

# Comparison of letrozole or clomifene for ovulation induction in women with polycystic ovarian syndrome

<b>Submission date</b> 16/12/2019	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered
<b>Registration date</b> 07/01/2020	<b>Overall study status</b> Completed	<input checked="" type="checkbox"/> Protocol
<b>Last Edited</b> 13/06/2025	<b>Condition category</b> Nutritional, Metabolic, Endocrine	<input checked="" type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data
		<input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Polycystic ovary syndrome (PCOS) affects 20% of women. Women with PCOS may not release eggs from their ovaries; this is called anovulation. The first line treatment for anovulation is a medicine called clomifene (formerly known as clomiphene). Current clinical guidelines in the UK recommend the use of clomifene with or without another medicine, metformin, for a maximum of 6 menstrual cycles. Clomifene treatment does not result in pregnancy for approximately 70% of women despite prolonged treatment. Furthermore, clomifene is associated with numerous side effects and a 10-fold increase in the risk of multiple pregnancy.

Recently there has been growing interest in the use of another medicine, letrozole, to treat infertility in women with PCOS. Letrozole works differently to clomifene and has fewer side effects, including a lower risk of multiple pregnancy. A recent review of studies involving all available medicines for women with PCOS and infertility has indicated that letrozole may be more effective than clomifene when used alone, and there may be additional value when it is combined with metformin.

This trial has been developed in consultation with two patient representation groups, Fertility Network UK and the Women's Network of the RCOG.

### Who can participate?

Adult women diagnosed with PCOS seeking fertility treatment to participate in this study

### What does the study involve?

Participants will be allocated to clomifene or letrozole, which they will take for 5 days at the beginning of each menstrual cycle. Participants will also be given metformin or a dummy drug to be used alongside clomifene or letrozole but this use will continue up until the first 14 weeks of pregnancy. Clomifene or letrozole treatment will be offered for up to 6 treatment cycles, to match the current guidelines. The allocation of treatment will be decided at random by a computer, and neither the participants nor the researchers will know what treatment a patient is receiving; this arrangement is necessary to test the treatments fairly. The main outcome evaluated will be whether a participant has a live birth. A number of other key outcomes such as ovulation rate, miscarriage, multiple pregnancy and newborn outcomes will also

What are the possible benefits and risks of participating?

#### Benefits

At the moment there is not enough evidence to say which treatment is best for ovulation induction and a successful pregnancy outcome.

We do not know whether participants will benefit personally from taking part in this study, but the knowledge gained will inform future treatment and potentially lead to improved treatment for ovulation induction for women in the future.

#### Risks/side effects

The most common side effect of taking clomifene or letrozole is hot flushes, as well as occasional fatigue and dizziness. Metformin can often cause stomach upset and sickness. Treatment with letrozole is off-license as the drug company has not applied for a specific license to allow treatment for fertility and is therefore not approved for ovulation induction.

Where is the study run from?

Birmingham Clinical Trials Unit, UK

When is the study starting and how long is it expected to run for?

March 2020 to August 2025

Who is funding the study?

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC), UK

Who is the main contact?

Georgia Mitchell, g.mitchell.1@bham.ac.uk

## Contact information

#### Type(s)

Scientific

#### Contact name

Ms Georgia Mitchell

#### Contact details

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## Additional identifiers

Clinical Trials Information System (CTIS)

2018-004641-16

## **Integrated Research Application System (IRAS)**

257918

## **ClinicalTrials.gov (NCT)**

Nil known

## **Protocol serial number**

CPMS 42795, IRAS 257918

# **Study information**

## **Scientific Title**

Letrozole or clomifene, with or without metformin, for ovulation induction in women with polycystic ovary syndrome: a 2x2 factorial design randomised trial (the LOCI trial)

## **Acronym**

LOCI

## **Study objectives**

Current study hypothesis as of 25/02/2025:

In women with PCOS and infertility, letrozole versus clomifene, metformin versus placebo, and letrozole plus metformin versus clomifene plus metformin increases the live birth rate ( $\geq 34$  weeks of gestation) by at least 10%.

Previous study hypothesis:

In women with PCOS and infertility, letrozole plus metformin versus clomifene plus metformin increases the live birth rate ( $\geq 34$  weeks of gestation) by at least 10%

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Approved 18/12/2019, West Midlands - Edgbaston Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)2071048089; Edgbaston@nhs.net), ref: 19 /WM/0364

## **Study design**

Interventional randomized controlled trial

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Polycystic ovarian syndrome

## **Interventions**

Participants will be randomised on-line via a secure internet facility at the level of the individual in a 1:1 ratio to either letrozole or clomifene and at the same time randomised to metformin or placebo.

Planned IMP interventions: Letrozole oral tablet 2.5-7.5mg daily or clomifene 50-150mg daily for 5 days of each menstrual cycle for up to 6 treatment cycles, with concomitant randomisation to an escalating dose of metformin to 1500mg or placebo daily. Letrozole, clomifene, metformin and placebo will be provided as over-encapsulated tablets in numbered treatment packages. The Metformin/placebo will be provided at the same time as letrozole/clomifene.

Dose: The ideal dose of letrozole and clomifene for ovulation induction is not known. The choice of 2.5mg for letrozole and allowing for 2 dose escalations up to 7.5mg was made after a) careful review of the existing literature, b) a survey of UK health professionals who use letrozole for this indication, and c) reviewing the safety profile of the drug in a previous large randomised trial involving letrozole.<sup>14</sup> Summary of Product Characteristics and the British National Formulary<sup>15</sup> suggest a starting dose of 2.5mg. The choice of clomifene 50mg with 2 dose escalations up to 150mg was based on NICE recommendations.<sup>3</sup> Our systematic review of literature and UK-wide survey of health professionals supported these regimens. The choice of metformin dose was based on our systematic review of literature and the UK-wide survey of health professionals. However, when clinicians feel the participant should be started on a higher dose because of previous cycle experience or preference, this will be allowed for a maximum of 3 tablets daily.

Route: All drugs are recommended for oral use.

Regimen: Letrozole and clomifene will be given for 5 days starting on day 2 or 3 of the menstrual cycle or following the start of withdrawal bleeding for up to 6 treatment cycles (Table 1). This regimen was the most commonly used in our survey of UK health professionals. The dose of metformin will be increased gradually from 500mg daily for the 1st week, 500mg twice daily for the 2nd week, and 500mg thrice daily from the 3rd week, and continued until the end of treatment or up to 14 weeks of pregnancy (Table 2). The gradual increase of metformin was suggested by our national investigator group to minimise the side-effects of metformin. Metformin will be continued up to 14 weeks of pregnancy as this was the most commonly used regimen in our national survey of UK health professionals. However, when clinicians feel the participant should be started on a higher dose because of previous experience or preference, this will be allowed for a maximum of 3 tablets daily.

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Clomifene, letrozole

## **Primary outcome(s)**

Current primary outcome measure as of 25/02/2025:

Live births at and beyond 34 completed weeks of gestation, as a proportion of all women randomised - measured by patient records

Previous primary outcome measure:

Live births at and beyond 34 completed weeks of gestation measured using patient records

## **Key secondary outcome(s)**

Current secondary outcome measures as of 25/02/2025:

Measured using patient records:

1. Treatment outcomes: ovulation rate, pregnancy time, cycles for pregnancy/live birth at end of ovulation induction, 240 days since randomisation, booking scan form (11-14 weeks) or at pregnancy outcome (~9 months)
2. Pregnancy end outcomes: ongoing pregnancy, loss, termination, stillbirth, ectopic, multiple births at booking scan (11-14 weeks) or pregnancy outcome
3. Live birth  $\geq 24$  weeks: time to delivery, gestational age, mode of birth, birth weight, APGAR score at pregnancy outcome
4. Antenatal outcomes: antepartum haemorrhage, hypertension, pre-eclampsia, cholestasis, gestational diabetes at 28 days post pregnancy outcome
5. Intrapartum outcomes: chorioamnionitis, fetal growth restriction, macrosomia at pregnancy outcome
6. Postpartum outcomes: haemorrhage at pregnancy outcome
7. Maternal outcomes: HDU/ITU admission at 28 days post live birth
8. Neonatal outcomes: discharge, early infection, retinopathy, NEC, intraventricular haemorrhage, RDS, ventilation at 28 days post birth
9. Neonatal survival: 28-day survival at 28 days post live birth
10. Health economic evaluation: EQ-5D-5L at baseline, booking scan (month 4-9), and end of trial (month 2-18)

Previous secondary outcome measures:

Measured using patient records:

1. Miscarriage rate (defined as delivery before 24 weeks of gestation).
2. Ongoing pregnancy at 12 weeks (range 11 to 14 weeks) of gestation.
3. Multiple pregnancies.
4. Ovulation rate
5. Time to pregnancy

**Completion date**

30/08/2025

## Eligibility

### Key inclusion criteria

Current inclusion criteria as of 17/10/2022:

1. Women diagnosed with PCOS (according to Rotterdam criteria) and evidence of anovulation (defined as irregular cycles lasting  $< 21$  or  $> 35$  days, fewer than 8 periods per year, or absence of raised serum progesterone  $> 20$  nmol/l seven days prior to a period)
2. Presentation with infertility or wishing to conceive
3. Male partner with normal sperm count ( $\geq 15$  million/ml) and progressive motility  $\geq 32\%$  or total motility  $\geq 40\%$  in the last 3 years
4. Willing and able to give informed consent
5. Aged  $\geq 18$  to  $\leq 42$  years at randomisation
6. Body Mass Index  $\leq 35$  kg/m<sup>2</sup>

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Previous inclusion criteria:

1. Women diagnosed with PCOS (according to Rotterdam criteria) and evidence of anovulation (anovulation is defined as irregular cycles lasting  $< 21$  or more than 35 days or less than 8 periods per year OR absence of raised serum progesterone greater than 20nmol/l 7 days prior to a

period)

2. Presentation with infertility or wishing to conceive

3. Male partner with normal sperm count ( $\geq 15$  million) and progressive motility ( $\geq 32\%$ ) in the last 3 years

4. Willing and able to give informed consent

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Upper age limit**

42 years

### **Sex**

Female

### **Total final enrolment**

1739

### **Key exclusion criteria**

Current exclusion criteria as of 17/10/2022:

1. More than six previous ovulation induction treatments (cycles) with either letrozole or clomifene in the previous 12 months
2. Intention to continue current use of metformin treatment for ovulation induction or for other indications
3. Metformin use in the previous 14 days
4. Women opting for alternative methods of ovulation induction or treatment (GnRH agonists and antagonists, gonadotropins), triggering ovulation with hCG, or performing intrauterine or intracervical insemination
5. Contraindications to letrozole, clomifene, metformin use and/or pregnancy
6. Woman has previously participated in the LOCI trial

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Previous exclusion criteria:

1. Age  $< 18$  or  $> 43$  years at randomisation
2. Body Mass Index  $\geq 35$  kg/m<sup>2</sup>
3. Three or more previous ovulation induction treatments with either letrozole or clomifene
4. Currently on metformin treatment or inositol supplements for ovulation induction or for other indications
5. Women opting for alternative methods of ovulation induction or treatment (GnRH agonists and antagonists, gonadotropins), triggering ovulation with hCG, or performing intrauterine or intracervical insemination
6. Contraindications to letrozole, clomifene, metformin use and/or pregnancy (see section 7.2

for full details on contraindications)

7. Woman has previously participated in the LOCI trial

**Date of first enrolment**

01/03/2020

**Date of final enrolment**

29/02/2024

## **Locations**

**Countries of recruitment**

United Kingdom

England

Scotland

Wales

**Study participating centre**

**Ashford and St Peter's Hospitals NHS Foundation Trust**

Chertsey

United Kingdom

KT16 0PZ

**Study participating centre**

**Barts Health NHS Trust**

The Royal London Hospital

Whitechapel Road

London

United Kingdom

E1 1FR

**Study participating centre**

**Barking, Havering and Redbridge University Hospitals NHS Trust**

Romford

United Kingdom

RM7 0AG

**Study participating centre**

**Birmingham Women's and Children's NHS Foundation Trust**

Steelhouse Lane

Birmingham  
United Kingdom  
B4 6NH

**Study participating centre**  
**Bolton NHS Foundation Trust**  
Bolton  
United Kingdom  
BL4 0JR

**Study participating centre**  
**Cambridge University Hospitals NHS Foundation Trust**  
Addenbrookes Hospital  
Hills Road  
Cambridge  
United Kingdom  
CB2 0QQ

**Study participating centre**  
**Manchester University NHS Foundation Trust**  
Cobbett House  
Oxford Road  
Manchester  
United Kingdom  
M13 9WL

**Study participating centre**  
**Countess of Chester Hospital**  
Chester  
Cheshire  
United Kingdom  
CH2 1UL

**Study participating centre**  
**County Durham and Darlington NHS Foundation Trust**  
Durham  
United Kingdom  
DL3 6HX

**Study participating centre**  
**Dartford and Gravesham Nhs Trust**  
Dartford  
United Kingdom  
DA2 8DA

**Study participating centre**  
**Royal Derby Hospital**  
Uttoxeter Road  
Derby  
United Kingdom  
DE22 3NE

**Study participating centre**  
**East Lancashire Hospitals Nhs Trust**  
Blackburn  
United Kingdom  
BB2 3HH

**Study participating centre**  
**East Suffolk and North Essex Nhs Foundation Trust**  
Colchester  
United Kingdom  
CO4 5JL

**Study participating centre**  
**Guy's and St Thomas' NHS Foundation Trust**  
Great Maze Pond  
London  
United Kingdom  
SE1 9RT

**Study participating centre**  
**King's College Hospital Nhs Foundation Trust**  
London  
United Kingdom  
SE5 9RS

**Study participating centre**

**Leeds Teaching Hospitals NHS Trust**

Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**

**Liverpool Women's NHS Foundation Trust**

Liverpool  
United Kingdom  
L8 7SS

**Study participating centre**

**London North West University Healthcare NHS Trust**

Harrow  
United Kingdom  
HA1 3UJ

**Study participating centre**

**The Newcastle Upon Tyne Hospitals Nhs Foundation Trust**

Newcastle-upon-Tyne  
United Kingdom  
NE7 7DN

**Study participating centre**

**NHS Grampian**

Aberdeen  
United Kingdom  
AB15 6RE

**Study participating centre**

**NHS Greater Glasgow and Clyde**

Glasgow  
United Kingdom  
G12 0XH

**Study participating centre**

**NHS Lothian**  
Edinburgh  
United Kingdom  
EH1 3EG

**Study participating centre**  
**Nottingham University Hospitals Nhs Trust**  
Nottingham  
United Kingdom  
NG7 2UH

**Study participating centre**  
**Oxford University Hospitals Nhs Foundation Trust**  
Oxford  
United Kingdom  
OX3 9DU

**Study participating centre**  
**Salisbury Nhs Foundation Trust**  
Salisbury  
United Kingdom  
SP2 8BJ

**Study participating centre**  
**South Tees Hospitals Nhs Foundation Trust**  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**  
**Southend University Hospital Nhs Foundation Trust**  
Southend-on-Sea  
United Kingdom  
SS0 0RY

**Study participating centre**

**University College London Hospitals Nhs Foundation Trust**  
London  
United Kingdom  
NW1 2PG

**Study participating centre**  
**University Hospitals Birmingham Nhs Foundation Trust**  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**  
**University Hospital Southampton Nhs Foundation Trust**  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**  
**University Hospitals Coventry And Warwickshire Nhs Trust**  
Coventry  
United Kingdom  
CV2 2DX

**Study participating centre**  
**University Hospitals Of Leicester Nhs Trust**  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**University Hospitals Of North Midlands Nhs Trust**  
Stoke-on-Trent  
United Kingdom  
ST4 6QG

**Study participating centre**

**Wirral University Teaching Hospital Nhs Foundation Trust**

Wirral  
United Kingdom  
CH49 5PE

**Study participating centre**

**Worcestershire Acute Hospitals Nhs Trust**

Worcester  
United Kingdom  
WR5 1DD

**Study participating centre**

**Wrightington, Wigan And Leigh Nhs Foundation Trust**

Wigan  
United Kingdom  
WN1 2NN

**Study participating centre**

**Buckinghamshire Healthcare Nhs Trust**

Amersham  
United Kingdom  
HP7 0JD

**Study participating centre**

**South Tyneside Nhs Foundation Trust**

South Shields  
United Kingdom  
NE34 0PL

**Study participating centre**

**Princess of Wales Hospital**

Coity Road  
Bridgend  
Bridgend County Borough  
United Kingdom  
CF31 1RQ

**Study participating centre**

**Royal Gwent Hospital**

Cardiff Road  
Newport  
United Kingdom  
NP20 2UB

**Study participating centre****Forth Valley Royal Hospital**

Stirling Road  
Larbert  
United Kingdom  
FK5 4WR

**Study participating centre****Bolton Royal Hospital**

Minerva Road  
Farnworth  
Bolton  
United Kingdom  
BL4 0JR

**Study participating centre****West Wales General Hospital**

Dolgwili Road  
Carmarthen  
United Kingdom  
SA31 2AF

**Sponsor information****Organisation**

University of Birmingham

**ROR**

<https://ror.org/03angcq70>

**Funder(s)****Funder type**

Government

### Funder Name

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/116/01

### Funder Name

National Institute for Health Research (NIHR) (UK)

### Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

### Funding Body Type

Government organisation

### Funding Body Subtype

National government

### Location

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

### IPD sharing plan summary

Data sharing statement to be made available at a later date

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Protocol file</a>	version 7.0	28/11/2023	20/02/2024	No	No
<a href="#">Protocol file</a>	version 8.0	14/02/2025	13/06/2025	No	No
<a href="#">Statistical Analysis Plan</a>	version 1.0	12/12/2023	16/02/2024	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes