

Statistical methods to determine the minimal clinically important difference in health-related quality of life questionnaires

Célia Touraine, Ahmad Ousmen, Nina Deliu, Francesco Cottone, Franck Bonnetain, Fabio Efficace, Anne Brédart, Sophie Gourgou, Caroline Mollevi, Amélie Anota

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Context

- Health-related quality of life (HRQoL) as an endpoint in cancer clinical trials

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- ↪ To determine a threshold beyond which a change is clinically important

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MCID definitions

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- **Others definitions** and nuances in the terminology, see:
 - King, M. T. (2011). "A point of minimal important difference (MID): a critique of terminology and methods." *Expert review of pharmacoeconomics & outcomes research*, 11(2), 171-184.

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Anchor-based methods

■ Principle

- Change in the HRQoL is linked to an external criteria (anchor)
- Score differences in the distinct groups of the anchor are likely to be meaningful

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- Subjective assessments of patient status

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- Change in the HRQoL is linked to an external criteria (anchor)
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■ Two kind of anchors

- Objective indicators
- Subjective assessments of patient status

■ Score differences can be determined

- Cross-sectionally (a single time point)
- Longitudinally
 - Prospective anchors
 - Retrospective anchors

Cross-sectional anchor-based methods

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Clinical anchors to categorize patients into distinct groups

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Clinical anchors to categorize patients into distinct groups

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PS	0	1	2	3	4
mean score	65.4	61.3	57.9	55.1	51.9

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Mean score differences between adjacent clinically distinct categories

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MCID definition

Mean score differences between adjacent clinically distinct categories

Example: MCID ranges from 2.8 to 4.1:

	0 vs. 1	1 vs. 2	2 vs. 3	3 vs. 4
MCID	4.1	3.4	2.8	3.2

Longitudinal anchor-based methods

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Clinical anchors (prospective)

- HRQoL *and anchor* assessed prospectively at T_1 and T_2
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Example: ECOG Performance status (PS) at T_1 and T_2 :

	much worse	worse	same	better	much better
PS change	-2 to 4	-1	0	+1	+2 to 4
MCID 1	-8	-2	1.5	8.8	15.4
MCID 2		-3.5		7.3	

Longitudinal anchor-based methods

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- HRQoL assessed prospectively at T_1 and T_2
- At T_2 , the patient is asked to assess the HRQoL change between T_1 and T_2 :
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Limitations: Recall bias
Influence of patients' current health state

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Methods based on sample variation

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0.2	small change
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- Standardized response mean (SRM) = $\frac{\text{mean change}}{\text{SD of change}}$
- Responsiveness statistic = $\frac{\text{mean change}}{\text{SD of change}_{|G}}$ where G is a group of stable patients

Methods based on the sample variation

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Methods based on the sample variation

- Standard error of measurement (SEM)

$$\text{SEM} = (\text{SD at baseline}) \times \sqrt{1 - r}$$

where r = reliability coefficient

→ **MCID**: 1 SEM, 1.96 SEM

- Growth curve analysis

→ **MCID**: based on empirical Bayes slope estimates

Advantage: all available data are used

Limitation: requires large samples to provide stable estimates

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Distribution-based	Ability to account for change beyond some level of random variation
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Some recommendations

- Multiple anchors
- Correlation ≥ 0.3 between the anchor and the HRQoL domain
- To combine both approaches
 - Simple comparison
 - Considering anchor-based estimates as MCID only if $> \text{MDC}$ where $\text{MDC} = \text{minimal detectable change (based on the SEM)}$
 - Considering anchor-based estimates as MCID if $0.2 \leq \text{ES} \leq 0.5$

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Remark

- No method taking into account the response shift effect (RS) (RS = patient's adaptation to the disease treatment)

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Step	Description
WP 1:	Literature review
WP 2:	Impact of RS on the determination of the MCID
WP 3:	Methodology to take into account the RS effect
WP 4:	Simulation study
WP 5:	Implementation of the methodology in an R package

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WP1 : Literature review

A systematic literature review of the methods for MCID determination in HRQoL cancer questionnaires

- 1 To identify the existing methods
- 2 To provide an overview of the most widely used methods
- 3 To identify the main limitations in the MCID determination methodology and give some guidelines

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Impact of RS on the determination of the MCID

- Using 3 data bases
 - Adjuvant breast cancer (n=381)
 - Resistant ovarian cancer (n=361)
 - Unresectable glioblastoma (n=134)
- Analyses
 - 1 MCID determination
 - 2 Characterization of the RS effect
 - 3 Adjusted MCID determination (taking account the RS effect)