International Society for Quality of Life Research

Volume 11 Issue 1 *Newsletter for ISOQOL Members* *April 2006*

PRESIDENT'S MESSAGE

Peter Fayers, PhD
Aberdeen, UK

One major event since the last newsletter has been the long-awaited publication of the US Food and Drug Administration (FDA) guidelines. This document is bound to affect all of us who are involved in assessing quality of life in clinical trials – even people like me, a statistician in a UK university who has not been involved in any pharma RCTs for many years. So despite at present only being the draft version, and despite its lengthy and off-putting title, we should all be paying attention to the "Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims (Draft Guidance)". The reason for its undoubted impact is that, firstly, all pharmaceutical organisations around the world are interested in the US market as well as markets in their own regions, and this document for the first time spells out in a comprehensive manner the issues that the FDA will have in mind when reviewing licensing applications. Secondly, now that there is a detailed, published standard for use in clinical trials, we can expect many funding and ethical agencies in other countries to adopt aspects of this document for appraisal of clinical trials being submitted as new projects. Thirdly, the implications of this will carry through to all aspects of HRQoL assessment. For example, if developers of instruments expect their questionnaires to be used by drug companies, they will have to demonstrate that they have satisfied the guidance requirements.

A link to the full document is available on the ISOQOL website. In 32 pages, it covers all aspects of evaluating patient reported outcome (PRO) instruments, designing studies that assess PROs, analysing the data, and interpreting study results. At present, as I have emphasised, this is a draft version. Although many of us have concerns about particular issues, I am hearing quite consistently favourable reactions to the overall content.

When the ISOQOL board last met (at the annual conference in San Francisco) we were aware of the impending release of these FDA guidelines. Although the date for their release remained vague, it appeared to be imminent. We discussed the need for ISOQOL to react rapidly once the guidelines appeared. As a consequence, we have initiated all the following activities on your behalf:

1. When the draft guidance was made public on 2 February, we promptly made it available on the ISOQOL website, and encouraged members to submit comments via our website. This was urgent – comments had to be submitted within 60 days! A collective response on behalf of ISOQOL is being submitted to the FDA.
2. A small ISOQOL Task Force on PRO Regulatory Issues was convened under the leadership of Dennis Revicki, to coordinate our activities.
3. The ISOQOL board voted to endorse the Mayo FDA-Guidance workshop, the success of which is reported later in this newsletter.
4. ISOQOL has arranged a one-day summer meeting (June 29th), aimed at the pharmaceutical industry.
5. Immediately prior to our annual conference in Lisbon, a one-day satellite meeting has been arranged (October 10th). This will require separate registration from the conference itself, and is anticipated to attract delegates from the European Pharma industry. This meeting will contrast the (European) EMEA and (US) FDA regulatory requirements.
6. In parallel, and avoiding overlap, the organising committee for our Lisbon annual conference is arranging a special plenary session involving key representatives from both the FDA and European EMEA.
7. Linked to these meetings, we will prepare on behalf of ISOQOL a report to be submitted to Quality of Life Research for publication consideration.

Thus there has been quite a flurry of activity, and I am sure there will be much discussion in Lisbon about the guidance and its import. Meanwhile, those of you who have not looked at our website are encouraged to do so. Anyone who is developing HRQoL instruments, or using them in clinical trials, will undoubtedly be affected by the content of this document sooner or later!

IN THIS ISSUE . . .

The ISOQOL Newsletter is published three times a year by the International Society for Quality of Life Research with the cooperation of Degnon Associates.

Newsletter Editor
Kathleen Wyrwich, PhD, *USA*

Deadline for articles for our next issue is June 1, 2006

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LET'S TALK

Kathleen Wyrwich, PhD
St. Louis, MO, USA

In my first column on substantive issues in the measurement of health-related quality of life, I asked:

> **Is "quality of life at the end of life" a different construct from the "quality of life" that we generally measure and study?**

Two ISOQOL members weighed in on this question. First, Mogens Groenvold, MD, PhD, in the Department of Palliative Medicine at Bispebjerg Hospital, Copenhagen, Denmark wrote:

Hi Kathleen- Based on the 2005 ISOQOL Annual Meeting session on palliative care (where I was one of the presenters in a very small session), you ask for comments to the question of whether QOL at the end of life is different from what we generally measure and study. This is really a very large question; I will give a few brief comments.

First of all, I think we should avoid the trap of talking of 'what is QOL': if we have the ambition of 'measuring QOL' we will always fail (and while doing so we hamper the reputation of our research). Because of the infinite diversity of human values and aspects there are - and will not come, I think, any definitions which allow us to devise universally accepted specific measures of QOL (good definitions may point at relevant, overall measures, though). This is why I have a slide which I have used over and over again while teaching for fifteen years now:

> *QOL cannot be measured - but aspects that are very important to QOL can*

(The problem is that we do not know what was behind the answers to the broad, overall questions about QOL.)

The consequence of this is that the researcher needs to define which aspect of QOL are of interest (or: the researcher needs to make others define what to measure - but, again, this requires that the researcher starts by asking the right questions). In other words, many diffuse discussions about 'What is QOL' and 'Can QOL be measured' origin from conceptual laziness in the first place.

Based on these general views I will return to the question: is QOL a different construct at the end of life? The first answer following for the arguments above is that the question is too diffuse and should therefore not be answered.

A second answer could be a reformulation of the question - for example to: does the relative importance of various aspects of QOL change during life? Of course they do, and clearly people at the end of life value some aspects of QOL much more (and others less) than they have done previously. However, this does not mean that the QOL construct is different: the things that are important at the end of life have always been there - but maybe we were too busy thinking of e.g. some existential issues.

Our conceptual/methodological laziness also has the implication that we frequently forget that the relevance of the composition of questionnaires varies according to their use; they may be well suited for one purpose but badly for another.

This has the consequence that even though the QOL construct is the same (and still not easily operationalised) the methods we want to use at different stages of life are likely to be different, reflecting that the relative importance of and attention given to various aspects of life have changed. As you suggest, generic HRQOL measures may be partly irrelevant at the end of life.

This was exemplified in our recent study leading to the development of the EORTC QOLQ-C15-PAL: role function (work, leisure time) is probably an extremely important aspect of life at ear-

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MAYO/FDA MEETING ON THE FDA DRAFT GUIDANCE ON PATIENT REPORTED OUTCOMES

Amylou Dueck, PhD, Marlene H. Frost, RN, PhD, Michele Y. Halyard, MD, Jeff A. Sloan, PhD

From the Mayo Clinic in Rochester, Minnesota and Scottsdale, Arizona

In February, the U.S. Food and Drug Administration (FDA) released a draft guidance document for industry in the use of patient reported outcomes (PROs) in drug approval applications and labeling claims (available at www.fda.gov/cder/guidance/5460dft.pdf). The draft guidance outlines how the FDA evaluates PROs used as efficacy endpoints in clinical trials, and how sponsors can develop and use study results based on PROs in labeling claims. The Mayo Clinic College of Medicine and the FDA Center for Drug Evaluation and Research (CDER) co-sponsored an open-registration meeting following the release of the draft guidance to facilitate discussion, dissemination, and operationalization of the guidance document. The meeting, titled, "FDA Guidance on Patient Reported Outcomes: Discussion, Dissemination, and Operationalization," was held three weeks after the release of the draft guidance on February 23-25, 2006, in Chantilly, Virginia.

As part of this meeting, five teams of 25 PRO experts drafted manuscripts addressing anticipated PRO guidance issues prior to the meeting (and prior to the release of the draft guidance). The five major themes covered by the manuscripts were conceptual issues, PRO instrument selection, PRO instrument development, PRO instrument validation, and analysis, interpretation, and presentation of PRO data. The format of the meeting involved five sessions comprised of a 30-minute presentation of each of the five manuscripts by the writing team, a brief response from the FDA with regard to select manuscripts, and an hour discussion session in which audience members could ask the writing team and representatives from the FDA questions.

The conference opened with an introduction of the draft guidance via a formal presentation lead by Laurie Burke, director of the Study Endpoints and Label Development Team of the FDA. During this session and throughout the meeting, FDA representatives on several occasions clarified that "PRO", "quality of life", and "health-related quality of life" are not interchangeable terms or concepts (i.e., "PRO `" QOL `" HRQL"). Quality of life as a general concept has never been approved in a labeling claim and FDA representatives doubted that it ever would be used successfully. However, the FDA representatives expressed that they considered health-related quality of life a possible endpoint if the psychometric properties were well-developed and documented.

The FDA also gave a formal response to the meeting on the final day of the meeting. Also on the final day of the meeting, David Osoba (QOL Consulting, West Vancouver, British Columbia, Canada), Ann O'Mara (National Cancer Institute), Neil Aaronson (European Organisation for Research and Treatment of Cancer), and Catherine Acquadro (European Regulatory Issues on Quality of Life Assessment) presented their perspectives of PROs in the clinical trials setting. Another highlight of the meeting on the final day was a moving presentation by Cynthia Chauhan, cancer survivor and patient advocate for the North Central Cancer Treatment Group. She presented her impressions of the meeting and stressed that broader PRO measures of symptom impact and health-related quality of life are as important if not more important than simple measures of symptoms: "You name that patient experience 'symptoms' and you have spent a great deal of time differentiating or arguing against differentiating symptoms from HRQL much less QOL. I understand the need for partializing in problem solving as long as one holds onto the knowledge that the whole is equal to and perhaps greater than the sum of its parts." The meeting concluded with a humorous group sing-a-long lead by David Cella of Northwestern University of "Give PROs a Chance," sung to the tune of John Lennon's "Give Peace a Chance".

Dave Cella singing "All we are saying, is give PROs a chance"

The FDA representatives throughout the meeting advocated for open communication between trial sponsors and the FDA throughout the drug development process. Particularly, PRO endpoints should be discussed, developed, and agreed upon prior to the phase III trial. Documentation of reliability, validity, and interpretability of PROs should be available, and potentially submitted, as part of the drug application. However, the level of documentation needed remains unclear, particularly for modifications to existing validated PRO instruments including language translations or items selected from a previously validated PRO instrument. The FDA representatives did suggest that the level of documentation needed for supporting a single-item symptom measure is less than what would be required for a multidimensional measure comprised of several items or intended to measure a complex concept (e.g., a physical functioning measure). The FDA representatives also indicated that PRO instruments previously used in trials are not "grandfathered" for use in future labeling claims (i.e., previous use does not imply reliability, validity, or interpretability), rather adequate documentation of the psychometric properties in the context of the clinical trial needs to be submitted.

***Mayo/FDA**, continued on page 11*

A REPORT FROM THE ISOQOL *GOOD PRACTICES WORKING GROUP*

By Jordi Alonso, Health Services Research Unit, Institut Municipal d'Investigació Mèdica (IMIM-IMAS), and Universitat Autònoma de Barcelona, Spain

The Good Practices Working Group was initially formed in 2002 with the aim of exploring the terms of use of HRQL instruments. The group was convened by past ISOQOL president Ivan Barofsky in order to assess the degree of accessibility of instruments measuring health status and HRQL for end users around the world. The operational objectives of the group were to summarise and illustrate the expected wide array of conditions for obtaining permission to use an HRQL instrument, and indeed, to obtain the instrument itself. The group discussed the potential interest of carrying out a formal evaluation of the situation and to make the conclusions of such evaluation available to the ISOQOL Board of Directors. With such a background, the Board could then produce an official statement.

A survey of the access to HRQL Instruments

We decided to focus our review on the terms or the requirements for accessing to the original instruments (and adapted versions) to end users. Items that were considered of interest in the revision were: requirements, costs and timelines for distribution. We also considered how long it would take to obtain an instrument.

We decided to survey well-known instruments that reflected different content areas, a variety of countries of origin as well as a representation of different populations (e.g., age groups). We fixed the number of instruments to review in 20, five of which would be generic HRQL instruments for adults (SF-36, WHOQOL, EQ-5D, NHP, OARS), three generic measures for children and adolescents (CHIP, CHQ, and Kindl), eight instruments, disease specific (EORTC, FACIT, VF-14, SGRQ, AQLQ, QLI-Epilepsy, WOMAC, and QUALEFO) and 3 additional instruments from psychopathology, a pioneer field in questionnaires assessing health status (PWI, GHQ, and HADS).

These instruments also represented a number of countries but obviously a limited list (the US, the UK, Germany, France, Canada and Australia) plus Europe (EORTC) and an international organisation (the WHO). Obviously the list is but a minimal part of the large number of existing HRQL instruments.

A team of researchers at the Health Services Research Unit of the Institut Municipal d'Investigació Mèdica (IMIM-IMAS) in Barcelona, Spain working in collaboration with the ISOQOL Secretariat, made use of two major resources of information: the QOLID database, a major international repository of HRQL instruments, hosted by the MAPI Research Institute (web page address: www.proqolid.com), and the Spanish Network for Health Outcomes and Services Research virtual library of HRQL instruments in Spanish (Red IRYSS, web page address: www.rediryss.net). In addition, there were many direct contacts with developers or contact persons, when ever feasible. Data collection was carried out in several waves, with the last update completed on March 2005.

Data collected included: the name of the instrument, the content area, the country where the instrument was originally developed, the terms of use, the copyright information; and the contact person and address/es.

Conditions of access to HRQL instruments

Current practice is that users of HRQL instruments need to sign an *agreement* or *contract* for the use of their instrument. With exceptions, the access to questionnaires is *not free* for everybody. The typical *divide* is between academics, who get free access to the instrument, and for-profit, typically pharmaceutical, companies who must pay fees for the use of the instrument. In addition, in many cases the user (both academic and for-profit companies) is requested to *buy an instrument manual*. It is also very common that academics are requested to *share their instrument data* with the developers of the instrument. We were unable to identify any formal description of particular policies towards those requesting use from *developing countries*.

As per type of instrument, *generic HRQL* and *psychological* instruments are mostly granted permission with fees, with the noticeable exception of the WHOQOL, but half of these questionnaires developers request them only for commercial/pharmaceutical companies with free access for academics. *Disease specific* questionnaires are more frequently freely accessible than the generic ones.

It is important to note that some information about the accessibility of the instruments that we obtained through the QOLID database was also upon a registration fee (while the Red IRYSS network is a completely free-access web site, but only for questionnaires in Spanish language).

ISOQOL and the Good Practices in the access to HRQL instruments

Although the task described here may be incomplete, the group discussed the possibility that ISOQOL produced a statement on good practices in accessing HRQL instruments, which would differ according to users. The statement would consider, amongst other issues, the perspective of researchers working for non-profit bodies, uses within public tax funded projects, or researchers work in a non-convertible currency country. Another important issue to consider is whether or not the development of the instrument occurred with public financing. A final issue for consideration is a general strategy for obtaining a return of the research costs.

Please find more information at: **http://www.isoqol.org/gpwg.pdf**

***Good Practices**, continued on page 6*

THE PATIENT REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS): A UNITED STATES NATIONAL INSTITUTES OF HEALTH EFFORT TO BUILD BANKS AND BRIDGES

Susan Yount and David Cella, PROMIS Statistical Coordinating Center, Evanston, Illinois

In May 2002, the Director of the National Institutes of Health (NIH) initiated a series of meetings to chart a "roadmap" for medical research in the 21st century. The purpose of the NIH Roadmap is to identify major opportunities and gaps in biomedical research that no single Institute could tackle alone but that NIH as a whole must address to make the biggest impact on the progress of medical research. One of the initiatives within the Roadmap concerns the adoption of a systematic infrastructure to accelerate and strengthen the clinical research process. In support of this initiative, the NIH funded a 5-year multicenter cooperative group, referred to as the Patient Reported Outcomes Measurement Information System (PROMIS). PROMIS is a program of research designed to develop, validate, and standardize item banks to measure patient-reported outcomes (PROs) that are relevant across common medical conditions in an effort to revolutionize the way patient-reported outcome tools are selected and employed in clinical research and practice evaluation. The purpose of PROMIS is to encourage common language and communication about PROs, not to mandate their use or suppress further important research that will be necessary and even vital for the field after project completion.

The PROMIS Network Structure

The PROMIS initiative establishes a collaborative relationship between NIH and individual research teams through a cooperative agreement (U01) mechanism. The PROMIS network of clinicians, clinical researchers, and measurement experts is organized around four functional components: six primary research sites (PRSs), a statistical coordinating center (SCC), NIH project scientists representing several institutes, and a Scientific Advisory Board (SAB).

Primary Research Sites

The PROMIS PRSs include: Duke University, Stanford University, Stony Brook University, University of North Carolina at Chapel Hill, University of Pittsburgh, and University of Washington in Seattle.

Statistical Coordinating Center

The PROMIS SCC is based at the Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University Medical School. The SCC provides and manages a secure, customizable, coordinated data management system for the collection, storage, and analysis of data collected by the PRSs. It coordinates, facilitates, and maintains information exchange and dissemination across scientific, administrative and advisory tiers of the PROMIS network.

NIH Scientific Staff

Several NIH scientists are involved in the PROMIS and have overall responsibility for program oversight and stewardship. NIH scientific staff members also serve the as scientific liaison between the awardees and other NIH program staff and between the PROMIS network and other NIH-sponsored research collaborations. Each grant (PRS/SCC) is also assigned an NIH Science Officer who has substantial scientific/programmatic involvement.

Scientific Advisory Board

Appointed by NIH and selected for their broad expertise, the SAB consists of approximately 10 scientists who are not closely affiliated with any of the funded sites. SAB members provide their expert advice regarding study objectives, strategies, designs, data collection instruments, analysis plans, and results. The SAB oversees coordination among funded projects and evaluates their progress toward the goals of the PROMIS initiative.

Network Activities

PROMIS network activity over the first year (2005) is organized around the creation of the PROMIS Item Library and three interrelated protocols: Archival Data Analysis, Conceptual Framework for PROMIS Dimensions and Domains and Qualitative Item Review, all of which are integrated and inform one another.

The PROMIS Item Library

A critical first step in the creation of item banks was the creation of an "item library," an extensive relational database of items gathered from existing PROs. The purpose of the library is to support the identification, cataloguing, and refinement of items that will serve as candidate items for future PROMIS item banks. Due to the library's size (approximately 7,000 items) and the amount of content redundancy among items, a selection process was undertaken, known as "binning and winnowing." First, all items in each domain were classified according to content ("binning"). Next, a smaller set of items (approximately 1100) was reviewed and revised by domain experts through the QIR process ("winnowing") to eliminate items that were dissimilar to the identified domain (face invalidity) or similar to a better-worded item (redundancy). This information was catalogued in the Item Library.

Archival Data Analysis Protocol

Data analyses are driven by a statistical analysis plan based on item-response theory (IRT), developed with extensive input from a team of 20 co-investigators and consultants. To support the building of the initial item banks, data analysis of 15 available large datasets was undertaken with the goal of better understanding dimensionality in the five PROMIS domains, inform the revision of items in the item library, inform the identification of the most useful re-

***PROMIS**, continued on page 12*

AN UPDATE ON PROGRESS WITH THE 2006 ISOQOL CONFERENCE

Andrew Bottomley, 2006 Conference Committee Chair and Henning Flechtner, Co-Chair, on behalf of the Conference Committee

Planning for the 13th ISOQOL Annual Conference, scheduled for October 11 through 14, in the exciting, historical coastal city of Lisbon, in sunny Portugal, is in full swing.

The co-chairs, organizing committee and excellent team at Degnon Associates are all working extremely hard to pull together an exciting, dynamic and innovative 2006 Conference program.

Immediately preceding the conference on Tuesday, October 10, we have planned a special pre-conference satellite meeting where key-regulatory issues will be discussed. This will be followed by a full day of workshop offerings on Wednesday October 11, made possible through the efforts of Dr. Carol Moinpour, Chair of the workshop subcommittee. More than 14 workshops, aimed at both basic and advanced levels, covering all key and the most topical issues in HRQOL research to date, will be offered. These are often well subscribed sessions, so be sure to register as soon as the planning is finalized and the information is posted on the ISOQOL website (www.isoqol.org) which will occur in the next few weeks. In addition, a workshop planned for local researchers and clinicians, and conducted mainly in Portuguese, has been scheduled for Wednesday, October 11.

This main conference will focus on HRQOL making a difference in the real world. Dr. Peter Fayers, the ISOQOL President, will open the Conference with an innovative and insightful welcome address. Dr. António Correia de Campos, The Minister of Health for Lisbon will welcome us to the wonderful city of Lisbon; we hope he will tell us how to best enjoy the QOL offered by the city!

We have planned a special plenary session on HRQOL and regulatory issues with speakers representing FDA views and presenting the newly minted FDA PRO guidelines. Also Dr. Mira Pavlovic, key contributor to the new EMEA HRQOL guidelines, will give her view of the value and impact of these. The differences and impact the FDA and EMEA guidelines could have for HRQOL researchers globally will be discussed in detail.

The keynote address by Dr. Gordon Guyatt will excite and challenge us about how we can improve HRQOL research making it more useful to the clinical community. We have several symposia exploring incorporating HRQOL evaluation into the real world, integrating values and preferences into clinical practice guidelines and HRQOL, and global public health policy, among others. The President's award this year will be given to none other than the eminent and charming Dr. David Osoba. He will inspire us with his wisdom about the influence of historic HRQOL and the development he sees over the coming decades.

We plan a panel discussion on how to publish research results, not only in specialized journals such as *Quality of Life Research* (QLR), but also in mainstream journals, with *The Lancet* editor Dr. David McNamee giving tips and engaging discussion about the challenges of publishing HRQOL material. Don't miss this opportunity for an open and frank exchange of views.

There will be time for our global special interest groups to meet and network, along with time for national chapters to meet and discuss progress and events for the coming years.

In addition to all these activities, we will soon be reviewing submitted symposium topics, scheduling extra workshops, setting up the useful mentor-mentee meetings, and reviewing the hundreds of important abstracts to make up a memorable and enjoyable Conference. Please send in your best new work to give yourself the best chance to present to your fellow researchers your efforts and move HRQOL research forward in leaps and bounds....

We look forward to seeing you all in Lisbon....

2006 Annual Meeting
Key Dates and Deadlines

- Symposium, Paper and Poster submissions due: May 12
- Scholarship Applications due: May 12
- Outstanding Article of the Year Award nominations due: July 15
- Early bird registration: August 18
- Satellite Meeting (PRO Regulatory Issues in Europe and the USA): October 10
- Workshops: October 11
- Conference: October 12-14

***Good Practices**, from page 4*

Acknowledgements: *The members of the Good Practices Working Group were: Jordi Alonso, David Cella, Geoffrey Norman, Donald Patrick and John E. Ware. Data collection for this survey was carried out by: Sali Santed, Sarah Shiffert, Montse Ferrer, José María Valderas and Jordi Alonso. This work has been partially supported by the Instituto Carlos III (Red de Investigación Cooperativa en Resultados y Servicios de Salud G03/202).*

ISOQOL PATIENT REPORTED OUTCOMES AND FDA REGULATORY GUIDANCE MEETING

Opening Reception: Wednesday, June 28, 2006, 6:00 - 7:30pm
Meeting: Thursday, June 29, 2006, 9:00am - 5:30pm

Renaissance Mayflower Hotel
Washington, DC

Chairs
Dennis Revicki, William Lenderking, Jeff Sloan

Wednesday, June 28
6:00 - 7:30pm
Opening Reception

Thursday, June 29
9:00 - 9:45am
Opening Plenary Session
Draft FDA PRO Guidance and What it Means to You
FDA respondent (TBC): Overview of the PRO guidance
Discussants
Albert Wu
Margaret Rothman (TBC)

9:45 - 10:45am
Plenary Session 2
Conceptual Framework and Guidance on Statements about PRO Findings in Product Labels and Promotional Materials
Dennis Revicki, David Cella, Neil Aaronson, William Lenderking
FDA respondent (TBC)

10:45 - 11:00am
Break

11:00am - 12:00 noon
Plenary Session 3
Best Practices for PRO Instrument Development (Including Recall Period, etc.) and Validation
David Cella, Ron Hays, Jakob Bjorner, Peter Fayers, Neil Aaronson, William Lenderking
FDA respondent (TBC)

12:00 noon - 1:15pm
Lunch on your own

1:15 - 2:15pm
Plenary Session 4
Standards for Evaluation and Documenting Psychometric Qualities of PRO Instruments
Neil Aaronson, Jakob Bjorner, Ron Hays, Diane Fairclough
FDA respondent (TBC)

2:15 - 3:15pm
Plenary Session 5
Statistical Analysis Issues for PROs: Missing Data, Multiplicity, and Longitudinal Data Structure
Jeff Sloan, Peter Fayers, Diane Fairclough, Jakob Bjorner, Dennis Revicki
FDA respondent (TBC)

3:15 - 3:30pm
Break

3:30 - 4:30pm
Plenary Session 6
Interpreting PRO Results: Methods for Determining Responsiveness and MID
Ron Hays, Dennis Revicki, Jeff Sloan, David Cella, William Lenderking
FDA respondent (TBC)

4:30 - 5:30pm
Plenary Session 7
Commentary and Closing Session: PROs and You: Where Do We Go From Here?
Moderators: William Lenderking; Dennis Revicki; Jeff Sloan
This session will include a mix of academic, FDA and industry representatives who will comment on and discuss the presentations made during the day.

PAPER OF THE YEAR INTERVIEW

Kathleen Wyrwich, USA

I recently had the opportunity to interview Galina Velikova, MD, first author of ISOQOL's Paper of the Year Award in 2005. Here is an edited transcript of our trans-Atlantic telephone conversation.

KATHLEEN: Hi Galina. Your paper, "Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial," that appeared in the February 2004 *Journal of Clinical Oncology* (15;22(4):714-24), was selected as Article of the Year at the ISOQOL 2005 Annual Meeting. Can you summarize the aims and achievements for the paper?

GALINA: Well, I wanted to see whether introducing the use of quality of life data into routine patient care would have a positive effect. And I have to say, my thinking started with, "Could we measure a positive effect of assessing quality of life of patients on patients' well-being first?" And then I started thinking backwards about what we expect to see— what are the intermediate steps to achieve that goal? And that's when I began investigating the hypothesis that if we measure quality of life, we can improve patient outcomes in terms of their well-being, and that will it have an impact on the process of care. And I decided to focus on communication—what is happening during the patient-clinician consultations.

So that's – that's how it all started. We conducted these studies using a randomized design with a proper control group and develop a step-wise protocol of the different elements that this kind of intervention involves. I did quite a lot of initial pilot work with some of my oncology colleagues to see how best to fit QOL measurement into clinical practice.

KATHLEEN: Why do you think this is an important contribution to quality of life measurement and use of quality of life measures?

GALINA: Well, this is the first study showing that it's possible to use these measures in individual patient care in a way that benefits the patients. We've used the QOL measures in clinical trials and we do get results, but the actual translation of those results in individual care is a long process. So I think that's the first study demonstrating the principle that it's possible to use these measures, incorporate them into patient care and actually benefit these individual patients who contribute the data. In other clinical trials, patients contribute the data and then it goes on to analysis and conclusions, but that cycle of involving the patients and getting immediate benefit for them is rather long.

And, also, it's difficult to change clinical practice. In this study we do a little bit of that by training and suggesting to the physicians ways of using the QOL data. And some of this worked, but I don't think it worked absolutely for everybody. Nonetheless, I think it's important to prove the principle that this is possible to do and then develop it further.

KATHLEEN: What do you think are the next steps for this type of investigation?

GALINA: Oh, it has to be repeated, I think, with better instruments. Therefore, what I'm doing in my work now is trying to see if we can improve the instruments. I want to improve them specifically for clinical practice—to make them a bit more flexible, more individualized, and then test whether this is better. And I also think we need models where these measures are actually incorporated and used directly in clinical practice. I'm a clinician and do see patients, but I don't use the measures routinely in my practice. So…I think that's the next step is to try and incorporate them into day-to-day practice on a small scale initially and see whether it will work and how it will work. It's following the model for clinical trials that they have Phase I, II, III, and then Phase IV is actually application of the findings of Phase III trials and seeing whether they apply on a wider scale in – in normal life. Also it will be good if more people replicate these findings because it's only one finding at present—the effect on quality of life. I think we have already several trials showing effect on the process of care. I think we have, perhaps, enough studies to encourage us to think that there is some effect, but we need more studies to show benefits for the patients.

KATHLEEN: Is there any anecdote or special story that would like to share about your participants in this study?

GALINA: There were several anecdotes about patients in the study from the physicians seeing them. The clinicians realized that they've missed things going on with their patients. We had one story of a patient receiving interferon who was generally fine with interferon. But the doctor only spotted a problem with social functioning because of the QOL results and said, "What's this thing about?" It turned out that the effects of interferon are such that this patient, who had a farm, couldn't look after the farm, so he and his wife were selling the farm and totally changing their lives. The physician was so impressed that he missed all of that; he had seen the patient several times and felt, "He's fine." Interferon has quite serious side effects in principle, but this patient seemed to be coping well. The physician wasn't aware of all that was going at the background, so he felt that the QOL data was quite helpful to actually realize the impact the treatment was having on this patient.

Interestingly, after the study was concluded, I had some of the physicians who took part in the study coming back to me and say, "Well, I already missed the QOL reports because they were so helpful to see at a glance that the patient is fine or there's an area that we need to ask that I wouldn't otherwise asked."

***Paper of the Year**, continued on page 10*

***Let's Talk**, from page 2*

lier stages of life but the role function items of the EORTC QOLQ-C30 were not considered important by patients or health care professionals when evaluating the outcome of palliative care. This highlights the old point that it is important to reconsider the composition of instruments before using them in a population different from what they were developed for. While our study showed that several of the other domains included in the EORTC QOLQ-C30 were viewed as very important (and thus should be retained) it also confirmed that aspects not included may also be extremely relevant. We concluded that our new measure, the EORTC QOLQ-C15-PAL, contains items that measure 'aspects that are very important to QOL' (mainly physical and emotional function and not claim that it covers all aspects that are relevant to QOL at the end of life. No single measure can do so; depending on the research questions it will clearly be important to consider which other aspects should be included (we intend to develop supplementary 'modules' measuring some of the important aspects).

Second, Nancy E. Mayo, BSc(PT), MSc, PhD, from McGill University in Montreal, Canada wrote:

Dear Kathy -I liked your column of do we need another term for quality of life at end of life. I am involve peripherally in palliative care research (I teach a protocol development course as part of a palliative care training grant). I also supervised a palliative care physician who is working on her Master of Science degree in Epidemiology and Biostatistics looking at health care at end of life. This has produced several publications and a model.

However, what struck me the most useful for thinking about these issues is more at a personal level where a close friend of mine lost her husband to a very awful and aggressive form of head and neck cancer.

My friend coined the term "quality of death" – of which he had none. She had already abandoned that he had any quality of life – this was close to zero after undergoing 2 (two) 22 hour operations on his jaw, etc.

She herself is an academic in the field of rehabilitation and had higher expectations of the health care system. Having lived this horror, she is interested in writing up this experience and I said that I would help her. I think this will bring some closure for her on his death (he was 59) but also her description of quality of death, I found informative from my own perspective as a quality of life researcher. So for what ever this is worth, this is my 2 cents worth. I think there are 2 constructs, quality of life and then quality of death.

Many thanks to Mogens and Nancy for their replies to a question that I feel is very important in our field. The new question that I would like to toss around comes for an email recently sent by a colleague who stated:

"With 3000 diseases listed in the ICD-9, 250 nations in the United Nations and a total of perhaps 500 distinct languages, and at least 2 different ways (generic or disease-specific) of measuring QOL, it seems that there's a potential for millions of publications of the form "Adapting the measure of some disease or other to patients with a slightly different disease in an altogether different language."

My question for your thoughts in this issue is:

Are we currently putting too much effort and publication space into the translation and validation of QOL measures for use in other nations and languages? And secondly, are there minimum criteria that this publications genre should report in the publication of results?

What do you think? I look forward to reading and compiling members' responses in our next issue, so please send your ideas, comments, references, etc. to me via email at wyrwichk@slu.edu.

SEEKING AN ASSOCIATE EDITOR

Quality of Life Research, The Official Journal of the International Society for Quality of Life Research, is seeking an Associate Editor. The deadline for submission of applications is June 1, 2006. We are seeking someone with advanced knowledge of statistical methods and analysis, but we will consider applications regardless of area of expertise.

The candidate for Associate Editor (AE) should have:

- A broad knowledge of the field of quality of life research and its applications in health care settings.
- A strong record of peer-reviewed publications in the field of quality of life research.
- A commitment to the peer-review process and the editorial responsibilities including: Identifying appropriate referees for submitted manuscripts; Evaluating the merits of manuscripts, based on both referee reports and her/his own judgment, and making final decisions regarding the disposition of those manuscripts; Communicating effectively with authors, peer reviewers, other members of the editorial board, and the publisher (Springer Netherlands).
- Experience as a peer reviewer is required. Previous experience with comparable editorial activities is desirable.
- Doctoral degree in statistics or biostatistics is preferred.

The Springer Netherlands central editorial office carries out day-to-day administrative work (i.e., preparing correspondence, tracking of manuscripts, etc.).

AEs can expect to spend at least one-half day a week on their editorial du-

***Seeking Editor**, continued on page 13*

***Paper of the Year**, from page 8*

I had a few of the more negative comments, however, particularly for patients who are medically quite unwell, such as those patients that come in with symptoms of spinal cord compression. This is time when it's a medical emergency and these QOL questionnaires are, perhaps, irrelevant. Although the patients did complete them, doctors felt that in those situations, they're not really of much use, as well as in other situations where the physicians had to tell bad news to the patients because of the progression of cancer: i.e. "The cancer's worse, and no further options, etc." Again, they felt it's not particularly helpful to have the QOL data because, obviously, the patient will be distressed and the emphasis of that particular encounter will be quite different. But apart from that I had quite a few positive interpretations from the physicians participating in the study.

KATHLEEN: Good.

GALINA: Yes, it's interesting. Patients will comment, as well, and we did have quite a few very positive comments from patients in a subsequent study of focus groups about these questionnaires. One patient said, "Yes, it was quite good" because she felt she wasn't written off altogether, that is, people still wanted to know things about her.

KATHLEEN: That's great. You had quite a complex experimental design and it was very helpful to have the diagram that you included in the paper so that everyone can see it both pictorially and then in text in your method section. In retrospect, is there anything that you would have changed on your experimental design?

GALINA: I thought that the study was perhaps a bit too long. I did the study based on a six-month timeframe. For some patients that was too long. Patients who had treatments every couple of weeks ended up with ten or fifteen interventions during the study. Therefore, I felt that for these patients, that was too long and too much. And in future study I will count the number of times they come back to clinic. For examples, let's say six clinic attendances rather than six months time—and then control for time in the analysis.

In designing this study, I thought it was important to address all potential confounders — like the contamination of doctors, although I couldn't address that in my setting and therefore led to the quite a complex study. And I still can't see a way around this. Perhaps another way of doing the study to simplify it a bit is to do a cluster randomization. That would involve doing the study in several centers and do the intervention in one center and the control in another center, or do multiple centers and randomize the centers. Nonetheless, it's quite a complex study to do in a multicenter trial. I'm currently doing a study in three centers and it's a nightmare to actually ensure the same quality in all three places, although they're all regional and we control it centrally.

KATHLEEN: You talked earlier about how the physicians were trained in interpretating the questionnaire data. Can you tell me about this training?

GALINA: I did the pilot study with three physicians whom I interviewed after every patient they saw with QOL data to see what they're looking at. We only did ten patients per physician. And then at the end of that period, I sat down with them and asked them what would help them to interpret the data easier—to make things easier for them to understand.

Then I developed written guidelines on interpretation, although they apply for groups of patients, so they can not be directly translated to individuals. I created case reports of patients pulled out from previous studies. In these cases studies, I had several scores of quality of life with a brief summary of the patient's medical chart notes. I tried to match what's in the records with the quality of life for interpretation. I also met individually with every physician who was joining the study and went through how the scores are created, and although we don't have norms, we can use the population norms as a guide. I explained one case study to them and then gave them another one which has the quality of life scores and some clinical details and asked them to try and interpret it, and then another one if we had time. I tried to make it as practical as possible. And that was the initial training.

Then to enforce that intervention, I asked each one of them to complete a brief checklist. I had two purposes—first, to see their perception about they used the QOL scores and how much it helped, but also to try and reinforce the process so that they did not forget the information.

I also displayed posters in the offices with the two questionnaires' scores and the possible scores in a graphical format so that if they look role function and thought, "Oh, I wonder what – what's that?" then the poster had the items on role function and the possible scores.

Also during the study, I did regular presentations in our research meetings to try to reinforce that the study's ongoing, the number of enrolled patients, the number of patients each doctor has seen on the study, and so on— just trying to keep them interested. I was running like a competition who will see most patients!

GALINA: I just want to mention here something, Kathy, which came later, after we completed the study, and I don't know whether you're aware of that work. The Medical Research Council of UK-MRC has now published on their website guidelines for how to do trials of complex intervention (http://www.mrc.ac.uk/pdf-mrc_cpr.pdf). And, actually, what we did in this study falls quite neatly into their definition of complex intervention. And the way we developed our study actually falls quite nicely into the stages they recommend to be done when you have a complex intervention. Basically, a complex intervention is any intervention that you have several active elements. So in that framework we have the patients com-

pleting the questionnaires and the doctors having the information, the patients talking to the doctors, so there are several elements. And that framework recommends that early pilot work actually looks at which are the elements that work and how to put them together, finalize that complex intervention, and then do a study to test its effect. So I think for future studies that's a useful framework to have. We sort of worked it out using common sense, but now we have that framework in the UK.

KATHLEEN: To measure the quality of life of cancer patients we usually see either the EORTC QOL C30 or the FACT-G family of instruments being used. Rarely do we see both. Tell me how you came to use both.

GALINA: We decided on EORTC QOL C30 for reasons of being European, and also from a clinical perspective—it has specific symptoms items. I think that's quite important if you're trying to sell a questionnaire to clinicians that it has things they understand (symptoms) and in addition, they can see the emotional functioning, the physical functioning, etc. That's the reason I preferred the QOL C30 for use in clinical settings.

Then when we were designing the study, there was an issue of using the same instrument as your intervention and your outcome measure. I was talking at that stage to people who have done studies in health services research and they said you can't use the same measure; it's not good practice and it will confound your study. I think at that stage the FACT-G was a natural choice because we wanted a common measure of cancer QOL. I think that was an important decision to use cancer-specific questionnaire, and that's how we ended up using both.

In Detmar's work, they used SF-36. I suppose to some extent I've learned from them, as well, because at the stage when we were starting, they were finishing their study and they knew there wasn't an effect on SF-36. I think one of the reasons is the SF-36 is not cancer specific, so it's not sensitive enough for that population. Therefore, I went for FACT-G as a cancer-specific outcome instrument.

KATHLEEN: Galina, this has been excellent. Is there anything else you would like to add?

GALINA: Yes, there's another thing perhaps I want to add. I'm particularly pleased that the paper was published, and I am also pleased that quite a few people have contacted me wanting to do similar studies. I think dissemination is difficult to measure, but I feel particularly pleased about that people liked the design of the study and it clearly inspired them to do more work in that area. So, I'm really eager to see how these studies will develop and whether they get similar results.

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***Mayo/FDA**, from page 3*

The FDA representatives acknowledged the importance of PROs and did not want sponsors to be dissuaded from using PROs in clinical trials. The FDA assured registrants that the FDA is working towards requiring documentation of the properties of all efficacy endpoints in labeling claims for PROs and other clinical endpoints.

In the coming months, the writing teams will revise the draft manuscripts to address issues raised by the release of the FDA draft guidance, and to incorporate issues raised from discussions held at the February meeting. These manuscripts will be submitted to the FDA for its consideration in preparing the final PRO guidance document. The FDA will also prepare a manuscript in response to the meeting to be published with the five manuscripts in a peer-reviewed journal of high scientific merit. Since FDA guidance documents are concise by design, the manuscripts from this meeting are intended to provide details of the recommendations provided in the FDA draft guidance and by FDA representatives at the meeting. The published manuscripts are intended to effectively operationalize the FDA guidance document for those submitting labeling claims to the FDA. Additionally, the manuscripts will be a vital resource for researchers and clinicians regarding sound practice of the use of PROs and the interpretation and understanding of future label claims.

In addition, consumers were encouraged to submit formal comments to the Federal Register by the April 4, 2006 deadline. This meeting was neither the last opportunity for interacting with the FDA regarding the draft guidance nor the last opportunity for consumers to raise issues with the draft guidance. Consumers are encouraged to attend upcoming meetings regarding PROs and the FDA draft guidance including ***ISOQOL Patient Reported Outcomes and FDA Regulatory Guidance*** on June 29, 2006 in Washington, DC and ***Patient-Reported Outcomes Assessment in Cancer Trials: Evaluating and Enhancing the Payoff to Decision Making*** on September 20-21, 2006, in Rockville, MD.

All in all, the meeting was a huge success in terms of integrating theory and practice into a framework of PRO measurement and informing attendees, writing teams, and representatives of the FDA, alike. The success is due to planning and tremendous hard work by the meeting executive committee, collaboration of the writing teams, active participation by meeting registrants, and open feedback and willingness of representatives of the FDA to sit "on the hot seat" for three days. Information regarding the meeting and the related publications can be found at www.qolpro.org or via email to dueck@mayo.edu.

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***PROMIS**, from page 5*

sponse sets, and guide new item construction.

Conceptual Framework for PROMIS Dimensions and Domains Protocol
A second and parallel task was development of a domain map (framework) that portrayed the structure of each target domain and its hierarchical structure. Consensus on domain framework and priority domains for first wave bank development was driven by a modified Delphi approach with multiple rounds of revisions until consensus was reached. The resulting framework retains the World Health Organization (WHO) 3-domain framework: physical health, mental health, and social health. PROMIS experts within these three domains reviewed and refined the framework by specifying the unidimensional sub-domains they believed to constitute the domain. From this framework, pain, fatigue, emotional distress, physical functioning, and social role participation were selected along with general health perceptions (global PROs) for the first wave of PROMIS network testing.

Qualitative Item Review Protocol
Qualitative item review began with expert classification and review of existing questions from commonly used instruments. Expert classification is evaluated and supported by input from several focus groups to evaluate the comprehensiveness of the PROMIS domain framework and note any conceptual gaps in the domain definitions. To evaluate comprehension and relevance of items flagged for inclusion in PROMIS banks, cognitive assessment interviews will be conducted with various patient populations. Items will be revised as needed to improve clarity, precision, readability, translatability, and fit to a CAT framework. Informed by consensus definitions of each domain and IRT analyses of item performance in archival datasets, new items will be written to attempt to cover the full continuum of each of the five selected domains. Each domain group identified key instruments to be considered "legacy" instruments, which will be included in future testing to aid in validation testing of the PROMIS item banks.

Future Plans
Network testing of items in the five preliminary domains is anticipated to begin in the summer of 2006. Data collection will primarily take place using internet–based testing, with off-line computers provided as a back-up. In total, over 1,000 items will be tested in a cross-country sample in excess of 7,000 individuals. The items to be administrated include the item bank items, demographics and general health items, and existing "legacy" instruments for future co-calibration and validation. We will also create a publicly available system to administer the instruments developed by the PROMIS network for use in clinical research. The system will be designed to enable easy modifications and will allow clinical researchers to access a common repository of items and computerized adaptive tests (CAT). Information on the requirements of end-users is currently being gathered from network research scientists, study coordinators, research assistants, psychometricians, statisticians, technology experts, and a wide range of external advisors. The platforms for the software will include stand-alone computers, websites, Personal Digital Assistants (PDA's), and Integrated Voice Response (accessible from any telephone). Under the leadership of an independent project at the University of Washington, all systems are being developed to insure easy accessibility to people with special needs. We welcome all to learn more and participate over time in the efforts of PROMIS to build bridges for PRO research.

Please attend our inaugural PROMIS Conference, to be held **September 11-13, 2006, at the Gaithersburg Marriott Washingtonian Center, Gaithersburg, MD, USA.** Please register for this FREE conference at http://meetings.promis.iqsolutions.com.

Further information and updates about PROMIS overall are available at http://www.nihpromis.org.

ISOQOL WELCOMES NEW MEMBERS

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John Wei MD
Ann Arbor, MI USA

INTRODUCING NEW WORKING PARTY

Charles Cleeland, PhD, Houston, TX, USA and Andrei Novik, MD, Moscow, Russia

Quality of Life and Symptoms Working Party has been recently established within the European Hematology Association (EHA).

There are several reasons to establish Quality of Life and Symptoms Working Party within EHA. By now novel treatment strategies have led to the improvement in outcomes for patients with different hematological malignancies. While prolongation of survival duration remains elusive in these conditions, all efforts must be made to ensure that the quality of life (QoL) is optimized. In addition, hematological diseases are often characterized by pronounced distress due to symptoms caused by the disease itself or its treatment and, in doing so, significant impairment of QoL takes place. In many conditions, such as multiple myeloma, new choices of treatment may be made based on reduction of symptom burden as well as survival. So far continuous symptom management is worthwhile. Measurement of symptoms and their impact makes it possible to cast symptom burden as a reasonable summary measure of both disease- and treatment-outcome status. Moreover, in cases when curative treatment is not possible, effective symptom palliation is of great importance to support and/or improve the patients' QoL. There are several obstacles to the implementation of QoL assessment in clinical practice. First, standard methods of assessing symptoms and overall of QoL evaluation in hematology are lacking. Second, there is a gap between physicians and researchers involved in QoL studies. Third, there is a lack of knowledge among physicians on how to interpret symptom and QoL data and use them in everyday practice. In addition, the attitude toward symptom management and QoL research varies across different countries and different cultures, which also may be considered an obstacle to promotion of QoL studies in hematology.

Coordination of QoL and symptom research within the new Working Party in EHA will improve quality of care for patients with hematological diseases, will help formulate symptom outcome measures of hematologic clinical trials that should result in better treatment outcomes, and will provide data for health-policy decision.

The aims of the Working Party are:

- To promote all aspects associated with quality of life and symptom research in the field of hematology;
- To develop unified recommendations for quality of life and symptom assessment in hematology;
- To attempt standardization of quality of life and symptom assessment within EHA affiliating centers;
- To develop practical clinical and research recommendations on quality of life and symptom assessment in hematology;
- To provide education and training in assessment for of symptoms and quality of life for those planning clinical trials.
- To explore national, cultural, and linguistic aspects of symptom and quality of life research.

Among the Working Party activities it is worthwhile to mention the following:

- Dissemination of knowledge among physicians and researchers in order to maintain high common standards in the field of quality of life research;
- Training in the field of quality of life and symptom research in hematology;
- Preparation of publications on the core issues of quality of life and symptom research in hematology as well as on new data in the field;
- Maintenance of liaisons with other associations, centers, leagues involved in QoL research;
- Regular meetings to coordinate and to support initiatives in quality of life research in hematology.

The Chair of the Working Party is C. S. Cleeland, McCullough Professor of Cancer Research, Chair of Department of Symptom Research, the University of Texas M. D. Anderson Cancer Center, Houston, USA. Its co-Chair is A. A. Novik, Professor of Internal Medicine and Hematology, Chair of Hematology/BMT Department, National Medical Surgical Center, Moscow, Russia. At present the Working Party unites specialists from different European counties and the USA.

Thus, Quality of Life and Symptoms Working Party is the first Working Party within the EHA to focus on symptom and quality of life measurement, and its relationship with treatment studies. The establishment of such a Working Party will be beneficial in terms of bridging the gap between the experts in QoL research and health-care givers.

The new Working Party is looking forward for cooperating with such groups as the International Society for Quality of Life Research and initiating joint projects.

The first meeting of Quality of Life and Symptoms Working Party will be held at European Hematology Society Congress on 17th June 2006, Amsterdam, The Netherlands.

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Seeking Editor, *from page 9*

ties. They do not receive financial compensation for their service, but previous AEs have found the experience to be rewarding. Many of them appreciated the opportunity to contribute to the advancement of quality of life research.

If you are interested, please submit an email with your curriculum vitae and a brief indication of your specific areas of interest and expertise to: Ron D. Hays, PhD, Editor-in-Chief, *Quality of Life Research*, drhays@ucla.edu.
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