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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process

Assessing minimum important difference/responder definition in clinical evaluation of rare diseases

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Plan:

Minimal important difference:

- what is it, how to estimate

Applying the MID

- proportion who benefit

Br J Dermatology, 2004

- effect of alefacept on quality of life in 553 patients with psoriasis
- alefacept significantly reduced (improved) mean Dermatology Quality of Life Scale scores compared with placebo: 4.4 vs. 1.8 at 2 weeks after the last dose ($P < 0.0001$) and 3.4 vs. 1.4 at 12 weeks after the last dose ($P < 0.001$).
- effect size?
 - trivial, small but important, large?

Minimally important difference

- smallest change that patients would consider important
- approaches
 - patient scenarios
 - between-patient ratings
 - within-patient ratings
 - global ratings of change
 - are you the same, a little better, a lot better

Establishing Interpretability

- Chronic Respiratory Questionnaire (CRQ)
- Chronic Heart Failure Questionnaire (CHQ)
- 20 Items
 - Dyspnea
 - Fatigue
 - Emotional Function
- evidence for validity, responsiveness

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
- 7 NOT AT ALL SHORT OF BREATH

Establishing Interpretability

- clinical impression
 - MID 0.5 per question
- 31 patients respiratory rehab program
 - before, 2, 6, 12, and 24 weeks after
- 24 CAL patients in bronchodilator trial
- 20 patient with CHF in digoxin trial

Global rating of change

Overall, has there been any change in your shortness of breath since the last time you saw us?

1 WORSE

2 ABOUT THE SAME

3 BETTER

- 1 ALMOST THE SAME, HARDLY ANY WORSE AT ALL
- 2 A LITTLE WORSE
- 3 SOMEWHAT WORSE
- 4 MODERATELY WORSE
- 5 A GOOD DEAL WORSE
- 6 A GREAT DEAL WORSE
- 7 A VERY GREAT DEAL WORSE

All Trials Combined Mean Change per Question

Global Rating of Change in CRQ and CHQ	0	1 - 3	4 - 5	6 - 7
Dyspnea	0.10	0.43	0.96	1.47
Fatigue	0.03	0.46	0.88	0.96
Emotional Function	0.02	0.49	0.81	0.86

Mean change per question - adults with asthma -- AQLQ

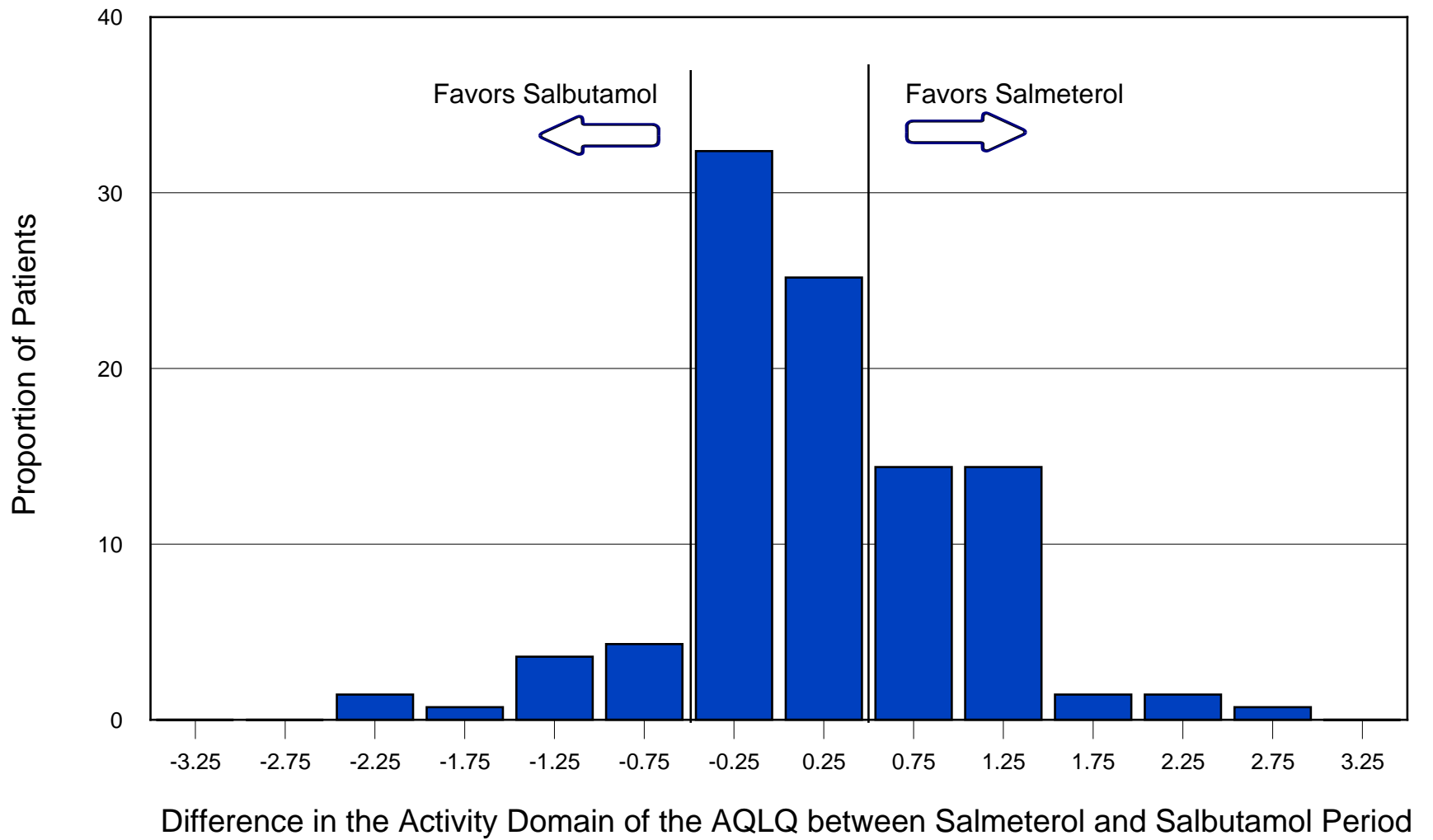
<i>Global ratings</i>	0 - 1	2 - 3	4 - 5	6 - 7
Overall QOL	0.11	0.52	1.03	2.29
Activity Limitations	0.12	0.47	0.87	1.83
Symptoms	0.20	0.49	1.13	2.21
Emotional Function	0.20	0.58	1.51	2.70

Applying the MID

- assume MID is 0.50 and patients mean improvement is 0.25
- does this mean no one benefits?
- what if 0.6 - everyone benefits?
- if 0.25 mean change could mean:
 - 75% have 0 improvement
 - 25% have 1.0
 - RD 25%, NNT of 4

NNT in a cross-over trial

- multicentre blinded crossover RCT
- 12 weeks duration, 140 patients
- medications
 - salmeterol (50 ug, twice daily) plus salbutamol p.r.n.
 - salbutamol (200 ug, qid) plus salbutamol p.r.n.
 - placebo plus salbutamol p.r.n.
- AQLQ at end of each period



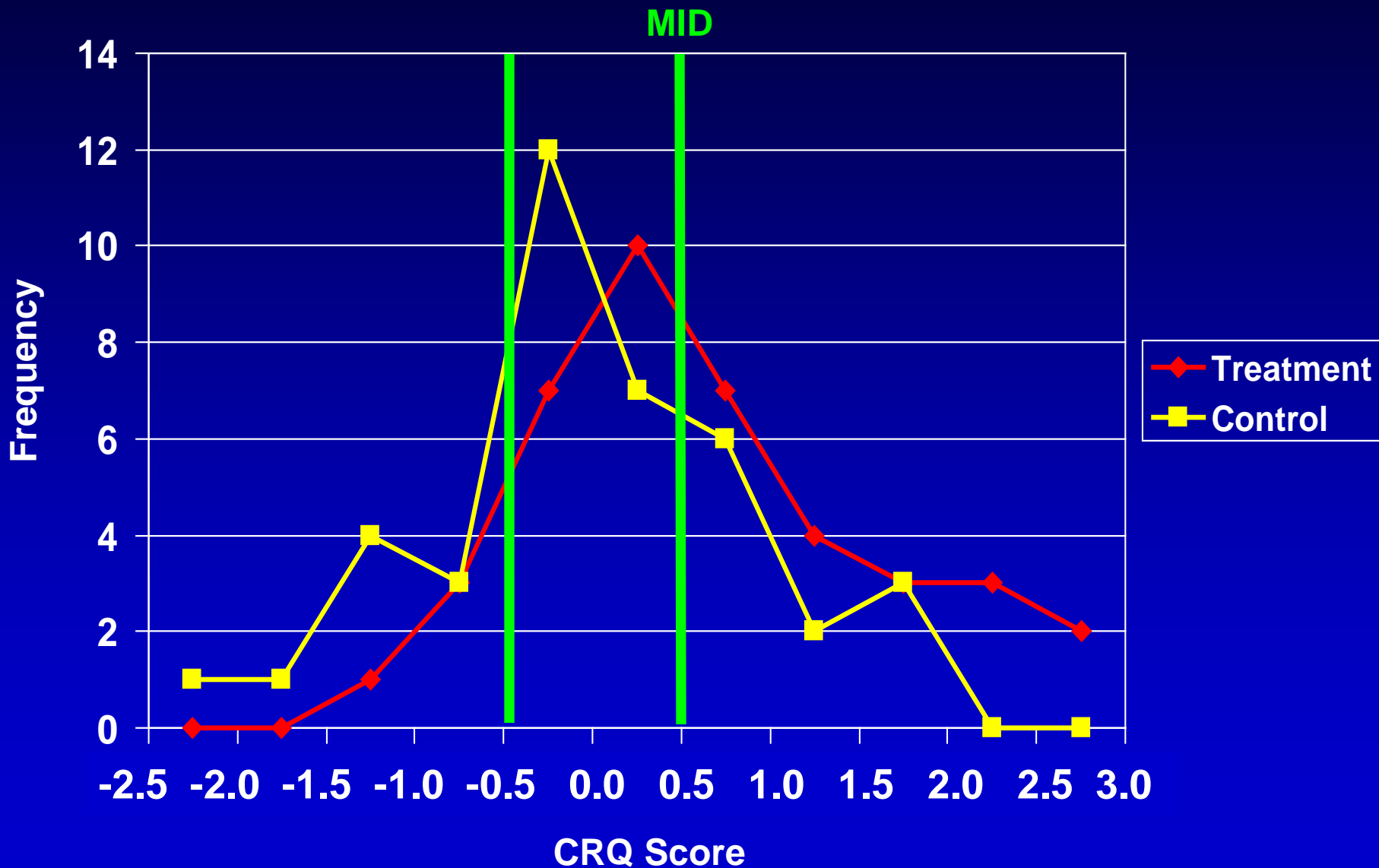
Differences between groups given different treatments for asthma: salmeterol v salbutamol

AQLQ domains	Difference between treatments		Proportion better on salmeterol	Proportion better on salbutamol or placebo	Proportion who benefited	No NNT for a single patient to benefit
	Mean	P value				
Symptoms	0.50	<0.0001	0.42	0.12	0.30	3.3
Limitations on activity	0.30	<0.0001	0.32	0.10	0.22	4.5

Differences between groups given different treatments for asthma: salmeterol v placebo

AQLQ domains	Difference between treatments		Proportion better on salmeterol	Proportion better on salbutamol or placebo	Proportion who benefited	No NNT for a single patient to benefit
	Mean	P value				
Symptoms	0.68	<0.0001	0.50	0.09	0.41	2.4
Limitations on activity	0.43	<0.0001	0.42	0.08	0.34	2.9

CRQ Dyspnea Change Scores



Differences between rehabilitation and conventional care in CAL

CRQ domain	Difference between groups		Estimated proportion better on rehabilitation	Estimated proportion better on conventional care	Proportion benefiting from rehabilitation	No NNT for a single patient to benefit
	Mean	P value				
Dyspnoea	0.60	0.0003	0.47	0.28	0.19	5.2
Fatigue	0.45	0.06	0.45	0.23	0.23	4.4
Emotional function	0.40	0.001	0.47	0.17	0.30	3.3
Mastery	0.71	0.0001	0.54	0.15	0.39	2.5

Steps to making qol RCT data compelling

- determine the MID
- report mean differences
 - in terms of MID
- calculate proportion benefit, NNT