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Design and Analysis of a Multi-Frequency PRO Collection Strategy in a Clinical Trial

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ABSTRACT

This paper presents a practical framework for implementing a multi-frequency patient-reported outcome (PRO) collection design in clinical trials. Illustrated with the EORTC QLQ-C30 (v 3.0) and its subset IL163, it shows how full questionnaires and subsets can be administered at different frequencies to optimize clinical outcomes and reduce patient burden. The workflow covers scheduling, data quality checks, and CDISC-compliant SDTM and ADaM standardization and analysis, underscoring critical roles of the sponsor, eCOA provider, and analytic team. Practical data QC examples and standardized datasets demonstrate how multi-frequency PRO data can be validated and analyzed within CDISC standards to support patient-centered trial designs.

INTRODUCTION / BACKGROUND

Patient-reported outcomes (PROs) capture patients' perspectives on symptoms, functioning, and overall health condition, and are increasingly recognized by regulatory agencies such as the U.S. Food and Drug Administration (FDA) as important components of benefit-risk assessment. PROs are often collected using full questionnaires at fixed intervals, but different domains may change at different rates in response to intervention. Symptoms can fluctuate quickly, while functioning and quality of life (QoL) may change more slowly. Collecting responses to all instruments at a high frequency increases sensitivity for fast changing symptoms but also increases patient burden and may reduce compliance. A multi-frequency strategy addresses this by collecting items of interest more often and broader domains less frequently. Figure 1 illustrates the workflow and key responsibilities across functional groups.

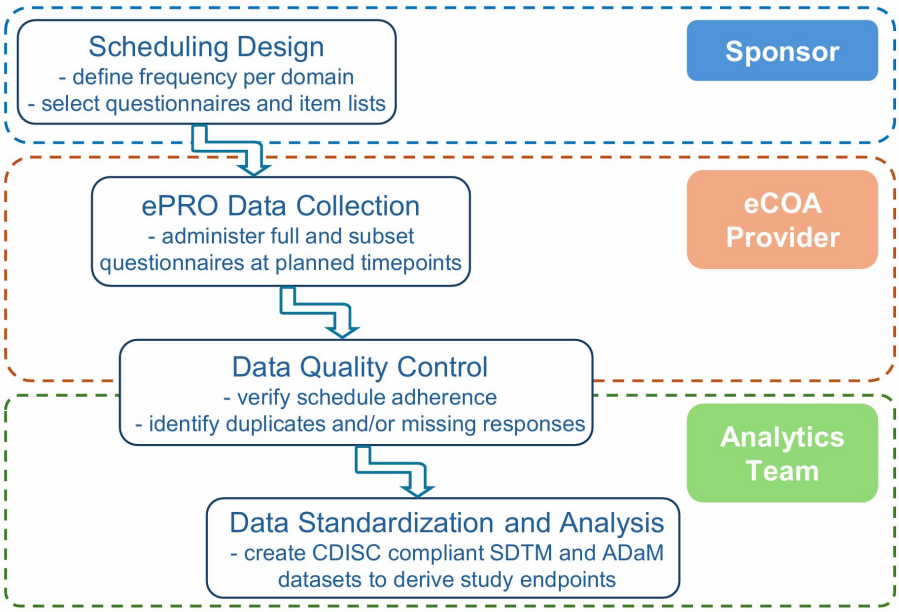

Figure 1 A cross-Function workflow with key responsibilities for implementing multi-frequency PRO collection. eCOA: Electronic clinical outcome assessment.

CASE STUDY

1. STUDY BACKGROUND

In an oncology study, subjects receive Treatment X or placebo weekly. Prior studies show that at least 20% of subjects receiving Treatment X experienced diarrhea, making it a key symptom to monitor. The sponsor selects the EORTC QLQ-C30 (v 3.0) as the core PRO instrument to assess time to deterioration (TTD) for symptoms and QoL. The EORTC Item Library is then used to identify a higher frequency symptom subset. The existing item list IL163, which contains seven items including Q17 ("Have you had diarrhea?"), is selected to support more sensitive symptom monitoring with reduced burden. Additional information about the EORTC QLQ C30 is available at https://qol.eortc.org/questionnaires/core/eortc-qlq-c30/ and the IL163 questionnaires can be found on the EORTC platform (https://itemlibrary.eortc.org).

2. STUDY SCHEDULING DESIGN

As shown in Table 1, subjects completed the full QLQ-C30 prior to first dose of treatment and this assessment serves as baseline. During treatment, IL163 is administered weekly (QW) and the full QLQ-C30 every four weeks (Q4W). This design allows weekly monitoring of all IL163 items, including diarrhea, while assessing the QoL and other broader domains every 4 weeks.

Table 1. Example schedule of assessments.

Instruments	Intervention period (cycle length = 7 Days)					
	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1+ (visit window ± 3 days)
IL163		x	x	x		Weekly until treatment discontinuation
EORTC QLQ-C30	x				x	Q4W until treatment discontinuation

* Subjects complete PRO assessments prior to each treatment infusion.
* The two questionnaires should never be administered at the same timepoint.

3. DATA COLLECTION AND DATA QUALITY CONTROL

During data collection, the eCOA provider uses digital devices to administer PRO questionnaires at planned timepoints.

Before analysis, data quality control should be performed by both the eCOA provider and the analytic team to confirm accurate scheduling and a consistent data structure. Key checks include:

1. Confirming that each instrument is collected at scheduled visits.
2. Ensuring that full questionnaire and its subset are not administered at the same timepoint.
3. Verifying that only one response per subject per item per timepoint.
4. Ensuring missing responses are captured in the raw data.
5. Reviewing any unscheduled or duplicate responses due to deviations prior to analysis inclusion.

Figure 2 shows an example of visual check, with weekly peaks for IL163 and four-week peaks for QLQ-C30, demonstrating adherence to the planned schedule.

a

```
data selected;
 set qs (where=(QSTESTCD ='EOR0117'));
 length QSTESTCD_ $200;
 if SRCDATA='IL163' then QSTESTCD_ ='Q17 from IL163';
 if SRCDATA='EORTC QLQ-C30' then QSTESTCD_ ='Q17 from EORTC QLQ-C30';
run;

proc freq data =selected (where=(1 <= QSDY<= 35)) ;
  tables QSTESTCD_*QSDY / out= freq_selected ;
run;

ods graphics / width=900px height=500px;
proc sgplot data=freq_selected;
  styleattrs datacontrastcolors=(biyg blue);
  scatter x=QSDY y=count / group=QSTESTCD_ jitter markerattrs=(symbol=circlefilled);
  xaxis label="Study day" type=discrete labelattrs=(color=black size=15);
  yaxis label="Number of responses" labelattrs=(color=black size=15 );
  keylegend / title ="" location=inside position=topright across=2;
run;
```

b

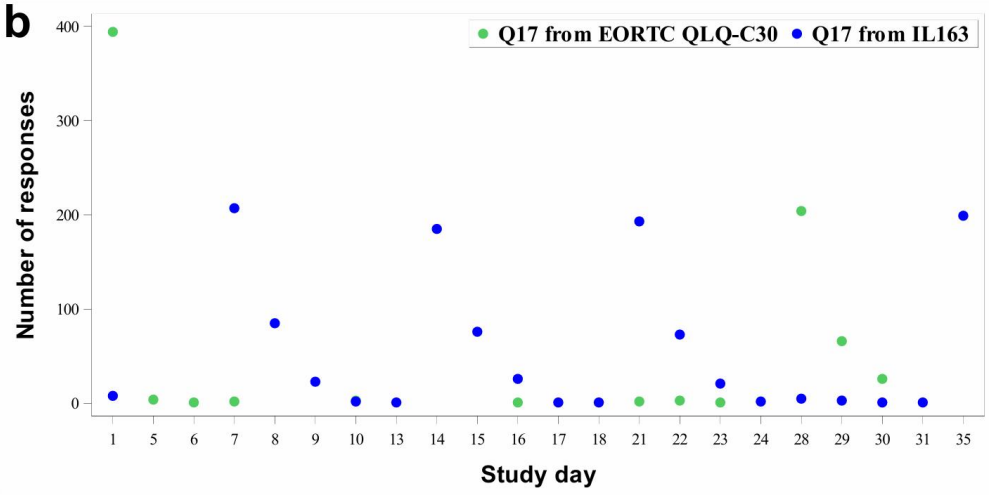

Figure 2. a Example code.

b Responses frequency for item Q17 from IL163 and QLQ-C30 across study days.

4. SUBMITTING DATASETS:

After quality checks are complete, the PRO data is structured and analyzed following CDISC SDTM and ADaM standards. The example datasets in Table 2, 3 and 4 illustrate how QLQ-C30 and IL163 data coexist in the SDTM QS domain and are transformed into ADQS (Analysis Questionnaire Data) and ADQSTTE (Analysis Questionnaire Time-to-Event Data) using the Basic Data Structure.

Example SDTM dataset

Table 2 presents an example subset of the QS dataset. The combination of QSCAT and QSSCAT identifies the data source. Missing PRO assessment are represented.

Missing data

- When the PRO questionnaire is partially or completely missed, a CRF page for reviewing PRO completion status should be reviewed to confirm the visit status and reason for non-completion.
- Missing PRO assessment should be recorded and presented in the dataset.

Example ADQS dataset

In ADQS, raw item responses are converted into standardized 0-100 scores per the EORTC scoring manual. Parameters for Diarrhea are derived from both weekly IL163 data and Q4W QLQ-C30 data, while QoL scores are derived from Q4W QLQ-C30 items (Table 3).

Traceability

Traceability is maintained through the PARCAT variables. PARCAT1 classifies the analysis parameter, and PARCAT2 indicates data sources. All records, including those with missing responses, are retained to ensure transparency and alignment with CDISC principles.

Clinical Interpretation

A change of more than 10 points from baseline is considered clinically meaningful. For symptom scales, an increase reflects deterioration and a decrease reflects improvement. For functioning and QoL scales, the interpretation is reversed. These rules support consistent interpretation across analyses and facilitate downstream TTD derivations.

Example ADQSTTE dataset

ADQSTTE is used to derive TTD endpoint (Table 4), defined as the time from C1D1 to the first clinically meaningful deterioration confirmed at a later visit. Subjects without an event are censored at their last evaluable assessment.

Table 2. Subset of example QS dataset (key variables only).

Row	USUBJID	VISIT	QSCAT	QSSCAT	QSTESTCD	QSTEST	QSORRES	QSSTRESN	QSSTAT	QSREASND	QSBLFL	QSDTC	QSDY
1	A001	CYCLE 1 DAY 1	EORTC QLQ-C30		EOR0117	EOR01-Have You Had Diarrhea	A Little	2			Y	2025-09-08	1
2	A001	CYCLE 2 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea	A Little	2				2025-09-14	7
3	A001	CYCLE 3 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea	Quite a Bit	3				2025-09-21	14
4	A001	CYCLE 4 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea	Quite a Bit	3				2025-09-28	21
5	A001	CYCLE 5 DAY 1	EORTC QLQ-C30		EOR0117	EOR01-Have You Had Diarrhea	A Little	2				2025-10-05	28
6	A001	CYCLE 6 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea	A Little	2				2025-10-12	35
7	A001	CYCLE 7 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea	Not at All	1				2025-10-19	42
8	A001	CYCLE 8 DAY 1	EORTC QLQ-C30	IL163	EOR0117	EOR01-Have You Had Diarrhea			NOT DONE	SUBJECT FORGOT		2025-10-26	49
9	A001	CYCLE 9 DAY 1	EORTC QLQ-C30		EOR0117	EOR01-Have You Had Diarrhea	Not at All	1				2025-11-02	56
10	A001	CYCLE 1 DAY 1	EORTC QLQ-C30		EOR0129	EOR01-Rate Your Overall Health	4	4			Y	2025-09-08	1
11	A001	CYCLE 1 DAY 1	EORTC QLQ-C30		EOR0130	EOR01-Rate Your Overall Quality of Life	5	5			Y	2025-09-08	1
12	A001	CYCLE 5 DAY 1	EORTC QLQ-C30		EOR0129	EOR01-Rate Your Overall Health	5	5				2025-10-05	28
13	A001	CYCLE 5 DAY 1	EORTC QLQ-C30		EOR0130	EOR01-Rate Your Overall Quality of Life	5	5				2025-10-05	28
14	A001	CYCLE 9 DAY 1	EORTC QLQ-C30		EOR0129	EOR01-Rate Your Overall Health	6	6				2025-11-02	56
15	A001	CYCLE 9 DAY 1	EORTC QLQ-C30		EOR0130	EOR01-Rate Your Overall Quality of Life	5	5				2025-11-02	56

Table 3. Subset of ADQS dataset (derived parameters only).

Row	USUBJID	VISIT	AVISIT	PARCAT1	PARCAT2	PARAMCD	PARAM	AVAL	PARAMTYP	QSSTAT	BASE	CHG	CHGCAT1	ADT	ADY
1	A001	CYCLE 1 DAY 1	BASELINE	Symptoms	EORTC QLQ-C30	ILDASC	Diarrhea Score (QW)	33.33	DERIVED					2025-09-08	1
2	A001	CYCLE 2 DAY 1	C2D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)	33.33	DERIVED		33.33	0	NO CHANGE	2025-09-14	7
3	A001	CYCLE 3 DAY 1	C3D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)	66.67	DERIVED		33.33	33.34	DETERIORATION	2025-09-21	14
4	A001	CYCLE 4 DAY 1	C4D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)	66.67	DERIVED		33.33	33.34	DETERIORATION	2025-09-28	21
5	A001	CYCLE 5 DAY 1	C5D1	Symptoms	EORTC QLQ-C30	ILDASC	Diarrhea Score (QW)	33.33	DERIVED		33.33	0	NO CHANGE	2025-10-05	28
6	A001	CYCLE 6 DAY 1	C6D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)	33.33	DERIVED		33.33	0	NO CHANGE	2025-10-12	35
7	A001	CYCLE 7 DAY 1	C7D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)	0	DERIVED		33.33	-33.33	IMPROVEMENT	2025-10-19	42
8	A001	CYCLE 8 DAY 1	C8D1	Symptoms	IL163	ILDASC	Diarrhea Score (QW)		DERIVED	NOT DONE	33.33		MISSING	2025-10-26	49
9	A001	CYCLE 9 DAY 1	C9D1	Symptoms	EORTC QLQ-C30	ILDASC	Diarrhea Score (QW)	0	DERIVED		33.33	-33.33	IMPROVEMENT	2025-11-02	56
10	A001	CYCLE 1 DAY 1	BASELINE	EORTC QLQ-C30	EORTC QLQ-C30	EODASC	Diarrhea Score (Q4W)	33.33	DERIVED					2025-09-08	1
11	A001	CYCLE 5 DAY 1	C5D1	EORTC QLQ-C30	EORTC QLQ-C30	EODASC	Diarrhea Score (Q4W)	33.33	DERIVED		33.33	0	NO CHANGE	2025-10-05	28
12	A001	CYCLE 9 DAY 1	C9D1	EORTC QLQ-C30	EORTC QLQ-C30	EODASC	Diarrhea Score (Q4W)	0	DERIVED		33.33	-33.33	IMPROVEMENT	2025-11-02	56
13	A001	CYCLE 1 DAY 1	BASELINE	EORTC QLQ-C30	EORTC QLQ-C30	EOQLSC	QoL Score (Q4W)	58.33	DERIVED		58.33	0	NO CHANGE	2025-09-08	1
14	A001	CYCLE 5 DAY 1	C5D1	EORTC QLQ-C30	EORTC QLQ-C30	EOQLSC	QoL Score (Q4W)	66.67	DERIVED		58.33	8.34	NO CHANGE	2025-10-05	28
15	A001	CYCLE 9 DAY 1	C9D1	EORTC QLQ-C30	EORTC QLQ-C30	EOQLSC	QoL Score (Q4W)	75	DERIVED		58.33	16.67	IMPROVEMENT	2025-11-02	56

Table 4. Subset of example ADQSTTE dataset (key variables only).

Row	USUBJID	PARCAT1	PARCAT2	PARAMCD	PARAM	AVAL	ADT	CNSR	EVNTDESC
1	A001	Symptoms	IL163	ILDATD	Diarrhea TTD (QW)	14	2025-09-21	0	Confirmed deterioration
2	A001	EORTC QLQ-C30	EORTC QLQ-C30	EODATD	Diarrhea TTD (Q4W)*	56	2025-11-02	1	Last evaluable assessment
3	A001	EORTC QLQ-C30	EORTC QLQ-C30	EOQLTD	QoL TTD (Q4W)	56	2025-11-02	1	Last evaluable assessment

*In actual studies, Diarrhea (Q4W) analysis is not included when a weekly version is available but is included here for illustration.

CONCLUSION

The multi frequency PRO collection design provides a flexible way to align assessment timing with clinical relevance, and this paper showed how to implement it from scheduling and data review through SDTM and ADaM dataset creation and endpoint analysis. By outlining functional group responsibilities and illustrating key data checks and CDISC compliant structures, the examples demonstrate that multiple assessment schedules can coexist within a single PRO instrument while maintaining consistency and traceability. Overall, this framework offers a practical and scalable approach that supports more patient centered, efficient, and data driven clinical trial designs.

REFERENCES

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