Validation of the Polycystic Ovary Syndrome Health-Related Quality of Life (PCOSQ) in the Clinical Community in our Gynaecological Endocrine Clinic

NKOSINATHI NCUBE

STUDENT NUMBER NCBNKO005

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SUPERVISORS: PROF ZM VAN DER SPUY AND PROF PS STEYN

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

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Declaration by the Candidate

I, *NKOSINATHI NCUBE*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Declaration by the Supervisors

Professors, Z M van der Spuy and P S Steyn supervised the research undertaken by NKOSINATHI NCUBE and the presentation of this dissertation.

We are satisfied that this is NKOSINATHI NCUBE'S original work and that this dissertation should be submitted in fulfilment of the requirements for the M Med in Obstetrics and Gynaecology.

Supervisor: Prof ZM van der Spuy

Signature: Signed by candidate

Date: 07.11.2015

Supervisor: Professor PS Steyn

Signature: Signed by candidate

Date:

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and impacts negatively on their health related quality of life (HRQoL). The Polycystic Ovary Syndrome Questionnaire (PCOSQ) is a disease specific questionnaire used to measure HRQOL in affected women. This questionnaire has not been validated for use in the clinical population of South Africa. This study aimed to assess the psychometric properties of the PCOSQ in our population and to compare findings with those from the WHOQOL-BREF, a generic questionnaire that measures HRQoL.

Methods: This was a cross sectional analytical study of women with PCOS as defined by the Rotterdam criteria attending the Gynaecological Endocrine Clinic at Groote Schuur Hospital in Cape Town. The PCOSQ and WHOQOL-BREF were administered at the first interview and a repeat PCOSQ interview was conducted telephonically within a period of 2 to 7 days. The clinical data of the participants at initial diagnosis were obtained from the clinical records.

Results: A total of 105 consenting women were recruited over a period of 8 months from November 2013 to July 2014. Sixty-seven participants responded to the second follow up interview for test-retest reliability. The test-retest reliability was good with intra-class correlation coefficients from all domains being above 0.8 (0.820-0.929, $P<0.001$). The Cronbach's alpha coefficients of internal consistency were above 0.7 in all domains with the exception of the menstrual domain, which scored 0.65. Construct validity was demonstrated by a statistically significant correlation between the corresponding domains of the WHOQOL-BREF ($P<0.05$). Secondary factor analysis confirmed the domain structure of the PCOSQ. The scores from all domains were reflective of an impaired quality of life. Weight had the most

impact on the HRQoL. The WHOQOL-BREF demonstrated a poor internal consistency in the study population.

Conclusions: The PCOSQ is a valid questionnaire for measuring the HRQoL in our clinical population and is preferred above the WHOQOL-BREF. The incorporation of the domain on acne and further exploration of the domain of menstrual problems could be undertaken to strengthen its factor structure. PCOS has an adverse effect on the HRQoL. Weight has the biggest impact on the HRQoL. The WHOQOL-BREF is suboptimal in measuring HRQoL in women with PCOS, as it is not specific to the condition.

Abbreviations

AN	Acanthosis Nigricans
ASRM	American Society for Reproductive Medicine
BMI	Body Mass Index
DHEAS	Dehydroepiandrosterone Sulphate
ESHRE	European Society for Human Reproduction and Embryology
FAI	Free Androgen Index
GEC	Gynaecologic Endocrine Clinic
G:I	Fasting Glucose/ Fasting Insulin ratio
HDL	High Density Lipoprotein
HOMA	Homeostatic Model Assessment of insulin resistance
HRQoL	Health Related Quality of Life
IR	Insulin Resistance
LDL	Low Density Lipoprotein
MS	Metabolic Syndrome
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
PCOSQ	Polycystic Ovary Syndrome Questionnaire
SHBG	Sex Hormone Binding Globulin
TG	Triglycerides
WC	Waist Circumference
WHO	World Health Organisation
WHOQOL-BREF	World Health Organisation Quality of Life – BREF questionnaire
WHR	Waist: Hip ratio

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Normal Reference Values for Women

17α HYDROXYPROGESTERONE	0.5 -14.2 nmol/l
BMI (WHO)	18.50-24.99 kg/m^2
BLOOD PRESSURE	<130mm Hg systolic and/or < 85mm Hg diastolic
DHEAS	Adolescents 1.8-10 µmol/l
	Adults 2.7-9.2 µmol/l
FAI (Free Androgen Index)	[A] 0.4-5.9
	[B] 0.3-5.6
FASTING GLUCOSE	4.1-5.9 mmol/l
FASTING INSULIN	2.6-24.9 µmol/ml
G:I (Fasting Glucose: Insulin ratio)	> 4.5
HDL-CHOLESTEROL	> 1.2 mmol/l
HOMA-IR	< 2.5
LDL-CHOLESTEROL	< 3.0 mmol/l
SHBG	26.1-110 nmol/L
TESTOSTERONE	[A] 0.2-2.9 nmol/L
	[B] 0.3-1.7 nmol/l
TRIGLYCERIDES	< 1.7 mmol/l
TOTAL CHOLESTEROL	< 5.0 mmol/l
WAIST CIRCUMFERENCE	68-80 cm
WHR	< 0.80

The assay method for testosterone was changed on the 5th of July 2010. [A] denotes the reference ranges prior to this date, and [B] refers to the reference range after that date

Chapter 1: Introduction and Literature Review

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with a reported prevalence of between 5 and 10% in the developed world according to the National Institutes of Health (NIH) criteria for definition (1,2). The broader Rotterdam consensus definition for diagnosis of PCOS has indicated a prevalence of up to 15% (3). According to the Rotterdam Consensus meeting of 2003, the diagnosis of PCOS requires at least two of the following three criteria: *1)* oligo- or anovulation, *2)* clinical and/or biochemical hyperandrogenism, and *3)* at least one ovary as assessed by ultrasound with a polymorphic appearance as defined in the literature (3,4). Other causes of hyperandrogenism must be excluded before the diagnosis is made. These include congenital adrenal hyperplasia, Cushing's syndrome, androgen secreting neoplasm and high exogenous androgens (3).

In adolescents the diagnostic criteria pose a challenge as traits of normal puberty overlap with the diagnostic criteria and often all symptoms are not fully developed. The hyper-androgenic clinical characteristics of PCOS are not always associated with the condition in this age group (5). Acne is common in adolescents and is not specific to PCOS (5). Hirsuitism associated with PCOS develops later on in life (5). Biochemical hyperandrogenism may be a more consistent feature of PCOS in this age group (5,6). In adolescents irregular menses are common in the period after menarche. Studies have revealed that up to 85% of the menstrual cycles are anovulatory in the first year after menarche and as many as 59% in the third year (5). The raised body mass index has been found to be significantly associated with persistent anovulation (6). Quite often a trans-abdominal scan is performed to visualise the ovaries and this limits the optimal characterization of the ovaries. In addition, only 40% of adolescents

with menstrual irregularities have polycystic ovary morphology on ultrasound (5). Diagnosis at this age group has lifelong psychological and social implications for these teenagers. A careful evaluation and identification of risk factors such as family history, obesity, irregular menses, hirsutism and biochemical hyper-androgenism is crucial in this age group to avoid misdiagnosis that has long-term implications (7,8).

The exact origin of PCOS is still an enigma (9,10). Genetic and environmental causes may play a role in the development of PCOS (11). Affected women may have a family history of PCOS, although with varying severity. Given the clustering of this syndrome in families, a polygenetic background has been suggested (11). Some studies have found a positive association in girls born small for gestational age and those with early pubarche and early menarche. This suggests the intrauterine environment also plays a role in the pathogenesis (11,12).

PCOS is frequently first identified during the early reproductive years, and at this stage diagnostic challenges are often encountered as highlighted above (3). Presenting symptoms may include amenorrhoea and/or oligomenorrhoea, acne, hirsutism, anovulatory infertility and obesity (13). PCOS has a heterogeneous presentation and there is considerable phenotypic variation among individuals and population groups and symptoms may change over time (14,15). Despite androgen production decreasing with ovarian age and decreasing production by the adrenal glands in the fourth decade of life, hirsutism that is already established usually persists (16). In addition to the hyper-androgenism, the metabolic syndrome is often present, manifesting partially or in full with all the components of its

diagnostic criteria present. There is an established relationship between hyper-androgenism and the metabolic syndrome (17,18).

The metabolic effects of PCOS include insulin resistance (IR), which can promote enhanced androgen secretion by the ovary further worsening the hyper-androgenism (19). These metabolic disturbances become more pronounced with age as insulin resistance increases and obesity worsens. Insulin resistance may be attributable to obesity but there may well also be a genetic trait as many lean PCOS patients have insulin resistance (17-20).

The ESHRE/ASRM-sponsored PCOS working group has now hosted a number of workshops resulting in three consensus publications. In 2003 they reviewed the diagnostic criteria for PCOS and the Rotterdam criteria were subsequently published in 2004 (3). In 2008 infertility management in PCOS was reviewed (21). In 2012, during the latest workshop that was held in Amsterdam, important areas that need on-going research and input were addressed (5). These include various aspects of PCOS during the reproductive and post-reproductive years such as PCOS presentation in adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, sexual health, ethnic variations, pregnancy complications, long-term health and cancer risk and the quality of life in women with PCOS (3,5). In published studies, reviewing the quality of life among women with PCOS, the general finding is that PCOS is associated with a relatively poor HQOL (22). In addition to addressing the clinical condition, it is important to address the psychological wellbeing in women affected by this lifelong condition (23).

Quality of Life and PCOS

The presentation and symptoms of PCOS can be assessed relative to the age of the patient. The diagnosis is often made at an early reproductive age and adolescents may present with acne and menstrual problems (5,6,24-26). In addition the fear of subsequent reproductive problems is frequently already evident at the initial presentation (25). In later reproductive life the issue of menstrual problems, obesity, infertility and hirsutism are more prominent (27). As menopause approaches the metabolic long-term complications become more evident but these may have already presented at a relatively young age (24,28). The risk of endometrial cancer has been well documented (5). These risk factors include obesity, hyper-insulinaemia and diabetes mellitus. These create a hyper-oestrogenic environment that promotes excessive endometrial proliferation. This results in abnormal uterine bleeding patterns and endometrial abnormalities, which are precursors of malignancy (29).

With increased age there is an inherent propensity towards the development of the Metabolic Syndrome (MS) and Insulin Resistance (IR). As stated in the literature, some indicators of the metabolic syndrome are already established as early as adolescence (6,19,30,31). Insulin resistance (IR) has a significant role in the development of obesity, diabetes, and cardiovascular disease. If identified early enough, measures such as weight loss, exercise, dieting and medication can be prescribed to contain these metabolic effects. These complications manifest as excessive weight gain, hirsutism, acne and reproductive complications, which adversely affect the women's physical appearance and psychological integrity (22,29).

If diagnosed early enough, insulin resistance can be managed to a certain extent before becoming fully established. There are several methods used to measure insulin resistance. The hyper-insulinaemic euglycaemic glucose clamp is the gold standard (32). This test is time and labour intensive, which limits its use in clinical practice. Alternative methods to measure insulin resistance include the fasting glucose/insulin ratio (G:I ratio) and the homeostasis model assessment (HOMA) (32). Table 1 summarises the use of these two tests. Insulin resistance contributes to the development of the metabolic syndrome making it an essential surrogate test for monitoring these women. The metabolic syndrome manifests with cardiovascular effects, hypertension, central obesity, dyslipidaemia, pro-thrombotic states, and a relative increase in pro-inflammatory markers, which are not ideal for a healthy vascular endothelium (12,19,28).

Table 1: Measures of Insulin Resistance (IR) (32)

Method	**Comment**	**Formula**	**Reference Values**
Glucose/Insulin ratio	Sensitive & specific for insulin sensitivity. Surrogate ratio for measuring insulin resistance	G/I [a]	> 0.45
Homeostasis model assessment *(HOMA-IR)*	Assesses β-cell function and insulin sensitivity.	*(G×I)* [a] */22.5*	< 2.5

[a.] *G = fasting glucose: I = fasting insulin*

The criteria for diagnosis of metabolic syndrome in adult women with PCOS require at least three of the five parameters listed in Table 2.

Table 2: Criteria for the Diagnosis of Metabolic Syndrome (3)

Risk factor	**Reference value**
Abdominal obesity (waist circumference)	> 88 *cm*
Triglycerides	> 1.695 *mmol/L*
HDL-Cholesterol	< 1.295 *mmol/L*
Blood pressure	Systolic ≥130 *mmHg* diastolic ≥*85 mm* Hg
Fasting and 2 hour glucose from glucose tolerance test (GTT)	Fasting: 6.105-6.993 *mmol/L*: 2 hour glucose: 7.77-11.0445 *mmol/l*

The impact of the clinical manifestations of PCOS on the HRQoL, i.e. the hyper-androgenism and the metabolic effects has been explored across different populations, cultures, races and geographical areas. These clinical presentations impact on the HRQoL across different populations, albeit in different ways (10, 29).

Schmid *et al.* (2004) demonstrated that despite a similar symptom profile, Austrian immigrant Muslim women were more affected in terms of their HRQOL compared to other Austrian women with PCOS (33). Infertility was identified as a major problem because of the high reproductive pressure in that sector of the Austrian society. Himelein and Thatcher (2008), in North Carolina reviewed the literature and reiterated the differences across

cultures of the impact of PCOS on the HRQOL (34). Hashimoto *et al.* (2003), from the study they performed noted that Brazilian women were more worried about facial hair compared to Austrians despite scoring higher on the weight scale than their European counterparts. The authors attributed this finding to the greater importance of being thin in Western countries than in developing countries (34). Kumarapeli *et al.* (2010), in a study that compared South Asian women with PCOS to their white European counterparts found that PCOS adversely affected the psychological wellbeing and the HRQOL in South Asian women. The psychological distress was attributed to hirsutism rather than weight, as was the case with affected European women (35).

Jones *et al.* (2010) from their study in the United Kingdom found that despite there being HRQOL differences between South Asian and Caucasian women in the general population, this was not replicated in the women with PCOS. A compromised HRQoL was noted in both populations regardless of ethnicity (36). Ladson *et al.* (2011) in the USA reviewed the racial impact on PCOS phenotype and concluded that Black women with PCOS were very similar reproductively to their white counterparts, although some biochemical differences were present (37). In a meta-analysis by Li *et al.* (2011) from the People's Republic of China, found that women with PCOS scored lower in each dimension of the SF-36. The SF-36 is a widely used health related quality of life (HRQoL) measuring tool. The lowest score was in the emotional role function (38). The overall impression from the current literature is that of compromised HRQoL in women with PCOS. Evaluating patients in order to address these psychological morbidities in the context of local culture and geography cannot be over-emphasized.

Besides the physiological disturbances that are found in PCOS, considerable psychological manifestations of this syndrome have been described. These adversely impact the health related quality of life in the affected women. Mental health problems include depression and anxiety, suicide attempts, body dissatisfaction, eating disorders, diminished sexual satisfaction, and lowered health-related quality of life (13,15,39,40). The psychological impact of PCOS has been explored with respect to the phenotypic expression of the syndrome, reproductive impairment and biochemical derangements (23). Biochemical hyper-androgenism may lead to an improved libido but worsen the hirsutism as the induced androgen sensitivity of the hair follicles remains for the rest of the life cycle (16). Hirsutism has been found to be crippling emotionally and socially in some studied population groups (41). There is an established correlation between hyper-androgenism and obesity (20). These effects cumulatively impact adversely on the quality of life for these women.

Anovulatory infertility is common in women with PCOS. These women may struggle to conceive. Obesity and insulin resistance further compromises their reproductive function (29). This weighs negatively on the affected women's outlook on life. In addition to the impaired fertility, pregnancy itself is medically challenging as some of these women are at a relatively higher risk of miscarriage and other pregnancy complications because of the abnormal metabolic status (31). The impact of different aspects of PCOS on quality of life needs to be assessed so that relevant therapeutic interventions such as psychological counselling are instituted (23).

Health Related Quality of Life

Health related quality of life (HRQoL) focuses on the quality of life in the context of health and disease (42). This measure is based on the individual's perception of their current wellbeing and their perception of the future (43). HRQoL is defined by the World Health Organisation (WHO) as ' *an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns* '(42). This definition embraces the physical, psychological and social aspects of life in relation to a particular disease or its treatment (34). The burden of chronic diseases and the impact they have on the HRQoL has necessitated the need for these subjective measures. The impact of interventions to alleviate these conditions can thus be quantitatively measured (44). Questionnaires that measure relevant psychometric properties are used to assess the HRQoL (43). These are either generic or disease specific questionnaires. Disease-specific questionnaires have a greater sensitivity than generic assessments when measuring the HRQOL within a specific medical condition (45,46).

The WHOQOL-BREF Questionnaire

The WHOQOL-BREF is a generic HRQoL measuring instrument. This is an abbreviated 26-item version of the WHOQOL-100 developed by the WHOQOL group in 15 international field centres simultaneously (47). The WHOQOL-BREF has four domains of QOL namely physical, psychological, social and environmental. In addition there are two questions on overall quality of life and general health. These are not part of the items in the domains. Each

question is scored on a five point Likert scale. The lowest score is one, indicating maximum impairment in the HRQoL with five being the optimum score with the least impairment. The responses reflect how the respondents felt in the preceding two weeks (47,48). The WHOQOL-BREF is a cross culturally validated questionnaire with good to excellent psychometric properties of reliability (47). This follows analysis of its test-retest reliability, internal consistency, item-total correlations, and secondary factor analysis; construct validity and discriminant validity (47).

The cross-cultural validity offers more practicality in the administration of the WHOQOL-BREF in the assessment of HRQoL in a culturally diverse population (49). In a systematic and critical review of cross culturally developed generic HRQOL questionnaires by Bowden *et al.* (2003), the WHOQOL was found to have evaluated cross-cultural equivalence rigorously, and was likely to provide more valid scores for comparison across diverse settings (50).

The PCOS Quality of Life Questionnaire (PCOSQ)

Cronin and associates developed a PCOS specific questionnaire in the USA in 1998. This questionnaire was developed to measure the health related quality of life in women with PCOS (45). This is a self-administered questionnaire. The PCOSQ was developed to complement the generic HRQOL instruments such as the Standard Short-Form health survey questionnaire (SF-36), the General Health Questionnaire (GHQ), and the World Health Organisation Quality Of Life Questionnaire (WHOQOL-BREF) which were perceived as having insufficient sensitivity in measuring the impact of PCOS symptoms (47). Qualitative

interviews with women with PCOS have also demonstrated that generic questionnaires can underestimate the full impact of PCOS on their HRQoL, as they do not explore issues specific to PCOS (51).

The PCOSQ is a 26-item questionnaire. The items are grouped into five domains namely, emotions (8 items), body hair (5 items), weight (5 items), infertility (4 items) and menstrual problems (4 items) (45). The instrument was developed using semi-structured interviews, a health professional survey and an extensive literature review to identify 182 items that seemed relevant to PCOS to include in the initial questionnaire. Following the initial interviews an item reduction phase was initiated which 100 patients with PCOS completed (45). Each item was weighed through its impact score on how frequently it featured among these patients. The impact score method was then applied to identify the 44 most important items (45). Factor analysis, a statistical method used to describe variability among observed correlated variables was used to identify 5 domains and reduced the total number of items from 44 to 26, which have been retained in the final questionnaire. In its present form, the PCOSQ has 26 questions clustered into 5 domains (45). Each question is scored on a Likert scale of 1-7. The least impairment in the HRQoL has a score of 7 and the most impairment score is 1 for each question. The scores reflect the respondent's feelings in the preceding two weeks (45).

The PCOSQ has been used in several studies to measure psychological morbidity, treatment intervention outcomes, and the psychological impact of PCOS across different generations (51). The questionnaire has also been used to compare the impact of PCOS in different

cultures and geographic areas (36,52). Several studies have assessed the impact of PCOS on various aspects of quality of life in affected women. Comparisons have been made with general populations, different ethnic groups, adolescents and different geographical areas. In addition sexual function, psychological morbidity, obesity and hirsutism have been reviewed independently in some studies and the general consensus is that PCOS is associated with relatively poor health related quality of life (22,38). Cronin *et al.* (1998) recommended testing of the PCOSQ either prior or concurrent with its use (45). Prior to its utilisation, the PCOSQ has been validated in the respective populations that were studied. This enabled the investigators to assess its appropriateness, robustness and applicability in different population settings and contexts (52,53).

Validation of the PCOSQ in the Literature

The PCOSQ is specific to women with the PCOS. This patient-reported outcome measure was designed to quantitatively measure the HRQoL in PCOS patients. Before using this questionnaire, the PCOSQ has to be assessed through a validation process and statistical tests of reliability mainly test-retest, internal consistency, construct and face validity. In essence, the process of validation reliability testing assesses the questionnaire's acceptability, responsiveness and interpretability in a specific population (51). Table 3 summarises validation studies where the PCOSQ has been used.

Table 3: Validation of the PCOSQ in the Literature

Reference	Study Aim	Findings	Population
Guyatt *et al* (2004) (52)	To examine the psychometric properties of the PCOSQ	Good discriminative and longitudinal validity, and responsiveness	Canada
Jones *et al* (2004) (53)	To examine the psychometric properties of the PCOSQ	PCOSQ is a reliable instrument however the validity needs improvement by incorporating the dimension of acne	United Kingdom
McCook *et al* (2005) (22)	To evaluate the influence of obesity, fertility status and hyper-androgenic effects on HRQoL in women with PCOS	Good internal consistency and reliability, however the item on late menstrual periods loaded better on the menstrual subscale rather than the emotions	United States of America
Coffey *et al* (2006) (54)	To examine whether women with PCOS have poorer HRQoL than women in the general population and patients with other medical conditions	Good internal reliability, good concurrent validity and good discriminant validity	United Kingdom
Barnard *et al* (2007) (55)	To estimate the prevalence of depression in a community sample with PCOS, to examine whether the factor structure of the PCOSQ can be reproduced with the addition of the acne subscale and to determine HRQoL in PCOS.	Added the acne subscale and strengthened face validity of the scale	United Kingdom
Jedel *et al* (2008) (40)	To determine the test-retest reliability and to confirm the domain structure of the Swedish version of the PCOSQ	Confirmed the reliability of the Swedish version of the PCOSQ	Sweden
Amini et al (2011) (56)	To translate the PCOSQ and determine the reliability and validity of the HRQOL for women with PCOS in Tehran	The Iranian version of the PCOSQ was reliable and valid except for menstrual problems domain	Iran
Bazarganipour et al (2012) (57)	To examine the psychometric properties of the modified PCOSQ in which they added the Acne domain	Satisfactory internal consistency, intraclass correlation coefficients and the six factor model was retained	Iran
Juhyae and Ju Hee (2014) (58)	To examine the reliability and validity of the Korean version of the PCOSQ	The Korean version of the PCOSQ was a reliable and valid instrument for use locally	Korea

The patients' perceptions of the psychosocial impact of PCOS should be interpreted in the context of their locale, ethnicity, age, race, religion and culture. These have been found to influence the HRQoL. Findings from different populations may be unique because of the environmental and social dynamics. Before using the PCOSQ within our clinical population, the questionnaire had to be validated and its psychometric properties examined. Psychometrics is the study of the principles and ways of psychological measurement. It involves the construction and validation of questionnaires. Validity and reliability are essential elements for determining the quality of any test. A reliable measure is one that measures a construct consistently across time, individuals, and situations (59). A valid measure is one that measures what it is intended to measure (59,60).

Aim of the Study

This study aimed to evaluate the psychometric properties of the PCOSQ in a clinical population in South Africa, and to utilize the WHOQOL-BREF, a generic HRQoL questionnaire to assess general health and wellbeing as a comparator. The objectives were to get clinical information on the women with PCOS, to validate the PCOSQ in our clinical population and to compare the outcomes with those of the WHOQOL-BREF. The validated PCOSQ will be used in the future in our clinical population to identify issues associated with the HRQoL in women with PCOS and we will be able to compare findings generated locally with those from studies performed elsewhere.

Chapter 2: Methods

Study Design, Site and Population

This was a cross-sectional analytical study of women diagnosed with PCOS, as defined by the Rotterdam Consensus criteria (2003), at the Gynaecological Endocrine Clinic (GEC) at Groote Schuur Hospital in Cape Town. This clinic has the largest database in Africa, which contains over 1600 women diagnosed with PCOS.

A clinical research team who were not involved in the direct management of the patients recruited the participants from the Gynaecological Endocrine Clinic (GEC). The research team was trained to conduct the initial and the follow up re-test interviews. The recruitment period spanned eight months, from November 2013 to July 2014.

The inclusion criteria for participation were:

- Women with a diagnosis of PCOS according to the Rotterdam criteria (2003).
- Women who were at least 18 years old at the time of the study.
- Women who had a good comprehension of the study and were willing to participate.
- Women who were able to complete the questionnaire in English.

The exclusion criteria for participation were:

- Women with significant chronic co-morbidities that were often not related to PCOS.

- Women who were pregnant at the time of the study.
- Women who were not willing to participate in the study.
- Women who were unable to understand the study because of language or other difficulties.

Recruitment of Participants

The research team approached individual women attending the GEC. The study was explained to them and information leaflets with contact details of the principal researcher and the Research Ethics Committee were given to each participant. Participants were made aware that this study was not part of their on-going care and declining to participate would not compromise their level of care. The potential participants were given a description of the study and information leaflets were provided as well (Appendix 1). The participants signed an informed consent before the initial interview (Appendix 2). Counselling service was readily available for participants whom at the time or following the interview felt adversely affected.

The PCOSQ (Appendix 3) and the WHOQOL- BREF (Appendix 4) were used concurrently in the initial interview and only the PCOSQ for the retest interview. Baseline clinical data (Appendix 5) were collected from the clinical records. The data collection tools were assigned case numbers for de-identification to ensure the confidentiality of participants' information. A member of the research team administered the questionnaires on a one to

one basis in a private interview room. The participants were given answer templates to assist in completing each questionnaire (Appendix 6 and 7). Answers were selected from the options on the template derived from the respective questionnaire. The two questionnaires took about 20 minutes to administer.

The participants were given an answer template for the PCOSQ (Appendix 6) to take with them for the subsequent telephonic interview for the re-administration of the PCOSQ. This second interview was scheduled at the convenience of the participant no less than two days but not longer than seven days following the first interview. This interval was elected in order to minimise recall bias i.e. patients recalling answers without reading the questionnaire in the second interview, and was well within the two-week recall as required by the questionnaire. Participants did not receive any treatment intervention that would have altered their HRQOL during the two to seven days interval.

The data were collected over a period of eight months to reach the sample size required for statistical analysis as stated above. The study aimed to recruit at least 100 participants to enable factor analysis (61). There was no monetary incentive for the participants.

Statistical Analysis

The data from the questionnaires were captured into a Microsoft Excel Spreadsheet. Two research team members independently captured the data. The spreadsheets were then compared using the software Spreadsheet Compare and the differences reconciled from the

source documents. Statistical analysis was carried out using IBM SPSS Statistics Version 22. Descriptive statistics were done, followed by univariate tests of association. Reliability analysis (tests of internal consistency as well as test-retest reliability) and secondary factor analysis were performed. Reliability is the ability of a questionnaire to measure outcomes by different individuals or on different occasions in a reproducible manner (62). This is a function of the questionnaire, the participants and the circumstances (62). This was assessed by the questionnaire's internal consistency and test-retest reliability (53). Validity is the degree to which the questionnaire measures what it is supposed to measure. It is concerned with the meaning and interpretation of the score, and is a function of the scale, the participants and the circumstances (62).

Test-Retest

Test-retest reliability measures how stable the questionnaire is over time. It is important particularly when the purpose of the PCOSQ is to measure outcome (63). The two sets of questionnaires were compared by correlational analysis. The Spearman's correlational analysis together with the Wilcoxon nonparametric-signed rank test was used to calculate statistical differences between the scores at times 1 and 2. The intra-class correlation coefficients were calculated to examine the relationship between the scale scores at time 1 and 2. The results were taken as significant if $P < 0.05$ (52).

Internal Consistency

Internal consistency is an indication of how well the items within a scale are associated with each other. Cronbach's alpha is the measure used. Cronbach's alpha reliability coefficient ranges between 0 and 1. The closer the Cronbach's alpha is to 1, the greater the internal consistency of items on the scale (64). Scores >0.7 usually indicate that scale items are measuring related constructs (64). A value very close to 1 may however indicate redundancy of that item. Item-total consistency was calculated to check the internal reliability of a dimension. The item-total statistics and the corrected item-total correlation measure the correlation between that item and the sum of the responses on the remaining items. The Cronbach's Alpha was re-calculated after deleting individual items from the domain. When recalculated if the alpha coefficient score increases after a question is removed, then that question does not correlate with others in that domain. Removing it would make the scale more reliable.

Face Validity

Face validity is a subjective judgement of the expert clinicians (63). This looks at how appropriate, relevant and understandable items on the questionnaire are with regard to the focus and aim of the questionnaire. The purpose was to identify items that are irrelevant and may side track participants resulting in omissions or responses that are not genuine (63). This can improve the co-operation of respondents completing a questionnaire, identify any ambiguities in wording of items and identify any irrelevant or missed out items (65). To check face validity originally, expert clinicians were given the questionnaire to comment and

input any aspect of the PCOS that they found significant enough to be included. In addition on conclusion of the interviews, the participants in this study were asked for their opinions of the questionnaire.

Construct Validity

Construct validity reflects the ability of the questionnaire to measure a construct (62,66). This allows comparison of equivalent domain scores in the two questionnaires. Construct validity is demonstrated by supporting the hypothesis in the test score. In this study there was a concurrent administration of WHOQOL-BREF for this purpose. Domains that measured related concepts were compared using Spearman's correlational analysis. The scale scores in the PCOSQ are measured from one to seven whereas on the WHOQOL-BREF the scores are on a scale of one to five. To enable comparison the scales of both questionnaires were converted to a new scale of zero to one hundred. For the WHOQOL-BREF, syntax was used to convert the scores. The PCOSQ scores were converted to a new scale of 0-6 and applying the formula *(total of raw scores for each item in the scale/maximum possible raw scores × 100)* to end up with an equivalent scale score of 0-100 (53). The final scales for both questionnaires range from 0 indicating the worst health status and 100 being the best health status.

Secondary Factor Analysis

Secondary factor analysis enables the underlying scales/domains of a questionnaire to be determined (61). The domain structure of the PCOSQ was re-examined with in our local population. We wanted to see it the original domains will be retained or revised according to the responses from the participants.

A minimum sample size ranging from 100 to 150 is sufficient for this analysis (67,68). Larger sample sizes of up to 1:10 ratios of questions to sample size solely for factor analysis, have been criticized by Sapners and Zeller (2002) in the literature as often associated with a large data set which is a challenge with respect to management, time factor and the accompanying financial costs (68). The data from the first PCOSQ interview were analysed using principal component analysis (Varimax rotation) as used in the development of the original questionnaire (PCOSQ).

Research Ethics Consent and Copyright Permission

The University of Cape Town Human Research Ethics Committee granted us permission to conduct the study (HREC REF 535/2013) (Appendix 8). We applied to the Endocrine Society in (USA) for the permission to use the PCOSQ as they hold the copyright of the questionnaire. The original authors and the Endocrine Society approved this and allowed us to purchase the rights to use the questionnaire. Permission to use the WHOQOL-BREF was granted by the WHO Publications office (Appendix 9).

Chapter 3: Results

Recruitment and Demographic Characteristics

During the eight months of recruitment, a total number of 105 participants completed the PCOSQ and the WHOQOL-BREF at the first interview. Sixty-seven participants (64%) completed the repeat PCOSQ questionnaire between 2 and 7 days following the first interview. One participant was excluded because she was subsequently found to be pregnant. Of the participants who did not take part in the telephonic follow up interview the reasons included unavailability because of work and other commitments and some did not answer the phone despite agreeing to the follow up interview. The mean age of the participants was 28 years (range 18-49, SD ±6.8). The majority (94.3%) of the participants were of mixed ancestry. In addition, there were 2 white (1.9%), 3 Asian (2.9%) and one woman, originally from West Africa (1%). No black South African women were recruited to this study.

The baseline clinical characteristics of the participating women are summarised in Table 4. These measurements were taken at the time of initial diagnosis, before any treatment interventions and not at the time of conducting this study. This explains the age range for the clinical assessments starting from 14 years which otherwise would not have been eligible for recruitment into the study.

Table 4: Clinical Characteristics of the participants at the time of diagnosis[1]

	Range	Mean (SD) [2]	Reference value [7]
Age *(years)*	14.0-43.0	25.3 (5.8)	
Weight *(kg)*	38.0-174.5	91.2 (26.2)	
Height *(m)*	1.5-1.8	1.6 (0.1)	
BMI *(kg/m^2)*	17.3-54.0	34.0 (8.4)	19-25
Waist *(cm)*	64.0-148.0	103.5 (18.7)	>80
Hip *(cm)*	1.6-152.0	113.7 (21.3)	
W-H Ratio	0.6-1.1	0.9 (0.1)	<0.85
0estradiol *(pmol/l)*	2.6-1239.0	248.4 (209.2)	46-608
Testosterone *(nmol/l)* [3]	0.6-4.1	1.99 (0.87)	See footnote [3]
	0.2-4.1	1.43 (0.72)	See footnote [4]
SHBG *(nmol/l)*	7.3-165.0	35.9 (31.7)	26.1-110
FAI [4]	0.5-29	7.43 (7.02)	See footnote[5]
	0.2-24.6	6.5 (5.13)	See footnote [6]
FSH *(IU/l)*	0.1-10.4	5.1 (1.8)	1.7-21.5
LH *(IU/l)*	0.1-42.2	9.8 (7.3)	1.0-95.6
DHEAS *(µmol/l)*	1.1-60.2	6.8 (7.0)	2.7-9.2
17α OH progesterone *(nmol/l)*	0.8-20.3	5.6 (3.7)	0.7-14.2
Fasting Glucose *(mmol/l)*	2.8-19.3	5.3 (1.7)	6.1-6.993
Fasting Insulin *(mIU/l)*	1.0-73.4	24.4 (15.3)	<24.9
Fasting Glucose: Insulin ratio	0.1-2.58	0.26 (0.29)	>0.45
HOMA	0.7-28.01	5.96 (4.34)	<2.5
Fasting Cholesterol *(mmol/l)*	3.3-7.7	4.9 (0.9)	<5.2
Fasting triglycerides *(mmol/l)*	0.4-4.6	1.3 (0.9)	<1.7
Fasting HDL *(mmol/l)*	0.6-2.1	1.2 (0.3)	>1.6
Fasting LDL *(mmol/l)*	1.1-40.0	3.5 (3.9)	2.6-3.3

[1]*The time of diagnosis was when the patients initially presented to the clinic.*
[2] *Standard deviation.*
[3]*The reference range of normal testosterone before the 5th of July 2010 was (0.2-2.9 nmol/l).*
[4] *After the 5th of July 2010 reference range was (0.3-1.7 nmol/l). This was due to a change in the assay method from that date.*
[5] *FAI reference values were adjusted from (0.4-5.9) before the 5th of July 2010.*
[6] *After the 5th of July 2010 the new reference range was changed to (0.3-5.6).*
[7] *The values were based on our local laboratory references.*

Insulin resistance was calculated from the fasting glucose/insulin ratio (G:I) and the homeostatic model of assessment (HOMA) criteria as previously highlighted in Table 1. The formula used in the HOMA was (Glucose X Insulin) / 22.5. Values of 2.5 or above were diagnostic of insulin resistance. Of the 105 participating women, eight (7.6%) did not have fasting glucose and insulin measurements in their clinical records. As per the HOMA calculation 75 (77.3%) of the women had insulin resistance and 22 (22.7%) did not have insulin resistance. The G:I ratio was regarded as indicative of insulin resistance if less than 0.45. Through this calculation 77 (79.4%) of the women had insulin resistance compared to 20 (20.6%) who did not demonstrate insulin resistance. Table 5 summarises the results of measurements for insulin resistance.

Table 5: Assessment for insulin resistance (IR) (N=97)

	G: I [a] Number of women (Percentage)	**HOMA** [b] Number of women (Percentage)
Insulin resistance present	77 (79.4)	75 (77.3)
Insulin resistance Absent	20 (20.6)	22 (22.7)

[a] *G:I = fasting glucose : fasting insulin ratio*

[b] *HOMA = homeostatic model assay*

The Pearson's chi-squared test was performed to explore the relationship between insulin resistance and the presence of acanthosis nigricans. A statistically significant association between these two clinical entities was demonstrated. There was a positive association between acanthosis nigricans and insulin resistance in this group of women.

Metabolic syndrome was present in 23 participants (24%). However 85% of the participants had at least one of the components and 2% had all the components of the metabolic syndrome. The waist circumference was the most frequent contributor followed by the elevated HDL-cholesterol. Table 6 presents a summary of the clinical characteristics of the participants with respect to the features of metabolic syndrome.

Table 6: Clinical Characteristics of the Participants (N=105)

	Reference value	**Women affected**	**Percentage**	**Total** [3]
Blood pressure	≥ 130/≥85mmHg	35	35	99
Waist circumference	> 88cm	62	81	77
Triglyceride levels	≥ 1.695mmol/l	19	20	95
LDL-Cholesterol	>3.3mmol/l	35	36	96
HDL-Cholesterol	< 1.295mmol/l	51	54	95
Total cholesterol	>5.2mmo/l	35	36	97
Fasting Glucose	> 6.993mmol/l	5	5	99
G:I ratio	>0.45	77	74.4	97
FAI raised	(See footnote 4)	76	72.4	84
Metabolic syndrome[1, 2]		23	24	97

[1] *As defined in Table 2*

[2] *Eight of the participants had absent measurements for the diagnosis of metabolic syndrome:*

[3] *The total count for the measurement excludes values that were missing from the clinical records:*

[4] *The free androgen index assay was changed on the 5th of July 2010 from a reference range (0.4-5.9) to (0.3-5.6)* after a new assay for testosterone was introduced*. This was taken into consideration in this study.*

PCOSQ Results

A total of 105 participants completed the PCOSQ at the first interview. This was labelled PCOSQ-1. Participants had relatively low scores in all domains, indicating impairment in the HRQoL. Table 7 presents the mean PCOSQ-1 domain scores. Weight was the most concerning issue with the lowest mean score. Infertility and menstrual problems had a similar impact on the HRQOL and were the second most troubling issues. Emotions had a moderate impact on the HRQOL and body hair was the least worrying issue.

Table 7: Summary of the Domain Scores of the PCOSQ

Domain	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean [a]	Standard Deviation
Emotions	1.13	2.38	3.25	5.00	7.00	3.69	1.55
Body hair	1.00	2.80	4.60	6.80	7.00	4.72	2.01
Weight	1.00	1.60	2.60	4.00	7.00	3.09	1.74
Infertility problems	1.00	1.50	3.00	5.50	7.00	3.47	2.01
Menstrual problems	1.00	2.25	3.00	4.50	6.75	3.47	1.58

[a] *The values assigned were between 1 and 7. 1 indicating the most impairment and 7 represented the least impairment of the HRQOL.*

A notable large number of participants selected lower scores in all domains except that on body hair as illustrated in figures 1-5. The cluster tables illustrate the number of responses the scores elicited from the participants. These tables are graphical representation of where the participants scored their HRQoL. Participants with the worst impairment were

represented by a score of 1, whilst those with the least impact on their HRQoL were represented by a score of 7.

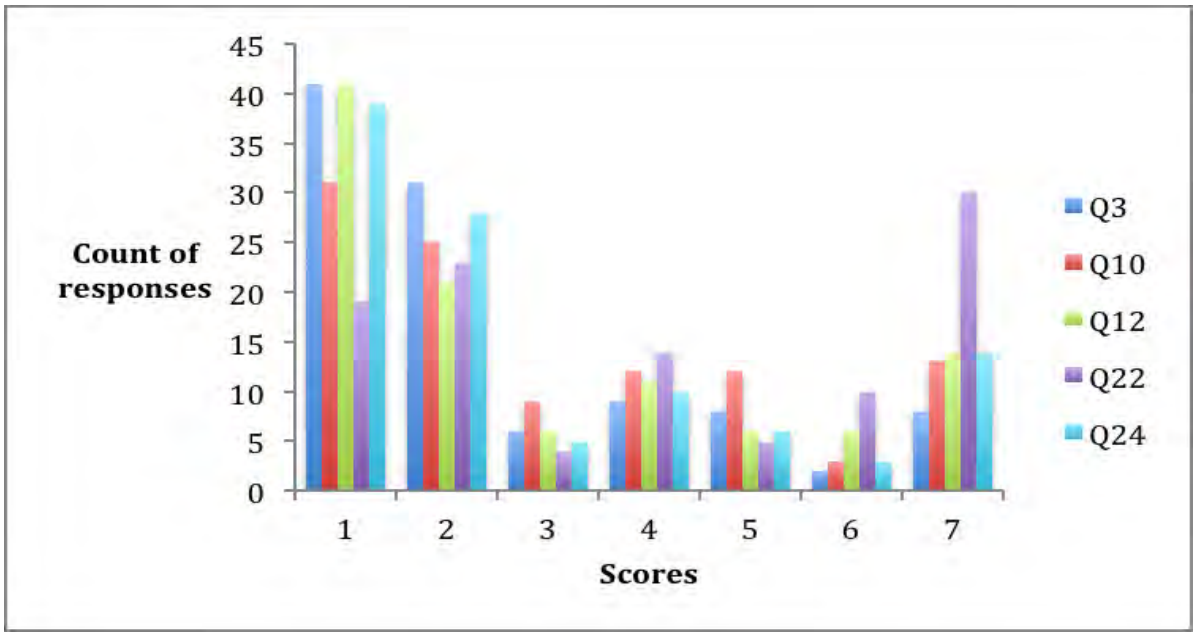

Figure 1: **Weight domain** frequency distribution of scores. The least impairment of the health related quality of life is indicated by a score of 7 and 1 indicates the worst impairment. Q3, Q10, Q12, Q22, 24 are the individual questions in this domain.

The weight domain had most participants selecting low scores as shown in figure 1. This domain had the most impact on the HRQoL. Figure 1 illustrates the frequency of the responses to each question for each score in the weight domain. Majority of the participants selected score of 1 or 2 except for Q22 *(How much of the time in the last two weeks did you feel like you are not sexy because of being overweight?).* This distribution indicated that weight impacted heavily the HRQoL in most of them. Figure 2 illustrates the frequency of the responses in the domain of body hair. Most of the participants selected the highest score of seven indicating the least impairment in their HRQoL. Body hair was the least bothersome problem in the majority of the participating women.

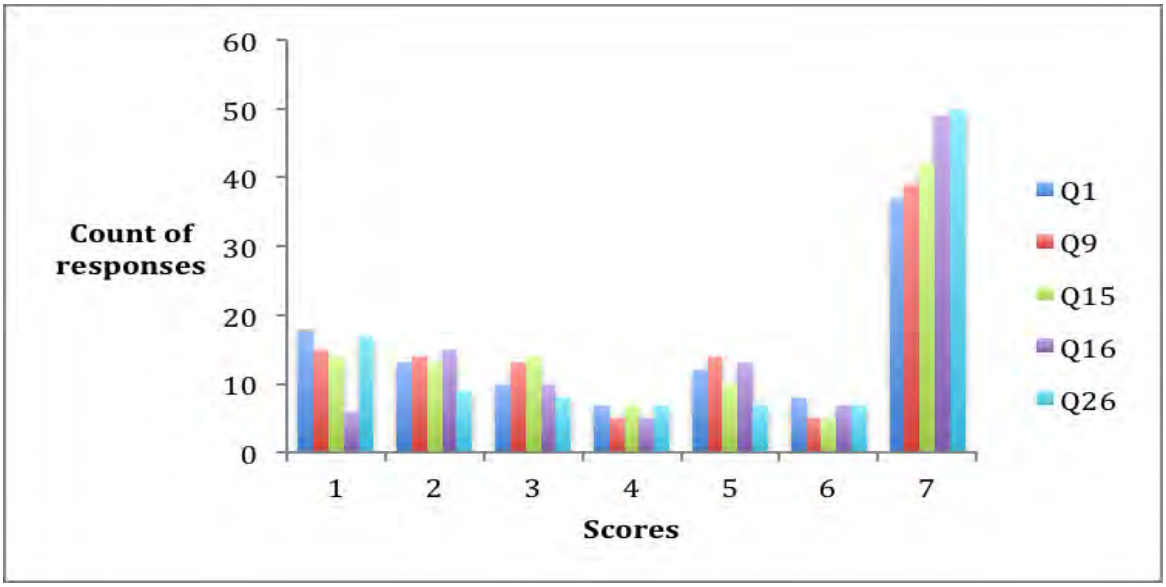

Figure 2: **Body hair** domain frequency distribution of scores. The least impairment of the health related quality of life is indicated by a score of 7 and 1 indicates the worst impairment. Q1, Q9, Q15, Q16 and Q26 refer to the questions in this domain.

The infertility domain frequency distribution of scores is illustrated in figure 3. The majority of the participants scored the lowest possible score of 1. There was a sizable number also scoring 7 suggesting the least impairment on the HRQoL. This problem of infertility impacted negatively the HRQOL in participating women with PCOS. Figures 4 and 5 present the frequency of the responses to each score the domains of menstrual problems and emotions. The lower scores had relatively more participants than the higher scores selecting them indicating a compromised HRQoL.

Table 8 presents the mean scores for the individual items in each domain. Some of the questions did not get responses. These were either erroneously omitted or were irrelevant to the respondent. These were questions referring to infertility and sexual relations in participants who were not sexually active Q13 (feeling afraid of not being able to have

children) and, Q25 (feeling sad because of infertility problems). Q7 (headaches on menstruation) and Q6 (moody as a result of PCOS) were omitted in error by two of the participants.

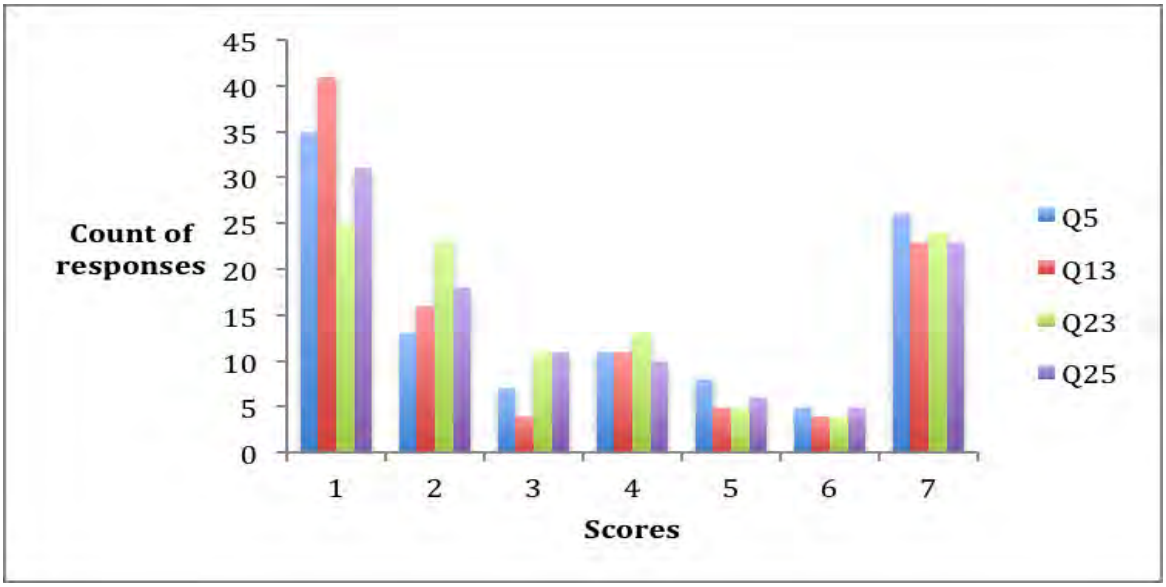

Figure 3: **Infertility domain** frequency distribution of scores. The least impairment of the health related quality of life is indicated by a score of 7 and 1 indicates the worst impairment. Q5, Q13, Q23, Q25 refer to the questions in this domain

Across all domains of the PCOSQ with the exception of the domain of body hair, there was a noticeable trend of the majority of participants selecting average or lower scores. This projected a compromised HRQoL in most of the participants. Weight was the most concerning issue and body hair had the least impact on the HRQoL.

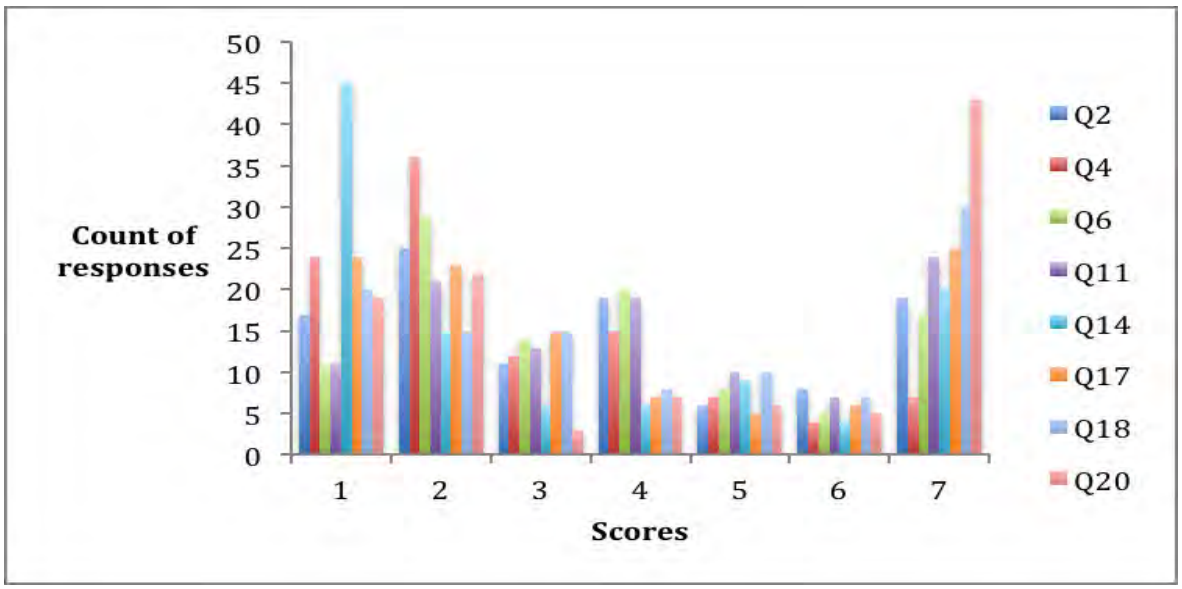

Figure 4: **Emotions domain**, frequency distribution of scores. The least impairment of the health related quality of life is indicated by a score of 7 and 1 indicates the worst impairment. Q2, Q4, Q6, Q11, Q14, Q17, Q18, Q20 refer to the questions constituting this domain.

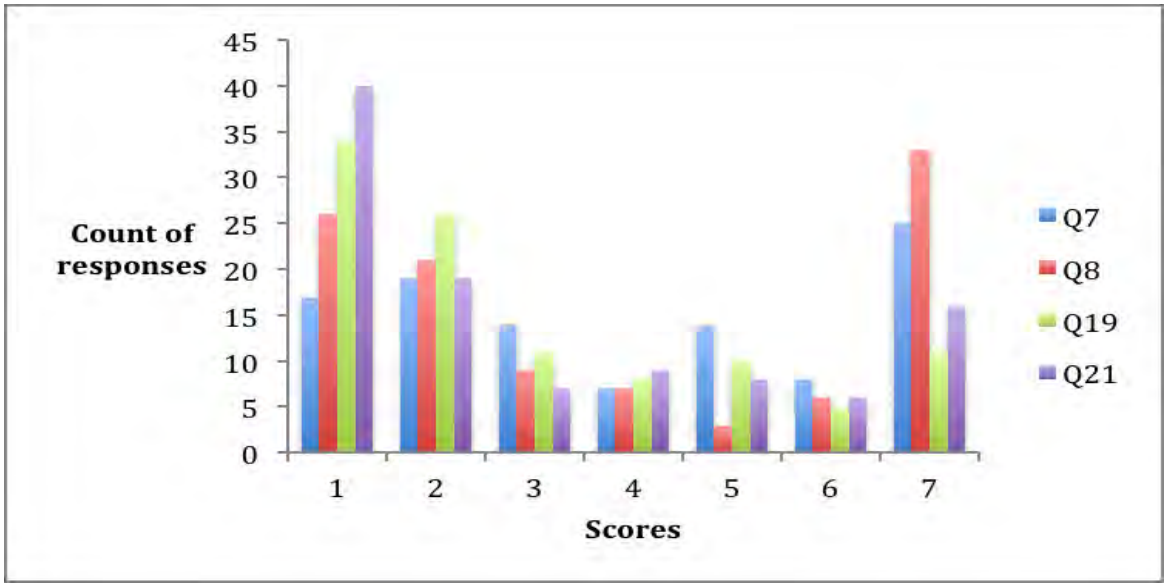

Figure 5: **MENSTRUAL problems domain**, frequency distribution of scores. The least impairment of the health related quality of life is indicated by a score of 7 and 1 indicates the worst impairment. This domain comprises of questions Q7, Q8, Q19 and Q21.

Table 8: Distribution of responses and percentages (%) for the scores of the PCOSQ

		Score N (%) [b]							
Domain	**Question**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total**
Emotions	**Q2**	17 (16.2)	25 (23.8)	11 (10.5)	19 (18.1)	6 (5.7)	8 (7.6)	19 (18.1)	105 (100.0)
	Q4	24 (22.9)	36 (34.3)	12 (11.4)	15 (14.3)	7 (6.7)	4 (3.8)	7 (6.7)	105 (100.0)
	Q6	11 (10.6)	29 (27.9)	14 (13.5)	20 (19.2)	8 (7.7)	5 (4.8)	17 (16.3)	104 (100.0)
	Q11	11 (10.5)	21 (20.0)	13 (12.4)	19 (18.1)	10 (9.5)	7 (6.7)	24 (22.9)	105 (100.0)
	Q14	45 (42.9)	15 (14.3)	6 (5.7)	6 (5.7)	9 (8.6)	4 (3.8)	20 (19.0)	105 (100.0)
	Q17	24 (22.9)	23 (21.9)	15 (14.3)	7 (6.7)	5 (4.8)	6 (5.7)	25 (23.8)	105 (100.0)
	Q18	20 (19.0)	15 (14.3)	15 (14.3)	8 (7.6)	10 (9.5)	7 (6.7)	30 (28.6)	105 (100.0)
	Q20	19 (18.1)	22 (21.0)	3 (2.9)	7 (6.7)	6 (5.7)	5 (4.8)	43 (41.0)	105 (100.0)
Body hair	**Q1**	18 (17.1)	13 (12.4)	10 (9.5)	7 (6.7)	12 (11.4)	8 (7.6)	37 (35.2)	105 (100.0)
	Q9	15 (14.3)	14 (13.3)	13 (12.4)	5 (4.8)	14 (13.3)	5 (4.8)	39 (37.1)	105 (100.0)
	Q15	14 (13.3)	13 (12.4)	14 (13.3)	7 (6.7)	10 (9.5)	5 (4.8)	42 (40.0)	105 (100.0)
	Q16	6 (5.7)	15 (14.3)	10 (9.5)	5 (4.8)	13 (12.4)	7 (6.7)	49 (46.7)	105 (100.0)
	Q26	17 (16.2)	9 (8.6)	8 (7.6)	7 (6.7)	7 (6.7)	7 (6.7)	50 (47.6)	105 (100.0)
Weight	**Q3**	41 (39.0)	31 (29.5)	6 (5.7)	9 (8.6)	8 (7.6)	2 (1.9)	8 (7.6)	105 (100.0)
	Q10	31 (29.5)	25 (23.8)	9 (8.6)	12 (11.4)	12 (11.4)	3 (2.9)	13 (12.4)	105 (100.0)
	Q12	41 (39.0)	21 (20.0)	6 (5.7)	11 (10.5)	6 (5.7)	6 (5.7)	14 (13.3)	105 (100.0)
	Q22	19 (18.1)	23 (21.9)	4 (3.8)	14 (13.3)	5 (4.8)	10 (9.5)	30 (28.6)	105 (100.0)
	Q24	39 (37.1)	28 (26.7)	5 (4.8)	10 (9.5)	6 (5.7)	3 (2.9)	14 (13.3)	105 (100.0)
Infertility problems	**Q5**	35 (33.3)	13 (12.4)	7 (6.7)	11 (10.5)	8 (7.6)	5 (4.8)	26 (24.8)	105 (100.0)
	Q13	41 (39.4)	16 (15.4)	4 (3.8)	11 (10.6)	5 (4.8)	4 (3.8)	23 (22.1)	104 (100.0)
	Q23	25 (23.8)	23 (21.9)	11 (10.5)	13 (12.4)	5 (4.8)	4 (3.8)	24 (22.9)	105 (100.0)
	Q25	31 (29.8)	18 (17.3)	11 (10.6)	10 (9.6)	6 (5.8)	5 (4.8)	23 (22.1)	104 (100.0)
Menstrual problems	**Q7**	17 (16.3)	19 (18.3)	14 (13.5)	7 (6.7)	14 (13.5)	8 (7.7)	25 (24.0)	104 (100.0)
	Q8	26 (24.8)	21 (20.0)	9 (8.6)	7 (6.7)	3 (2.9)	6 (5.7)	33 (31.4)	105 (100.0)
	Q19	34 (32.4)	26 (24.8)	11 (10.5)	8 (7.6)	10 (9.5)	5 (4.8)	11 (10.5)	105 (100.0)
	Q21	40 (38.1)	19 (18.1)	7 (6.7)	9 (8.6)	8 (7.6)	6 (5.7)	16 (15.2)	105 (100.0)

[a] *Q1-Q26 are the individual questions. N=105 is the total no of participants.*

[b] *Scores for each question range from 1-7 from the most impairment (1) to the least impact on the HRQOL(7)*

WHOQOL-BREF Results

The SPSS Syntax was used to process the data into domains for analysis. The syntax was used to transform the domain scores from a scale of 1 to 5 to that of 0 to 100. This transformation enabled us to perform comparative tests with the scores from the PCOSQ. Q1 *(How would you rate your quality of life?)* and Q2 *(How satisfied are you with your health?)* from the WHOQOL-BREF were assessed separately as they were not part of the domains. Table 9 presents the distribution of scores for Q1 and Q2. Most participants scored 4 when rating their quality of life implying a good quality of life. However, most participants were not satisfied with their health as indicated by a score of 2.

Table 9: The distribution of scores for Q1 and Q2 of the WHOQOL-BREF (N=105)

	[a] Frequency of responses for each score (percentage)				
	1	**2**	**3**	**4**	**5**
Q1. How would you rate your quality of life?	1 (0.8%)	9 (7%)	31(24.2%)	**55**[b] (43%)	9 (7%)
Q2. How satisfied are you with your health?	12 (9.4%)	**33**[b] (25.8%)	28 (21.9%)	26 (20.3%)	6 (4.7%)

[a] *The scores ranged from 1 to 5. A maximum impairment of the HRQOL was indicated by a score of 1 and the least impairment scoring 5*

[b] *Bold type highlights the most frequent score from the participants.*

The WHOQOL-BREF scores are presented in Table 10. The physical domain had the most impaired HRQoL. The social relationships domain had the least impairment in the HRQoL. The environment and psychological domains had scores between these two domains.

Table 10: The WHOQOL-BREF transformed domain scores [a]

Domain	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean	Standard Deviation
Physical	25.00	42.86	53.57	60.71	78.57	52.04	11.91
Psychological	25.00	54.17	62.50	70.83	91.67	61.35	13.47
Social Relations	8.33	54.17	75.00	91.67	100.00	69.91	22.90
Environment	28.13	50.00	59.38	71.88	90.63	59.11	14.77

[a] *The scores were transformed to a scale of 0-100. A score of 0 denotes the most impairment and 100 is the least impairment of the HRQoL.*

WHOQOL-BREF Internal consistency

The Cronbach's alpha test of internal consistency was performed in order to test how well the individual questions in the WHOQOL-BREF measured the same construct (HRQoL) in our women with PCOS. The expectation was that the questions would correlate, as they were all measuring HRQoL. A high correlation would indicate that the WHOQOL-BREF is a reliable measure of HRQoL in our population group. A poor correlation could mean either the question is poorly worded or does not belong. The Cronbach's alpha scores for the domains are presented in Table 11.

Table 11: WHOQOL-BREF Internal Consistency Reliability – Cronbach's alpha

Domain	Label	No. Of cases	No. Of items	Cronbach's Alpha
1	Physical	105	7	0.241
2	Psychological	105	6	0.437
3	Social Relationship	[a] 91	3	**0.705**
4	Environment	105	8	**0.704**

[a] *13 participants omitted Q21(How satisfied are you with your sex life?) stating that they were not sexually active 1 participant omitted Q20 (How satisfied are you with your personal relationships?) because she felt it did not apply to her as she was not in a relationship.*

The physical and psychological domains had Cronbach's alpha reliability coefficients less than 0.5 indicating poor internal consistency reliability. As a rule of thumb, George and Marley (2003) stated that values above 0.5 are acceptable for internal consistency reliability (64). Each domain was then assessed individually in a matrix to identify those items that were not correlating i.e. items when omitted from the domain, would result in a better correlation of the remaining items i.e. a higher alpha coefficient. The Cronbach's alpha was recalculated. In the physical domain, the highest Cronbach's alpha score of 0.53 was obtained after removing Q3 (*To what extent do you feel pain prevents you from doing what you need to do*). This made the reliability coefficient above 0.5, which was acceptable; implying the omission of this question would improve the physical domain internal consistency. In the psychological domain, the Cronbach's alpha score went up to 0.715 when Q26 was omitted *(How often do you have negative feelings, i.e. blue mood, despair, and depression)*. This showed that removing this question with improve the internal consistency of the questions in the psychological domain. The internal consistency of the WHOQOL-BREF improved with the omission of questions 3 and 26.

PCOSQ Validation

Test-Retest

To determine test-retest reliability, the PCOSQ was administered twice to participants at two separate times. The second interview was at least 2 days later and not beyond 7 days. Sixty-seven (64%) of the 105 participants completed the second PCOSQ (PCOSQ-2). The interviews were conducted telephonically two to seven days later. All the participants were offered the second telephonic interview, however some declined because of a busy work schedule while others were not contactable on their phones. Table 12 is a summary presentation of the domain scores of the PCOSQ-2. The results from the second interview mirrored the findings from the first interview. Weight impacted most on the HRQOL and body hair was the least concerning issue.

Table 12: PCOSQ-2, Domain raw scores (N=67) [a]

Domain	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean	Standard Deviation
Emotions	1.38	2.25	4.00	4.75	7.00	3.79	1.59
Body hair	1.00	2.80	5.40	7.00	7.00	4.83	2.04
Weight	1.00	1.80	2.80	4.60	7.00	3.14	1.77
Infertility problems	1.00	2.00	3.25	5.25	7.00	3.66	1.95
Menstrual problems	1.50	2.25	3.50	5.25	7.00	3.87	1.72

[a] *67 participants completed the second interview*

The PCOSQ-1 data from the initial interview was processed for comparative analysis. The questionnaires from participants who did not have the second interview were excluded from this comparison. The scores from both questionnaires were transformed from a scale of one to seven, to that of 0 to 100. This was achieved through re-coding each question score scale from 1-7 to that of 0-6 in order to get a minimum score of 0. We applied the formula shown below to achieve a new scale of 0-100 (53).

Scale score = total of raw scores for each item in the scale/maximum possible raw score x 100

The transformation enabled us to compare the scores from the PCOSQ with those from the WHOQOL-BREF as described later when construct validity was assessed. Table 13 presents the transformed scores from the PCOSQ-1 and PCOSQ-2 from the 67 participants in each set who completed the questionnaire twice. In this test-retest reliability analysis questionnaires from participants who completed the follow up interview were used. As a result, thirty-eight questionnaires from the initial PCOSQ interview were left out.

The Wilcoxon Sign rank test for paired data was used to perform the test-retest calculations of the PCOSQ. The intra-class correlations of the individual questions were calculated. The results are presented in Table 14 with a heat-map to illustrate the strength of the correlations. The darker colour indicates a stronger the correlation and the less intense colour reflecting a statistically weaker correlation. All the individual items demonstrated a statistically significant correlation with p-values less than 0.05.

Table 13: Summary of the transformed scores of the PCOSQ-1[A] and PCOSQ-2[B, C]

Domain	Minimum	25th Percentile	Median	75th Percentile	Maximum	Mean	Standard Deviation
Emotions PCOSQ-1	2.08	22.92	37.50	66.67	100.00	44.66	25.59
Body hair PCOSQ-1	0	30.00	60.00	96.67	100.00	62.00	33.52
Weight PCOSQ-1	0	10.00	26.67	50.00	100.00	34.86	28.92
Infertility problems PCOSQ-1	0	8.33	33.33	75.00	100.00	40.99	33.47
Menstrual problems PCOSQ-1	0	20.83	33.33	58.33	95.83	41.07	26.29
Emotions PCOSQ-2	6.25	20.83	50.00	62.50	100.00	46.42	26.54
Body hair PCOSQ-2	0	30.00	73.33	100.00	100.00	63.83	34.01
Weight PCOSQ-2	0	13.33	30.00	60.00	100.00	35.62	29.51
Infertility problems PCOSQ-2	0	16.67	37.50	70.83	100.00	44.22	32.60
Menstrual problems PCOSQ-2	8.33	20.83	41.67	70.83	100.00	47.89	28.70

[A] PCOSQ-1 = Questionnaires from the first interview:

[B] PCOSQ-2 = Questionnaires from the second interview: Both questionnaire scores were converted to a scale of 0-100 from that of 1-7 as described in the text.

[C] 67 participants completed the PCOSQ on two occasions.

The intra-class correlations for the test-retest analysis were performed on the corresponding domains, i.e. PCOSQ-1 domains and PCOSQ-2 domains. The domain correlation coefficients were then calculated and the results are presented in Table 15. All

the domains showed statistically significant correlations, implying that the PCOSQ-1 questions correlated to their counterparts in PCOSQ-2.

Table 14: Individual question Intra-class Correlation PCOSQ-1 vs. PCOSQ-2

Questions	Number of responses	Correlation Coefficient	p-value
Q1	67	0.833	<0.005
Q2	67	0.680	<0.004
Q3	67	0.726	<0.003
Q4	67	0.604	<0.002
Q5	66	0.720	<0.001
Q6	67	0.524	<0.001
Q7	67	0.626	<0.001
Q8	67	0.575	<0.001
Q9	67	0.763	<0.001
Q10	67	0.714	<0.001
Q11	67	0.845	<0.001
Q12	67	0.701	<0.001
Q13	67	0.826	<0.001
Q14	67	0.642	<0.001
Q15	67	0.862	<0.001
Q16	67	0.716	<0.001
Q17	67	0.702	<0.001
Q18	67	0.733	<0.001
Q19	67	0.794	<0.001
Q20	67	0.587	<0.001
Q21	67	0.761	<0.001
Q22	67	0.801	<0.001
Q23	67	0.592	<0.001
Q24	67	0.771	<0.001
Q25	66	0.880	<0.001
Q26	67	0.732	<0.001

The P-value was < 0.05 in all the domains indicating statistically significant correlation of individual questions.

The intra-class correlation coefficients were above 0.8 demonstrating good test-retest reliability in all domains. This means that the PCOSQ gave consistent scores at both times it was administered. The PCOSQ demonstrated good test-retest reliability in this study.

Table 15: Domain Intra-class Correlation PCOSQ-1 vs. PCOSQ-2

Domain	N	Correlation Coefficient	P-value
Emotions	67	0.909	<0.001
Body hair	67	0.929	<0.001
Weight	67	0.856	<0.001
Infertility problems	67	0.867	<0.001
Menstrual problems	66	0.820	<0.001

The P-value was < 0.05 in all the domains indicating statistically significant correlations.

Internal Consistency of the PCOSQ

The Cronbach's Alpha coefficient was used to assess the internal consistency of the PCOSQ. The reliability of the PCOSQ items making up each of the domains was tested through the inter-item correlations. This measures how items at a particular point relate i.e. if the scores remained consistently related independent of their magnitude. The Cronbach's alpha coefficients were above 0.7 in all domains with the exception of the menstrual domain, which scored 0.65. Cronbach's alpha scores less than 0.5 represent weak correlations. According to the rule of thumb by Gliem and Gliem in 2003 the internal consistency was good in all domains of the PCOSQ in this study (64).

Table 16 presents a summary of the Cronbach's alpha scores. Domain 5 of menstrual problems had the lowest alpha coefficient of 0.650. An item correlational matrix was performed subsequently to identify questions which when omitted would improve the alpha score. There were no improvements in the alpha score even from the correlational matrix calculations. The alpha score of 0.650 was still acceptable as indicative of good internal consistency. Overall, the PCOSQ demonstrated a good internal consistency.

Table 16: Internal consistency reliability analysis of the PCOSQ – Cronbach's alpha

Domain		Respondents	Questions	Cronbach's Alpha
1	Emotions	104	8	0.850
2	Body hair	105	5	0.920
3	Weight	105	5	0.876
4	Infertility problems	103	4	0.873
5	Menstrual problems	104	4	0.650

The alpha score was at least 0.65 in all domains, indicative of good internal consistency of the PCOSQ. The lowest score was observed in the domain of menstrual problems

Construct Validity

This test was performed to see how well the PCOSQ measured the HRQoL in our population sample. To determine the construct validity, the PCOSQ domain scores from the first interview were compared with those from the WHOQOL-BREF. The hypothesis was that, certain domains from the two questionnaires measured related constructs (concepts); therefore they should have statistically coherent outcomes. The psychological domain from the WHOQOL-BREF was correlated with the emotions and infertility domains of the PCOSQ. The physical domain of the WHOQOL-BREF was correlated with the body hair, weight and menstrual domains of the PCOSQ. The Spearman's nonparametric correlations calculation was used to compare the matched domains. The PCOSQ scores from the first interview were transformed from a scale of 1-7 to that of 0-100 (as described previously) in order to match those of the WHOQOL-BREF. WHOQOL-BREF data were edited using the SPSS Syntax file. This enabled the scores to be converted from 1-5 to a scale of 0-100. Table 17 presents the correlation outcomes from the 2 questionnaires.

Table 17: Spearman's correlation analysis of the PCOSQ and the WHOQOL-BREF (N=105)

PCOSQ Domain		WHOQOL-BREF Domain	
		Psychological	Physical
Emotions	Correlation Coefficient	0.277	
	P-value	**0.004**[a]	
Infertility problems	Correlation Coefficient	0.218	
	P-value	**0.026**	
Body hair	Correlation Coefficient		0.133
	P-value		0.176
Weight	Correlation Coefficient		0.247
	P-value		**0.011**
Menstrual problems	Correlation Coefficient		0.213
	P-value		**0.029**

[a] P < 0.05 = *Bold type denotes a statistically significant correlation. Transformed domain scores were used in the correlational analysis. A total of 105 participants completed both questionnaires at the initial interview.*

The psychological domain of the WHOQOL-BREF correlated with the emotional and infertility domains of the PCOSQ. The physical domain from the WHOQOL-QOL correlated with the domains of weight and menstrual problems as shown in Table 17. However, the physical domain did not demonstrate a statistically significant correlation with the body hair domain from the PCOSQ. Overall, this comparison illustrated a good construct validity of the PCOSQ.

Factor Analysis

Factor analysis was performed in order to determine if the questions would remain in their respective domains of the original PCOSQ i.e. to confirm the domain structure of the PCOSQ. The sample size for this analysis was 105. This analysis was performed on responses from the first interview.

The Principal Components method of extraction was used to determine the number of domains in which the questions would cluster from the responses of the participants. This was followed by Varimax rotation, an orthogonal rotation method that we used to identify the distribution of the questions in the identified domains.

Before determining the number of domains, a value called communality was calculated for each question. Communality is the estimate of an individual question's common variance from the rest of the questions in the questionnaire. Communalities greater than 0.3, were considered for component extraction i.e. identification of the number of domains. All questions had communalities greater than 0.3. The Eigenvalue and the Kaiser Normalisation criterion were used to determine how many components to extract. The Cattell's Scree Plot of questions (items), with Eigenvalue greater than 1 was used to determine the number of domains in the questionnaire. The point of inflexion indicated 5 domains as in the original questionnaire as shown in Figure 6.

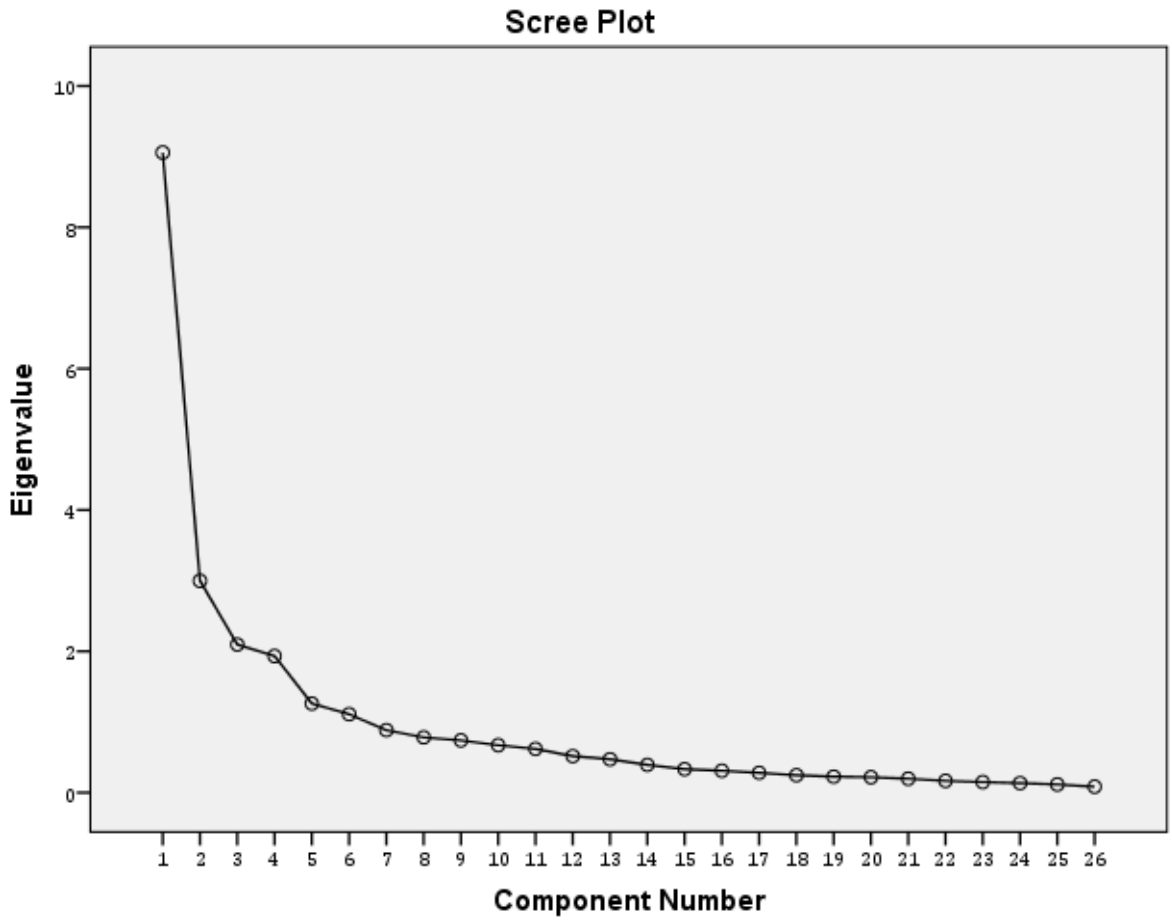

Figure 6: The Cattell's Scree Plot. Questions with the Eigenvalue greater than 1 were considered.

The components above the inflexion point (elbow) of the curve were retained. Five components were identified as shown in Figure 6. These accounted for 71% of the variance even after rotation. This indicated that from the participant responses, five domains were identified. Finally, in order to determine the distribution of these questions in the five domains, a Varimax Rotation was performed. A rotated component matrix was produced to determine how these questions would load in each of the five domains.

Table 18: Factor analysis of the PCOSQ rotated component matrix

PCOSQ-Question	Domain	Rotated component matrix [a]				
		1	2	3	4	5
Q 26	Hair	**0.869**[b]				
Q 15	Hair	**0.856**[b]				
Q 1	Hair	**0.855**[b]				
Q 9	Hair	**0.838**[b]				
Q 16	Hair	**0.795**[b]				
Q 10	Weight		**0.86**[b]			
Q 3	Weight		**0.837**[b]			
Q 24	Weight		**0.825**[b]			
Q 12	Weight		**0.778**[b]			
Q 22	Weight		**0.631**[b]			
Q 23	Weight		**0.517**			
Q 2	Emotions			**0.726**[b]		
Q 7	Emotions			**0.65**		
Q 11	Emotions			**0.641**[b]		
Q 19	Emotions			**0.637**		
Q 6	Emotions			**0.632**[b]		
Q 21	Emotions			**0.561**		
Q 18	Emotions			**0.53**[b]		
Q 4	Emotions			0.449[b]		
Q 17	Emotions			0.43[b]		
Q 14	Emotions			0.389[b]		
Q 13	Infertility				**0.917**[b]	
Q 25	Infertility				**0.871**[b]	
Q 5	Infertility				**0.823**[b]	
Q 8	Menstrual					**0.808**[b]
Q 20	Menstrual					**0.796**

Extraction method: Principal component analysis: Varimax rotation with Kaiser Normalization. Loading of communalities above 0.3:

[a] Rotation Convergence in six iterations:

[b] Loads in the same factor as in the PCOSQ, Cronin et al (1998): Bold type indicates factor loading values ≥ 0.5.

The cells were sorted and conditionally formatted so that larger numbers are darker on the heat map as shown in Table 18. Values above 0.5 were considered as belonging to that

respective domain, while those with values less than 0.5 were suggestive of a less than optimal fit to the domain.

All but questions 7, 19, 20, 21 and 23 retained the positions in their respective domains as in the original questionnaire by Cronin *et al* (1998) (45). The first 5 questions loaded on Factor one (body hair), were retained as in the original questionnaire.

The next 6 questions loaded on factor two (weight), however Q23 (*lack of control over the situation with PCOS*) which in the PCOSQ is in the infertility domain, loaded in this weight domain. Intuitively this question could be moved to either the infertility or the weight domain depending on how the participants perceived the impact of lack of control over the situation with PCOS in weight as more overwhelming than that in infertility.

The next 7 questions (Q2, 7, 11, 19,6,21 and 18) loaded on factor three (emotions). Q 2, 11, 6, and 18 were retained in this domain as in the original questionnaire. Questions 7, 19 and 21, which fall in the menstruation domain in the original questionnaire, loaded in the emotions domain. Questions 4, 17 and 14 do not load highly on the emotions domain but intuitively fit into this domain. Questions 13, 25 and 5 loads on Factor four (infertility) as in the original questionnaire, however question 23 loaded in the weight domain in our analysis. The last 2 questions (Q8 and 20) load on Factor five (menstrual problems). This domain managed to retain Q8 only from the original questionnaire. Q20, which refers to the menstrual periods, loaded in this domain and seemed intuitively appropriate.

As highlighted earlier on, some of the factors can be assigned intuitively to the best fitting domain. Even though some of the questions were rearranged in the secondary factor analysis, the principal domains were retained. In essence, the original domain structure of the PCOSQ was retained in secondary factor analysis, thus confirming the domain structure of the PCOSQ from our participants' responses.

Face Validity

The gynaecological endocrine specialists and nursing sisters reviewed the questionnaire. The PCOSQ was found to be practical and appropriate for use in the clinical population of South Africa. Most participants acknowledged that the PCOSQ addressed all the issues that bothered them. They identified the issues addressed by the questionnaire. Participants welcomed this questionnaire especially when it came to issues of sexual health which most of them found hard to express. None of the participating women requested counselling following the interview. All the participants completed the questionnaire. The questionnaire was satisfactory for use in our clinical population, as the respondents easily understood and accepted it.

Correlating PCOSQ Domain Scores with FAI, IR and Metabolic Syndrome

This analysis was undertaken to look for associations between the domains of the PCOSQ with the categories of the metabolic syndrome, insulin resistance and free androgen index.

The median weight domain had a statistically significant correlation with both the metabolic syndrome and insulin resistance categories. There was a statistically significant difference between the weight domain and the categories of metabolic syndrome. This finding reinforced the role of weight in insulin resistance and metabolic syndrome among the participants. However the median scores in the domains of emotions, body hair, menstrual problems and infertility did not show any statistically significant correlation with the metabolic syndrome, insulin resistance categories and free androgen index categories. Table 19 summarises the relations and the calculated P-values.

Table 19: Correlation of the PCOSQ domains with the categories of MS, IR and FAI [b]

Domain	**Wilcoxon-Mann-Whitney U test P-value**		
	MS	IR	FAI
Emotions	0.104	0.425	0.325
Body hair	0.345	0.914	0.836
Weight	**0.025**[a]	**0.001**[a]	0.927
Infertility problems	0.067	0.258	0.239
Menstrual problems	0.298	0.445	0.789

The level of significance is P< 0.05:

[a] bold type indicates a significant correlation:

[b] MS = metabolic syndrome, IR=insulin resistance FAI=free androgen index

The weight domain correlated with the metabolic syndrome and the insulin resistance categories. This meant that there was a statistically demonstrated relationship between the quality of life scores from the weight domain and the presence of metabolic syndrome and insulin resistance.

Chapter 4: Discussion

This study aimed to evaluate the psychometric properties of the PCOSQ and obtain baseline information on a clinical population in South Africa. The study established that the PCOSQ is valid for use in this clinical population.

The participants were recruited from the Gynaecological Endocrinology Clinic at Groote Schuur Hospital (GSH) in Cape Town. These patients presented with clinical problems related to PCOS including infertility, hyper-androgenism and menstrual problems among others. There are over 1600 patients recorded in the database of the PCOS clinic. The ethnic composition of the patients is 88 % mixed ancestry, 10 % black, 1 % white and 1% Asian ancestry. The general gynaecological outpatients comprise of 30% Black South African women 65% mixed ancestry and 3% white and less than 1% Asian. This is against a background population distribution in Cape Town in which 42% of the population is of mixed ancestry, 39% Black, 16% White, and 1.4% Asian, according to the 2011 National population census (69). Within these groups there are also cultural and religious differences.

Notable in the study sample was the absence of local Black patients presenting for follow up management or on-going care. This racial disparity in the presentation and health seeking trends in this population group in our community needs to be explored further as we do not have information on the prevalence of PCOS in all local ethnic groups.

From the development of the PCOSQ, Cronin *et al.* (1998) noted the impact scores of the infertility items among the African-American ethnic group in their study group in the USA to be the highest compared to other population groups (45). Ladson *et al.* (2011) in the USA noted some minor racial differences between the black and white women in the PCOS phenotype but recommended further research on the impact of race on PCOS treatment effects (37). Further studies on patterns of presentation, perceptions and impact of PCOS in Black South African women are needed.

The metabolic syndrome was present in 24 % of the participating women. Components of metabolic syndrome were present even in participants who had not yet developed the syndrome. Erhmann *et al.* (2006) in a multicentre trial concluded that metabolic syndrome and its individual components are common in PCOS, particularly among women with high insulin levels and raised BMI (31). This is in keeping with findings from our study, which we found the presence of the components of metabolic syndrome alongside insulin resistance and high BMI.

The mean scores of the PCOSQ reflect the poor HRQoL in the participants. PCOS had a negative impact on the HRQOL among the women. The weight domain had the lowest mean score. This impacted the most on the HRQOL of these women with PCOS. The body hair domain had the highest mean score. This domain was the least concerning to the participants. The domains of infertility, menstrual problems and emotions also impacted negatively on the HRQOL. The impact of weight on the HRQOL among women with PCOS

cannot be over emphasized. Addressing weight issues has a positive influence on the metabolic syndrome, insulin sensitivity and fertility.

Jones *et al.* (2004) in the United Kingdom had similar findings that highlighted the importance of addressing the weight related issues (53). Weight impacted most on the HRQOL in studies by Guyatt *et al.* (2004) in the United Kingdom, McCook *et al.* (2005) in the USA and Barnard *et al.* (2007) in the United Kingdom (22,52,55). Barnard *et al.* (2007) compared the impact of weight in PCOS patients and weight-matched controls, noted that weight concerns were more severe in the PCOS group (55). Locally, studies are needed to compare healthy control groups to PCOS to ascertain the overall net impact of PCOS in the overweight population subgroup (55). Weight and infertility issues among women with PCOS have been studied in the literature and found to affect the psychological wellbeing of patients with PCOS (21). Coffey *et al.* (2006) in the United Kingdom found that even women with PCOS with normal weight at one time in their lives have possibly been overweight at some point (54). These women constantly felt that they have problems with their weight and had a poor HRQOL. Weight loss has been shown to improve the HRQOL (54). Addressing issues related to weight gain is important when managing women with PCOS.

McCook *et al.* (2014) in the USA looked at the different contributions of PCOS manifestations (infertility, hirsutism, obesity and menstrual problems) to psychological symptoms (23). They validated the link between the manifestations of PCOS and the psychological symptoms using the Brief Symptom Inventory and the PCOSQ (23). From that study it was noted that participants had poor scores in the subset of psychological wellbeing

further reinforcing the above finding of a negative quality of life in women with PCOS. They also found that each domain had a unique subset of psychological symptoms and that the menstrual domain had the most salient features and deserved particular attention as a marker for psychological risk (23). This finding justifies the importance of addressing all issues pertaining to the PCOS manifestations. The psychological manifestation of these symptoms may not necessarily parallel those of HRQOL. The importance of addressing all the issues pertaining to the presentation of PCOS cannot be overemphasized, and each symptom must be weighed cautiously bearing in mind the physical and psychological effects that impact the HRQoL.

The WHOQOL-BREF was used to assess general health and wellbeing of the participants. This is a generic tool for measuring the HRQoL. The scores from this tool were indicative of a compromised quality of life in participating women with PCOS. These results were parallel to those from the disease specific PCOSQ. This may be related to the psychological morbidity due to the manifestations of PCOS as highlighted by McCook *et al.* (2014) (23). The WHOQOL-BREF is not specific to patients with PCOS and on its own lacks the specificity to address the relevant issues pertaining to PCOS. Despite its generic nature, results from this study pointed towards a compromised health related quality of life among the participating women.

The WHOQOL-BREF was elected over the SF-36 because of its multinational and diverse cultural development origins. The WHOQOL-BREF internal consistency was assessed using

the Cronbach's alpha coefficient score. The social and environment domains had alpha scores greater than 0.7 demonstrating a good internal consistency. However, the physical and psychological domains had alpha scores of 0.24 and 0.437 respectively; which demonstrated a poor internal consistency in these domains. These are domains impacted by the PCOS i.e. the physical and psychological wellbeing as highlighted by McCook *et al.* (2014) (23). The WHOQOL-BREF is not specific for measuring HRQOL in women with PCOS.

These two domains i.e. the physical and psychological of the WHOQOL-BREF were explored to identify individual questions that may have attributed to the poor internal consistency. A correlational matrix of the items in the domains was performed. By removing each question from its respective domain and recalculating the Cronbach's alpha coefficient, we identified questions that when omitted improved the score. In the Physical Domain, the highest Cronbach's alpha score of 0.53 was obtained after removing Q3 *(To what extent do you feel pain prevents you from doing what you need to do).* This made the reliability coefficient above 0.5, which was acceptable. This question could be explored further as pain is a subjective perception that has cultural, physical and emotional components. This question is also not specific, as it does not state the type of pain and the context of in which it is perceived. In the Psychological Domain, the Cronbach's alpha score went up to 0.715 when Q26 was omitted *(How often do you have negative feelings, i.e. blue mood, despair, and depression).* This question was perceived as being too broad and would have been improved by splitting the items. This question needs to be examined in future studies.

Skevington *et al.* (2004) recommended that despite its strengths of a cross-cultural developmental history, the WHOQOL-BREF needs more work on validity, sensitivity and feasibility (47). The WHOQOL-BREF lacked in internal consistency in measuring the health related quality of life in women with PCOS particularly in the physical and psychological domains.

The WHOQOL-BREF was used to measure the construct validity of the PCOSQ. The PCOSQ demonstrated good construct validity. We hypothesized that the domains from the PCOSQ that measure related constructs with the domains of the WHOQOL-BREF should show a statistically significant correlation. The domains of emotions and infertility from the PCOSQ correlated with the psychological domain of the WHOQOL-BREF. The domain of weight and menstrual problems demonstrated a statistically significant correlation with the physical domain from the WHOQOL-BREF. The domain of body hair, however, failed to show a statistically significant correlation with the physical domain. As noted in from the results this domain had the least impact on the HRQOL. The PCOSQ demonstrated good construct validity.

The internal consistency of the PCOSQ in our study was good. The Cronbach's alpha correlation coefficient values were above 0.8 in the domains of emotions, body hair, infertility problems and weight. The lowest score of 0.65 was from the menstrual domain. A correlational matrix was performed in this domain to identify questions that could have resulted in the lowest score from the menstrual domain. The Cronbach's alpha coefficient scores remained unchanged. This was still an acceptable internal correlation coefficient

according to George and Marley (2003) (64). Studies elsewhere have come up with similar findings.

Jones *et al.* (2004) in the United Kingdom evaluated the psychometric properties of the PCOSQ, and had similar findings with respect to the menstrual domain (53). Guyatt *et al.* (2004) in Canada attributed the low alpha coefficient in their study to the question referring to headaches in the menstruation domain (52). They noted that this item did not relate strongly to its counterparts and questioned its appropriateness in the PCOSQ (52). Amini *et al.* (2011) in Iran found an adequate validity and reliability of the PCOSQ in all the domains except the menstrual problems domain (56). Bazarganipour *et al.* (2014) in Iran found that moving the question on irregular menstrual periods *(Question 8)* from the emotional domain to the menstrual domain significantly improved the reliability of both domains (70). The domain of menstrual problems requires further evaluation in our clinical population.

Test-retest reliability of the PCOSQ showed intra-class correlations above 0.8 in all the domains. This demonstrated the stability and consistency of the PCOSQ over time. This is despite the fact that the set up for the second interview was done in a different environment i.e. telephonically in the comfort of the patient's home environment. According to a study by Keszei *et al.* (2010), test-retest reliability coefficients between 0.7 and 0.8 are acceptable for research tools (63).

The interval of two to seven days between the interviews was elected to reduce recall bias while still remaining within two weeks as stated by the questionnaires. In their study, Barnard *et al.* (2007) used the Internet to conduct interviews citing its acceptability,

affordability and anonymity as the advantages (55). A review of the studies in the literature found no difference in Internet samples compared to other samples obtained through the telephone and physical mail. The limiting factors of the Internet are its limited accessibility and the target population that tends to be the younger age group (55).

Secondary factor analysis was performed to confirm the domain structure of the PCOSQ. The sample size of 105 participants was adequate for this analysis, which was a ratio of 1:4 items to participants (61). The domain structure was retained maintaining the original domains of infertility problems, menstrual problems, weight and emotions. The composition of the domains however was different. There was rearrangement of 5 questions, with the remainder retaining positions in their respective domains. The composition of the menstrual domain was the most affected retaining one question *(Q8)* and gaining *(Q20)*, which refers to the menstrual periods. This seemed intuitively appropriate. *(Q7)* (Headaches *in relation to menstruation*), Q19 (*Abdominal bloating in relation to menstruation*) and Q21 (*menstrual cramps*) loaded on the emotions domain instead. These could intuitively be reassigned to the menstrual domain to retain the domain structure of the PCOSQ.

Face validity was performed to identify any items that the expert clinicians perceived as irrelevant. These if not identified could affect the participant's responses by either causing a low response rate or questions being taken less seriously. In this study we identified none such items. The participants' impression of the questionnaire in general was that the PCOSQ was relevant to them as it addressed all issues they were concerned about. There were no

items identified as missing and which needed to be included. As we continue to use the questionnaire in our clinical population it is possible that some items may be adopted and or revised in future studies. Jones *et al.* (2004) and Coffey *et al. (*2006) perceived Question 14 *(During the past two weeks, how much of the time have you felt afraid of getting cancer?)* as causing unnecessary worry among the participants (53,54). This was not realised in participants from this study.

The psychometric properties of the PCOSQ were in keeping with findings from studies done by Coffey *et al.* (2006) in the United Kingdom, Guyatt *et al.* (2004) in Canada, Jones *et al.* (2004) in the United Kingdom and Jedel *et al.* (2008) in Sweden (52-54,71). Jones *et al.* (2004) suggested the addition of the acne subscale in their validation study and Barnard *et al.* (2007) added this subscale (55). From our sample 44 out of 105 (42%) of the participants had acne among their presenting symptoms. This item, absent in the original questionnaire is prevalent enough to warrant an inclusion in our clinical population. Cronin *et al.* (1998) considered items that were endorsed by at least 50% of the participants (45). During the development of the original questionnaire, acne was not an issue among their selected group of patients interviewed. This led to the omission of this item. Jones *et al.* (2004) and Jedel *et al.* (2008) recommended the inclusion of the acne subscale from their respective studies (53,71). Barnard *et al.* (2007) added acne to the PCOSQ when they evaluated the HRQOL in PCOS their findings were that the acne subscale strengthened the face validity and contributed to the factor structure (55). This item needs further examination for inclusion in the PCOSQ in future studies in our population.

The strength of the study was the sample size that was sufficient to enable factor analysis and test-retest reliability. A limitation was that the study recruited women attending the gynaecological endocrine clinic for their follow up care. These women had presented with gynaecologic complications associated with PCOS. This sample automatically excluded women who presented elsewhere e.g. dermatology and medical endocrine clinics with metabolic complications that are specific to those clinics.

This study recruited participants with PCOS as defined by the Rotterdam criteria (2003). The PCOSQ was developed from participants with the syndrome as defined by the NIH criteria. This study offered us an opportunity to test this questionnaire in our population of women with PCOS as per the Rotterdam PCOS definition (2003). The psychometric properties of the questionnaire were valid in our study sample. Despite these differences of definitions the questionnaire can be used in our PCOS population as demonstrated from our study results.

Validation of the PCOSQ in local languages of Afrikaans and Xhosa will be undertaken following this study.

Further studies are needed to explore the contributions of the different elements of PCOS to the psychological morbidity and HRQOL. Also, future studies that will compare the general health related quality of life in women with PCOS with healthy controls and with other non-PCOS related chronic conditions. Validation in local languages should be undertaken to cover a more diverse population. The questionnaire's longitudinal and discriminant validity also needs to be tested in randomised controlled trials to test its sensitivity to the effect of interventions and change in our local population. This will enable

us to use the questionnaire to measure treatment effect on HRQoL, and to compare the effects on HRQoL from different interventions.

Chapter 5: Conclusions

The psychometric properties of the PCOSQ are valid for use in the clinical population of South Africa. The domain on acne needs further evaluation for possible inclusion into the PCOSQ in future studies. The domain of menstrual problems needs further evaluation to strengthen the factor structure of the PCOSQ in the clinical population of South Africa.

The WHOQOL-BREF did not have a good internal consistency when compared to the PCOSQ when measuring HRQOL in women with PCOS particularly in the physical and psychological domains. This questionnaire is not specific to PCOS unlike the PCOSQ.

In our study PCOS impacted negatively on the health related quality of life in affected women. The concurrent use of a generic measure of health, the WHOQOL-BREF highlighted the poor general quality of life in women with PCOS. Attention should be given to the psychological and mental wellbeing of women affected by PCOS in addition to addressing their physical symptoms.

Weight was the highest contributor of the compromised HRQOL in our study participants. Hirsuitism had a less impact on the HRQOL. A positive association between insulin resistance and acanthosis nigricans was observed. The metabolic syndrome and insulin resistance

contributed significantly to the morbidity associated with PCOS. Addressing issues around weight gain is crucial in improving the HRQOL.

The PCOSQ is a valid tool for measuring HRQOL in the clinical population of South Africa. Translation and validation in local languages should be undertaken to broaden its use in our clinical population.

References

(1) Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Task Force on the Phenotype of the Polycystic Ovary Syndrome of the Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009;91:456-488.

(2) Franks S. Polycystic ovary syndrome. N Engl J Med 1995;333:853-61.

(3) The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Consensus Statement: Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-47.

(4) Balen AH, Laven JS, Tan S, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update 2003;9:505-514.

(5) Fauser B, Tarlatzis BC, Rebar R, Legro R, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). Human Reprod 2012;27(1):14-24.

(6) Diamanti-Kandarakis E. PCOS in adolescents. Best Pract Res Clin Obstet Gynaecol. 2010;24:173-183.

(7) Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Obstet Gynecol 2010;203:201-205.

(8) Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. Reprod Endocrinol 2014(6 (20)):22-35.

(9) Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev Endocr Metab Disord. 2007;8(2):127-141.

(10) Balen A. Pathogenesis of polycystic ovary syndrome—the enigma unravels? Lancet 1999;354(9183):966-967.

(11) Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol 2014 Oct;171(4):P1-29.

(12) Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, et al. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. Int J Reprod Med 2014;2014.

(13) Chang WY, Knochenhauer ES, Bartolucci AA, Azziz R. Phenotypic spectrum of polycystic ovary syndrome: clinical and biochemical characterization of the three major clinical subgroups. Fertil Steril 2005;83:1717-1723.

(14) Solomon CG. The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. Endocrinol Metab Clin of North Am 1999;28:247-263.

(15) Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab 1999;84(6):1897-1899.

(16) van der Spuy ZM, Le Roux PA, Matjila MJ. Cyproterone acetate for hirsutism. Cochrane Database Syst Rev. 2003; 4:CD00019:1-15

(17) Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989 Sep;38:1165-1174.

(18) Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or Hyperinsulinemia. J Clin Endocrinol & Metab 1987;65:499-507.

(19) Sam S, Dunaif A. Polycystic ovary syndrome: syndrome XX? Trends in Endocrinol Metab 2003;14:365-370.

(20) Hsu M. Changes in the PCOS phenotype with age. Steroids 2013;78:761-766.

(21) Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod 2008;23:462-477.

(22) McCook JG, Reame NE, Thatcher SS. Health-Related Quality of Life Issues in Women With Polycystic Ovary Syndrome. J Obstet Gynecol Neonatal Nurs 2006;34:12-20.

(23) McCook JG, Bailey BA, Williams SL, Anand S, Reame NE. Differential Contributions of Polycystic Ovary Syndrome (PCOS) Manifestations to Psychological Symptoms. J Behav Health Serv Res 2014:1-12.

(24) Liang SJ, Hsu CS, Tzeng CR, Chen CH, Hsu MI. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:3443-3449.

(25) Trent M, Austin SB, Rich M, Gordon CM. Overweight status of adolescent girls with polycystic ovary syndrome: body mass index as mediator of quality of life. Ambul Pediatr 2005;5:107-111.

(26) Harris-Glocker M, Davidson K, Kochman L, Guzick D, Hoeger K. Improvement in quality-of-life questionnaire measures in obese adolescent females with polycystic ovary syndrome

treated with lifestyle changes and oral contraceptives, with or without metformin. Fertil Steril 2010;93(3):1016-1019.

(27) Panidis D, Tziomalos K, Macut D, Delkos D, Betsas G, Misichronis G, et al. Cross-sectional analysis of the effects of age on the hormonal, metabolic, and ultrasonographic features and the prevalence of the different phenotypes of polycystic ovary syndrome. Fertil Steril 2012;97(2):494-500.

(28) Hart R, Doherty DA, Mori T, Huang R, Norman RJ, Franks S, et al. Extent of metabolic risk in adolescent girls with features of polycystic ovary syndrome. Fertil Steril 2011;95:2347-2353.

(29) Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol 2013;98(12):4565-4592.

(30) Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab 2006;91(2):492-497.

(31) Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:48-53.

(32) Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes 2010 May 15;1:36-47.

(33) Schmid J, Kirchengast S, Vytiska-Binstorfer E, Huber J. Infertility caused by PCOS:health-related quality of life among Austrian and Moslem immigrant women in Austria. Hum Reprod 2004;19:2251-2257.

(34) Himelein MJ, Thatcher SS. Polycystic ovary syndrome and mental health: a review. Obstet Gynecol Surv 2006;61:723-732.

(35) Kumarapeli V, Seneviratne RA, Wijeyaratne C. Validation of WHOQOL-BREF to measure quality of life among women with polycystic ovary syndrome. Sri Lanka J Coll Community Physicians 2006;11:01-10

(36) Jones GL, Palep-Singh M, Ledger WL, Balen AH, Jenkinson C, Campbell MJ, et al. Do South Asian women with PCOS have poorer health-related quality of life than Caucasian women with PCOS? A comparative cross-sectional study. Health Qual Life Outcomes 2010;8(1):149-156.

(37) Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, et al. Racial influence on the polycystic ovary syndrome phenotype: a black and white case-control study. Fertil Steril 2011;96:224-229.

(38) Li Y, Li Y, Yu Ng EH, Stener-Victorin E, Hou L, Wu T, et al. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. Fertil Steril 2011;96:452-458.

(39) Agrawal R, Sharma S, Bekir J, Conway G, Bailey J, Balen A, et al. Prevalence of polycystic ovaries and polycystic ovary syndrome in lesbian women compared with heterosexual women. Fertil Steril 2004;82(5):1352-1357.

(40) Jedel E, Waern M, Gustafson D, Landén M, Eriksson E, Holm G, et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. Hum Reprod 2010;25:450-456.

(41) Klimczak D, Szlendak-Sauer K, Radowicki S. Depression in relation to biochemical parameters and age in women with polycystic ovary syndrome. Eur J Obstet Gynecol and Reprod Biol 2015;184:43-47.

(42) Romero M, Vivas-Consuelo D, Alvis-Guzman N. Is Health Related Quality of Life (HRQoL) a valid indicator for health systems evaluation? SpringerPlus. 2013;2:664.

(43) Naughton M, Shumaker S, Anderson R, Czajkowski S. Psychological aspects of health-related quality of life measurement: tests and scales. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven USA 1996;15:117-131.

(44) Bobadilla J, Cowley P. Designing and implementing packages of essential health services. J Int Dev 1995;7(3):543-554.

(45) Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab 1998;83:1976-1987.

(46) Wiebe S, Guyatt G, Weaver B, Matijevic S, Sidwell C. Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol 2003;56:52-60.

(47) Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004;13(2):299-310.

(48) Saxena S, Carlson D, Billington R, Orley J. The WHO quality of life assessment instrument (WHOQOL-Bref): the importance of its items for cross-cultural research. Qual life Res 2001;10(8):711-721.

(49) Acquadro C, Jambon B, Ellis D, Marquis P. Language and translation issues. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven USA.1996;2:575-585.

(50) Bowden A, Fox-Rushby JA. A systematic and critical review of the process of translation and adaptation of generic health-related quality of life measures in Africa, Asia, Eastern Europe, the Middle East, South America. Soc Sci Med 2003;57:1289-1306.

(51) Malik-Aslam A, Reaney MD, Speight J. The suitability of polycystic ovary syndrome-specific questionnaires for measuring the impact of PCOS on quality of life in clinical trials. Value Health 2010;13:440-446.

(52) Guyatt G, Weaver B, Cronin L, Dooley JA, Azziz R. Health-related quality of life in women with polycystic ovary syndrome, a self-administered questionnaire, was validated. J Clin Epidemiol 2004;57:1279-1287.

(53) Jones GL, Benes K, Clark TL, Denham R, Holder M, Haynes T, et al. The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ): a validation. Hum Reprod 2004;19(2):371-377.

(54) Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). Gynecol Endocrinol 2006;22:80-86.

(55) Barnard L, Ferriday D, Guenther N, Strauss B, Balen A, Dye L. Quality of life and psychological well being in polycystic ovary syndrome. Hum Reprod 2007;22:2279-2286.

(56) Amini L, Ghorbani B, Montazeri A. Iranian version of polycystic ovarian syndrome health related quality of life questionnaire (PCOSQ): translation, validity and reliability. Payesh J 2011;11:213-219.

(57) Bazarganipour F, Taghavi SA, Montazeri A, Ahmadi F, Chaman R, Khosravi A. The impact of polycystic ovary syndrome on the health-related quality of life: A systematic review and meta-analysis. Iran J Reprod Med 2015 Feb;13(2):61-70.

(58) Oh J, Kim JH. Validity and Reliability of a Korean version of Polycystic Ovary Syndrome Questionnaire. Korean J Women Health Nurs 2014;20(4):255-265.

(59) Olsen J. Epidemiology deserves better questionnaires. Int J Epidemiol 1998;27(6):935-935.

(60) Juul L, Van Rensburg J, Steyn P. Validation of the King's Health Questionnaire for South Africa in English, Afrikaans and isiXhosa: South African journal of Obstetrics and Gynaecology 18.3 (2012).

(61) MacCallum RC, Widaman KF, Zhang S, Hong S. Sample size in factor analysis. Psychol Methods 1999;4(1):84.

(62) Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. : Oxford university press; 2014.

(63) Keszei AP, Novak M, Streiner DL. Introduction to health measurement scales. J Psychosom Res 2010;68(4):319-323.

(64) Gliem JA, Gliem RR. Calculating, interpreting, and reporting Cronbach's alpha reliability coefficient for Likert-type scales. : Midwest Research-to-Practice Conference in Adult, Continuing, and Community Education;2003:82-88. Available at: http://www.alumniosu.org/midwest/proceeding.html

(65) Jenkinson C, McGee HM. Health status measurement: a brief but critical introduction. : Radcliffe Medical Press, Oxford; 1998.

(66) Sushil S, Verma N. Questionnaire validation made easy. Eur J Sci Res 2010;46(2):172-178.

(67) Stephenson MT, Holbert RL. A Monte Carlo simulation of observable versus latent variable structural equation modeling techniques. Commun Res 2003;30(3):332-354.

(68) Sapnas KG, Zeller RA. Minimizing sample size when using exploratory factor analysis for measurement. J Nurs Meas 2002;10(2):135-154.

(69) City of Cape Town 2011 Census. Strategic Development Information and GIS Department, City of Cape Town 2011 and 2001 Census data. Statistics South Africa. December 2012. Retrieved from: https://www.capetown.gov.za/en/stats/Documents/2011%20Census/2011_Census_Cape_Town_Profile.pdf. Accessed 24 October 2015.

(70) Bazarganipour F, Ziaei S, Montazeri A, Faghihzadeh S, Frozanfard F. Psychometric properties of the Iranian version of modified polycystic ovary syndrome health-related quality-of-life questionnaire. Hum Reprod. 2012;27:2729-2736.

(71) Jedel E, Kowalski J, Stener-Victorin E. Assessment of health-related quality of life: Swedish version of polycystic ovary syndrome questionnaire. Acta Obstet Gynecol Scand 2008;87:1329-1335.

Appendices

Appendix 1: Participant Information Leaflet

This informed consent is for women who have Polycystic Ovary Syndrome attending the Gynaecological Endocrine Clinic at Groote Schuur Hospital in Cape Town.

Name of Principal Investigator: **Nkosinathi Ncube**

Supervisors: **Professor ZM van der Spuy**

Professor PS Steyn

This Informed Consent Form has two parts:

(1) Information Sheet (to share the information about the research with you)

(2) Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form.

Introduction

The Reproductive Medicine Unit (RMU) in the Department of Obstetrics and Gynaecology is doing a research on the health related quality of life in patients with Polycystic Ovary Syndrome (PCOS). We are doing a research on the health related quality of life in patients with Polycystic Ovary Syndrome. In order for us to do so, we need to gather information from willing participants with Polycystic Ovary Syndrome using questionnaires developed in the United States of America (USA) and the World Health Organization (WHO). This information will relate to the different aspects of health related quality of life in patients with Polycystic Ovary Syndrome. The questionnaire known as the Polycystic Ovary Syndrome Questionnaire (PCOSQ) was developed in the United States of America for this purpose. We will also use a well-researched questionnaire WHOQOL-BREF developed by the World Health Organization.

Why are we doing this research?

This questionnaire has not been used in our local clinical environment and in this study we want to assess its value for use within our clinical population.

What do I have to do if I agree to participate?

We will also be using another questionnaire at the same time. This questionnaire is called the WHOQOL-BREF. This questionnaire measures the health related quality of life in the general population and is not specific for Polycystic Ovary Syndrome. The WHOQOL-BREF has been used before in South Africa successfully. Its concurrent use will allow us to assess if the PCOS questionnaire measures the problems encountered by women with PCOS more accurately.

You will be asked the questions from both questionnaires and at 4-8 weeks review you will be asked the same set of similar questions. The purpose of this is to test if these questionnaires can gather the same information at different times.

Who can participate in this study?

Patients with Polycystic Ovary Syndrome attending The Gynaecologic Endocrine Clinic at Groote Schuur hospital are invited to participate.

Do I have to participate?

No. Your participation in this research is entirely voluntary. It is your choice whether you participate or not. Your decision will not affect your care in our clinic in any way. You are allowed to change your mind later on and stop participating at any stage of the research with no consequences to your care at the hospital.

How long will it take?

Your participation in this research involves completing two sets of questionnaires 4-8 weeks apart during your usual scheduled review appointment.

Are there any adverse outcomes for participating in this research?

There are no adverse outcomes from participation in this research project.

Are there any benefits for participating in this project?

There may be no benefits for you personally, but your participation is likely to help us with identifying problems encountered by women with PCOS.

Will I be reimbursed?

Any transport costs additional to your usual clinic attendance will be met and if you attend for the second interview you will be given a gift voucher.

Will my details be kept confidential?

We will not be sharing the identity of those participating in the research project. The information that we collect from this research will be kept confidential. The information from the questionnaire will be safely recorded and only the researchers will be able to access this. All information will be analysed anonymously.

How will the results of the research be disseminated?

The knowledge that we get from doing this research will be shared with fellow health workers and anyone interested through meetings. After these meetings, we will publish the results in order to benefit others interested in the research. The research will also be used to contribute towards the specialist degree MMed in Obstetrics and Gynaecology for Dr Nkosinathi Ncube.

Do I have the right to decline or withdraw from the study?

You do not have to take part in this research if you do not wish to do so. Declining to participate will not affect your treatment at this hospital in any way. You will still have all the benefits of attending this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.

Who can I contact if I need further information?

If you have any questions you may ask them now or later on. If you wish to ask questions later, you may contact the principal investigator Dr N Ncube, the supervisors or Human Ethics Research Committee. The contact details are listed below.

Dr Nkosinathi Ncube
Department of Obstetrics and Gynaecology
University of Cape Town
Phone 0786155117
Email drnncube@yahoo.com

If you want to talk to someone not involved on the study you may contact

Dr M Patel

Department of Obstetrics and Gynaecology

University of Cape Town

Phone 0214046020

malikahassan@wol.co.za

Professor Marc Blockman

Chairperson, Faculty of Health Sciences

Human Research Ethics Committee

Phone 0214066338

Mark.Blockman@uct.ac.za

This proposal has been reviewed and approved by the Human Ethics Research Committee (HERC), which is a committee whose task is to make sure that research participants are protected from harm.

Appendix 2: Participant Consent Form

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire information document. All of my questions have been answered to my satisfaction in a language of my choice.
- The study's purpose, procedures, risks and possible benefits have been explained to me in a language of my choice.
- I agree to let the study team use the health information and other information gathered for this study to assess the value of these questionnaires.
- I voluntarily agree to participate in this research study. I agree to follow the study procedures as directed. I have been told that I can withdraw at any time.
- I understand this study will involve me completing two questionnaires with the assistance of the research team on two separate occasions.

PARTICIPANT NAME SIGNATURE

_____

INTERVIEWER NAME SIGNATURE

_____

WITNESS SIGNATURE

NAME

_____

DATE

_____

Appendix 3: PCOSQ

Instructions: This questionnaire is designed for women with Polycystic Ovary Syndrome. In the questionnaire, we will refer to the Polycystic Ovary Syndrome by its initials: PCOS. The questions concern your health and health-related issues. Please respond to each question by checking the box with the rating that best reflects how you feel. For each question, you have seven rating options. Option 1 represents the greatest possible impairment, while Option 7 represents the least impairment. Choose only one option for each question. There is no right or wrong answer. Just choose the option that is closest to how you feel.

Date:

Study No:

Interview No: 1 / 2 PCOSQ

To what extent have you felt that growth of visible hair on your chin has been a problem for you during the **last two weeks:**

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q1. Growth of visible hair on chin?	☐	☐	☐	☐	☐	☐	☐

During **the past two weeks,** how much of the time have you felt?

	All the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
Q2. Depressed as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐
Q3. Concerned about being overweight?	☐	☐	☐	☐	☐	☐	☐
Q4. Easily tired?	☐	☐	☐	☐	☐	☐	☐

Q5. Concerned with infertility problems?	☐	☐	☐	☐	☐	☐	☐
Q6. Moody as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐

In addition to your last menstruation, how much were the following issues a problem for you?

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q7. Headaches?	☐	☐	☐	☐	☐	☐	☐
Q8. Irregular menstrual periods?	☐	☐	☐	☐	☐	☐	☐

To what extent has growth of visible hair on your upper lip been a problem for you **the last two weeks?**

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q9. Growth of visible hair on upper lip?	☐	☐	☐	☐	☐	☐	☐

During the **past two weeks,** how much of the time have you**:**

	All the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
Q10. Had trouble dealing with your weight?	☐	☐	☐	☐	☐	☐	☐
Q11. Had low self-esteem as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐
Q12. Felt frustration in trying to lose weight?	☐	☐	☐	☐	☐	☐	☐
Q13. Felt afraid of not being able to have children?	☐	☐	☐	☐	☐	☐	☐
Q14. Felt frightened of getting cancer?	☐	☐	☐	☐	☐	☐	☐

Over the **last two weeks** to what extent the following issues have been a problem for you:

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q15. Growth of visible hair on your face?	☐	☐	☐	☐	☐	☐	☐
Q16. Embarrassment about excessive body hair?	☐	☐	☐	☐	☐	☐	☐

During the **past two weeks** how much of the time have you been:

	All the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
Q17. Worried about having PCOS?	☐	☐	☐	☐	☐	☐	☐
Q18. Self-conscious as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐

In relation to **<u>your last menstruation</u>**, how much the following issues were a problem for you:

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q19. Abdominal bloating?	☐	☐	☐	☐	☐	☐	☐
Q20. Late menstrual period?	☐	☐	☐	☐	☐	☐	☐
Q21. Menstrual cramps?	☐	☐	☐	☐	☐	☐	☐

How much of the time during the **<u>last two weeks</u>** did you**:**

	All the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
Q22. Feel like you are not sexy because of being overweight?	☐	☐	☐	☐	☐	☐	☐

Q23. Feel a lack of control over the situation with PCOS?	☐	☐	☐	☐	☐	☐	☐
Q24. Have difficulties staying at your ideal weight?	☐	☐	☐	☐	☐	☐	☐
Q25. Feel sad because of infertility problems?	☐	☐	☐	☐	☐	☐	☐

To what extent has growth of visible body hair been a problem for you the **last two weeks?**

	A severe problem	A major problem	A moderate problem	Some problem	A little problem	Hardly any problem	No problem
Q26. Growth of visible body hair?	☐	☐	☐	☐	☐	☐	☐

THIS QUESTIONNAIRE WAS DEVELOPED BY AND OBTAINED FROM:

L. Cronin, G. Guyatt, L. Griffith, E. Wong, R. Azziz, W. Futterweit, D. Cook, A. Dunaif. Development of a Health-Related Quality-of-Life Questionnaire (PCOSQ) for Women with Polycystic Ovary Syndrome (PCOS) Journal of Clinical Endocrinology and Metabolism 1998;83(6):1976-1986*

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Appendix 4: WHOQOL-BREF

Date:

Study No:

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. ***Please choose the answer that appears most appropriate.*** *If you are unsure about which response to give to a question, the first response you think of is often the best one. Please keep in mind your standards, hopes, pleasures, and concerns. We ask that you think about your life* ***in the last two weeks.***

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life	1	2	3	4	5

	to be meaningful?					
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied

16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5
20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living space?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

_____
_____
_____

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	Domain 1	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:
28.	Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:
29.	Domain 3	Q20 + Q21 + Q22 ☐ + ☐ + ☐	a. =	b:	c:
30.	Domain 4	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:

Appendix 5: Baseline Clinical Data

Date:

Study No:

AGE

GSH FOLDER NUMBER: ETHNIC GROUP:

PARITY: GRAVIDITY:

BMI (Kg/m^2):

MEASUREMENT WAIST: HIP : WAIST: HIP RATIO:

MENSTRUAL CYCLE:

Prim. amen / sec. amen / oligo / regular / irregular / menorrhagia / other

HIRSUTISM:

Ferriman-Gallwey score

FERTILITY:

Never attempted / prim. infertility / second. infertility / no problems

MISCARRIAGES:

0 / 1 / 2 / 3 / 4 / 5

ACNE:

Nil / mild / moderate / severe

ACANTHOSIS NIGRICANS:

Yes / No

BLOOD PRESSURE (mmHg):

Mean of three readings in recumbent position, 5 minutes apart.

Date:

Study No:

FASTING BLOOD SAMPLES

1. Testosterone nmol/l :
2. Estradiol pmol/l:
3. SHBG nmol/l: FAI:
4. FSH IU/L:
5. LH IU/L:
6. DHEAS µmol/l:
7. 17-OHP nmol/l:
8. Glucose mmol/l:
9. Insulin µunits/ml:
10. Lipid profile:

Cholesterol mg/dl	Triglyceride mg/dl	HDL mg/dl	LDL mg/dl	LDL Fractionation

Appendix 6: PCOSQ Answer Template

A

A SEVERE PROBLEM	**A MAJOR PROBLEM**	**A MODERATE PROBLEM**	**SOME PROBLEM**	**A LITTLE PROBLEM**	**HARDLY ANY PROBLEM**	**NO PROBLEM**

B

ALL THE TIME	**MOST OF THE TIME**	**A GOOD BIT OF THE TIME**	**SOME OF THE TIME**	**A LITTLE OF THE TIME**	**HARDLY ANY OF THE TIME**	**NONE OF THE TIME**

Appendix 7: WHOQOL-BREF Answer Template

A

VERY POOR	**POOR**	**NEITHER POOR NOR GOOD**	**GOOD**	**VERY GOOD**

B

VERY DISSATISFIED	**DISSATISFIED**	**NEITHER SATISFIED NOR DISSATISFIED**	**SATISFIED**	**VERY SATISFIED**

C

NOT AT ALL	**A LITTLE**	**A MODERATE AMOUNT**	**VERY MUCH**	**AN EXTREME AMOUNT**

D

NEVER	**SELDOM**	**QUITE OFTEN**	**VERY OFTEN**	**ALWAYS**

Appendix 8: Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

23 October 2013

HREC REF: 535/2013

Dr N Ncube
c/o Prof Z van der Spuy & Prof Steyn
Obstetrics & Gynaecology
H-Floor, OMB

Dear Dr Ncube

PROJECT TITLE: VALIDATION OF THE POLYCYSTIC OVARY SYNDROME HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (PCOSQ) IN THE CLINICAL COMMUNITY IN OUR GYNAECOLOGICAL ENDOCRINE CLINIC

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 8th October 2013.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th October 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulaton Part 50, 56 and 312.

Appendix 9: WHOQOL-BREF User Agreement

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This agreement is between the World Health Organization ("WHO") and NKOSINATHI NCUBE. WHO hereby grants the User a nonexclusive, royalty-free license to use the World Health Organization Quality of Life Questionnaire and/or related materials (hereafter referred to as "WHOQOL-100" or "WHOQOL-BREF") in User's study outlined below. The term of this User Agreement shall be for a period of 1 year, commencing on (date) 20 NOVEMBER 2013

The approved study for this User Agreement is:

Study Title	VALIDATION OF THE Polycystic Ovary Syndrome (PCOSQ) Questionnaire in our Gynaecology endocrine clinic
Principal Investigator	NKOSINATHI NCUBE
Sample characteristics	Patients with polycystic ovary Syndrome
Sample size	100
Treatment intervention	Nil
Total number of assessments	105
Assessment time points	November 2013 to April 2014
"WHOQOL-100" or WHOQOL-BREF version – PLEASE SPECIFY	WHOQOL - Bref
Other measures	PCOSQ

This User Agreement is based upon the following conditions:

1. User shall not modify, abridge, condense, translate, adapt, recast or transform the WHOQOL-100 or BREF in any manner or form, including but not limited to any minor or significant change in wording or organization, or administration procedures, of the WHOQOL-100 or BREF. If User thinks that changes are necessary for its work, or if translation is necessary, User must obtain written approval from WHO in advance of making such changes.

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3. User agrees to provide WHO with an annual update regarding activities related to the WHOQOL-100 or BREF.

4. User agrees to provide WHO with a complete copy of User's raw data and data code books, including the WHOQOL-100 or BREF and any other instruments used in the study. This data set must be forwarded to WHO upon the conclusion of User's work. While User remains the owner of the data collected in User's studies, these data may be used in WHO analyses for further examining the psychometric properties of the WHOQOL-100 or BREF. WHO asserts the right to present and publish these results, with due credit to the User as the primary investigator, as part of the overall WHOQOL-100 or BREF development strategy.

5. WHO shall be responsible for preparing and publishing the overall WHOQOL-100 or BREF results under WHO copyright, including:

a. the overall strategy, administrative set-up and design of the study including the instruments employed;

b. common methods used by two or more Users;

c. the data reported from two or more Users ;

d. the comparisons made between the data reported from the Users;

e. the overall findings and conclusions.

6. User shall be responsible for publications concerning information developed exclusively by User and methods employed only by User. Publications describing results obtained by User will be published in User's name and shall include an acknowledgement of WHO. User agrees to send to WHO a copy of each such paper prior to its submission for publication.

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Signed by candidate

Please confirm your agreement with the foregoing by signing and returning one copy of this letter to WHO, whereupon this letter agreement shall become a binding agreement between User and WHO.

WHO:

Signed by candidate

Dr. Somnath Chatterji
Health Statistics and Health Information Systems (HSI)
World Health Organization
Avenue Appia
Geneva 27
CH-1211 Switzerland

Date: 26/08/2014

USER:

By: N ROSINATHI NCUBE
Title: Dr
Institution: University of Cape Town
Address: Department of Obstetrics and gynaecology
Faculty of Health Sciences
Anzio Road, OBSERVATORY, CAPE TOWN South AFRICA
Date: 26/08/2014.