

**PharmaSUG 2020 - Paper DS-195**  
**Standardizing Patient Reported Outcomes (PROs)**

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## **ABSTRACT**

Any health outcome directly reported by the subject in the trial is referred to as Patient reported Outcome (PROs). It is an addendum to the data reported by the investigator and/or study staff who are conducting the trial. Patient-reported data helps in better understanding of the subject's perspective. In addition to providing physiological effects, it is critical in evaluating the safety and efficacy of a drug administered. The patient-reported data is typically collected through subject diary. Subject diary, often called patient diary, is a tool used during a clinical trial or a disease treatment to assess the patient's condition or to measure treatment compliance. The use of digitized patient-reported data, or patient-reported data, is on the rise in today's health research setting. Subject diary can collect the information about: Daily symptoms, daily activities, safety assessment, usage of the study medication to measure the compliance, usage of the concomitant medication and disease episodes on frequent basis. In this presentation, we will be exploring the standardization of the diary data with standard SDTM domains in different therapeutic areas.

## **INTRODUCTION**

Data in a clinical trial are generated and collected by: The investigator, Study staff or/and Directly by patients. Data generated by patients, is a health outcome directly reported by the subject in the trial experiencing it. Patient-reported outcomes (PROs) are commonly collected in clinical trials and should provide impactful evidence on the effect of interventions on patient symptoms and quality of life. Patient-reported outcomes (PROs) can be included in clinical trials as primary or secondary endpoints and are increasingly recognized by regulators, clinicians, and patients as valuable tools to collect patient-centered data. PROs provide unique information on the impact of a medical condition and its treatment from the patient's perspective; therefore, PROs can be included in clinical trials to ensure the impact of a trial intervention is comprehensively assessed. PRO is becoming an important component in the evaluation of prescription drugs in registration, reimbursement, and labeling claims.

This paper elaborates the standardization of these patient reported data and converting them into standard SDTM domain for further analysis purposes.

## **PROS – BACKGROUND**

FDA quotes - "A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts

Medical technology enables us to measure physiological and biochemical data of patients, psychometric evaluation of the patient cannot be accommodated by these technologies, which contributes to the effectiveness of the drug being tested. Patients can perceive some important factors during the trial which



## TECHNICAL METHOD

An electronic hand-held system such as a tablet or text messaging (SMS) is used. Also, technical tools that can be used to receive these data in an efficient, participant-friendly manner are rapidly evolving.

Asking patients to provide their data electronically has many advantages: the quality of data is better, and these systems allow the site staff ongoing understanding of how the patient is doing, and whether the data are entered reliably or not. With paper diaries, this only becomes obvious at the next patient visit when they bring the diary to the site. ePROs also reduces the study data entry workload for the site staff.

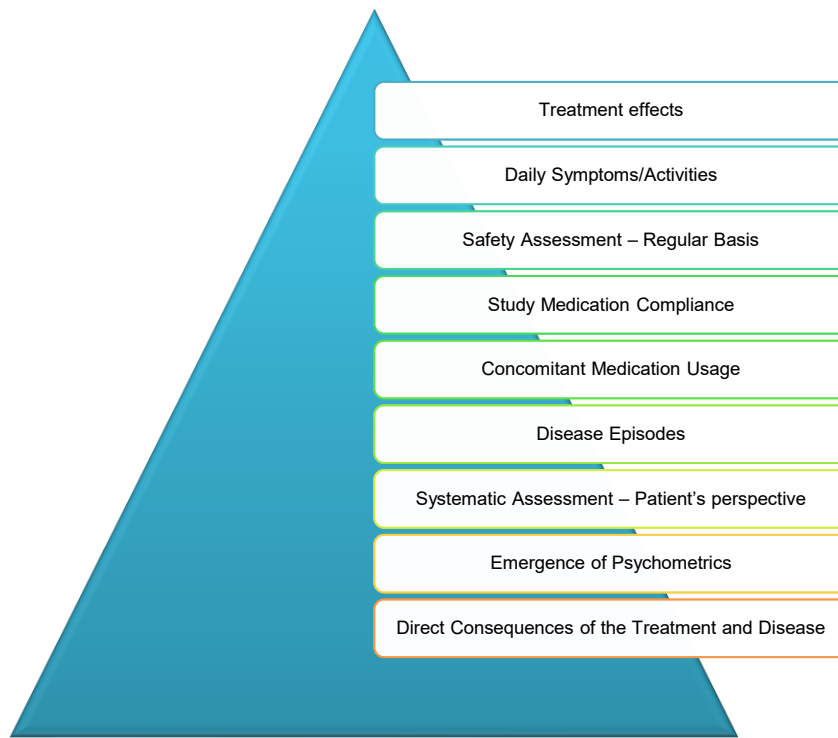


Figure 2. Technical method of data

<p><b>Traditional</b></p>	<p>Slow completion /DB Lock of Clinical trials</p> <p>In efficient and poor data</p> <p>Uncontrolled authentication</p> <p>Not clear if changes made to data. Cannot confirm when data was filled or back filled.</p> <p>Paper diaries are submitted via the investigator – through the clinical site.</p> <p>Loss of Paper Diary data, cannot get back the data entered</p>	<p><b>Technical</b></p>
	<p>Enhance efficiency and speed and accelerated DB locks of clinical trials</p> <p>Efficient data management</p> <p>Passwords and device identification methods.</p> <p>Patient cannot change the data once reported.</p> <p>Accurate date and time stamping</p> <p>Electronic Diaries' often deployed by a third-party service provider on behalf of the sponsor</p> <p>Lost of device may not impact on the already entered data, as the entered data will be in Data base.</p>	

Table 1. Comparison between traditional and technical method of data collection

## SCENARIOS/SITUATIONS FOR COLLECTING DIARY DATA



**Table 2. List of Scenarios**

## CASE STUDIES

### E-DIARY DATA COLLECTED IN VACCINE TRIALS

An important aspect of vaccine development is the assessment of the vaccine's reactogenicity. Reactogenicity refers to the property of a substance to produce an expected or common adverse reaction when introduced into the body.

Reactogenicity event refers to a specific expected or common reaction following vaccine administration. In vaccine studies, a reactogenicity event(s) is typically caused by an inflammatory response to the vaccine under study and may include reactions like fever or redness at the site of administration. Reactogenicity describes immediate short-term reactions to vaccines, not long-term sequelae.

Reactogenicity is assessed in studies by monitoring a pre-defined set of adverse events over a pre-defined observation period. Pre-defined means identified prior to the start of the trial to support reactogenicity assessments of one or more investigational product(s) in the study protocol. The pre-defined observation period starts immediately after the administration of one or more investigational product(s) and lasts a pre-defined number of days as stated in the study protocol.

The schedule daily assessments of reactogenicity for a pre-defined period following the vaccination are usually performed by the study subject and recorded in a diary. Many pharma companies opt for the electronic version of the diaries for easier and hassle-free data collection. According to TAUG for vaccines, when the diary data is collected electronically Flat model to be implemented on those data collected for standardization.

### Flat model

All the daily assessments are transcribed/loaded from the diary card and a global event record is created, whether a reactogenicity event occurred during the pre-defined assessment interval.

The daily assessments are captured in the FACE domain, with FATESTCD=OCCUR, following the SDTM IG rules. The CE domain is created by a global summary record of the each reactogenicity event assessed

	USUBJID	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FATPTREF	FATPT
1	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY1
2	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY2
3	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY3
4	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY4
5	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY5
6	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY6
7	1001	OCCUR	Occurrence Ind..	Fatigue	REACTOGENI..	SYSTEMIC	N	VACCINATION..	DAY7
8	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY1
9	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY2
10	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY3
11	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY4
12	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY5
13	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY6
14	1001	OCCUR	Occurrence Ind..	Redness	REACTOGENI..	ADMINISTRAT..	N	VACCINATION..	DAY7

**Table 3. SDTM FACE DATASET For E-Diary Observations**

### QUESTIONNAIRE IN ONCOLOGY TRIALS

In oncology trials, the PRO is interpreted in context of survival and other outcome evidence to evaluate the treatment effectiveness. Questionnaires in oncology is important consideration as both the disease and treatments impact several aspects of life.

The questionnaires should have clearly defined methods and procedures, ensuring consistent measurement of data. The questionnaire should be designed in wholesome manner covering different aspects of QOL. Below are some of the generic questionnaires available:

- ❖ EuroQol-5D (EQ-5D)
- ❖ 36-Item Short Form Health Survey (SF-36)
- ❖ European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

The questionnaires are standardized into the QS domain as per the SDTMIG. When huge amount of data is collected through various questionnaires, we can also standardize it into individual split domains based on the questionnaires used.

	USUBJID	QSTESTCD	QSTEST	QSCAT	QSORRES	QSSTRESN	VISIT
1	1001	EQ5D0201	EQ5D02-Mobility	EQ-5D-5L	I HAVE NO PROBLEMS WALKING	1	CYCLE1DAY1
2	1001	EQ5D0201	EQ5D02-Mobility	EQ-5D-5L	I HAVE NO PROBLEMS WALKING	1	CYCLE2DAY1
3	1001	EQ5D0202	EQ5D02-Self-Care	EQ-5D-5L	I HAVE NO PROBLEMS WASHING OR DRESSING MYSELF	1	CYCLE1DAY1
4	1001	EQ5D0202	EQ5D02-Self-Care	EQ-5D-5L	I HAVE NO PROBLEMS WASHING OR DRESSING MYSELF	1	CYCLE2DAY1
5	1001	EQ5D0203	EQ5D02-Usual Activities	EQ-5D-5L	I HAVE NO PROBLEMS DOING MY USUAL ACTIVITIES	1	CYCLE1DAY1
6	1001	EQ5D0203	EQ5D02-Usual Activities	EQ-5D-5L	I HAVE NO PROBLEMS DOING MY USUAL ACTIVITIES	1	CYCLE2DAY1
7	1001	EQ5D0204	EQ5D02-Pain/Discomfort	EQ-5D-5L	I HAVE NO PAIN OR DISCOMFORT	1	CYCLE1DAY1
8	1001	EQ5D0204	EQ5D02-Pain/Discomfort	EQ-5D-5L	I HAVE NO PAIN OR DISCOMFORT	1	CYCLE2DAY1
9	1001	EQ5D0205	EQ5D02-Anxiety/Depression	EQ-5D-5L	I AM NOT ANXIOUS OR DEPRESSED	1	CYCLE1DAY1
10	1001	EQ5D0205	EQ5D02-Anxiety/Depression	EQ-5D-5L	I AM NOT ANXIOUS OR DEPRESSED	1	CYCLE2DAY1
11	1001	EQ5D0206	EQ5D02-EQ VAS Score	EQ-5D-5L	99	99	CYCLE1DAY1
12	1001	EQ5D0206	EQ5D02-EQ VAS Score	EQ-5D-5L	88	88	CYCLE2DAY1

**Table 4. SDTM QS Dataset for EQ-5D**

	USUBJID	QSTESTCD	QSTEST	QSCAT	QSORRES	QSSTRESN	VISIT
1	1001	EOR0101	EOR01-Trouble Doing Strenuous Activities	EORTC QLQ-C30 V3	A LITTLE	2	CYCLE1DAY1
2	1001	EOR0101	EOR01-Trouble Doing Strenuous Activities	EORTC QLQ-C30 V3	VERY MUCH	4	CYCLE2DAY1
3	1001	EOR0102	EOR01-Trouble Taking Long Walk	EORTC QLQ-C30 V3	NOT AT ALL	1	CYCLE1DAY1
4	1001	EOR0102	EOR01-Trouble Taking Long Walk	EORTC QLQ-C30 V3	QUITE A BIT	3	CYCLE2DAY1
5	1001	EOR0103	EOR01-Trouble Taking Short Walk Outside	EORTC QLQ-C30 V3	NOT AT ALL	1	CYCLE1DAY1
6	1001	EOR0103	EOR01-Trouble Taking Short Walk Outside	EORTC QLQ-C30 V3	A LITTLE	2	CYCLE2DAY1
7	1001	EOR0104	EOR01-Stay in Bed/Chair During the Day	EORTC QLQ-C30 V3	NOT AT ALL	1	CYCLE1DAY1
8	1001	EOR0104	EOR01-Stay in Bed/Chair During the Day	EORTC QLQ-C30 V3	A LITTLE	2	CYCLE2DAY1
9	1001	EOR0105	EOR01-Need Help Eating/Dressing/Washing	EORTC QLQ-C30 V3	NOT AT ALL	1	CYCLE1DAY1
10	1001	EOR0105	EOR01-Need Help Eating/Dressing/Washing	EORTC QLQ-C30 V3	NOT AT ALL	1	CYCLE2DAY1

**Table 5. SDTM QS Dataset for EORTC QLQ-C30**

## CONCLUSION

The integration of Pros with traditional endpoints in clinical trials provides a comprehensive evaluation of the intervention under study. Data derived from PROs can provide valuable evidence for benefit-risk assessment that can be used to communicate the effect of a treatment on patient symptoms, functioning and QOL on medical treatments and are subsequently useful for market adoption and consideration for value-based framework assessments. The Pharma companies have to ensure that trial design, study endpoints and select PRO measures in a way that it generates meaningful data that would be beneficial throughout the lifecycle of the medicinal product.

## REFERENCES

- Shilpakala Vasudevan (2018), Going Pro with PROs: Implementation and Analysis of Patient Reported Outcomes PhUSE US Connect 2018 - Paper AB10
- Amie Bissonett (2017), A SAS®sy Study of eDiary Data PharmaSUG 2017 - Paper BB14
- Amy Chu, Christine Teng and Jia He(2019), Compliance Report for Patient-Reported Outcomes PhUSE US Connect 2019 - Paper DH13

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## RECOMMENDED READING

- *Study Data Tabulation Model Implementation Guide: Human Clinical Trials, Version 3.2, CDISC Submission Data Standards Team (November 26, 2013).*
- *Study Data Tabulation Model, Version 1.4, CDISC Submission Data Standards Team*
- *Therapeutic Area Data Standards User Guide for Vaccines Version 1.1 (Provisional)*

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