

## REVIEW OF NIH/NIDDK MEETING ON MEASUREMENT OF URINARY SYMPTOMS (MOMUS)

NATIONAL INSTITUTES OF HEALTH, BETHESDA, USA, November 14-15 2011

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A most interesting and thought-provoking brainstorming meeting was held by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) at the National Institutes of Health in Bethesda, USA and was attended by an impressive array of speakers and participants including urologists, gynaecologists, researchers, basic scientists, epidemiologists, psychologists, biostatisticians, anaesthesiologists, with representatives from the pharma industry, U.S. Food and Drug Administration (FDA), the Centres for Medicare and Medicaid Services, and the Agency for Healthcare Research and Quality and last but certainly not least the all-important patients and advocacy groups. It was a gruelling schedule, testing even the fittest, covering 1½ days, starting at 7 am when we were collected by bus to go to the National Institutes of Health and ended around 7 pm on the first day. The second day, Tuesday, also began with a 7 am bus call and ended around mid-day.



The objectives of this meeting were defined by the NIDDK as to:

- *Discuss the uses and shortcomings of current symptom-based instruments in research of LUTD.*
- *Disseminate state-of-the-art methodology to improve patient reported outcomes (PRO) of LUTD symptoms.*
- *Discuss the validation and qualification process of new measurement tools, and patient phenotyping.*
- *Align the new LUTD symptom measurement tool among involved parties.*

In other words, a better tool for measuring urinary symptoms and pain needs to be found. This meeting also included much about interstitial cystitis, a condition that was repeatedly raised by many of the speakers.

### **Monday 14 November**

Opening the meeting, Griffin Rodgers, MD, Director of the NIDDK, explained that an immense number of men and women suffer from urinary symptoms and that these symptoms lead to a significant decrease in their quality of life. Since both incidence and prevalence rates increase with age and we have an aging population, treatment costs pose a major financial challenge now and in the future. The American Urological Association (AUA) symptom score, originally intended for benign prostatic hyperplasia (BPH) patients and in use for 20 years, is widely used in clinical practice and has been translated into multiple languages. This symptom score is often used as an endpoint in clinical trials to assess symptom-based clinical improvement in benign lower urinary tract disease. However, its use for research purposes has now come into question. Using the current AUA symptom score may not only be misleading clinically and correlate weakly with patient satisfaction, but also can be scientifically invalid and impede scientific progress. This means that we need a better measurement tool that focuses on patient reported outcomes (PRO) in order to quantify early, late, transient and persistent symptoms of lower urinary tract dysfunction in both men and women. Rodgers emphasised that the patient point of view is extremely important here. Janine Clayton, MD, NIH Acting Director Office of Research on Women's Health, went on to add that these challenging topics need interdisciplinary and multidisciplinary approaches.

## Session I: Public Health Importance of Measuring Lower Urinary Tract Dysfunction

*Speakers: Paul Abrams (represented by Marcus Drake), Mark Litwin, William Lawrence, William Riley, Laurie Burke.*

The first session on the public health importance of measuring lower urinary tract dysfunction was to be opened by Paul Abrams, MD, from Bristol Urological Institute, but due to flu his role was taken over by Marcus Drake, MD, also from Bristol. He discussed the International Consultation on Incontinence Modular Questionnaire (ICIQ) project which was established to provide a range of questionnaires to assess pelvic problems, to develop fully validated international standard questionnaires for lower urinary tract dysfunction, vaginal symptoms and lower bowel dysfunction, to form a consensus over the most suitable questionnaires for use and to facilitate wide use of questionnaires. Further information about this modular project can be found at <http://www.iciq.net>.

At the 1<sup>st</sup> meeting of the ICI in 1998, they recognised that there was a plethora of LUTD questionnaires, in which patients had largely not been involved, whereas it is essential to capture the patient perspective for such questionnaires to be effective. For the patients, symptoms are of the highest importance, according to Drake. He asked why questionnaires need to be used in LUTD, explaining that they are for:

- Diagnostic purposes
- To assess symptoms and the bother they cause patients and the effect on quality of life
- Clinical measures and questionnaires measure *different* but *related* aspects
- Valid questionnaires capture the patient perspective

Quoting Fairclough 2004, he noted that “*While we can measure a biological response, we may not be able to determine whether that response makes a noticeable difference to the patient*”.

On the subjects of translations, the speaker emphasised the need for translations to be culturally adapted as well as linguistically validated.

The proposition put forward was as follows:

- That the ICIQ should be implemented as a LUTD assessment standard, noting that the 4<sup>th</sup> ICI recommended that the ICIQ modules should become the standard instruments for assessing LUTD.
- Can a new generic tool for LUTD assessment be justified, taking into account that it would be time-consuming and expensive to develop and that there is no evidence that a more useful instrument would result?

Mark Litwin, Professor and Chair of Urology at the David Geffen School of Medicine, Los Angeles, speaking on the public health importance of measuring LUTD symptoms and defining the burden of illness, gave a few figures relating to cost in the USA:

### *ANNUAL MEDICARE EXPENDITURE:*

<i>Benign Prostatic Hyperplasia:</i>	<i>\$ 776 million</i>
<i>Adult male urinary tract infections:</i>	<i>\$ 480 million</i>
<i>Adult female incontinence:</i>	<i>\$ 234 million</i>
<i>Interstitial Cystitis:</i>	<i>\$ 119 million</i>
<i>Adult male incontinence:</i>	<i>\$ 39 million</i>

This shows that while IC features clearly on the list, it is not the most expensive by any means. This list also indicates a possibility that many men may not be doing anything about their incontinence problems.

If we take a look at the figures for **Annual Office Visits**, the picture is rather different:

<i>Adult female urinary tract infections:</i>	<i>9.0 million</i>
<i>Benign Prostatic Hyperplasia:</i>	<i>7.8 million</i>
<i>Interstitial Cystitis:</i>	<i>4.1 million</i>
<i>Adult female incontinence:</i>	<i>2.1 million</i>
<i>Adult male urinary tract infections:</i>	<i>2.0 million</i>
<i>Prostatitis:</i>	<i>1.8 million</i>

Now we can see that IC features higher on the list for office visits and a further graph showed that this figure is rising.

It can also be seen that urinary tract infections are extremely high in women.

Litwin emphasised that there is a clear need to survey patients and to talk to them directly in order to achieve patient-centred outcomes.

More information is available in the book **Urologic Diseases in America**, available chapter by chapter on the NIDDK website at: <http://kidney.niddk.nih.gov/Statistics/UDA/index.aspx>  
Here you will find a chapter **on Interstitial Cystitis and Painful Bladder Syndrome** by J. Quentin Clemens, Geoffrey F. Joyce, Matthew Wise and Christopher Payne. This chapter is a separate pdf file comprising 34 pages which you may find useful.

Further information on **Urologic Diseases America – UDA Online** can be found at:  
<http://www.udaonline.net/>

William Lawrence, MD, outcomes and evidence researcher (see: <http://www.ahrq.gov>), speaking on the topic “Can Intervention for Symptoms Always Provide Patient Goal Achievement?”, said that for healthcare interventions to be effective, they must maintain or improve outcomes that are important to patients. *“As we move forward towards new measures of outcomes of interventions for lower urinary tract dysfunction, it is important that we evaluate not only the symptoms, but also the impact of these symptoms on patients’ function and their quality of life. A broader evaluation of patient-centred outcomes will allow future patients to better weigh the potential for benefit and harm from interventions, and make informed decisions about their own care.”*

Consideration of symptoms alone is not enough for the patient, you also have to take into account their preferences and the impact on functioning and quality of life, he added.

See also: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

William Riley, Programme Director, Division of Cardiovascular Sciences at the NIDDK, discussed Patient Reported Outcomes (PRO) – the PROMIS initiative.

**Patient Reported Outcomes Measurement Information System (PROMIS)**, funded by the National Institutes of Health (NIH), is a system of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient-reported health status. Further information can be found at: <http://www.nihpromis.org>

Laurie Burke, Associate Director for Study Endpoints and Labelling, Office of New Drugs at the US Food and Drug Administration (FDA), also emphasised that “We cannot talk about measurement without talking with patients”. She was therefore happy to see that there were a number of patient representatives in the auditorium.

Discussing treatment benefit, she stressed that this is the impact of treatment on how patients survive, feel or function in their daily lives, measured as effectiveness or comparative safety. Treatment benefit can be measured directly (e.g. symptoms) or indirectly (e.g. biomarker). Treatment labelling must not be false or misleading, she said.

On Clinical Trial Outcomes Assessment (COAs), she explained that COAs are used as study endpoints to demonstrate treatment benefit and are critical to understanding drug benefits and harms. COAs require rigorous development before they can be adopted in clinical trials. In order to reduce scientific uncertainty AND regulatory uncertainty, COAs are needed that are well-defined and reliable in a clinical trial context. Laurie Burke stressed that the FDA encourages COA developers to continue to pursue better ways of capturing the impact of therapies [using the values and points of view of the patients who will receive the treatments](#).

On the topic of “Validity”, she gave two relevant quotations:

- It is wrong to speak of a “reliable and valid” test. Reliability and validity are [not immutable, inherent properties of a scale](#) but rather a result of interactions between the CFOA and the [context of use](#). (*paraphrased from Streiner and Norman*)

- “...validity usually is a matter of degree rather than an all-or-none property, and validation is an unending process... Strictly speaking, one validates the use to which a measuring instrument is put rather than the instrument itself. Tests are often valid for one purpose but not another.” (*Nunnally JC 7 Berstein IH*)

**In closing, she underlined that patients who are contemplating the use of a new treatment need to know its possible impact on how they will feel and function in their daily lives.**

## Session II A Patient Session: A Patient-Focused Approach To An Invisible Condition

The next session comprised a patient panel of US patients with different conditions, including post-prostatectomy, incontinence and leakage, chronic prostatitis and interstitial cystitis, giving an intensely moving yet down-to-earth and honest patient perspective. All of them spoke of the psychological dimensions, what it is like to be constantly asking where the toilet is and desperately wondering whether you are going to make it on time.

Laura Santurri, representing the ICA, gave a poignant description of what it is like to be an IC patient, stressing to the audience that questionnaires must be able to measure quality of life issues as well as symptoms. While basic symptoms include pain, urinary urgency and frequency, she noted that *“it is important to focus on other symptoms including sexual dysfunction and potentially significant pelvic and abdominal pain. The consequences of those symptoms, including social isolation and lack of sleep, also must be recognised and addressed in order to improve the health-related quality of life of those living with IC”*.



The presentations by this patient panel led to many questions from the doctors and researchers in the audience and clearly demonstrated the value of having the patient perspective at such a meeting.

### Session III: What is Currently Missing in the Measurement of LUTD Symptoms?

Speakers: Johannes Vieweg (not present), Claus Roehrborn, Marcus Drake, Michael Albo, William Steers, John Wei, Jerry Blaivas.

One of the important points raised here concerned the level of literacy of the patients who are filling in these questionnaires. Do they understand the questions and do they have the ability to explain their symptoms and answer the questions correctly? Claus Roehrborn, speaking on “Is The AUA SS Still the Best Instrument for Clinical Research?”, looked at the AUA Symptom Score which was developed by the AUA Measurement Committee in 1992 and was adopted shortly afterwards by the WHO as I-PSS. It is the most commonly used symptom score in the world and he said that, realistically speaking, the fact that this symptom score has been translated into 56 languages makes it very difficult to change in practical terms. He suggested that perhaps an extra set of questions could be added on. Marcus Drake from Bristol, UK, speaking on “How Do We Measure Incontinence?” noted that *“measuring incontinence is currently an unreliable assessment, and the challenges in developing a means to quantify urinary leakage in a standardised approach should not be underestimated.”* He further explained that quantifying leakage underpins decision-making for the selection of treatment and for research. More severe incontinence, for example, may justify more invasive treatment.

However, measuring severity is complex when dealing with a varied range of attitudes on the part of both the patient and the doctor. He quoted the following:

- *The stoical patient: “I cope fine with 4 pads a day”, “others are worse off than me”*
- *Seeking perfection: “incontinence is curable”, “life is appalling, ...I don’t need pads”*
- *Scornful doctors: “only 5mls”, “it’s not exactly serious”, “it’s only the bladder”*
- *“What do you expect, you’re getting old”*

Taking a look specifically at pad tests, he noted that there are practical difficulties such as embarrassment, that patients adapt their behaviour to reduce the severity of incontinence, such as restricting fluid intake and limiting exercise and that the exertion level varies. He concluded that since each patient is likely to report that differing circumstances substantially influence the incontinence severity, a generic solution has to ensure a comprehensive and flexible approach.



In this session, we once again heard that discrepancies exist between clinical measures of symptom severity and the patient’s perceptions of the symptoms. Symptom measurement must incorporate the perceived impact in addition to the quantification of symptoms. It is important to discover which symptoms are most bothersome to the patient and which symptoms have the most negative impact on their life. This is obviously going to be very individual and depend on many different circumstances.

William Steers speaking on “Bother” said that bother was the most important reason for treating lower urinary tract symptoms and can be influenced by the patient’s character. It may also explain the gap between prevalence and patients seeking treatment. He noted that there are age, gender and race differences in bother. While bother is distinct from worry, it is related to but not identical to quality of life. The question was asked: does a second condition displace or add to bother?

#### **Session IV. How are PROs measured in Other Conditions?**

*Speakers: Rosalind Ramsey-Goldman, Fred Friedberg, J. Quentin Clemens.*

This was a particularly interesting session for IC patients since it included topics such as autoimmune disease (using SLE as an example), IBS, Fibromyalgia and Chronic Fatigue Syndrome (FM/CFS) and Urological Chronic Pelvic Pain Syndromes (UCPPS).

The first speaker in this session, Rosalind Ramsey-Goldman, MD, from Chicago discussed “How Do We Measure Symptoms And Flares In SLE?”, looking at how to identify challenges in developing measures of symptoms and flares in Systemic Lupus Erythematosus (SLE) and assessing the current status of SLE flare definitions. SLE or Lupus as it is commonly known is a chronic autoimmune inflammatory multi-system (“systemic” or “generalised”) disease characterised by flares and remissions and by immune dysregulation, loss of tolerance to self-antigens, production of autoantibodies, and by immune complex-mediated tissue damage. Measuring disease activity and damage presents challenges because patients greatly vary in their disease manifestations, the course of the disease is unpredictable in individual patients, and there is a lack of concordance between clinical symptoms and blood test results. There are currently a number of validated measures of disease activity and damage, but have limitations. They are divided into two main categories: activity assessments (implying reversibility) and damage measurement (implying irreversibility). A specific challenge lies in using disease activity measure to quantify flares in SLE

The Lupus Foundation of America (LFA) convened an international working group to obtain a consensus definition of disease flare in lupus.

*Ruperto N et al. International Flare Consensus Initiative. International consensus for a definition of disease flare in lupus. Lupus. 2011 Apr;20(5):453-62. Epub 2010 Dec 10.*

Their definition was as follows:

*"A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment."*

This group examined the difference between disease activity and a flare.

*Disease activity* encompasses all the signs and symptoms related to lupus pathophysiology. It is determined at one point in time and is unrelated to the prior amount of disease activity.

*A flare* is an increase in disease activity as compared to a previous assessment, it implies potential reversibility of disease activity, and usually consideration of change or increase in treatment modality.

- Need to identify a beginning and end time point
- Need to define levels of flare, degree of change and threshold to move from one category to another, i.e. minimal clinically significant difference.

The speaker then presented a flare study in patients with SLE to illustrate the challenges of defining a flare in SLE. This study concluded that no flare versus any flare, and severe flare type are identifiable and that more work is needed to optimise the capture of mild and moderate flare.

This presentation was particularly interesting in light of the fact that many chronic pelvic pain syndromes such as IC and CP/CPSP are subject to flares and remissions, as was discussed later on in this meeting.

Lin Chang, MD, Professor of Medicine in Los Angeles, then discussed **What tools are available for symptom measurement in IBS?** She defined IBS according to Rome III 2006 as “*a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation*”. Other commonly reported symptoms are urgency, straining, bloating, visible abdominal distension, sensation of incomplete evacuation and mucus in the stool. The speaker noted that IBS is still a symptom-based condition that cannot yet be reliably diagnosed or monitored with biomarkers alone. Symptoms as reported by the patients are essential for diagnosis, to assess the severity of the overall disease, to guide treatment and evaluate outcomes. While the Rome III criteria are used to diagnose IBS and bowel habit subtypes, stool form has been shown to be a better predictor of diarrhoea and constipation subtypes. She mentioned the Bristol Stool Form Scale (BSFS). Lin Chang discussed rectal hypersensitivity in IBS being associated with greater symptom severity, noting that pain and bloating are independently associated with rectal hypersensitivity, with reference to an article by *Posserud I et al* that concluded that altered rectal perception is common in IBS and seems to be one important pathophysiologic factor associated with GI symptom severity in general and pain and bloating in particular.

She summarised by saying that:

- IBS is a symptom-based disorder without a reliable biomarker
- It is a multi-symptom heterogeneous condition
- Symptoms are largely measured using patient-reported outcomes
- Objective tools are being studied, but not currently used as primary endpoints in IBS
- Active efforts are being made to develop a valid and reliable PRO for IBS and gastrointestinal symptoms

Useful reading:

-*Spiegel BM, Bolus R, Agarwal N, et al. Measuring symptoms in the irritable bowel syndrome: development of a framework for clinical trials. Alimentary Pharmacology and Therapeutics 2011;32:1275-91.*

-*Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-4.*

-*Posserud I, Syrous A, Lindström L, Tack J, Abrahamsson H, Simrén M. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. Gastroenterology. 2007 Oct;133(4):1113-23. Epub 2007 Jul 25.*

Fred Friedberg, PhD, Research Associate Professor in Psychiatry, Stony Brook, then took us on to **Symptom Measurement in FM/CFS.**

He began by defining Chronic Fatigue Syndrome (CFS) as follows:

- At least 6 months persistent fatigue
- Substantial impairments
- Fatigue not medically explained
- Flu-like symptoms
- Pain symptoms
- Unrefreshing sleep
- Post-exertional malaise >24 hours
- 

He discussed the McGill Pain Questionnaire (MPQ) which distinguishes different pain syndromes, and the Fibromyalgia Impact Questionnaire (FIQ) which was superseded in 2009 by the FIQR.

See:

*Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL.*

*The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009;11(4):R120. Epub 2009 Aug 10.*

This is an open access paper: <http://www.myalgia.com/FIQR%20ART%20Paper.pdf> which describes the revised version of the FIQ. The authors believe that the FIQR has sound psychometric properties, discriminates between fibromyalgia patients and patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and major depressive disorder (MDD), takes just over one minute to complete, is easy to score and it can be used in online surveys. A further pluspoint is that it correlates

well with the old FIQ and consequently provides the ability to compare the results of studies using the older FIQ with studies using the revised version. It is used by clinicians and researchers.

J Quentin Clemens, MD, urologist from Michigan, then looked at **Urologic Chronic Pelvic Pain Syndromes, Measuring Pain and Flares.**

The term Urologic Chronic Pelvic Pain Syndromes (UCPPS) is a term created informally by the NIDDK for the MAPP project and refers to the disorders interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. IC/BPS is defined as an unpleasant sensation (pain, pressure and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms (LUTS), in the absence of infection or other identifiable causes. CP/CPSS refers to pain in the perineum, suprapubic region, testicles or tip of the penis, in the absence of a urinary tract infection or other obvious pathology. The pain is often exacerbated by urination or ejaculation. It is often accompanied by a sense of incomplete bladder emptying and/or urinary frequency. Both of these conditions are based on symptoms and have no reliable objective tests for diagnosis. With regard to definitions, Clemens pointed out that while there was no controversy surrounding CP/CPSS, IC/BPS had been very controversial, the subject of multiple meetings and consensus conferences. There are many reasons for this including the definition of urgency, and the problem of how to distinguish IC from similar conditions such as OAB, vulvodynia etc.

He discussed the Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) which are tandem instruments. (These can be found on the ESSIC website at: <http://www.essic.eu/pdf/ICSlandICPI.pdf>). He then looked at the overlap of pain and lower urinary tract symptoms in both men and women. He briefly mentioned some questions raised by the MAPP project:

1. *What factors are associated with longitudinal symptom variability?*
2. *How does this variability impact quality of life, resource utilisation?*
3. *What is meant by a 'flare'? How do patients describe a flare?*

A few interesting thoughts raised by Dr Clemens were:

- Symptom = subjective evidence of disease or physical disturbance observed by the patient
  - pain, pressure, burning, discomfort
  - urgency
- Behaviour = anything that an organism does involving action and response to stimulation
  - urinary frequency, nocturia
- Urgency is a type of pain
- Pain and urgency are afferent symptoms

Highlighting the overlap between afferent, efferent and structural abnormalities in the presentation of lower urinary tract disorders, he presented an interesting slide with **Conceptual Grouping** as follows:

**Sensory/Afferent Abnormalities**

- Interstitial cystitis/bladder pain syndrome
- Chronic prostatitis/chronic pelvic pain syndrome
- OAB dry/urgency-frequency syndrome
- Orchalgia
- Chronic epididymitis

**Motor/Efferent Abnormalities**

- Detrusor failure\*
- OAB wet/Urge incontinence/Detrusor overactivity\*
- Detrusor Sphincter dyssynergia\*
- Dyfunctional voiding\*

**Structural Abnormalities**



- Stress incontinence\*
- Pelvic prolapsed\*
- Diminished bladder compliance\*
- Bladder outlet obstruction\*

\* Have objective signs/diagnostic tests

### **Session V: Phenotypes, Clinical Conditions, and Impact on Measurement**

*Speakers: Tomas Griebing, Keven McVary, Steven Jacobsen, Aruna Sarma, Firouz Daneshgari, William Steers.*

In this session we heard about **Healthy Aging. What is the impact of LUTD** from Thomas Griebing followed by a presentation by Kevin McVary on **What did we learn from MTOPS?**

*(Marberger M. The MTOPS Study: New Findings, New Insights, and Clinical Implications for the Management of BPH. European Urology Supplements Volume 5 Issue 9 Pages 628-633 (June 2006).*

Open access: <http://download.journals.elsevierhealth.com/pdfs/journals/1569-9056/PIIS1569905606001485.pdf>).

### **Phenotyping**

This meeting also concerned the issue of phenotyping and William Steers, MD Professor and Chair of Urology in Virginia, as last speaker of the first day, addressed the topic of phenotyping patients with lower urinary tract symptoms. He began by discussing why phenotyping is necessary. Current treatment for lower urinary tract symptoms is usually a question of trial and error. Most treatment or trials are solely based on symptoms or bother, rather than targeting the underlying cause or reversing the disease process. Clinical trials sponsored by industry are often designed to capture the largest population with common symptoms rather than sub-groups characterised by phenotypes. Treatments are showing a mediocre effect compared to placebo. This is resulting in great inefficiency and cost-wasting, with frustrating patients going from one doctor to another in the hope of finding a treatment that works. Phenotyping may provide insight into the pathophysiology. An indication that phenotyping may improve outcomes is the fact that some treatment shows dramatically good results in a few patients, but not in others. So the average response appears to show that the treatment is not effective. The ultimate goal would be to provide the right treatment to the right patients at the right time and at the right dose. He looked at the UPOINT system with domains: urinary, psychosocial, organ, infection, neuro/systemic, tenderness, and the UPCANS system: urinary, psychosocial/character traits, childhood history, associated organs, neuro/systemic, sex. For future directions, he suggested: trials linked to potential risk factor categories, serum or urine biomarkers; longitudinal studies or registry of LUTS by phenotype; the right drug for the right patient at the right dose; data mine current FDA trial data and combine data sets from multiple trials to look for signals.

### **Tuesday, 15 November**

#### **Session VI: Better Understanding of the Symptomatic LUTD Patient: the Future**

*Speakers: Matthew Barber, Elizabeth Platz, Claire Snyder, Kevin Weinfurt, James Griffeth, Stephen Van Den Eenden, Kevin McVary and John Wei.*

We were by now into day 2 with Matthew Barber, Professor of Surgery at the Cleveland Clinic, as first speaker addressing the issue of **What Measures are Needed and for What Purposes?** He emphasised that lower urinary tract dysfunction (LUTD) has multiple causes, resulting in a wide variety of clinical presentations, prognoses, and impact of individual patients. Patients may suffer from a single urinary disorder, multiple symptoms or a symptom complex such as OAB. While it is common in both men and women, he explained, the most common symptoms, natural history of disease, impact on daily functioning, interpretation/description of common symptoms, and response to treatment are very

different between genders, reflecting clear differences in underlying pathophysiology and pelvic anatomy. Given these differences, it is important for gender-specific measures to be developed. He added that “validation” in both genders is not enough; it must be demonstrated that instruments have the same properties/interpretation in both men and women before adoption across both populations.

**Patient-reported outcomes (PROs)** also formed an important topic in this session. Why are PROs necessary?

Quoting R. Temple, Dir. FDA Office of Medical Policy:

*“The patient, properly queried, is the best source of information about he or she feels.”*

Many treatment effects are known only to the patient, for example pain, bother, quality of life, satisfaction. PRO instruments minimise measurement error, improve consistency and interpretability over informal interviews. Beyond the boundaries of research, they can be used in clinical practice to enhance the treatment of patients.

A survey of patients, physicians and nurses found that subjective measures and improvement in health-related quality of life (HRQOL) were regarded by all groups as the most important outcomes in urogynaecology studies. Tincello et al suggested that these should become primary outcome measures in all future clinical trials and audits of incontinence treatments.

*Tincello DG, Alfirevic Z. Important clinical outcomes in urogynecology: views of patients, nurses and medical staff. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(2):96-8; discussion 98.*

It was also noted that while many validated instruments assessing multiple domains already exist, they were constructed using Classical Test Theory and few were based on patient focus groups. While a variety of tools are used in clinical research, only a handful are broadly accepted and used. Once again it was emphasised that in most circumstances gender-specific tools are needed. Diagnostic instruments that accurately identify clinically relevant phenotypes should be a priority. Since many instruments currently exist, harmonization and direct comparisons of common instruments are needed to identify the best toolbox of instruments.

It was suggested a number of times that new modules could be created to add on to existing tools such as the AUA SS to make them more comprehensive. This would also make it unnecessary to revise the AUA SS and retranslate into multiple languages.

On the topic of **questionnaires**, a look was taken at the desirable characteristics of a questionnaire: It should ask the right questions, it should be comprehensive (ensure that treatments/assessment address patients’ concerns), measure treatment outcome, phenotype patients (identify different subgroups of patients), should be inclusive (can be completed by people with a low literacy level, by blind people etc), should be accepted by patients and clinicians, and last but not least should be brief yet precise.

John Wei ended the session with a presentation on **Barriers to Moving Forward**, stating that measurement of LUTD must be aimed at improving research quality and be clinically useful and that there must be standardisation and FDA/regulatory compliance. Phenotyping LUTD also plays an important role here. Barriers include: disagreement as to whether the current tools are adequate, e.g. the AUA SS, the ICS measures. We have to decide whether we want a clinical tool to more comprehensively measure LUTS, a research tool, or a tool that can do both. This decision will determine the scope and feel of any new questionnaire. A decision is also needed on what domains to be included. While BOO/LUTS, OAB, detrusor failure should be clearly included, what about pain, urinary incontinence, prolapsed, bowel issues, sexual issues? And what about impairment, bother, adaptation, expectations and satisfaction issues? And more besides. What is the optimal PRO

approach? Should you create more (validated) condition specific instruments using classical test theory? Should you merge existing instruments to maintain reliability/validity, i.e. a panel approach? Should you create item bank(s), meta-analyses of FDA data, use IRT/CATI, “harmonize” the scales? Wei then asked: should we extend beyond patient-reported outcomes? What about clinician RO or observer RO, or objectives measures e.g. UDS and biomarkers? Where do you draw the line?

Wrapping up the session, Robert Star, Division Director NIDDK Kidney, Urologic & Hematologic Disease, stressed the importance of “talking to the patient and retalking” and of the construct that the doctor places on what the patient says.

This was followed by breakout sessions in 4 groups:

1. What is missing in current measurement tools for male LUTD?
2. What is missing in current measurement tools for female LUTD?
3. How to validate the new measurement instrument?
4. How to phenotype the patients with symptomatic LUTD?

It now remains to be seen what the follow-up will be. Hopefully there will be a more detailed evaluation report by the NIDDK on this meeting with their conclusions available in the coming months.

*The MOMUS programme details can be seen at:*

<http://www2.niddk.nih.gov/News/Calendar/MOMUS2011.htm>

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