International PCOS guideline clinical research priorities roadmap: a co-designed approach aligned with end-user priorities in a neglected women's health condition

H. J. Teede,[a,b,*] M. Gibson,[a,b,c] J. Laven,[b,d] A. Dokras,[e] L. J. Moran,[a,b] T. Piltonin,[f] M. Costello,[g] A. Mousa,[a,b] A. E. Joham,[a,b] and C. T. Tay,[a,b] on behalf of the International PCOS Network[h]

[a]Monash Centre for Health Research and Implementation, Monash University, Melbourne, VIC, Australia
[b]National Health and Medical Research Council Centre for Research Excellence in Women's Health in Reproductive Life, Australia
[c]National Centre for Women's Health Research Aotearoa, Faculty of Health, Victoria University of Wellington, Wellington, New Zealand
[d]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, the Netherlands
[e]Department of Obstetrics and Gynaecology, University of Pennsylvania, Philadelphia, PA, USA
[f]Research Unit of Clinical Medicine, University of Oulu and Oulu University Hospital, Oulu, Finland
[g]University of New South Wales, New South Wales, Australia

eClinicalMedicine 2024;78: 102927
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102927

Summary

Background Polycystic ovary syndrome (PCOS) is a common endocrinopathy with significant reproductive, metabolic, and psychological complications. Consensus on PCOS clinical research priorities across end-users is fundamental and necessitates a robust co-development of a clinical research roadmap to guide international research efforts.

Methods A multistage process included: i) international surveys of women and healthcare providers to identify research priorities and unmet needs; ii) interrogation of systematic reviews conducted for the International PCOS Guideline to identify research gaps; iii) International PCOS Guideline Network consensus generated clinical research roadmap; and iv) international peer review for external validation.

Findings A codesigned survey engaging 1278 women with PCOS and 1474 healthcare providers found general concordance on research priorities. International PCOS Guideline development processes identified gaps in the literature and coproduced over 150 research priorities throughout the women's life course, affirmed in international peer review. Key themes included: 1) Optimizing PCOS diagnosis; understanding natural history across diverse populations and life stages; detecting and preventing complications, and integrating and interrogating large data assets; 2) developing evidence-based resources, exploring optimal modes for information provision and models of care; 3) exploring effective lifestyle and weight management strategies; minimising weight stigma; 4) exploring intervention effects (including treatment efficacy, safety, cost-effectiveness, and long-term follow-up) on diverse features of PCOS across subgroups; and 5) optimising preconception care and fertility treatments in PCOS.

Interpretation This rigorously coproduced International PCOS Guideline clinical research roadmap addresses stakeholder priorities to guide future clinical research in this common yet neglected condition. The roadmap complements the established PCOS Core Outcome Set to enhance research quality, and tackles evidence-practice gaps to improve health outcomes for women with PCOS throughout their life course.

Funding The survey, International PCOS Guideline Network and 2018 and 2023 International PCOS Guidelines were funded by the Australian National Health and Medical Research Council (NHMRC) Centres of Research excellence in PCOS (APP1078444) and in Women's Health in Reproductive life (APP1171592). Guideline partners, American Society for Reproductive Medicine (ASRM), Endocrine Society, European Society of Human Reproduction and Embryology (ESHRE), and European Society of Endocrinology (ESE), provided additional funding and assisted in guideline development. HT and AM are NHMRC Research Fellows. LM was funded by a Heart Foundation Future Leader and Veski Fellowship and CTT by the NHMRC Centres of Research excellence in Women's Health in Reproductive life. All disclosures of interest were declared before commencing GDG involvement and updated before

*Corresponding author. Monash Centre for Health Research and Implementation, Monash University, Locked Bag 29, Clayton, Victoria 3168, Australia.
E-mail address: helena.teede@monash.edu (H.J. Teede).
[h]The members of International PCOS Network group are listed in the Acknowledgements section.

all major milestones and are available alongside the PCOS Guideline (https://www.monash.edu/__data/assets/pdf_file/0009/3371292/Register-of-disclosures-of-interest.pdf).

Keywords: Polycystic ovary syndrome; Public and patient involvement; Consumer and community involvement; Research; Infertility; Diabetes mellitus; Evidence-based medicine

Research in context

Evidence before this study

Polycystic ovary syndrome (PCOS) is a common yet significantly neglected endocrine disorder characterized by profound reproductive, metabolic, and psychological features. The relative lack of adequate education, research, and models of care have negatively impacted timely diagnosis and health outcomes, prompting widespread dissatisfaction globally. Traditionally, research has been investigator-driven, assuming alignment with patient, healthcare provider, and policy priorities. Yet, growing evidence shows stark gaps between current research priorities and activities versus those of end-users'. Stakeholder consensus on PCOS research priorities including with end-users, is fundamental to addressing these gaps. We aimed to collaborate internationally and coproduce an international clinical research roadmap to guide advocacy, research efforts, and improve health outcomes.

Added value of this study

To overcome the lack of stakeholder-driven research priorities in PCOS, this study generates a rigorously coproduced international clinical research priority roadmap. Robust and multistage methods included online international surveys of women and healthcare providers, finding general alignment of perspectives among these stakeholder groups on priorities for PCOS research. These findings were then incorporated into International PCOS Guideline development methods including best practice evidence synthesis. The International PCOS Guideline Network including consumer groups and spanning six continents, then applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence to decision framework, capturing past evidence and gaps for moving forward. International peer review refined these and together this process generated over 150 research priorities.

Implications of all the available evidence

While there is a recognised fundamental need for greater understanding of the pathophysiology and genetics underlying PCOS, discovery science research falls outside the scope of this International PCOS Guideline clinical research roadmap which focuses on enhancing current clinical practices and alignment with immediate clinical care needs for PCOS. Grounded in the collective insights and expertise of both patients and healthcare providers, this clinical research roadmap represents a valuable resource to guide future global clinical research endeavours in this common but diverse and neglected condition. To maximise the roadmap's impact, it should be integrated with the established PCOS Core Outcome Set to ensure that future clinical research and outcome measures are both relevant and impactful. Jointly these efforts seek to address clear knowledge gaps, optimise care, and improve outcomes for the one in eight women affected by PCOS globally.

Introduction

Polycystic ovary syndrome (PCOS) poses a significant global public health challenge and is the most common long-term endocrinopathy affecting women with a prevalence of 12%.[1–6] This complex syndrome is now understood to be caused by genetic and epigenetic interactions between metabolic and endocrine factors that manifests with cardiometabolic (obesity, type II diabetes, cardiovascular risk factors, and increased cardiovascular disease),[1–4,7,8] reproductive (ovulatory disturbance, infertility, and pregnancy complications),[9] psychosocial (depression and anxiety symptoms, disordered eating, and poor quality of life),[10] and dermatological features, impacting quality of life. These features vary across the lifespan, within and between individuals, necessitating patient-centred multidisciplinary approaches.[1–5,11]

Evidence-practice gaps persist in PCOS care provision through delayed diagnosis, inconsistent and fragmented care, inadequate information provision, suboptimal lifestyle management, and under-recognition of the broader features of PCOS globally.[12,13] In addition to narrow perceptions of PCOS as a reproductive/fertility disorder, exacerbated by the current name of the condition, progress is further hindered by lack of health professional education and limited dedicated models of care.[14,15] PCOS is also impeded by being a women's health condition, which alongside conditions such as endometriosis and menopause, is subject to inherent gender bias in research and clinical care.[16] Whilst research is vital to pursue solutions, an under-appreciation of the broad and profound impact of PCOS, coupled with inadequate prioritization and research funding,[14] has ultimately compromised progress with small and often low-quality studies generating low certainty of evidence.[1–4,6]

Traditionally, research objectives have been investigator or researcher-driven.[17,18] Relevance to research

end-users, including patients, healthcare providers, and policy makers is usually assumed, rather than rigorously validated.[19] A recent study reported that up to 86% of research priority-setting by the World Health Organization (WHO) was based on expert consultation with nearly one-third reporting this as the sole method.[18] Yet, increasing evidence highlights discrepancies between conducted research and end-user priorities.[19,20] Given that the community is ultimately both the funder and beneficiary of most health related research, co-production of research priorities, incorporating patients'[21] and healthcare provider perspectives[20] is key to ensure research relevance, adoption of research findings into policy and practice, and research impact.[22] Developing and incorporating end-user research priorities and standardised outcomes (core outcome sets) are proposed to maximise research impact and eliminate evidence gaps.[23,24] A clinical research core outcome set has been co-produced in PCOS,[25] however, evidence of stakeholder-derived research priorities remains a major gap in PCOS.

To address these key gaps, we conducted a multistage international research end-user priority setting process for PCOS involving: i) an extensive online cross-sectional survey of international women and multidisciplinary healthcare providers to identify end-user research priorities and unmet needs; ii) extensive systematic reviews for the International PCOS Guideline following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[1–6,26] to identify research limitations and gaps; iii) International PCOS Guideline Network consensus using the GRADE Evidence to Decision framework to plan out a clinical research roadmap[1–6,26]; and iv) international peer review as part of the International PCOS Guideline process for validation. The ultimate aim was to co-produce strategic stakeholder-informed PCOS clinical research priorities to accelerate progress in clinical research and to drive evidence-based healthcare, and improved health outcomes (Fig. 1).

Methods

Study design, setting and participants

Surveys included a community sample of international women with PCOS who were mainly recruited from the two largest PCOS support organisations worldwide: 1) PCOS Challenge (United States) and 2) Verity: The PCOS Charity (United Kingdom), which also have international membership. Women accessed the questionnaire by visiting the PCOS support organisations' websites, receiving an invitation to participate via the organisations' mailing lists or through social media links. Eligibility criteria included age ≥18 years and a self-reported diagnosis of PCOS made by a medical professional. Healthcare providers were recruited from partnering societies: American Society for Reproductive Medicine, American College of Obstetricians and Gynaecologists, Androgen Excess and PCOS Society, Federation of Obstetrics and Gynaecological Societies of India, European Society of Human Reproduction and Embryology, Finnish Society of Obstetrics and Gynaecology, Finnish Society of Endocrinology, Danish Society of Endocrinology, Danish Society of Obstetrics and Gynaecology, Norwegian Society for Gynaecology and Obstetrics, Norwegian Society of Endocrinology,

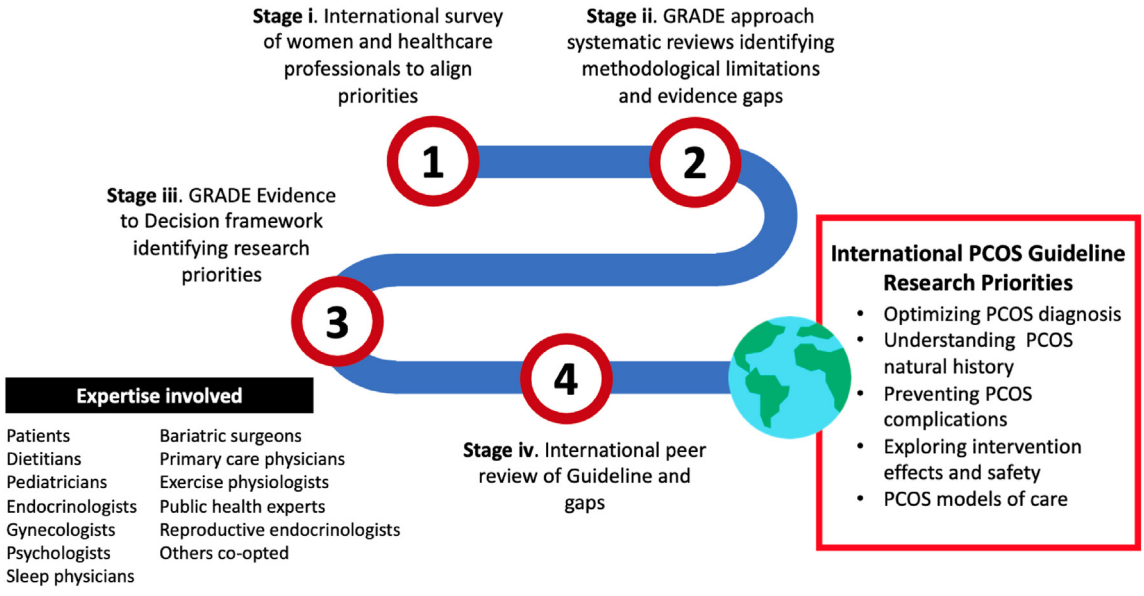

Fig. 1: Summary of multistage process to develop International PCOS Guideline research priority roadmap.

Estonian Society of Gynaecology and Estonian Society of Endocrinology. Physicians received email invitations to participate through these societies or could access a link on society websites. Members of the Nordic PCOS Network identified specialists and sent direct email invitations. To achieve a 3% margin of error with 95% confidence intervals, a sample size of 1067 is required for both an estimated global population of 500 million women with PCOS and a global population of 12 million healthcare professionals.

Members of the International PCOS Evidence-based Guideline Network were nominated by the 39 participating patient and professional societies, providing robust and transparent governance.[1–5] This included specialists, general practice, nursing, allied health and researchers alongside experts with lived experience of PCOS. International and public peer review was through dissemination by the International PCOS Guideline Network partner and collaborating organisations to validate the findings.

Stage i: international online survey to identify end-users research priorities and unmet needs

This study, conducted in 2015–2016, was approved by the University of Pennsylvania Institutional Review Board (protocol number: 822,252) and other relevant ethics committees as required regionally. Completion of the surveys was considered consent to participate (implied consent).

Methods for this exploratory survey development have been reported previously.[12,13,27] In summary, a multidisciplinary expert advisory group developed a questionnaire which was then piloted with women with PCOS. The questionnaire was further refined with insights gained from previous study as well as discussions involving women, healthcare professionals and international experts. For those with PCOS, research priority questions were integrated into a broader survey on demographics, diagnosis experience, information provision, PCOS concerns or priorities, and the name of the condition. Healthcare provider surveys included demographics, diagnosis and management practices, awareness of PCOS features, the name of the condition, clinical care priorities, professional development needs and research priorities.

PCOS research priority questions were "Which of the following do you think are the most important areas to research in PCOS?" (Supplemental File S1). The topics addressed included: understanding, treating and preventing insulin resistance, diabetes and heart disease; developing lifestyle interventions and weight management; addressing infertility; understanding and preventing PCOS at adolescence; addressing hyperandrogenism; integrated models of care; improving quality of life; understanding long-term effects after menopause; addressing pregnancy complications; understanding and preventing endometrial cancer; and natural or alternative treatment methods. This exercise was designed to identify and understand women's and healthcare providers' initial research priorities and unmet needs.

Variables and statistical methods

For the surveys, statistical analysis was performed using Stata (version 14, StataCorp, College Station, TX). Variables were presented as count and percentage responses. Comparisons of demographic characteristics across world regions were conducted using chi-squared tests or Fisher's exact test as appropriate. A p-value < 0.05 was considered statistically significant. Multivariable logistic regression analyses generated odds ratios (ORs) and 95% confidence intervals (CIs) within each of the two samples for associations of the ten most commonly selected research priorities. For women with PCOS, the covariate considered in the regression was women's age [18–25 years, 26–35 years (reference category), 36–45 years, or >45 years] and world region of residence [North America (reference category), Europe or other]; for healthcare providers, the covariates considered were world region of residence/practice [North America (reference category), Europe or other], and healthcare providers' specialty [obstetrician/gynaecologist (reference category), endocrinologist or other].

Stage ii: international PCOS guideline systematic evidence reviews to identify research gap

End-users research priorities and unmet needs identified in Stage i informed the 52 clinical topics to be address by the International PCOS Guideline in 2018. These clinical topics were carried over for the 2023 Guideline with additional 3 clinical topics (mechanisms of weight gain, weight stigma and PCOS model of care). Tools and methods for Guideline co-production and peer review have been previously reported and followed best practice methods.[1–4,26] To underpin the International PCOS Guideline, 40 systematic reviews were undertaken during the 2018 Guideline[5] and 52 new and updated reviews for the 2023 Guideline[1–4] were undertaken in 2022. Details are accessible in the Guideline Technical Report,[6] as a supplementary resource to the Guideline. All reviews underwent rigorous appraisal using the GRADE approach, encompassing assessments of external and internal validity to gauge risk of bias and appraise sources of inconsistency, indirectness, imprecision or publication bias.[6,26] Here, information about risk of bias and certainty of evidence was extracted from the technical report and synthesised to identify common methodological limitations and identify evidence gaps.

Stage iii: international PCOS Guideline Network consensus on clinical research priority roadmap

Informed by the evidence from Stage ii, the multidisciplinary expert and consumer Guideline Development

Group (GDG) members applied the GRADE Evidence to Decision framework[26] to enable robust discussion and transparent documentation of decisions underpinning evidence-based recommendations. The GRADE Evidence to Decision framework consists evaluation of evidence from Stage ii, clinical expertise and patient preferences across multiple domains: priority of the problem, desirable and undesirable effects of the intervention; certainty of the evidence; values associated with the outcomes of the recommended intervention; balance of effects; resource requirements; cost-effectiveness; equity; acceptability, and feasibility.[26] Via an iterative and collaborative approach over extensive advisory, project board and multiple GDG meetings over nine months in 2022, evidence-based and consensus clinical recommendations were co-produced. Additionally, a clinical research priority was developed to address end-users' unmet needs identified in Stage i and research gaps identified in Stage ii.

Stage iv: validation from international peer review

As an integral part of the International PCOS Guideline development process, the draft guideline and clinical research priority roadmap were disseminated online for public and targeted collaborating partner peer review in the first half of 2023. This stage included women with PCOS, healthcare providers, and academics worldwide. The Guideline documents containing consolidated priorities derived from the multistage longitudinal process were circulated online, inviting feedback which were thoughtfully incorporated into the final Guideline and clinical research roadmap.

Role of funding

The survey, International PCOS Guideline Network and 2018 and 2023 International PCOS Guidelines were funded by the Australian National Health and Medical Research Council (NHMRC) Centres of Research excellence in PCOS (APP1078444) and in Women's Health in Reproductive life (APP1171592). Guideline partners, American Society for Reproductive Medicine (ASRM), Endocrine Society, European Society of Human Reproduction and Embryology (ESHRE), and European Society for Endocrinology (ESE), provided additional funding and assisted in guideline development. HT and AM are NHMRC Research Fellows. LM was funded by a Heart Foundation Future Leader and Veski Fellowship and CTT by an RACP fellowship.

Results

Stage i: international online survey

Participation and demographics

Overall, 1550 women completed the survey. Of these, 272 were excluded: one was <18 years of age, 67 were not diagnosed with PCOS, 204 did not complete demographic or research priority questions; leaving 1278 participants. Most resided in North America (53%) or Europe (42%) (Table 1) and represented a range of life-stages, with approximately half aged 26–35 years and half having been diagnosed with PCOS for over five years (Table 1).

For healthcare providers, 1870 completed the survey, with 364 excluded with missing data on demographics research priorities or health care provider status. The final survey comprised 1474 participants who resided predominantly in North America (42%) and Europe (41.0%) and were mainly obstetrician-gynaecologists (60%) or reproductive endocrinologists (27%) (Table 1).

Priorities for those with PCOS

We identified several research priorities, the highest were understanding and treating insulin resistance, diabetes risk, and preventing heart disease (71%); understanding and treating hyperandrogenism, hirsutism, scalp hair loss, and acne (69%); and understanding and treating PCOS-related infertility (63%). Developing lifestyle interventions, achieving weight loss and preventing weight gain (59%) and models of care were also prioritised (Fig. 2). Young women prioritised lifestyle interventions and weight (adjusted OR (aOR) 1.4; 95% CI 1.1–2.0), and understanding and preventing PCOS in adolescence (aOR 1.5; 95% CI 1.1–2.1), but not integrated models of care (aOR 0.7; 95% CI 0.5–0.9). Other research topics did not demonstrate a significant relationship (Supplemental Table S1). Women aged 36–45 years were less likely to prioritise infertility (aOR 0.5; 95% CI 0.4–0.6), pregnancy complications (aOR 0.4; 0.3–0.6), and endometrial cancer (aOR 0.6; 95% CI 0.4–0.8) than younger women as areas of research priority, while other research topics showed no significant associations. Women aged >45 years were more likely to select metabolic implications of PCOS (aOR 2.5; 95% CI 1.3–4.5), integrated models of care (aOR 1.6; 95% CI 1.1–2.5), and effects of PCOS after menopause (aOR 4.7; 95% CI 2.9–7.6), and less likely to select infertility (aOR 0.3; 95% CI 0.2–0.4) and pregnancy complications (aOR 0.3; 95% CI 0.1–0.6). No significant relationships were observed for other research topics.

Adjusting for age, women living in Europe were less likely to select research priorities relating to metabolic implications of PCOS (aOR 0.7, 95% CI 0.5–0.9) and complementary therapies (aOR 0.5; 95% CI 0.4–0.6) than North American women (Supplemental Table S1). Other world regions prioritised understanding and preventing PCOS at adolescence (aOR 1.7; 95% CI 1.1–3.0) and pregnancy complications (aOR 2.0; 95% CI 1.1–3.4) over North American women. Other research topics did not reveal significant correlations.

Priorities for healthcare providers

Insulin resistance, diabetes and heart disease (85%), lifestyle interventions (59%), and infertility (54%) were the most commonly selected priorities (Fig. 2).

Women: n (%)	Overall n = 1278	North America n = 678	Europe[a] n = 541	Other regions[b] n = 59	p-value
Age in years (n = 1278)					
18–25	171 (13.4)	90 (13.3)	72 (13.3)	9 (15.3)	0.083
26–35	655 (51.3)	367 (54.1)	254 (47.0)	34 (57.6)	
36–45	366 (28.6)	181 (26.7)	170 (31.4)	15 (25.4)	
45 or older	86 (6.7)	40 (5.9)	45 (8.3)	1 (1.7)	
Years since diagnosis (n = 1266)					
1 or less	146 (11.5)	96 (14.3)	41 (7.6)	9 (15.3)	<0.001
Between 1 and 5	314 (24.8)	172 (25.6)	123 (23.0)	19 (32.2)	
Between 5 and 10	321 (25.4)	163 (24.3)	140 (26.1)	18 (30.5)	
More than 10	485 (38.3)	240 (35.8)	232 (43.3)	13 (22.0)	
Healthcare providers: n (%)	**Overall n = 1474**	**North America n = 625**	**Europe[c] n = 604**	**Other regions[d] n = 245**	**p-value**
Profession (n = 1474)					
Obstetrician-gynaecologist	887 (60.2)	398 (63.7)	371 (61.4)	118 (48.2)	<0.001
Reproductive Endocrinologist	402 (27.3)	175 (28.0)	122 (20.2)	105 (42.9)	
Other[e]	185 (12.5)	52 (8.3)	111 (18.4)	22 (9.0)	
Gender n = 1461					
Female	932 (63.8)	404 (65.3)	415 (69.5)	113 (46.1)	<0.001
Male	529 (36.2)	215 (34.7)	182 (30.5)	132 (53.9)	
Women with PCOS seen in last year (n = 1458)					
Less than 50	725 (49.7)	314 (50.6)	349 (58.5)	62 (25.7)	<0.001
50–200	589 (40.4)	254 (41.0)	218 (36.5)	117 (48.6)	
more than 200	144 (9.9)	52 (8.4)	30 (5.0)	62 (25.7)	

[a]Northern Europe: 497, Southern Europe: 34, Western Europe: 8, Eastern Europe: 2. [b]Oceania: 32, Southern Africa: 7, West Asia: 6, South Asia: 5, Central and South America: 3, East and South East Asia: 4, North and West Africa: 2. [c]Northern Europe: 419, Southern Europe: 76, Western Europe: 61, Eastern Europe: 46, not stated: 2. [d]South Asia: 62, South America: 42, West Asia: 38, Central and East Asia: 29, Central and Latin America: 28, Oceania: 19, North and West Africa: 14, South East Asia: 9, Southern Africa: 4. [e]Medical endocrinologist: 83, nurse, midwife or nurse practitioner: 31, general practitioner/internist or general physician: 29, embryologist: 17, medical student: 10, psychologist or psychiatrist: 6, other (e.g., dietitian, complementary or alternative medicine practitioner, physician assistant) 9.

Table 1: **Demographic characteristics of women and healthcare providers completing an online questionnaire about PCOS research priorities.**

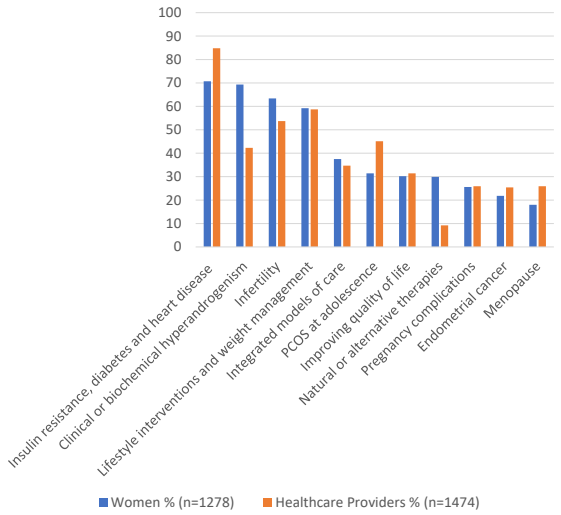

Fig. 2: Research priorities selected by women with PCOS and healthcare providers. Other research priorities included diagnosing and treating anxiety and depression (women: 19.6%, healthcare providers: 9.6%), achieving regular menstrual cycles (women: 19.3%, healthcare providers: 22.9%), understanding impacts in pregnancy (women: 11.4%, healthcare providers: 18.8%), understanding liver effects (women: 10.6%, healthcare providers: 8.1%) and understanding and improving sleep quality (women: 9.8%, healthcare providers: 3.8%). PCOS: polycystic ovary syndrome.

Adjusting for profession, reproductive endocrinologists focused on lifestyle interventions (aOR 1.4; 95% CI 1.1–1.8), PCOS at adolescence (aOR 1.7; 95% CI 1.4–2.2), models of care and pregnancy complications (aOR 1.4; 95% CI 1.1–1.8), and less on hyperandrogenism (aOR 0.7; 95% CI 0.6–0.9) and endometrial cancer (aOR 0.6; 95% CI 0.4–0.8), compared with obstetrician-gynaecologists (Supplemental Table S2). There were no significant associations identified for addressing PCOS related metabolic issues, infertility, quality of life, menopause, and natural or alternative treatments. Other healthcare providers highlighted models of care (aOR 1.6; 95% CI 1.1–2.2), improving quality of life (aOR 1.9; 95% CI 1.4–2.7) and complementary therapies (aOR 1.9; 95% CI 1.1–3.0), with no significant relationships observed for other research topics over obstetrician-gynaecologists. Adjusting for geographic location, providers in Compared to North American healthcare providers, providers from both Europe and other world regions were more likely to select infertility (Europe aOR 1.6; 95% CI 1.3–2.1; other aOR 2.0; 95% CI 1.5–2.7) and pregnancy complications (Europe aOR 1.9; 95% CI 1.5–2.5; other aOR 2.1; 95% CI 1.5–2.9) (Supplemental Table S2). Additionally, those in Europe were less likely to select adolescence (aOR 0.8; 95% CI 0.6–0.9), models of care (aOR 0.7; 95% CI 0.5–0.9) and endometrial cancer (aOR 0.7; 95% CI 0.5–0.9), while those from other world regions were more likely to select menopause (aOR 1.6; 95% CI 1.2–2.2) and complementary medicine (aOR 2.2; 95% CI 1.4–3.5) as research priorities. Other research topics did not show significant correlations.

Stage ii: international PCOS guideline systematic evidence reviews

More than 950 studies were ultimately included in the evidence reviews conducted and are detailed in the nearly 6000-page technical report and multiple published systematic reviews completed for the 2023 Guideline.[6] Only one quarter of the studies were low risk of bias, and over two-thirds of the outcomes were affected by very low- or low-level certainty of evidence with methodological weaknesses (Table 2). For observational studies, cross-sectional, and case-control studies predominated over cohort studies with limited representative community-based or unselected cohorts, generating bias. For observational and randomised

Observational trials	Randomised controlled trials	PCOS-specific methodologies
- Inadequate description of participant recruitment and selection methods. - Inadequately powered studies leading to wide 95% confidence intervals. - Utilization of inappropriate study designs, with a prevalence of cross-sectional studies instead of longitudinal studies, and a reliance on case-control studies rather than cohort studies. - Limited representation of community-recruited cohorts, often biased towards selected clinic populations.	- Inadequate description of participant recruitment and selection methods. - Inadequately powered studies leading to wide 95% confidence intervals. - Inadequate or unclear concealment of participant allocation. - Insufficient or unreported blinding of participants, investigators, and outcome assessors. - Ambiguity regarding whether all participants were analyzed according to their allocated groups (intention to treat). - Absence of direct comparisons between groups or unreported p-values. - Inadequate reporting of medication compliance, side effects, withdrawals, or participant loss to follow-up.	- Inconsistent definitions of PCOS features, including ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology. - Inadequate representation of diverse ethnic backgrounds and age groups within the evidence base. - Ambiguity concerning selective outcome reporting and incomplete reporting of anthropometric, metabolic, reproductive, psychological, and clinical parameters.

Table 2: **Common methodological weaknesses of the included studies in the evidence-based guideline process.**

controlled trials (RCTs), inadequate description of recruitment, limited sample size, and single site studies were common. For RCTs, inadequate or unclear concealment of participant allocation, insufficient or unreported blinding of participants, investigators and outcome assessors, and ambiguity on intention to treat analyses were common. Inadequate reporting of compliance, side effects, withdrawals or loss to follow-up were notable. Important PCOS-specific methodological limitations included inconsistent definitions of PCOS features, such as ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology. There was inadequate representation of diverse ethnicities and age groups, ambiguity on selective outcome reporting with incomplete anthropometric, metabolic, reproductive, and especially psychological outcomes, with limited application of the PCOS core outcome set.[25] These deficiencies underpinned priorities for better funded, designed, multisite, and quality studies in diverse populations applying the core outcome set.

Stages iii and iv: international PCOS Guideline Network consensus and international peer review

Via a series of international GDG meetings over nine months, a clinical research priority roadmap consisting of over 150 research recommendations throughout the life course of women with PCOS was generated to guide future clinical research (Table 3). These were categorised across the five topic areas in the International PCOS Guideline: 1) Screening, diagnostic assessment, risk assessment, and life stage; 2) Psychological features and models of care; 3) Lifestyle management; 4) Management of non-fertility features; and 5) Assessment and treatment of infertility. Clinical research priorities revolved around five key themes: 1) greater insights into accurate diagnosis, deeper understanding of natural history and complication prevention of PCOS across diverse subgroups, age groups including adolescence and post menopause, ethnicities and weight categories; 2) developing evidence-based resources and tools and exploring optimal modes for information provision (e.g., AskPCOS app), developing optimal models of care and strategies for shared decision making; 3) exploring effective lifestyle and other weight management strategies and minimising weight stigma in PCOS; 4) examining impact of interventions on the interconnected aspects of PCOS across reproductive, metabolic, and psychological well-being; and conducting thorough comparisons of treatment efficacy, safety, and cost-effectiveness with a focus on long-term follow-up assessments; and 5) optimising preconception care and fertility treatments in PCOS. Finally, public and stakeholder feedback during the international peer review process informed refinement of the final International PCOS Guideline clinical research priority roadmap, providing valuable external validation of the relevance of the roadmap to the global PCOS research community (Table 3).

Discussion

This unique body of work brings together the knowledge and experiences of over 2800 women, healthcare providers, and academic experts internationally to coproduced an International PCOS Guideline clinical research priority roadmap. Online surveys demonstrated alignment of clinical research priorities between women and healthcare providers, with a strong call for enhanced focus on the metabolic impact of PCOS, exploration of infertility including underlying causes and treatment options, and lifestyle management strategies. The Guideline systematic reviews identified limitations and key gaps in clinical research, calling for better funded, well-designed, multisite, and high-quality studies in diverse populations, applying the core outcome set. The International PCOS Guideline

Question #	Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:
Guideline Development Group 1	**Screening, diagnostic assessment, risk assessment and life-stage**
Theme 1. Optimizing PCOS diagnosis; understanding subgroups and natural history across diverse populations and life stages; detecting and preventing complications, and harmonising, integrating and interrogating large data assets.	
Q 1.1. Irregular cycles and menstrual dysfunction	• Longitudinal studies to identify early predictors and natural history of PCOS in adolescents from different ethnic backgrounds, targeted to allow for timely and accurate diagnosis. • Quality and current normative data across ethnicities and BMI assessing pubertal development with and without PCOS.
Q 1.2. Biochemical hyperandrogenism	• Large-scale quality studies comparing testosterone, DHEAS and androstenedione measured by reference standard tandem mass spectrometry, including predefined cut-off thresholds, prospectively tested and validated in independent cohorts of women with well characterised PCOS and women without PCOS. • Evaluate the diagnostic value of the active 11-oxygenated androgens in detecting biochemical hyperandrogenism in PCOS, comparing it to the diagnostic performance of recommended androgens. • Characterising a large cohort of women with PCOS from different ethnic backgrounds to comprehensively identify biochemically defined clusters of women and relationships to clinical features of PCOS.
Q 1.3. Clinical hyperandrogenism	• In an unselected population of adolescents and adults, determine the predictive value biochemical hyperandrogenism and/or PCOS status across acne alone, female pattern hair loss alone, hirsutism alone. • Determine the naturally occurring 'abnormal' cut-off value of the mFG score for defining hirsutism by ethnicity, and BMI, in large unselected populations. • Exploring simpler methods of assessing hirsutism (including validity of self-reported hirsutism)
Q 1.4. Ultrasound and polycystic ovarian morphology	• Study natural history of ovarian morphology in community-based populations across the lifespan and across the globe. • Examine the relationship of polycystic ovary morphology with PCOS-related health outcomes over the lifespan. • Establish rigor and reproducibility in measuring and reporting of ovarian ultrasonographic markers in a clinical workflow. • Study the impact of combined oral contraceptive pill on polycystic ovary morphology
Q 1.5. Anti-Mullerian hormone	• Normative data assessing AMH levels in adolescents and in different age groups. • Longitudinal studies to assess AMH levels in women with PCOS compared to controls. • Cost effectiveness studies comparing pelvic US and AMH assessments. • Study the impact of combined oral contraceptive pill on serum AMH levels. • Study the relationship between BMI, ethnicity and serum androgen levels and AMH
Q 1.1. – 1.5.	• Explore cluster analyses integrating all core diagnostic features for more accurate diagnosis across ethnic groups
Q 1.6. Ethnic variation	• Assess PCOS prevalence in diverse populations, including the African and South American continents. • Study ethnic variation, including prevalence, and characteristics in adolescents and adults. • Study migrant populations assessing the impact of migration and environment
Q 1.7. Menopause life-stage	• Study features of PCOS in the postmenopause, including variation by ethnicity and BMI. • Long-term cohort studies post menopause to assess health outcomes including androgen levels, clinical hyperandrogenism, cardiometabolic disease, bone health, psychosexual function (accounting for impacts of treatment).
Q 1.8. Cardiovascular Disease	• Long-term, large, longitudinal studies for assessment of cardiovascular disease events. • Cardiovascular risk prediction models to be developed and validated in PCOS, considering ethnic variation. • Cost effectiveness in screening and prevention programs for cardiovascular disease in PCOS
Q 1.9.1. Impaired glucose tolerance and type 2 diabetes	• Evaluation of relative risk of diabetes across ethnicities and age ranges, including postmenopausal. • Exploring risk of type 2 diabetes in different subgroups including ethnic variation and by degree of hyperandrogenism. • The rate of progression of prediabetes into diabetes in women with and without PCOS.
Q 1.9.2. Glycaemia monitoring	• Compare accuracy of different diagnostic tests against the oral glucose tolerance test including a combination of diagnostic strategies for glucose testing incorporating a combination of parameters to simplify glycaemic evaluation in settings where oral glucose tolerance test may not be practical.
Q 1.10. Obstructive sleep apnoea	• Validate existing screening tools for obstructive sleep apnoea in PCOS. • Explore mechanisms of obstructive sleep apnoea in PCOS and relationships with metabolic and psychological features. • Study adherence and effectiveness of treatment for obstructive sleep apnoea in PCOS.
Q 1.11. Endometrial cancer	• Mechanisms including the impact of insulin and androgen excess on endometrial cancer development. • Long-term natural history of endometrial hyperplasia and incidence of endometrial cancer across ethnicities. • The impact of COCP treatment.
Q 1.12. Risk in relatives	• Studies in families of women with PCOS including male and female relatives, including exploration of mechanisms. • Studies including daughters of women with PCOS who are at least 8 years post menarche are a key gap.
Guideline Development Group 2	**Psychological features and models of care**
Theme 2. Developing evidence-based resources and tools (e.g., AskPCOS app) and exploring optimal modes for information provision and models of care for shared decision making and better outcomes.	
Q 2.1. Quality of life	• Studies in adolescents/adults to develop a PCOS specific health related quality of life tool to overcome current limitations.
Q 2.2. Depression and Anxiety	• Explore aetiology and pathophysiology of mental health disorders in PCOS, which may inform more targeted therapy. • Where regions, ethnic, population subgroups and life stages (including perinatal period) have not been adequately included, prevalence studies could be justified. Otherwise, further prevalence studies are not warranted. • Longitudinal follow up to determine frequency of screening for depressive and anxiety symptoms. • Effectiveness of treatment for depression or anxiety in PCOS, including impact on PCOS treatment and outcomes.

(Table 3 continues on next page)

Question #	Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:
(Continued from previous page)	
Q 2.3. Psychosexual function	• Psychosexual function in combination with sexual distress (psychosexual dysfunction) to be assessed across cultures. • Effect of lifestyle or pharmacological intervention on psychosexual dysfunction by treatment type. • Interventional studies in PCOS to include psychosexual dysfunction as an outcome, where appropriate.
Q 2.4. Body image	• Study body image in adolescents. • Validate existing body image measurement tools. • Determine clinically meaningful differences in body image scores. • Assess preferences of women with PCOS on treatment of body image issues, considering diversity. • Examine impact of PCOS treatment on body image.
Q 2.5. Disordered eating	• Prevalence of eating disorder/disordered eating in PCOS, including subgroups (e.g., adolescents, ethnicities), using a structured clinical interview and considering all types of eating disorders. • Adapt and validate existing screening and assessment tools in PCOS, including diverse groups. • Examine impact of treating eating disorders/disordered eating on outcomes and on effectiveness of PCOS treatment.
Q 2.6.1. Information resources	• Exploration of optimal delivery methods of health information for end users. • Exploration of needs, satisfaction and impact of education strategies on practice and health outcomes. • Identify avenues of integration into models of care.
Q 2.6.2. Models of care	• Develop benchmarking and performance indicators that address all aspects of multidisciplinary service. • Develop and implement a best practice framework outlining critical and aspirational elements of a PCOS model of care.
Q 2.6.3 Family and interpersonal interactions	• Understand impact of PCOS on wider family and interpersonal relationships. • Explore role of family, social and peer support in providing psychological support. • Investigate stigma and explore strategies to reduce stigma, considering cultural contexts
Q 2.6.4. Interactions	• How to implement well-established and effective frameworks for sharing news and shared decision-making in PCOS. • Evaluate effectiveness of these frameworks for outcomes that matter to patients (e.g., decision quality, causal understanding, agency, good health). • Explore how biases manifesting in interactions around sharing news and shared decision-making can be addressed.
Q 2.7. Psychological therapy	• Examine role and efficacy of psychological intervention for depression and/or anxiety, disordered eating, body image distress, self-esteem, gender identity or psychosexual dysfunction in adults and adolescents with PCOS. • Examine stepped care models incorporating evidence-based interventions and delivery modes (e.g., telehealth, apps).
Q 2.8. Anti-depressants and anxiolytics	• Understand aetiology and pathophysiology of mental health disorders in PCOS, which may inform targeted therapy. • Explore role and efficacy of various therapies in mental health disorders in PCOS in adults and adolescents. • Examine impact of PCOS treatment on depression or anxiety.
Guideline Development Group 3	**Lifestyle Management**
Theme 3. Exploring effective lifestyle and other weight management strategies, and minimising weight stigma in PCOS.	
Q 3.1. Effectiveness of lifestyle interventions	• Large, high quality RCTs and pragmatic implementation lifestyle trials, specifically: ○ Codesigned interventions and delivery methods (app based for example) with longer term sustainability and outcomes. ○ Improved outcome capture including reproductive (menstrual cycle, ovulation, pregnancy, live births) and psychological. ○ Study across ethnicities in low resource environments and across life stages. ○ Role and benefits in non-overweight populations. ○ Effects of lifestyle in the preconception period in women, reporting on live birth and obstetric outcomes.
Q 3.2. Behavioural interventions	• Clear, consistent definition of behavioural lifestyle interventions and outcomes. • Evaluate outcomes, alongside feasibility including cost-effectiveness. • Efficacy of behavioural interventions to optimise health behaviours and/or weight with lifestyle on anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes.
Q 3.3. Diet interventions	• High-quality research to determine the impact of different dietary interventions on a range of outcomes across the BMI range. • Investigate impact of range of diet interventions on anthropometric, metabolic, hormonal, reproductive, psychological outcomes in PCOS. • Monitoring safety and harm of specific dietary interventions (including disordered eating) and long-term follow-up
Q 3.4. Exercise interventions	• Explore exercise types, intensity, duration and duration of effect to optimise efficacy and efficiency. • Strategies to increase engagement and address barriers, cultural factors, acceptability, feasibility and sustainability. • Medium to longer term exercise studies (6–12 months or greater). • Impact of improvements in cardiorespiratory fitness and/or strength on PCOS features. • Assess the impact of reducing sedentary behaviour on clinical outcomes
Q 3.5. Weight gain	• Examine more precise quantification of diet, physical activity, appetite hormone regulation, appetite, insulin and energy expenditure in women with and without PCOS and examine relationships with weight/weight change across BMI range. • Primary longitudinal studies assessing: ○ Physiological, behavioural and psychosocial predictors of weight gain in PCOS, across age and BMI ranges. ○ Mechanisms including food or nutrient intake on adipokines, gastrointestinal appetite hormones, functional MRI, meal induced thermogenesis, metabolic flexibility and neuropeptide responses, linked to energy homeostasis. ○ Total energy expenditure in PCOS using doubly labelled water, diet intake measures and physical activity measures by accelerometry.

(Table 3 continues on next page)

Question #	Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:
(Continued from previous page)	
Q 3.6. Weight stigma	• Extent of weight-stigma in PCOS (across weight spectrum) by health professionals, family, workplace and community. • Health professionals' awareness of their own weight-stigmatising beliefs and behaviours and implementation of weight-neutral/weight inclusive care in PCOS. • Impacts of weight-neutral/weight-inclusive care on the biopsychosocial wellbeing of women with PCOS. • Consideration of other sources of stigma in PCOS (e.g., infertility, acanthosis nigricans, hirsutism, alopecia etc.).
Guideline Development Group 4	**Management of non-fertility features**
Theme 4. Examining intervention effects (including treatment efficacy, safety, cost-effectiveness and long-term follow-up). On diverse features of PCOS and across subgroups	
Q 4.2. & Q 4.3. COCP and combination COCP	• Large scale population-based studies to capture side effects and risks in individuals with PCOS. • Large scale comparative studies in adolescents to determine optimal COCP preparation including progestins and doses. • Efficacy of COCP on acne, hair loss, hirsutism and psychological outcomes. • Adverse events including weight, metabolic effects and psychological outcomes. • Efficacy of progestin only preparations (including intrauterine system, implant, progesterone only pills etc.).
Q 4.4. Metformin	• Explore metformin adherence and adverse effects in adults/adolescents by dose, preparation type and longer duration. • Explore across the BMI range to understand potential differential effect of metformin associated with BMI. • Study efficacy of combination therapy including metformin in addressing PCOS clinical features. • Assess Vitamin B12 levels in women on metformin to inform frequency of monitoring.
Q 4.5. Anti-obesity agents	• Compare efficacy of anti-obesity medications versus placebo in adolescents and adults with PCOS. • Assess impacts on metabolic, reproductive, psychological and pregnancy outcomes and adverse effects. • Explore role and adverse effects of long-term therapy
Q 4.6. Anti-androgens (AA)	• Determine optimal AA preparation and schedules including benefits and harms. • Determine optimal combination therapies by BMI groups.
Q 4.7. Inositol	• Optimal formulations, dose and adverse effects. • Critical clinical outcomes including ovulation, clinical pregnancy and live birth as well as quality of life, metabolic, reproductive, psychological and pregnancy outcomes and adverse effects. • High priority for independent funding as a consumer priority
Q 4.8. Hair reduction	• COCP alone or COCP + antiandrogens versus laser. • Feasibility and efficacy of laser treatment of hirsutism in different age subgroups and breastfeeding women. • More clarity on best laser treatment by skin type (given the heterogeneity of skin types in the studies). • Evaluation of laser efficacy in general body areas other than face. • Adverse events and side effects and cost effectiveness of laser treatment.
Q 4.9. Bariatric surgery	• Evaluate bariatric surgery impacts including comparison to anti-obesity therapy and by ethnicity. • Compare different types of bariatric/metabolic surgical procedures by outcomes. • Pre-conception and pregnancy requirements post bariatric/metabolic surgery. • Cost effectiveness studies. • Individual and patient cohorts long-term is critical, including psychological, pregnancy and child outcomes.
Q 4.10. Pregnancy complications	• Identify PCOS-status in antenatal care and follow-up PCOS versus non- PCOS, registering predefined outcomes. • Explore how phenotype, age and preconception BMI and ART affect adverse outcomes in addition to PCOS-status on individual patient data meta-analysis across international cohorts.
Q 4.11. Metformin in pregnancy	• Understand mechanisms of metformin action in pregnancy. • Timing, dosing, duration and subgroups that benefits most in pregnancy. • Explore potential long-term health effects in the next generation of metformin-exposure in utero.
Guideline Development Group 5	**Assessment and treatment of infertility**
Theme 5. Optimising preconception care and fertility treatments in PCOS	
Q 5.1. Preconception risk	• Individual patient data meta-analysis of preconception risk factors in PCOS and impact on fertility outcomes. • Explore ethnic and geographical variation in PCOS reproductive outcomes and fertility treatment responses. • Impact of age on fertility and fertility treatment outcomes in PCOS. • Cumulative weight gain over the reproductive life course and the impact on fertility and pregnancy outcomes. • Impact of underweight on fertility outcomes in PCOS.
Q 5.2. Tubal patency	• Explore if tubal patency tests should be done during infertility work-up to identify the optimal timing and method of assessing tubal patency in PCOS and infertility due to anovulation alone with normal semen analysis, considering cost effectiveness and quality of life.
Q 5.3. Aromatase inhibitors	• Establish ideal number of cycles of ovulation induction with letrozole before other treatments. • Validation of prediction models for first line ovulation induction agents and dose. • Study combination therapies of aromatase inhibitors with other inexpensive and widely available medications with different mechanisms of action such as metformin, inositol and clomiphene citrate. • Best therapies for drug naïve versus drug resistant/drug failure patients.
Q 5.4. Clomiphene and metformin	• Exploring side-effects and mitigation. • Best time for cessation of metformin in pregnancy. • A definitive trial to assess magnitude of efficacy on critically important outcome of live birth by BMI and metformin status.

(Table 3 continues on next page)

Question #	Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:
(Continued from previous page)	
Q 5.5. Gonadotrophins	• Compare letrozole versus gonadotrophins in women with anovulatory PCOS who are therapy naïve for clinical and cost effectiveness and Quality of life
Q 5.6. Ovarian surgery	• Understand how LOS restores ovulatory function. • Compare LOS with other ovulation induction agents in PCOS. • Explore profiles in PCOS who may respond to LOS. • Determine minimal effective intervention of LOS (i.e., number of drillings, energy level, modality and unilateral/bilateral).
Q 5.7. Stim IVF/ICSI	• Explore benefits of stimulated IUI versus IVF in PCOS. • Comparing IVM-ICSI to Stimulated-ICSI only.
Q 5.7.1. GnRH protocol	• Compare effectiveness of GnRH antagonist protocol versus GnRH long protocol to improve reproductive outcomes.
Q 5.7.2. Trigger type	• Ascertain whether combination of GnRHa trigger and intensive luteal steroid support in the OHSS high-risk patient is associated with better clinical outcomes than GnRHa trigger and subsequent frozen embryo transfer.
Q 5.7.3. Choice of FSH	• Compare different types of FSH in PCOS in controlled ovarian (hyper) stimulation for IVF/ICSI using GnRH antagonist or agonist long protocol on live birth rate per cycle, cumulative live birth rate from one egg retrieval, OHSS, cost effectiveness.
Q 5.7.4. Exogenous LH	• Investigate dose of exogenous LH in addition to FSH appropriate for follicular development on live birth rate and OHSS. • Explore groups that will benefit from exogenous LH addition to FSH in IVF ± ICSI.
Q 5.7.5. Adjuvant metformin	• RCTs of adjunct metformin before and/or during IVF/ICSI with GnRH antagonist protocol assessing benefits and harms, optimal start and finish times for metformin for pregnancy rate, live birth rate and infant outcomes.
Q 5.7.6. In Vitro Maturation	• Optimal IVM protocol for PCOS. • Long term health of offspring with IVM.
Q 5.8/5.9 Anti-obesity, Inositol	See 4.5 and 4.7

Table 3: **Research priorities emerging from the international polycystic ovary syndrome (PCOS) evidence-based guideline (EBG) process 2018 and 2023.**

Network consensus process built on prior stages and generated a clinical research priority roadmap consisting of over 150 research recommendations across diagnosis, broad features of PCOS and diverse population groups, which were further validated by international peer review.

Discrepancies between researcher-driven studies and end-user needs have been observed in various health conditions.[20,28] Such discrepancies have been attributed to a lack of involvement of research end-users in research priority setting.[29] Through our multistage coproduction process, we have generated an International PCOS Guideline clinical research priority roadmap to guide future clinical research in this neglected women's health condition. We show general concordance between women and healthcare providers with key clinical research priorities focusing on improving diagnosis concomitantly with expanding the understanding of long-term metabolic implications of PCOS, especially given the worldwide obesity epidemic. Notably and regretfully, PCOS remains underrepresented in diabetes and endocrine journals, guidelines and funding initiatives, despite robust evidence linking PCOS to type II diabetes and other metabolic conditions which is independent of excess weight and exacerbated by PCOS-related weight gain.[30] Infertility remains a research priority for all stakeholders, however, there is evidence that PCOS research remains underfunded compared even to other reproductive conditions.[14]

PCOS poses significant global health burden due to its multifaceted nature and wide-ranging impact on affected women. Precision medicine offers promising avenues for alleviating this burden by tailoring prevention, diagnosis and treatment strategies to individuals with PCOS. However, to effectively harness the potential of precision medicine, a comprehensive approach that integrates both discovery science and clinical research is required.[31] Discovery research in PCOS is vital to understand the pathophysiological causes and mechanisms of PCOS and often involves laboratory-based studies, animal models, genetic and molecular analyses as outlined in our recent contribution in Nature Disease Reviews Primer.[32] This is key to understanding PCOS, including the various subtypes as well as the identification of novel or personalised interventions targets. While we fully acknowledge that discovery research in PCOS remains an important priority, discovery research is not addressed in this current International PCOS Guideline clinical research roadmap as it is dedicated to the immediate clinical care needs in PCOS as a multifaceted, complex and neglected syndrome. Here, clinical research, focuses on human research on the natural history, presentation, diagnosis, treatment, models of care and outcomes of the condition through epidemiological and qualitative studies and clinical trials, often taking discovery research into applications to improve health outcomes. By identifying clinical research priorities through an international, rigorous, and inclusive

multistage co-production process involving women, healthcare providers, and academic experts globally, this roadmap ensures that the perspectives of those directly affected by PCOS and their healthcare providers, shaped the clinical research landscape. Our clinical roadmap can also help guide the development of PCOS discovery research initiatives to closely align with the clinical needs and priorities of key stakeholders. Through this coordinated approach, we can bridge the gap between research and clinical practice, ultimately advancing the field of precision medicine in PCOS.

Precision medicine operates initially on group-level predictions derived from large datasets, which serve as a foundation for tailoring interventions to individual patients.[31,33] As we look to the future, there is a compelling case for consolidating data across studies to unlock the potential of "big data" in advancing our understanding and application of precision medicine of this complex syndrome. The integration of data from various sources, including clinical, genetic and epigenetic data holds significant promise to elucidate the multifaceted nature of PCOS and its diverse manifestation across different populations and life stages. Creating international data repositories is of high research priority. One key aspect is establishing common core data standards to harmonise data collection methods, variables and format, enabling seamless integration and comparison of findings from different study cohorts.[34] This collaborative effort will provide researchers access to a wealth of information for analysis and interpretation, and lay foundation for the development of sophisticated machine learning models, facilitating the development of personalised prevention and treatment in PCOS, with work already underway.[35]

We recommend that the International PCOS Guideline clinical research priority roadmap be used in conjunction with key tools including the guide for high quality harmonised observational studies[34] and the Harmonizing Research Outcomes for PCOS (HARP) core outcome set.[25] The HARP core outcome set defines a set of outcomes that should be measured and reported in PCOS clinical research based on the end-points reported in evidence synthesis and patient consultations conducted for the 2018 Guideline, followed by a modified Delphi survey and workshop.[25] It offers a standardized framework for assessing relevant and important outcomes in PCOS clinical research, thereby enhancing comparability across studies and minimise research wastage. Designing future clinical research in PCOS which aligns with this International PCOS Guideline clinical research priority roadmap and the HARP core outcome set will assist in streamlining research efforts to address critical knowledge gaps and enable comprehensive evaluation of the effectiveness of interventions and management strategies' in PCOS. This approach increases the likelihood of research findings being adopted into clinical practice and health policy, leading to tangible improvements in PCOS management and patient outcomes.

The exploratory surveys were conducted in English and primarily engaged those in Europe and North America by convenience sampling, therefore the findings may not be representative of priorities of women and healthcare providers worldwide, especially in developing countries. Logistic regression modelling using age in categorical format in stage i can be subject to unmeasured confounding. However, categorising age into groups here was intentional to align with our objective of exploring research priorities across different life stages. Subsequent stage ii and iii processes also involved experts and consumers from six continents and stage iv involved public consultation online internationally for peer review. The number of studies included in the International PCOS Guideline evidence reviews is an estimate because a study may have contributed to answering more than one clinical question for the guideline, and the estimates of level of certainty of the evidence may differ between endpoints within the same study. Despite these limitations, this process by the International PCOS Guideline Network is the only one to comprehensively explore the PCOS research priorities of women and healthcare providers on an international scale. Subsequent extensive engagement in evidence synthesis, GRADE processes, and peer review encompassed six continents. The findings are enriched here by the multistage co-production process and the robust best practice guideline development with an embedded, transparent and systematic process for decision-making, involving the perspective of those with PCOS lived experience and of multidisciplinary clinical and academic experts as part of the PCOS Guideline GDG.

The International PCOS Guideline clinical research priority roadmap, developed through an unprecedented and rigorous multistage co-production process, has engaged stakeholders worldwide, and represents a pivotal step in addressing the major challenges and clinical care needs posed by this common and overlooked condition. Here, clinical research priorities include both core principles for improving research quality as well as specific clinical areas for focused research. Building on the International PCOS Guideline and Network, prioritizing key areas through the clinical research roadmap and integrating with the PCOS core outcome set, will position this field for improved consistency, comparability, quality and relevance of research and better translation of research findings into practice. For optimal progress, the Guideline also recommends that government bodies, policy makers, and funding organizations recognize the breadth, health and quality of life impact of PCOS, and calls for greater equity and research funding in this neglected field. Adequate funding and resources should be allocated to facilitate consumer partnership and large-scale, well-

designed, multicentre studies that align with the research priorities and core outcome set. By developing and advancing these recommendations and priorities, together stakeholders can accelerate the generation and translation of evidence into practice to overcome inherent gender and reproductive health bias in research and, ultimately improve outcomes for the one in eight women affected by PCOS.

Contributors

HT: obtained funding, engaged stakeholders and created the International PCOS Guideline Network, led the Guideline development processes in 2018 and 202, participated in study design, execution, analysis, manuscript drafting and critical discussion.

MG: participated in study design, Guideline development, execution, analysis in Stage i, manuscript drafting and critical discussion.

JL, AD, LM, TP, MC, and AJ were Guideline Development Group chairs and had a role in funding, design, execution and peer review responses as well in manuscript review.

CTT and AM: participated in study execution, had a lead role in evidence synthesis and Guideline development, and in manuscript drafting and critical discussion.

The International PCOS Guideline Network members and included authors were trained in evidenced-based guideline development, attended multiple meetings, interpreted the evidence synthesis and generated evidence-based recommendations transparently, whilst also agreeing on next steps in research priority settings.

Data sharing statement

All data that support the findings of this study, including deidentified individual-participant data, are available after publication on request from the corresponding author (Helena.teede@monash.edu). Additionally, the data that support the findings of Stage ii and iii of International PCOS Guideline process are openly available in the PCOS Guideline Technical Report at https://www.monash.edu/__data/assets/pdf_file/0010/3379591/TechnicalReport-2023.pdf.

Declaration of interests

All disclosures of interest were declared before commencing GDG involvement and updated before all major milestones and are available alongside the PCOS Guideline (https://www.monash.edu/__data/assets/pdf_file/0009/3371292/Register-of-disclosures-of-interest.pdf).

JL declared grants or contracts from AnshLabs, Ferring, Merck, Titus Health Care and Roche Diagnostic; consulting fees from AnshLabs, Ferring and Gedeon Richter; and participation on Advisory Board for LOCI Trial.

MG declared payment or honoraria from Sharesies NZ Ltd, Women's Health Seminar Series 2022; and support for meeting and/travel for attendance of the PCOS Guideline development meeting from the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life.

TP declared grants or contracts from Research Council of Finland, Novonordisk, Sigrid Juseliud Foundation and Roche; consulting fees from Organon, Roche and Gedeon Richter; support for attending meetings and/or travels from Gedeon Richter, Ferring, and Exceltis; and leadershio role in Androgen Excess and PCOS Society and NFGO Scientific.

Acknowledgements

The authors gratefully acknowledge all the women and healthcare providers who participated in this research. The authors thank the following organisations for their assistance with survey dissemination: PCOS Challenge, Verity UK, the American Society for Reproductive Medicine, American College of Obstetricians and Gynaecologists, Androgen Excess and PCOS Society, Federation of Obstetrics and Gynaecological Societies of India, European Society of Human Reproduction and Embryology, national societies in Nordic countries and Estonia, and the Nordic PCOS Network. The extensive international contributions to the evidence synthesis and Guideline process is much appreciated. We acknowledge the use of ChatGPT for language editing of this manuscript.

The survey, International PCOS Guideline Network and 2018 and 2023 International PCOS Guidelines were funded by the Australian National Health and Medical Research Council (NHMRC) Centres of Research excellence in PCOS (APP1078444) and in Women's Health In Reproductive Life (APP1171592). Guideline partners, American Society for Reproductive Medicine (ASRM), Endocrine Society, European Society of Human Reproduction and Embryology (ESHRE), and European Society of Endocrinology (ESE), provided additional funding and assisted in guideline development. HT and AM are NHMRC Research Fellows. LM was funded by a Heart Foundation - Australia Future Leader and Veski Fellowship and CTT by the NHMRC Centres of Research excellence in Women's Health in Reproductive life.

International PCOS Guideline Network: Wiebke Arlt, Ricardo Azziz, Adam Balen, Lisa Bedson, Lorna Berry, Jacky Boivin, Jacqueline Boyle, Leah Brennan, Wendy Brown, Tania Burgert, Maureen Busby, Carolyn Ee, Rhonda M Garad, Cheryce Harrison, Roger Hart, Marie Misso, Rachel Morman, Angelica Lindén Hirschberg, Tuong Ho, Kathleen Hoeger, Sonia Jitpiriyaroj, Cailin Jordan, Richard S Legro, Rong Li, Marla Lujan, Ronald C Ma, Darren Mansfield, Kate Marsh, Edgar Mocanu, Robert J Norman, Sharon Oberfield, Dawn Kimberly Hopkins, Malika Patel, Alexia Peña, Leanne Redman, Luk Rombauts, Daniela Romualdi, Duru Shah, Poli Mara Spritzer, Elisabet Stener-Victorin, Fahimeh Ramezani Tehrani, Shakila Thangaratinam, Mala Thondan, Eszter Vanky, Bassel H. Al Wattar, Chandrika Wijeyaratne, Selma Witchel, Dongzi Yang, Bulent O Yildiz.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102927.

References

1 Teede HJ, Tay CT, Laven J, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril*. 2023;120(4):767–793.
2 Teede HJ, Tay CT, Laven J, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndromedagger. *Hum Reprod*. 2023;38(9):1655–1679.
3 Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Eur J Endocrinol*. 2023;189(2):G43–G64.
4 Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2023;108(10):2447–2469.
5 Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Clin Endocrinol*. 2018;89(3):251–268.
6 Mousa A, Tay CT, Teede H. *Technical report for the international evidence-based guideline for the assessment and management of polycystic ovary syndrome*. Melbourne: Monash University; 2023.
7 Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. *Trends Endocrinol Metab*. 2015;26(3):136–143.
8 Zhang J, Xu JH, Qu QQ, Zhong GQ. Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: a meta-analysis of cohort studies. *Front Cardiovasc Med*. 2020;7:552421.
9 Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, Chen HY. Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Reprod Biol Endocrinol*. 2013;11:56.
10 Dokras A, Stener-Victorin E, Yildiz BO, et al. Androgen Excess-Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome. *Fertil Steril*. 2018;109(5):888–899.
11 Dapas M, Dunaif A. Deconstructing a syndrome: genomic insights into PCOS causal mechanisms and classification. *Endocr Rev*. 2022;43(6):927–965.

12 Gibson-Helm M, Dokras A, Karro H, Piltonen T, Teede HJ. Knowledge and practices regarding polycystic ovary syndrome among physicians in Europe, North America, and internationally: an online questionnaire-based study. *Semin Reprod Med*. 2018;36(1):19–27.
13 Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2017;102(2):604–612.
14 Brakta S, Lizneva D, Mykhalchenko K, et al. Perspectives on polycystic ovary syndrome: is polycystic ovary syndrome research underfunded? *J Clin Endocrinol Metab*. 2017;102(12):4421–4427.
15 Tay CT, Joham AE, Moran LJ, Teede H. Better care for women with polycystic ovary syndrome - a proposal for an international evidence based best practice framework to improve care. *Curr Opin Endocrinol Diabetes Obes*. 2022;29(6):514–520.
16 Gupta GR, Oomman N, Grown C, et al. Gender equality and gender norms: framing the opportunities for health. *Lancet*. 2019;393(10190):2550–2562.
17 Piil K, Jarden M. Patient involvement in research priorities (PIRE): a study protocol. *BMJ Open*. 2016;6(5):e010615.
18 Terry RF, Charles E, Purdy B, Sanford A. An analysis of research priority-setting at the World Health Organization - how mapping to a standard template allows for comparison between research priority-setting approaches. *Health Res Policy Syst*. 2018;16(1):116.
19 chalmers I, Essali A, Rezk E, Crowe S. Is academia meeting the needs of non-academic users of the results of research? *Lancet*. 2012;380:S43.
20 Crowe S, Fenton M, Hall M, Cowan K, Chalmers I. Patients', clinicians' and the research communities' priorities for treatment research: there is an important mismatch. *Res Involvement Engag*. 2015;1(1):1–10.
21 de Wit MP, Berlo SE, Aanerud GJ, et al. European League against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. *Ann Rheum Dis*. 2011;70(5):722–726.
22 Moher D, Glasziou P, Chalmers I, et al. Increasing value and reducing waste in biomedical research: who's listening? *Lancet*. 2016;387(10027):1573–1586.
23 Elwyn G, Crowe S, Fenton M, et al. Identifying and prioritizing uncertainties: patient and clinician engagement in the identification of research questions. *J Eval Clin Pract*. 2010;16(3):627–631.
24 Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. *Lancet*. 2000;355(9220):2037–2040.
25 Al Wattar BH, Teede H, Garad R, et al. Harmonising research outcomes for polycystic ovary syndrome: an international multistakeholder core outcome set. *Hum Reprod*. 2020;35(2):404–412.
26 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
27 Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. *Fertil Steril*. 2017;107(6):1380–1386.e1.
28 Sacristan JA, Aguaron A, Avendano-Sola C, et al. Patient involvement in clinical research: why, when, and how. *Patient Prefer Adherence*. 2016;10:631–640.
29 Shafiei T, Small R, McLachlan H. Women's views and experiences of maternity care: a study of immigrant Afghan women in Melbourne, Australia. *Midwifery*. 2012;28(2):198–203.
30 Rodgers RJ, Avery JC, Moore VM, et al. Complex diseases and comorbidities: polycystic ovary syndrome and type 2 diabetes mellitus. *Endocr Connect*. 2019;8(3):R71–R75.
31 Franks PW, Cefalu WT, Dennis J, et al. Precision medicine for cardiometabolic disease: a framework for clinical translation. *Lancet Diabetes Endocrinol*. 2023;11(11):822–835.
32 Stener-Victorin E, Teede H, Norman RJ, et al. Polycystic ovary syndrome. *Nat Rev Dis Primers*. 2024. In press.
33 Ye Y. Unleashing the power of big data to guide precision medicine in China. *Nature*. 2022;606(7916):S49–S51.
34 Azziz R, Kintziger K, Li R, et al. Recommendations for epidemiologic and phenotypic research in polycystic ovary syndrome: an androgen excess and PCOS society resource. *Hum Reprod*. 2019;34(11):2254–2265.
35 Kiconco S, Mousa A, Azziz R, et al. PCOS phenotype in unselected populations study (P-PUP): protocol for a systematic review and defining PCOS diagnostic features with pooled individual participant data. *Diagnostics*. 2021;11(11):1953.