



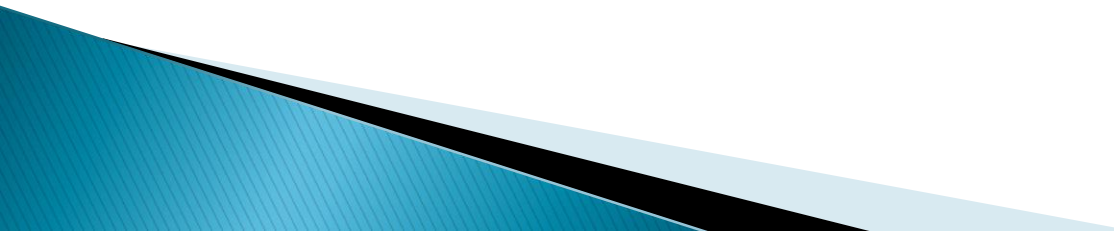
Analysis of Patient Reported Outcome (PRO) Endpoints in Clinical Trial

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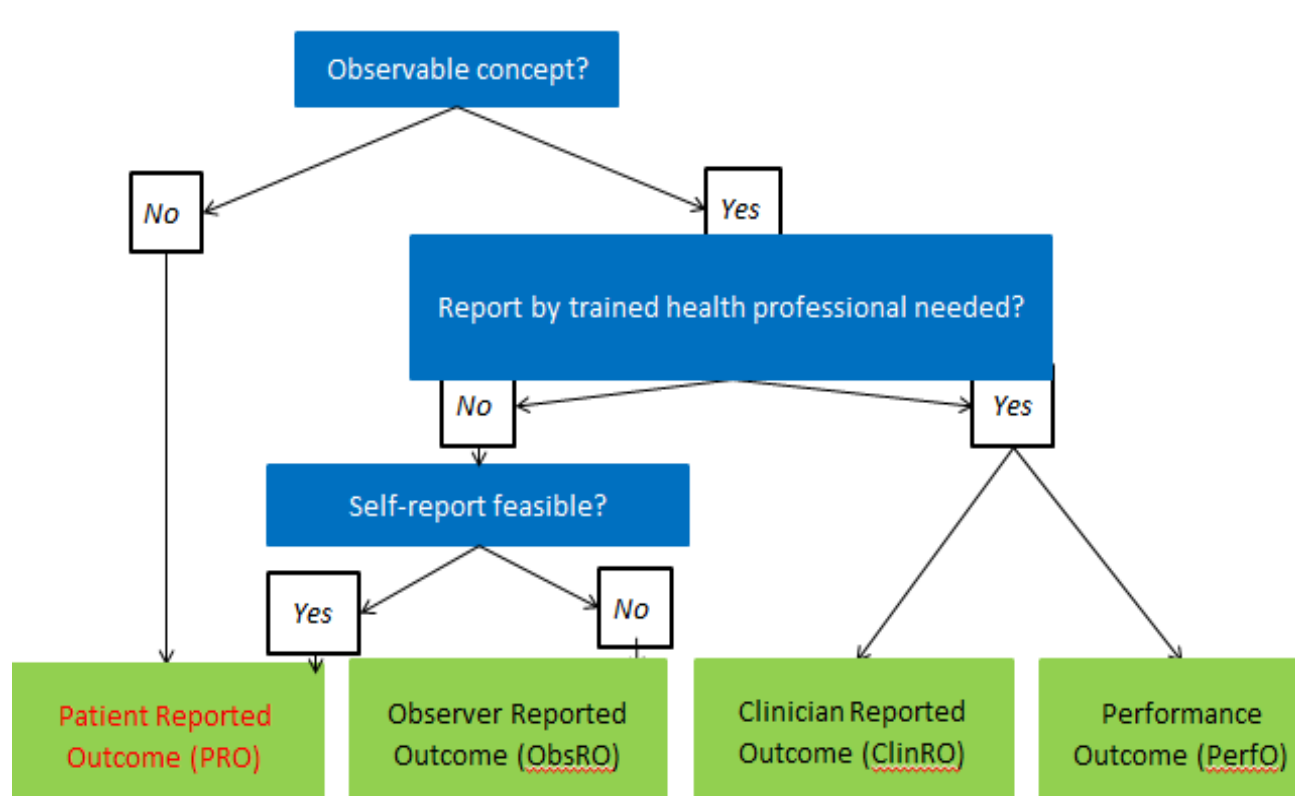
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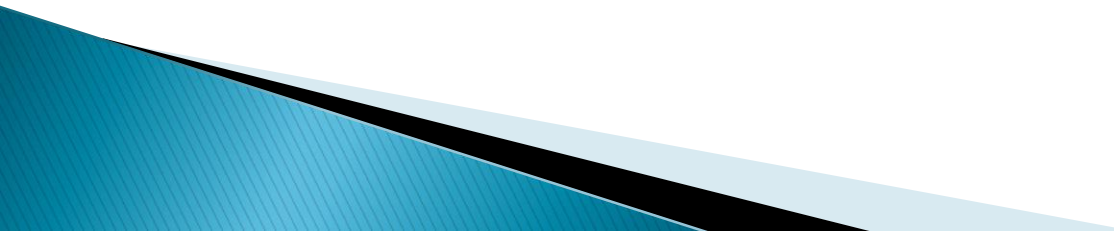
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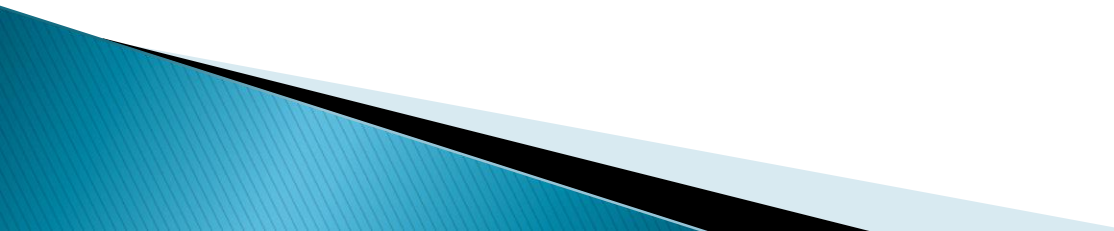
What is PRO



What is PRO

- ▶ Endpoint/outcome that is directly reported by a patient without interpretation by physicians or others.
 - Symptoms (e.g., pain, nausea)
 - Impact of disease on patient Function
 - Patient opinion about a drug product preference and satisfaction
 - ▶ PROs are typically measured with questionnaires, which are made up of items (questions) grouped into one or more subscales, or domains, which purport to measure some underlying construct.
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Why PRO Analysis

- ▶ PRO have been widely used in clinical trials and other types of health research and played a significant part in the development and evaluation of preventive, psycho-social, and therapeutic interventions.
 - ▶ PRO is increasingly important in the field of oncology studies. The FDA has specific guidance on PRO data to support labeling claims and Health Technology Assessment submissions.
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Case Example 1

- ▶ Study on the treatment of overactive bladder
- ▶ King's Health Questionnaire (KHQ)
- ▶ KHQ is a patient self-administered self-report and has 3 parts consisting of 21 items.

Parts	Domain (9 in number)	Sub items (21 in number)	Responses	Score
Part I	1. General health perception	1. Self-perceived health	5 (Very good, Good Fair, Poor, Very poor)	0 to 100
	2. Incontinence impact	2. Life burden due to disease	4 (Not at all, A little, Moderately, A lot)	0 to 100
Part II	3. Role limitations	3. House hold tasks	4 (Not at all, A little, Moderately, A lot)	0 to 100
		4. Limitation of daily activities	4 (Not at all, A little, Moderately, A lot)	0 to 100
	4. Physical limitations	5. Limitation of physical activities	4 (Not at all, A little, Moderately, A lot)	0 to 100
		6. Limitation of daily activities	4 (Not at all, A little, Moderately, A lot)	0 to 100
	5. Social limitations	7. Limitation of social life	4 (Not at all, A little, Moderately, A lot)	0 to 100
		8. Inability to visit friends, relatives	4 (Not at all, A little, Moderately, A lot)	0 to 100
	6. Personal relationships	9. Partner relationship	4 (Not at all, A little, Moderately, A lot)	0 to 100
		10. Sex life	4 (Not at all, A little, Moderately, A lot)	0 to 100
		11. Family life	4 (Not at all, A little, Moderately, A lot)	0 to 100
	7. Emotions	12. Depression	4 (Not at all, A little, Moderately, Very much)	0 to 100
		13. Anxiety, nervousness	4 (Not at all, A little, Moderately, Very much)	0 to 100
		14. Feeling bad	4 (Not at all, A little, Moderately, Very much)	0 to 100
	8. Sleep/energy	15. Sleep deprivation	4 (Not at all, A little, Moderately, All the time)	0 to 100
		16. Tiredness	4 (Not at all, A little, Moderately, All the time)	0 to 100
	9. Severity measures	17. Pad usage	4 (Not at all, A little, Moderately, All the time)	0 to 100
		18. Fluid restriction	4 (Not at all, A little, Moderately, All the time)	0 to 100
		19. Change of underclothes	4 (Not at all, A little, Moderately, All the time)	0 to 100
		20. Urinary odour	4 (Not at all, A little, Moderately, All the time)	0 to 100
Part III	Symptom severity scale	21. Ten bladder related symptoms such as frequency, nocturia, urgency, urge & stress incontinence, bedwetting, intercourse incontinence, urinary infection, dysuria and dribbling.	For each sub question: 4 (Nil, Mild, Moderate, Severe)	0 to 30

eCRF



SDTM



ADaM



TFL

King's Health Questionnaire

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol. 1997; 104: 1374-1379
The electronic copy of the instrument provided here is not intended for use with or administration to study subjects. Copies of the instrument will be separately provided to the study site for that purpose.

1.	Enter date collected if different from visit date	/ /
2.	1. How would you describe your present overall health?	☐ Very good ☐ Good ☐ Fair ☐ Poor ☐ Very poor

3.	2. How	QSDTC		QSGRPID	QSTESTCD	QSTEST		QSCAT		QSORRES			
		2012-07-10		KHQ	KHQ01	Describe Your Present Overall Health		KINGS HEALTH QUESTIONNAIRE		FAIR			
4.	3. Does	2012-07-10		ADT	ADY	PARAM		PARAMCD	PARAMN	PARAMTYP	PARAMCAT	AVAL	AVALC
		2012-07-10		10JUL2012	1	Bladder Prob Affects Ability to Travel		KHQ06	4060		KINGS HEALTH QUESTIONNAIRE	4	A LOT
5.	4. Does	2012-07-10		10JUL2012	1	Bladder Problem Limits Social Life		KHQ07	4070		KINGS HEALTH QUESTIONNAIRE	2	SLIGHTLY
		2012-07-10		10JUL2012	1	Bladder Problem Limits Visiting Friends		KHQ08	4080		KINGS HEALTH QUESTIONNAIRE	2	SLIGHTLY
6.	5. Does	2012-07-10		10JUL2012	1	Bladder Prob Affects Relation w/partner		KHQ09	4090		KINGS HEALTH QUESTIONNAIRE	0	NOT APPLICABLE
		2012-07-10		10JUL2012	1	Bladder Problem Affects Your Sex Life		KHQ10	4100		KINGS HEALTH QUESTIONNAIRE	0	NOT APPLICABLE
7.	6. Does	2012-07-10		10JUL2012	Summary of Baseline King's Health Questionnaire (KHQ)								
		2012-07-10		10JUL2012	All Randomized Subjects								
		2012-07-10		10JUL2012									

Summary of Baseline King's Health Questionnaire (KHQ) All Randomized Subjects

		Drug A		Drug B		Total	
		n	(%)	n	(%)	n	(%)
	Subjects in population	XXX		XXX		XXX	
	1. How would you describe your present overall health?						
	Very good	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	Good	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	Fair	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	Poor	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	Very poor	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	NULL	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	2. How much do you think your bladder problem affects your life?						
	Not at all	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	A little	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	Moderately	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	A lot	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)
	NULL	XX	(XX.X)	XX	(XX.X)	XX	(XX.X)

Case Example 2

- ▶ PRO endpoints in the field of oncology are neither pure efficacy nor pure safety endpoints as they are affected by both disease progression and treatment tolerability. It is usually measured by
 - EORTC QLQ-C30 (common across cancers)
 - EORTC QLQ-LC13 (lung cancer specific)
 - EuroQol-5D (EQ-5D)
 - FACT-G, FACT-L

Quality of Life (QoL)

- ▶ Quality of life refers to the degree to which a person enjoys important possibilities of his or her life, and includes both subjective and objective indicators. It is a reflection of individual's sense of well-being and satisfaction with life.

EORTC QLQ-C30

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised) [†]	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised) [†]	PF2	5	3	1 to 5	F
Role functioning (revised) [†]	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

EORTC QLQ-C30

Analysis of Change from Baseline of EORTC QLQ-C30 Global Health Status/Quality of Life at Cycle X
FAS population

Treatment	N	Baseline Mean (SD)	Cycle X Mean (SD)	Global health status/quality change from baseline at Cycle X	
				Mean (SD)	LS Mean (95% CI)
Control	xxx	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX XX.XX)
Drug x mg/kg	xxx	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX XX.XX)
Drug xx mg/kg	xxx	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX)	XX.XX (XX.XX XX.XX)
Pairwise Comparison				Difference in LS Means (95% CI)	p-value
Drug x mg/kg vs. Control				XX.XX (XX.XX XX.XX)	x.xxx
Drug xx mg/kg vs. Control				XX.XX (XX.XX XX.XX)	x.xxx
Drug x mg/kg vs. Drug xx mg/kg				XX.XX (XX.XX XX.XX)	x.xxx

Analysis Methods

- ▶ Many studies that use PROs are longitudinal. cLDA analysis is usually applied to evaluate
 - ▶ between arm differences of longitudinal changes from baseline to pre-specified post-baseline.
- ▶ In recent years, time-to-event models such as the time-to-HRQoL score deterioration (TTD) have also been proposed as an approach to the analysis of longitudinal HRQoL in oncology, calculated using the Kaplan-Meier method and compared using the log-rank test.
- ▶ However, one of the major concerns about PRO analysis has been that of missing data.

Missing Data

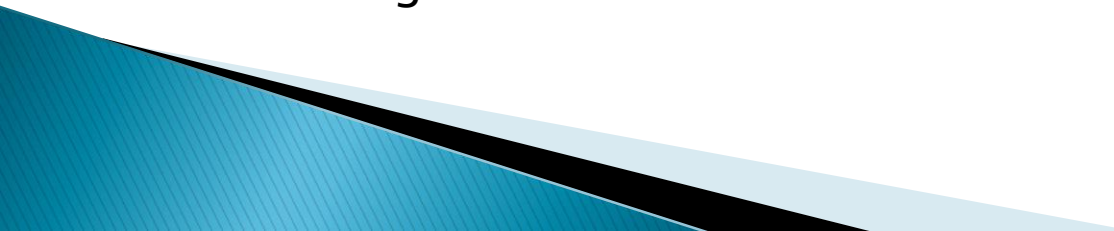
▶ Reason

- Avoidable reasons: Missing data because of study design and administration or the complexity of questionnaire. By improve study design and procedure, avoidable missing data could be minimized
- Non-avoidable reasons: Missing data due to disease process, such as death. At the beginning of study, non-avoidable missing data should be evaluated and pre-specified rules should be developed.

▶ Type

- Non-response: the whole response for the specific visit is missing.
- score/unit drop out: part of the response is missing

▶ Pattern

- Missing completely at random:
 - Missing at random
 - Missing not at random
- 

Statistical Programming Consideration (1)

- ▶ The cLDA model implicitly treats missing data as missing at random (MAR), which is reasonable if the missing data does not depend on the unobserved value. Sensitivity analyses through imputations may also be performed against the robustness of the MAR assumption.
- ▶ The cLDA model is specified as follows:
- ▶ $E(Y_{ijt}) = \gamma_0 + \gamma_{jt}I(t > 0) + \beta_{it}X_i$, $j=1,2,3$, $t=0,1,2,3$,
- ▶ where Y_{ijt} is the PRO score for subject i , with treatment assignment j , at visit t , γ_0 is the baseline mean for all treatment groups, γ_{jt} is the mean change from baseline for treatment group j at time t , X_i is the stratification factor, and β_{it} is the coefficient vector for stratification factor at time t .

Statistical Programming Consideration (2) – Sensitivity analyses

- ▶ The imputation could be based on the missing pattern and the reason for the missing data. Specifically, the following multiple-imputation rule could be applied for EORTC QLQ-C30:
 1. Impute missing data with the reason for the missing data being too ill to complete due to disease under study, too ill to complete due to side effects of treatment, or in hospital or hospice from the worst 15th percentile outcomes observed in raw scale score;
 2. Death will be imputed as the worst outcome possible in raw scale score.
 3. Impute missing data due to disease progression and without any PRO assessment falling into the visit window based on the observed scores of the progressed patient subgroup.
 4. Impute missing data with missing reason unreachable or questionnaire translation not available in subjects' language and other based on the estimated analysis model of the patient's own arm, i.e., assuming those missing data are missing at random.

Statistical Programming Consideration (3) – Sensitivity analyses

- ▶ Another sensitivity analysis (MNAR)
- ▶ All the monotone missing values (i.e., there are no reported data at a later visit after the time point of missing data.) could be multiply-imputed based on the analysis model built based on the control group, regardless of missing reasons.
- ▶ All intermediate missing or baseline missing data will be imputed firstly based on the MAR assumption using the MCMC method in SAS PROC MI.

Conclusion

- ▶ Patient reported outcomes could be measured and analyzed in a stable and reliable ways, though there are still potential issues need special attentions.
- ▶ Currently PRO may be used in some therapeutic areas like oncology or psychology, but in the future, it may be wildly used in clinical trials of all disease as its importance in health technology assessment.
- ▶ One of the major concerns about PRO analysis is missing data. Missing data lead to decrease in precision and power caused by the reduction in data, and the potential for bias in the estimation of both between (e.g., treatment effect) and within group effects (e.g., change over time). Reducing missing data during study conduct is more important and helpful than modeling.

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