Workshop

Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials II: the Rheumatology Common Toxicity Criteria v.2.0

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ABSTRACT. ***Objective.*** The OMERACT Drug Safety Working Group focuses on standardization of assessment and reporting of adverse events in clinical trials and longitudinal and observational studies in rheumatology. This group developed the Rheumatology Common Toxicity Criteria (RCTC) in 1999, building on the Oncology Common Toxicity Criteria. At OMERACT 8, a workshop group reviewed the use of the RCTC and other instruments in rheumatology clinical trials to date, to revise and to stimulate its implementation.

Methods. The Working Group drafted a revision of the RCTC after an iterative examination of its contents, terms, and definitions. The RCTC were compared with the Oncology Common Toxicity Criteria (CTC v.2.0), and the Common Terminology Criteria for Adverse Events (CTCAE v.3.0). In addition a pharmaceutical company focus group met to clarify the challenges of application of RCTC terms and definitions, relative to the standard in pharmaceutical clinical trials, i.e., verbatim recording of adverse events followed by mapping to Medical Dictionary of Drug Regulatory Activities (MedDRA) terms. The workshop focused on the proposed revision of RCTC to version 2.0 and on the research agenda, including a validation of the RCTC in future trials.

Results. At OMERACT 8, breakout groups amended the contents of the 4 current and 2 new categories of adverse event terms within the draft RCTC v.2.0. Participants recognized the need to standardize the definitions for disease flares, infection, malignancy, and certain syndromes such as drug hypersensitivity and infusion reactions. Moderate consensus (62%) was reached in the final plenary session that the amended RCTC v.2.0 should be promulgated and tested in available trials of anti-tumor necrosis factor agents.

Conclusion. The RCTC has face validity and construct validity. However, documentation of discrimination and feasibility (the other elements of the OMERACT filter) is needed. Collaboration with drug safety working groups in rheumatology professional organizations is necessary to enable this project. (J Rheumatol 2007;34:1401–14)

Key Indexing Terms:
DRUG SAFETY ADVERSE EVENT REPORTING SAFETY PROFILES

The mission of OMERACT, to facilitate standardization of outcome measures in rheumatology clinical trials, has resulted in the ability to compare the efficacy of a variety of novel therapies developed for the treatment of rheumatoid arthritis (RA)[1]. However, understanding the comparative safety profiles of such agents in the treatment of rheumatic diseases remains a problem. Whereas the use of MedDRA* (*Medical Dictionary for Drug Regulatory Activities*) has resulted in

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standard terminology being applied to designation/description of adverse events, methods for elicitation, characterization, and severity grading are less well standardized in rheumatology.

The assessment of therapy-associated adverse events in clinical trials remains highly variable, resulting in difficulty in assessment of risk/benefit during the regulatory review process, and lack of clarity in product labeling for communication to practitioners regarding comparative risks of various rheumatologic therapies. We ascribed this variability to differences in investigator experience and training, as well as to differences in sensitivity to the impact of various side effects on patient well-being. In international clinical trials, variability in adverse event reporting also likely occurs due to language and cultural differences. We also recognized that in many cases, baseline patient status, such as severity of disease, likely influenced assessment of severity of side effects. We hypothesized that the development of a standardized, face- and content-valid assessment tool that was easy to use would facilitate consistency of adverse event reporting. Such a tool should provide uniform definitions of different types of toxicity, and also should supply a basis for describing degrees of severity for observed adverse events, recognizing the influence of disease status on severity.

In April 1996 a group of individuals interested in addressing the challenges of adverse event reporting in rheumatology clinical trials met at OMERACT 3, and the Drug Safety Working Group was formed. We believed that this effort would be especially important in light of the many new therapies, some with potentially narrow therapeutic indices, being developed for serious rheumatologic diseases, most with associated significant baseline signs, symptoms, and laboratory abnormalities. The development of this instrument might be useful both for regulatory agencies and to provide summary estimates of safety that could be used in a risk/benefit analysis. Members include individuals from academia, industry, and regulatory agencies with substantial and diverse clinical trials experience.

At the November 1998 American College of Rheumatology (ACR) meeting a "working version" of the Rheumatology Common Toxicity Criteria (RCTC) was presented to the group and approved for posting on the website of the International League of Associations for Rheumatology (ILAR) to facilitate acquisition and use by clinical trial groups. A plan was established to pilot these RCTC on a voluntary basis in clinical trials that were being conducted by groups interested in and willing to provide feedback to the Toxicity Working Group. We hoped this approach would allow review of experience with the application of these RCTC at OMERACT 5. RCTC v.1.0 was then published[2].

Subsequently, various national and international efforts have been established to increase the focus on the safety and evaluation of risk/benefit of novel antirheumatic therapies in development and clinical practice. To improve the interpretability of studies that comprise these initiatives, it is desirable to apply consistent methodology to characterization of adverse events, using standard terminology and definitions to describe them and grade their severity. At OMERACT 8, the Drug Safety Working Group recommitted to facilitating standardization of assessment and reporting of adverse events using the RCTC. The Workshop consisted of 3 parts:

1. Distribution of a proposed revision of RCTC as v.2.0 for discussion, in parts, by 4 breakout groups, in order to reach consensus regarding terminology and grading definitions;
2. A comprehensive compilation, by survey within each breakout group, of methods for assessment of adverse events currently in use in (rheumatology) clinical trials, needs for reporting, and recommended methods for application in clinical trials, to facilitate implementation of RCTC v.2.0 more broadly; and
3. Development of a prospective project to examine and report the ability to efficiently compare safety profiles of novel antirheumatic therapies in development and postmarketing pharmacovigilance. Details of this project, as well as a followup project for patient self-reporting of adverse events, may be found in completed protocols, which will be posted separately as they are developed.

Methods

Meetings were held at OMERACT 4, 5, 7[3,4], and 8, and at gatherings such as ILAR, EULAR, and the ACR, as well as periodically by teleconference. Initially, the group conducted a review of tools used by other subspecialties, such as oncology[5] and infectious disease (AIDS)[6], in clinical trials. Written materials were circulated to members prior to meetings, with the anticipated outcome of obtaining input and consensus on the tools being proposed. These background materials included the WHO Common Toxicity Criteria (CTC), the Common Toxicity Criteria of the US National Cancer Institute and the European Organization for Randomized Trials in Oncology

* *MedDRA – the Medical Dictionary for Regulatory Activities*: A pragmatic, medically valid terminology with an emphasis on ease of use for data entry, retrieval, analysis, and display, as well as a suitable balance between sensitivity and specificity within the regulatory environment. It was developed by the International Conference on Harmonisation (ICH) and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH Steering Committee.

MedDRA terminology applies to all phases of drug development, excluding animal toxicology. It also applies to the health effects and malfunction of devices.

The Maintenance and Support Services Organization (MSSO) serves as the repository, maintainer, and distributor of MedDRA as well as the source for the most up to date information regarding MedDRA and its application within the biopharmaceutical industry and regulators. MedDRA subscribers submit proposed changes to the terminology. The MSSO includes a group of internationally based physicians who review all proposed subscriber changes and provide a timely response directly to the requesting subscriber.

The Japanese Maintenance Organization (JMO) is a partner of the MSSO that provides MedDRA support to companies with headquarters in Japan, and maintains and distributes *MedDRA/J*. The JMO assists the MSSO in providing MedDRA related information and services in Japan.

(EORTC), the Division of AIDS Tables for Grading Severity of Adverse Experiences, and various modified WHO and CTC tables developed by pharmaceutical companies and researchers involved in rheumatology clinical trials. We also tried to integrate our efforts with other groups engaged in revision of CTC, using the Oncology CTC v.2.0 as our primary reference because this was the tool most frequently used for rheumatology clinical trials, by default. To develop acceptable terminology, we originally selected terms from the MedDRA (http://www.meddramsso.com/MSSOWeb/index.htm) with attention to the following:

• Intended use in pharmaceutical development, in randomized controlled clinical trials, and in postmarketing studies, and with attention as well to the origin of terms used in the late 1990s:

• From the UK MCA's medical terminology (ADROIT)

• Also incorporating WHO-ART, HARTS, COSTART, and International Classification of Diseases-Revision 9 in the instrument.

The RCTC v.1.0 included the following categories:

- Allergic/immunologic
- Cardiac
- Constitutional (general)
- Dermatologic
- Ear, nose, throat
- Gastrointestinal
- Laboratory/metabolic
- Musculoskeletal
- Neuropsychiatric
- Ophthalmologic
- Pulmonary

Within each system, specific symptoms or signs are described, with characteristics for each that define the severity grade, using the general definitions clarified in preparation for OMERACT 8 and given in Table 1.

In preparation for OMERACT 8, input was sought from users of various CTC instruments, including the recently published CTCAE revision of the Oncology CTC, and a focus group was held with members of a pharmaceutical company Phase II/III rheumatology development team, who were working on integrated safety reports for 2 biologics being developed for rheumatologic diseases. The method used to capture, assess, and record adverse events was open questioning ("How has the treatment affected you?"); verbatim recording of the event (with subsequent mapping of the term in MedDRA), and application of the oncology CTC v.2.0, mainly because it had been used in oncology programs for one of the study agents. No explicit training of investigators had taken place regarding the application of this method, although it was described in the protocol.

The purpose of the OMERACT 8 focus groups was to gain input on key issues identified in their method and to consider future actions to improve databasing and interpretation of adverse events. As a result, the following recommendations were made for development of RCTC v.2.0 at OMERACT 8:

• Add definitions for reporting an RA flare as an adverse event, as opposed to lack of efficacy

• Describe a method to report key aspects of infection

• Update definitions for reporting new autoimmune syndromes.

Additional new categories considered for the RCTC v.2.0 in preparation for OMERACT 8 included growth and development, hematologic, infection, malignancy, sexual/reproductive function, and syndromes.

Following an overview of available data and brief descriptions of needs for the performance of this instrument (based on current approaches used by participating pharmaceutical companies and an academic group conducting postmarketing pharmacovigilance studies)[7], 4 breakout groups focused on the contents of 4 current and 1 or 2 proposed new categories of adverse event terms. This included attention to severity grading within the proposed RCTC v.2.0, to gain consensus on the final version to be published. Recommendations were collated following the workshop. The RCTC v.1 was modified to produce the current version of the instrument, as determined in the final group discussion completing the workshop, and subsequently the final OMERACT 8 plenary session.

Table 1. Grading severity of adverse events observed in rheumatology clinical trials.

1. Mild Event	2. Moderate Event	3. Severe Event	4. Includes Life Threatening
Asymptomatic, or transient	Symptomatic	Prolonged symptoms, reversible	At risk of death
Short duration (< 1 week)	Duration 1–2 weeks	Major functional impairment	Substantial disability, especially if permanent
No change in lifestyle	Alter lifestyle occasionally		
No medication or over-the-counter	Medications give relief (may be prescription)	Prescription medications/partial relief; hospitalized < 24 hours	Hospitalized > 24 hours
		Temporary or permanent study drug discontinuation	Permanent study drug discontinuation

Results

In the OMERACT 8 Drug Safety Workshop there were 72 active participants, most of whom were clinical trialists; 14% were patients with various rheumatic diseases. The majority (90%) agreed with the desirability of standardizing the assessment of adverse events throughout drug development and postmarketing surveillance. However, only 36% of the participants had experience using an adverse event guideline, and only about half had had specific training in the assessment of adverse events in clinical trials.

As a result of the workshop and 4 breakout groups, the following recommendations were incorporated into implementation of RCTC v.2.0:

- Develop a working definition to facilitate reporting of disease flares separately, but as an adverse effect (as part of the research agenda to include developing a data-driven definition)
- Report disease-related surgeries as concomitant treatment if expected, as adverse events if emergent or unexpected
- Expand methods of reporting infection, malignancies, autoimmune syndromes, and infusion reactions to gather key data to clarify the nature, treatment, response, outcome, and effects on patients of these adverse events
- It was also recognized that a method for investigator and study team training in the use of RCTC is needed to achieve investigator and data management acceptance, thus:
  - Develop a training guide to facilitate implementation
  - Convene additional pharmaceutical company focus groups, especially regarding feasibility, and effective training guidance
  - Monitor implementation — this would ideally be a website tool to facilitate timely feedback
- Carry forward the following research agenda:
  - Develop a method to characterize, describe, and communicate safety profiles, to facilitate comparison of different therapies
  - Continue development of the patient-centered tolerability assessment tool, begun at OMERACT 7[3,16,17,18].

As MedDRA has become the accepted dictionary for reporting adverse events in regulatory submissions, we used this terminology, and together with the Revised Oncology CTCAE v.3.0, we revised the RCTC v.2.0 and achieved consensus on its implementation in the final plenary session at OMERACT 8. The voting in the final plenary session also indicated support to produce guidelines for reporting adverse events of special interest such as infections, malignancies, disease flares, infusion reactions, and joint surgeries.

The Rheumatology CTC, version 2.0, as it was developed at OMERACT 8 is given in the Appendix. This includes consensus-derived additional terms suggested at the workshop. Terms used were selected from the MedDRA and CTCAE, v.3.0 (National Cancer Institute website: http://ctep.cancer.gov/reporting/ctc.html), and are based on consensus among the rheumatologists, other clinical researchers, and patients attending OMERACT 8 and the Drug Safety Workshop, regarding adverse events commonly observed in rheumatology clinical trials. For designation of adverse events not shown here, the approach described in Table 1 is recommended, keeping in mind that for industry-sponsored clinical trials, verbatim terms taken from adverse event report forms are routinely mapped to MedDRA terms: *select or designate the preferred term best describing the adverse event, and apply the revised definitions in Table 1 to determine the severity grade*.

Discussion

The overall goal for this project was the development, for rheumatology clinical trials, of an adverse event assessment tool that would provide a basis for use of common terminology, and an assurance of consistency of reporting severity of side effects observed within clinical trials and during postmarketing surveillance, as well as during observational studies[8-11]. The primary result should be the development of an outcome measure that fulfills the OMERACT criteria and can (1) improve the consistency of assessment and reporting of adverse events in clinical trials; (2) facilitate the ability of investigators, regulators, and practitioners to differentiate safety profiles of individual and combination therapies for rheumatic diseases; and (3) facilitate management of adverse event data[12-17].

Other issues to be considered are the technical requirements for registration of pharmaceuticals for human use, assuring compatibility with International Committee on Harmonization (ICH) consensus definitions:

- Adverse drug reaction (ADR): Noxious/unintended response to a therapeutic agent at doses normally used for prophylaxis, diagnosis, or therapy of disease
- Adverse event (AE): Any untoward medical occurrence that may be present during treatment with a therapeutic agent, which does not necessarily have a causal relationship with this treatment
- Side effect: Any unintended effect of a therapeutic agent at doses normally used, related to its pharmacological properties.

We emphasize that the RCTC is a guideline, not a "checklist," so that elicitation of adverse events should continue to use a standard "open question" approach[18-20]. As some agents are also being evaluated in other diseases characterized by immune dysregulation as well as, possibly, in transplantation or/and cancer, these RCTC may also facilitate characterization of an agent's safety profile across indications. For clinical trials, the RCTC can also be used to develop a standard approach to characterization of stopping rules and thresholds for acceptable adverse events.

Version 2.0 of the RCTC has been developed by individuals with broad experience in the conduct of rheumatology clinical trials, as a result of their recognition of the desirability of being able to compare safety profiles of novel

antirheumatic therapies as they are being developed, and just as importantly, in postmarketing pharmacovigilance. The approach should assure ongoing assessment to provide evidence that the instrument meets the OMERACT filter, that is:
• Accuracy to characterize safety profiles of various types of antirheumatic therapies (Truth)
• Ability to differentiate the safety/toxicity profiles of such therapies in clinically meaningful ways (Discrimination)
• Ease of use in clinical trials, observational studies, and postmarketing pharmacovigilance (Feasibility).

The group is also interested in the utility of the instrument to influence selection of treatment for individual patients as a result of increased clarity of risk/benefit.

While face validity was reasonably established by the process by which the Rheumatology CTC was developed, the other aspects of validation, discrimination, and feasibility remain to be specifically examined, and are part of the research agenda established in the OMERACT 8 workshop.

Implementation approach
• Communication through national/international professional meetings
• Direct interaction with pharmaceutical companies to stimulate use in clinical trials, including development and application of training tools
• Provide instructional tools on OMERACT, EULAR, ACR, the Bone and Joint Decade, and ILAR websites
• Assure methods for feedback and periodic revision.

Research agenda
• Provide a data-driven definition of RA flare; conduct a retrospective analysis of the assessment of this event in at least 3 phase III clinical trials
• Develop method and approach pharmaceutical company clinical development groups, to compare final safety databases for studies using RCTC; compared to those that have not done this
• Develop methods and conduct an evaluation to examine effects of investigator/study team training in adverse event assessment
• Consider a project to characterize continuous (rather than categorical) measures of adverse event severity.

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REFERENCES

1. Boers M, Brooks P, Strand V, Tugwell P. The OMERACT filter for outcome measures in rheumatology. J Rheumatol 1998;25:198-9.
2. Woodworth TG, Furst DE, Strand V, et al. Standardizing assessment of adverse effects in rheumatology clinical trials. Status of OMERACT Toxicity Working Group March 2000: towards a common understanding of comparative toxicity/safety profiles for antirheumatic therapies. J Rheumatol 2001;28:1163-9.
3. Lassere MN, Johnson KR, Boers M, et al. Standardized assessment of adverse events in rheumatology clinical trials: summary of the OMERACT 7 drug safety module update. J Rheumatol 2005;32:2037-41.
4. Lassere MN, Johnson KR, Woodworth TG, et al. Challenges and progress in adverse event ascertainment and reporting in clinical trials. J Rheumatol 2005;32:2030-2.
5. Mahoney MR, Sargent DJ, O'Connell MJ, Goldberg RM, Schaefer P, Buckner JC. Dealing with a deluge of data: an assessment of adverse event data on North Central Cancer Treatment Group trials. J Clin Oncol 2005;23:9275-81.
6. Ionnidas JP, Lau J. Improving safety reporting from randomized trials. Drug Saf 2002;25:77-84.
7. Peloso PM, Wright JG, Bombardier C. A critical appraisal of toxicity indexes in rheumatology. J Rheumatol 1995;22:989-94.
8. Hetland ML, Unkerskov J, Ravn T, et al. Routine database registration of biological therapy increases the reporting of adverse events twenty-fold in clinical practice. First results from the Danish Database (DANBIO). Scand J Rheumatol 2005;34:40-4.
9. Askling J, Fored M, Geborek P, et al. Swedish registers to address drug safety and clinical issues in rheumatoid arthritis. Ann Rheum Dis 2006 Jan 13 (Epub ahead of print).
10. Liauw WS, Day RO. Adverse event reporting in clinical trials: room for improvement. Med J Aust 2003;179:426-8.
11. Santiago LM, Debanne SM, Neuhauser D. Tracking adverse events in RCTs: lack of agreement among regulatory institutions. Qual Saf Health Care 2003;12:234-5.
12. Prieto L, Sacristan JA, Gomez JC. The validity and reliability of the global index of safety (GIS). Curr Med Res Opin 2004;20:1825-32.
13. Etminan M, Carleton B, Rochon PA. Quantifying adverse drug events: are systematic reviews the answer? Drug Saf 2004; 27:757-61.
14. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004;140:795-801.
15. Edwards IR. The WHO World Alliance for Patient Safety: a new challenge or an old one neglected? Drug Saf 2005;28:379-86.
16. Welch V, Singh G, Strand V, et al. Patient based method of assessing adverse events in clinical trials in rheumatology: the revised Stanford Toxicity Index. J Rheumatol 2001;28:1188-91.
17. Lassere MN, Johnson KR, Van Santen S, et al. Generic patient self-report and investigator report instruments of therapeutic safety and tolerability. J Rheumatol 2005;32:2033-6.
18. Bent S, Padula A, Avins AL. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med 2006;144:257-61.
19. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004;22:3485-90.
20. Basch E, Artz D, Dulko D, et al. Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 2005;23:3552-61.

Appendix: Rheumatology Common Toxicity Criteria v.2.0

Based on Woodworth TG, *et al.* Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Antirheumatic Therapies

	1 – Mild Asymptomatic, or transient Short duration(<1 week) No change in life style No medication or OTC	**2 – Moderate** Symptomatic Duration (1-2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/ partial relief May be hospitalized <24hr Temporary study drug discontinuation, or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised >24 hr Study drug discontinued
A. ALLERGIC / IMMUNOLGIC				
A1. Allergic reaction/ hypersensitivity (includes drug fever)	Transient rash: drug fever < 38°C: transient, asymptomatic bronchospasm	Generalised urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g. vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g. hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g. transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post-nasal discharge)	Transient, non-prescription meds relieve	Prescription med. required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy

A5. Vasculitis	Localised, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Generalised, parenteral corticosteroids required or/and short duration hospitalisation	Prolonged, hospitalisation, ischemic changes, amputation
B. CARDIAC				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalisation required; parenteral meds
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g. 1 + feet/calves), self-limited, no therapy required	Symptomatic (e.g. 2 + feet/calves), requires therapy	Symptoms limiting function (e.g. 3 + feet/calves, 2 + thighs), partial relief with treatment, prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, *transient* increase by > 20 mm Hg (diastolic) or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mm Hg (diastolic), requiring and responding readily to treatment	Symptomatic increase >150/100, > 20 mmHg, persistent, requiring multi-agent therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mm Hg	Symptomatic, without interference with function, recurrent or persistent > 20 mm Hg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infacrtion, arrthymia or/and CHF
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest X-ray, dyspnoea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery
B8. Phlebitis/thrombosis/ Embolism (excludes injection sites)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism

C. GENERAL (constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation;
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7-38.5ºC	Symptomatic, recurrent 38.6-39.9ºC. Relieved by meds	≥ 40ºC; ≤24h, persistent symptoms; partial response to meds.	≥ 40ºC, debilitating, > 24h, hospitalisation; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.
C4. Insomnia	Difficulty sleeping, short term, not interfering with function	Difficulty sleeping Interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalisation; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalisation; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/hospitalization >24 hr
C7. Weight gain	5-9.9%	10-19.9%	20-30%	NA
C8. Weight loss	5-9.9%	10-19.9%	20-30%	NA

D. DERMATOLOGIC				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete, or irreversible even if patchy
D2. Bullous eruption	Localised, asymptomatic	Localised, symptomatic, requiring treatment	Generalised, responsive to treatment; reversible	Prolonged, generalised, or requiring hospitalisation for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1-2 wks controlled with emollients	Generalised, interfering with ADL >2 wks, persistent pruritis, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain, pruritis, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1-2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery

D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalised, responsive to treatment; reversible	Prolonged, irreversible, disabling
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systematic corticosteroids	Generalised exfoliation or hospitalisation
D7. Pruritis	Localised, asymptomatic, transient, local treatment	Intense, or generalised, relieved by systematic medication	Intense or generalised; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/popular eruption; pruritus transient; TOC or no meds	Diffuse macular/popular eruption or erythema with pruritus; dry desquamation; treatment required	Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids
D9. Indurartion/fibrosis/ Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms
E. Ear/Nose/Throat				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support; residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalise	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition

F. EYE/OPHTHALMOLOGIC				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA

F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g. blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophtalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight
G. GASTROINTESTINAL				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2-3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4-6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g. incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤2 units needed; responds to treatment	Haematemesis, transfusion 3-4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation

G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤2 units, reversible	Recurrent, transfusion > 3-4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent >2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatitic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required.
H. MUSCULOSKELETAL				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalisation required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds
I. NEUROPSYCHIATRIC				
I-1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self

I-2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
I-3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily routine	Debilitating/disabling and permanent; toxic psychosis
I-4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
I-5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
I-6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I-7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
I-8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I-9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraesthesias interfering with function	NA
I-10. Seizure	NA	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures
I-11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization

J. PULMONARY				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating

J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitation, requiring hospitalisation
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO)	76-90% of pre-treatment value	51-75% of pre-treatment value	26-550% of pre-treatment value	≤25% of pre-treatment value

LABORATORY DATA

K. HAEMATOLOGY				
K1. Hgb (g/dl) decrease from pre-treatment	1.0-1.4	1.5-2.0	2.1-2.9, or Hgb<8.0, >7.0	≥3.0;or Hgb < 7.0
K2. Leukopenia (total WBC) X 1000	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
K3. Neutropenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
K4. Lymphopenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
K5. Platelets (X 1000)	75-LLN	50-74.9	20-49.9; platelet transfusion required	< 20; recurrent platelet transfusions
L. CHEMISTRY				
L1. Hypercalcaemia (mg/dl)	1.1 X ULN – 11.5	11.6 – 12.5	12.6 – 13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140 – 160	161 – 250	251 – 500	> 500, or associated with ketoacidosis > 7.0 or any arrhythmia

L3. Hyperkalaemia (mg/dl)	5.5 – 5.9	6.0 – 6.4	6.5 – 7.0 or any ECG change	
L5. Hypocalcaemia (mg/dl)	0.9 X LLN – 7.8	7.7 – 7.0	6.9 – 6.5; or associated with symptoms	< 6.5 or occurrence of tetany
L6. Hypoglycemia (mg/dl)	55 – 64 (no symptoms)	40 – 54 (or symptoms present)	30 – 39 (symptoms impair function)	< 30 or coma
L7. Hyponatraemia (mg/dl)	-	125 – 129	120 – 124	< 120
L8. Hypokalaemia (mg/dl)	-	3.0 – 3.4	2.5 – 2.9	< 2.5
L9. CPK (also if polymyositis-disea	1.2 – 1.9 X ULN	2.0 – 4.0 X ULN	4.0 X ULN with weakness but without life-threatening signs or symptoms	> 4.0 X ULN with signs or symptoms of rhabdomyolysis or life-threatening
L10. Serum uric acid	1.2 – 1.6 X ULN	1.7 – 2.9 X ULN	3.0 – 5.0 X ULN or gout	NA
L11. Creatinine (mg/dl)	1.1 – 1.3 X ULN	1.3 – 1.8 X ULN	1.9 – 3.0 X ULN	> 3.0 X ULN
L12. SGOT (AST)	1.2 – 1.5 X ULN	1.6 – 3.0 X ULN	3.1 – 8.0 X ULN	> 8.0 X ULN
L13. SGPT (ALT)	1.2 – 1.5 X ULN	1.6 – 3.0 X ULN	3.0 – 8.0 X ULN	> 8.0 X ULN
L14. Alkaline phosphatase	1.1 – 2.0 X ULN	1.6 – 3.0 X ULN	3.0 – 5.0 X ULN	> 5.0 X ULN
L15. T. bilirubin	1.1 – 1.4 X ULN	1.5 – 1.9 X ULN	2.0 – 3.0 X ULN	> 3.0 X ULN
L16. LDH	1.3 – 2.4 X ULN	2.5 – 5.0 X ULN	5.1 – 10 X ULN	> 10 X ULN
M. URINALYSIS				
M1. Haematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusion required
M2. Proteinuria (per 24 h)	300 – 500 mg (tr/1+)	501 – 1999 mg (2+)	2 – 5.0 g (3+) nephrotic syndrome	5.0 g (4+) anasarca
M3. WBC in urine	NA	NA	Indicating acute interstitial nephritis	Associated with acute renal failure
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (eg renal colic)	Causing renal outflow obstruction and hospitalization

OTC: over-the-counter medication; ADL: activities of daily living; IV: intraveneous; ECG: electrocardiogram; CHF: congestive heart failure; MRI: magnetic resonance imaging; Hb: haemoglobin; LLN: lower limit of normal; ULN: upper limit of normal; WBC: white blood cells; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies; H-2 blockers: histamine-2 blockers; FVC: forced vital capacity