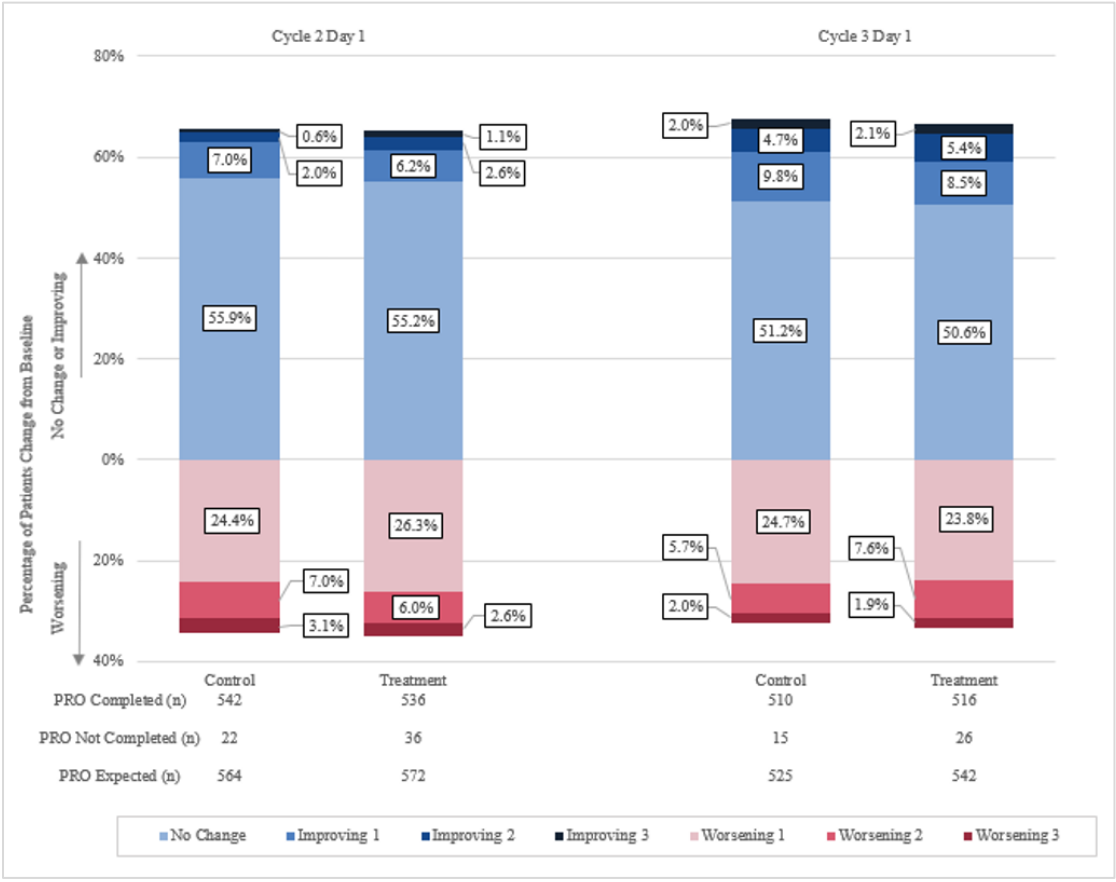


Table A11. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)[26]

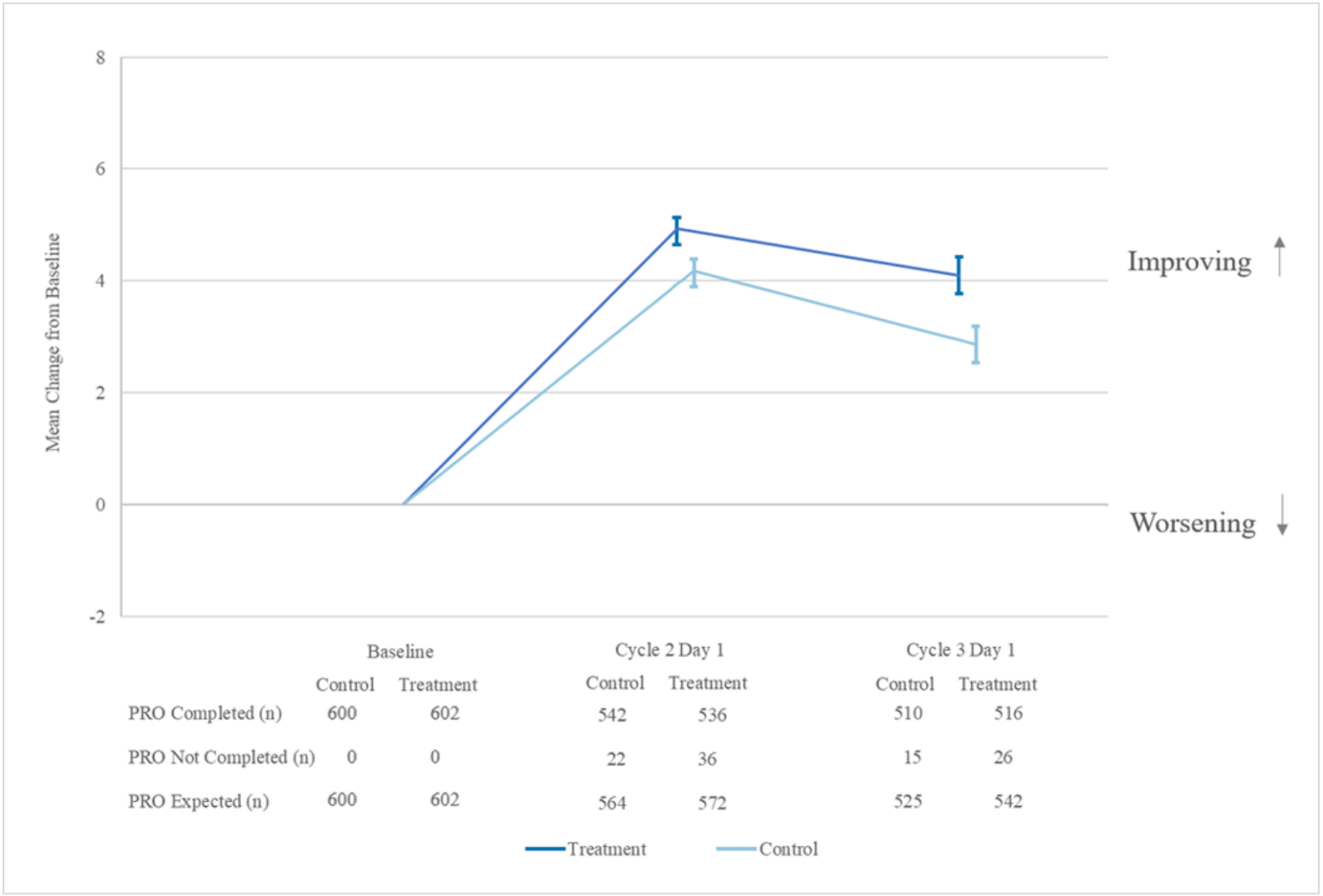
Analysis Visit		Treatment	Control
Cycle 2 Day 1	PRO Expected[27] (N)	564	572
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)
	Summary Statistics[28]		
	Mean	4.9	4.5
	Standard Deviation	4.0	1.7
	Standard Error	0.17	0.19
	Median	5.0	4.2
	Minimum	-1.1	-1.3
	Maximum	10.3	9.0
Cycle 3 Day 1	PRO Expected[1] (N)	525	542
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)
	Summary Statistics		
	Mean	4.1	2.9
	Standard Deviation	5.7	5.6
	Standard Error	0.25	0.24
	Median	4.2	2.9
	Minimum	-1.6	-1.4
	Maximum	8.0	8.5

[26] Denominator used to calculate percentages for PRO Completed and PRO Not Completed is PRO Expected.

[27] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.

[28] Summary Statistics are calculated based on PRO Completed.

Figure A8. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)[29] [30]



[29] The 'Improving' and 'Worsening' labels are provided as examples within the figure. Labels of directionality should align with what is provided in the scoring manual for the PRO measure used.
[30] Error bars based on a 95% confidence internal for the mean are represented within the line plot.

5.3.7 *Incidence of Healthcare Utilization*

Table A12. Incidence of Healthcare Utilization (Safety and Tolerability Example where Denominator = PRO Expected)[31]

Analysis Visit	Treatment Arm	Randomized Patients	PRO Expected[32] (N)	Healthcare Utilization Intervention, n (%)					
				Emergency Department (ED) Visits	Hospitalizations	Opiates	Supportive Care Medications (e.g., Steroids, Transfusions, Growth Factors)	Supportive Care Procedures (e.g., Palliative: Hospice, Nephrostomy)	Other (Describe)
Baseline	Control	600	600	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	564	5 (0.9%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	0 (0.0%)
	Treatment	602	572	5 (0.9%)	3 (0.5%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Cycle 3 Day 1	Control	600	525	7 (1.3%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
	Treatment	602	542	7 (1.3%)	3 (0.6%)	0 (0.0%)	2 (0.4%)	5 (0.9%)	0 (0.0%)

[31] Denominator used to calculate percentages is PRO Expected.

[32] When PRO data are used to inform the evaluation of safety and tolerability, the PRO measure may not be expected to be completed after a patient discontinues from treatment as shown in the table. The PRO Expected column excludes patients who discontinued from treatment and is determined where PRO Expected Flag (PROEXPFL) equals 'Y'.