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The Suitability of Polycystic Ovary Syndrome-Specific Questionnaires for Measuring the Impact of PCOS on Quality of Life in Clinical Trials

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ABSTRACT

Objectives: Generic patient-reported outcome (PRO) measures underestimate the impact of polycystic ovary syndrome (PCOS) on quality of life (QoL). The aim of this review was to identify PCOS-specific QoL measures and establish whether their development history and measurement properties support their use in clinical trials.

Methods: A systematic search was conducted using terms synonymous with "PCOS" and "QoL." Following identification of measures, further searches were undertaken using the questionnaire name and abbreviation to explore its use, development history, and demonstrated measurement properties.

Results: Of 56 abstracts screened, 21 reported using PRO measures. One PCOS-specific QoL measure was identified: the PolyCystic Ovary Syndrome Questionnaire (PCOSQ). Nine papers show that the PCOSQ's development history is somewhat incomplete, and that it does not have good content validity. The PCOSQ subscales demonstrate acceptable levels of reliability (0.70–0.97) and partial known-groups validity as well as convergent/divergent validity with other PRO instruments. Responsiveness to change is variable and minimally important differences have not been established.

Conclusions: The PCOSQ is the only condition-specific measure of the impact of PCOS on QoL. Additional research is required to ensure its comprehensiveness, sensitivity, and to guide interpretation prior to including in clinical trials.

Keywords: polycystic ovary syndrome, quality of life, questionnaire.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, affecting approximately 5% to 10% of women in the Western world [1,2]. Women with PCOS exhibit a wide range of symptoms presenting in varying combinations. These include amenorrhea, oligomenorrhea, menorrhea, hirsutism, subfertility or infertility, anovulation, weight gain or obesity, acne vulgaris, androgenic alopecia, excess androgen production, and insulin resistance [3,4]. Furthermore, growing research indicates PCOS as a risk factor for endometrial cancer [2,5], as well as conditions resulting from metabolic disturbances (e.g., type 2 diabetes, cardiovascular disease, dyslipidemia, and hypertension) [1,2,5–7].

Because of the variability in symptomatology, PCOS has proven challenging to diagnose. The Rotterdam diagnostic criteria [7] (developed in 2003 to aid clinicians in the systematic and accurate diagnosis of PCOS), state that two of the following three criteria should be present for a diagnosis: 1) oligoovulation or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; and 3) polycystic ovaries. Furthermore, the likelihood of other similar illnesses (such as Cushing's syndrome) should first be systematically excluded. New criteria have recently been proposed by the Androgen Excess and PCOS Society [8], which suggest tighter definitions are required by focusing on only two criteria: 1) hyperandrogenism (clinical hirsutism or biochemical hyperandrogenamia, or both); and 2) ovarian dysfunction (oligo-ovulation or anovulation, or polycystic ovaries, or both).

Increasingly, importance is placed on understanding the impact of a condition, its symptoms and treatment from the patients' perspective, and the overall impact of these on patients' quality of life (QoL) [9,10]. The variability of PCOS symptoms (and the potentially significant and varied impact of these on QoL) makes it paramount to understand PCOS from the patients' perspective. With this information, it is possible to gain a better understanding of how the condition and any treatment impacts outcomes in ways that are significant for the patient. Furthermore, novel treatments and therapies can then be targeted toward improving those outcomes which are most important for the individual concerned.

Despite growing interest in assessing the impact of a condition and its treatment on QoL, little consensus has been reached on the definition of QoL [11] and a "remarkably wide range of meanings is implied by the choice of instruments used to measure quality of life" [9]. In the absence of a universally agreed and specific definition of QoL, researchers have often reported a variety of patient-reported outcomes (such as treatment satisfaction or health status) as indicative of (or even synonymous with) QoL. There is, however, some consensus that QoL is a multidimensional (involving assessment of physical, psychological, and social aspects of life), subjective, and dynamic concept unique to the individual concerned relating to the discrepancies between their perceived and attained goals [12].

Developers of pharmacological therapy are increasingly concerned with the demonstration of a decrease in the impact of a condition on QoL (known as health-related quality of life (HRQL)) following intervention. Many phase III clinical trial programs include a secondary (or coprimary) objective of HRQL improvement as a point for treatment differentiation. The lack of consensual QoL definition, and the mis-conceptualization and mis-labeling of PROs as measures of QoL has led to inaccurate statements pertaining to QoL benefits (and lack of benefits) [13]. For example, a previous review [14] reported that many studies had used the Short-Form 36 (SF-36) to measure the

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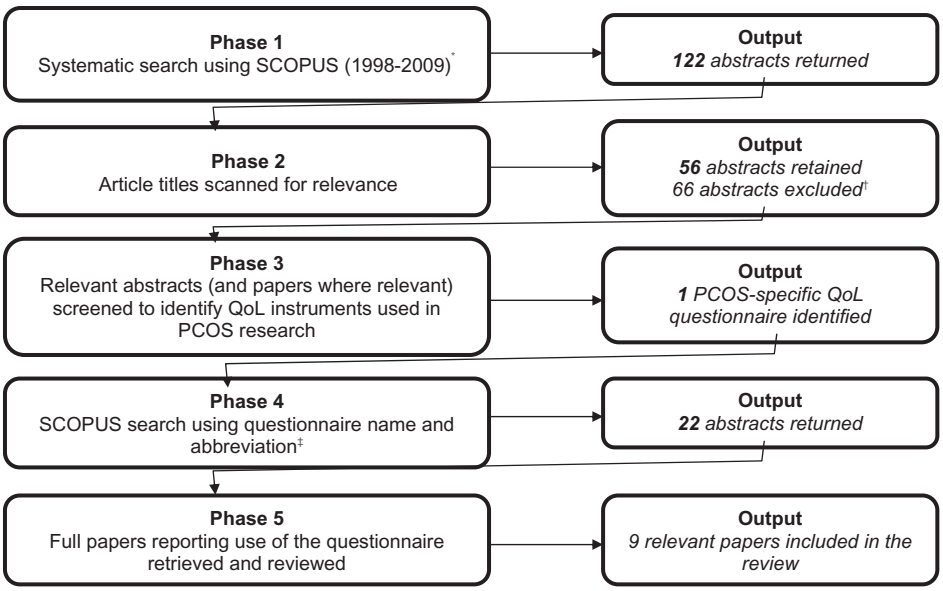

* Search conducted in the title and abstract fields using terms synonymous with "PCOS" in combination with terms associated with "QoL" to identify PCOS-specific QoL measures (for a list of search terms please refer to Table 1. Search was limited to include only articles published in the English language.
† Abstracts excluded as the search returned many articles focusing on type 2 diabetes and epilepsy.
‡ Search was undertaken in Scopus (all fields from the year of the questionnaire development publication-January 2009).

Figure 1 Process of identifying quality of life (QoL) measures used in polycystic ovary syndrome (PCOS) research and articles reporting use of the PCOS-specific QoL questionnaire.

impact of PCOS on QoL despite the fact that the SF-36 was conceived (and is most accurately described) as a measure of generic health status.

Consequently, European and US regulatory guidance [15,16] has been developed to offer advice and standards regarding the use of patient-reported outcome (PRO) measures in medical product development. The European Medicines Agency reflection paper [15] stipulates that claiming any improvement in the impact of a condition on QoL (i.e., HRQL) implies that all relevant domains specific to the condition for which the questionnaire has been developed have been identified and measured. Furthermore, the Food and Drug Administration FDA draft guidance [16] specifically outlines the standards against which the development history and measurement properties of a PRO instrument will be judged. It specifies that the development of a PRO measure needs to be guided by a conceptual framework informed by existing literature, expert opinion, and, importantly, by patient input (e.g., focus groups or interviews). A further requirement is that the instrument development process should be documented throughout. Once a pilot instrument has been developed, the measurement (or psychometric) properties of the instrument need to be examined. This can include statistical tests of reliability (test–retest, internal consistency, interrater reliability), validity (content, convergent, divergent, known groups), acceptability, responsiveness, and interpretability. Therefore, the selection of a PRO instrument for use in a clinical trial needs to be based on the suitability of an instrument's development history and measurement properties (in addition to other more practical issues, such as availability of translations, respondent burden).

The aim of this review is to update and build on Jones's paper [14], which identified PRO measures used previously to assess the impact of symptoms and treatment on the HRQL of women with PCOS. Jones detailed the use of both generic and PCOS-specific instruments, but did not critique them according to the regulatory guidance outlined above. Their suitability for clinical trial research cannot therefore be established from that review alone. The current review details the use of PCOS-specific measures of HRQL only. Our previous qualitative interviews with women with PCOS [17] have indicated that generic measures are likely to underestimate the full impact of PCOS on QoL because of the notable absence of items of specific relevance to the condition. Thus, this article critiques PCOS-specific QoL measures in accordance with regulatory guidance [15,16], to establish whether their development history and measurement properties support their use in clinical trials.

Methods

The search process followed a comprehensive five-phase approach (Fig. 1) using the search terms in Table 1.

In accordance with the regulatory guidance [15,16], the development history and measurement properties of identified PCOS-specific instruments were examined. Specifically, this included examining:

- reliability (internal consistency, test–retest reliability);
- validity (face/content, convergent, divergent, known groups);
- acceptability (concerning the targeting of an instrument to a sample);
- responsiveness (whether the measure detects expected changes following an intervention);
- interpretability (establishment of minimally important differences (MIDs)).

Results

The results of the search process are outlined in Figure 1. Although 21 studies reported the use of 12 PRO measures to

Table 1 Search terms for systematic search strategy to identify PCOS-specific QoL measures

PRO terminology	Condition
"Quality of life"	"polycystic ovary syndrome"
QOL	"polycystic ovaries"
HRQOL	PCOS
HRQL	
Psycholog*	
Psychosocial	
Well-being	
Wellbeing	
Satisfaction	
"Health status"	
"Functional status"	

*Used here to indicate truncated search terms.
Rows within a column were combined using the Boolean operator "or"; columns were then combined using the Boolean operator "and."

study the impact of PCOS on QoL (Table 2), only one PCOS-specific QoL questionnaire was identified—the Polycystic Ovary Syndrome Questionnaire (PCOSQ) [18]. The PCOSQ has been used in nine research projects since its development, including one randomized controlled trial.

The PCOSQ

The PCOSQ was developed by Cronin et al. [18] to be a PCOS-specific HRQL measure. The PCOSQ encompasses five multi-item domains designed to measure Emotions, Body Hair, Weight, Infertility, and Menstrual problems, informed by both patient and expert (health-care professional) interviews, and a literature review. The development history of the PCOSQ was found to be comprehensive (Fig. 2). However, contrary to the recommendations of the FDA's draft guidance, the development of the PCOSQ does not appear to have been guided by a conceptual model and framework, although these could be developed post hoc from the results of the qualitative development studies and literature review.

A summary of the measurement properties of the PCOSQ are reported in Table 3 and discussed in detail below.

Table 2 Patient-reported outcome instruments used in PCOS research

Reference	PCOSQ	Other PRO instruments
Cronin et al. (1998) [18]	✓	
Trent et al. (2002) [19]		CHQ-87
Elsenbruch et al. (2003) [20]		SCL-90R, SF-36
Trent et al. (2003) [21]		CHQ-87
Guyatt et al. (2004) [22]	✓	
Isoppo et al. (2004) [23]		PPP, PSQ, SQ
Jones et al. (2004) [24]	✓	SF-36
Schmid et al. (2004) [25]	✓	
Clayton et al. (2005) [26]		HADS, WHOQOL-BREF
Hahn et al. (2005) [27]		SCL-90R, SF-36
McCook et al. (2005) [28]	✓	
Trent et al. (2005) [29]		CHQ-87
Elsenbruch et al. (2006) [30]		LSQ, SCL-90R, SF-36
Himelein & Thatcher (2006) [31]		BDI, MBSRQ-AS
Coffey et al. (2006) [32]	✓	
Barnard et al. (2007) [33]	✓	
Ching et al. (2007) [34]	✓	GHQ
Jedel et al. (2008) [35]	✓*	
Sundararaman et al. (2008) [36]		GHQ
Tan et al. (2008) [37]		BDI, SCL-90R, SF-36

*This paper was not included in the review as it was validating a Swedish version of the PCOSQ.
BDI, Beck Depression Inventory; CHQ-87, Child Health Questionnaire (used in adolescent studies only); GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; LSQ, Life Satisfaction Questionnaire; MBSRQ-AS, Multi-dimensional Body-Self Relations Questionnaire-Appearance Scales; PCOSQ, Polycystic Ovary Syndrome Questionnaire; PPP, Psychophysiological Stress Profile; PSQ, Pisa Stress Questionnaire; SCL-90R, Symptom Checklist-90 (Revised); SF-36, Short-Form 36; SQ, Symptom Questionnaire; WHOQOL-BREF, World Health Organization Quality of Life Bref.

Reliability

Internal consistency reliability. Cronbach's alpha for all domains were reported in five of the nine articles. For all five subscales of the PCOSQ, internal consistency reliability was acceptable [22,24,28,32,33] ($\alpha = 0.70$–0.97) in three articles [24,32,33], but two of the subscales did not demonstrate internal consistency in other studies [22,28]. Guyatt et al. [22] found alpha levels for the Menstruation subscale to be lower ($\alpha \geq 0.62$ at baseline and 0.54 at a 44-week follow up) than acceptable levels. McCook et al. [28] also found alpha levels for the Emotion subscale ($\alpha \geq 0.56$) and Menstruation subscale ($\alpha \geq 0.60$) to be lower than is generally accepted. Furthermore, McCook et al. [28] reported that the alpha levels of the Emotion and Menstruation subscales improved considerably (to $\alpha \geq 0.86$ and 0.81, respectively) when one item ("worry about late period") was moved from the Emotion subscale to the Menstruation subscale.

Test–retest reliability. Jones et al. [24] found the PCOSQ to have acceptable test–retest reliability when readministering the questionnaire after a 3 to 6-day interval, with people who reported no change to their "health status" during that time. Correlation coefficients ranged from 0.89 to 0.95 for all subscales and these were found to be statistically significant ($P \leq 0.001$ for all domains). In this case, the time between the first and second

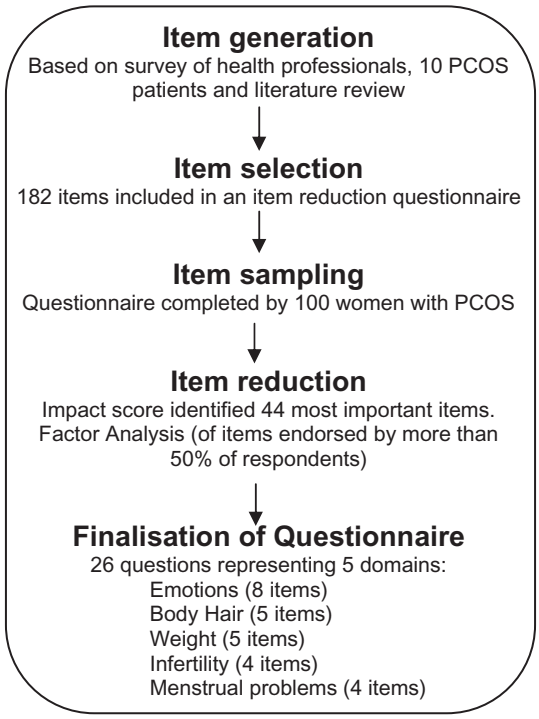

Figure 2 Polycystic Ovary Syndrome Questionnaire development history. PCOS, polycystic ovary syndrome. Adapted from Cronin et al. [18].

Table 3 Measurement properties of the PCOSQ

Reference	Country	Reliability		Validity				Acceptability	Responsiveness
		Internal consistency	Test–retest reliability	Face/ content	Convergent	Divergent	Known groups		
Cronin et al. (1998) [18]	USA	—	—	×	—	—	—	—	—
Guyatt et al. (2004) [22]	Canada, UK, USA	✓	—	×	?	—	✓	✓	?
Jones et al. (2004) [24]	UK	✓	✓	×	✓	—	—	—	—
Schmid et al. (2004) [25]	Austria	—	—	—	—	—	—	—	—
McCook et al. (2005) [28]	USA	?	—	—	—	—	✓	—	—
Coffey et al. (2006) [32]	UK	✓	—	—	✓	✓	✓	—	—
Barnard et al. (2007) [33]	UK	✓	—	×	—	✓	✓	—	—
Ching et al. (2007) [34]	Australia	—	—	—	—	—	✓	—	—
Jedel et al. (2008) [35]	Sweden	—	✓	×	—	—	—	—	—

✓, satisfactory; ×, unsatisfactory; ?, partially demonstrated; —, not reported.

administration of the questionnaire is unusually short, particularly given that the PCOSQ has a 2-week recall period.

Jedel et al. [35] found the PCOSQ to have acceptable test–retest reliability when readministering the questionnaire after a 7-day interval. However, no attempt was made to assess whether the women reported any change in their health during this time. Agreement between all 26 items and individual domains of the PCOSQ were examined using the Kappa statistic together with the intraclass correlation coefficient (ICC). For the 26 items, ($k = 0.29$–0.69) and for the five domains ($k = 0.30$–0.75). The ICC for the domains ranged from 0.78 to 0.96. Significance levels were not reported.

Validity

Face/content validity. The PCOSQ's face/content validity was examined in five of the nine articles. Overall, the face/content validity of the PCOSQ was found to be poor. In the original PCOS development paper [18], the authors reported that items were included in the factor analysis only if they had been endorsed by 50% of respondents (N = 100). Although, all five studies supported a five-factor structure for the PCOSQ (to represent the five subscales of Emotion, Body Hair, Weight, Infertility, and Menstruation), the variance explained by a five-factor solution (67.8%) was found to be lower than the variance explained by six- (78.8%) or seven-factor solutions (80%) [24,33]. Jedel et al. [35] found a six-domain structure to be the best solution (statistics not reported), with the Menstrual problems subscale being divided into two separate scales. Alongside a factor analysis of the PCOSQ, Jones et al. [24] conducted interviews with women with PCOS to assess the validity of the items in the questionnaire. Twenty-five percent of the women interviewed expressed concern over the noticeable omission of items concerning acne and hair loss (the hair subscale of the PCOSQ includes items pertaining to body hair growth rather than hair loss). Barnard et al. [33] therefore modified the PCOSQ to include an additional acne subscale and further divided the Menstrual subscale into two distinct scales, thereby creating a seven-subscale version of the PCOSQ, which explained 80% of the variance.

Convergent validity. Convergent validity (i.e., the extent to which PCOSQ subscales correlate with similar scales) was examined in two of the nine articles and was found to be satisfactory [24,32]. Both studies compared scores on the PCOSQ against scores on subscales of the SF-36 [38], a generic measure of health status comprising eight subscales forming two component summary scores of physical health and mental health. Jones et al. [24] found there to be strong correlations between the Emotion subscale of the PCOSQ and the SF-36 mental health ($r = 0.62$, $P \leq 0.01$) and role–emotional subscales ($r = 0.49$, $P \leq 0.01$). Coffey et al. [32] also found significant correlations between the SF-36 mental component summary score and each PCOSQ domain (Emotion: $r = 0.61$, Body Hair: $r = 0.32$, Weight: $r = 0.51$, Infertility: $r = 0.49$, Menstruation: $r = 0.25$).

Divergent validity. Divergent validity (i.e., the extent to which PCOSQ subscales does not correlate with dissimilar scales) has been examined in two studies. Coffey et al. [32] found that the Hair and Weight subscales of the PCOSQ did not correlate significantly with the SF-36 physical component summary score and reported this to demonstrate adequate divergent validity. Barnard et al. [33] found there to be moderate significant correlations between scores on the PCOSQ and scores on the Zung Depression Scale [39].

Known groups validity. Five of the nine studies examined known groups validity (i.e., the extent to which the PCOSQ is able to discriminate between different populations as expected). Guyatt et al. [22] found that PCOSQ scores correlated weakly with objective measures of hair growth, menstrual cyclicity and hyperandrogenemia. Furthermore, it was found that the proportion of normal menstrual cycles correlated only with the Infertility subscale ($r = 0.17$, $P \leq 0.01$) at baseline but correlated with both the Infertility subscale ($r = 0.27$, $P \leq 0.01$) and Menstruation subscale ($r = 0.24$, $P \leq 0.01$) at 44-week follow-up.

McCook et al. [28] found that body mass index (BMI) was significantly negatively correlated with the PCOSQ Weight subscale ($r = -0.33$, $P \leq 0.001$). As predicted, the greater (higher) the BMI, the lower the Weight score, suggesting greater weight-related concerns. The F/G score (a measure of hirsutism) was negatively correlated with the Body Hair subscale ($r = -0.63$, $P \leq 0.001$) and Emotion subscale ($r = -0.23$, $P \leq 0.001$). Moreover, significant differences were found for scores on the Infertility subscale between women with PCOS who had experienced pregnancy losses or were unsuccessful in establishing a pregnancy and women who had at least one infant ($P \leq 0.001$).

Coffey et al. [32] compared scores on the PCOSQ for women with PCOS and a generic version of the PCOSQ (where the term "PCOS" was replaced by "health") for the general population. Significant differences were found on all domains between women with PCOS and the general population.

Barnard et al. [33] found BMI to be moderately correlated with the PCOSQ Weight subscale ($r = -0.60$ & $r = -0.47$, $P \leq 0.05$). Additionally, women with PCOS on anti-androgen medication reported significantly worse PCOSQ scores than those not taking such medication ($P < 0.05$). Finally, Ching et al.

[34] found BMI to be significantly negatively correlated with all domains on PCOSQ except for the Body Hair subscale ($P \leq 0.01$ for all, correlations not reported).

Acceptability

The acceptability of the PCOSQ was examined in only one article. Guyatt et al. [22] found that the proportion of patients with minimum or maximum results on the questionnaire was ≤5% except in two of the five subscales (the Body Hair subscale (5.5% at baseline) and the Weight subscale (12.9% at baseline and 7.9% at 44-week follow-up).

Responsiveness

Responsiveness to change was examined in one only study with mixed results. Guyatt et al. [22] found that scores on the PCOSQ were responsive to treatment effects (treatment using insulin sensitizing drugs to treat endocrine abnormalities and improve infertility), with greater improvements in higher dose treatment groups being found for scores on the Infertility, Emotion, and Menstrual subscales. However, no difference was found for scores on the Body Hair and Weight subscales.

MIDS

None of the articles identified in the review established MIDs for the PCOSQ.

Discussion

Our systematic review aimed to identify PRO measures designed specifically to assess the impact of PCOS on QoL and examine their suitability according to recent regulatory guidance for the use of PRO measures in medical product development [15,16]. Specifically, this involved examining the development history and measurement properties of the instruments identified. Since its development, the PCOSQ [18] has dominated PCOS-specific research relating to the psychosocial aspects of PCOS; our systematic search identified nine studies in which the PCOSQ has been used, almost half of the total published PRO research studies in PCOS.

We found that the development history of the PCOSQ is relatively comprehensive and has been documented systematically [18]. However, the PCOSQ has limited face/content validity which can be understood through examination of the PCOSQ's development history. First, the development of the PCOSQ does not appear to have been guided by a conceptual model or framework. The omission of such a step can have crucial implications when considering the use of the questionnaire in a clinical trial. The development of a conceptual model would have meant that all significant issues and aspects of life that can impact the QoL of an individual with PCOS would have been accounted for. Two studies reported the notable omission of items relating to acne and hair loss [24,33], both of which are significant symptoms of PCOS and have the potential to impact negatively on the QoL of women with PCOS. In addition, our own qualitative research confirms that the PCOSQ is inadequate in its current form to assess the impact of PCOS on QoL [17]. Second, the developers report that one of the criteria for inclusion of items in the questionnaire was that they had have been endorsed by 50% of respondents with PCOS. This implies that many crucial issues that can impact the QoL of women with PCOS may have been omitted. The variability in PCOS symptomatology [3,4] makes the experience of PCOS unique for every woman and therefore the impact on one woman may not necessarily match that experienced by another. A comprehensive measure of the impact of PCOS on QoL needs to consider the impact of symptoms and their treatment on all aspects of life relevant to a larger majority of women with PCOS.

The review identified a number of generic measures that have been used with the intention of assessing HRQL in women with PCOS, although most of these more accurately measure health status, depression, anxiety, and stress. Examination of the domains represented by the subscales and items of the PCOSQ suggests that the PCOSQ would be better conceptualized as a measure of symptom bother and psychological well-being rather than QoL. The items and subscales of the PCOSQ pertain mainly to the symptoms of PCOS (i.e., Body Hair, Weight, Infertility, and Menstrual problems) with the exception of the Emotion subscale which can be argued to relate more closely to psychological well-being than QoL. The Emotion subscale alone cannot be deemed substantial enough to capture the full impact of PCOS on QoL. Accordingly, our previous research [17] assessing the impact of PCOS on QoL using the Schedule for the Evaluation of Individual Quality of Life (SEIQoL; an interview method developed to assess generic QoL from the individual's perspective [40]) has highlighted how a variety of aspects of life important for QoL can be impacted by PCOS. These include work/career, general health, everyday activities, relationships (family, friends, partners), self-esteem, social life/leisure, and spiritual life. Our qualitative study (more than twice the size of the study that informed the development of the PCOSQ) indicates that the PCOSQ has limited relevance as a measure of the impact of PCOS on QoL, despite it assessing the bother associated with many of the symptoms. Measures based on interviews designed to assess the individualized impact of a condition on QoL have been developed in other conditions [41–43] and have proven to be highly sensitive to the benefits of new treatments and interventions designed to minimize the impact of the condition on QoL [44].

In terms of measurement properties, the PCOSQ appears to be a reasonable measure that performs well in studies of women with PCOS. However, measurement properties alone are not indicative of suitability. The PCOSQ appears to have reasonable convergent, divergent and known groups validity but none of these properties substantiates the claim for the PCOSQ to be a good measure of the impact of PCOS on QoL. Only the assessment of face/content validity can attest to the suitability of the PCOSQ in this respect and evidence to date is lacking. Finally, and by no means least important in the context of clinical trials, evidence for the responsiveness of the PCOSQ is both limited and mixed, and MIDs have not been established.

Based on the regulatory guidance [15,16], current evidence does not support the use of the PCOSQ in a clinical trial program without modification and additional validation. Although, developing a conceptual framework/model at this juncture would be ineffective in informing the development of the questionnaire, it could still be a useful exercise. For instance, the development of a conceptual model and framework could demonstrate that the items included in the questionnaire are all pertinent in understanding the bothersomeness of PCOS symptoms. Furthermore, additional validation work in terms of further research to establish responsiveness and MIDs (to aid interpretability of the questionnaire) and evaluate administrative and respondent burden would be required. In addition to the brief guidance on how to analyze the PCOSQ included in the original development paper, it would be helpful to develop a user manual to specify how to incorporate the PCOSQ into a clinical trial while minimizing administrator burden, respondent burden, missing data, and poor quality data.

Regardless of gaps in the evidence for the PCOSQ being filled by purposefully designed studies, there remains a need for a PCOS-specific QoL measure that encompasses all the relevant elements of life that can be impacted by PCOS. Such a measure needs to be developed in accordance with a conceptual model and framework informed by interviews with patients [17]. This would offer the potential for full and holistic evaluation of the impact of PCOS (including its many symptoms) and its treatment on QoL.

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