

## **Invitation for expression of interest (EOI)**

**“To undertake a multi centric randomized controlled trial for evaluating the efficacy of Metformin vs Inositol to improve fertility and birth outcomes among PCOS women”**

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### **Overview:**

Polycystic ovarian syndrome (PCOS) is a complex disorder ranging from mild to severe disruptions in reproductive, endocrine, and metabolic functions, with key features including irregular menstrual periods (anovulation), hyperandrogenism, insulin resistance, and abnormal gonadotropin secretion. The prevalence of infertility in women with PCOS is high, varying between 70 and 80% [1]. Moreover, PCOS women have been found to have increased prevalence of pregnancy complications and less favorable pregnancy outcomes (live births, miscarriage, pregnancy rate) compared with women without PCOS [2].

In contemporary practice, use of Metformin and Inositol for the treatment of PCOS is widespread. However, present evidence on the efficacy of these two drugs in terms of improvement in fertility and other related outcome is insufficient. A Finnish study suggested that, as compared to placebo, metformin improved the pregnancy rate, live birth rate and ovulation rate in the studied population [3]. However, a Cochrane review with meta-analysis including three other smaller studies reported that as compared with placebo, metformin may have only marginal benefit for live birth rate outcome [4].

Additionally, there is very limited data available globally on effectiveness of Inositol for PCOS women, especially for birth outcome and cycle regulation [5]. Evidence on the efficacy of both metformin and inositol in the Indian context is almost non-existent. To address the knowledge gap and to generate evidence on the management of PCOS for improving birth outcomes in the Indian context, the current ICMR call is being proposed.

### **Purpose of the call:**

ICMR is looking to partner with interested researchers for the development of a multicentre randomized controlled trial for the management of PCOS in Indian women. The drugs that have been recommended by experts for this purpose are Metformin and Inositol. The selected researchers shall be invited to join the research team and shall collaborate to develop a full research proposal and roll out the multi-centre research project which will be coordinated by

ICMR. The process of development of proposal and research project implementation shall be reviewed by an independent Expert Committee.

ICMR invites EOI to address the following research question:

**Priority Research Question:**

Among women with Polycystic Ovary Syndrome (PCOS), how does inositol in comparison to metformin in terms of efficacy and safety on outcomes including pregnancy conception, menstrual cycle regularization, and improvement in endocrinological and metabolic parameters?

**Design:** A multicenter randomized controlled trial.

**Who can submit the EOI?**

1. Researchers (PIs and Co-PIs) who have regular employment in Medical Institutes/ Research Institutes/ Universities/ Colleges/Government and semi- government organizations and NGOs.
2. A team of researchers should be identified along with the principal investigator. The research team should have credentials for relevant skills, experience and demonstrated ability to solve health problems under consideration.
3. The team should have prior experience in conducting RCTs, preferably in PCOS or reproductive health.

**Review process:**

The EOI documents will be evaluated by the Indian Council of Medical Research (ICMR). The ICMR team will screen the applications for technical accuracy and eligibility. The shortlisted teams will be invited to collaborate and develop one single detailed proposal to be implemented in all the selected sites under the guidance of ICMR HQ. A two day workshop will be envisaged to draft and finalize the SOPs for each activity planned within the study. An expert group will evaluate the developed proposal for the technical and operational aspects. The budget will be developed in consultation with ICMR HQ.

**How to Submit the EOI?**

The EOI can be submitted through ONLINE MODE ONLY by the Principal Investigator on behalf of the proposed team. **Interested parties should fill out the Google form at the below link and submit an Expression of Interest (EOI) as per the (Annexure I) in PDF format.**

Link:

[https://docs.google.com/forms/d/e/1FAIpQLSe28PES\\_SPJJ0A6RMlfey8lhjXKtJMy93abyvCNVT\\_Err1QXXA/viewform?usp=pp\\_url](https://docs.google.com/forms/d/e/1FAIpQLSe28PES_SPJJ0A6RMlfey8lhjXKtJMy93abyvCNVT_Err1QXXA/viewform?usp=pp_url)

*Only shortlisted PI will be contacted via e-mail.*

### **Timelines**

<b>Timeline Activities</b>	<b>Date</b>
Release of Call	30.09. 2024
End of Call	21.10.2024
Shortlisting of EOIs	12.11.2024
SOP Development Workshop	21.11.2024-22.11.2024

**For any queries related to the call, please contact**

Dr. Taruna Arora

Scientist - 'D'

RCN Division, ICMR Headquarters, V Ramalingaswami Bhawan,  
Ansari Nagar, New Delhi-110029

Email: [tarunakatyal@gmail.com](mailto:tarunakatyal@gmail.com)

## References

1. Rasquin LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. [Updated 2022 Nov 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459251/>
2. Collée, J., Mawet, M., Tebache, L., Nisolle, M., & Brichant, G. (2021). Polycystic ovarian syndrome and infertility: overview and insights of the putative treatments. *Gynecological Endocrinology*, 37(10), 869-874.
3. Morin-Papunen, L., Rantala, A. S., Unkila-Kallio, L., Tiitinen, A., Hippeläinen, M., Perheentupa, A., et al. (2012). Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): A multicenter, double-blind, placebo-controlled randomized trial. *Journal of Clinical Endocrinology and Metabolism*, 97, 1492–1500. <https://doi.org/10.1210/jc.2011-3393>
4. Morley, L. C., Tang, T. M. H., Balen, A. H., (2017). Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome. *Scientific Impact Paper No. 13. BJOG*, 124, e306–e313. <https://doi.org/10.1111/1471-0528.14764>
5. Teede, H. J., Tay, C. T., Laven, J. J. E., et al. (2023). Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Journal of Clinical Endocrinology and Metabolism*, 108(10), 2447-2469. <https://doi.org/10.1210/clinem/dgad463>

## **Format of Expression of Interest (EOI) to be submitted**

1. Title of the proposal:
2. Name of the Principal Investigator:
3. Address with email id and phone no. of PI:
4. Name of the Institute:
5. Type of Organization: Government/ Private/ Non-Government Organization
6. Study outline in PICO format
7. Rationale of choice of sites (states and districts) to be included where the study shall be carried out (< 300 words). (Kindly mentioned the expected number of relevant PCOS patients in their set up, that they will be able to recruit in the study, if approved)
8. Work plan/ methodology aligned to objectives (< 1000 words)
  - a) Study design including details of randomization process
  - b) Sampling technique and sample size estimation
  - c) Participant recruitment
  - d) Baseline assessment
  - e) Details of the intervention
  - f) Details of comparator
  - g) Outcome measurement
  - h) Data analysis
  - i) Ethical consideration
  - j) Timeline
  - k) Budget

The final budget for the proposal will be developed by the selected research team/s in discussion with ICMR. In this EOI, we request you to provide an estimated budget outline (no budget justification required at this stage) under the following headings: staff, recurring/contingency, data management, travel and equipment.

9. Study deliverables, Monitoring and evaluation plans& future scope (<300 words)
10. Collaboration with ICMR or contribution to ICMR activities in last 5 years (maximum 250 words).
11. Research Team (<500 words)  
Summarize and justify the composition of the research team, based on the expertise of the individual team members in designing and implementing the project. Also, highlight the skill set and expertise the members shall bring to the research team that shall be constituted by the ICMR Hqrs for the development of final protocol and research project implementation.
12. Two-page CV of the principal investigator and other key investigators in a single pdf  
Please provide a Two-page CV of the PI and other key investigators from each identified area. Each CV should include:
  - a) Academic and professional qualifications
  - b) Current position and affiliation
  - c) Up to five most relevant previous research grants
  - d) Up to five most relevant previous publications
  - e) Experience in undertaking projects on PCOS

**Signature of PI**