## **APPENDIX S1** World Health Organization trial registration data set

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| Primary Registry and Trial Identifying Number | Dutch trial register (NL8950) |
| Date of Registration in Primary Registry | 2 October 2020 |
| Secondary Identifying Numbers | n/a |
| Source(s) of Monetary or Material Support | Amsterdam Reproduction and Development (AR&D) |
| Primary Sponsor | Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands |
| Secondary Sponsor(s) | n/a |
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| Public Title | APRIL 4-year follow-up |
| Scientific Title | Long-term outcomes following antenatal exposure to low-dose aspirin: Study protocol for the 4-year follow-up of the APRIL randomised controlled trial. |
| Countries of Recruitment | Netherlands |
| Health Condition(s) or Problem(s) Studied | Low-dose aspirin (75-150 mg) is prescribed to a large and increasing proportion of pregnant women for the prevention of obstetric complications such as preeclampsia. This raises a question on the long-term effect of antenatal exposure to aspirin on child health and development. Evidence on this topic is scarce and has several limitations. |
| Intervention(s) | Original trial: low-dose aspirin 80 mg versus placebo, 1:1 ratio, parallel assignment, double-blind. |
| Key Inclusion and Exclusion Criteria | The study population consists of the singleton children born to women who participated in the APRIL trial during pregnancy (n=387). All infants who were alive at the corrected age of three months (n=379) will be eligible for follow-up assessment at the corrected age of 4 years. Non-Dutch speaking participants will be excluded. |
| Study Type | Follow-up of a randomised controlled trial |
| Date of First Enrollment | September 2020 |
| Sample Size | Since the sample size is determined by the power calculation of the original trial, the maximum number of participants in the follow-up study is fixed: 188 in the aspirin group and 191 in the placebo group. We calculated the minimum number of participants needed to find a significant difference (for a medium effect size with 80% power, $\alpha$=0.05 and $\beta$=0.2) for the two main outcomes in the offspring: (neuro)development and behaviour. Based on a previous study, we expect to find 20.7% mildly abnormal ASQ scores in our study population. To find an OR of 2.5 comparing aspirin to placebo, a sample of 93 children per group would be required, and for an OR of 3.0 a sample of 63 per group. For the SDQ, we expect to find to find a mildly abnormal score in 11.6% of our population. To find an OR of |

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| | 2.5 comparing aspirin to placebo, a sample of 135 children per group would be required and for an OR of 3.0 a sample of 90 per group. |
| Recruitment Status | Recruiting |
| Primary Outcome(s) | (Neuro)development as assessed by the Ages and Stages questionnaire (ASQ) and behaviour in children as assessed by the strengths and difficulties questionnaire (SDQ) at the corrected age of 4 years |
| Key Secondary Outcomes | Child mortality (from perinatal death to child death up to the corrected age of 4 years); the incidence of health-related problems (e.g. medical conditions, the need for a medical specialist and/or developmental care, medication use in the past and present, hospital admissions and need for surgery); child's growth; a composite outcome of mortality up to 4 years of age and abnormal child outcome (abnormal ASQ or abnormal SDQ). |
| Ethics Review | IRB-approval was obtained from the Medical Research Ethics Committee from Amsterdam Medical Center (W20 289#20.325). |
| Completion date | n/a |
| Summary Results | n/a |
| IPD sharing statement | n/a |