constructs. A new mathematical approach (Rasch analysis) then allows for formal tests of unidimensionality in ordinal scales. Questions, or tasks which are summated in some fashion to give an overall score must be unidimensional. Furthermore, at the same level of ability (for example in walking), the probability of a patient doing a task must be the same irrespective of whether they are male or female, young or old, underlying pathology (cross-diagnostic validity) or country of use (cross-cultural validity) – the absence of DIF.

Once these fundamental requirements of measurement are met, tests of reliability, validity and responsiveness may proceed. In this way, those working in the field of arthritis can be confident that evaluation of interventions are supported by high quality measurement.

SP0059 CROSS-CULTURAL VALIDATION OF PERCEIVED HEALTH STATUS MEASURES

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Since difference in country, language or culture make people vary in disease expression, in perception of health problems and quality of life, and in their use of health care systems, there is a need for measures tailored to their particular need. It is also increasingly necessary to have standardised instruments for international use in research and practice. To resolve this paradox, the process of cross-cultural validation will particularly focus on the achievement of equivalence in concept measured across culture.

Perceived health status measures are complex scales in the form of interview or self-report questionnaires. Their validation shall follow the standards of psychometric validity (content, construct, reliability and sensitivity to change). The content validity is particularly challenging the cross-cultural validation. Among options to conduct validation of the content, it is possible to achieve it by:

- building an instrument concomitantly in several countries. It allows to work together in the generation and selection of items, as has been done with disease-specific (QUALEFFO, Womac), or generic instruments (WHOQOL).
- developing a standard methodology to cross-culturally adapt an established instrument offering guarantee of equivalence between source and target. The participation of the developers to the process is highly contributive to clarify concept explored in the original language

Researchers are most frequently facing the situation where the original version has been developed and validated in a foreign language. Thus the second option will be particularly useful.

Simple translation/back-translation is far from meeting basic requirements for equivalence in content. Perfect bilingual experts are scarce, if any.

Guidelines are proposed to ensure cross-cultural content equivalence. They include:

- several translations, with appropriate translators
- expert committee review, including various experts (health professionals, patients) and having specified tasks
- several back-translations, with standardised rules
- testing with patients to probe understandability

The place and role of back-translation has been debated, since its contribution to the process may be overestimated. It is as fallible as translations, and not any (back) translator would be capable of assessing proximity between versions.

From qualitative research, it is now clear that a thoughtful committee working on several translations achieved by adequate translators may well achieve the goal.

One aspect of the cross-cultural adaptation is the potential bias introduced when adapting answer modalities. The scalability of the adapted instrument can be assessed using the Rasch modelling statistic.

Other aspects of validation of the cross-culturally adapted measure should be clearly considered separately. As far as the population in the target culture may differ in many aspects compared to the original targeted population, especially in many characteristics relating to culture, a standard procedure of validation should be conducted:

- construct validity will consider how items and dimensions are clearly exploring separate and complementary facets of the concept, i.e. health status, and the coherence of scales (factor structure and internal consistency)
- convergent validity will be documented by the relation to variables exploring a similar construct,
- discriminant validity will be documented by checking how groups with known difference will be recognised as different by the instrument
- reliability will be documented by the ability of the measure to produce the same value when exploring the same phenomenon
- sensitivity to change will be its power to detect intra individual changes over time.

These steps are mandatory requirements to document the equivalence of the measurement, at the same degree of reliability in different cultural settings. Because it is much shorter process than developing a new instrument in each and every country, and since many instruments are already available, the cross-cultural adaptation and validation of existing perceived health status and quality of life measures is highly recommended.

State of the art lecture – Friday 15 June, 10.00-10.30/Congress Hall

SP0060 DISEASE MODIFYING DRUGS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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The last several years have been very exciting for the therapy of rheumatoid arthritis (RA). One major advance has been the acceptance of a core set of disease activity measurements and definition of improvement. The American College of Rheumatology (ACR) core set of disease measurements includes tender and swollen joint count, physician and patient assessment of disease activity, patient assessment of pain, physical function and acute phase reactants (Arthritis Rheum. 36:729,1993). The ACR definition of response requires a 20% improvement in both tender and swollen joint count and a 20% improvement in three of the five remaining ACR core set measures (Arthritis Rheum.38:727,1995). Another disease activity response rate developed by Dutch investigators is called the DAS (Disease

Activity Score) (Ann. Rheum. Dis 916,1990). The US Food and Drug Administration has also developed several different labels for drugs in RA including improvement in signs and symptoms, function and quality of life, stabilisation in radiographic progression and complete clinical response and remission.

Methotrexate remains the most most widely studied and popular therapy to treat RA. Leflunomide, the oral pyrimidine inhibitor, was recently approved for RA. One randomised trial of 359 pts compared leflunomide (20 mg/day) to sulfasalazine (2 gr/day) and to placebo (Lancet 353:259,1999). At week 24, 29% of the placebo patients met ACR 20% response criteria compared to 55% in the lef group and 56% in the ssa group. There was less radiographic progression in the lef and ssa group as compared to placebo. In a study of 482 pts leflunomide (20 mg/day) was compared to methotrexate (7.5 to 15.0 mg/wk) and to placebo (Arch. Intern. Med.159:2542,1999). Of those patients who completed 52 weeks of therapy, 41% of patients on lef met an ACR 20% criteria compared to 35% on MTX and 19% on placebo. There was significantly more radiographic progression as measured by Sharp score in those receiving placebo as compared to either MTX or lef (Arthritis Rheum. 43:495, 2000). Leflunomide has received the signs and symptoms claim and the radiographic label.

Infliximab, the chimeric monoclonal antibody, that down regulates TNF activity is the first biologic that reported efficacy in RA. In the pivotal study, 428 patients who had active RA were maintained on chronic MTX therapy and were randomised to receive placebo or one of four dosing regimens of infliximab (Lancet 354, 1932, 2000, NEJM 343:1594, 2000). Patients were dosed with infliximab either every 4 or 8 weeks at doses of either 3.0 or 10.0 mg/kg or placebo. At week 52, there was sustained clinical response with ACR 20% being noted in 52% of the infliximab groups as compared to 17% in the placebo group. At wk 52 a reduction in the rate of radiographic progression was observed with all doses and dosing regimens of infliximab as compared to placebo plus MTX. Infliximab has received the signs and symptoms claim and the radiographic label. Etanercept, the p75 TNF receptor, has been extensively studied in trials in North America. One study of 234 patients with active RA evaluated 25 mg or 10 mg of etanercept injected twice per week versus placebo for 6 months (Ann Intern Med. 130:478, 1999). At month 6, 59% of the 25-mg group and 11% of the placebo achieved an ACR 20% response. In a 24-week double-blind study, 89 patients on chronic MTX patients were randomised to receive either etanercept 25 mg twice a week or placebo (NEJM 340:253,1999). At week 24, 71% of those patients receiving etanercept plus MTX and 27% of those receiving placebo plus MTX met ACR 20% response criteria. In another trial 632 patients with early RA (less than 3 years) were randomised to receive either MTX or etanercept (NEJM 343:1586, 2000). Patients were treated for one year with either etanercept 25 mg twice a week, etanercept 10 mg twice a week or MTX at a dose that was rapidly escalated to a dose of 20 mg/wk. There was a more rapid effect with etanercept as compared to MTX in the first several months of treatment but both drugs lead to significant improvements in ACR response criteria and a reduction in radiographic progression. Etanercept has received the signs and symptoms claim and the radiographic label.

Fibromyalgia is a central nervous system disorder – Friday 15 June, 10.00-11.45/ Forum Hall

SP0062 FIBROMYALGIA: EVIDENCE FOR A CENTRAL NERVOUS SYSTEM DISORDER

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This presentation reviews evidence from several studies in our laboratory regarding central factors associated with abnormal pain sensitivity in fibromyalgia (FM). We have found that, compared to healthy controls, clinic patients with FM and community residents who meet criteria for FM but have not consulted a physician (FM non-patients) display significantly lower pain thresholds in response to pressure stimulation and exhibit significantly higher cerebrospinal fluid (CSF) levels of substance P. In addition, during exposure to suprathreshold levels of pressure stimulation, controls and FM patients differ in changes in brain regional cerebral blood flow (rCBF). That is, controls show significant rCBF increases in the contralateral thalamus, somatosensory cortex, and the anterior cingulate cortex, whereas patients with FM show significant and bilateral increases in rCBF in these brain structures. Finally, patients with FM show greater cardiovascular responses to stress than controls. Moreover, stress produces greater increases in thermal pain unpleasantness ratings among FM patients compared to controls. Together, these findings indicate that FM patients show abnormal central processing of nociceptive stimuli that tends to be exacerbated by stress. We plan to determine whether the effects of stress on pain unpleasantness in FM (a) are associated with abnormal rCBF changes in the anterior cingulate cortex; and (2) may be mediated by abnormal cortisol release or cytokine production.

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SP0063 GENETIC FACTORS IN FIBROMYALGIA

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