## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | MAGDALENA: Study protocol of a randomised, placebo-controlled trial on cognitive development at two years of age in children exposed to SSRI in utero. |
| **AUTHORS** | Heinonen, Essi; Szymanska - von Schultz, Barbara; Kaldo, V; Nasiell, Josefine; Andersson, Ewa; Bergmark, Mikaela; Blomdahl-Wetterholm, Margareta; Forsberg, Lisa; Forsell, Erik; Forsgren, Anna; Fröojd, Sandra; Goldman, Amy; Nordenadler, Eva-Marie; Sklivanioti, Myrto; Blennow, Mats; Wide, Katarina; Gustafsson, Lars |

## VERSION 1 – REVIEW

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| **REVIEWER** | Steven Miller & Emma Duerden<br>The Hospital for Sick Children, Canada |
| **REVIEW RETURNED** | 25-Apr-2018 |

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| **GENERAL COMMENTS** | In "MAGDALENA: Study protocol of a randomised, placebo-controlled trial on cognitive development at two years of age in children exposed to SSRI in utero." Heinonen and colleagues describe their proposed clinical trial examining the association of antenatal exposure to sertraline with long-term outcome of young children. This trial addresses an important issue in the care of mothers and children.<br><br>This study will be a valuable contribution to research in maternal mental health and functional outcomes in children antenatally exposed to selective serotonin reuptake inhibitors (SSRIs).<br><br>Additional discussion of the following issues in the manuscript is recommended:<br><br>1. Sample size calculation: The hypothesis reads that the sample is based on an equivalence study yet the sample size calculation is based on a superiority trial. This issue can be clarified or discussed.<br><br>2. Why is sertraline the antidepressant of choice for this trial?<br><br>3. Do the authors see any risks of assigning mothers to the placebo group with a non-standard treatment of depression (i.e. internet based cognitive behavioural therapy)?<br><br>4. How are babies born preterm handled in the trial and analysis?<br><br>5. The authors note that 2.4% of Swedish pregnant women are treated with SSRIs in the Introduction – however in the diagram in Figure 2 would indicate that 5% of women are treated with SSRIs. The Introduction and figure should be consistent – please provide clarification or references. |

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| | 6. Is longer term follow up planned to address aspects of neurodevelopmental outcome that may not be fully apparent by age 2 years (i.e. autism spectrum disorder)? |

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| **REVIEWER** | Lars Henning Pedersen<br>Aarhus University & Aarhus University Hospital, Denmark |
| **REVIEW RETURNED** | 29-Apr-2018 |

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| **GENERAL COMMENTS** | The protocol describes an RCT that aims to investigate the adverse effect on the offspring of antidepressant treatment initiated during pregnancy. Better studies on pharmacological treatment in pregnancy are much needed. In this specific case, both maternal depression and antidepressants may adversely affect the development of the fetal and neonatal brain. Observational studies have struggle to adjust for severe confounding and bias. An RCT will potentially bring the field an important step forward.<br>The protocol is in accordance with recognised standard.. In particular, given the subject matter, the specific and abundant ethical considerations have been taken into account. The study seems sufficiently powered for the primary outcome and will further be able to answer a number of important questions. |

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer(s) Reports:**
**Reviewer: 1**
**Reviewer Name: Steven Miller & Emma Duerden**

**Institution and Country: The Hospital for Sick Children, Canada**

Please state any competing interests or state ‘None declared’: None Declared

Please leave your comments for the authors below
In "MAGDALENA: Study protocol of a randomised, placebo-controlled trial on cognitive development at two years of age in children exposed to SSRI in utero." Heinonen and colleagues describe their proposed clinical trial examining the association of antenatal exposure to sertraline with long-term outcome of young children. This trial addresses an important issue in the care of mothers and children.

This study will be a valuable contribution to research in maternal mental health and functional outcomes in children antenatally exposed to selective serotonin reuptake inhibitors (SSRIs).

Additional discussion of the following issues in the manuscript is recommended:

1. Sample size calculation: The hypothesis reads that the sample is based on an equivalence study yet the sample size calculation is based on a superiority trial. This issue can be clarified or discussed.

2. Why is sertraline the antidepressant of choice for this trial?

3. Do the authors see any risks of assigning mothers to the placebo group with a non-standard treatment of depression (i.e. internet based cognitive behavioural therapy)?

4. How are babies born preterm handled in the trial and analysis?

5. The authors note that 2.4% of Swedish pregnant women are treated with SSRIs in the Introduction – however in the diagram in Figure 2 would indicate that 5% of women are treated with SSRIs. The Introduction and figure should be consistent – please provide clarification or references.

6. Is longer term follow up planned to address aspects of neurodevelopmental outcome that may not be fully apparent by age 2 years (i.e. autism spectrum disorder)?

**Reviewer: 2**
**Reviewer Name: Lars Henning Pedersen**

**Institution and Country: Aarhus University & Aarhus University Hospital, Denmark**

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The protocol describes an RCT that aims to investigate the adverse effect on the offspring of antidepressant treatment initiated during pregnancy. Better studies on pharmacological treatment in pregnancy are much needed. In this specific case, both maternal depression and antidepressants may adversely affect the development of the fetal and neonatal brain. Observational studies have struggle to adjust for severe confounding and bias. An RCT will potentially bring the field an important step forward.
The protocol is in accordance with recognised standard.. In particular, given the subject matter, the specific and abundant ethical considerations have been taken into account. The study seems sufficiently powered for the primary outcome and will further be able to answer a number of important questions.

**FORMATTING AMENDMENTS (if any)**
Required amendments will be listed here; please include these changes in your revised version:
- Kindly re-upload each figure with at least 300 dpi resolution in either TIFF or JPG format.

- Patient and Public Involvement:
Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.

This should provide a brief response to the following questions:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?
How did you involve patients in the design of this study?
Were patients involved in the recruitment to and conduct of the study?
How will the results be disseminated to study participants?
For randomised controlled trials, was the burden of the intervention assessed by patients themselves?
Patient advisers should also be thanked in the contributorship statement/acknowledgements.
If patients and or public were not involved please state this.