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Research Priorities for Endometriosis

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Research priorities for endometriosis: recommendations from a global consortium of investigators in endometriosis

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Abstract

The 3rd International Consensus Workshop on Research Priorities in Endometriosis was held in São Paulo on 4 May 2014, following the 12th World Congress on Endometriosis. The workshop was attended by 60 participants from 19 countries, and was divided into five main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management, and research policy. This research priorities consensus statement builds on earlier efforts to develop research directions for endometriosis (Rogers, D'Hooghe et al. 2009, Rogers, D'Hooghe et al. 2013). Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 41 remained unchanged, 13 were updated, and two were deemed to be completed. Fifty two new research recommendations were made at the 2014 meeting in Sao Paulo, which in addition to the 13 updated recommendations resulted in a total of 65 new recommendations for research. The research recommendations published herein, as well as those from the two previous papers from international consensus workshops, are an attempt to promote high quality research in endometriosis by identifying and agreeing on key issues that require investigation. New areas included in the 2014 recommendations include infertility, patient stratification, and research in emerging nations, in addition to an increased focus on translational research. A revised and updated set of research priorities which builds on this document will be developed at the 13th World Congress on Endometriosis to be held 17 -20 May 2017, in Vancouver, Canada.

Introduction

The 3rd International Consensus Workshop on Research Directions in Endometriosis was held in São Paulo on 4 May 2014, the day following the 12th World Congress on Endometriosis (WCE). The workshop was supported by the World Endometriosis Society (WES) and the World Endometriosis Research Foundation (WERF). Previous research directions workshops have been held in conjunction with earlier WCE meetings in Melbourne in 2008 and Montpellier in 2011, both resulting in the publication of a number of research recommendations (Rogers, D'Hooghe et al. 2009, Rogers, D'Hooghe et al. 2013).

The São Paulo workshop, attended by 60 participants from 19 countries, was divided into 5 main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management and research policy. Within each session, speakers provided updates on areas of significant research progress in the past three years, followed by suggestions for new research directions. On each topic, discussion was opened to all workshop participants and new research recommendations were developed. Following the workshop, each speaker was asked to scrutinise a transcript of the meeting and using the 56 research recommendations from 2011 as a starting point, (1) to list recommendations that are still relevant and should remain unchanged, (i.e.: do not need updating), (2) to identify recommendations that are no longer relevant (i.e.: have been completed or superseded), and (3) from the transcript of the meeting, list new or updated recommendations that were suggested at the workshop. This paper records the new and updated recommendations from the workshop. The status of recommendations from 2011 (Rogers, D'Hooghe et al., 2013) is provided in Table 1.

To broaden thinking and generate new ideas, speakers were also asked to consider three new themes across all of the sessions: (i) novel concepts or approaches that endometriosis researchers can emulate from research successes in other complex diseases; (ii) enhancing research in emerging regions; (iii) prioritization of translational research: where should we be focusing our research efforts? Where relevant, these themes are incorporated into this report. In addition, compared to the 2011 meeting, the workshop included an enhanced focus on symptoms of endometriosis, with sessions on pain, infertility, and the patients' perspective.

Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 44 remained unchanged, 8 were updated, and only 4 were deemed to be no longer relevant, with 2 superseded and 2 completed. 57 new research recommendations were made at the 2014 meeting in Sao Paulo, which in addition to the 8 updated recommendations gives a total of 65. These are listed below.

Background

Endometriosis is a common and costly disorder affecting 6-10% of reproductive-aged women (Burney and Giudice 2012) and the most common cause of chronic pelvic pain (Hickey, Ballard et al. 2014). The financial burden of endometriosis on the healthcare system is substantial, with the direct and indirect annual costs of endometriosis estimated at US $12,419/woman (approx. €9,579)(Simoens, Dunselman et al. 2012). The same authors reported decreased quality of life as the most important predictor of direct health care and total costs. The economic burden associated with endometriosis is similar to other chronic diseases such as diabetes, Crohn's disease, rheumatoid arthritis (Simoens, Dunselman et al. 2012).

There is a delay of up to 9 years between symptom onset and definitive diagnosis of endometriosis depending on healthcare settings (Nnoaham, Hummelshoj et al. 2011) (Culley, Law et al. 2013). It has been estimated that affected women lose, on average, 10.8 hours of work weekly, mainly owing to reduced effectiveness while working. Loss of work productivity translates into significant costs, ranging from US$208 in Nigeria to US$23,712 in Italy per woman/year (Nnoaham, Hummelshoj et al. 2011). There is currently no known cure for endometriosis. Following surgical management, symptomatic recurrence ranges from 20-40% and many women require additional surgery at a later time (Vercellini, Barbara et al. 2009).

The research recommendations published in this report, as well as those from the two previous papers from international consensus workshops, are aimed at promoting high quality research into endometriosis by identifying and agreeing on the key issues that require investigation. While the recommendations are offered as a guide only, it is notable that the 2009 and 2013 papers have been cited 79 and 27 times respectively (Web of Science data September 2015) by other publications, suggesting that they have been of considerable use to the endometriosis research community. Considerable research effort is occurring in all aspect of endometriosis: between the 2011 and 2014 WCE meetings, a total of 2,524 new scientific publications on endometriosis were recorded on PubMed. Despite this research activity, and somewhat disappointingly, only 2 of the 56 recommendations from the 2011 Research Directions Workshop were deemed to have been satisfactorily addressed.

One key area of progress since the 2011 meeting has been in research policy. To encourage and facilitate the required large, international collaborations, the World Endometriosis Research Foundation (WERF) launched the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) (http://endometriosisfoundation.org/ephect/), led by Stacey Missmer of Harvard University and Krina Zondervan from University of Oxford (Becker, Laufer et al. 2014, Fassbender, Rahmioglu et al. 2014, Rahmioglu, Fassbender et al. 2014, Vitonis, Vincent et al. 2014). The WERF EPHect team includes 34 experts from 16 countries as well as three industry sponsors - many of whom were present at the WES/WERF Research Workshop. Together this group developed and published freely available clinical and surgical data collection tools along with protocols to standardise collection of biological samples to support discovery and innovation.

Pathogenesis and Pathophysiology

Epidemiology
The consensus approached epidemiology from its two definitions. First as the discipline focused upon determining WHO is at risk for endometriosis (which of a girl or woman's characteristics or exposures are associated with her endometriosis), and HOW those characteristics and exposures cause or impact endometriosis pathogenesis and pathophysiology. Second as the science underlying the methods by which valid human studies must be conducted: it matters who we choose to sample from among the population of girls and women and who we compare to whom for our studies of pathogenesis and pathophysiology. The broad consensus was that future studies need to be large and diverse to quantify and evaluate powerfully the importance or insignificance of the diversity of disease presentation, whether it be in macroscopic subtypes (superficial peritoneal, ovarian, and deep infiltrating endometriosis; propensity for scaring and adhesions), symptom presentation (dysmenorrhea, acyclic pelvic pain, dyspareunia, infertility), and treatment response.

Two topics summarize the new recommendations: 1) a need for our field to thoughtfully and actively determine what data are needed to quantify endometriosis disease burden and to facilitate discovery that takes into account phenotypic variation, and 2) endometriosis must be addressed and consistent data must be collected for research and clinical needs across the life course; in adolescence, pregnancy, and throughout adulthood. Adolescents in particular are an underserved group with high morbidity and social impact, and yet this age is likely the critical window for disease etiologic discovery and intervention (Shah and Missmer 2011). Endometriosis macroscopically appears and behaves differently among patients. However, what patterns and differences are important to target for etiologic discovery, treatment development and ultimately cure - and perhaps prevention - remain unclear. Scientific progress has been limited in part due to small studies and geographic restrictions that make identification of these unique disease groups impossible.

There were no recommendations from the 2011 meeting that are no longer relevant; 2 remain current.

Since the 2011 World Congress to this 2014 consensus meeting, only two epidemiological study papers evaluated outcomes comparing and contrasting subtypes of macro disease presenation of endometriosis. One included superficial peritoneal, ovarian, and deep infiltrating categories. (Reis, Luisi et al. 2012). The other applied the ASRM classification system and the Endometriosis Fertility Index (Zeng, Xu et al. 2014). There was nothing published comparing patients by categories of symptomatology or peritoneal lesion types. There were many publications with "stage" as a keyword; however none evaluated stage by comparing the study outcomes among cases stratified by stage.

Regarding diet, there were seven studies published; they included focus on micronutrients, a gluten-free diet, fish oil, flavonoids, and systemic antioxidant capacity. There were a rich range of methods and expertise: animal models, small human trials, cohort studies (Savaris and do Amaral 2011, Herington, Glore et al. 2012, Marziali, Venza et al. 2012, Rudzitis-Auth, Korbel et al. 2012, Darling, Chavarro et al. 2013, Durak, Kokcu et al. 2013, Harris, Chavarro et al. 2013). In a chimeric mouse model, dietary fish oil supplementation inhibited formation of endometriosis-associated adhesions (Herington, Glore et al. 2012). The cohort studies reported a significantly decreased risk of endometriosis among women who consumed larger quantities of dairy foods rich in vitamin D, calcium, or magnesium (Harris, Chavarro et al. 2013). They also observed a decreased risk with greater vitamin B and C intake, but from food sources, not from supplements (Darling, Chavarro et al. 2013).

Two body mass index (BMI) studies reinforced the robustly observed higher prevalence of endometriosis among lean women (Lafay Pillet, Schneider et al. 2012, Shah, Correia et al. 2013). Overall, those with lean BMI at age 18 (<18.5 kg/m^2) had 20-25% greater risk of endometriosis compared to women with healthy BMI (of 18.5-24.9 kg/m^2), 40% greater than overweight women, and nearly double the risk of morbidly obese women (p-value, test for linear trend <0.0001).

There was little published regarding exploration of other risk factor associations, and no publications regarding underlying etiologic pathways related to these factors.

Finally, with respect to environmental toxins, three studies were published since the last congress (Kvaskoff, Bijon et al. 2013, Upson, De Roos et al. 2013, Wolff, Sun et al. 2013). The study of environmental toxin risk factors was the only topic that included data evaluating

the importance of age at exposure, with studies that included *in utero* exposure, childhood exposure, and exposure during adulthood. Earlier life exposures to toxins may be the critical window for impacting initiation or promotion of endometriosis development, while later life exposures may impact symptom severity or treatment resistance.

New Recommendations:
1. **Recommendation (new):** Facilitate and prioritize collection of country / region-specific endometriosis prevalence data to facilitate calculation of disease burden statistics. This is particularly critical in emerging regions.
2. **Recommendation (new):** Document the social impact of endometriosis using standardised instruments. This is particularly critical for inclusion of adolescents.
3. **Recommendation (new):** Devise standardized questions, or tools, for participant query and medical record abstraction of endometriosis and endometriosis-related symptom data that could validly facilitate adding these data to many large ongoing international cohorts.

Genetics, Epigenetics and Genomics
Genetic and environmental factors contribute to endometriosis risk and the disease is inherited as a complex trait (Montgomery, Nyholt et al. 2008, Rahmioglu, Nyholt et al. 2014). Substantial progress has been made in discovery of genomic regions contributing to endometriosis risk. New genome-wide association (GWA) studies (Albertsen, Chettier et al. 2013), replication studies (Pagliardini, Gentilini et al. 2013, Sundqvist, Xu et al. 2013) and meta-analyses (Nyholt, Low et al. 2012, Rahmioglu, Nyholt et al. 2014) show remarkable consistency in the size and direction of effect for risk variants across studies and across ethnic groups. There are at least six genomic regions showing significant association with endometriosis of any disease stage (Rahmioglu, Nyholt et al. 2014). In addition to these, , association between markers near the interleukin 1A gene (*IL1A*) first reported in Japanese patients was confirmed recently (Hata, Nakaoka et al. 2013, Sapkota, Low et al. 2014).

The combined data show the genetic contribution to endometriosis results from a large number of variants of small effect. Results from the estimated contributions of the known genomic regions (Nyholt, Low et al. 2012, Albertsen, Chettier et al. 2013, Rahmioglu, Nyholt et al. 2014) and the SNP heritability (Lee, Harold et al. 2013) suggest many more variants remain to be identified. Knowing and understanding the effects, of these variants will aid understanding of disease origin and progression, and the identification of biomarkers for disease as well as novel drug targets. To this end, genotyping is being completed in additional case-control samples to conduct new GWA studies and combine results in a large new meta-analysis that will increase the sample size to at least 15,000 cases. This sample size increase will increase power for gene discovery, but is still modest compared with current projects of 50,000 – 100,000 cases in other diseases. In addition, an important objective for future studies is to use genetic approaches to help understand the similarities and differences between different subtypes of endometriosis including peritoneal disease, ovarian endometriomas and deep infiltrating disease. Most of the large samples used for GWA studies lack detailed information on disease subtypes and there is an important need for new large studies where detailed phenotypic data, medical records and genotype data are available for combined epidemiological and genetic studies (Montgomery, Zondervan et al. 2014).

There were no recommendations from the 2011 meeting that are no longer relevant; 2 recommendations remain current.

4. **Recommendation (new):** Establish databases for appropriate samples and clinical information to facilitate future large-scale multi-centre collaborations on genetic contributions to endometriosis.
5. **Recommendation (new)**: Collect large sample sets with appropriate clinical and phenotypic information about endometriosis for future functional studies.

One objective of genetic studies is to identify the specific genes and biological pathways responsible for increasing disease risk. The gene discovery phase only identifies genomic regions associated with disease and the next critical steps are to link the DNA sequence variation to the altered regulation and function of specific genes. Defining these molecular mechanisms for each genomic region is a major challenge (Edwards, Beesley et al. 2013, Montgomery, Zondervan et al. 2014). The general approaches include 'fine mapping' of the association signal in each region with additional genotyping, functional annotation, expression quantitative trait locus (eQTL) studies for target-gene identification using global and local gene expression studies, and evaluation of likely causal SNPs and target genes by genomic and functional studies. Studies would be strengthened if there were comprehensive data available for global regulation of gene expression and epigenetics in relevant reproductive tissues, but these data are not currently available.

There is accumulating evidence that epigenetic mechanisms (that are able to alter the effect of genes without changing the DNA 'code') may play an important role in endometriosis. Most epigenetic-focused studies to date have been investigations of promoter methylation of genes known to be differentially regulated in endometriosis: either silenced (e.g., *p21*, *CDH1*, *PRB*, *HOXA10*, *17HSD2*, aromatase and *ESR1*) or up regulated (e.g., *SF1*)(Wu, Halverson et al. 2005, Wu, Strawn et al. 2006, Wu, Strawn et al. 2007, Bulun, Cheng et al. 2010). Together, these molecular aberrations may sustain the survival and growth of ectopic implants, and explain differences in disease aggressiveness and invasive properties (Smuc, Hevir et al. 2009) (Brosens, Brosens et al. 2012) (Cakmak and Taylor 2010).

While DNA methylation has received considerable attention, little is known about the role of histone modifications in endometriosis. Histone deacetylase inhibitors (HDACi) and other epigenetic modulators are emerging as a class of promising cancer therapeutics (Mai and Altucci 2009, Chen, Hardy et al. 2011). During the last decade, many drugs with HDAC inhibiting action have been shown to induce growth arrest, apoptosis and differentiation of tumor cells (Crisanti, Wallace et al. 2009, Hagelkruys, Sawicka et al. 2011). It was recently shown that different types of lesions vary in the expression of histone deacetylases (HDACs) (Colon-Diaz, Baez-Vega et al. 2012) (Samartzis, Noske et al. 2013), and that tissues (lesions and endometrium) from patients have different levels of H3K9 and H4K16 acetylation compared to control tissues (Monteiro, Colon-Diaz et al. 2014) (Xiaomeng, Ming et al. 2013). Thus, evidence has started to accumulate that endometriotic lesions have a characteristic histone code, and that global H3 and H4 acetylation within promoter regions of candidate genes is differentially modulated in lesions.

More recently, histone methylation has been identified as another potential target for therapy, following the discovery of enzymes that modulate this specific modification of histones, histone methyltransferases (HMTs) and histone de-methyl transferases (HDMTs) (Piekarz and Bates 2009, Spannhoff, Hauser et al. 2009). A growing number of HMTs inhibitors

(HMTi) are undergoing intense research efforts as potential treatments for cancer, based on the observation that these enzymes are at increased levels in various cancer types. It will be of interest to explore this new, promising avenue for targeted treatments of endometriosis. In conclusion, based on the data obtained to date, endometriosis may have an important epigenetic component involving nucleoside and histone modifications; as such, this disease is a good candidate for epigenetic reprogramming through HDACi and HMTi that should be explored further (Wu and Guo 2006, Kawano, Nasu et al. 2011).

6. **Recommendation (new):** Studies should be undertaken on all aspects of epigenetic regulation of endometriosis.

Functional Biology

There were a total of 25 recommendations relating to pathophysiology of endometriosis developed at the 2011 Montpellier consensus conference. The consensus of the participants was that each of these remained relevant and that none had been fully addressed. Among the earlier recommendations, some were updated in 2014 to conform more closely to evolving research opinions. Examples of this include new data emerging about the location of putative progenitor cells as well as studies in models highlighting the inherent 'plasticity' of cells within the endometrium that make likely the existence of cells that may change their identity via mesenchmal/epithelial transition.

7. **Recommendation (updated):** Further research is required into all aspects of endometrial progenitor cell biology, including their origins, their potential to adopt different cell lineages and whether inhibiting the recruitment and differentiation of progenitor cells will limit the progression of endometriosis.

8. **Recommendation (updated):** Research should be directed towards understanding the phenotype of immune cells such as macrophages and mast cells in endometriosis lesions.

9. **Recommendation (new):** There should be investigation of the epithelial-to-mesenchymal transition state, well-characterized in cancer metastasis, which may prove to be informative regarding the invasiveness of endometriosis lesions (Matsuzaki and Darcha 2012, Cousins, Murray et al. 2014, Nakamura, Ono et al. 2015, Proestling, Birner et al. 2015).

Despite the many unchanged recommendations from 2011, it was noted that the literature on endometriosis continues to be compromised by studies that fail to differentiate between the location and type of lesion being studied. It was suggested that reviewers should insist on this information being included before papers are accepted and suggested that WERF EPHect's Surgical Form be utilized for harmonization of data reporting.

Several updated or new recommendations on the functional biology of endometriosis were tabled at the 2014 Sao Paulo workshop, covering animal models, imaging, immune and progenitor cells, peritoneum, and pain. A new mouse model using 'menstrual' uterine tissue from a donor mouse has been developed: insights from this model include the potential for immune cells such as macrophages that are shed into the peritoneal cavity at time of menses persisting in lesions and contributing to the growth of both vascular (angiogenesis) and nerve cells (neurogenesis) within the lesions (Greaves, Cousins et al. 2014). In the last three years there has been a much greater appreciation that macrophages are not the only cell type that has the potential to play an important role in establishment of lesions and development of pain symptoms, as well as a major re-evaluation within the macrophage research community of their phenotypic classification (Noy and Pollard 2014).

10. **Recommendation (new):** Studies focusing on the role of macrophages should consider the contribution from the endometrium (Thiruchelvam, Dransfield et al. 2013) as well as the peritoneum and use new macrophage classification systems (Guilliams, Ginhoux et al. 2014).
11. **Recommendation (new):** Studies on mast cells should be conducted to assess their contribution to development of pain and other symptoms (Kirchhoff, Kaulfuss et al. 2012); building on historical preliminary data (Matsuzaki, Canis et al. 1998).

New insights have been gained from studies on peritoneum highlighting changes in women with chronic pain, even if they do not have active endometriosis (Greaves, Grieve et al. 2014), metabolic changes and a role for TGFbeta (Young, Brown et al. 2014, Young, Brown et al. 2014). These studies will inform future development of non-surgical treatments. The link between pain and pathology has only been possible because of the use of standardised measures of pain intensity (Vitonis, Vincent et al. 2014).
12. **Recommendation (updated):** Studies on the peritoneum should be encouraged and used to complement those on endometriosis lesions. Cell models including mesothelium from the peritoneum of women suffering chronic pain should be used to extend investigations on intact human lesions/peritoneal tissue.

Symptoms

Pain

Very little progress has been made recently in either understanding the mechanisms underlying endometriosis-associated pain or in identifying effective treatment strategies for this symptom. It is now well established in the pain community (amongst both scientists and clinicians) that central changes occur in all chronic pain conditions, and that the nervous system can both modulate pain or may itself be responsible for generating the sensation of pain (Tracey and Bushnell 2009). There is good evidence that these changes also occur in conditions associated with pelvic pain (Kaya, Hermans et al. 2013, Brawn, Morotti et al. 2014, Stratton, Khachikyan et al. 2015) (Kaya, Hermans et al. 2013, Brawn, Morotti et al. 2014) including endometriosis. However, in the majority these studies are descriptive, providing no information on cause and effect nor relating central changes to potential pain generators in the periphery.

A large number of factors have been found to be altered in the pelvises of women with endometriosis when compared to controls (e.g. inflammatory mediators, neoangiogenesis, nerve density, TRPV1 expression), which may plausibly be involved in generating pain (Morotti, Vincent et al. 2014). However, there is little relationship between the magnitude of these alterations and the intensity of the pain experienced.

Two recent studies have demonstrated how by combining information about the structure or function of the nervous system with clinical descriptors and peripheral measures, insights into the mechanisms generating pain can be found. In the first it was shown that levels of cytokines in the peritoneal fluid of women with endometriosis (particularly TNFα) were related to neurophysiological measures of central hyperexcitability in response to painful stimuli (Neziri, Bersinger et al. 2014). In the second, brain volume was investigated in four groups of women: (1) healthy controls, (2) women with chronic pelvic pain (CPP) without endometriosis, (3) women with CPP and endometriosis and (4) women with endometriosis but no associated pain (As-Sanie, Harris et al. 2012). Perhaps unsurprisingly, women with CPP had alterations in gray matter volume consistent with findings in other chronic pain

conditions (May 2011), whether or not they had endometriosis. However, more interestingly, the women with endometriosis but no pain had an increased volume of the peri-aqueductal gray (PAG), a key region of the descending pain modulatory system (DPMS). As the DPMS acts to control the amount of information ascending to the brain from the dorsal horn of the spinal cord, and dysfunction within this system has been proposed as a potential mechanism leading to pain vulnerability (Denk, McMahon et al. 2014), this may be an example of adaptive brain plasticity preventing some women with endometriosis from experiencing pain. Of note, there is now an increased interest in dysmenorrhoea within the pain community (Berkley 2013) since the recent publication of four studies demonstrating long lasting structural and functional changes within the brains of women with dysmenorrhoea (Tu, Niddam et al. 2009, Tu, Niddam et al. 2010, Vincent, Warnaby et al. 2011, Tu, Niddam et al. 2013). Furthermore, dysmenorrhoea was recently reclassified as a chronic pain condition by the International Association for the Study of Pain (IASP) (Baranowski, Abrams et al. 2012).

Endometriosis is unusual in the context of chronic pain conditions, because of the number of different types of pain (e.g. dysmenorrhoea, non-cyclical pelvic pain, dyspareunia, etc.) that can be experienced by any one woman, potentially all with different underlying mechanisms and associations. Moreover, the relative severity of this pain varies between patients and over time. Potentially one of the factors hampering progress in our understanding of endometriosis-associated pain is the use of crude or inadequate measures of pain, that do not account for these differing types of pain, nor for the quality of the pain (stabbing, burning, aching, etc.) or for variation with the menstrual cycle. The use of standardized questionnaires for data collection as proposed by EPHect (Vitonis, Vincent et al. 2014) is expected to help in this respect with regards to mechanistic and biomarker studies. However, for clinical trials the design of a novel patient report outcome measure (PROM) that is meaningful to patients is necessary. IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) have previously defined core outcome measures that should be included in any trials in chronic pain (Turk, Dworkin et al. 2003) and it was proposed a few years ago that these should be adapted for clinical trials in endometriosis-associated pain rather than designing completely new unvalidated measures (Vincent, Kennedy et al. 2010). Any such PROM should include measures of other factors contributing to the pain experience such as psychological state and pain catastrophising as these have also been shown to contribute to perceived quality of life (Tripp, Curtis Nickel et al. 2004, Tripp, Nickel et al. 2006) and success of treatment (Martin, Johnson et al. 2011, Carey, Martin et al. 2014).

Two new animal models have been used to investigate the link between estrogen and pain. Evidence that estrogenic ligands may directly regulate factors such as Slits (Greaves, Collins et al. 2014) and production of inflammatory factors by macrophages (Greaves, Temp et al. 2015) known to regulate nerve cell migration has been obtained using the new mouse model, demonstrating its potential as a platform for basic research and testing of potential therapies to treat endometriosis associated pain using Von Frey and other techniques. A rat model has been developed in which endometrial tissue is transplanted to the gastrocnemius muscle; this has subsequently been used to explore the role of leptin in estrogen-dependent chronic pain (Alvarez, Chen et al. 2012, Alvarez, Bogen et al. 2014, Alvarez, Giudice et al. 2014).

Five recommendations on endometriosis-related pain were unchanged from 2011, while two were either no longer relevant or superseded.

13. **Recommendation (updated):** All studies collecting any form of biological measure (e.g. inflammatory marker, gene expression, nerve density etc) need also to collect detailed pain information rather than a single rating of "generalised pelvic pain intensity" to allow a better understanding of pain mechanisms in endometriosis.

14. **Recommendation (updated):** An endometriosis or female pelvic-pain specific patient report outcome measure (PROM) should be developed to capture the various different types of pain (dysmenorrhoea, dyspareunia, non-cyclical pelvic pain, dyschezia, dysuria etc), their quality (e.g. burning, aching, stabbing) and any cyclicity.
15. **Recommendation (new):** Where possible, endometriosis-associated pain should be phenotyped by its underlying mechanisms (e.g. inflammatory, neuropathic, central, etc.)(Loeser and Treede 2008).
16. **Recommendation (new):** Encourage the use of new rodent models to test existing drugs that may be suitable for repurposing as treatments for inflammation/pain in women with endometriosis.
17. **Recommendation (new):** Engage the leaders of large multinational studies launched recently to evaluate adolescent brain development with biobanking of brain imaging data, to ensure that pain and dysmenorrhea data as well as endometriosis diagnoses are included in their data collection efforts.

In common with other chronic pain conditions, potential novel treatments for endometriosis-associated pain have rarely been successful in early phase clinical trials. One potential explanation for this observation is that the mechanisms generating pain are so variable in this heterogenous population that there will not be a "one size fits all" treatment. The strategy of sensory phenotyping, which has been proposed particularly in neuropathic pain but also applied to other chronic pain conditions, is particularly interesting in this context. This strategy uses the pattern of sensory symptoms and pain qualities derived from the completion of questionnaires and the results of quantitative sensory testing (QST) to classify patients on the basis of the potential site(s) of dysfunction of the pain processing pathways. Detailed analysis of large numbers of patients with neuropathic pain with a variety of aetiologies has shown that it is feasible to subgroup patients with this strategy and moreover, retrospective analysis of clinical trial data has shown the sensory phenotype to predict the response to treatment (Reimer, Helfert et al. 2014). Thus any PROM designed for women with CPP/endometriosis should contain sufficient information to allow such stratification to be performed and to facilitate multi-centre proof of concept studies to confirm that such a strategy is appropriate in endometriosis. It is promising, however, that in other conditions not classically considered as neuropathic pre-operative central measures have been shown to both predict the response to surgery and the development of chronic post-operative pain (Yarnitsky, Crispel et al. 2008, Weissman-Fogel, Granovsky et al. 2009, Gwilym, Oag et al. 2011).

Whilst it is disappointing that endometriosis rarely features on the programmes of specialist pain meetings there is a similarly poor inclusion of pain neuroscience in the majority of Endometriosis or Women's Health conferences. Given that CPP, with or without endometriosis, affects millions of women worldwide inclusion of pain neuroscience more broadly in health and research meetings is essential. Furthermore, many of the topics discussed at the World Congress on Endometriosis in Sao Paolo (e.g. the role of gases such as nitric oxide and hydrogen peroxide in generating pain; neurogenic inflammation; pain genetics; and patient tailored treatment) were also discussed in headache and pain meetings that same year (15th World Congress on Pain, 6-11th October 2014, Buenos Aires, Argentina. 2nd Joint Symposium of IASP/IHS [International Association for the Study of Pain/International Headache Society], 23-26th April 2014, Siena, Italy). Thus it is proposed that the collaboration and sharing of knowledge and experience with pain neuroscientists will be key to unraveling the peripheral and central mechanisms generating the clinical experience of pain in women with endometriosis.

18. **Recommendation (new):** A joint research symposium between pain researchers and endometriosis researchers should be organised to share knowledge, identify areas of overlap, optimise potential collaborations, and avoid "reinventing the wheel".
19. **Recommendation (new):** Research should be undertaken to analyse community attitudes to chronic pelvic pain (CPP) using sociological methods.

Infertility
It is estimated that up to 35-50% of women with infertility have endometriosis (Meuleman, Vandenabeele et al. 2009). Whether endometriosis contributes to infertility has long been debated, and underlying mechanisms resulting from the presence of disease and classified by stage possibly affecting fertility potential are poorly understood, although inflammation and reactive oxygen species are believed to contribute significantly (Gupta, Goldberg et al. 2008, Burney and Giudice 2012). To date, data support abnormal folliculogenesis, including compromised granulosa cell and follicle immune homeostasis, poor oocyte quality and reduced ovarian reserve, lower fertilization rates, altered embryo development and abnormalities in the eutopic endometrium that affect implantation success in a disease stage-specific manner (Garrido, Navarro et al. 2002, Gupta, Goldberg et al. 2008, Aghajanova and Giudice 2011, Shah 2013). There are also consequences of anatomical distortion that may compromise fertility (Gupta, Goldberg et al. 2008), and there are mixed data on pregnancy outcomes in women with disease (Stephansson, Kieler et al. 2009, Brosens, Brosens et al. 2012). Human in vitro fertilization and embryo transfer (IVF-ET) and ovum donor/recipient cycles serve to test hypotheses generated from experimental data obtained in animal models and with human endometrial and endometriosis tissues and cells (Simon, Gutierrez et al. 1994, Pellicer, Oliveira et al. 1995). Overall, studies of various factors contributing to endometriosis-related infertility show conflicting results (Navarro, Garrido et al. 2003). This lack of identified factors underscores the need to have rigorous epidemiologic and clinical data to understand mechanisms underlying effects of endometriosis on female fertility, assess approaches to mitigate these abnormalities for treatment and also for diagnosis and prevention, and understand short-term and long-term effects of endometriosis-related infertility and treatment on the health of affected women and their offspring.
As there were no previous recommendations on infertility associated with endometriosis, herein only new recommendations proposed.

20. **Recommendation (new):** Research is needed to elucidate the causal relation, if one exists, between endometriosis and infertility, taking into account the importance of evaluating the relation between pelvic pain and infertility, independent of endometriosis.
21. **Recommendation (new):** Determine the relative contribution of anatomic versus non-anatomic endometriosis associated lesions, including the role of adhesions, to infertility in general and embryo implantation rates in particular.
22. **Recommendations (new):** Develop validated screening tools including clinical history and physical examination to reduce the number of patients treated by laparoscopy, so that when laparoscopy is used for endometriosis-related infertility, it is used effectively.

Oocyte competence, folliculogenesis, embryo quality and development
Several studies strongly support the view that oocytes from women with endometriosis have reduced competence. The pro-inflammatory environment in which the oocyte matures likely affects its developmental potential, and several animal studies support this view (Mansour, Sharma et al. 2010). Clinical IVF studies that have assessed fertilization rates, embryo

quality, and implantation rates with oocytes from women with endometriosis have either not found significant differences (Suzuki, Izumi et al. 2005, Matalliotakis, Cakmak et al. 2007) or have found significantly decreased oocyte competence (Simon, Gutierrez et al. 1994). Reduced oocyte competence results in early embryonic growth arrest (Yanushpolsky, Best et al. 1998) and reduced embryo quality and implantation rates (Kumbak, Kahraman et al. 2008). A retrospective meta-analysis of IVF outcomes in endometriosis patients has highlighted a progressive decrease in oocyte quality with increasing stage of disease (Barnhart, Dunsmoor-Su et al. 2002), and more compromised oocyte quality in women with endometriomas (Suzuki, Izumi et al. 2005). Also, the latter sub-type have lower ovarian reserve that can translate to lower oocyte quality/competence.

23. **Recommendation (new):** Investigate the effects of endometriosis on folliculogenesis, oocyte competence and subsequent fertilization and embryo quality. Studies should include detailed information on endometriosis stage and involvement of the ovaries with disease.

24. **Recommendation (new):** Investigate the mechanisms underlying diminished ovarian reserve in women with endometriosis, the degree to which this is spontaneous or due to surgical intervention, and determine how much of the observed diminished ovarian reserve is reversible.

Endometrial abnormalities and pregnancy outcomes

There are abundant data to suggest that the endometrium of women with endometriosis demonstrates abnormalities in gene expression, global transcriptome, signalling pathways, in response to steroid hormones, and having a pro-inflammatory environment (Aghajanova, Velarde et al. 2010, May, Villar et al. 2011, Lessey, Lebovic et al. 2013). Only a few studies have looked at the influence of disease stage (Aghajanova, Velarde et al. 2010) or considered other uterine and pelvic abnormalities as confounders (Tamaresis, Irwin et al. 2014). To date women with more advanced compared to early stage disease have more difficulty conceiving, (D'Hooghe, Debrock et al. 2003), significantly lower implantation rates (13.7% vs. 28.3%, respectively; p<0.05) and pregnancy rates (22.6% vs. 40.0%, respectively; p<0.01), but not fertilization or miscarriage rates (Kuivasaari, Hippelainen et al. 2005), and significantly lower IVF pregnancy rates (13.84% vs. 21.12% respectively; p<0.001) (Barnhart, Dunsmoor-Su et al. 2002), underscoring a potential endometrial origin of these differences. Also, subjects with advanced disease demonstrate diminished ovarian response and higher cancellation rates in IVF cycles, but after surgery show improved implantation, pregnancy, miscarriage, and delivery rates, similar to those of women with tubal factor infertility (Matalliotakis, Cakmak et al. 2007), suggesting that removal of disease improves endometrial receptivity to embryonic implantation.

25. **Recommendation (updated):** There is a need for reliable and comprehensive epidemiologic data on pregnancy outcomes in women who have endometriosis who become pregnant naturally, by infertility therapy and assisted reproduction.

26. **Recommendations (new):** Data on clinical outcome after infertility treatment, whichever type, medical, surgical, expectant, should be collected with time to pregnancy as a key important event, using life table analysis and cumulative pregnancy rates at the expected level of quality in any fertility trial

27. **Recommendations (new):** Capture a history of endometriosis (stage, treatment to achieve pregnancy if relevant) in obstetrical records, working with professional organisations to promote the inclusion of endometriosis as a diagnosis in the obstetrical record.

Pain and optimal fertility therapies for women with endometriosis, disease status

An unmet need was identified to assess pain during fertility treatment and management of pain, including safety, efficacy, and effects on quality of life.

28. **Recommendations (new):** There is a need to determine whether women with endometriosis experience pain during infertility therapy, and if they do, whether it is exacerbated by fertility treatment, and if/how the pain affects both quality of life and fertility. There is also a need to determine if treatments for pain during fertility therapy are safe and efficacious, and whether they alter the efficacy of fertility treatments.

Patient perspectives

While previous research priorities workshops in 2008 and 2011 included consumer representatives, there were no recommendations specifically formulated towards research either into, or driven by, patient perspectives. The 2014 workshop sought to remedy this and agreed that future workshops should continue to include a session on the perspectives of women with endometriosis. A number of new recommendations were developed.

29. **Recommendation (updated):** Patient views on the most pressing topics in endometriosis research and clinical priorities should be sought and subcategorized into different demographic groups including age, symptoms, ethnicity, and economic background.

30. **Recommendation (new):** Research should be undertaken on how treatment costs, including for IVF, impact on the patients' decisions around diagnosis and treatment.

31. **Recommendation (new):** In both developed and emerging countries, adolescent beliefs about not having periods and about the use of contraceptives when they are not sexually active should be explored. The need for improved education programmes and/or patient support organisations should be quantified, particularly in emerging countries.

Diagnosis, Classification and Prognosis

Surgery
Diagnostic surgery for endometriosis
The clinical utility of the rASRM classification system (1997) for endometriosis-related infertility, pain and deep infiltrating endometriosis is limited. A surgical classification system for endometriosis-associated infertility (Adamson and Pasta 2010) has been developed and its clinical prognostic usefulness validated in independent trials. Classification systems for deep infiltrating endometriosis are also being developed and validated (AAGL and ENZIAN).

The meeting recognized the need for improved education and training to increase uptake of minimally invasive diagnostic imaging technologies. Preoperative imaging will reduce the likelihood of laparoscopic procedures which have to be abandoned because of unexpectedly severe disease. In the future, symptomatic women who have been diagnosed preoperatively with moderate to severe disease by imaging modalities should be offered excisional surgery as a first line treatment. If imaging studies reveal no obvious signs of endometriosis then "see and treat" surgery should be considered for women with pain or infertility who are refractory to non-surgical therapies.

Diagnostic imaging modalities allow for better pre-operative planning and counselling for patients scheduled to undergo excisional surgery for deep endometriosis reducing both the morbidity and treatment cost of endometriosis (Exacoustos, Manganaro et al. 2014). Reduced reliance on diagnostic and 'staging' surgery and improved education about, and access to

endometriosis-specific ultrasonographic and magnetic resonance imaging techniques is desirable (Piessens, Healey et al. 2014). However, diagnostic surgery is still relevant for superficial and/or mild peritoneal disease which remains difficult to detect using imaging modalities alone in symptomatic women (Dunselman, Vermeulen et al. 2014)

Controversy also remains in young women, who are likely to have mild disease, as to the need for a surgically defined diagnosis when treating pain symptoms (Brosens, Gordts et al. 2013). It was acknowledged that imaging techniques, such as TVUS, may be inappropriate and less able to detect disease in this group (Reese, Reddy et al. 1996). For this reason, it is still recommended that adolescents who have failed hormonal and pain therapies be offered surgery to establish a diagnosis as more than two-thirds will likely have disease (Laufer, Goitein et al. 1997, Janssen, Rijkers et al. 2013).

> **32. Recommendation (new):** The development, validation, and implementation of new endometriosis classification systems should continue.

Recommendation (new): For patients at low risk of deep endometriosis, efforts should be made to improve and evaluate the development of low cost advanced diagnostic surgical techniques (e.g., single port entry and NOTES methods) in centers with high training and accreditation standards.

Imaging

Different imaging modalities play an essential role in the diagnosis and perioperative treatment of endometriosis. While operator experience, as well as lack of sensitivity to detect minimal and mild endometriosis can be problematic, ovarian endometriosis (endometrioma) and deep endometriosis can be readily recognized using transvaginal ultrasound and/or magnetic resonance imaging (MRI). Diagnostic test accuracy studies and meta-analyses have been performed and show that transvaginal ultrasound and MRI techniques can diagnose endometriomas, rectosigmoid, and deep infiltrating endometriosis with a similar sensitivity and specificity to that of surgery.

At the 2011 meeting it was recognised that technological advances in imaging were evolving rapidly and that consequently imaging techniques should be monitored on an ongoing basis for application to endometriosis. This recommendation was updated in 2014.

There have been significant advances in MRI and imaging related to pain since the 2011 meeting. Recent work in an animal model to detect endometriosis non-invasively using Dynamic Contrast-Enhanced MRI (DCE-MRI) with gadofosveset-trisodium as a contrast agent (Schreinemacher, Backes et al. 2012) found that contrast enhanced MRI gave better visualisation than conventional MRI. MRI, including diffusion tensor imaging (DTI) DTI with tractography is a non-invasive means of detecting changes in the microarchitecture of the sacral nerve roots. MRI is increasingly used for endometriosis and chronic pelvic pain (CPP), and tractography can be used to show altered microstructure of sacral roots affected by endometriosis and CPP (Manganaro, Porpora et al. 2014).

It is now possible under certain circumstances to image nerves and alterations in nerve properties non-invasively, to image receptor level expression and inflammatory processes in injured tissue, to image astrocyte and glial roles in neuroinflammatory processes, and to image pain conduction functionally in the trigeminal ganglion (Linnman and Borsook 2013). These advances will ultimately allow description of the pain pathway from injury site to behavioural consequence in a quantitative manner. Such a development could lead to

diagnostics determining the source of pain (peripheral or central), objective monitoring of treatment progression, and, hopefully, objective biomarkers of pain. (Linnman and Borsook 2013)

32. **Recommendation (updated):** More research is needed with emerging imaging modalities to define whether or not they are suitable for identifying lesions and peripheral pain pathways.
33. **Recommendation (new):** To undertake longitudinal studies based just on imaging techniques to track the course of the disease and determine which patients ultimately require surgery.
34. **Recommendation (new):** To investigate clinical outcomes in patients randomised to surgical versus non-surgical treatment based on diagnostic imaging.
35. **Recommendation (new):** To develop a validated screening tool based on history and physical examination to identify women who should undergo imaging, particularly for adolescents and early stage lesions.
36. **Recommendation (new):** Prospective studies should be undertaken that can define changes in clinical practice and any resulting cost savings when diagnostic imaging tests are introduced into clinical algorithms.
37. **Recommendation (new):** More high quality diagnostic test accuracy (DTA) studies based on Quality Assessment of Diagnostic Accuracy Studies (QUADAS) to ensure accurate assessment of the best diagnostic imaging modalities.

Biomarkers

Of the two recommendations from 2011 concerning biomarkers, both were considered still relevant and not in need of updating. In addition, a number of new recommendations were put forward. There was emphasis placed on the need for the discovery of new biomarkers to assist with diagnosis and classification of endometriosis.

Laparoscopic identification coupled with histological verification is currently the gold standard for diagnosis of endometriotic lesions (Dunselman, Vermeulen et al. 2014). Benefits of this approach include the simultaneous treatment of the condition and reassurance for both patient and clinician. However, as various medical treatments are often similarly successful, but associated with side-effects and surgery whilst being effective in some cases is still associated with the risk of morbidity and mortality, the availability of robust biomarkers to aid clinical decision-making continues to be a central unmet clinical need.

Two systematic reviews using well-defined Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria summarized the results from existing biomarker studies (May, Conduit-Hulbert et al. 2010, May, Villar et al. 2011). The authors included 343 studies conducted since January 1984 on biomarkers in peripheral blood, saliva and urine as well as eutopic endometrium. Despite an abundance of potential candidates, no biomarker was found to be suitable for clinical application (Dunselman, Vermeulen et al. 2014). Almost all studies were underpowered, had significant methodological issues or demonstrated a poor choice of control subjects. In addition, in some cases different studies investigating the same marker demonstrated opposing findings, largely a result of factors such as the heterogeneity of the disease, patients and controls, different collection and processing techniques of biological samples, and non-standardized assessment of clinical data. Many of these standardization issues have been addressed by the recent EPHect publications (Becker, Laufer et al. 2014, Fassbender, Rahmioglu et al. 2014, Rahmioglu, Fassbender et al. 2014, Vitonis, Vincent et al. 2014).

A paper published in the pre-WERF EPHect era tested a panel of 28 biomarkers identified from the literature in 232 women with endometriosis and 121 control women (Vodolazkaia, El-Aalamat et al. 2012). A strength of this study is that the findings from a training set were then validated with the test set. A lack of validation studies was one of the main points of criticism of all the other existing studies.

38. **Recommendation (new):** Large databases from collaborative efforts using harmonized and robust sample and data collection tools such as described in WERF EPHect are needed to help identify and validate the bio-phenome of endometriosis.

39. **Recommendation (new):** Multi-centre studies of the bio-phenome should incorporate well-selected control populations including women with other pelvic diseases to achieve a high sensitivity and specificity and should focus on both discovery and validation phases.

40. **Recommendation (updated):** Efforts should be made to combine non-invasive biomarkers, imaging and clinical characteristics to improve diagnostic test accuracy.

It is important to emphasize the lack of data on endometriosis in adolescent girls. It has been recognized that the condition and associated symptoms are present in this age group, but that the few existing studies involve small numbers of patients, which make it impossible at present to draw any reliable clinical conclusions (Brosens, Gordts et al. 2013). Therefore, a research focus on adolescent girls with symptoms suggestive of endometriosis is urgently needed. One such clinical observation that may point to early onset endometriosis is neonatal uterine bleeding detected in 5% of neonatal girls around day 4. This withdrawal bleed resulting from maternal hormone withdrawal may be refluxed into the pelvic cavity due to the functional occlusion of the long neonatal cervix. Endometrial stem cells so delivered may remain dormant until menarche where they become activated to initiate growth of endometriosis lesions (Gargett et al 2014). Although some 10 years will be required to collect this data prospectively, it will determine if neonatal menstruation is a risk factor and potential biomarker for adolescent disease (Brosens et al 2015).

41. **Recommendation (new):** In addition to adolescents and women with pain symptoms, emphasis should be put on biomarker studies in adolescents and women with sub-fertility.

42. **Recommendation (new):** Systematic registration of neonatal menstruation should be encouraged in maternity services as a potential biomarker of early onset endometriosis.

Accumulating evidence demonstrates that genetic factors play a role in endometriosis (see above). Genome-wide association studies have identified single nuclear polymorphisms (SNPs) linked to increased risk of endometriosis at a number of genetic loci in women, especially in those with extensive disease (Uno, Zembutsu et al. 2010, Painter, Anderson et al. 2011, Nyholt, Low et al. 2012, Albertsen, Chettier et al. 2013, Rahmioglu, Nyholt et al. 2014). Increasing progress in laboratory techniques and network analysis now allow for large-scale functional, multiplex studies combining results from different approaches, which may not only advance our understanding of disease pathogenesis mechanisms, but also identifying novel target candidates for diagnosis and treatment.

43. **Recommendation (new):** Results from large scale genetic studies should be followed-up by functional multiplex biomarker studies.

Disease and Symptom Management

Surgery

There has been significant progress made on surgery-related recommendations formulated at the 2008 Research Directions Workshop (Rogers, D'Hooghe et al. 2009), as summarized in the following two paragraphs.

Combined surgery and ovarian suppression results in better outcomes in pain patients (Brown and Farquhar 2014). Laparoscopic surgery to treat mild and moderate endometriosis reduces overall pain and increases live birth or ongoing pregnancy rates. There is low quality evidence that laparoscopic excision and ablation were similarly effective in relieving pain, although there was only one relevant study (Duffy, Arambage et al. 2014). Reasonable data have demonstrated that laparoscopic treatment has adverse outcomes no worse than other surgical interventions. Shaving, disc resection and bowel resection all have a role in management of bowel endometriosis, but further elucidation of their application is needed (Abrao, Petraglia et al. 2015).

The Endometriosis Fertility Index (EFI) (Adamson and Pasta 2010) has been validated as a useful clinical tool in 10 additional published studies. Excisional surgery improves spontaneous pregnancy rates in the nine to 12 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone (Brown and Farquhar 2014). Ovarian reserve may be reduced with treatment of endometriomas, but its clinical significance is variable (Muzii, Di Tucci et al. 2014, Georgievska, Sapunov et al. 2015).

There were five major recommendations relating to surgery from the 2011 workshop (Rogers, D'Hooghe et al. 2013), and all of these still remain relevant. In addition, two new recommendations have been made in 2014. Perhaps the most important of these arise from the recognition that no classification system predicts pelvic pain outcomes following surgery (Brown and Farquhar 2014).

44. **Recommendation (new):** Principles utilized in development of the EFI (Adamson and Pasta 2010) should be utilized in development of a classification system for management of pelvic pain.

45. **Recommendation (new):** The optimal application of surgery and specific surgical techniques, including energy techniques, need to be elucidated for endometrioma, bowel, bladder, ureter and deep infiltrating endometriosis. Short and long term outcomes, including efficacy related to symptoms of infertility and pain, cost and safety, need to be evaluated against non-surgical techniques such as ovarian suppression, mind/body approaches, ART and other medical and holistic interventions. This will provide information to develop improved comprehensive management approaches over time.

Medication
Disappointingly, there has been little research progress in medical management for endometriosis over the last three years due to the typically poor quality of the trials in this field. In March 2014, Brown and Farquhar published a summary of the evidence from Cochrane systematic reviews on treatment options for women with pain (or subfertility) associated with endometriosis (Brown and Farquhar 2014). They noted that the quality of the trials for specific comparisons ranged from 'very low' to 'moderate'. The main reason identified for the poor trial quality was bias: inadequate reporting of allocation concealment and randomisation methods, and a lack of blinding.

46. **Recommendation (updated):** There is a need for more well designed, adequately powered, multi-center randomized controlled trials, and long-term follow-up studies comparing different endometriosis treatment options ideally against placebo and against defined outcome measures.

Although there were 31 'open' (recruiting, or about to start) relevant trials at the time of the Sao Paulo meeting addressing treatment efficacy of endometriosis registered on ClinicalTrials.gov and the EU Clinical Trials Register, only one trial (PRE-EMPT http://www.controlled-trials.com/ISRCTN97865475) directly addresses a 2011 recommendation. This trial aims to determine whether effective medical adjuvant therapies exist to prevent or limit the recurrence of lesions and symptoms following surgery.

As a consequence of the overall lack of progress in clinical trials, most recommendations from 2011 remain substantially unchanged, although a number have been updated.

The precise mechanisms by which endometriosis causes pain are not completely understood (see above). However, there is increasing evidence that pain may be due to neuropathic, in addition to nociceptive and inflammatory, mechanisms (Stratton and Berkley 2011). The efficacy of neuromodulatory drugs has been documented for a number of neuropathic pain conditions (Moore, Derry et al. 2012, Wiffen, Derry et al. 2013), but not for endometriosis-associated pain specifically. In some of these trials, neuromodulators also improved sleep, mood and other elements of quality of life.

47. **Recommendation (updated):** Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including neuromodulatory drugs used in the treatment of other chronic pain conditions.

Current treatment strategies for endometriosis are restricted to surgical excision of the lesions or suppression of ovarian function and estrogen action. In up to 75% of cases, symptoms recur after surgery, and long-term ovarian suppression is often ineffective, suppresses fertility and has unwelcome side effects (Giudice 2010). What women with endometriosis want is a therapy that can (i) reduce the painful symptoms associated with the condition (ii) preserve their ability to conceive whilst on medication, and (iii) have no, or limited, side effects. There is therefore an unmet clinical need for new non-hormonal treatments for endometriosis.

48. **Recommendation (updated):** Novel non-hormonal medical treatments for endometriosis should be investigated.

The incorporation of genomic profiling into routine clinical practice has already been adopted for some tumours, such as human epidermal growth factor receptor 2 (HER2) testing in breast cancer, providing a guide to treatment selection that is not afforded by histological diagnosis alone (Slamon, Leyland-Jones et al. 2001). There is also increasing consensus that clinical trials should be more stratified for, or be performed only, in similarly 'molecularly defined' subsets to avoid overtreatment and to save valuable resources (Deley, Ballman et al. 2012). This approach results in smaller numbers of more phenotypically and genotypically well-defined patients being eligible for such trials.

49. **Recommendation (new):** We need to transform our clinical study design to integrate genomic profiling for patient stratification.

Other therapies
There were no formal recommendations concerning complementary and alternative medicine (CAM) from the 2011 workshop, although it was noted that Chinese herbal medicine (CHM)

was widely used in China to treat symptoms of endometriosis such as pain and infertility, and that more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis (Zhu, Hamilton et al. 2011, Flower, Liu et al. 2012). CAM therapies utilized by patients with endometriosis include herbs, acupuncture, CHM enema, microwave physiotherapy, and psychological intervention (Hou, Chen et al. 2014). The same authors state that although CAM therapies have been gradually accepted in some countries, a range of issues hinders more widespread application of CAM therapies throughout the world. These include: (1) selective publication of only positive results with varying study qualities and standards, (2) lack of large-sample sizes and randomized controlled trials, (3) the lack of confirmatory animal studies with therapies such as auricular acupoint, Chinese herbal enema, microwave physiotherapy, and psychological intervention (Hou, Chen et al. 2014).

50. **Recommendation (new):** There should be more research, including pre-clinical animal studies and randomized controlled trials, into the effectiveness of complementary and alternative medicines, compared to conventional therapies, for the treatment of endometriosis. These studies should include decreasing pain as well as enhancing fertility, pregnancy outcomes and safety.

Diet and nutrition continue to be issues that women seek advice on when confronted with endometriosis. Clinical experience from practitioners present at the workshop noted that if women do modify their diet, it is often by trial and error to work out what their own triggers are. Some will find a beneficial effect on their pain levels, but consensus on what works is not common. A similar lack of clear findings about diet and endometriosis risk is also found in the published literature, where evidence supporting a significant association between diet and endometriosis is at best equivocal (Parazzini, Vigano et al. 2013). Women with endometriosis seem to consume fewer vegetables and omega-3 polyunsaturated fatty acids and more red meat, coffee and trans fats but these findings could not be consistently replicated (Parazzini, Vigano et al. 2013). Others have concluded that specific types of dietary fats are associated with endometriosis and/or dysmenorrhoea, thereby indicating that there may be modifiable risk factors (Hansen and Knudsen 2013). However, findings were equivocal and further research was recommended. There has also been a meta-analysis that found no evidence for an association between coffee/caffeine consumption and the risk of endometriosis (Chiaffarino, Bravi et al. 2014).

51. **Recommendation (updated):** Randomized controlled trials are needed to elucidate the role of diet in modifying recorded symptoms and underlying disease of endometriosis.

Patient stratification
A number of recommendations from 2011 had some relationship to patient stratification, nearly all of which remain unchanged in this context. Patient stratification or personalized medicine is a novel concept in endometriosis. A PubMed search on 4 May 2014, using the key words "endometriosis AND patient stratification", identified only 13 papers, with just one linking patient stratification to outcome (Beste, Pfaffle-Doyle et al. 2014). These authors reported on a clinically relevant inflammatory network that may serve as an objective measure for guiding treatment decisions for endometriosis management, and in the future may provide a mechanistic endpoint for assessing efficacy of new agents aimed at curtailing inflammatory mechanisms that drive disease progression.

Patient stratification is an active area of research in gynecological cancer and chronic inflammatory conditions that are common in women, especially in breast and ovarian cancer, but also in rheumatoid arthritis and Crohn's disease. It is important to try to apply insights

from patient stratification in these related diseases to patient stratification for endometriosis. A systematic review approach is warranted to stratify predefined outcomes in endometriosis research with family history, symptoms, clinical exam, dynamic imaging/pain reporting, surgical staging, and systemic or tissue biomarkers.

Standardised baseline characteristics should be reported in clinical trials evaluating reproductive outcome in women with endometriosis, specifying completed child wish (proven fertility), absent child wish, or present child wish (active child wish at present, active child wish in the future, infertile (inability to become pregnant during the last 12 months)) (Meuleman, Tomassetti et al. 2011, Meuleman, Tomassetti et al. 2011, Meuleman, Tomassetti et al. 2014).

52. **Recommendation (new):** To stratify reproductive outcome in women with endometriosis-associated infertility according to their true reproductive status and plans.

The phenotype of each patient needs to be determined and harmonized on the level of clinical symptoms, signs during clinical examination, imaging and surgical staging. The WERF EPHect tools allow for standardized (consistent) collection of clinical symptoms and surgical findings in the context of biomarker studies (Becker, Laufer et al. 2014, Vitonis, Vincent et al. 2014), but harmonization is also needed with respect to definitions and reporting of data related to clinical exam and imaging, in order to relate these data (ie: ovarian mass, adhesions, deep nodules, other pathology, presence/absence of pain in specific areas during exam, co-existing morbidities like adenomyosis and fibroids) to surgical data.

53. **Recommendation (new):** To stratify clinical outcome data in medical or surgical therapeutic trials for endometriosis-associated pain and/or infertility according to predefined clinical symptoms, signs, imaging and surgical staging.

The concept of recurrence is used differently by different authors in different studies, due to the lack of a universally accepted definition which can be used in clinical research (Meuleman, Tomassetti et al. 2012, Meuleman, Tomassetti et al. 2014).

54. **Recommendation (new):** To seek agreement on the definition of recurrence of endometriosis and endometriosis-associated symptoms after medical or surgical treatment.

Low income countries and low resource settings
Previous endometriosis research priorities workshops have not considered research in low income countries and low resource settings.

55. **Recommendation (new):** The Workshop on Research Priorities in Endometriosis should include statements addressing the needs of low resource settings.

Over 2 billion people live in severe poverty (World Bank data: 2.2 billion people lived on less than US $2 a day in 2011). The different approaches required in low resource settings dictate that researchers appropriately consider the needs of the tens of millions of women in these situations. Challenges regarding culturally sensitive distribution of information, effective implementation of programs, the role of centers of excellence, private vs. public initiatives/collaborations and organizational collaborations, play a critical role in developing successful interventions and research programs in low resource settings. With the trend of delayed child bearing in developing countries following similar patterns as has occurred in developed countries (Eltigani 2001), it is expected that endometriosis prevalence will rise. However, in many developing countries there is a lack of awareness of endometriosis among

doctors, patients, and families, and there is a huge lag between developing and developed countries regarding endometriosis research and centres of excellence for endoscopic surgery.

56. **Recommendation (new):** Research programs run by developing nations, targeting endometriosis-related issues specific to those nations, should be implemented.

57. **Recommendation (new):** Researchers working in developed nations should ensure that progress resulting from endometriosis research will, where possible, be of benefit in low resource settings.

58. **Recommendation (new):** Programs and projects that provide international support and enhance regional collaboration in low resource settings should be implemented, involving both health care professionals and patient organizations.

59. **Recommendation (new):** We should encourage centres of excellence in developed countries to take more active role in training and supporting research program in centres dealing with endometriosis in low income countries and this should be part of their accreditation process.

There are almost no data on diagnosis and classification of endometriosis in low resource settings. There has been no organized approach to obtaining such data. An endometriosis management program involving history, physical examination, testing and management that is culturally-appropriate and cost-effective and that can be used in low resource settings needs to be developed and taken to the World Health Organization (WHO) to engage them and through them health departments in the governments of the world to bring endometriosis diagnosis and treatment into their primary and secondary healthcare systems.

60. **Recommendation (new):** Innovative approaches and tools such as WERF EPHect, The FIGO Fertility Toolbox™, the International Committee Monitoring ART registry and Low-cost IVF should be evaluated for their possible contributions to endometriosis research in low resource settings.

In very low resource settings, effective family and social support may be the most important intervention to reduce the burden of disease, and is applicable in any setting.

61. **Recommendation (new):** Research into culturally appropriate and cost-effective social support systems that mitigate the personal impact of endometriosis in low resource settings should be performed.

Research Policy

Prioritisation and collaboration
At the 2011 Research Directions Workshop in Montpellier, 14 different recommendations were made under the overall banner of research policy. Of these, significant progress has been made on several, with the most obvious being the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect). This global initiative involving 34 clinical/academic and three industrial collaborators from 16 countries, developed consensus on standardization and harmonization of phenotypic surgical/clinical data and biological sample collection methods in endometriosis research. To facilitate large-scale internationally collaborative, longitudinal, epidemiologically robust, translational, biomarker and treatment target discovery research in endometriosis, WERF EPHect provides evidence-based guidelines on: [1] detailed surgical, clinical, and epidemiological phenotyping (phenome) data to be collected from women with and without endometriosis to allow collaborative sub-phenotype discovery and validation analyses; and [2] standard operating procedures (SOPs) for collection, processing, and long-term storage of biological samples from women with and without endometriosis (Becker,

Laufer et al. 2014, Fassbender, Rahmioglu et al. 2014, Rahmioglu, Fassbender et al. 2014, Vitonis, Vincent et al. 2014).

Other recommendations from 2011, such as submission of genetic and genomic data into online repositories so as to be available for all researchers, are covered by the requirement from most international peer-reviewed journals that this is a prerequisite prior to publication. Some recommendations remain unchanged and were reinforced in 2014, the most notable being the need for a multi-disciplinary, and where appropriate, multi-centre approach to all aspects of endometriosis research.

There were 2 new recommendations under the heading of research prioritization.
62. **Recommendation (new):** As a priority, we should undertake multi-disciplinary research aimed at producing translatable patient-based outcomes, with a particular focus on pain and infertility.
63. **Recommendation (new):** WERF should consider forming a clinical trials advisory group to provide feedback to assist researchers in developing high quality studies that are appropriately designed and powered to achieve meaningful outcomes.

Funding strategies
There were three recommendations from 2011 concerning lobbying and funding. All of these were deemed as relevant in 2014 as they were in 2011. With the global funding for research becoming more and more competitive, it has become increasingly challenging to secure funds for research in endometriosis, which despite its huge personal and healthcare cost is classified as a "benign" disease. Endometriosis, however, is not benign for those who may suffer for decades with harsh and enduring impacts on their lives (Nnoaham, Hummelshoj et al. 2011), a neither is it benign when taking into consideration the personal and societal costs (Simoens, Dunselman et al. 2012).

Funding sources can be divided into 3 broad categories: government, philanthropic, and industry. To successfully secure funding from any of these sources, it is necessary to position endometriosis as a disease priority, and commence strategic lobbying to ensure its place in national health care and research budgets. Specific funding asks (i.e., for research initiatives) may aid this process in raising awareness about the disease. To obtain philanthropic funding, endometriosis must have its profile raised through high profile awareness campaigns, as well as targeted proposals to wealthy individuals who have the means to support women's health initiatives, and who may have a vested interest in supporting the eradication of a disease that may have impacted family and friends.

To ensure ongoing industry collaboration and financial support for investment in research into endometriosis disease mechanisms and improved treatments, convincing arguments must be collectively put forward to pharma to assist them in the process of internal prioritisation of specific disease investment. A disease affecting an estimated 176 million women worldwide (Adamson, Kennedy et al. 2010), which is not caused by preventive lifestyle factors, should provide tremendous potential for wider industry investment.

It is crucial that there is one, clear message from a large collective group of global collaborators of what needs to be done, how it will be done, and where money needs to be invested to make the goal of targeted treatments and prevention of endometriosis a reality.
64. **Recommendation (new):** Develop lobbying and fundraising resources suitable to take to government, industry and philanthropy that highlight the social and economic

cost of endometriosis, as well as the need for research to improve outcomes for women with this disease.

Lobbying resources could include regularly updated fact sheets suitable for inclusion in letters to government, online resources, and videos where women and families speak about the disease and how it has affected their lives. Successful patient advocacy groups from other diseases such as breast cancer and diabetes may be able to provide guidance and examples of approaches that have been successful in the past. The meeting noted that WERF and WES may be appropriate bodies to develop and regularly update a portfolio of suitable facts and figures for groups to use in lobbying.

Discussion
The research recommendations developed by the 2014 consensus workshop provide important new insights into the evolving challenges facing endometriosis researchers, practitioners and patients. New areas included in these recommendations include infertility, patient stratification, epigenetics, and research in emerging countries. Patient symptoms relating to pain and infertility are the two areas with the most new recommendations, followed by diagnosis under headings such as imaging, biomarkers and diagnostic surgery. This shift to more translational research priorities reflects a broader focus by government funding agencies, and society in general, towards translational research. There is also a recognition of the need to involve and harness research insights in disciplines that intersect with endometriosis (e.g., pain neuroscience) and the need to broaden multidisciplinary approaches to understanding and treating endometriosis.

It is interesting to follow the evolution of research priorities from the 2008 and 2011 workshops (Rogers, D'Hooghe et al. 2009, Rogers, D'Hooghe et al. 2013) to present. In 2008, several of the research recommendations centred around the recognition that multidisciplinary approaches were needed, and that individual silos of expertise could only make limited progress. In 2011, by far the majority of recommendations were around functional biology and disease mechanisms, although a significant advance was the recognition of the need for more research into all aspects of endometriosis associated pain. A key theme for 2014 has been translation to better patient outcomes.

This 2014 research priorities consensus statement builds on earlier efforts to develop research directions in endometriosis. Forty one of the 56 recommendations from 2011 remain current. Despite this, significant progress has been made by the international research community, with more than 2,500 new scientific papers listed on PubMed between the 2011 and 2014 workshops. Of note, and directly emanating from recommendations at the 2011 workshop are the publications from the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) (Becker, Laufer et al. 2014, Fassbender, Rahmioglu et al. 2014, Rahmioglu, Fassbender et al. 2014, Vitonis, Vincent et al. 2014). Lack of progress in other research areas may reflect the complexities of problems to be addressed, as well as the relatively slow pace of research and limited funding globally.

It is the hope of the workshop organizers and participants that this international consensus document will be a useful tool in aiding researchers to develop new and relevant research proposals and obtain increased funding support. The recommendations also provide a document to assist in the ongoing lobbying effort for increased research funding for endometriosis research from government, industry and philanthropy. This is particularly

important in procuring funding from non-traditional sources to support research in domains that intersect with endometriosis, such as pain.

Combining the 41 recommendations that are unchanged from 2011 with the 65 new ones from 2014 gives a total of 106 current endometriosis research recommendations. A task for the participants of the next endometriosis research priorities workshop to be held at the 13th World Congress on Endometriosis from 17-20 May 2017, in Vancouver, Canada will be to consolidate and prioritise these 106 recommendations, as part of developing a revised and updated set of research priorities.

THE COMPLETE ALPHABETICAL LIST REPRESENTING THE WES/WERF CONSORTIUM FOR RESEARCH PRIORITIES IN ENDOMETRIOSIS

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DISCLOSURES

G.D.A. is the owner of Advanced Reproductive Care, Inc. and Ziva, and is a consultant to Bayer Pharma and AbbVie. H.A. is employed by Juneau Biosciences LLC and has direct financial interest in Juneau Biosciences. M.A-J. has nothing to disclose. C.A. is a consultant to AbbVie, Actavis, and Bayer Pharma. J.A. has nothing to disclose. Y.A. DISCLOSURE. M.B. has nothing to disclose. C.M.B. holds a research grant from Bayer Healthcare. M.A.B. has nothing to disclose. C.C-J. has nothing to disclose. S.C.F. DISCLOSURE. K.C. is an employee of AbbVie in which he holds stock and stock options. H.C. has received travel support from AbbVie, Bayer Pharma, Gedeon Richter, Preglem and Vifor Pharma, and holds research grants from Bayer Pharma and Preglem. M.F.F. has nothing to disclose. T.M.D. reports only conflicts of interest outside the scope of the submitted paper. He has served as advisor for Bayer Pharma, Proteomika, Pharmaplex, Astellas, Roche Diagnostics, Actavis, has received grants from Ferring, Merck Serono, MSD, Besins, Pharmaplex, and has received travel support from Ferring, Merck Serono and MSD. On October 1st 2015, he became Vice-President and Head of Global Medical Affairs Infertility for Merck Serono and will continue on a part time basis his academic appointment as Professor of Reproductive Medicine at the

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