

# Impact and integration of the occurrence of missing data in the longitudinal analysis of health-related quality of life in oncology

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- HRQoL assessment is based on patients' responses to questionnaires
- In RCTs, HRQoL is assessed at several measurement times :
  - ▷ at baseline (before the beginning of treatment, before randomization)
  - ▷ during the treatment
  - ▷ at the end of the treatment

### Aim

To study the impact of treatment on patient's HRQoL level over time

- Correlation between patient's HRQoL measures over time
  - **Longitudinal analysis**
- Major challenge for longitudinal analysis of the HRQoL
  - **The occurrence of missing data (MD)**

(Fairclough DL, *Stat Med*, 1998)

## Patterns of missingness

- **Intermittent :**

Patient fails to complete a questionnaire at one or more measurement times, but HRQoL data are available after this occurrence

- **Monotone :**

No further data are available for a patient after the occurrence of MD

→ **Mainly corresponding to withdraw of some patients before the planned end of the study or death**

(Diggle P, *Applied statistics*, 1994)

→ **informative of the HRQoL level of the patient**

- **Mixed :** period of intermittent missingness followed by monotone missingness


	Assessment 1	Assessment 2	Assessment 3	Assessment 4	Assessment 5
Complete data	x	x	x	x	x
Intermitent MD	x x x	x	x x	x  x	x x x
Monotone MD	x x x	x x x	x x	x	
Mixed MD	x x x		x	x x	

## Profiles of MD

- **Completely at random (MCAR)** : independent of observed data and unobserved HRQoL level
- **At random (MAR)** : depend on observed data
- **Not at random (MNAR)** : depend on unobserved HRQoL level

(Little RJ, New York : John Wiley & Sons, 1987)

## Problem of MD

- MD MCAR are uninformative → no bias
  - MD MAR are uninformative
    - no bias only if we consider observed data dependent on the MD
    - MD considered as MCAR
  - MD MNAR are informative → bias
-  MD can induce a bias in the longitudinal analysis of the HRQoL and always a statistical power decrease

- Direct impact of the occurrence of MD → **the study population**
- Preferable method to prevent bias and enables comparison between studies  
→ **intent-to-treat (ITT) population**
- ITT population
  - ▷ all patients enrolled
  - ▷ regardless of the treatment received
  - ▷ regardless of the respect of the eligibility criteria
- Due to the occurrence of MD → **definiton of an ITT population subset**
- modified ITT (m-ITT) population
  - ▷ ITT population subset
  - ▷ all ITT patients with HRQoL data available at baseline

- Different methods were proposed for the longitudinal analysis of the HRQoL
- The most used methods :

→ **linear mixed models (LMMs)**

(Cnaan A, *Stat Med*, 1997)

→ **time to HRQoL score deterioration (TTD)**

(Bonnetain F, *Eur J Cancer*, 2010 ; Anota A, *QoL Research*, 2015 ; Hamidou Z, *The Oncologist*, 2011)

## LMMs

- Assesses the evolution of the HRQoL scores over time
- **Fixed effects**
  - ▷ arm effect : corresponds to the global  $\neq$  between the two arms which is present since baseline
  - ▷ time effect : corresponds to the global time effect between the two arms
  - ▷ interaction effect arm  $\times$  time : to study if the HRQoL level changes  $\neq$  between the two arms
- **Random effects**
  - ▷ patients effect
  - ▷ time effect

} take into account the individual variations

## TTD

- Different definitions
  - **Adjuvant situation : TTD**
    - ▷ 1<sup>st</sup> clinically significant HRQoL score deterioration  $\geq 5$  points compared to the baseline score (Hamidou Z, *The Oncologist*, 2011)
  - **Advanced/metastatic situation : Time until definitive deterioration**
    - ▷ with no further improvement  $\geq 5$  points compared to the baseline score
    - ▷ including or not death as an event (**QoL deterioration-free survival**)

(Bonnetain F, *Eur J Cancer*, 2010)
  - Minimal clinically important difference included in event definition
- (Anota A, *QoL Research*, 2015)

## Consideration of MD

- MD are ignored in LMMs and TTD methods
- HRQoL level remains constant between two consecutive measurement times



## Objectives

- To explore and to compare methods to take into account the occurrence of MD in the longitudinal analysis of HRQoL data
- Project focused on two approaches : **TTD** and **LMMs**
- All patterns of missingness and profiles of MD will be explored
- Profiles of MD at baseline and over time
- The methods investigated to take into account the occurrence of MD will be adapted to the longitudinal analysis method used

- **WP1 : Literature review**

- ▷ to determine the profile of MD
- ▷ to take into account the occurrence of MD on the longitudinal data

### Objectives

- to study the advantages and disadvantages of each method
  - to ensure the exhaustiveness of the methods explored
- **WP2 : Evaluation and comparison of  $\neq$  approaches for dealing with MD**
    - ▷ application to database from several clinical trials
    - ▷ according to the TTD method (**WP2.a**)
    - ▷ according to the LMMs method (**WP2.b**)
  - **WP3 : Simulations**
    - ▷ to complete and to validate the results obtained on real data
  - **WP4 : Development of an R package**

- Other methods could be used according to the results of the literature review
- **MCAR** : Simple and multiple imputations
- **MAR** :
  - ▷ Multiple imputation taking into account the observed data
  - ▷ IPTW method of the propensity score (only for the TTD)  
(Anota A, *Plos one*, 2015)
- **MNAR** :
  - ▷ Imputation by extreme values (worst case analysis)

## TTD

- ▷ Competitive risk analysis between the HRQoL deterioration and death
- ▷ To consider death as an event
- ▷ To consider the patient in deterioration just a day after the last available HRQoL measure, if no deterioration is observed before

## LMMs

- ▷ Pattern mixture model

- All patterns of missingness and profiles of MD will be investigated
  - **Treatment of MD at baseline and over time**
- To propose some recommendations for the longitudinal analysis of HRQoL according to the patterns of missingness and profiles of MD
  - **Reliable and robust interpretation of the results**
  - **Switch from m-ITT population to ITT population**
- Standardisation of the treatment of MD in the longitudinal analysis of HRQoL
  - **SISAQoL and QRECISt projects supported by the EORTC**

(Bonnetain F, *JCO*, 2016 ; Bottomley A, *The Lancet Oncology*, 2016)

**Thank you for your attention**