

Minimal Clinically Important Improvement and Patient Acceptable Symptom State for Subjective Outcome Measures in Rheumatic Disorders

FLORENCE TUBACH, PHILIPPE RAVAUD, DORCAS BEATON, MAARTEN BOERS, CLAIRE BOMBARDIER, DAVID T. FELSON, DESIRÉ van der HEIJDE, GEORGE WELLS, and MAXIME DOUGADOS

ABSTRACT. The concepts of minimal clinically important improvement (MCII) and patient acceptable symptomatic state (PASS) could help in interpreting results of trials involving patient-reported outcomes by translating the response at the group level (change in mean scores) into more clinically meaningful information by addressing the patient level as “therapeutic success (yes/no).” The aims of the special interest group (SIG) at OMERACT 8 were to discuss specific issues concerning the MCII and PASS concepts, especially the wording of the external anchor questions used to determine the MCII and PASS estimates, and to move toward a consensus for the cutoff values to use as the MCII and PASS in the different outcome criteria. The purpose of this SIG at OMERACT 8 was to inform participants of the MCII and PASS concepts and to agree on MCII and PASS values for pain, patient global assessment, and functional impairment. (*J Rheumatol* 2007;34:1188–93)

Key Indexing Terms:

MINIMAL CLINICALLY IMPORTANT DIFFERENCE
RESPONSE TO THERAPY
PATIENT ACCEPTABLE SYMPTOMATIC STATE
OUTCOME CRITERIA
PATIENT’S PERSPECTIVE

From the Département d’Epidémiologie, Biostatistique et Recherche Clinique, Hôpital Bichat, Paris, France; INSERM, U738; Université Paris 7 Denis Diderot; St. Michael’s Hospital, Institute for Work and Health, University of Toronto, Toronto, Ontario, Canada; Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; Arthritis Center, Boston University, Boston, Massachusetts, USA; Department of Rheumatology, University Hospital Maastricht, Maastricht, The Netherlands; Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada; Department of Rheumatology B, Cochin Hospital, Paris, France and Université René Descartes, Paris 5.

Dr. Tubach obtained a EULAR/OMERACT Travel Bursary to attend the OMERACT 8 meeting.

F. Tubach, MD, INSERM, U738; AP-HP, Département d’Epidémiologie, Biostatistique et Recherche Clinique; Université Paris 7, UFR de médecine, Paris; P. Ravaud, MD, PhD, INSERM, AP-HP, Hôpital Bichat, Département d’Epidémiologie, Biostatistique et Recherche Clinique, Paris; D. Beaton, BScOT, PhD, St. Michael’s Hospital, Institute for Work and Health, University of Toronto; M. Boers, MD, PhD, Professor of Clinical Epidemiology, Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam; C. Bombardier, MD, FRCPC, Institute of Medical Sciences, Institute for Work and Health, Faculty of Medicine, University of Toronto, Department of Medicine, Mount Sinai Hospital; D.T. Felson, MD, MPH, Professor, Clinical Epidemiology Research and Training Unit, Arthritis Center, Boston University;

D.M. van der Heijde, MD, Professor of Rheumatology, Department of Rheumatology, University Hospital Maastricht; G.A. Wells, PhD, Professor, Department of Epidemiology and Community Medicine, University of Ottawa; M. Dougados, MD, Paris-Descartes University, Medicine Faculty; AP-HP, Department of Rheumatology B, Cochin Hospital, Paris.

*Address reprint requests to Dr. F. Tubach, Département d’Epidémiologie, Biostatistique et Recherche Clinique, INSERM E0357, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France.
E-mail: florence.tubach@bch.aphp.fr*

Most rheumatologic diseases are chronic and symptomatic conditions. Thus, the aim of treatment is to improve patient symptoms, function, and well-being, rather than to cure the disease. Consequently, patient-reported outcomes are widely used in assessing the result of care in clinical practice, clinical trials, and longitudinal epidemiological studies^{1,2}. Most of the tools evaluating these subjective criteria in rheumatic disorders measure continuous variables (scores). Thus, with the exception of summary indices such as American College of Rheumatology response instruments ACR20/50/70³, results of clinical trials for symptoms (e.g., pain) and signs (e.g., joint count) are usually expressed as continuous data at the group level (e.g., mean change or effect size), which are difficult to interpret and cannot easily be translated to the level of an individual response. Clinicians need to know how many patients showed a response, what was their level of response, and how many patients are doing well. But what constitutes a clinically relevant therapeutic success with patient-reported outcomes? Translating these continuous criteria [e.g., by Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score] to more clinically meaningful information such as “therapeutic success (yes/no)” would be helpful in better understanding the results of trials. However, the cutoff used for the dichotomization must be clinically relevant.

Two concepts can be distinguished in interpreting patient-reported outcome scores at the individual level: (1) the concept of improvement (which can be relative or absolute), and (2) the concept of a state of well-being. For the concept of

improvement, the minimal clinically important difference (MCID)⁴⁻⁶ or minimal clinically important improvement (MCII)⁷, defined as the smallest change in measurement that signifies an important difference/improvement in a symptom, could be used. In this report, because the direction of effect in most trials is signified by improvement, and because of differences (now documented) in the MCID for deterioration and improvement⁸, we focus only on the MCII. For the concept of status of well-being at any point in time (usually after treatment in a trial setting), a few definitions are being used, as follows — the patient acceptable symptom state (PASS)⁹; low disease activity (LDA)¹⁰, now renamed minimal disease activity (MDA); and remission. The PASS is defined as a symptom state that the patients consider acceptable. MDA is now defined in rheumatoid arthritis (RA) as “that state deemed a useful target of treatment by both the physician and the patient given current treatments and knowledge,” and is thus located between activity of disease and (close to) remission¹¹. The MDA for RA is based on the opinion of physician and patient, whereas the PASS is strictly a patient reported outcome. Classifying individuals’ conditions as being below a threshold level of disability or pain allows for the description of the proportion of therapeutic success or failure (patients who have improved or achieved an acceptable state or not) in addition to mean effects at the group level. Such analysis would add useful information and aid in the interpretation of trial and longitudinal results to decide whether a treatment should be used. Accurate methods for such analysis would result in improved decision tools that are dependent on a “responder analysis” at each node in a decision tree.

The question of what constitutes an important improvement or an acceptable state is an issue of increasing interest. At the moment, no consensus exists on the methods that should be used to determine the MCID/MCII. During OMERACT 5, 6, and 7, the anchor-based method, an external judgment of the importance of change as the anchor, was recommended^{12,13}. Moreover, the patient’s perspective was recommended as the perspective to use for the anchor¹⁴. Further, the importance of standardizing the wording of the anchor question has been raised¹⁵ and remains to be addressed.

The concept of MDA was addressed during OMERACT 6 and 7. These OMERACT modules aimed at seeking a consensus on the definition of MDA in RA based on patients’ profiles. So the MDA state was defined for a prespecified core set of criteria in RA. Similarly, the ASessments in Ankylosing Spondylitis Working Group (ASAS) has developed partial remission criteria for ankylosing spondylitis, based on an aggregation of a core set of items. However, the main outcome criterion in clinical trials often concerns a single domain of symptom (e.g., pain, function), and the concept of MDA for these specific domains has not been thoroughly evaluated.

Since OMERACT 7, knowledge in the field of MCID/MCII and MDA/PASS has increased, moving from

theory to practice. In particular, the determination of MCII and PASS estimates from several studies in different diseases allows investigation of some of the properties of these criteria.

During OMERACT 8, the aim of the SIG was to discuss specific issues concerning the MCII and PASS concepts and to move toward a consensus for use of the MCII and PASS — Which external anchor should be used? Should the MCII, the PASS, or both, be recommended? What should the MCII and PASS values be? Should the effect of some covariates be taken into account?

Specific issues

Standardization of the wording of the external anchor question to determine the MCII and PASS

Various questions with different wordings have been used as an external anchor for the MCII and PASS. In addition, the response modalities and the group for which MCII is defined (patients with fair response to therapy, good response to therapy, very good response to therapy, etc.) have been shown to influence the MCII estimates¹⁵. For the PASS value determination, the issue of the time spent in the state is very important for the wording of the anchor question (i.e., Was the patient asked if his symptom state was acceptable if he was to remain in that state for 48 hours, 3 months, or for the rest of his life?). Standardization is needed to allow comparison across studies, diseases, and languages.

The review of these different issues was the basis of a discussion that led to the survey we report below.

Should the MCII and PASS be treatment-specific or the same whatever the treatment evaluated?

Determining treatment-specific MCII and PASS values [i.e., a PASS for evaluating nonsteroidal antiinflammatory drug (NSAID) therapy different from a PASS for evaluating anti-tumor necrosis factor- α (TNF- α) therapy] allows for taking into account the different levels of patients’ expectations for the treatment. Indeed, it is not known whether patients consider a state (or a change) satisfactory independent of the treatment they receive (i.e., whether the PASS values are related to patients’ expectations of the treatment). One may hypothesize, for instance, that patients expect stronger effects from a TNF- α antagonist than from NSAID therapy and thus would consider a lower level of symptoms as satisfactory with TNF- α antagonist therapy. This issue should be investigated in a further study. The drawback of using treatment-specific PASS or MCII values is that these values would be updated regularly as treatment options and knowledge and expectations about them evolve^{2,4}.

Relation between MCII and PASS

The relative meaning of the MCII and PASS was unknown. Whether the concept of improvement, remission, or both should be recommended was discussed and was addressed in a survey following the SIG session, reported below. The

results on how the MCII and PASS are interrelated in a study of hip and knee osteoarthritis (OA) and acute rotator cuff syndrome¹⁶ were presented. In pain and function scores, the resulting MCII values corresponded with the amount of improvement needed to reach the level defined by the PASS. The MCII appears to be the amount of change in status required that will allow the patient to achieve the PASS. It seems that patients consider that they experienced an important improvement only if this improvement allows them to achieve a satisfactory state, a state in which they feel good. Consequently, it seems that what is important to patients is to feel good (the concept of PASS) rather than to feel better (the concept of MCII).

Review of the existing values determined for MCII and PASS for different outcome criteria in different diseases

MCID values have been determined in some rheumatic diseases, such as chronic low back pain¹⁷ and hip or knee OA¹⁸⁻²⁰.

The MCII has been estimated for pain, patient global assessment, and the WOMAC function subscale in French patients with hip and knee OA⁷. The definition of MCII and PASS was chosen by a group of expert rheumatologists, who are members of this OMERACT SIG: the external anchor was

patients' evaluation of their response to therapy on a 5-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 defined as the 75th percentile of the change in score between the baseline and final visit among patients whose final evaluation of response to therapy was good. The MCII was defined in the group of patients whose evaluation of response to therapy was "good," because one is always looking for clinically important differences. Patients whose evaluation of response to therapy was "excellent" were not included, since our target was the minimal change important in the patient's perspective. Following the same methodology, the MCII was estimated in acute rotator cuff syndrome in France, for pain and Neer index¹⁶, a score of shoulder function²¹, and in AS in Norway for pain, night pain, patient's global assessment, with the Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index¹⁵.

The PASS has been determined in studies of hip or knee OA, acute rotator cuff syndrome, and AS, defined as the 75th percentile of the score at the final visit for patients who considered their state satisfactory at the end of the study.

Table 1. Results of the first survey about the MCII and PASS given to OMERACT 8 special interest group members.

Three questions were voted on:	
1) In addition to the conventional way of reporting results of trial using patient-reported outcomes measured with continuous variables (e.g. mean change in pain 0-100 VAS), should OMERACT recommend adding reports of percentage of improved patients (MCII concept) and/or percentage of patients in an acceptable state (PASS concept)	88% YES 12% NO
2) If yes, are you in favor of	
- Reporting the percentage of improved patients at the end of the study (MCII).....	10%
- Reporting the percentage of patients in an acceptable symptomatic state at the end of the study (PASS)	45%
- Reporting both	45%
3) OMERACT members should consider adding external anchors ("gold standard" questions) to their clinical studies in order to estimate MCII or PASS values and to contribute to our understanding of how they work in practice.	84% YES 16% NO

At the SIG session, MCII and PASS estimates were presented from a multinational cohort study of similar design in the main outcome criteria in hip and knee OA, hand OA, RA, AS, and low back pain for disease-specific criteria (e.g., BASDAI in AS) and for generic criteria (e.g., pain measured on a numeric rating scale). This study involved 8 countries (6 languages): France, Spain, United Kingdom, Belgium, The Netherlands, Australia, Lebanon, and Morocco. These results

provided a basis for discussion on the best values for the MCII and PASS in different outcome criteria.

The data supported moving toward a consensus on cutoff values for generic criteria (pain, patient's global assessment of disease activity, and function, all measured with visual analog scale or numeric rating scale), but not for disease-specific criteria (e.g., BASDAI in AS), for which more work was needed (Table 2).

Table 2. Results of the second e-mail survey about the MCII and PASS sent to OMERACT 8 special interest group members.

1) The wording of the external anchor	
1) Should the external anchor be symptom specific (i.e. addressing improvement in a particular symptom) or general ?	
Symptom specific	42%
General	50%
Both	8%
Don't know	0%
If you answered 'symptom specific', which one do you prefer?	
<i>Examples for the MCII (same issue for the PASS)</i>	
"Has there been a change in your level of functional impairment since you started the study?"	61%
"Think only about the difficulty you had in doing daily physical activities due to your (name of rheumatic disease) during the last 48 hours. Compared to when you started the study, how has the level of difficulty been during the last 48 hours?"	39%
If you answered 'general', which one do you prefer?	
<i>Examples for the MCII (same issue for the PASS)</i>	
"Taking into account all the ways your (name of rheumatic disease) is affecting you, your level of pain and your functional impairment, how would you rate your response to the medication you have received for your arthritis for 4 weeks ?"	38%
"Think about all the ways your (name of rheumatic disease) has affected you during the last 48 hours. Compared to when you started the study, how have you been during the last 48 hours?"	62%
2) What should be the time frame in the external question to estimate the PASS?	
no time frame: "Taking into account all you have to do during your daily life, your level of pain, and your functional impairment, do you consider that your current state is satisfactory?"	43%
"Think about all the ways your (name of rheumatic disease) has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable or unacceptable to you?"	43%
"Think about all the ways your (name of rheumatic disease) has affected you during the last 48 hours. If you were to remain for the rest of your life as you were during the last 48 hours, would this be acceptable or unacceptable to you?"	9%
3/35 (8.6%)	
Others	6%

Table 2. Continued

<p>3) Do you agree that we have enough data to propose the endorsement of estimates of MCII and PASS for the 3 generic criteria (pain, patient global assessment of disease activity and one-item global function)?</p>		
	YES	40%
	NO	29%
	Don't know	31%
<p>4) If yes, what is the best proposal for these different criteria?</p>		
<p>MCII (abs*) for Pain</p>	<p>MCII (rel**) for Pain</p>	<p>PASS for Pain</p>
-107%	-10%0%	207%
-1527%	-15%7%	3033%
-2053%	-20%40%	3513%
-307%	-30%33%	4040%
-407%	-50%20%	507%
<p>MCII (abs*) for Patient global assesement</p>	<p>MCII (rel**) for Patient global assesement</p>	<p>PASS for Patient global assesement</p>
-107%	-10%0%	2019%
-1520%	-15%0%	3013%
-2060%	-20%40%	3519%
-307%	-30%29%	4044%
-407%	-50%29%	506%
<p>MCII (abs*) for function</p>	<p>MCII (rel**) for function</p>	<p>PASS for function</p>
-1027%	-10%0%	2013%
-1533%	-15%23%	3013%
-2027%	-20%54%	3525%
-307%	-30%15%	4044%
-407%	-50%8%	506%

What is the effect of various parameters on the MCII and PASS estimates?

In the hip or knee OA study, the MCII was shown to vary greatly across tertiles of baseline scores and age. This influence of the baseline level of symptoms was reduced in part only when relative change instead of absolute change was used. Gender and disease duration did not appear to affect the MCII value. The influence of the baseline value had also been demonstrated by Riddle and colleagues¹⁷ in their investigation of low back pain, in which the MCID varied between 3 and 13 depending on the baseline range of scores (from the Roland-Morris Back Pain Questionnaire). Patients dealing with the most severe symptoms have to experience a greater absolute change to consider themselves improved.

In the hip or knee OA study, the PASS was more constant across tertiles of the baseline score than the MCII, and age, gender, and disease duration did not affect the PASS⁹.

An important aspect of any desirable state is the time spent in that state. In the AS study, the PASS was shown to be stable over 10 weeks²². This key finding supports the use of PASS values to describe patients achieving and maintaining such a state for a specified period of time. This finding remains to be confirmed in a study with a longer followup.

Would modification of the values for the MCII and PASS have an effect on the evaluation of the treatment effect?

One of the objectives of the SIG was to move toward consensus on the MCII and PASS value to recommend, so knowing whether there is an influence of the choice of the cutoff value on the evaluation of the treatment effect is important. Would it be relevant to propose rounded values, for instance, for a goal of simplicity? Members of the group are investigating this point.

Summary of progress at OMERACT 8

The SIG session was attended by patients, researchers, and clinicians. One point of debate was the place of the MCII and PASS in rheumatology. Some participants raised the important issue of the loss of power, which is the cost of dichotomizing continuous variables²³⁻²⁵. The group made it clear that the MCII and PASS aim at reporting the proportion of improved patients and the proportion of patients in an acceptable state, in addition to the conventional way of reporting results (e.g., difference in mean change). The aim is to provide complementary and more meaningful information to assist interpretation of trial results. Participants also suggested that these concepts were interesting tools to enhance physician-patient communication.

Using feedback from the SIG session, we proposed a survey of session attendees during the OMERACT 8 meeting. A total of 35 people completed the survey (2 patients, one clinician, 25 academic researchers, 7 industry researchers); participants confirmed the relevance of use of the MCII and PASS in rheumatology. Most respondents considered that OMERACT should recommend reporting of the percentage of patients in an acceptable state plus or minus the percentage of improved patients, and that OMERACT members should consider adding external anchors to determine MCII and PASS estimates in their clinical studies (Table 1).

The next step was an e-mail survey after OMERACT 8 addressed to the SIG participants, to seek direction on the wording of the external anchors and the best values of the MCII and PASS in the generic outcome criteria: for a given criterion, the same MCII and PASS values whatever the disease (Table 2). A total of 36 people completed the e-mail survey (5 patients, 2 clinicians, 26 academic researchers, 3 industry researchers). Advice was divided on whether the external anchor should be symptom-specific or general. Most participants felt that the external anchor to estimate the PASS should contain no element of timeframe, or a short timeframe (“in the next few months” or “in the next week”) rather than “for the rest of your life.” Of the respondents, 40% thought that we have enough data to propose the endorsement of cutoff values for the MCII and PASS (52% among the academic researchers). The MCII value most frequently chosen for absolute change was -20 for pain and patient global assessment, but opinion was divided for function (-10 , -15 , or -20). The MCII value most frequently chosen for relative change was -20% for pain, patient global assessment, and function. The PASS value most frequently chosen was 40 for pain (i.e., patients are considered in an acceptable state if their pain score is below 40 on a 0–100 scale), patient global assessment, and function.

In summary, this SIG session at OMERACT 8 allowed productive discussions of the MCII and PASS concepts and validation of the usefulness of these concepts in rheumatology by the OMERACT participants, with examples of their application to pain, patient global assessment, and function (measured on visual or numeric rating scale). More work is needed to move to a consensus on the wording of the external anchor, and to propose MCII and PASS values for disease-specific criteria, using a data-driven approach in different diseases and with different wordings of the anchor question. Including external anchors in clinical studies to determine the MCII and PASS, especially for disease-specific criteria, will be very useful.

REFERENCES

1. Fairclough DL. Patient reported outcomes as endpoints in medical research. *Stat Methods Med Res* 2004;13:115-38.
2. Willke R, Burke B, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Control Clin Trials* 2004;25:535-52.
3. Felton DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
4. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Curr Opin Rheumatol* 2002;14:109-14.
5. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10:407-15.
6. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81-7.
7. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient-reported outcomes in knee and hip osteoarthritis: the Minimal Clinically Important Improvement. *Ann Rheum Dis* 2005;64:29-33.
8. Schwartz AL, Meek PM, Nail LM, et al. Measurement of fatigue. Determining minimally important clinical differences. *J Clin Epidemiol* 2002;55:239-44.
9. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient-reported outcomes in knee and hip osteoarthritis: the Patient Acceptable Symptom State. *Ann Rheum Dis* 2005;64:34-7.
10. Wells G, Boers M, Shea B, et al. MCID/Low Disease Activity State Workshop: low disease activity state in rheumatoid arthritis. *J Rheumatol* 2003;30:1110-1.
11. Wells GA, Boers M, Shea B, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005;32:2016-24.
12. Wells G, Anderson J, Beaton D, et al. Minimal clinically important difference module: summary, recommendations, and research agenda. *J Rheumatol* 2001;28:452-4.
13. Wells G, Beaton D, Shea B, et al. Minimal clinically important differences: review of methods. *J Rheumatol* 2001;28:406-12.
14. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56:395-407.
15. Pham T, Tubach F, Ravaud P, et al. Minimal clinically important improvement determination in patients with ankylosing spondylitis is dependent on the response modalities [abstract]. *Arthritis Rheum* 2005; Suppl 52:S636.
16. Tubach F, Dougados M, Falissard B, Baron G, Logeart I, Ravaud P. Feeling good rather than feeling better matters more to patients. *Arthritis Rheum* 2006;55:526-30.
17. Riddle DL, Stratford PW, Binkley JM. Sensitivity to change of the Roland-Morris Back Pain Questionnaire: part 2. *Phys Ther* 1998;78:1197-207.
18. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol* 2002;29:131-8.
19. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials — results of a consensus development (Delphi) exercise. *J Rheumatol* 1992;19:451-7.
20. Ehrlich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. *J Rheumatol* 2000;27:2635-41.
21. Neer CS 2nd, Watson KC, Stanton FJ. Recent experience in total shoulder replacement. *J Bone Joint Surg Am* 1982;64:319-37.
22. Tubach F, Pham T, Skomsvoll JF, et al. The patient acceptable symptomatic state in outcome criteria in ankylosing spondylitis is stable over time. *Arthritis Rheum* 2006;55:960-3.
23. MacCallum R, Zhang S, Preacher K, Rucker D. On the practice of dichotomization of quantitative variables. *Psychol Methods* 2002;7:19-40.
24. Cohen J. The cost of dichotomization. *Appl Psychol Meas* 1983;7:249-53.
25. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ* 2006;332:1080.