www.mapi-trust.org

www.eriqa-project.com

PRO Methods Group
www.cochrane-pro-mg.org

Educational Program onPatient-Reported Outcomes in Clinical Trials

The PROmats

BACKGROUND

The need to assess the patient's perception on the impact of disease and treatment in clinical trials has gained in importance for the **pharmaceutical industry.**

*The term "patient-reported outcomes" (PROs) has evolved to include any endpoint derived from patient reports, whether collected in the clinic, in a diary, or by other means, including single-item outcome measures, event logs, symptom reports, formal instruments to measure health-related quality of life (HRQL), health status, adherence, and satisfaction with treatment.

At the same time, the **Food and Drug Administration (FDA)** has become increasingly concerned about the use of PRO and data yielded by its assessment in both labeling and promotional claims.

Similarly, the **European Agency for the Evaluation of Medicinal Products (EMEA)** emphasizes key issues to be addressed, such as the added value of HRQL/PRO, psychometric properties of validated instruments and analysis/ interpretation of PRO data.

To meet the needs of clinical trials reviewers and pharmaceutical companies, we have developed **PROmats**, an **Educational Program on PRO assessment**, in collaboration with the **Cochrane Patient-Reported Outcomes Methods Group** and the **ERIQA group.** This educational program provides practical information on instruments for health outcomes assessment, utilization of the instruments in clinical trials, and interpretation of the results.

OBJECTIVES

- **Facilitate the dialogue** between regulators, members of pharmaceutical companies and health-care providers, as well as improve intra-company communications.

- Help reviewers and experts of regulatory agencies understand PRO issues better, in order to improve the decision making process while reviewing the files submitted to their agency.

*Wilke R.J, Burke L.B., Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Controlled Clinical Trials 2004: 25; p.535-552.

METHODOLOGY OF THE PROMATS

Each PROmat is a large sheet of paper divided into three parts:

- A brief **Background** introducing the theme;
- A summary of **Objectives** to achieve during the discussion;
- A list of **Assignments** to be completed by the participants.

Our **PROmats** training emphasizes **Interactive Learning** in a group setting to facilitate the understanding of key concepts. Participants are separated into small working groups and complete the assignments through group discussions. Then, each group shares its answers with the other participants in order to reach (or not) a consensus.
The entire process is under the supervision of two facilitators who use their experience and expertise in the field of PRO to make the sessions more meaningful.

We distribute the following materials to each participant in order to provide additional background information on PRO:

- A **Workbook**
- A copy of the **slide presentation**
- Copies of key **PRO instruments**

CONTENT AND OBJECTIVES OF EACH **PROMAT MODULE** *:

PROmats	Content & Objectives
1 Objectives	**How do disease and treatment impact upon a patient – from the patient's perspective?** • To identify the impact of health conditions and treatment from a patient's perspective • To distinguish the different ways diseases and treatment can affect the life of patients from their own perspective
2 Objective	**Deciding which PRO to use to assess the impact of disease and treatment** • To define the relevant domains and items depending on the conditions studied
3 Objective	**How is a new PRO questionnaire developed?** **1st Steps: Development of items and item reduction** • To describe the process of item generation and item reduction
4 Objectives	**How is a new PRO questionnaire developed?** **2nd Steps: Psychometric validation and cultural adaptation** • To describe the evaluation of psychometric properties: reliability, validity, and responsiveness • To describe the process of cultural adaptation
5 Objectives	**Choosing an appropriate existing measure** • To explore the process for selecting an appropriate PRO instrument for use in a specific clinical trial scenario • To examine the trade-offs in the selection process • To review the criteria necessary to evaluate a PRO instrument appropriately • To identify and evaluate established questionnaires for use in a specific patient group
6 Objectives	**Analysis of PRO data** • To identify the issues and potential problems in designing a statistical analysis plan for PRO data • To understand the different methods of dealing with missing data • To gain the knowledge and skills needed to analyze differences in PRO data between two or more treatments
7 Objectives	**Presentation and interpretation of PRO included in clinical trials** • To critically evaluate published literature describing PRO surveys • To interpret PRO data that are reported in the published literature

*** PROmats 3, 4, 6 and 7 are available with Respiratory specific assignments**

PROMAT EXAMPLE

HRQL Methods Group

6- ANALYSIS OF PRO DATA

BACKGROUND

Patient-Reported Outcomes (PRO) scores are increasingly included in clinical trials of new medical treatments. Before analysing PRO data, it is important to review the collected data for completeness, missing values, and to calculate scale scores. The statistical analysis of PRO data requires an understanding of how the data were collected and the underlying disease indication and the potential impact of the comparative treatments.

Attention also needs to be paid to missing assessments, especially missing data due to mortality or other illness-related reasons (eg hospitalization).

Decisions need to be made regarding the statistical model, how to deal with multiple statistical tests, variations between clinical centres and repeated measurements of PRO during the clinical trial.

It is important to evaluate the impact of missing data on the treatment comparisons. The key is to conduct the data analysis in a way that results in fair and unbiased treatment comparisons and PRO findings.

ASSIGNMENTS

Assignment 1:
For this assignment, you should review the clinical trial design and hypothesis together with PRO generated during the trial. Are you able to identify any problems with the data that may pose problems in the statistical analysis? Can you recognise the types of missing data?

Assignment 2:
Discuss the results from the clinical trial presented and decide how the differences in the missing data will affect the PRO analysis.

Assignment 3:
Using the tabulated results of the hypothetical clinical trial, this assignment will show you how to evaluate different techniques for addressing missing questionnaires or scores.

Assignment 4:
Using the clinical trial design presented, you will consider various methods for addressing the issue of multiple testing. The method must be chosen carefully to optimise the chance of a successful PRO claim.

ASSIGNMENT 1

Preparing PRO data for statistical analysis

For this assignment, review a sample of tabulated PRO data from the completed Clinical trial shown below. Based on your review, identify up to 4 problems that you observe in the sample PRO data that are likely to impact on the statistical analysis.
How would you categorise the type of missing data (see below)?

Problem 1:	
Problem 2:	
Problem 3:	
Problem 4:	

Clinical Trial Hypothesis

A hypothetical clinical trial has been designed to evaluate the two different antiretroviral treatments in patients with moderately symptomatic HIV disease with CD4 counts under 200. A total of 600 male patients, ages 30-50, were randomly assigned to one to two treatments and PRO data were collected at baseline and every four months for one year (a total of 4 PRO assessments). Study patients were recruited from 10 clinical centres. The main hypothesis is that treatment A will result in improved energy, increased ability to engage in everyday activities, and improved psychological weel-being compared to treatment B. The HIV Health Survey is used as the measure of PRO (a copy is supplied). A hypothetical set of group means for 300 asymptomatic HIV patients is also provided.

Treatment Group	Site Number	Patient Number	Visit	PF	VT	MH	GH	SF
A	1	0101	0	45	40	61	58	50
A	1	-	1	50	45		61	62
A	1	-	2	52	51	64	66	59
A	1	-	3	57	60	70	68	
A	1	0102	0	67	65		74	70
A	1	-	1	60	64		70	65
A	1	0103	0			65	55	
A	1	-	1	55	57	61	58	59
A	1	-	2	61	65	65	61	
A	1	0104	0	52	51	54	61	55
A	1	-	1	57	60		68	65
A	1	-	2	67	65	75	74	70
A	1	-	3	60	64	70	70	
A	1	0105	0	51	53		55	55
A	2	0151	0		40	61	58	50
A	2	-	1		45	55	61	
A	2	0153	0		51	64	66	59
A	2	-	1		60		68	65
A	2	0162	1		65	75	74	
A	2	-	0	60	64	70	70	65
A	2	0163	0	51	53	65	55	55
A	2	-	1	55	57	61	58	59
A	2	-	2	61	65	65	61	
A	2	0164	0	52	51		61	55
A	2	-	1	57	60	60	68	65
A	2	-	2	67	65	75	74	
A	2	-	3	60	64	70	70	65
A	2	0165	0	51	53	65	55	
A	2	-	1	60	59		61	62
A	3	0166	0	55	50	54		58
B	1	0111	0	45	40	61	58	
B	1	-	1	50	45	55	61	52
B	1	-	2	52	51	64	66	59
B	1	-	3	57	60	70	68	65
B	1	0112	0	57	55		54	60
B	1	-	1	60	54	50	50	65
B	1	0113	0	51	53	65	55	55
B	1	-	1	55	57	61	58	59
B	1	-	2	61	65		61	58
B	1	-	3	60	64	63	60	54
B	1	0114	0	52	51	54	61	55
B	1	-	1	57				
B	1	-	2	67	65		74	70
B	1	-	3	60	64	70	70	65
B	1	0115	0	51	53		55	55
B	2	-	1	55	57	65	60	60
B	2	0121	0	45	40	61	58	50
B	2	-	1	50	45	55	61	52
B	2	-	2	52	51		66	59
B	2	0131	0	57	60		68	65
B	2	0132	0	57	55	55	54	60
B	2	-	1		54	50	50	65
B	2	0143	0		53		55	55
B	2	-	1	55	57	61	58	59
B	2	-	2	61	65	65	61	68
B	2	-	3	60	64		60	54
B	2	0144	0	52	51	54	61	55
B	2	-	1		60	60	66	65
B	2	-	2	67	65	75	74	70
B	2	-	3		64		70	65
B	2	0145	0		53	65	55	55
B	2	-	1	55	57	65	60	60
B	2	0171	0	50	53		47	55
B	2	-	1	52	55	62	51	55
Asymptomatic Means				74	70	60	69	75

ASSIGNMENT 2

Evaluating the impact of missing data in the statistical analysis of PRO data

For this assignment, assume that once the clinical trial was completed you have the following pattern of completed PRO assessments by treatment group.

	Treatment A (T_A)	Treatment B (T_B)
Baseline N (T_0)	300	300
Month 4 assessment (T_1)		
Complete data	280	270
Missing, died	10	25
Missing, discontinued	10	5
Month 8 assessment (T_2)		
Complete data	250	240
Missing, died	35	45
Missing, discontinued	15	15
Month 12 assessment (T_3)		
Complete data	230	200
Missing, died	45	75
Missing, discontinued	25	25

Based on your review of the available data, do you think that differential mortality between the two groups will create problems for the PRO data analysis?
Write down possible problems and solutions.

How do you think that the differential mortality between the treatment groups may impact on the PRO findings?

_____

_____

ASSIGNMENT 3

Evaluating techniques for addressing missing questionnaires/scores

Listed below are six techniques for dealing with missing data in PRO data analyses. Evaluate each approach based on the example clinical trial and describe their advantages and disadvantages.

1. Exclude all patients who died, dropped out of the study or who had missing scores and examine differences across treatments at baseline and last data collection point (end of follow-up complete case analysis).
Advantages / Disadvantages: _____

2. Perform available case analysis at each timepoint.
Advantages / Disadvantages: _____

3. Impute a fixed value for missing scores (observed mean or median, worst observed score).
Advantages / Disadvantages: _____

4. Impute a value for missing scores based on the LOCF (Last Observed Value Carry Forward).
Advantages / Disadvantages: _____

5. Impute values for missing scores based on methods such as hot deck imputation (selection at random of an observed score), regression imputation (prediction of missing scores from a regression), or Markov chain (using probability of transition).
Advantages / Disadvantages: _____

6. Perform multiple imputation (different values are attributed to missing scores).
Advantages / Disadvantages: _____

ASSIGNMENT 4

Possible methods for addressing multiple testing

- Adjustment of alpha (for example using the Bonferroni procedure: α /number of tests).
- Choice of one domain as primary endpoint for the PRO analysis.
- Choice of one timepoint as primary endpoint for the PRO analysis.
- Use of multivariate analysis (MANOVA, mixed-effect model, repeated measures model).
- Development of summary measures (post-treatment mean, mean change from baseline, last value minus baseline, average rate of change over time, maximum value, area under the curve, time to reach a specific value).

Which method of analysis would you recommend for the study?

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PREVIOUS SESSIONS: HEALTH AUTHORITIES AND REVIEWERS

Health Authorities

- Agence Française de Sécurité Sanitaire des Produits de Santé **(AFSSAPS)**; 2002/2003, France
- Food and Drug Administration **(FDA)**;2002, USA
- Agence Nationale d'Accréditation et d'Evaluation en Santé **(ANAES)**; 2003, France
- Institut National d'Assurance Maladie Invalidité **(INAMI)**; 2003, Belgium
- European Medicines Agency **(EMEA)**; 2005, UK

Cochrane Collaboration

- Xth International Cochrane Colloquium; 2002, Norway
- XIth International Cochrane Colloquium; 2003, Spain
- XIIth International Cochrane Colloquium; 2004, Ottawa

ADDITIONAL INFORMATION

We organize **on-site courses**.
Our **PROmats** training is a **flexible** program; it can be tailored to suit your company's specific needs.
You choose the modules that are best suited for your team and your work schedule.

In the table below you have examples of possible formulas:

Duration	½ day	1 day
Number of Workmats	2-4	5-7
Participants	12-20	12-20
Facilitator(s)	2	2

Additional explanatory lectures are available to clarify key concepts (Promats 1 & 2) & interpretation issues (Promat 7)

DEVELOPMENT TEAM

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