Endpoints of Clinical Trials for Asthma

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Standardized endpoints in clinical trials

- The **assessment of asthma control** is pivotal to the evaluation of treatment response in individuals and in clinical trials.

- Consensus recommendations on **standardized definitions and data collection methods** for assessing **asthma control, asthma severity, and asthma exacerbations** were provided.

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Standardized endpoints in clinical trials

American Thoracic Society Documents

An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations

Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice

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Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Current clinical control	Future risk of adverse event	
Symptom-free days	Exacerbations (mild, moderate, severe)	Direct measurement
Reliever use	Post-BD FEV1 (for lung function decline)	
Composite scores (ACT, ATAQ, ACQ)	Composite scores (ACT, AQLQ, ACQ)	
Exacerbation (within last 1-4 wk)	Treatment side effects	
Quality of life	Pre-BD FEV1 (for predictor of exacerbation)	Indirect assessment

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Current clinical control
Symptom-free days
Reliever use

Symptom-free days and beta2-agonist use (reliever-free days and occasions/day) may be ascertained from a **diary** or from a **visit-based questionnaire.**

If a visit-based questionnaire or composite score is used, **the period of assessment for reliever use and symptom-free days should be no more than 4 wk**. **Symptom-free days** are **not suitable** as an outcome measure for study populations with **very frequent or very infrequent symptoms.**

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Current clinical control

Composite scores (ACT, ATAQ, ACQ)

At least one, and **preferably two**, validated composite measures (e.g., ACQ, ATAQ, ACT) should be recorded.

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Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Current clinical control

Quality of life is **not** in itself **a measure of clinical asthma control**.

Quality of life

Quality of life is a measure of the **impact of the level of asthma control on the patient's well being**.

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Post-BD FEV1 is defined as **FEV1 recorded 15 min after** administration of 400 mg of **albuterol** or equivalent.

It is **not considered** necessary to specify whether **LABA or study medication should be withheld**, as FEV1 is close to **plateau levels after 400 mg albuterol**.

Future risk of adverse event

Post-BD FEV1 (for lung function decline)

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Future risk of adverse event

Side effects relevant to **study medication**(s), as-needed medications, or exacerbation medications, and **any withdrawals due to adverse events**.

Some side effects related to asthma medications (e.g., **dysphonia [ICS] or mood changes [OCS]**) may not be perceived by patients as "health problems" and therefore **may be underestimated by routine Adverse Event questioning**.

Treatment side effects

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Minimum Set of Measures (Essential)

Future risk of adverse event

Pre-BD FEV1 is defined as FEV1 recorded **after appropriate withholding of short-acting and long-acting bronchodilator,** if used.

Pre-BD FEV1
(for predictor of exacerbation)

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Desirable Set of Measures

Current clinical control	Future risk of adverse event	
On treatment FEV1	Symptom, Reliever use, lung function (PEF) diary	Direct measurement
Symptom, Reliever use, lung function (PEF) diary	Health care utilization (corticosteroid use, ER visits, hospitalizations)	
Indirect measures (Corticosteroid use, Health care utilization)	Mortality due to asthma	
	Airway hyperresponsiveness (as predictor of future risk)	Indirect assessment
	Biomarkers (as predictor of future risk)	

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Desirable Set of Measures

Current clinical control

On treatment FEV1

"**On-treatment FEV1**" is defined as **FEV1 recorded without withholding of study medication**. To standardize the measurement, it should be **performed 6 hours after SABA** where possible.

"On-treatment FEV1" is only substantially different from "Pre-BD FEV1" for studies in which subjects are taking LABA. In such studies, **preference should be given to recording "Pre-BD FEV1" (where LABA is withheld)** because of the additional information that this measure **provides about future risk.**

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Desirable Set of Measures

Current clinical control	Future risk of adverse event
	Symptom, Reliever use, lung function (PEF) diary
Symptom, Reliever use, lung function (PEF) diary	**Health care utilization (corticosteroid use, ER visits, hospitalizations)**
Indirect measures (Corticosteroid use, Health care utilization)	

Diary measures should be obtained from **validated diary questions** and, where possible, using **electronic data collection** to **improve data quality and avoid data fabrication**. **Morning PEF** is the **most consistently reported** lung function variable from diaries

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Desirable Set of Measures

Airway hyperresponsiveness is a marker of **underlying disease activity**, and **the extent to which this has been modified by treatment**.

It allows **assessment of discrepancies with the observed level of clinical control** (e.g., with **masking by LABA monotherapy**).

In the assessment of treatment effect, airway hyperresponsiveness also serves as **a predictor of future risk**.

Future risk of adverse event

Airway hyperresponsiveness (as predictor of future risk)

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Desirable Set of Measures

Biomarkers (e.g., sputum eosinophils, sputum neutrophils, exhaled nitric oxide) are markers of **underlying disease activity**, and **the extent to which this has been modified by treatment**.

They allow **assessment of discrepancies with the observed level of clinical control** (e.g., with masking by LABA monotherapy).

In the **assessment of treatment effect**, some biomarkers also serve as **predictors or surrogate measures of future risk.**

Future risk of adverse event

Biomarkers
(as predictor of future risk)

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Optional Set of Measures

Current clinical control
Biomarkers
Airway hyperresponsiveness
Post-BD FEV1

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Definition of severity of exacerbation in asthma

- **Severe exacerbation**

  : Events that **require urgent action to prevent a serious outcome (hospitalization or death)**

- **The definition of a severe exacerbation for clinical trials**

  ➔ Should include at least one of the followings:

  1) **Use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days** (separated by ≥1 week are considered as separate events)

  2) **A hospitalization or ER visit** because of asthma, requiring systemic corticosteroids.

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Definition of severity of exacerbation in asthma

- **Moderate exacerbation**

  : Events that should result in **temporary changes in treatment** to prevent severe exacerbation

- **The definition of a moderate exacerbation for clinical trials**

  ➔ One or more of the followings for ≥2 days

  1) deterioration in **symptoms**

  2) deterioration in **lung function**

  3) increased **rescue bronchodilator use**

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Definition of severity of exacerbation in asthma

- **Mild exacerbation**

  : Only just outside the normal range of variation for the individual patient

  : Cannot be distinguished from transient loss of asthma control

  ➔ Currently, no standardized definition of a "mild" exacerbation can be offered.

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Criteria for mild exacerbation	References
15% decrease in morning PEF	Eur Respir J 2000;16:226–235.
20% decline in clinic FEV1	Am J Respir Crit Care Med 2000;162:578–585.
Increase in reliever medication use	Chest 2003; 123:1480–1487

➔ Subtle differences in criteria for exacerbation days resulted in large differences in risk of event or efficacy of an intervention

Thorax 2003;58:204–210.

Contents

Importance of MCID

- **Quantifying statistical significance** (using P-value in the context of null hypothesis testing)

  ➔ One of the most widely used methods to guide decision making in medical research

- However, **statistical significance dose not necessarily imply clinical relevance.**

  ➔ Statistical significance is linked to the sample size.

  ➔ Given a large enough sample, statistical significance between groups may occur with very small differences that are clinically meaningless

- **Bridging the gap between statistical and clinical significance in clinical trials**

  ➔ **Minimal clinically important difference (MCID)**

Definition

- **Minimal clinically important difference (MCID)**

  : The **smallest change of difference** in an outcome measure that is perceived as **beneficial** and would lead to a **change** in patients' medical management

- Assuming the absence of excessive side-effects and costs

- **Identical changes** on a numerical scale **may have diverse clinical importance** in different subjects and populations

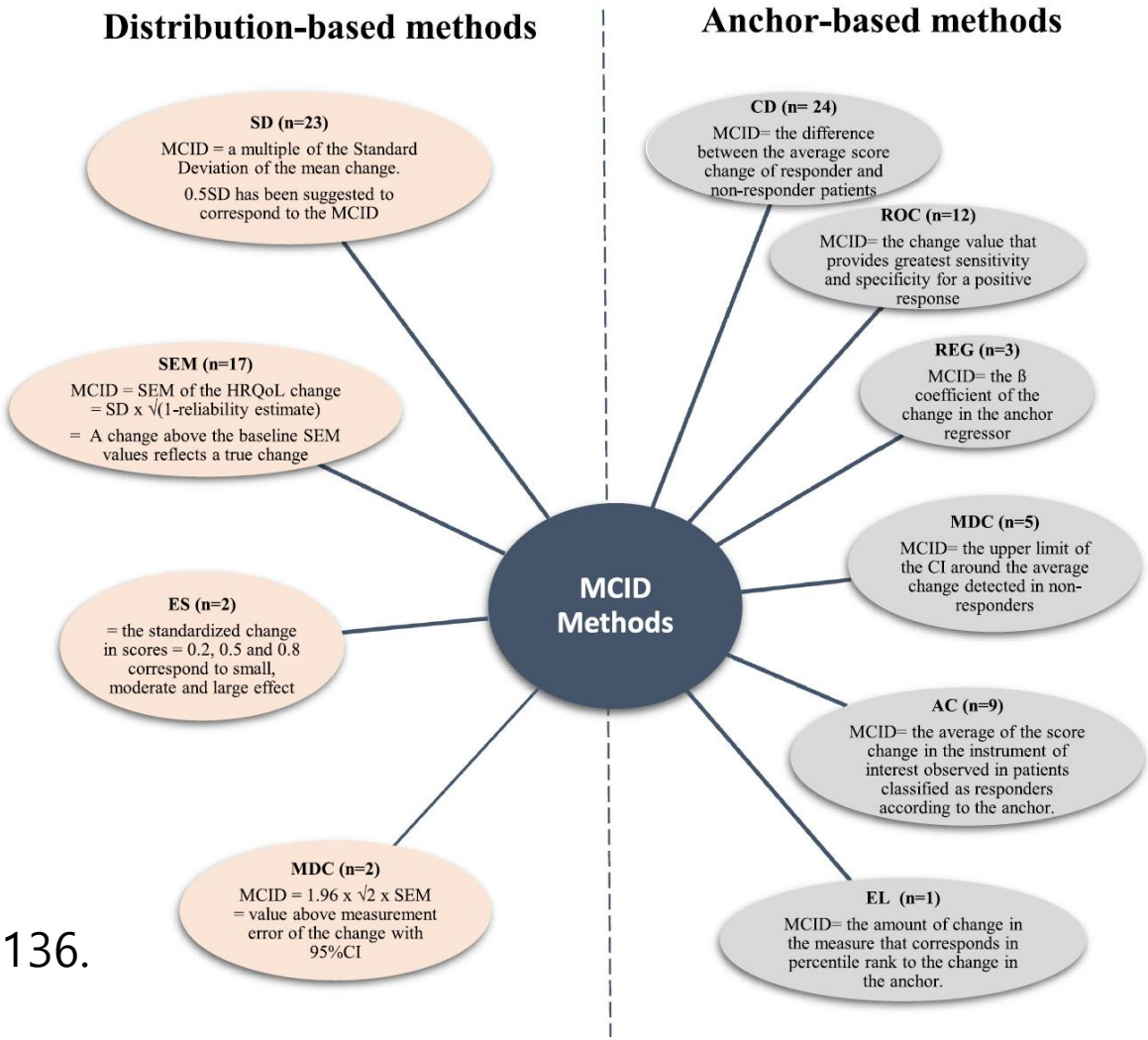
Control Clin Trials. 1989 Dec;10(4):407-15.
JAMA. 2014 Oct 1;312(13):1342-3.

Benefit of using MCID as endpoints

- **The MCID in clinical trials**
  - Represents the best standard for **determining effectiveness of a given intervention**
  - **Describes patient satisfaction** regarding a given intervention

Methods for establishing MCID

- Mainly clustered in three broad categories
  - ✓ **Consensus-based method**
  - ✓ **Distribution-based method**
  - ✓ **Anchor-based method**



Health Qual Life Outcomes. 2020 May 12;18(1):136.

MCID: Minimal Clinically Important Difference, AC: Average Change, MDC: Minimal Detectable Change, CD: Change Difference, ROC: Receiver Operating Curve, REG: Regression analysis, EL: Equipercentile Linking, SD: Standard deviation, SEM: Standard error of measurement, ES: Effect size

Consensus-based method

- Known as the Delphi method
- Based on the opinion of the experts on which numerical value should represent a clinically relevant change for the considered end-point

Distribution-based method

- Rely on the distribution of observed scores in specific populations of patients
- Main advantage: **being easy to calculate**

- Most importantly they provide a minimal value below which a change in outcome scores for a given measure may be due to a measurement error

  ➔ it **neglects the core concept of MCID, which is to determine the clinical importance of a given change in outcome scores independently from their statistical significance**

J Allergy Clin Immunol. 1998 Jul;102(1):16-7.

Distribution-based method

Measure	Definition	Suggested MCID
Effect size	Standardised measure of change obtained by dividing the difference in scores from baseline to post-treatment by the standard deviation of baseline scores	<0.20: no change 0.20–0.49: small change 0.50–0.79: moderate change ⩾0.80: large change
Standard error of measurements	It represents the variation in patient-reported outcome scores attributed to instrument unreliability, in which a change smaller than the calculated SEM is likely due to measurement error rather than a true change	Threshold values of 1 SEM, 1.96 SEM and 2.77 SEM have been suggested
Standard deviation	Measure used to quantify the amount of variation or dispersion of a set of data values	⩾0.5 SD
Coefficient of variation	Standardised measure of dispersion of a frequency distribution	⩾1.65 CV
Minimal detectable change	The smallest threshold of change in scores that can be considered above the measurement error with a given level of confidence (usually 95% confidence)	⩾MDC
Reliable change index	Statistic that determines the magnitude of change score necessary of a given self-report measure to be considered statistically reliable It is calculated by dividing the individual patient change in score by the square root of the SEM	⩾1.96

Eur Respir Rev. 2020 Jun 3;29(156):190137.

Anchor-based method

- Linking a specific change in the outcome measure score to a meaningful external indicator, either clinical or patient reported

- The most widely used external criterion in the anchor-based approach is the global rating of change (GRC).

- Eg. Likert-type scale scored by the patient

Anchor-based method

- The original statistical strategy: based on the mean change of patients rating as having a small improvement or deterioration.

- Recently, the precision of MCID can be optimized by ROC curve analyses

- Longitudinal methods as more reliable, compared to cross-sectional ones, to determine a clinically important change.

J Clin Epidemiol. 2009 Apr;62(4):374-9.
J Clin Epidemiol. 2004 Nov;57(11):1153-60.

Anchor-based method

- Advantage

  : linking the change in a given score to the patient's perspective and provide insights on the importance of observed change from a subjective point of view

- Limitation

  1) do not take into account the **measurement precision** of the instrument
  2) do not provide any information about the **range of change by random variation alone**
  3) The **paradox** to **use a subjective measure, as a supposed external criterion**, for another subjective measure of the same or similar construct

What is the best strategy to determine MCID?

- Each of these methods has its **own limitations**
  - **Consensus-based method**: expert opinion could not coincide with patients' feeling
  - **Distribution-based method**: only identify minimal detectable effects and prevent the definition of the clinical importance of a given change
  - **Anchor-based method**: limited by the choice of an anchor, which is subjective and difficult to find it valid and reliable

Eur Respir Rev. 2020 Jun 3;29(156):190137.

What is the best strategy to determine MCID?

- The **best strategy to determine MCID** should be based on a multiple approach
  - Assigning the highest relative weight to **anchor-based methods**
  - Using **distribution-based measures** as supportive information

Eur Respir Rev. 2020 Jun 3;29(156):190137.

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Proximal airways parameters

- Forced expiratory volume in 1 s (FEV1)
- Peak expiratory flow (PEF)
- Forced vital capacity (FVC) [Complementary endpoint]

- Several attempts to identify MCIDs in lung function tests by the use of a **distribution-based method** have been carried out.

CV of FEV1 and FVC

- Acute change

Table 2—*Individual (Within Day) Coefficient of Variation*

Reference (No. of Patients, No. of Tests Each)	FVC	FEV_1	FEF 25-75%
McCarthy[7] (12, 10)	3	3	8
Pennock[8] (20, 9)	6.7	8.1	14
Hruby*[9] (15, 10)			
Normal	3	5	
Obstructive	6	7	
Restrictive	9	11	
Summary			
Normal	3	3	8
Obstructive	6.7	8.1	14

- Chronic change

Table 3—*Individual (Week-to-Week) Coefficient of Variation*

Reference (No. of Patients, No. of Tests Each)	FVC	FEV_1	FEF 25-75%
McCarthy[7] (20, 10) and (5, 25)	5	7	13
Spicer[10]			
Normal (11, 30-60)	7.8		
Bronchitic (7, 30-60)	13.5		
Asthmatic (10, 30-60)	14.1		
Pennock[8] (20, 5)			
Asthmatic	11.1	14.2	18.4
Summary			
Normal	6.4	7	13
Obstructive			18.4

Chest. 1981 Jul;80(1):97-9.

Threshold of FEV1 and FVC

- Threshold (significance at the 95 percent confidence limit)

Table 4—*Significance Level (Changes Greater than Percent Shown)*

	FVC	FEV_1	FEF 25-75%
Population mean	21	21	41
Within day			
Normal	5	5	13
Obstructive	11	13	23
Week-to-week			
Normal	11	12	21
Obstructive	21	23	30

Chest. 1981 Jul;80(1):97-9.

Proximal airways parameters

- Chronic change (year to year)

TABLE 12 Reported significant changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), mid-expiratory flow ($MEF_{25-75\%}$) and carbon monoxide diffusing capacity ($D_{L,CO}$) over time

	FVC	FEV_1	$MEF_{25-75\%}$	$D_{L,CO}$
Within a day				
Normal subjects	⩾5	⩾5	⩾13	>7%
COPD patients	⩾11	⩾13	⩾23	
Week to week				
Normal subjects	⩾11	⩾12	⩾21	>6 units
COPD patients	⩾20	⩾20	⩾30	>4 units
Year to year	⩾15	⩾15		>10%

Eur Respir J. 2005 Nov;26(5):948-68.

MCID of FEV1 and PEF

- ATS/ERS statement
  - **MCID for improvement and worsening in FEV1 in asthma**

: 20% in short-term trials (weeks)

: 15% in long-term trials (1-year)

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

- Some trials used **25L/min** as an **MCID for PEF** values

N Engl J Med. 2005 Apr 14;352(15):1519–1528.
N Engl J Med. 1996 Sep 19;335(12):841–847.

MPPI of FEV1 and PEF

- **MPPI** (minimal patient perceivable improvement)
- Post-hoc analysis of a RCT with 281 asthmatic patients (leukotriene antagonist)

Table 4. – Average (quartiles) changes in forced expiratory volume in one second (FEV_1) by patient global change category

Patient determined global category	n	Average (quartiles) change from baseline in FEV_1 L
Very much worse	1	-0.62
Moderately worse	2	-0.01
A little worse	10	0.08 (-0.10–0.26)
Unchanged	52	0.11 (-0.12–0.34)
A little better (MPPI)	86	0.23 (0.01–0.48)
Moderately better	74	0.25 (-0.14–0.55)
Very much better	48	0.38 (0.10–0.63)

Table 5. – Average (quartiles) changes in peak expiratory flow (PEF) by patient global change category

Patient determined global category	n	Average (quartiles) change from baseline in PEF $L \cdot min^{-1}$
Very much worse	1	-6.7
Moderately worse	2	-15.6
A little worse	10	-14.3 (-31.8–-0.8)
Unchanged	52	3.4 (-9.8–19.8)
A little better (MPPI)	86	18.8 (0.7–36.9)
Moderately better	74	22.1 (0.4–43.3)
Very much better	48	35.2 (12.9–55.2)

Eur Respir J. 1999 Jul;14(1):23-7.

Lung function variability

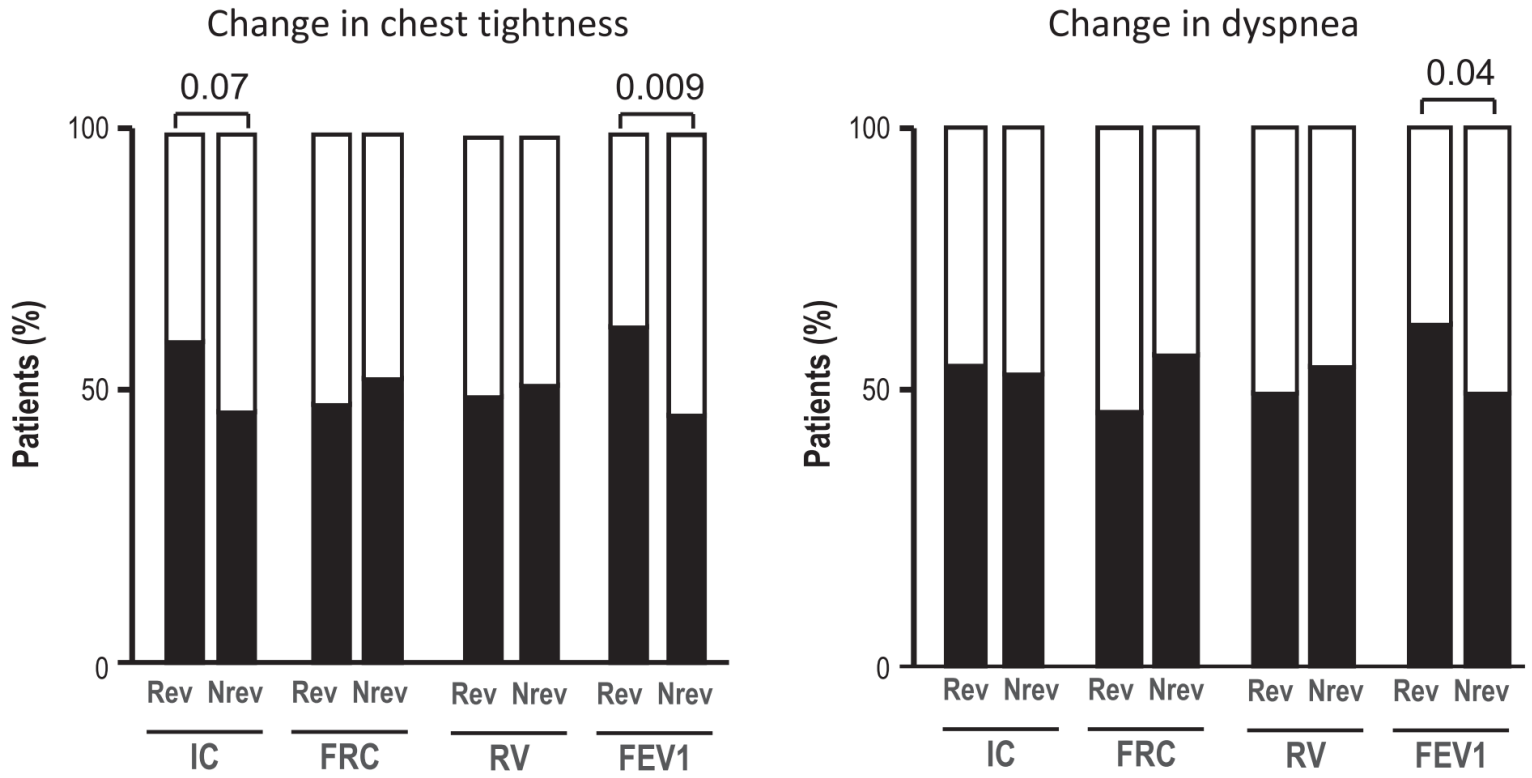
- **Airway hyperresponsiveness** (Fall of FEV1 ≥20% with standardized doses of methacholine)
- **Post-bronchodilator reversibility** (FEV1 and/or FVC >12% and 200 mL)

- Both are recommended for asthma diagnosis and in specific conditions for asthma control monitoring.

- **No specific MCID has been investigated.**

FEV1 reversibility

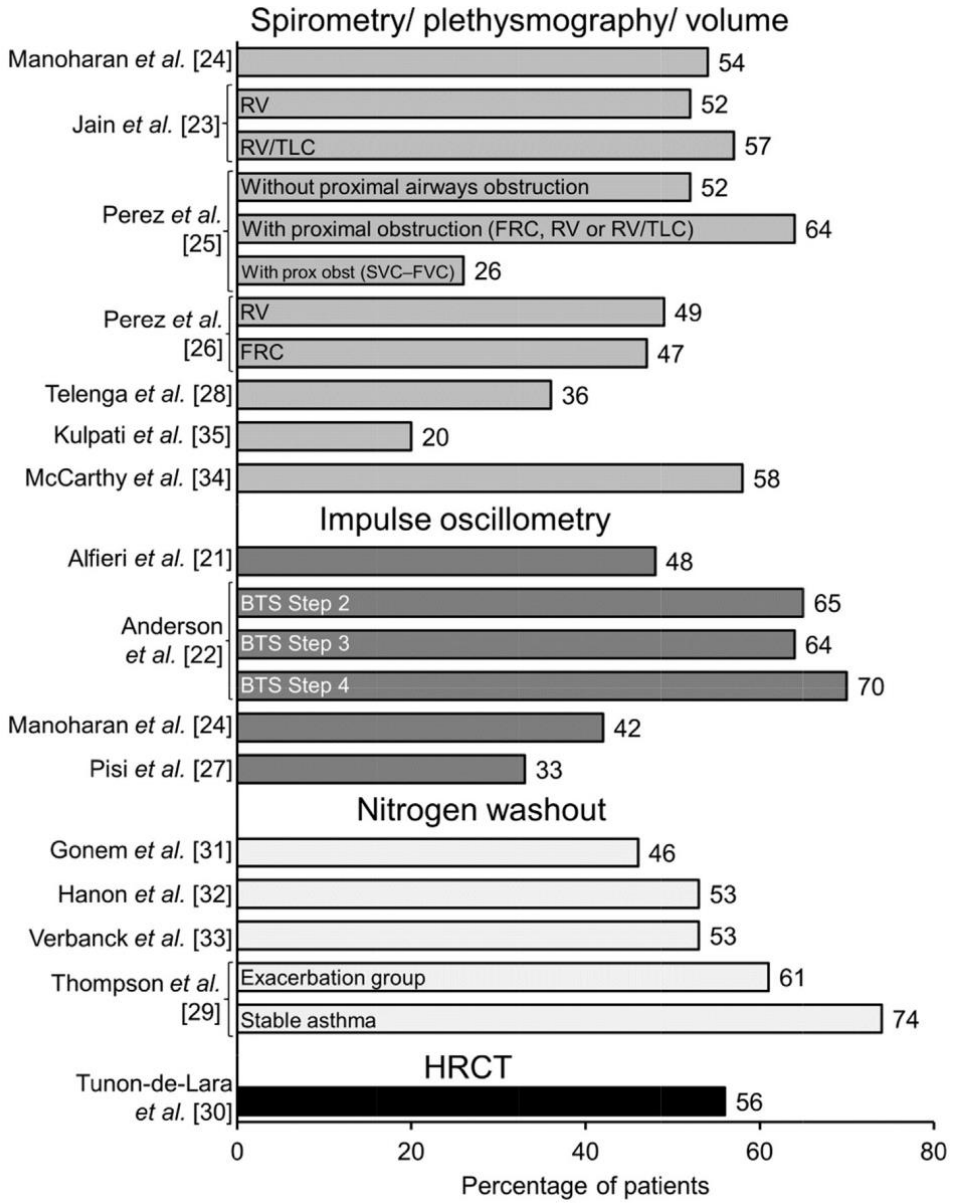
- FEV1 reversibility was the only parameter associated with a significant clinical improvement (change in visual analogue scale ≥2 cm)



Allergy. 2016 Jan;71(1):108-14.

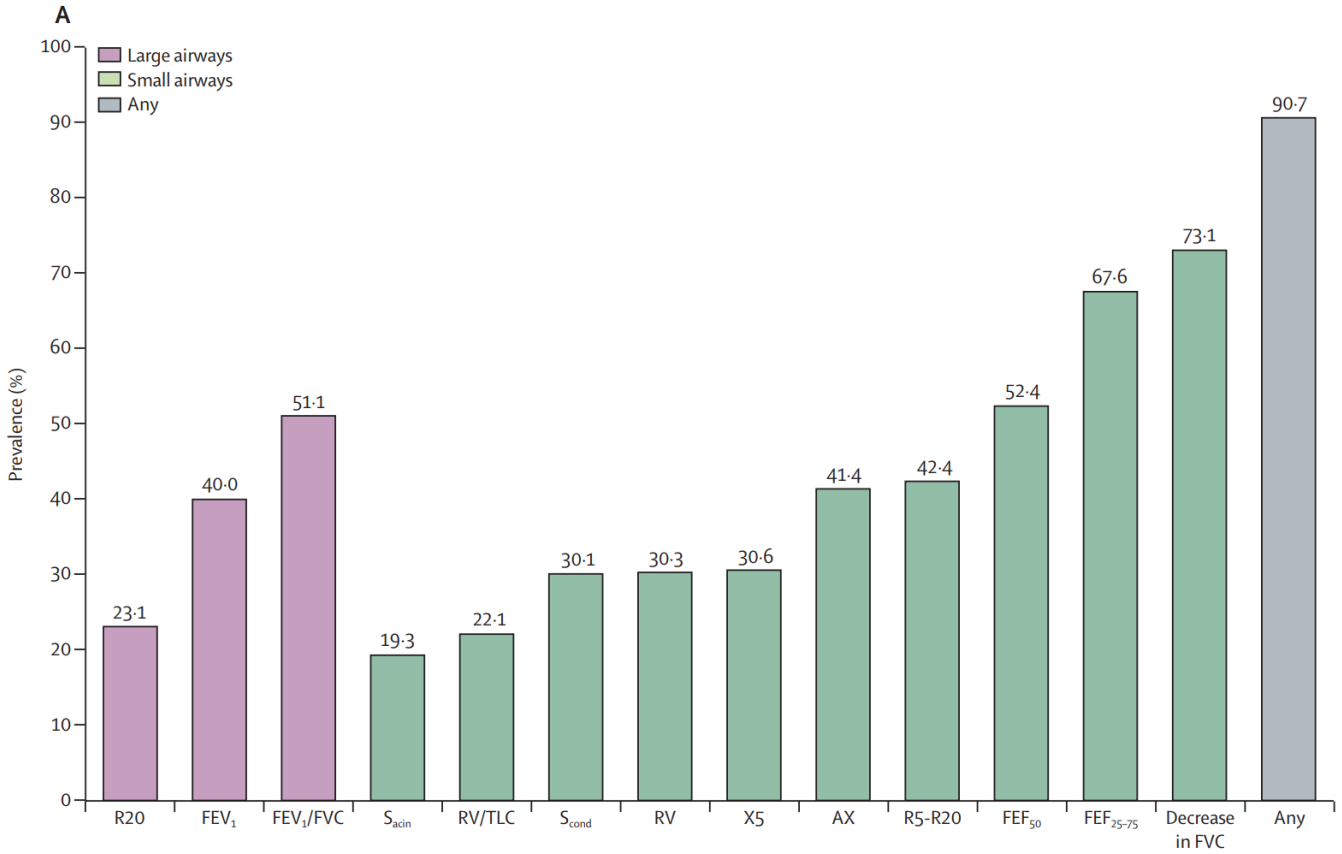
Peripheral airways parameters

- Variable prevalence of small airway dysfunction (20-74%) in asthma with different levels of severity and magnitude of airway obstruction



Respir Med. 2016 Jul;116:19-27.

Peripheral airways parameters



	GINA1 (n=135)	GINA2 (n=85)	GINA3 (n=207)	GINA4 (n=300)	GINA5 (n=46)
Spirometry					
FEF_{25-75}	41%	43%	51%	55%	80%
FEF_{50}	37%	49%	54%	55%	75%
Decrease in FVC	72%	68%	75%	73%	84%
Body plethysmography					
Residual volume/total lung capacity	14%	16%	19%	28%	31%
Functional residual capacity	16%	23%	19%	25%	27%
Impulse oscillometry					
R5–R20	30%	40%	37%	51%	71%
AX	32%	34%	35%	49%	68%
X5	23%	32%	29%	33%	53%
Multiple breath nitrogen washout					
S_{cond}	21%	20%	30%	33%	64%
S_{acin}	12%	18%	19%	21%	41%

Lancet Respir Med. 2019 May;7(5):402-416.

Peripheral airways parameters

- Forced expiratory flow between 25% and 75% of FVC (FEF25–75): Most popular

  ➔ Its use in clinical practice is limited by issues of measurement inconsistency.

  ➔ Therefore, assessing the MCID for this parameter is a difficult task.

  J Appl Physiol 2008; 104: 394–403.

- Serial measurements are indeed subjected to high variability and values are influenced by volume changes and obstruction of large airways.

Small airway dysfunction

- **SAD (small airways dysfunction) score**

  : Combination of lung function measurements (impulse oscillometry variables, FEF50 and FEF25–75 (%) and other parameters)

- SAD score was associated
  - Positively with: duration of asthma, ACQ-6, number of exacerbations
  - Negatively with: ACT, mini-AQLQ, EuroQol-5D-5L

Lancet Respir Med. 2019 May;7(5):402-416.

Peripheral airways parameters

- **MCID** for other lung function parameters reflecting **small airway involvement** has not been established.

- **Main limitations**: reproducibility, repeatability, acceptability (= reliability), and variability of each test

Exercise tolerance

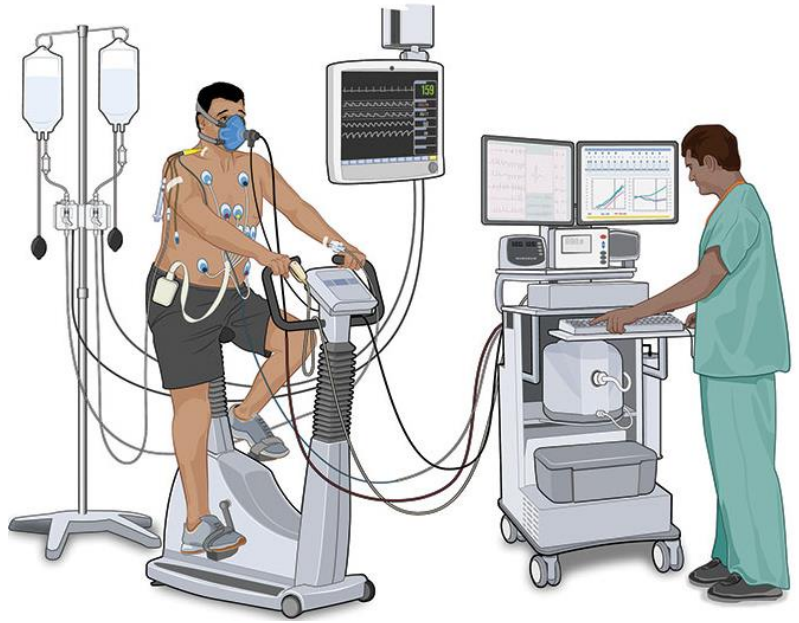
- **Exercise tolerance** can be defined as the ability to perform a physical task considered normal for a healthy person with the same characteristics.

- As it cannot confidently be predicted from variables such as FEV1, DLCO and LV-EF, **laboratory-based (eg. CPET) and field tests (eg. 6MWD)** were developed.

Cardiopulmonary exercise test

- **Symptom-limited incremental cardiopulmonary exercise testing** could be considered the **gold standard** for evaluating the causes of **exercise intolerance**.

- **Constant work-rate exercise test** is the **gold standard** to study **the effects of interventions** on the endurance time and/or other measurable parameters.



MCID of exercise test

Protocol and measure	MCID
Symptom limited incremental exercise testing	
$\dot{V}_{O_2}$	0.04±0.01 L·min^{-1}
Work rate	4±1 W
Inspiratory capacity	>0.14 L or >4.5% predicted
Dyspnoea score on modified Borg scale (10 points)	⩾2 points
Dyspnoea score on VAS (100 mm)	⩾10–20 mm
Constant work rate exercise testing	
Endurance time	>100 s or change >33% from baseline

Data refer to measurements at peak exercise. $\dot{V}_{O_2}$: oxygen uptake; VAS: visual analogue scale.

Eur Respir Rev. 2020 Jun 3;29(156):190137.

Exercise challenge test

- **Exercise challenge test** on treadmill or cycloergometer is the gold standard to elicit **exercise-induced bronchospasm** (EIB).

- If the FEV1 decreases ⩾10% at the end of exercise (up to 30 min after) the test is considered positive for EIB.

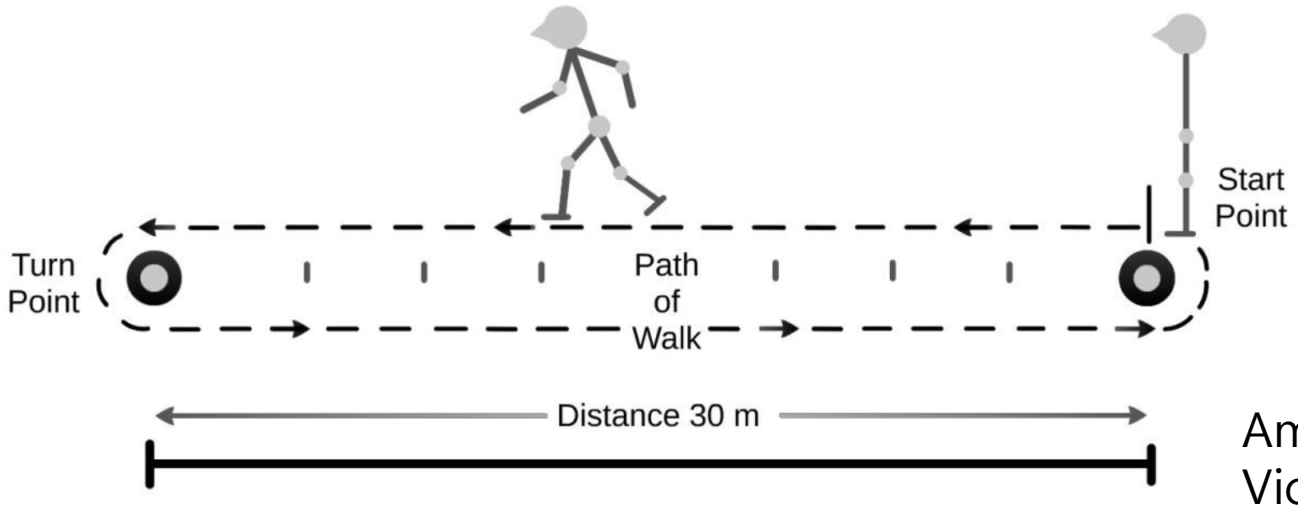
- Several RCTs have assessed the efficacy of pre-exercise use of bronchodilators in preventing EIB.

Curr Allergy Asthma Rep. 2011 Dec;11(6):482-90.

6-min walk test

- Self-paced test measuring the distance that a patient can quickly cover in a period of 6 min (6MWD), strongly related to important clinical outcomes.

- Measuring the response to interventions (mostly rehabilitation program rather than pharmacotherapy) in patients with moderate-to-severe heart or lung disease



Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.
Vicent Benavent-Caballer et al. doctoral thesis, 2016

MCID of 6-min walk test

- In healthy population

CHARACTERISTICS OF THE HEALTHY ADULT PARTICIPANTS

Characteristic	Median (5th, 95th percentiles) Men (*n* = *117*)	Women (*n* = *173*)
Age	59.5 (43.1, 77.0)	62.0 (45.0, 79.0)
Height, cm	176 (164, 185)	162 (151, 173)
BMI, kg/m^2	27.8 (22.1, 33.9)	25.5 (20.6, 32.4)
Baseline pulse	74 (58, 100)	80 (60, 105)
Change in pulse	+25 (−8, +79)	+20 (−6, +58)
Baseline Sa_{O_2}	96% (92, 98)	96% (93, 99)
Change in Sa_{O_2}	0.0 (−8.0, +2.0)	0.0 (−16.0, +2.0)
FEV_1, %pred	96% (75, 118)	106% (81, 125)
6MWD, m	576 (399, 778)	494 (310, 664)
	SE=97m	SE=90m

Am J Respir Crit Care Med. 1998 Nov;158(5 Pt 1):1384-7.

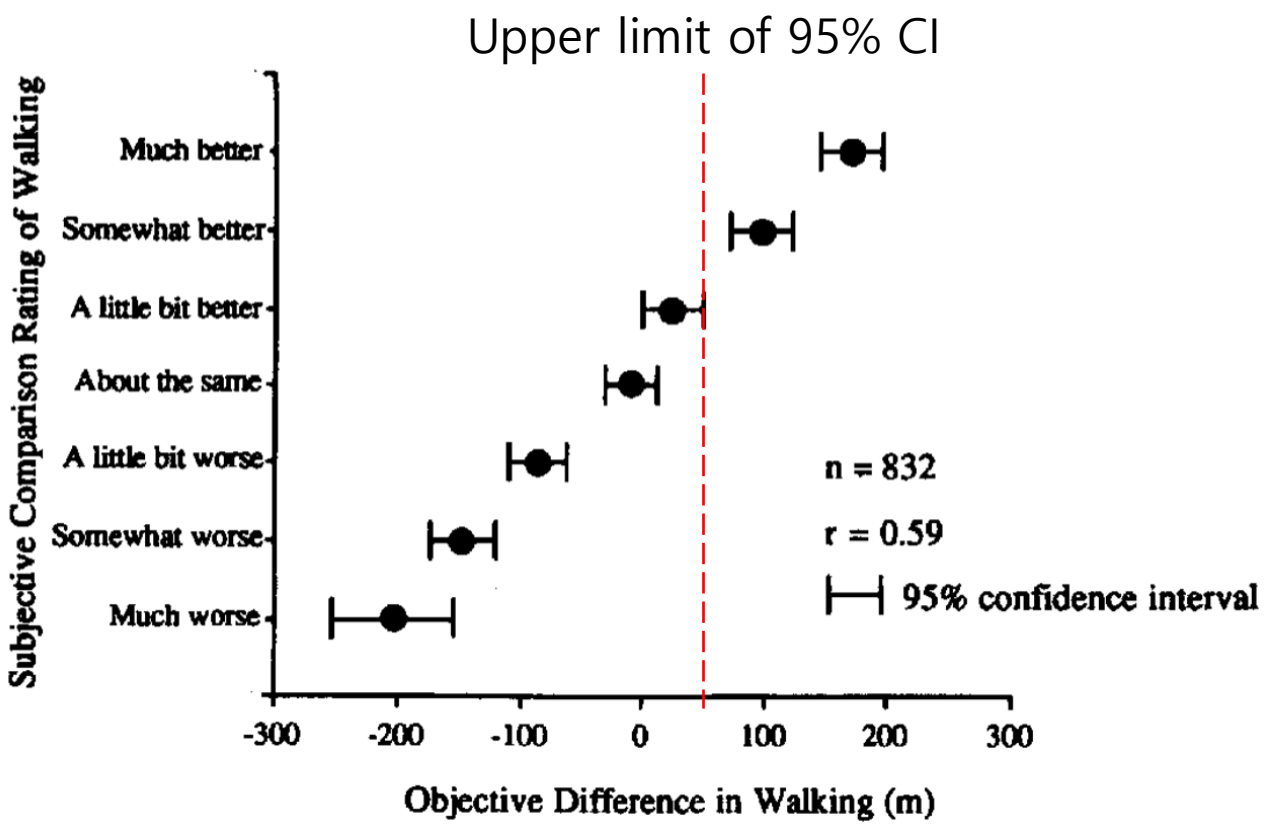
Characteristic	Total (n=259)	Male (n=95)	Female (n=164)
Resting HR, bpm	78.6±9.35	77.1±9.90	79.5±8.93
Resting SpO_2, %	97.9±0.85	97.6±0.90	98.2±0.74
6MWD, m	598.5±57.92	628.9±59.51	580.9±47.80
Borg after 6MWT	0.19±0.334	0.3±0.39	0.15±0.287
HR after 6MWT, bpm	115.4±19.49	112.5±21.63	117.2±17.98
% mHR after 6MWT	63.0±10.48	60.7±10.96	64.4±9.97
SpO_2 after 6MWT, %	97.2±1.21	96.7±1.35	97.6±0.97
Change in SpO_2, %	0.7±1.22	1.0±1.50	0.6±1.01

Tuberc Respir Dis (Seoul). 2014 Jun;76(6):269-75.

MCID of 6-min walk test

- In COPD patients, CV was 8% and initially proposed MCID was 54m.

Chest 2001; 119: 256–270.
Am J Respir Crit Care Med 1997; 155: 1278–1282.



MCID of 6-min walk test

- The available evidence suggests a MCID for 6MWD of 30 (25-33)m for adult patients with chronic respiratory disease.

Eur Respir J. 2014 Dec;44(6):1428-46.
Eur Respir J. 2014 Dec;44(6):1447-78.

- Factors such as age, height, weight and sex should be taken into consideration when interpreting the results of 6MWD.

Contents

Blood eosinophil

- Blood eosinophil is considered the most valuable biomarker of type-2 inflammation in respiratory diseases.

- However, low relevance in identifying asthma severity, specific clinical parameters (lung function, exhaled nitric oxide, exacerbation rate) and PROs.

J Allergy Clin Immunol 2013; 132: 72–80.
Respir Res 2015; 16: 142.
Lancet Respir Med 2015; 3: 849–858.
Ann Allergy Asthma Immunol 2014; 113: 19–24.

MCID of blood eosinophil

- In asthma, blood eosinophilia seems to be more accurate and reliable as a marker of treatment response than asthma severity.

- However, no MCIDs have been specifically investigated or suggested in either clinical trials or real-world data (including studies with biologic drugs targeting eosinophils [reslizumab and benralizumab]).

Chest 2016; 150: 789–798.
Chest 2016; 150: 799–810.
Lancet 2016; 388: 2115–2127.
Lancet 2016; 388: 2128–2141.

Blood IgE antibody

- Total or allergen-specific levels of IgE could not be wholly effective to predict a therapeutic response to omalizumab.

➔ IgE could not be used as a biomarker and a MCID cannot be assessed.

Allergy 2009; 64: 1780–1787.

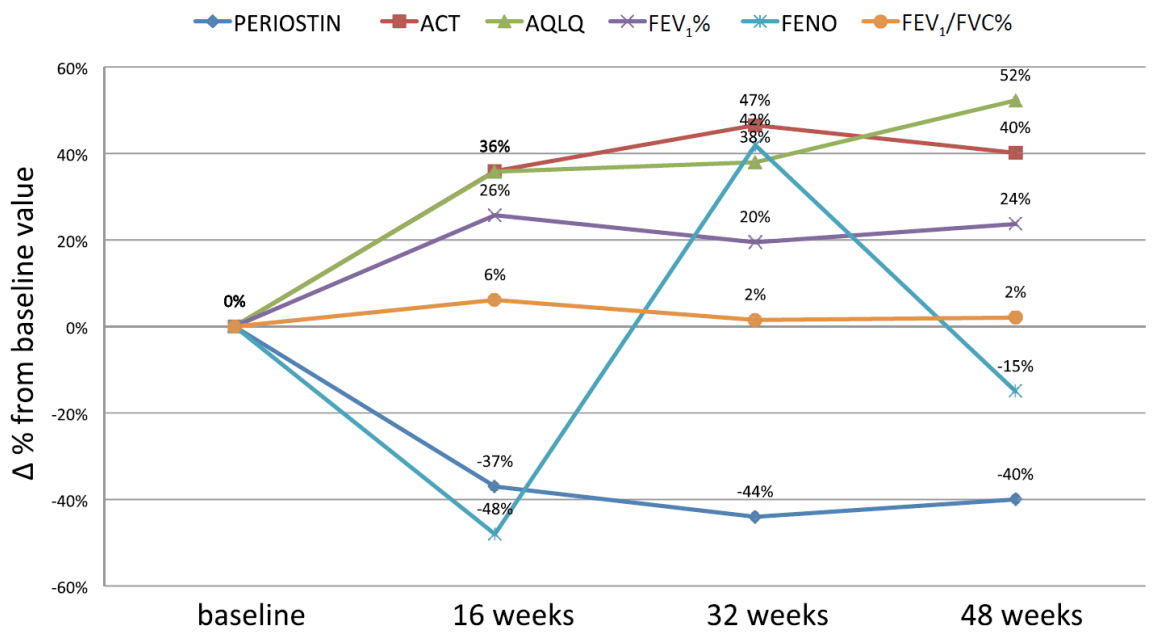
Blood periostin

- A valuable biomarker of T-helper (Th)2 airways inflammation

Eur J Intern Med 2017; 38: 12–16.

- Point-by-point parallelism between serum periostin level and lung function, exhaled nitric oxide fraction (FeNO) and PROs

- No specific association with a MCID has been explored



Ann Allergy Asthma Immunol. 2017 Nov;119(5):460-462.

FeNO, a biomarker in exhaled air

- In patients losing asthma control after steroid withdrawal, a mean increase in FeNO ranging from 16 ppb to 25 ppb, or a 60% increase from baseline.

Eur Respir J 2002; 19: 1015–1019.
Am J Respir Crit Care Med 2001; 164: 738–743.

- When asthma is not optimally controlled, a 40% FeNO of reduction is a reliable predictor of asthma control optimization, particularly for those low ICS doses (PPV 80%).

Eur Respir J. 2008 Mar;31(3):539-46.

MCID of FeNO

- Within-subject CV of FeNO
  - In healthy subjects: ~ 10% (4ppb)
  - **In asthma subjects: ~ 20%**

J Allergy Clin Immunol 2005; 115: 1130–1136.
Respir Med 2002; 96: 895–900.

- ATS clinical practice guideline
  - A change of at least **20% to indicate a significant rise or fall in FeNO** over time or following an intervention

Am J Respir Crit Care Med. 2011 Sep 1;184(5):602-15.

MCID of sputum eosinophil

- ATS/ERS statement
  - Standard MCID for sputum eosinophil counts**: 2-fold or 50% change**

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

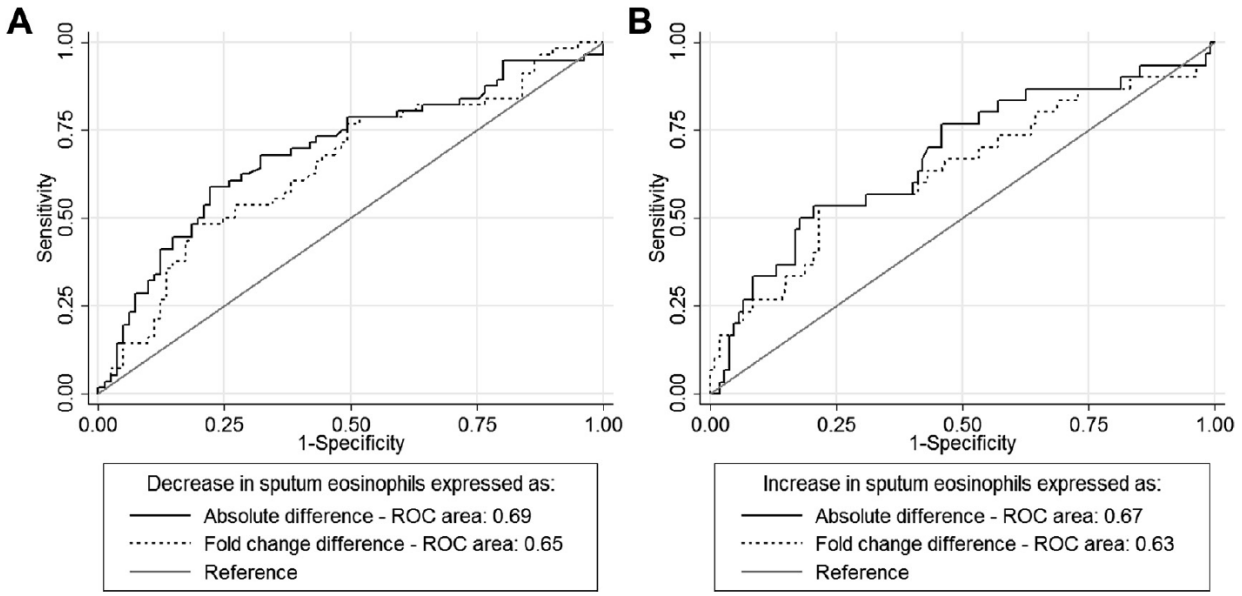
- In various severe asthma studies, a reduction in eosinophil counts was shown between 15% and 20%

  ➔ it may be reasonable to assume a **MCID of 15% absolute change**

Eur Respir J. 2013 Oct;42(4):1003-11.

MCID of sputum eosinophil

- The best cutoff points to discriminate patients measured by the **ACQ score**
  - **Improved asthma control**: absolute **decrease of 4.3% in sputum eosinophils**
  - **Worsened asthma control**: absolute **increase of 3.5% in sputum eosinophils**



J Allergy Clin Immunol Pract. 2017 Sep-Oct;5(5):1335-1343.e5.

Contents

Symptoms

- **Changes in asthmatic symptoms** can be measured by **validated symptom scales**

Eur Respir J 1999; 14: 23–27.

- Clinical research in asthma needs outcome standardization for symptoms
  - To examine and compare outcomes across clinical trials and studies
  - To interpret evaluations of interventions for asthma at a scale larger than single trial
  - Methodological aspects: validity; internal consistency; test-retest reliability; and responsiveness or sensitivity to change

Eur Respir Rev. 2020 Jun 3;29(156):190137.

Validated tools for symptoms

- **Validated** daily diaries and questionnaires for control of adult asthma symptoms

  : **Test-retest reliability + Internal consistency + Validity**

	Measurement	Report	Suggested MCID
Daytime Symptom Diary Scale and Nocturnal Diary Scale	4 items; daytime symptoms (0 to 6-point scale) 1 item; nocturnal awakening (0 to 3-point scale)	Mean score over 2 weeks	N/A
Asthma Symptom Utility Index	8 items; asthma symptoms 3 items; side-effects	Converting mean scores i nto utility (range 0–1)	0.09 points
Asthma Control Questionnaire	5 items; asthma symptoms 1 item; SABA use 1 item; FEV1	Converting mean scores i nto utility (range 0[b]–6[w])	0.5 points
Asthma Control Test	5 items; asthma symptoms and functioning	Range 5(w)–25(b)	3 points

Eur Respir Rev. 2020 Jun 3;29(156):190137.

Validated tools for QoL

Questionnaire	Type	Items /Scores	Reliability /Validation	Responsiveness	Domains	Suggested MCID
Medical Outcomes Study Short Form 36 (SF-36)	Generic	36 items / 0(w)-100(b)	Y	Y	Emotions / Physical	Various according to 8 subscales
Asthma Quality of Life Questionnaire - long version (AQLQ^{juniper} or AQLQ-J)	Asthma-specific	32 items / 1(w)-7(b)	Y	Y	Symptoms / Activities / Impact	0.5 points
AQLQ - short version (mini-AQLQ^{juniper})	Asthma-specific	15 items / 1(w)-7(b)	Y	Y	Symptoms / Activities / Impact	0.5 points
AQLQ^{marks} or AQLQ-S	Asthma-specific	20 items / 0(w)-4(b)	Y	Y	Breathlessness / Concerns / Mood / Social	N/A
Living with Asthma Questionnaire (LWAQ)	Asthma-specific	68 items / 0(b)-2(w)	Y	Y	Physical / Psychological / Social / Others	N/A
St. George's Respiratory Questionnaire (SGRQ)	Asthma-specific	50 (76) items / 0(b)-100(w)	Y	Y	Symptoms / Activities / Impact	4 units (mostly in COPD patients)
Asthma Questionnaire-20 (AQ20)	Asthma-specific	20 items / 0(b)-20(w)	Y	Y	Symptoms / Activities / Impact	N/A

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

Asthma Control Test

Question	Abbreviated text
Q1	Asthma limit your usual activities and enjoyment of everyday life
Q2	Felt fed up or frustrated because of your asthma
Q3	**Asthma keep you from getting as much done at work or home**
Q4	Asthma restrict you in performing your usual daily activities
Q5	Asthma keep you from socializing
Q6	**Rate your asthma control**
Q7	Had any asthma symptoms
Q8a	How often have you had wheezing
Q8b	How often have you had tightness or pain in your chest
Q8c	**How often have you had shortness of breath**
Q8d	How often have you had coughing
Q9	**Asthma symptoms wake you up at night or earlier than usual**
Q10	Awaken at your usual time in morning with asthma symptoms
Q11	How often did you have an asthma episode or attack
Q12	How many days did asthma limit your daily activities
Q13	How many days did asthma keep you at home for more than half a day
Q14	Asthma limit your ability to exercise
Q15	Missed any time from work or school because of asthma
Q16	**Used your rescue inhaler or nebulizer medication**
Q17	Stay in hospital overnight because of asthma
Q18	Visit an urgent care facility or emergency room because of asthma
Q19	Unscheduled visit to primary care physician because of asthma

TABLE II. Summary of forward selection of ACT items in logistic regression analyses (Specialist's rating on asthma control)

Item	Description	Number entered	Odds ratio (confidence limits)	Chi-square	*P* value
Q8C	Shortness of breath	1	1.25 (1.02, 1.61)	54.4273	0.0000
Q6	Patient rating of control	2	0.68 (0.48, 0.95)	14.1044	0.0002
Q16	Use of rescue medication	3	1.30 (1.02, 1.66)	7.1375	–0.0075
Q3	Asthma keeps you from getting much done at work/school	4	1.66 (1.15, 2.40)	5.8535	0.0155
Q9	Asthma symptoms wake you up	5	1.22 (1.04, 1.56)	4.1618	–0.0413

J Allergy Clin Immunol. 2004 Jan;113(1):59-65.

Asthma Control Test

Q1 In the **past 4 weeks,** how often did your asthma prevent you from getting as much done at work, school or home?

SCORE

All of the time 1 | Most of the time 2 | Some of the time 3 | A little of the time 4 | Not at all 5

Q2 During the **past 4 weeks,** how often have you had shortness of breath?

More than once a day 1 | Once a day 2 | 3 to 6 times a week 3 | Once or twice a week 4 | Not at all 5

Q3 During the **past 4 weeks,** how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more times a week 1 | 2 to 3 nights a week 2 | 1 night a week 3 | Less than 1 night a week 4 | Not at all 5

Q4 During the **past 4 weeks,** how often have you used your reliever medication (such as salbutamol)?

3 or more times a day 1 | 1 or 2 times per day 2 | 2 or 3 times per week 3 | Once a week or less 4 | Not at all 5

Q5 How would you rate your asthma contol during the **past 4 weeks**?

Not controlled 1 | Poorly controlled 2 | Somewhat controlled 3 | Well controlled 4 | Completely controlled 5

표 3-7. 한국어판 천식조절검사(Asthma control test: ACT)

1	2	3	4	5
지난 4 주 동안, 당신은 천식으로 인해 얼마나 많은 시간을 직장이나 학교나 집에서 평소에 했던 만큼 일하고 공부하고 활동하는데 지장을 받았습니까?				
항상 그랬다	대부분의 시간 동안 그랬다	다소의 시간 동안 그랬다	아주 약간의 시간 동안 그랬다	전혀 그렇지 않았다
지난 4 주 동안, 당신은 얼마나 자주 숨을 헐떡였거나 / 숨을 쉬기가 어려웠습니까?				
하루에 두번 이상 그랬다	하루에 한번 그랬다	일주일에 3-6번 그랬다	일주일에 1-2번 그랬다	전혀 그렇지 않았다
지난 4 주 동안, 당신은 천식증상(쌕쌕거리는 소리, 기침, 숨가쁨, 가슴답답함이나 통증) 으로 인해 얼마나 자주 밤에 잠을 깨거나 아침에 평소보다 일찍 일어났습니까 ?				
일주일에 4일 밤 이상을 그랬다	일주일에 2-3일 밤을 그랬다	일주일에 한번 그랬다	한 두번 그랬다	전혀 그렇지 않았다
지난 4주 동안, 당신은 응급약물(예를 들면 살부타몰, 페노테롤, 벤토린®, 베로텍® 등)을 얼마나 자주 사용했습니까 ?				
하루에 3번 이상 사용했다	하루에 1-2번 사용했다	일주일에 2-3번 사용했다	일주일에 한 번 이하로 사용했다	전혀 사용하지 않았다
당신은 지난 4주 동안 천식을 얼마나 잘 조절했다고 평가하겠습니까?				
전혀 조절하지 못했다	잘 조절하지 못했다	다소 조절했다	잘 조절했다	완벽하게 조절했다

천식 진료 지침 5차개정판, 2022, 대한결핵 및 호흡기학회

Asthma Control Questionnaire

1. On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
	1	Hardly ever
	2	A few minutes
	3	Several times
	4	Many times
	5	A great many times
	6	Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
	1	Very mild symptoms
	2	Mild symptoms
	3	Moderate symptoms
	4	Quite severe symptoms
	5	Severe symptoms
	6	Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
	1	Very slightly limited
	2	Slightly limited
	3	Moderately limited
	4	Very limited
	5	Extremely limited
	6	Totally limited

Eur Respir J 1999; 14: 902-907

Asthma Control Questionnaire

4. In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0	None
	1	A very little
	2	A little
	3	A moderate amount
	4	Quite a lot
	5	A great deal
	6	A very great deal
5. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0	None
	1	1–2 puffs most days
	2	3–4 puffs most days
	3	5–8 puffs most days
	4	9–12 puffs most days
	5	13–16 puffs most days
	6	More than 16 puffs most days
To be completed by a member of the clinic staff		
7. FEV_1 pre-bronchodilator:	0	>95% predicted
	1	95–90%
FEV_1 predicted	2	89–80%
	3	79–70%
FEV_1 % predicted	4	69–60%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59–50%
	6	<50% predicted

Eur Respir J 1999; 14: 902-907

Asthma Symptom Utility Index

1. How many days were you bothered by coughing during the past 2 weeks?

0 Not at all (skip to question 3)
1 1–3 days
2 4–7 days
3 8–14 days

2. On average, how severe was your coughing during the past 2 weeks?

1 Mild
2 Moderate
3 Severe

3. How many days were you bothered by wheezing during the past 2 weeks?

0 Not at all (skip to question 5)
1 1–3 days
2 4–7 days
3 8–14 days

4. On average, how severe was your wheezing during the past 2 weeks?

1 Mild
2 Moderate
3 Severe

5. How many days were you bothered by shortness of breath during the past 2 weeks?

0 Not at all (skip to question 7)
1 1–3 days
2 4–7 days
3 8–14 days

6. On average, how severe was your shortness of breath during the past 2 weeks?

1 Mild
2 Moderate
3 Severe

7. How many days were you awakened at night during the past 2 weeks?

0 Not at all (skip to question 9)
1 1–3 days
2 4–7 days
3 8–14 days

8. On average, how much of a problem was being awakened at night during the past 2 weeks?

1 Mild
2 Moderate
3 Severe

9. How many days were you bothered by side effects of your asthma medication during the past 2 weeks?

0 Not at all
1 1–3 days
2 4–7 days
3 8–14 days

10. If 1 day or more, what side effects did you have?

11. On average, how severe were the side effects of your asthma medication during the past 2 weeks?

1 Mild
2 Moderate
3 Severe

Chest. 1998 Oct;114(4):998-1007.

Asthma Quality of Life Questionnaire

1. Bicycling
2. Clearing Snow off Car
3. Dancing
4. Doing Home Maintenance
5. Doing Housework
6. Gardening
7. Hurrying
8. Jogging/Exercising/Running
9. Laughing
10. Mopping or Scrubbing the Floor
11. Mowing the Lawn
12. Playing with Pets
13. Playing with Children
14. Playing Sports
15. Shovelling Snow
16. Singing
17. Social Activities
18. Sexual Intercourse
19. Talking
20. Running Upstairs or Uphill
21. Vacuuming
22. Visiting Friends or Relatives
23. Going for a Walk
24. Walking Upstairs or Uphill
25. Woodwork or Carpentry
26. Work Activities

Subjects are asked to identify 5 activities in which they are limited by their asthma.

Remaining 27 questions within 2 weeks

DOMAINS

The items were grouped into four domains:
Activity limitations (items 1 to 5, 11, 19, 25, 28, 31, 32)
Symptoms (items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30)
Emotional function (items 7, 13, 15, 21, 27)
Exposure to environmental stimuli (items 9, 17, 23, 26).

27 questions	
Chest tightness	Morning awake
Felt having asthma	Afraid of not having medication
Short of breath	Heavy breathing
Symptom to smoking	Symptom to air pollution or weather
Wheezing	Night awake
Avoid smoking	Limit going outside d/t air pollution or weather
Coughing	Symptom to smell or perfume
Feel frustrated	Afraid of getting out of breath
Chest heaviness	Avoid smell or perfume
Need medication	Interfere sleep
Throat clearing	fighting for air
Symptom to dust	Range of activity limitation
Difficulty breathing	Activity limitation
Avoid dust	

Am Rev Respir Dis. 1993 Apr;147(4):832-8.

Limitations of symptom as an endpoint

- **Major limitations** as endpoints
  - Lack of convincing relationships between subjective feelings and objective outcomes
  - Possible influence of external features, like age and pharmacological treatments
  - Individual patients perceive symptoms differently and hence also perceive the magnitude of change in their asthma differently when answering the global change

Eur Respir Rev. 2020 Jun 3;29(156):190137.

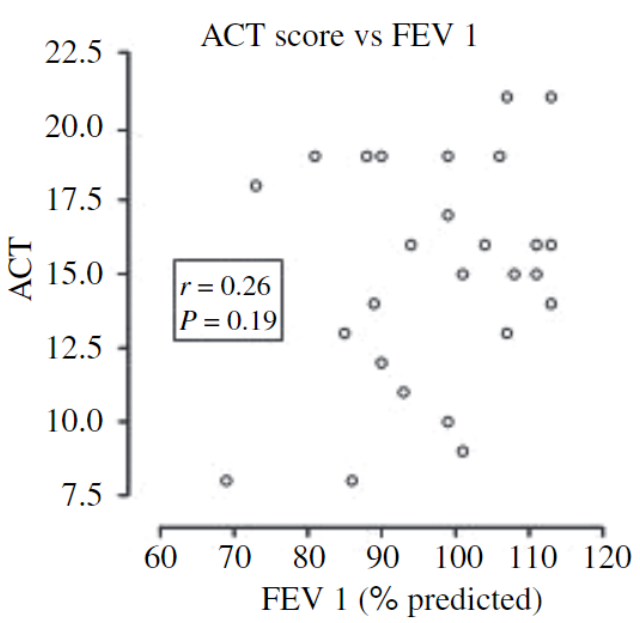
Difference between subjective/objective outcomes

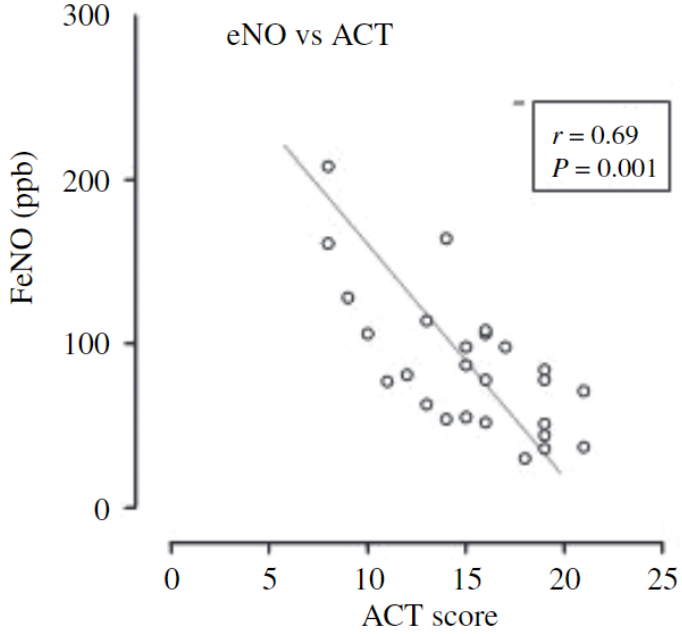
- The distributions of average **minimal patient perceivable improvement or deterioration scores** often do not correlate with values of **FEV1, PEF, and FeNO.**

LONGITUDINAL CONSTRUCT VALIDITY*

Value= r	Change in Asthma Quality of Life			
	Activities	Symptoms	Emotions	Environment
Change in clinical asthma				
FEV_1, % pred	0.28+	0.27+	0.43+	0.29+
PC_{20}, mg/ml	0.26+	0.26++	0.30	0.30+
Medications	0.45+	0.50++	0.30+	0.34+
Asthma control	0.57++	0.67+++	0.63++	0.40++
PEFR, L/min	0.41+	0.42+	0.38+	0.33+

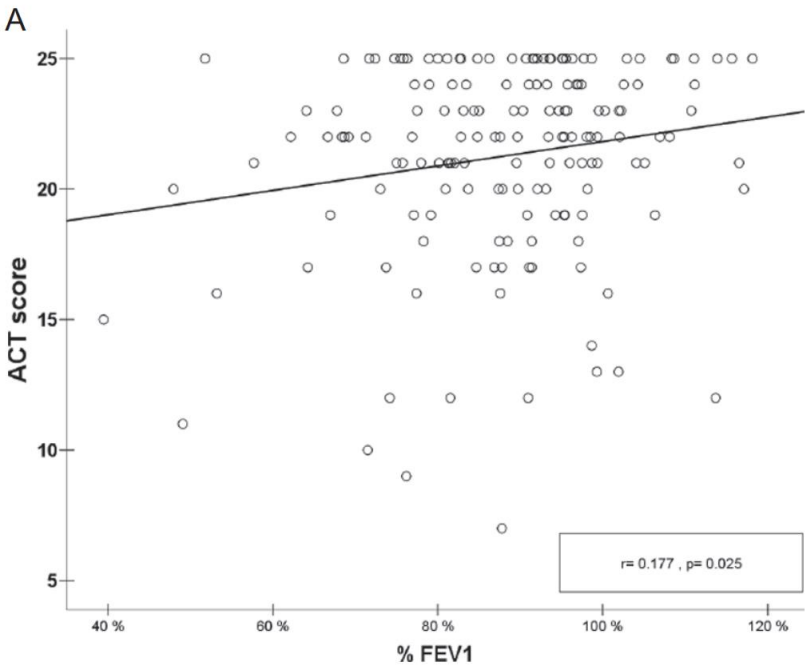
Am Rev Respir Dis. 1993 Apr;147(4):832-8.

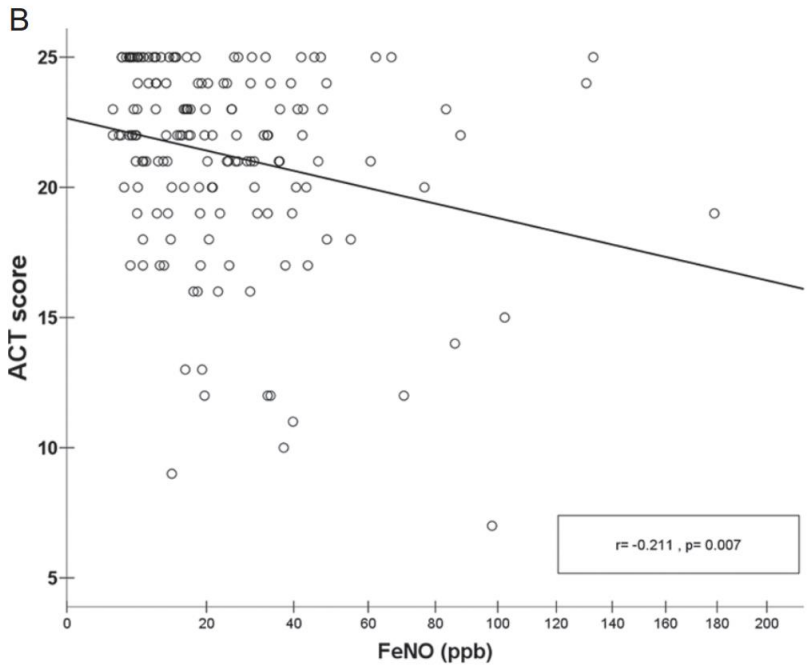




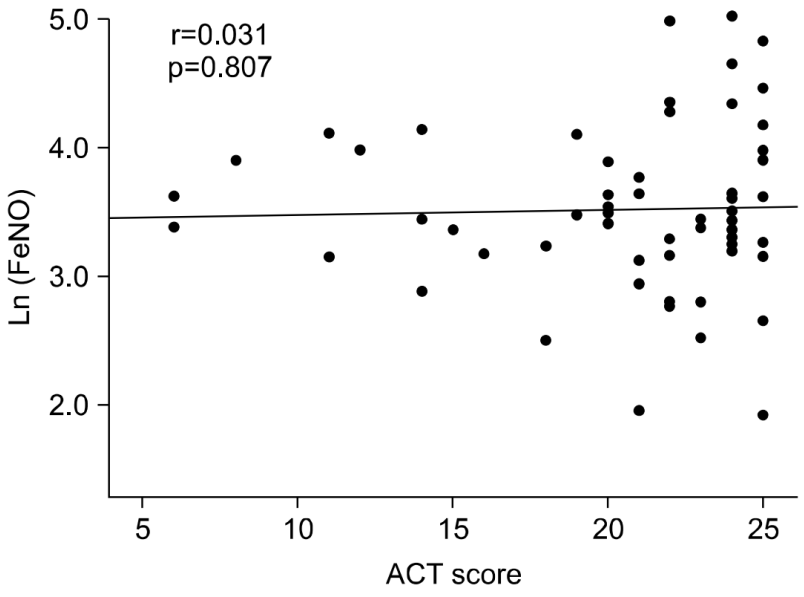
Allergy. 2007 Feb;62(2):207-8.

Difference between subjective/objective outcomes





J Asthma. 2011 Nov;48(9):901-6.



Tuberc Respir Dis 2011;71:106-113.

Difference according to age

- Small changes in asthma control measures correspond to higher levels of perceivable improvement in elderly than younger patients

Subgroups	MPPI n	Average MPPI from baseline for asthma measures: Diary scale score	FEV1 L	PEF $L \cdot min^{-1}$	β-agonist use $puffs \cdot day^{-1}$
Active treatment	67	-0.37	0.25	22.1	-1.03
Placebo treatment	19	-0.10	0.18	7.2	-0.04
Male	42	-0.29	0.25	19.0	-0.67
Female	44	-0.33	0.22	18.6	-0.94
Older than median age*	39	-0.19	0.17	19.4	-0.54
Younger than median age	47	-0.41	0.28	18.3	-1.03

Eur Respir J 1999; 14: 23-27

Exacerbation

- No validated MCID in reduction of severe asthma exacerbations is available.
  - Even a single episode of severe exacerbation can be considered clinically relevant.

- A reduction in annual exacerbation rate or in the risk of having a severe asthma-related event ranging from **20**–40**%** for a given asthma treatment regimen in RCTs

  ➔ MCID for severe exacerbations: **reduction >20%** (annual exacerbation rate)

Lancet 2003; 361: 1071–1076.
Lancet 2006; 368: 744–753.
Lancet Respir Med 2013; 1: 23–31.
N Engl J Med 2014; 371: 1198–1207.
Eur Respir Rev. 2020 Jun 3;29(156):190137.

Exacerbation in severe asthma with triple therapy

- IRIDIUM and ARGON studies

Outcome	Treatment	Active comparator	Delta	Suggested MCID	Beneficial clinically relevant effect
FEV_1	MD-MF/IND/GLY	MD-MF/IND	76 mL	>60 mL*	Yes
	MD-MF/IND/GLY	HD-FLU/SAL	99 mL		Yes
	HD-MF/IND/GLY	HD-MF/IND	65 mL		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	119 mL		Yes
	HD-MF/IND/GLY	HD-FLU/SAL + TIO	96 mL		Yes
Morning PEF	HD-MF/IND/GLY	HD-FLU/SAL + TIO	26.67%	>5.39%#	Yes
Evening PEF	HD-MF/IND/GLY	HD-FLU/SAL + TIO	28.72%		Yes
All exacerbations (mild, moderate, and severe)	MD-MF/IND/GLY	HD-FLU/SAL	−30%	>-20%	Yes
	HD-MF/IND/GLY	HD-MF/IND	−21%		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	−40%		Yes
Moderate or severe exacerbations	MD-MF/IND/GLY	HD-FLU/SAL	−19%		Borderline
	HD-MF/IND/GLY	HD-FLU/SAL	−36%		Yes
Moderate exacerbations	HD-MF/IND/GLY	HD-FLU/SAL + TIO	−43%		Yes
Severe exacerbations	HD-MF/IND/GLY	HD-MF/IND	−22%		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	−42%		Yes
ACQ-7	HD-MF/IND/GLY	HD-FLU/SAL	+8.2% responders	>0.5 points	A greater proportion of patients achieved the MCID
AQLQ	HD-MF/IND/GLY	HD-FLU/SAL + TIO	+8.1% responders	>0.5 points	A greater proportion of patients achieved the MCID
SGRQ	HD-MF/IND/GLY	HD-FLU/SAL + TIO	−2.00	>4 units	No

All exacerbations (mild, moderate, and severe)	MD-MF/IND/GLY	HD-FLU/SAL	−30%
	HD-MF/IND/GLY	HD-MF/IND	−21%
	HD-MF/IND/GLY	HD-FLU/SAL	−40%
Moderate or severe exacerbations	MD-MF/IND/GLY	HD-FLU/SAL	−19%
	HD-MF/IND/GLY	HD-FLU/SAL	−36%
Moderate exacerbations	HD-MF/IND/GLY	HD-FLU/SAL + TIO	−43%
Severe exacerbations	HD-MF/IND/GLY	HD-MF/IND	−22%
	HD-MF/IND/GLY	HD-FLU/SAL	−42%

J Exp Pharmacol. 2022 Jan 11;14:1-5.

Exacerbation in severe asthma with anti-IL5

Outcome measures	Importance	Measure unit	Minimal clinically important difference
Mortality	Critical*		
Exacerbation rate	Critical	Average reduction in the annual number of exacerbations	25% (a minimum reduction of 0,5 exacerbations per year)
		Number of patients who experience 0 exacerbations annually	10 percentage points
Oral corticosteroid-maintenance treatment	Critical	Average %-reduction in daily dose (maintenance-treatment)	20% (at least 2.5-mg prednisolone equivalent dose)
		Percentage of patients who are discontinued oral corticosteroid-maintenance treatment	5 percentage points
		Percentage of patients who experience ≥50% reduction of oral corticosteroid treatment	10 percentage points#
Lung function FEV_1	Important	Average change in lung function	200 ml
		Percentage of patients who experience an improvement of 200 ml or more	15 percentage points
Asthma control	Important	Average change in asthma control. A prioritised list of scores: · ACQ 5 (Asthma Control Questionnaire) · ACT (Asthma Control Test) · Other similar questionnaires	ACQ: 0.5 ACT: 3
Quality of life (QoL)	Important	Average change in QoL. A prioritised list of scores: · Astma Quality of Life Questionnaire (AQLQ) · Other questionnaires	AQLQ: 0.5 points
Serious adverse events (SAEs)	Important	The added number of SAEs	5 percentage points for the added number of SAEs
		Specific subgroups of SAEs, including anaphylaxis is assessed if they are distributed uniformly between the groups	No minimal clinically important difference is reported
Dropout rate	Important	The percentage of patients who dropped out when the study was completed (difference between intention-to-treat population and patients who completed the study)	10 percentage points
Sick leave	Important	Average number of sick leave days per year	5 days per year
Eosinophil count	Less	Eosinophils per microL	
Adverse events (AEs)	Less	The added number of AEs	

Eur Clin Respir J. 2018 Nov 7;5(1):1536097.

Summary

- **Standardized definitions and data collection** methods should be used for endpoints in RCTs

- **Essential endpoints** in RCTs
  - **For current control**: Symptom-free days, reliever use, composite scores, exacerbation, QoL
  - **For future risk**: Exacerbation, FEV1, composite scores, treatment side effects

- **How to determine the MCID**
  - **Primary: anchor-based methods**
  - **Secondary: distribution-based measures**

- **MCID of spirometric evaluation**
  - **FEV1:** 20% (short-term trials) / 15% (long-term trials) or 230mL
  - **PEF:** 25 or 18.8L/min

Summary

- **MCID of exercise test**
  - **Incremental exercise test**
    - ✓ VO2: 0.04 / Work rate: 4W / IC: 140ml or 4.5%
    - ✓ modified borg scale: 2 points
  - **Constant exercise test**
    - ✓ Enduration time: 100s or 33%
  - **6MWD**: 30m
- **MCID of inflammatory endpoints**
  - **FeNO**: 20%
  - **Sputum eosinophil**: 2-fold or 50% ➔ about 4%
- **MCID of clinical endpoints**
  - **Symptom**
    - ✓ ASUI: 0.09 / ACT: 3 / ACQ: 0.5 points
  - **QoL**
    - ✓ AQLQ: 0.5, min-AQLQ: 0.5, SGRQ: 4 points
  - **Limitation:** Lack of convincing relationships between subjective feelings and objective outcomes
  - **Exacerbation**: 20 (20~40)%

Thank you for your attention

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