**JLGTD Editorial**

# Core outcome sets for Clinical trials and Observational Studies in Vulvovaginal Disease

## I. Define the issue—general concepts

Clinical trials and observational studies in medical research have been criticized for lack of clearly defined, well-validated, reliable, and responsive outcome measures resulting in poor reproducibility and difficulty with cross-comparison of studies. Additionally, outcome assessment can vary greatly based upon the specific "stakeholder" involved (i.e. patient, medical researcher, practitioner, or healthcare payer). The collective recognition of the need for consensus in research outcomes methodology has spurred a number of major initiatives including but not limited to: Patient-Reported Outcomes Measurement Information System (PROMIS)[1], Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[2], Outcome Measures in Rheumatology (OMERACT)[3], and Harmonizing Outcome Measures for Eczema (HOME).[4] In addition to providing standard, condition-specific research guidelines, these initiatives provide excellent roadmaps for research methodology improvement in other health care fields. A recent 'call-to-action' in the field of women's health known as the Core Research Outcomes in Women's and Newborn health (CROWN) initiative has been endorsed by a substantial group of professional journals focused on women's health issues, including the *Journal of Lower Genital Tract Disease*.[5;6]

## II. Define the issue—specific to vulvovaginal disease

Evidence-based practice lags behind in this field, particularly when compared with other disciplines in women's health. The development of interventional clinical trials for vulvovaginal conditions is hampered by the lack of essential information required to inform trial design, including validated outcome measures that can be recommended for a core outcome set. As a result, many published randomised studies are heterogeneous, of poor methodological quality and difficult to combine in metaanalysis, meaning that they cannot be utilised to inform evidence based practice.

Other more "developed" disciplines in women's health such as gynecologic oncology, reproductive endocrinology, and maternal-fetal medicine have evolved productive research directions. Research in these disciplines has been facilitated through subspecialty development, preferential research funding, and a perception of significant societal impact from the respective disease states. In contrast, well-designed, vulvovaginal clinical trials and observational studies, such as in vulvodynia, lichen sclerosus and mucosal / erosive lichen planus, are relatively small in number.[7-9] In spite of the research neglect, vulvovaginal disorders fall within the top ten ambulatory visits by women and lead to multiple return visits, development of sexual dysfunction, progression of chronic pain, and a negative impact on overall quality-of-life[10]. Clinically, many vulvovaginal complaints are infrequently raised by patients in discussion with the healthcare provider, based on devastating biopsychosexual implications that results in a 'suffering-in-silence'.[11]

## III. What is a core outcome set (COS) and a domain?

A core outcome set is a **minimum** set of outcomes for all clinical trials of a particular condition/group of conditions and will enable trials to be compared in meta-analyses. Core outcome sets consist of measures of effectiveness that are relevant to patients, care providers, and all other stakeholders.

- 'Outcome domains' are distinct elements of a disease (including consequence of the disease) such as patient defined symptoms, physician defined signs, laboratory assessments including histopathology, duration of effect of treatment and quality-of-life.
- Outcome measures are 'instruments' that measure the domains.(Schmitt 2015)

There is a lack of consensus with regard to the selection of outcomes for clinical trials.[12] As a result, different outcomes are assessed in different trials on the same population and intervention, important outcomes are missed by many trials, and/or different ways of measuring the same outcome domain are used, causing inconsistencies in reporting and difficulties in comparing and combining the findings in systematic reviews and meta-analyses and eventually using (pooled) trial information for clinical decision making. Consensus-based COS development is key to improvement of observational research and clinical trial methods by facilitating multicenter collaboration, providing reproducible measures of outcomes (i.e. drug testing results, disease status changes, etc.), and strengthening between-study comparisons such as meta-analyses. Formally defined structure such as Delphi panels can provide the essential foundation for the construction of widely accepted core outcome sets.[13]

Core outcome sets should address the following points:

- Usually consist of measures of effectiveness or harm
- Relevant to patients and care providers
- Relevant to those making decisions about health care cost-effectiveness
- Need to be valid, reliable, responsive to change
- Easy to implement
- Core outcomes may be different for clinical trials and routine care
- Some core outcomes may be generalizable to a wide spectrum of conditions while other core outcomes may be disease-specific

Core outcome domains may cover:

- (patient-reported) symptoms
- (clinician-reported) signs
- quality of life
- long-term control
- costs

Examples of "instruments" that measure single items or measures of defined domains of a COS for vulvovaginal disease include:

- Quality of life indices
- Female Sexual Functioning Index[14]
- Patient Global Assessment of symptoms
- Visual Analog Scale (VAS) for daily pain or itch level
- Tampon Test for vulvodynia[15]
- Vaginal maturation index
- Physician's global assessment of signs
- Biopsy for histopathological investigation

It is important to realise that core outcomes are not necessarily the only outcomes to be included in a trial. Other outcomes in addition to the core outcomes may be included to suit the needs of each particular trial. Core outcomes do not necessarily need to be the primary trial outcomes.

## IV. Organization is needed for ongoing independent workgroups

Based on a collective recognition of need, a number of workgroups have begun to address improved outcomes research in vulvovaginal disorders. However, the ongoing initiatives lack a unified focus and integration of efforts. Inevitably, the various workgroups will uncover common ground with respect to sexual dysfunction, chronic pain / itching, emotional disorders such as depression, and quality-of-life experience. Diverse diagnoses such as vulvodynia, lichen sclerosus, erosive lichen planus, recurrent vulvovaginal candidiasis, and vaginal atrophy will be found to be connected, based on blurred diagnostic boundaries or linked disease relationships. There is, therefore, need for a unified, focused, integrated consensus effort.

## V. Proposal: Development of a broad-based COS for vulvovaginal disease (VVD)

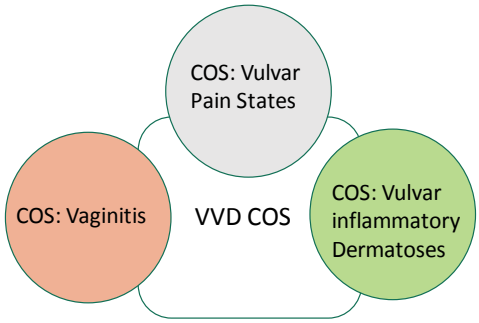
In spite of the relatively broad range of conditions encountered by specialists in the field, several factors argue for COS development that will span the spectrum of disease affecting the female lower genital tract:

- The diagnostic hallmarks of many vulvovaginal conditions, such as vulvodynia, lichen sclerosus, vaginal atrophy, and recurrent vulvovaginal candidiasis, are unclearly defined and are often coexisting.
- Diverse vulvovaginal afflictions promote a common psychosexual impact on the afflicted patient. This encourages a common assessment of patient reported quality-of-life outcomes across a spectrum of disorders.
- Developmentally, the three closely juxtaposed embryologic derivatives, making up the female lower genital tract may lead to confusing differences in tissue behavior within an anatomically unified region.[16] A classic example of physiologic variation based upon embryologic origin is seen in the difference in estrogen responsiveness between the vagina and vulvar vestibule.

The primary goal of a vulvovaginal disease COS initiative would be to develop consensus opinion concerning common domains and outcome measure instruments for vulvovaginal disorders. Publication of these consensus opinions would provide well defined, concrete direction for future research in the field.

We propose defining core domains, and identifying vulvovaginal disease COS and outcome assessment instruments that focus on at least three vulvovaginal disease subject areas:

- Vulvar inflammatory Dermatoses
- Vulvar Pain States (Vulvodynia)
- Vaginitis (Infectious (and non-infectious))




The vulvovaginal disease COS initiative should remain relatively broad in scope of medical conditions, be internationally-based, involve a broad stake holder group, and utilize recognized consensus methods such as Delphi panels and patient-centered focus groups.

## VI. The initial roadmap of COS development

Prior expert panel consensus initiatives such as IMMPACT[2] provide a clear roadmap for development of a series of major meetings covering all vulvovaginal COS areas and focused on three goals: 1) Delimiting clinical conditions and identifying core domains within each condition, 2) Identifying and defining core outcomes / instruments, and 3) Development of clinical research structure for randomized clinical trials (RCTs) in the respective subject areas. Core domains, such as *sexual dysfunction* and *pain,* would span all vulvovaginal conditions. Additional area-specific domains such as 'dermatologic architectural change' and 'laboratory assessment of vaginal milieu' would also be developed. Publication of internationally accepted core outcome measures for clinical trials and observational studies would enable the synthesis of evidence-based practice by facilitating cross-comparison and meta-analysis of studies.

Further points in COS development:

- **Language / cultural issues**: The vulvovaginal COS initiative should provide similar patient-directed measures across cultures and languages. Stakeholders must be internationally-based, including public, medical researchers, health care professionals, and health care policy experts with a global perspective. This will require appropriate translation. Cultural response differences will likely be recognized requiring alteration of measurement tools. PROMIS guidelines[1] will provide important direction in this instance.
- **HPV associated / neoplastic disease:** Updated consensus guidelines are in process of development and publication by a dedicated expert panel. HPV associated disease, therefore, will not be covered in this initiative. Future integration of COS for genital neoplasia will likely occur following the updated guideline roll-out.

- **Relationship to clinical recommendations**: This effort will be focused *on a minimum set of core outcomes (COS) for research* and should not be misinterpreted as clinical guidelines. Application to clinical practice, also known as *clinical practice guidelines,* will follow improved clinical research methodology and performance of appropriate clinical trials.
- **Publication of standards for performance of clinical trials research in lower genital tract disorders**: The *Journal of Lower Genital Tract Disease* (*JLGTD*) would facilitate a forum of discussion on COS development. Publications would necessarily undergo standard peer-review process but could develop a facilitated review process. Rapid turn-around from consensus meeting to publication should be ensured.
- **Continual review and update of COS should be anticipated:** COS development cannot be considered final or static. Rather, the concepts of outcome assessment would need regular review and updating based upon the existing state of the science.

*It is our intention, under the auspices of two major medical societies: the American Society for Colposcopy and Cervical Pathology (ASCCP) and the International Society for the Study of Vulvovaginal Disease (ISSVD), to provide overall direction, facilitate consensus meetings on vulvovaginal research outcomes measures, and publish consensus results. The consensus meetings may take several forms including a) expert panels, b) Delphi programs and c) Patient centered focus groups.*

References

1. Jeffery DD, Tzeng JP, Keefe FJ, et al. Initial report of the cancer Patient-Reported Outcomes Measurement Information System (PROMIS) sexual function committee: review of sexual function measures and domains used in oncology. Cancer 2009;115:1142-53.
2. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. [Review] [35 refs]. Pain 2003;106:337-45.
3. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. Journal of Rheumatology 1997;24:799-802.
4. Schmitt J, Apfelbacher C, Spuls PI, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. Journal of Investigative Dermatology 2015;135:24-30.
5. Khan KS, Romero R, Chief Editors of Journals participating in CI. The CROWN initiative: journal editors invite researchers to develop core outcomes in women's health. American Journal of Obstetrics & Gynecology 2014;211:575-6.
6. Andrews J. Lower Anogenital Tract Disease Therapy Outcomes, COMET, and CROWN: Call for Research Submissions. Journal of Lower Genital Tract Disease 2015;19:275-7.
7. Simpson RC, Thomas KS, Murphy R. Outcome measures for vulval skin conditions: a systematic review of randomized controlled trials. British Journal of Dermatology 2013;169:494-501.
8. Chi CC, Kirtschig G, Baldo M, Lewis F, Wang SH, Wojnarowska F. Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus. Journal of the American Academy of Dermatology 2012;67:305-12.
9. Kirtschig G, Becker K, Gunthert A, et al. Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus. Journal of the European Academy of Dermatology & Venereology 2015;29:e1-43.

10. Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. Vital & Health Statistics - Series 13: Data From the National Health Survey 2006:1-66.
11. Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia?[see comment]. Journal of the American Medical Womens Association 2003;58:82-8.
12. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet;374:86-9.
13. Prinsen CA, Vohra S, Rose MR, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials [Electronic Resource];15:247.
14. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. Journal of Sex & Marital Therapy;26:191-208.
15. Foster DC, Kotok MB, Huang LS, et al. The tampon test for vulvodynia treatment outcomes research: reliability, construct validity, and responsiveness. Obstetrics & Gynecology 2009;113:825-32.
16. Foster D. Site-specific mesenchymal control of inflammatory pain to yeast challenge in vulvodynia afflicted and pain-free women. Pain 2014.

Cheng S, **Kirtschig** G, Cooper S, Thornhill M, Leonardi-Bee J, Murphy R. Interventions for erosive lichen planus affecting mucosal sites. **Cochrane** Database Syst Rev. 2012 Feb 15;(2):CD008092. doi: 10.1002/14651858.CD008092.pub2.

Chi CC, **Kirtschig** G, Baldo M, Brackenbury F, Lewis F, Wojnarowska F.Topical interventions for genital lichen sclerosus.**Cochrane** Database Syst Rev. 2011 Dec 7;(12):CD008240. doi: 10.1002/14651858.CD008240.pub2.

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