Appendix A. Example MIDs for Specific Clinical Topics

Table 5. Minimal Important Differences in Outcomes in Women with Urinary Incontinence

Reference	Tool*	Conditions	Domain	Minimal Important Differences	Worst to Best
Quality of Life					
Amarenco, 2003[1]	CONT LIFE	Any/not specified	Global health and quality of life Daily Activities Emotions Sexual function Effort Activities Self-Image Well-Being	-7 to -20 (graph only), depending on the domain, in improved population defined by decrease of at least 50% in the number of urinary leaks under treatment	0 to 100
Klovning, 2009[2]	ICIQ-SF	Any/not specified	Frequency Severity Total QoL	With QoL* Mean 16.3 for very severe UI (defined by 2000 ISI) 12.3 for severe UI Without QoL 9.4 for very severe UI 6.8 for severe UI	21 to 0 with QoL 11 to 0 without QoL
Shumaker,1994;[3] Uebersax, 1995;[4] Hagen, 2002;[5] Barber, 2009[6]	IIQ	Any/not specified	Travel Physical activity Social Emotional Total QoL	-6.5 to -22 for stress UI -18 to -50 for UUI	100 to 0 for each domain
Patrick,1999;[7] Bushnell, 2005;[8] Wagner, 1996;[9] Oh, 2007;[10] Schurch, 2007;[11] Yalcin, 2006;[12] Yalcin, 2010;[13] Hollingworth, 2010[14]	I-QOL	Any/not specified Neurogenic UI	Avoidance and Limiting behavior Psychological impact Social embarrassment Total Qol	2 to 5 for UI 6.3 for the within-group MID: Patients appear to recognize important clinical value at reductions of 50-70% or more incontinence episodes frequency 2.5 for the between-group MID 4 to 11 for neurogenic UI A ≥10-point increase was associated with a 0.05 SF- 6D increase in patients with neurogenic UI	0 to 100

Reference	Tool*	Conditions	Domain	Minimal Important Differences	Worst to Best
Kelleher, 1997;[15] Reese, 2003;[16] Sand, 2007;[17] Kelleher, 2004[18]	KHQ	Any/not specified Urgency UI or OAB	Severity Incontinence impact Role limitation Physical limitation Social limitation Personal relationship Emotions Sleep and energy General health	-3 to -4 for general health and severity domains -5 to -6 for other domains "Very Much improved or Much improved" in PGI-I corresponds to a mean change in KHQ of 46 & 35 points (Range 17–60 points) with clear demarcation from those reporting "no change and/or worse condition" (mean 2 & -21; Range -25–10)*	100 to 0 for each domain
Rogers, 2001[19]	PISQ	Any/not specified	Behavioral/ emotive Physical activity Partner-related Total score	Not available	0 to 125
Hendriks, 2008;[20] Hendriks, 2008[21]	PRAF AB	Any/not specified	Protection Amount Frequency Adjustment Body image	>14 points for severe UI (>2 g/hour urine loss)* SUI: 2.5-3.1 Urgency UI: 3.0-4.0	20 to 5. 4 points/ item (1–4) with a total PRAFAB-Q score of 20 points
Stach-Lempinen, 2001[22]	UISS	Any/not specified	The amount of leakage the degree to which UI affects aspects of women's daily lives	>11.02 points for severe UI (>30 g/24 hour urine loss)*	100 to 0
Patient Satisfaction					
Pleil, 2005[23]	BSW	Urgency UI or OAB	Benefit Satisfaction Willingness to continue	-2.21 mean number of incontinence episodes per 24 hours for much benefit population	Categorized for each domain
Burgio, 2006[24]	PSQ	Any/not specified	One item for patient satisfaction	A 70% improvement in the frequency of incontinence episodes on bladder diary as a critical threshold	3 categories
Colman, 2008[25]	TBS	Urgency UI or OAB	One item for patient-reported benefits	UUI episodes/24 hours +1.31 in "4" group -0.52 in "3" group -1.62 in "2" group -2.38 in "1" group	4 to 1

Table 6. Minimal Important Differences in Outcomes in Patients with COPD Reported in Make B. (2007)[26]

Name	Domain	MID	Worst to Best
Forced expiratory volume in 1 second	Single domain/measure	100 ml	NA
Maximal exercise test	Single domain/measure	10 watts 3–5 watts for severe COPD	NA
Submaximal exercise endurance test	Single domain/measure	1.75 minutes	NA
Six-minute walk test	Single domain/measure	37–71 meters 24–28 for severe COPD	NA
Transition Dyspnea index	Functional impairment (FI) Magnitude of task (MT) Magnitude of effort (ME)	1 unit	-9 to +9
UCSD Shortness of Breath Questionnaire	Severity of shortness of breath during 21 activities of daily living, and three additional questions about fear of harm from overexertion, limitations, and fear caused by shortness of breath	5–7 units	120 to 0
Borg scale of perceived dyspnea	Single domain/measure	2 units	20 to 6
Visual analog scale of dyspnea	Single domain/measure	10–20	100 to 0
Breathlessness diary	Single domain/measure	0.2	4 to 0
St. George's Respiratory Questionnaire	Symptoms Activity Impacts	4 units	100 to 0
Chronic Respiratory Disease Questionnaire	Dyspnoea Fatigue Emotional functioning Mastery	0.5 units	1 to 7
Quality of Well-Being Scale	Mobility Physical activity Social activity 25 symptoms/problem complexes	0.03 units	0 to 1
Exacerbations	Single domain/measure	22% change; 1 exacerbation/year	NA

Table 7. Minimal Important Differences Reported in the Western Ontario McMaster Universities Osteoarthritis Index

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Dougados, 2000[27]	Anchor	(Varies) WOMAC, Lequesne Functional Severity Index, Global VAS	OARSI Responder Criteria—Proposition A: This emphasizes the domain 'pain'. A 'high' improvement in pain was sufficient to define a responder. However, using this set of criteria, a patient can be also considered as a responder if an improvement of 'moderate' magnitude is observed in two of the three domains, i.e., pain, function and patient's global assessment. OARSI Responder Criteria—Proposition B: This scenario applies equal importance to 'pain' and 'function', requiring a 'high' response of one OR the other. Alternatively, a 'moderate' magnitude of response could be present in two of the three domains..	MID was defined as an absolute improvement of ranging from 10 to 20 (normalized units) corresponding to moderate improvement in pain, function, and patient's global assessment:
Angst, 2001[28]	Anchor	10 to 0 (for each of the 24 items) WOMAC pain scale	The transition questionnaire was used to gather data from the patients about their current subjective health status in relation to the OA joint in terms of their general health. At the 3-month follow up, patients had to compare their general health status with that of 3 months earlier, i.e., with that at baseline examination, using the assessment categories "much worse," "slightly worse," "equal," "slightly better," and "much better."	The mean score difference between the "equal" group and the "slightly better" group =0.67 was the MID for improvement

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Tubach, 2005[29]	Anchor	100-0 WOMAC: function scale	At the final visit, patients assessed their response to NSAID treatment on a five point Likert scale (none=no good at all, ineffective drug; poor=some effect but unsatisfactory; fair=reasonable effect but could be better; good=satisfactory effect with occasional episodes of pain or stiffness;excellent=ideal response, virtually pain free).The MCII was determined in patients whose assessment of response to treatment was measured on a five point Likert scale and who had completed the final visit. The MCII was estimated for both the absolute (final value-baseline value) and the relative ((final value-baseline value)/baseline value) changes in each patient reported outcome. It was estimated by constructing a curve of cumulative percentages of patients as a function of the change in score (for example, difference in pain score) among patients whose final evaluation of response to treatment was ‘‘good, satisfactory effect with occasional episodes of pain or stiffness’’.	Patients with knee OA considered themselves clinically improved if the decrease in function score exceeded 9.1 on the WOMAC function scale
Tubach, 2005[30]	Anchor	100-0 WOMAC: function subscale	(1) “What is the level of pain above which you experience difficulties?” (This could be considered close to the external anchor for the PASS.) (2) “What is the level of pain above which you would consider taking a pain killer drug?” (This could be considered close to the external anchor for the LDAS.)	The MID in the high tertile of score is -20(absolute change)

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Weigl, 2006[31]	Anchor	Varies WOMAC; Transition scale (that investigates the current state of health of the OA joint at the 6 months follow-up compared to its state 6 months earlier(baseline examination)	The transition scale investigates the current state of health of the OA joint at the 6-month follow-up compared to its state 6 months earlier (at baseline examination).	Three different definitions of responder: (1) For the WOMAC global score, a percentage change (100*(change of score/baseline score)) greater or equal to 18% represents an MID in improvement; (2) patients who reported a slightly or a much better health status on the transition scale were classified as responders; (3) responders had to show an MID in improvement on the WOMAC global score and report a health improvement on the transition scale
Stratford, 2007[32]	Anchor	4-0 for each of the 5 items WOMAC LK 3.1	The five pain items of WOMAC that were analyzed were: (1) walking on flat ground; (2) going up or down stairs; (3) at night while in bed; (4) sitting or lying; and (5) standing upright.	90% of stable patients will display random fluctuations equal to or less than 3.94 when assessed on multiple occasions
Bieleman, 2009[33]	Anchor	68-0 WOMAC (Dutch versions)function scale	Functional Capacity Evaluation (FCE)	The cut-off point for the WOMAC scale the cut-off point was ≥21 where subjects had work limitations that corresponded to the physical work limitations on the FCE scale
White, 2010[34]	Anchor	WOMAC: physical function	The definitions of [MID] were that they were anchored to patient-based indicators of improvement and defined meaningful improvement relative to baseline WOMAC physical function scores. The definitions of [MID] 26% and [MID] Tertile were estimated in a group of people with knee pain reporting a “good, satisfactory effect with occasional episodes of pain or stiffness” following a 4-week course of nonsteroidal antiinflammatory drug (NSAID). The [MID] 17% definition was from a group of people with knee OA who underwent 3 to 4 weeks of inpatient rehabilitation.	3 definitions of [MID] for WOMAC physical function: [MID] 26% and [MID] 17% defines meaningful improvement as a 26% and 17% decrease in WOMAC physical function (final value minus baseline value/baseline value), respectively, with a minimum absolute decrease of 2 out of 68.
Escobar, 2007[35]	Anchor	100 to 0 WOMAC: pain subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “ a great deal better,” “somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC pain score of 37.58(19.71) was equivalent to patient reporting “A great deal better.”

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Escobar, 2007[35] (continued)	Anchor	100 to 0 WOMAC: function subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC function score of 34.58 (19.33) was equivalent to patient reporting “A great deal better.”
	Anchor	100 to 0 WOMAC: stiffness subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “a great deal better,” somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC stiffness score of 34.74(28.38) was equivalent to patient reporting “A great deal better.”
	Anchor	100 to 0 WOMAC: pain subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC pain score of 33.87(18.13) was equivalent to patient reporting “somewhat better.” This was considered the MID.
	Anchor	100 to 0 WOMAC: function subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC function score of 19.01(17.48) was equivalent to patient reporting “somewhat better.” This was considered the MID.
	Anchor	100 to 0 WOMAC: stiffness subscale	Patients had to answer a question about improvement in their knee at 6 months and 2 years after intervention. The possible responses were “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” and “a great deal worse.”	At 6 months: Mean change in WOMAC stiffness score of 14.53(26.50) was equivalent to patient reporting “somewhat better.” This was considered the MID.

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Quintana, 2006[36]	Anchor	100 to 0 WOMAC: pain subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The [MID] for pain subscale of WOMAC was at 22.85.
	Anchor	100 to 0 WOMAC: functional limitation subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The [MID] for functional limitation subscale of WOMAC was at 12.72.
	Anchor	100 to 0 WOMAC: stiffness subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The [MID] for stiffness subscale of WOMAC was at 29.14.

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Quintana, 2006[36] (continued)	Anchor	100 to 0 WOMAC: pain subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The MID for pain subscale of WOMAC was at 22.60.
	Anchor	100 to 0 WOMAC: functional limitation subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The MID for functional limitation subscale of WOMAC was at 17.67.

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Quintana, 2006[36] (continued)	Anchor	100 to 0 WOMAC: stiffness subscale	Six months after the intervention, patients were sent another letter with the questionnaires and additional questions on the clinical aspects of their disease and satisfaction with the intervention. The satisfaction question was dichotomized as being satisfied or not. At this time, patients answered a transitional question about their joint improvement after the intervention. The possible responses included “a great deal better,” “somewhat better,” “equal,” “somewhat worse,” or “a great deal worse.”	The MID for stiffness subscale of WOMAC was at 12.94.
Ornetti, 2011[37]	PASS	100 to 0 WOMAC: function subscale	All patients had to assess their current global state (global PASS) by answering ‘Yes’ or ‘No’ in answer to the question “Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?’”	Patients considered their global state as satisfactory if the WOMAC function was <28.06 (95% CI, 25.74 to 30.38.Global PASS is defined as the value of measurement beyond which patients consider their global state as satisfactory).
	PASS	100 to 0 WOMAC: function subscale	PASS for functional state: The PASS of each function scale was defined as the 75th centile of the absolute score among patients who considered their final state as satisfactory.	Patients considered their functional state as satisfactory if the WOMAC function was <28.40 (95% CI, 26.03 to 30.78). Function PASS is defined as the value of measurement beyond which patients consider their functional state as satisfactory.
	MCII	100 to 0 WOMAC: function subscale	All patients had to assess their degree of improvement of global state, on a three-point Likert scale (worsened function, no change, improved function). Among patients who improved, the degree of improvement was scored on a four-point Likert scale (poor, fair, good, excellent).	Patients considered their global state as improved for a change of WOMAC function scale >-17.13 (95% CI, -20.07 to -14.19).Global [MID] is defined as the smallest change in global state that signifies an important improvement in a patient's symptoms.

Author, Year	Method	Worst to Best Scale	Reference	Definition of Minimally Important Differences
Ornetti, 2011[37] (continued)	MCII	100 to 0 WOMAC: function subscale	[MID] for functional state: The [MID] of each function scale was defined as the 75th centile of the absolute change in score among patients whose final evaluation of response to NSAID was improved (improvement good or excellent).	Patients considered their functional state as improved for a change of WOMAC function scale >-17.02 (95% CI, -20.15 to -13.90). Functional [MID] is defined as the smallest change in functional state that signifies an important improvement in a patient's symptoms.

Table 8. Clinically Important Differences in Group Outcomes in Bone Density Studies Reported in (from a Systematic Cranney et al. (2001)[38]

Classification	Method	Spine	Femoral Neck
Minimum actually detectable beyond error in differences between groups and changes within group[39]	Calculated SD of short-term and long-term intra- and inter-subject variance for rates of change in g/cm^2/year as minimal detectable beyond error in group	Sample size decreased as length of follow-up and frequency of observations increased	NA
Differences between groups and changes within group observed in those estimated to differ/to have improved[40,41]	Effect size = mean in treatment less mean in placebo divided by SD of placebo	Better responsiveness for spine BMD than other sites	NA
Differences between groups and changes within group observed in those estimated to differ/to have improved[42]	Different cut-offs of % change in spine BMD used to define a responder in 3 year RCT (Liberman)	Choice of cut-off affects results of RCT	NA
Differences between groups and changes within group observed in those estimated to differ/to have improved[43]	Treatment response index = difference in % change between groups of RCT divided by standardized precision in 4 year RCT of hormone replacement therapy (HRT) for early, non-osteoporotic post-menopausal women	Treatment response index: DXA spine 10.4(0.5) DXA total hip 3.9(0.4) BUA 3.1(1.2) SOS 0.3(13.7) Stiffness 4.2(0.4)	NA
Differences between groups and changes within group observed in those estimated to differ/to have improved[44]	Compared dose-related % change in BMD in 2 RCTs and differences between treated and placebo groups Correlated changes in new region of interest in forearm to changes in BMD at the spine and hip	New region of interest in forearm is as responsive to change over time during therapy in an RCT as spine or hip BMD	New region of interest in forearm is as capable of detecting differences between groups
Differences between groups and changes within group observed in those estimated to have an important difference/improvement[45]	Clinician judgment that group difference or change should be greater than SD to be important	5%	8%

Classification	Method	Spine	Femoral Neck
Changes within group observed in population[46]	Used 3 arbitrary cut-offs (0%, 0–3%, >3% change in spine, hip, and femoral neck BMD)	>3% change predicted fewer vertebral fractures: Spine 6%, 4%, 3.7% Femoral neck 5.5%, 4.2%. 3.1% Total Hip 6.2%, 4.6%, 2.7%	
Differences between groups observed in those estimated to have an important difference/improvement[47]	Working party of 14 European experts in osteoporosis	15% reduction in fracture frequency suggested as MID, depending on unwanted effects	

Table 9. Reduction in Bone Fractures Corresponding to Importance of the Effect Reported in Cranney et al. (2001)[38]

Classification of Discrimination and Changes in Studies of Osteoporosis	Method	Outcomes
Differences between groups and changes within group observed in those estimated to differ /to have improved[40,41]	Effect size = mean in treatment less mean in placebo divided by SD of placebo	Better responsiveness for clinical vertebral in high risk subgroup with femoral neck BMD >2.5 SD
Differences between groups observed in population[48]	Tested if different criteria for diagnosis of vertebral fracture would change results of RCT of fluoride	Found no difference between difference between groups for any of the fracture definition criteria
Differences between groups observed in those estimated to have an important difference/ improvement[49]	Sample size calculation to detect difference in fractures associated with 1 SD decrease in bone mass	30% reduction in incidence of vertebral and non-vertebral fractures associated with low bone mass
Differences between groups observed in those estimated to have an important difference/ improvement[50]	Evaluated 7 methods of classifying/diagnosing vertebral fracture and calculated sample size for RCT	40% risk reduction in vertebral fracture
Differences between groups observed in those estimated to have an important difference/ improvement[51]	Sample size determination for FIT trial	40% risk reduction in vertebral fracture 90% power to detect 32% reduction
Differences between groups observed in those estimated to have an important difference/ improvement[52]	Sample size calculations for different definitions of vertebral fracture, from 5–30% reduction in height	50% risk reduction in vertebral fracture
Differences between groups observed in those estimated to have an important difference/ improvement[52]	Sample size calculation for 90% power, 2 tailed test, $p<0.05$ MORE RCT of 7705 post-menopausal women with ≥1 vertebral fracture	40% risk reduction in vertebral fractures
Differences between groups observed in those estimated to have an important difference/ improvement[53]	Sample size calculation for risedronate RCT of 2,458 post-menopausal women with ≥1 vertebral fracture	40% risk reduction in vertebral fractures
Differences between groups observed in those estimated to have an important difference/ improvement[51]	Sample size calculation for RCT of HRT, vitamin D/calcium in post-menopausal women	21% hip fracture reduction 20% reduction in combined fractures (vertebra, proximal femur, distal forearm, proximal humerus, pelvis)

Classification of Discrimination and Changes in Studies of Osteoporosis	Method	Outcomes
Differences between groups observed in those estimated to have an important difference/ improvement[47]	Working party of 14 European experts in osteoporosis	15% reduction in fracture frequency suggested as MCID depending on unwanted effects
Differences between groups observed in those estimated to have an important difference/ improvement[54]	Cost per averted hip fracture used to determine important difference needed for policy to change	10% difference in hip fracture incidence with thiazides is cost-neutral

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