Patient Based Methods for Assessing Adverse Events in Clinical Trials in Rheumatology. Progress Report for the OMERACT Drug Toxicity Working Party

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ABSTRACT. There has been increasing recognition in recent years that the measurement of drug related toxicities in rheumatology clinical trials has been sub-optimal. The OMERACT Drug Toxicity Working Party was established to address this issue. The first task of the working party was to identify a minimum set of attributes of drug related toxicity that would be important to patients, clinicians, investigators, and policymakers. The working party then developed consensus on a standard set of properties for instruments to measure these attributes. Existing instruments in the field of rheumatology were ascertained by literature review and by contact with experts in the field. Four instruments were ascertained and evaluated using the guidelines developed by the working party. This report outlines the progress and preliminary results of these activities. (J Rheumatol 1999;26:207–9)

Key Indexing Terms:
OUTCOME ASSESSMENT
RHEUMATIC DISEASES
ADVERSE EFFECTS
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BACKGROUND

In recent years there has been a profusion of literature focussing on standardizing the reporting of outcomes in clinical trials, particularly with regard to the assessment of efficacy in terms of health status[1]. However, the assessment of toxicity has until recently received relatively little attention[2]. Although the "risk–benefit ratio" of pharmacotherapies is frequently discussed, it is seldom documented or quantified[3]. Furthermore, input from patients is often not sought. Patient based approaches to the measurement of drug related toxicity in clinical trials need to cover all the attributes of potential interest to clinicians, investigators, and policymakers.

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TERMINOLOGY

The issue of drug safety assessment has until recently suffered from a confusion in terminology. Common terms such as "adverse drug reaction" (ADR), which has clear implications of causality, and "adverse event" (AE), which does not, have often been used interchangeably. The World Health Organization and the US Food and Drug Administration published consensus definitions for these terms for the first time in 1995 (Table 1).

OBJECTIVES

The goal of the Patient-Oriented Drug Toxicity Working Party is to provide data on testing and review of instruments that are apparently methodologically sound and that are

Table 1. Consensus definitions of commonly used terms in drug safety[4,5].

Term	Definition
Adverse reaction	Response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function
Adverse event/ experience	Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment
Side effect	Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug

used for the assessment of the adverse effects of interventions in clinical trials in rheumatology. This progress report describes the activities to date in reviewing existing instruments. Subsequent phases will address the issues of whether modifications of existing instruments are needed or whether new instruments are required. If so, strategies to develop these modifications (or new instruments) will need to be discussed.

PROGRESS

1. At the meeting in Washington in 1997, the Taskforce endorsed the following components/attributes of toxicity assessment instruments that would be important to one or more of patients, clinicians, policymakers, funders of healthcare, and investigators: frequency of events, severity of events, importance to the patient, importance to the clinician, effect upon activities, effect upon economic resources, and integration/tradeoff with the benefits of the intervention.

2. Existing instruments in the field of rheumatology were ascertained by literature review and by contact with experts in the field, yielding 4 instruments for evaluation: The Stanford Toxicity Index[6]; Patient Oriented Symptoms Index (POSI)[7,8]; Methotrexate Specific Toxicity Index[9,10]; and the Juvenile Arthritis Quality of Life Questionnaire (JAQQ)[11,12]. The authors of these 4 instruments were also contacted to obtain information regarding the instruments that were not available in published form.

3. The 4 instruments were then reviewed to identify which attributes each instrument assessed. Table 2 summarizes the results.

4. The measurement properties that reflect the "OMERACT filter" of "truth" "discrimination" and "feasibility"[13] and are relevant to the attributes in Table 2 have been transformed into extractable criteria. These are listed in Table 3. This information is currently being collated, with input from the designers of each instrument.

5. This document was discussed at a further meeting of the OMERACT Drug Toxicity Working Party at the Pan American League of Associations for Rheumatology meeting in Montreal in June 1998. It was agreed that the measurement properties listed in Tables 2 and 3 are important to measure. The Stanford group have already instituted a pilot study incorporating assessment of the importance of each adverse effect and have offered to discuss with the Working Party incorporation of the other attributes currently not included.

FUTURE DIRECTIONS

1. A more extensive literature review to ascertain other patient based instruments is being undertaken.

2. Contact with other experts in the field of outcomes assessment and health related quality of life measurement is also being made to ascertain any additional instruments or approaches for the measurement of drug related toxicities.

3. The results of the fuller review of existing instruments are expected to be available by late 1998. The task for the Toxicity Working Party will then be to decide if one of the current instruments, either in existing form or with some modifications, satisfies OMERACT criteria.

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Table 2. Existing instruments in the rheumatology field and the attributes of adverse events (AE) they assess.

Attribute Assessed	Instrument			
	Stanford Index[6]	POSI[7,8]	Morgan Index[9,10]	JAQQ[11,12]
Frequency	+	+	+	+
Severity	+	+	+	–
Importance to patient	–	–	–	+
Importance to clinician	+	–	+	–
Effect on activities	–	–	–	+
Effect on economic resources	–	–	–	–
Integration of benefit with AE (bipolar instrument)	–	–	–	–

Table 3. A framework for assessing the properties of instruments to measure adverse events associated with pharmacotherapies.

This framework will be used to assess whether each property is clearly specified (+) or not specified (–) either in published accounts of the instrument's development or from unpublished information obtained from the developers.

MEASUREMENT PROPERTY
1. TRUTH — Is this instrument measuring what it is supposed to measure?
(a) PURPOSE, POPULATION, SETTING
What concepts or attributes are being measured?
What will it be used for (classification, prognosis, evaluation)?
Why is this measurement needed?
Is the population clearly specified?
Is the setting clearly specified?
(b) CONTENT VALIDITY
Are there important omissions or inappropriate inclusions?
Are all relevant domains (e.g., symptoms, signs, laboratory abnormalities) included?
Within each domain, are all relevant items included?
Is there capacity to incorporate drug related complications? (i.e., hypertension, opportunistic infections)
Are all new events captured or is it restricted to AE that are attributed to medication by patient or physician?
If causality is assessed, is the assessment standardized?
Is the importance to the patient (as distinct from severity) assessed?
Is the importance to the physician assessed?
Is the effect upon physical function/ADL/psychosocial function assessed?
Is the effect on the patient integrated into the overall global assessment of improvement/deterioration?
Is the effect on costs assessed?
What was the method of selecting items for inclusion?
Is the breakdown of domains and/or categories appropriate?
(c) FACE VALIDITY
Is each element phrased in a suitable way?
Are the response categories for each element appropriate?
If a summary rating is calculated, is the method of aggregation appropriate?
Do the results allow the clinician to compare the magnitude of the toxicity to the benefits of the drug?
(d) CONSTRUCT VALIDITY†
Does the instrument behave in a fashion consistent with some theoretical framework?
2. DISCRIMINATION
(a) SENSITIVITY TO CHANGE* OR RESPONSIVENESS
(b) RELIABILITY
Does the instrument measure something in a reproducible fashion? Do measurements of individuals on different occasions, or by different observers, or by parallel tests, produce the same or similar results?
3. FEASIBILITY
Is it easy to understand?
Are there instructions and definitions provided?
Are procedures standardized?
Is it acceptable to the patient and observer?
Is the format for administration appropriate?
Is the administration time suitable?
Is the cost acceptable?

†Used when no "gold standard" measure available.
*Ability to detect the smallest clinically important changes over time.

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