Evaluating thresholds for minimal clinically important difference in patient-reported outcome measures in locally advanced or metastatic urothelial cancer: a systematic literature review

PCR237

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CONCLUSIONS

- **The interpretation of minimal clinically important differences (MCIDs) for patient-reported outcome measures (PROMs) is challenging**
- **MCID thresholds are useful in that they provide a benchmark for clinicians and researchers to assess whether clinically meaningful change has occurred**
- **In this systematic literature review (SLR), we found underreporting of MCID thresholds and heterogeneity in definitions of thresholds for the same PROMs in clinical trial publications and health technology assessment (HTA) submissions for locally advanced or metastatic urothelial cancer (la/mUC)**
  - **These issues hinder the ability to evaluate and compare changes in PROMs across studies**
- **Future research and collaboration should focus on defining and implementing consistent MCID thresholds in la/mUC research to capture patient perspectives on the effectiveness of different treatments**
  - **These efforts should include patient input**

PLAIN LANGUAGE SUMMARY

- **We reviewed all available published evidence from studies that evaluated quality of life as reported by people with locally advanced or metastatic urothelial cancer, a type of bladder cancer**
- **Our aim was to explore the thresholds used to define whether differences in quality of life are clinically meaningful, known as the minimal clinically important difference (MCID)**
- **We found that the majority of studies did not report MCID thresholds**
  - **Of the studies that did report MCID, we found that different studies used differing MCID thresholds, even for commonly used questionnaires**
- **As a result, it is difficult to compare quality of life outcomes reported in different studies**
- **We recommend that future research be conducted to establish common thresholds that adequately capture people's experiences, and people with bladder cancer should be involved in these studies**

BACKGROUND

- Increased use of PROMs in clinical research and policymaking requires reliable and consistent interpretation
- Suitable reference values for MCID thresholds facilitate interpretation of changes in patients' health-related quality of life (HRQOL), guiding treatment decisions and improving care
- MCID thresholds are context specific, meaning there is not one threshold that can be used for a single HRQOL instrument across all studies, diseases, and situations
- Additionally, different thresholds may be needed to evaluate improvement and worsening[1,2]
- Ultimately, the MCID concept is complex, with thresholds varying based on how they were estimated (ie, anchor based vs distribution based) (**Figure 1**)[3]

Figure 1. MCID fast facts

MCID thresholds can be estimated using different methods[3-5]	• Anchor-based methods compare measures of HRQOL to other measures that are clinically relevant • Distribution-based methods are based on statistical characteristics of the sample
Baseline impairment can influence thresholds[3]	• The amount of change that is considered clinically meaningful may differ between patients with severe baseline HRQOL impairment and those with milder impairment[3]
Change is not 100% clinical[3]	• Regression to the mean is a statistical phenomenon meaning that extreme scores tend to become less extreme at follow-up • Patients with greater impairment at baseline have more room to improve
Standardized thresholds do not exist[3]	• One MCID threshold cannot necessarily be used across all circumstances, especially when using distribution-based methods to establish the threshold (eg, effect size)
Research is mixed regarding whether similar thresholds can be used for improvement and worsening[3]	• Improvement may require a smaller amount of change than worsening to be considered clinically meaningful
Before establishing a threshold for MCID, the HRQOL instrument needs to be fully validated with evidence that it is responsive to change[3]	

HRQOL, health-related quality of life; **MCID**, minimal clinically important difference.

METHODS

- An SLR of interventional and observational studies reporting PROMs in la/mUC was conducted (May 29, 2024) to identify MCID thresholds
  - HTA submissions and ClinicalTrials.gov were also reviewed to include additional MCID thresholds not reported in publications
  - Documents from the following bodies were searched:
    - National Institute for Health and Care Excellence (NICE)
    - Canada's Drug Agency (CDA)
    - Institute for Comparative Effectiveness Research (ICER)
    - Scottish Medicines Consortium (SMC)
    - Institute for Quality and Efficiency in Health Care (IQWIG)
    - Pharmaceutical Benefits Advisory Committee (PBAC)
- Studies reporting MCID thresholds were analyzed for specific threshold definitions and whether thresholds were met

RESULTS

- The SLR identified 49 studies consisting of 37 clinical trials and 12 real-world evidence (RWE) studies reporting PROM data[6,7]
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EQ-5D were the most commonly reported PROMs
- Across PROMs, MCID thresholds were reported in 13 la/mUC trial publications, 1 ClinicalTrials.gov entry, 2 HTA submissions, and no RWE studies
- Various MCID thresholds were reported for the EORTC QLQ-C30 Global Health Status/Quality of Life (GHS/QOL) domain, with some publications specifying multiple thresholds to describe the degree of clinically meaningful change (**Table 1**)
  - The ClinicalTrials.gov publication did not report MCID results
  - Five publications reported meeting the MCID threshold, with an additional publication reporting this result in a subgroup of patients with moderate/severe pain at baseline
- MCID thresholds were also reported for the EQ-5D, Functional Assessment of Cancer Therapy – Bladder (FACT-Bl), National Comprehensive Cancer Network-FACT Bladder Symptom Index-18 (NFBlSI-18), and Brief Pain Inventory – Short Form (BPI-SF) (**Table 2**)
  - One of the publications was a validity study intended to establish MCID thresholds, whereas the remaining publications evaluated whether the MCID threshold was met
  - Consistency was observed for the reported EQ-5D visual analog scale (VAS) MCID threshold for improvement, which was met in 3 studies

Table 1. MCID thresholds for EORTC QLQ-C30 GHS/QOL in la/mUC research

Publication	Trial	Threshold definition(s)	Trial-defined threshold met (Y/N)
ClinicalTrials.gov 2015[8]	RANGE	10 points*	Not reported
Niegisch et al. 2016[9]	2 prospective trials of paclitaxel-based treatment	Minimal change: 5 to 10 points Moderate change: 10 to 20 points Strong change: 20 points	Y (minimal change)
Sharma et al. 2017[10]	CheckMate 275	10 points	N
Vaughn et al. 2018[11]	KEYNOTE-045	10 points	N
Holmsten et al. 2020[12]	VINGEM	Small clinical difference: 5 to 9 points Moderate clinical difference: 10 to 19 points	Y
O'Donnell et al. 2020[13]	Study 1108	10 points	Y
Morales-Barrera et al. 2022[14]	KEYNOTE-052	10 points	Y
van der Heijden et al. 2023[15]	CheckMate 901	10 points	N
Gupta et al. 2024[16]	EV-302	10 points	Y (subgroup with moderate/severe baseline pain)
Milowsky et al. 2024[17]	EV-103	Group-level change: 5 to 10 points Individual-level change: 10 points	N
Rosenberg et al. 2024[18]	EV-301	8 points	Y
IQWIG report[19]	EV-301	≥10 points*	N

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; **GHS/QOL**, Global Health Status/Quality of Life; **IQWIG**, Institute for Quality and Efficiency in Health Care; **la/mUC**, locally advanced or metastatic urothelial cancer; **MCID**, minimal clinically important difference.
*Threshold for worsening as opposed to improvement.

Table 2. MCID thresholds for other commonly used PROMs in la/mUC research

Publication	Trial	Threshold definition(s)	Trial-defined threshold met (Y/N)
EQ-5D utility index			
Grivas et al. 2023[20]	JAVELIN Bladder 100	0.09 to 0.12 points	N
CADTH report[21]	KEYNOTE-045	0.08 points	N
EQ-5D VAS			
Sharma et al. 2017[10]	CheckMate 275	7 points	Y
Ohyama et al. 2019[22]	CheckMate 275	7 points	Y
Morales-Barrera et al. 2022[14]	KEYNOTE-052	7 points	Y
IQWIG report[19]	EV-301	≥15 points*	N
Grivas et al. 2023[20]	JAVELIN Bladder 100	7 to 12 points	N
CADTH report[21]	KEYNOTE-045	7 points	N
FACT-Bl total score			
Degboe et al. 2019[23]	Study 1108	6 to 12 points	NA (validity study to establish threshold)
O'Donnell et al. 2020[13]	Study 1108	Half of a standard deviation	N
NFBlSI-18 total score			
Degboe et al. 2019[23]	Study 1108	4 to 7 points	NA (validity study to establish threshold)
Grivas et al. 2023[20]	JAVELIN Bladder 100	Group-level change: 3 to 6 points Individual-level change: 3 to 9 points	N
BPI-SF			
Milowsky et al. 2024[17]	EV-103	2 points	Y

BPI-SF, Brief Pain Inventory – Short Form; **CADTH**, Canadian Agency for Drugs and Technologies in Health; **FACT-Bl**, Functional Assessment of Cancer Therapy – Bladder; **la/mUC**, locally advanced or metastatic urothelial cancer; **MCID**, minimal clinically important difference; **NA**, not applicable; **NFBlSI-18**, National Comprehensive Cancer Network Functional Assessment of Cancer Therapy – Bladder Symptom Index-18; **VAS**, visual analog scale.
*Threshold for worsening as opposed to improvement.

LIMITATIONS

- The present research was limited by data availability; not all studies that reported PROM data provided MCID thresholds
- HTA reports from NICE, CDA, ICER, SMC, IQWIG, and PBAC were included in our searches; thus, considerations on MCID thresholds from other HTA agencies were not captured in the analysis

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