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# BMJ Open

**Child outcomes after induction of labour or expectant management in women with preterm prelabour rupture of membranes between 34-37 weeks of gestation: the PPROMEXIL Follow-up trial, a long-term follow-up study of the randomised controlled trials PPROMEXIL and PPROMEXIL-2.**

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3 1 **Child outcomes after induction of labour or expectant**  
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9 3 **membranes between 34-37 weeks of gestation: the**  
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11 4 **PPROMEXIL Follow-up trial, a long-term follow-up study of the**  
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14 5 **randomised controlled trials PPROMEXIL and PPROMEXIL-2.**  
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20  
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3 70 **ABSTRACT**  
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6 71 **Introduction:** Late preterm prelabour rupture of membranes (PROM between 34<sup>+0</sup> and 36<sup>+6</sup>  
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8 72 weeks gestational age) is an important clinical dilemma. Previously, two large Dutch  
9  
10 73 randomised controlled trials (RCTs) compared induction of labour to expectant management.  
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12 74 Both trials showed that early delivery does not reduce the risk of neonatal sepsis as  
13  
14 75 compared to expectant management, although prematurity related risks might increase. An  
15  
16 76 extensive, structured long-term follow-up of these children has never been performed.

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19 77 **Methods and analysis:** The PPROMEXIL Follow-up trial aims to assess long-term  
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21 78 childhood outcomes of the PPROMEXIL (ISRCTN29313500) and PPROMEXIL-2 trial (MEC  
22  
23 79 05-240, ISRCTN05689407), two multicenter RCTs using the same protocol, conducted  
24  
25 80 between 2007-2010 evaluating induction of labour versus expectant management in women  
26  
27 81 with late preterm PROM. The PPROMEXIL Follow-up trial will analyse children of mothers  
28  
29 82 with a singleton pregnancy (induction of labour n=359; expectant management n=353). At  
30  
31 83 10-12 years of (corrected) age all surviving children will be invited for a neurodevelopmental  
32  
33 84 assessment using the Wechsler Intelligence Scale for Children-V, Color-Word Interference  
34  
35 85 Test and the Movement Assessment Battery for Children-2. Parents will be asked to fill out  
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37 86 questionnaires assessing behaviour, motor function, sensory processing, respiratory  
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39 87 problems, general health and need for health care services. Teachers will fill out the Teacher  
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41 88 Report Form and answer questions regarding school attainment. For all tests means with  
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43 89 SD's will be compared, as well as predefined cut-off scores for abnormal outcome. Sensitivity  
44  
45 90 analyses consisting of different imputation techniques will be used to deal with loss-to-follow-  
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47 91 up.  
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52 92 **Ethics and dissemination:** The study has been granted approval by the MEC of the  
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54 93 AmsterdamUMC (MEC2016\_217). Results will be disseminated through peer-reviewed  
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56 94 journals and summaries shared with stakeholders. This protocol is published before analysis  
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58 95 of the results.  
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96 **Registration:** Dutch Trial registration number: NTR6953 (registration December 28<sup>th</sup>, 2017).

97 The study has been peer reviewed, approved and funded by ZonMW (843002826).

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99 **Key words:** Late preterm prelabour rupture of membranes, induction of labour, expectant

100 management, long-term outcome, child development, child health

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3 104 **ARTICLE SUMMARY**  
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5 105 **Strengths and limitations of this study**  
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- 8 106 • This long-term follow-up study will be the first study to evaluate long-term  
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10 107 developmental outcomes (cognitive, motor, and behavioural development, sensory  
11  
12 108 processing, respiratory problems, general health, children's need for health-care  
13  
14 109 services, and school attainment) in the offspring of women who have been treated  
15  
16 110 during pregnancy with induction of labour or expectant management for late preterm  
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18 111 prelabour rupture of membranes.  
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21 112 • Children will be evaluated at 10-12 years of age with internationally validated  
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23 113 measurements and questionnaires, translated for Dutch children, using norm scores  
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25 114 for Dutch children.  
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29 115 • A trained team consisting of a (neuro)psychologist and physician, masked to the  
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31 116 study group, will perform all neurodevelopmental tests.  
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34 117 • The study will be performed within the Dutch Consortium for Healthcare Evaluation  
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36 118 and Research in Obstetrics and Gynecology - NVOG Consortium 2.0, a collaboration  
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38 119 of approximately 70 obstetric hospitals (academic and non-academic hospitals) in the  
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40 120 Netherlands.  
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43 121 • Alongside this long-term follow-up study a separately reported economic evaluation  
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45 122 study will be planned to investigate cost-effectiveness of both treatments taking long-  
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47 123 term developmental outcomes into account.  
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## 125 INTRODUCTION

### 126 Background and rationale

127 Late preterm prelabour rupture of membranes (late preterm PROM) between 34<sup>+0</sup> and 36<sup>+6</sup>  
128 weeks gestation, is an important clinical problem occurring in 1.5% of pregnant women, of  
129 which 25% will deliver within 24 hours.(1) After PROM, the risk of infection increases for both  
130 mother and foetus. Recently, three large randomised controlled trials (RCTs) compared  
131 induction of labour to expectant management for women whose pregnancy was complicated  
132 by late preterm PROM.(2-4) The Dutch PPROMEXIL and PPROMEXIL-2 trial, and the  
133 Australian PPROMT trial showed that induction of labour does not reduce the risk of neonatal  
134 sepsis as compared to expectant management, while increasing prematurity related risks,  
135 such as hypoglycaemia and hyperbilirubinemia. Furthermore, an Individual Participant Data  
136 Meta-analysis (IPD-MA) investigating participant data of all three RCTs also concluded that  
137 expectant management is an acceptable alternative to induction of labour, as both  
138 treatments resulted in comparable rates of a composite of adverse neonatal outcomes.(5)  
139 Moreover, an economic analysis of the PPROMEXIL trial, showed that health care costs for  
140 induction of labour are slightly higher, although not statistically significant, with a mean  
141 difference of €754 (€8,094 for induction of labour versus €7,340 for expectant management,  
142 95% confidence interval (CI) -€335 to €1,802).(6) Therefore, currently most national  
143 guidelines advocate expectant management for late preterm PROM.(1, 7, 8)

144  
145 In 2015 our research team performed a follow-up study of children at two years of age, born  
146 to women who participated in the PPROMEXIL trial.(9) This follow-up study was performed  
147 with limited budget and used internationally validated screening questionnaires. Even though  
148 this study had a follow-up rate of 44% and no extensive neurodevelopmental assessments  
149 were used, an increase in neurodevelopmental impairment was found in the expectant  
150 management group as compared to the induction of labour group (abnormal score (-2  
151 standard deviation (SD)) in  $\geq 1$  domains of the Ages and Stages Questionnaire: 14%

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3 152 induction of labour group versus 26% expectant management group, difference in  
4  
5 153 percentage -11.4; 95% CI -21.9 to -0.98).(9) Hypothetically, a prolonged stay of the foetus in  
6  
7 154 an environment at risk for (subclinical) infections such as maternal placental inflammation  
8  
9 155 (histological or clinical chorioamnionitis) and foetal side placental inflammation (funisitis and  
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11 156 chorionic plate vasculitis) in case of expectant management could affect brain development  
12  
13 157 (i.e. neurological outcome) and therefore explain the neurodevelopmental impairment seen  
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15 158 at 2 years of age.(10) The developmental effects of induction of labour or expectant  
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17 159 management after late preterm PROM in children after 2 years are still unknown.  
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19 160 Furthermore, understanding the long-term effects on women's offspring of either treatment is  
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21 161 important for both clinicians and pregnant women when deciding how to manage late  
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23 162 preterm PROM.  
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28 164 Until now, no other study has performed or planned a comprehensive long-term follow-up of  
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30 165 children born after late preterm PROM. Study feasibility was investigated by an online  
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32 166 questionnaire filled out by parents and members of a Dutch patient organization representing  
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34 167 patients affected by preterm birth due to complications in pregnancy. Results showed that  
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36 168 89% of parents were willing to participate in an extensive follow-up study. Parents rated the  
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38 169 outcomes general health, behaviour, school attainment and respiratory problems as most  
39  
40 170 important outcomes (data not published). Additionally, a focus group meeting with mothers of  
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42 171 prematurely born children with or without preterm PROM was organized, to discuss the  
43  
44 172 different aspects of the child's long-term development. In general, mothers expressed  
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46 173 concerns regarding cognitive development, in particular executive functions, motor  
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48 174 development, social interaction and behaviour and the level of independency the child will  
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50 175 attain later in life (data not published).  
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## 55 177 **Objectives**

56 178 Therefore, the aim of this study is to conduct a structured follow-up of all children born to  
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58 179 women with late preterm PROM who were randomised to induction of labour or expectant  
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3 180 management in the PPROMEXIL and PPROMEXL-2 trial. Long-term cognitive, motor, and  
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5 181 behavioural development, sensory processing, respiratory problems, general health,  
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7 182 children's need for health-care services, and school attainment will be assessed at 10-12  
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9 183 years of age using internationally validated measurements and questionnaires, translated  
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11 184 and using norm scores for Dutch children.  
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## 186 **METHODS AND ANALYSIS**

### 187 **Study setting**

188 We will perform an extensive long-term follow-up study of two previously executed RCTs  
189 (PPROMEXIL Follow-up trial, NTR 6953, METC 2016\_217, NL58494.018.16) investigating  
190 long-term developmental outcomes (cognitive, motor, behavioural development), sensory  
191 processing, respiratory problems, general health, children's need for health-care services,  
192 and school attainment. This will be assessed at 10-12 years of corrected age in children born  
193 to women with a singleton pregnancy complicated by late preterm PROM (between 34+0 and  
194 36+6 weeks gestation), who participated in the RCTs PPROMEXIL, and PPROMEXIL-2 trial.  
195 Details of the PPROMEXIL (ISRCTN29313500) and PPROMEXIL-2 trial (amendment of the  
196 PPROMEXIL trial (MEC 05-240), ISRCTN05689407) have been published elsewhere.(2, 3)  
197 These two large RCTs, using the same study protocol and conducted between 2007 and  
198 2011 in 61 academic and non-academic hospitals in The Netherlands, assessed whether  
199 induction of labour versus expectant management would reduce the incidence of neonatal  
200 sepsis in women with late preterm PROM. In the induction of labour group, patients were  
201 induced within 24 hours after randomization. Patients in the expectant management group  
202 were monitored until the onset of spontaneous delivery or induced after 37+0 weeks  
203 according to national guidelines.(1)

### 204 **Participants and eligibility criteria**

205 All children born to women with a singleton pregnancy who participated in the PPROMEXIL  
206 trials will be invited for this long-term follow-up assessment. Children will be evaluated at 10-  
207 12 years of age. As the total number of multiple pregnancies in the PPROMEXIL- and  
208 PPROMEXIL-2 trials was very low (14/727 (1.9%) and equally distributed among treatment  
209 groups), only singleton pregnancies will be included in the analysis. See Figure 1. for the  
210 overview of PPROMEXIL follow-up participants.

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### 213 **Procedures and recruitment**

214 The study protocol is designed, constructed and reported according to the recommendations  
215 given in the Standard Protocol Items: Recommendations for Interventional Trials (See  
216 Additional file 1. SPIRIT checklist for reporting randomised trials; and Additional file 2.  
217 SPIRIT template for visualizing schedule of enrolment, interventions, and assessments of the  
218 women participating in PPROMEXIL trials and children participating in PPROMEXIL follow-  
219 up.)(11) The study will be performed within the Dutch Consortium for Healthcare Evaluation  
220 and Research in Obstetrics and Gynecology - NVOG Consortium 2.0, a collaboration of  
221 approximately 70 obstetric hospitals (academic and non-academic hospitals) in the  
222 Netherlands (<https://zorgevaluatienederland.nl/nvog>). Research nurses will be asked to  
223 crosscheck medical records for possible occurrence of death of women's offspring before  
224 contacting parents and their child for participating in this follow-up study. All parents will be  
225 contacted by post to announce this follow-up study, and if they give consent to be  
226 approached by the research team, they will be contacted by telephone or email to explain  
227 study details. Parents will be informed that participation is voluntary and that they may  
228 withdraw consent to participate at any time. They will be informed that declining participation  
229 will not affect their or their child's care. Parents will be given sufficient time to read the patient  
230 information and they will be given the opportunity to ask questions by telephone or email  
231 prior to signing the informed consent form. Written study information at children's reading  
232 level will be available for all children (specified for children <12 years of age and ≥12 years of  
233 age. An independent physician (i.e. not a member of the research team) will be available to  
234 answer any questions patients may have. Written informed consent will be obtained from  
235 both parents prior to the examination. Children ≥12 years of age have to sign their own  
236 informed consent, in addition to the informed consent of their parents, at the day of the  
237 assessment. A copy of the informed consent form(s) will be given to the parents/child. All  
238 study documents will be available through the study website.

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3 239 Concealment of treatment allocation at time of the PPROMEXIL and PPROMEXIL-2 trials  
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5 240 (i.e. induction of labour or expectant management) was not possible due to the type of  
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7 241 intervention, and therefore parents and children entered in this follow-up study will be aware  
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9 242 of treatment allocation. The research team performing the follow-up examinations and all  
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11 243 members of the research team performing data entry and data analyses will be masked to  
12  
13 244 treatment allocation.  
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15 245 All data will be collected, captured, and coded in accordance with existing policies to ensure  
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17 246 patient confidentiality. Data will be recorded using an electronic case record form and will be  
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19 247 stored in a web-secured database (available through the study website).(12) The  
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21 248 investigators will publish the results of this trial in a peer reviewed medical journal as soon as  
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23 249 appropriate. The Clinical Research Unit (CRU) of the Amsterdam UMC will monitor data  
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25 250 collection.  
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### 252 **Follow-up assessment and outcomes**

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33 253 During a single visit in an outpatient clinic of a local hospital close to the family's  
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35 254 neighbourhood, children will be assessed on long-term neurodevelopmental outcomes using  
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37 255 standardized and validated neurodevelopmental tests and questionnaires. A trained team  
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39 256 consisting of a (neuro)psychologist and physician, masked to the study group, will perform all  
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41 257 neurodevelopmental tests. Neurodevelopmental assessment of children has a structured  
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43 258 approach, is enjoyable for most children and is not invasive. During neurodevelopmental  
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45 259 assessment of the child, parents will be asked to fill out questionnaires on sensory  
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47 260 processing, behaviour, respiratory problems, and child's health. If necessary, parents will be  
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49 261 assisted with filling out questionnaires. All, but one, questionnaires are digital and can be  
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51 262 filled out on a tablet during the assessment or at any other time at home.  
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56 264 After completing all examinations, parents receive a short report on their child's test results.

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58 265 This short report will give information on total test scores and tell parents whether their child's  
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3 266 scores are above, on or below average. If test scores indicate that children would benefit  
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5 267 from supportive (health, developmental or educational) care, parents are advised to contact  
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7 268 their general practitioner for referral to a paediatrician or psychologist.  
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11 270 We consider our main outcomes to be: cognitive development (assessed by the WISC-V),  
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13 271 motor skills (assessed by the M-ABC-2) and behaviour (assessed by the CBCL).  
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### 16 272 *Assessment of cognitive development*

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18 273 Cognitive Development will be assessment using the Dutch version of the Wechsler  
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20 274 Intelligence Scale for Children (WISC-V).(13) The WISC-V is used worldwide to assess  
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22 275 cognition in children aged six to 16 years and consists of 10 subtests that are combined into  
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24 276 a Full Scale IQ score (FSIQ) and five primary indexes: verbal comprehension, visual spatial,  
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26 277 fluid reasoning, working memory and processing speed. Besides these primary indexes, an  
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28 278 additional mathematics subtest will be obtained to provide an objective measurement of this  
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30 279 area of academic attainment. The WISC-V total intelligence quotient (IQ) score and primary  
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32 280 indexes have a mean score of 100 points with a SD of 15 points. An index score  $\leq 70$  ( $\geq -2$   
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34 281 SD below the mean score) will be considered as a severe cognitive delay and will be  
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36 282 compared between groups. An index score  $> 70$  and  $\leq 84$  ( $\geq -1$  SD and  $< -2$ SD below the  
37  
38 283 mean score) will indicate a mild cognitive delay. Normal cognitive outcome is defined as no  
39  
40 284 severe or mild neurodevelopmental delay. A difference between the two treatment groups of  
41  
42 285 7.5 points (0.5 SD) could indicate a potential clinical relevant difference.  
43  
44

45  
46 286 Child's executive functioning will be tested using subtests of the WISC-V and the Color-Word  
47  
48 287 Interference Test (CWIT). The CWIT measures cognitive set shifting and the ability to inhibit  
49  
50 288 a dominant and automatic verbal response by separate and combined Color Naming and  
51  
52 289 Color Reading items. The CWIT subtests have a mean of 10 points with a SD of 2 points. An  
53  
54 290 CWIT index score of  $\leq 4$  (i.e. more than -2 SD below the mean score) is considered a severe  
55  
56 291 delay in executive functioning and will be analysed.  
57  
58  
59  
60

### 292 *Assessment of motor skills*

293 Child's motor function will be measured by the Movement Assessment Battery for Children-2  
294 (M-ABC-2).(14) The M-ABC-2 is the most commonly used tool used to examine fine and  
295 gross motor skills. The M-ABC-2 provides data about a child's performance of age-  
296 appropriate tasks within three domains; manual dexterity, aiming and catching, and balance.  
297 M-ABC-2 scores will be calculated as standard scores and percentiles for each domain, and  
298 as a total test score. The mean standard score for all domains and the total score is 10  
299 points, with a SD of 3 points. The age band two (7-10 years of age) and three (11-16 years of  
300 age) of the M-ABC-2 will be used, as appropriate according to the child's age. A standard  
301 score of  $\leq 5$  points, representing  $\leq 5^{\text{th}}$  percentile will be defined as a significant movement  
302 difficulty and a severe delay in motor skills and will be compared between treatment groups.  
303 A standard score of 6 or 7 points, representing  $>5^{\text{th}}$  to  $\leq 16^{\text{th}}$  percentile will indicate that the  
304 child is at risk of having a movement difficulty and therefore will be classified as mild delay in  
305 motor skills. A standard score of  $\geq 8$  points, representing  $>16^{\text{th}}$  percentile will be defined as no  
306 movement difficulty and normal development of motor skills.

307 Furthermore, parents will fill out the Movement-ABC-2 checklist, a questionnaire that consists  
308 of three sections on movement in static and/or predictable environment, movement in a  
309 dynamic and/or unpredictable environment and non-motor factors that may affect the child's  
310 movement. The sections on static and dynamic movements are summed up to a total score,  
311 with a higher score indicating a worse motor function. A total score of  $\geq 95^{\text{th}}$  percentile ( $\geq 9$   
312 points) indicates severe motor impairment and will be compared between both treatment  
313 groups.

### 314 *Assessment of behavioural development*

315 Child's behaviour will be measured by the Child Behaviour Checklist (CBCL), a parental  
316 questionnaire used to screen for behaviour problems in children.(15) It informs on eight  
317 narrow syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints,  
318 social problems, thought problems, attention problems, rule-breaking behaviour, and

1  
2  
3 319 aggressive behavior) and three broadband scales (internalizing, externalizing behavioural  
4  
5 320 problems and a total problems score) which are composed out of the narrow-band syndrome  
6  
7 321 scales. The CBCL broadband scales T scores have a mean of 50 points with a SD of 10  
8  
9 322 points. A score >90<sup>th</sup> percentile (>63 points) on one of the two broad dimensions scales  
10  
11 323 (internalizing problems or externalizing problems), or the total problem score (sum of all  
12  
13 324 scores) of the CBCL will be defined as abnormal and clinically relevant for indicating  
14  
15 325 behavioural problems. Scores ≥84<sup>st</sup> and ≤90<sup>th</sup> percentile (≥60 and ≤63 points) are considered  
16  
17 326 borderline and scores <84<sup>th</sup> percentile (<60 points) are defined as normal.

### 20 21 327 *Assessment of school attainment*

22  
23 328 Child's academic attainment and behaviour will be assessed using the Teacher's Report  
24  
25 329 Form (TRF).(16) The TRF assesses problem behaviour in the last two months and identifies  
26  
27 330 the same eight syndromes as the CBCL, and also inquires on academic attainment  
28  
29 331 (Academic Performance). With parental permission, the TRF will be filled out by the child's  
30  
31 332 school teacher (the teacher who has known the child in the school setting for more than two  
32  
33 333 months can complete the TRF). Accompanying the TRF, teachers will be asked some  
34  
35 334 additional questions regarding the child's need for additional educational support in- or  
36  
37 335 outside the classroom. For the TRF the cut-off percentiles of the broad band and total scores  
38  
39 336 as used in the CBCL will be applied. For Academic Performance a cut-off score of <10<sup>th</sup>  
40  
41 337 percentile (≤36 points) will be defined as abnormal. Scores between 10<sup>th</sup> and 16<sup>th</sup> percentile  
42  
43 338 are classified as borderline and ≥17<sup>th</sup> percentile are considered normal outcome.

### 46 47 339 *Assessment of sensory processing*

48  
49 340 Sensory processing will be determined using the Short Sensory Profile questionnaire (SSP-  
50  
51 341 NL).(17) The Short Sensory Profile contains sections corresponding to each sensory system,  
52  
53 342 sections that indicate the modulation of sensory input across sensory systems, and sections  
54  
55 343 that indicate behavioural and emotional responses that are associated with sensory  
56  
57 344 processing. This questionnaire consists of 38 items, classified into seven subscales (Tactile  
58  
59 345 Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Underresponsive/Seeks

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2  
3 346 Sensation, Auditory Filtering, Low Energy/Weak, and Visual/Auditory Sensitivity). For every  
4  
5 347 subscale parents will be asked how frequently their children respond in the way described by  
6  
7 348 each item using a 5 point Likert scale (nearly never, seldom, occasionally, frequently, almost  
8  
9 349 always). Lower scores on the total score and subscales indicate more sensory symptoms.  
10  
11 350 Subscales and the total scores will be used to classify as “definite difference” (cut off scores  
12  
13 351  $\geq -2$  SD below the mean) and will be compared between groups. “Typical performance” will  
14  
15 352 be defined as  $< -1$  SD below the mean, “probable difference” will be defined as  $\geq -1$  SD and  
16  
17 353  $< -2$  SD below the mean.

#### 20 354 *Assessment of respiratory problems*

21  
22  
23 355 Respiratory problems, such as asthma or other lung problems will be assessed using the  
24  
25 356 International Study of Asthma and Allergies in Childhood questionnaire (ISAAC  
26  
27 357 questionnaire) which informs on asthma, rhinitis and eczema.(18) The diagnosis of asthma  
28  
29 358 will be defined as a positive answers to the question: “In the last 12 (twelve) months, has  
30  
31 359 your child had wheezing?”, as this question has a sensitivity of 100%, specificity of 78%,  
32  
33 360 positive predictive value of 73%, and negative predictive value of 100% for the diagnosis of  
34  
35 361 asthma.(19)

#### 37 362 *Assessment of anthropometry and pubertal status*

38  
39  
40 363 Children will be asked to fill out the Puberty Developmental Scale (PDS), a self-report  
41  
42 364 measure of pubertal status.(20) Children will be asked questions regarding on e.g. growth in  
43  
44 365 height, skin changes, body or facial hair, deepening of the voice (for boys), and starting to  
45  
46 366 menstruate or developing breasts (for girls). Physical examination will be restricted to  
47  
48 367 measurement of height/weight and blood pressure. Results of physical examination  
49  
50 368 (height/weight, body mass index) will be used for baseline characteristics. Puberty status will  
51  
52 369 be used for baseline characteristics and subgroup analysis.

#### 53 370 *Assessment of child's health and need for health care services*

54  
55  
56 371 A general questionnaire consisting of 61 items, will be used to assess demographic  
57  
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3 372 characteristics and will ask questions regarding the present (last 12 months) and the past  
4  
5 373 health and health care use (from discharge after delivery until date of assessment) (also  
6  
7 374 used in previous follow-up studies such as ProTWINkids study at three and four years,  
8  
9 375 TripleP study(21-23)). Questions address child's health, need for health care services,  
10  
11 376 hospital visits, hospital admission, need for surgery, use of medication, psychological  
12  
13 377 problems, need for developmental therapies (such as physical therapists, remedial teaching,  
14  
15 378 speech therapist, occupational therapist). Health care use and (health) related problems will  
16  
17 379 be clustered into different clinically relevant groups (e.g. need for medical specialist and/or  
18  
19 380 developmental care, medication use in the past and present, hospital admissions and  
20  
21 381 surgery to give insight in the range of health related problems).  
22  
23  
24 382 Parents will be asked to give permission to gather medical information on the child's health  
25  
26 383 via the general practitioner and the preventive youth healthcare services if needed.  
27  
28

#### 29 384 *Economic analysis*

30  
31 385 Alongside this long-term follow-up study, an economic evaluation study will be planned to  
32  
33 386 investigate cost-effectiveness of both treatments taking long-term developmental outcomes  
34  
35 387 into account. Results of this economic evaluation will be reported separately from trial  
36  
37 388 results.  
38  
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40 389  
41  
42 390 At present, no additional long-term follow-up in later life (>12 years of age) is planned.  
43  
44 391 Permission to approach parents and children for additional follow-up research in later life will  
45  
46 392 be obtained with informed consent form during the current follow-up study. If additional long-  
47  
48 393 term follow-up of children at an adolescence age will be planned in the future, additional  
49  
50 394 approval of the Medical Research Ethics Committee will be sought.  
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53 395

#### 54 396 **Sample size**

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56  
57 397 Since this is a follow up study, the maximum number of study participants is already defined  
58  
59 398 by the two PPROMEXIL trials, excluding multiple pregnancies and deceased children (Figure  
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3 399 1 and Additional file 2.). Consequently, 712 children are eligible for inclusion, 359 born in the  
4  
5 400 induction of labour group and 353 born in the expectant management group. As we will not  
6  
7 401 be able to adjust the number of recruited children, a power calculation will not be of any use  
8  
9 402 to calculate a study sample size. However, this calculation can indicate the minimum  
10  
11 403 number of children that need to be tested in order to find a clinically significant difference for  
12  
13 404 the three most important outcomes in this study: cognitive development, motor skills and  
14  
15 405 behavioural development. All sample size calculations are with a power of 90%, a two-sided  
16  
17 406  $\alpha$  of 0.05 and  $\beta$  of 0.20. To be able to detect a clinically relevant difference in mean scores of  
18  
19 407 0.5 SD in all tests, 86 children per group will be sufficient (total 172 children). This 0.5 SD  
20  
21 408 equals a difference of 7.5 IQ points in the mean score of the WISC-V test (cognitive  
22  
23 409 development), a difference of 1.5 points on the mean total standard scores of the M-ABC-2  
24  
25 410 (motor skills) and a difference of 5 points on the mean T scores in any of the broadband  
26  
27 411 problem scales of the CBCL (behavioral development) between both groups. Thus, since  
28  
29 412 172 children comprise 24% of our total, also in case of limited follow up, differences of 0.5  
30  
31 413 SD can be picked up. Based on previous experience in our research team with follow-up  
32  
33 414 trials and based of existing literature, we expect to have a follow-up rate of 30 to 40% of the  
34  
35 415 children.(25)  
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## 417 **Statistical methods**

418 Differences in background characteristics and the maternal, pregnancy, delivery and  
419 neonatal outcomes between the induction of labour group and expectant management group  
420 will be compared using unpaired T-test, Mann-Whitney U test, Chi-square test or Fisher's  
421 exact test when appropriate. The same characteristics will be compared in children assessed  
422 at follow-up and for the original participants of the PPROMEXIL trials. This will allow us to  
423 assess whether selection or attrition bias may be present in our study (e.g. due to drop-out of  
424 healthy or unhealthy children). To compare the long-term developmental outcomes between  
425 both treatment groups mean differences and the corresponding 95% CI will be calculated.  
426 For dichotomous outcomes relative risk (RR) with corresponding 95% CI will be calculated.

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2  
3 427 Our main analyses shall be based upon the results from the children assessed in follow-up  
4  
5 428 (complete case analysis).(24)  
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7 429  
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9 430 The relatively simple statistical analysis described above can be justified by the fact that our  
10  
11 431 study is a follow-up of two RCTs and consequently no confounding measures are expectant  
12  
13 432 (See Additional file 4. Direct Acyclic Graph (DAG)). The DAG confirms that there are no  
14  
15 433 variables susceptible to have influenced the likelihood of receiving the intervention and  
16  
17 434 subsequently have influenced long-term outcome of the child. On the other hand, selection  
18  
19 435 bias may occur as a consequence of incomplete follow-up. We will evaluate the effect of  
20  
21 436 differences in background characteristics (such as maternal smoking, social-economic  
22  
23 437 status) and if applicable, report unadjusted and adjusted odds ratios for dichotomous  
24  
25 438 outcomes using logistic models and adjusted mean differences and the corresponding 95%  
26  
27 439 CI for continuous outcomes using general linear models.  
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31 440

#### 32 441 *Sensitivity analyses*

33  
34 442 Our pre-planned sensitivity analyses will only be performed for the WISC-V, the Movement-  
35  
36 443 ABC and the CBCL total scores to minimize the effect of multiple testing.

37  
38 444 Imputation missing data: A sensitivity analysis using imputation techniques will be performed  
39  
40 445 to impute missing data for children that are lost to follow-up. Imputation techniques will only  
41  
42 446 be applied when it can be assumed that data is (mostly) missing at random and the follow-up  
43  
44 447 rate is follow-up rate  $\geq 70\%$  (the group agreed on an arbitrary). If the loss to follow-up rate is  
45  
46 448 higher a best- and worst-case scenario will be performed. In these two scenarios the missing  
47  
48 449 cases are imputed either all as 'normal' (best case) or as 'abnormal' (worst case) outcomes.  
49  
50 450 These scenarios will provide some insight on the robustness of the complete case follow-up  
51  
52 451 results.  
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54  
55 452 Age and puberty adjusted scores: Despite the fact that most children are born late  
56  
57 453 premature/near term or full term, a sensitivity analyses will be performed using age-adjusted  
58  
59 454 scores (corrected for prematurity). Finally, a sensitivity analysis using results of the PDS  
60

1  
2  
3 455 indicating child's puberty status will be performed.  
4  
5 456

7 457 *Subgroup analyses exploring the potential impact of effect modification*

9 458 Dealing with the effect of 'down-stream' factors: During time to follow-up (due to loss to  
11 459 follow-up) a substantial difference in the prevalence 'down-stream' factors could potentially  
13 460 appear ('down-stream' factors are defined as potential effect modifiers appearing after  
15 461 randomization, such as sepsis at birth, positive GBS). In sensitivity analysis the potential  
17 462 interaction of the following 'down-stream' factors will be explored: gestational age at PROM,  
19 463 receiving antibiotics, receiving steroids for fetal maturation, receiving tocolysis, group B  
21 464 streptococci (GBS) positivity, a positive vaginal culture (including GBS and other pathogens  
23 465 not consistent with normal flora), neonatal sepsis, and for women who participated in the  
25 466 former follow-up study of children at 2 years of age.<sup>(9)</sup> The analysis will be stratified by these  
27 467 different factors and the potential differences in long term outcomes between the different  
29 468 strata will be explored.  
31  
32 469

34 470 A P-value of <0.05 was considered to indicate statistical significance. All analyses will be  
36 471 performed according to the intention-to-treat principle using IBM SPSS (NY, USA) or in  
38 472 RStudio (Boston, MA).  
40  
41 473

43 474 A statistical analysis plan (SAP), reporting a more detailed description of the statistical  
45 475 methods and analyses, will be published separately from the PPROMEXIL follow-up  
47 476 protocol.  
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49 477

51 478 **Patient and public involvement**

53 479 The Dutch association for parents of incubator children and the Dutch Collaboration of  
55 480 parent- and patient organisations endorsed the study and provided input on the study  
57 481 proposal. Parents from the Dutch association for parents of incubator children participated in  
59 482 an online survey. Additionally, mothers of prematurely born children participated in a focus



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3 483 group meeting organized by our research team, to discuss the different aspects of child's  
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5 484 long-term development to incorporate in long-term follow-up research.  
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8 485 **DISCUSSION**  
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10 486 Long-term follow-up of all children born to mothers participating in obstetric intervention trials  
11  
12 487 is of crucial importance.(25) The outcome late neurodevelopmental morbidity has been  
13  
14 488 identified and selected by parents as one of 13 core outcomes for studies evaluating  
15  
16 489 preventive interventions for preterm birth.(26) Furthermore, previous studies have stressed  
17  
18 490 the importance of long-term follow-up by demonstrating that interventions performed during  
19  
20 491 pregnancy can have unexpected long-term effects on children which may not be apparent at  
21  
22 492 birth or during neonatal assessment.(27) By assessing cognition, motor function, behaviour,  
23  
24 493 respiratory problems, general health and school attainment in an extensive and structured  
25  
26 494 follow-up, this study will have the unique opportunity to help understanding the long-term  
27  
28 495 effects of our current treatment regimen for late preterm PROM on women's offspring.  
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3 499 **ETHICS AND DISSEMINATION**

4  
5 500 **Ethics approval and consent to participate**

6  
7 501 The PPROMEXIL Follow-up trial aims to assess long-term childhood outcomes of the  
8  
9 502 PPROMEXIL trial (ISRCTN29313500) and PPROMEXIL-2 trial (MEC 05-240,  
10  
11 503 ISRCTN05689407), two multicentre RCTs using the same study protocol. The Medical Ethics  
12  
13 504 Committee of the Academic Medical Centre Amsterdam (MEC) has approved the  
14  
15 505 PPROMEXIL Follow-up trial (MEC2016\_217, NL58494.018.16). Table 1 describes the  
16  
17 506 chronology of submission and amendments to the MEC.  
18  
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20  
21 507 **Table 1.**

22 508 **Chronology submission and revisions PPROMEXIL follow-up study**

Version no.	Date (DD-MM-YYYY)	Main reasons for change
1	29-09-2016	N/A, first submission to MEC
2	20-12-2017	MEC2016_217#C20161752 Modifications requested by MEC d.d. 05-09-2016
3	04-01-2018	Modifications requested by MEC d.d. 04-01-2018 Additional information on informed consent about saving data (mother and child) up to 15 years after trial
3	10-01-2018	Approval MEC d.d. 10-01-2018
4	31-05-2018	Amendment 1: <ul style="list-style-type: none"><li>- Administrative modifications</li><li>- Change of acronym to PPROMEXIL follow-up</li><li>- Addition of two questionnaires (ISAAC and Puberty developmental scale)</li></ul>
4	04-07-2018	Approval amendment version 4 d.d. 04-07-2018
5	10-08-2018	Amendment 2: <ul style="list-style-type: none"><li>- Modification in protocol on how to recruit participants</li></ul>

		(via research nurses and PhD student) - Modification in Patient Information Files on recruitment
5	23-08-2018	Approval amendment version 5 d.d. 23-08-2018
6	06-11-2018	Amendment 3:  - Clarification on informed consent procedure, parents and participants will be counseled through the telephone and sign informed consent at home  - Minor modifications in the general health questionnaire
6	23-11-2018	Approval amendment version 6 d.d. 23-11-2018
7	03-04-2019	Amendment 4:  - Addition of patient information files for children age 12-15
7	12-04-2019	Approval amendment version 7 d.d. 12-04-2019

509

510 See <https://www.zorgevaluatienederland.nl/evaluations/ppromexil-follow-up> for the full study  
511 protocol and electronic case record form. Written informed consent will be obtained from both  
512 parents prior to the examination. Children  $\geq 12$  years of age have to sign their own informed  
513 consent, in addition to the informed consent of their parents, at the day of the assessment. A  
514 copy of the informed consent form(s) will be given to the parents/child.

515

### 516 **Dissemination**

517 No arrangements have been made concerning public disclosure. The trial is registered in the  
518 Dutch Trial register (Trial registration number: NTR6953. Date of registration December 28th  
519 2017). An overview of the WHO trial registration data set is described in Table 2.

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524 **Table 2.**  
525 **WHO trial registration data set**

Primary Registry and Trial Identifying Number	Trial NL6623 (NTR6953)
Date of Registration in Primary Registry	December 28 <sup>th</sup> , 2017
Secondary Identifying Numbers	n/a
Source(s) of Monetary or Material Support	ZonMW Dutch Healthcare efficacy program
Primary Sponsor	Academical Medical Center (AMC), Amsterdam, The Netherland
Secondary Sponsor(s)	n/a
Contact for Public Queries	Drs. Noor Simons Followup.ppromexil@amsterdamumc.nl
Contact for Scientific Queries	Prof. dr. Eva Pajkrt e.pajkrt@amsterdamumc.nl
Public Title	PPROMEXIL follow-up
Scientific Title	Child outcomes after induction of labour or expectant management in women with preterm prelabour rupture of membranes between 34-37 weeks of gestation: the PPRMEXIL Follow-up trial, a long-term follow-up study of the randomised controlled trials PPRMEXIL and PPRMEXIL-2.
Countries of Recruitment	The Netherlands
Health Condition(s) or Problem(s) Studied	Late preterm prelabour rupture of membranes (PROM between 34 <sup>+0</sup> and 36 <sup>+6</sup> weeks gestational age). Long-term effects of induction of labour versus expected management.
Intervention(s)	n/a
Key Inclusion and Exclusion Criteria	The PPRMEXIL Follow-up trial will analyse children of mothers with a singleton pregnancy (induction of labour n=359; expectant management n=353). At 10-12 years of (corrected) age all surviving children will be invited for follow-up.
Study Type	Follow-up of a randomized controlled trial
Date of First Enrollment	August 3 <sup>rd</sup> , 2018

Sample Size	All sample size calculations are with a power of 90%, a two-sided $\alpha$ of 0.05 and $\beta$ of 0.20. To be able to detect a clinically relevant difference in mean scores of 0.5 SD in all tests, 86 children per group will be sufficient (total 172 children). This 0.5 SD equals a difference of 7.5 IQ points in the mean score of the WISC-V test (cognitive development), a difference of 1.5 points on the mean total standard scores of the M-ABC-2 (motor skills) and a difference of 5 points on the mean T scores in any of the broadband problem scales of the CBCL (behavioral development) between both groups. Thus, since 172 children comprise 24% of our total, also in case of limited follow up, differences of 0.5 SD can be picked up.
Recruitment Status	Open for patient inclusion
Primary Outcome(s)	Cognitive development (Wechsler Intelligence Scale for Children, WISC-V) Motor skills (Movement-ABC-2) Behaviour (Child Behavior Checklist, CBCL).
Key Secondary Outcomes	Academic attainment and behavior (Teacher Report Form, TRF) Sensory processing (Short Sensory Profile, SSP) Respiratory problems (International Study of Asthma and Allergies in Childhood questionnaire, ISAAC questionnaire) Pubertal status (Puberty Developmental Scale, PDS) Height, weight, bloodpressure General health and demographics (questionnaires)
Ethics Review	The Medical Ethics Committee of the Academic Medical Centre Amsterdam (METC) has approved the PPROMEXIL Follow-up trial (METC 2016_217, NL58494.018.16).
Completion date	n/a
Summary Results	n/a
IPD sharing statement	n/a

526

527 Trial results will be submitted to a peer-reviewed journal, regardless of the outcome and  
528 made open access available in accordance with the Netherlands Organisation for Health  
529 Research and Innovation (ZonMW) policy. Results will be incorporated in national guidelines  
530 and patient information leaflets. Co-authorship will be based on the international committee

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3 531 of medical journal editor's guidelines. Contributors that not fulfil these criteria will be listed as  
4  
5 532 collaborators. The order of authors will be based on scientific input.  
6

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9 534 **Availability of data and materials**

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11 535 The datasets used and/or analysed during the current study will be available from the  
12  
13 536 corresponding author on reasonable request.  
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22 539 **FOODNOTES**

23  
24  
25 540 **Author's contributions**

26  
27 541 AdR, NS, JvtH, AvWL, CAM, MvW, GJvB, FV, DvdH, ASPvT, BWM, TR, EP are member of  
28  
29 542 the PPRMEXIL Follow-up trial study group and were involved in conception and design of  
30  
31 543 the study. AdR, NS, JvtH drafted the manuscript which follows the SPIRIT checklist for  
32  
33 544 reporting randomised trials. AdR, NS, JvtH, AvWL, CAM, MvW, GJvB, FV, DvdH, ASPvT,  
34  
35 545 TR, BWM, EP discussed and fine-tuned the final design of the study. All authors edited the  
36  
37 546 manuscript and read and approved the final version of the manuscript.  
38  
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40 547

41  
42 548 **Funding statement**

43  
44 549 The study group received funding by ZonMW, the Netherlands Organization for Health  
45  
46 550 Research and Development (governmental funding), grant number: 843002826. ZonMW  
47  
48 551 peer reviewed the primary study protocol, they had no other involvement in study design.  
49  
50 552 ZonMw will not have any involvement in data collection, nor in analysis or writing of the  
51  
52 553 manuscript.  
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57 555 **Competing interest statement**

58  
59 556 Dr. Ben Willem Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548). Dr.  
60

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3 557 Ben Willem Mol reports consultancy for ObsEva, Merck Merck KGaA and Guerbet. All other  
4  
5 558 authors did not report any conflicts of interest.  
6

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8  
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10  
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12  
13 562 Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology - NVOG  
14  
15 563 Consortium 2.0 as well as the Dutch Consortium Trialbureau for their efforts. The authors  
16  
17 564 thank the contributors of PPROMEXIL and PPROMEXIL-2 trial. For a list of contributors to  
18  
19 565 the PPROMEXIL and PPROMEXIL-2 trials see Additional file 3.  
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25 **567 List of abbreviations**

26  
27 568 CBCL; Child Behavior Checklist, CI; confidence interval, CWIT; Color-Word Interference  
28  
29 569 Test, DCD; Developmental Coordination Disorder, FSIQ; Full Scale IQ score, GA; gestational  
30  
31 570 age, GBS; group B streptococci, IPDMA; Individual Participant Data Meta-analysis, IQ;  
32  
33 571 intelligence quotient, ISAAC questionnaire; International Study of Asthma and Allergies in  
34  
35 572 Childhood questionnaire, ISRCTN; International Standard Randomised Controlled Trial  
36  
37 573 Number, M-ABC-2; Movement Assessment Battery for Children-2, M.D.; Doctor of Medicine,  
38  
39 574 MEC; Medical ethics committee; in Dutch: medisch ethische toetsingscommissie (METC),  
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41 575 NTR; Trial registration number, NVOG; the Dutch college of Obstetricians and  
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43 576 Gynecologists, in Dutch: Nederlandse Vereniging voor Gynaecologie en Obstetrie (NVOG),  
44  
45 577 PDS; Puberty Developmental Scale, PROM; prelabour rupture of membranes, PPROMEXIL  
46  
47 578 trial; Preterm Prelabour Rupture Of Membranes EXpectant management vs Induction of  
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49 579 Labour trial, PPROMT; the Preterm Pre-labour Rupture of Membranes close to Term Trial,  
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51 580 RCT; randomised controlled trial, RR; relative risk, SD; standard deviation, SSP-NL; Short  
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53 581 Sensory Profile, TRF; Teacher Report Form, WISC-V-NL; Wechsler Intelligence Scale for  
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3 584 **Figures and Tables**  
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5 585 **Figure 1.** Overview of PPROMEXIL follow-up participants  
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7 586 **Table 1.** Chronology submission and revisions PPROMEXIL follow-up study  
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9 587 **Table 2.** WHO trial registration data set  
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11 588 **Additional file 1.** Overview of PPROMEXIL follow-up participants  
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13 589 **Additional file 2.** Schematic diagram of enrolment PPROMEXIL follow-up participants.  
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15 590 **Additional file 3.** Authors PPROMEXIL randomised controlled trials.  
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17 591 **Additional file 4.** Direct Acyclic Graph (DAG) figure  
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19 592 **Additional file 5.** GRIPP2 short checklist PPROMEXIL follow-up  
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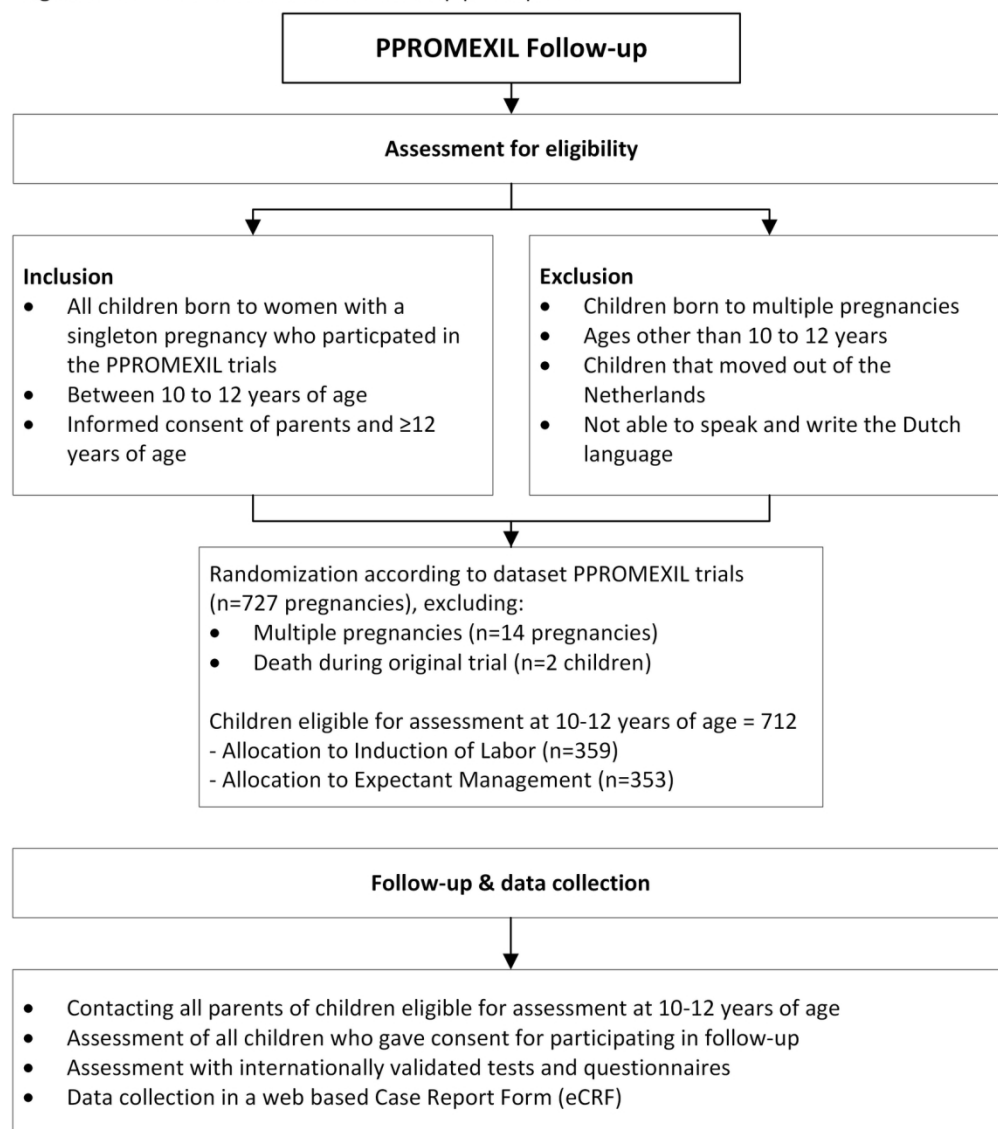
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For peer review only

Figure 1. Overview of PPROMEXIL follow-up participants



Overview of PPROMEXIL follow-up participants

144x170mm (300 x 300 DPI)

**Additional file 1.** SPIRIT checklist for reporting randomized trials

Section/item	Item No	Description	Adressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 10, 24-25
	2b	All items from the World Health Organization Trial Registration Data Set	5, 10, 24-25, Table1
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	5, 24-26,
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 26
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA / 26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10, 11

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

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4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-17
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13	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10, 17, Figure1, Additional file 2
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20	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17, 18
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26	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11, 12
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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36	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-12
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46	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-12
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52	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-12
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1 2 3 4 5 6 7 8 9 10 11 12 13	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

### Methods: Data collection, management, and analysis

14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-17, 23
		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
34 35 36 37 38 39 40 41 42	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-20
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19, 20
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19, 20



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3 **Methods: Monitoring**  
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6	Data monitoring	21a	Composition of data monitoring committee (DMC); 7 summary of its role and reporting structure; statement 8 of whether it is independent from the sponsor and 9 competing interests; and reference to where further 10 details about its charter can be found, if not in the 11 protocol. Alternatively, an explanation of why a DMC is 12 not needed	12
13		21b	Description of any interim analyses and stopping 14 guidelines, including who will have access to these 15 interim results and make the final decision to terminate 16 the trial	NA
17	Harms	22	Plans for collecting, assessing, reporting, and 18 managing solicited and spontaneously reported 19 adverse events and other unintended effects of trial 20 interventions or trial conduct	NA
21	Auditing	23	Frequency and procedures for auditing trial conduct, if 22 any, and whether the process will be independent from 23 investigators and the sponsor	NA
24	<b>Ethics and dissemination</b>			
25	Research ethics 26 approval	24	Plans for seeking research ethics 27 committee/institutional review board (REC/IRB) 28 approval	10, 22-23
29	Protocol 30 amendments	25	Plans for communicating important protocol 31 modifications (eg, changes to eligibility criteria, 32 outcomes, analyses) to relevant parties (eg, 33 investigators, REC/IRBs, trial participants, trial 34 registries, journals, regulators)	NA
35	Consent or 36 assent	26a	Who will obtain informed consent or assent from 37 potential trial participants or authorised surrogates, 38 and how (see Item 32)	11, 23
39		26b	Additional consent provisions for collection and use of 40 participant data and biological specimens in ancillary 41 studies, if applicable	NA

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24-27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11, 25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	26
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10, 11, 23
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license

**Additional file 2.** Schematic diagram of schedule of enrolment, interventions, and assessments of the women participating in PPRMEXIL trials and children participating in PPRMEXIL follow-up

	STUDY PERIOD			STUDY PERIOD		
	Original PPRMEXIL trials - women			PPRMEXIL Follow-up - children		
	Enrolment original trials	Allocation original trials	Outcomes original trials	Enrolment follow-up study	Assessment follow-up study	Close-out
TIMEPOINT	<i>Women with PPROM between 34 and 36+6 weeks of gestation</i>	t = 0	<i>Pregnancy, childbirth and neonatal period</i>	<i>After 10 – 12 years</i>	<i>Age 10-12 years</i>	<i>Age 10-12 years</i>
ENROLMENT:						
Eligibility screen	X			X		
Informed consent	X			X	X	
Allocation		X				
INTERVENTIONS:						
Induction of Labor		X				
Expectant Management		X				
ASSESSMENTS:						
<i>Baseline variables</i>	X	X		X		
<i>Outcome variables</i>			X		X	X

**Additional file 3.**

Contributors to the PPROMEXIL and PPROMEXIL-2 trials

David P. van der Ham, Christine Willekes, Jantien L. van der Heyden, Sylvia M. C. Vijgen,

Jan G. Nijhuis, Johannes J. van Beek, Brent C. Opmeer, Antonius L. M. Mulder, Rob

Moonen, Mariët Groenewout, Mariëlle G. van Pampus, Gerald D. Mantel, Kitty W. M.

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Pernet, Martina Porath, Jan F. M. Molkenboer, Simone Kuppens, Anneke Kwee, Michael E.

Kars, Mallory Woiski, Martin J. N. Weinans, Hajo I. J. Wildschut, Bettina M. C. Akerboom,

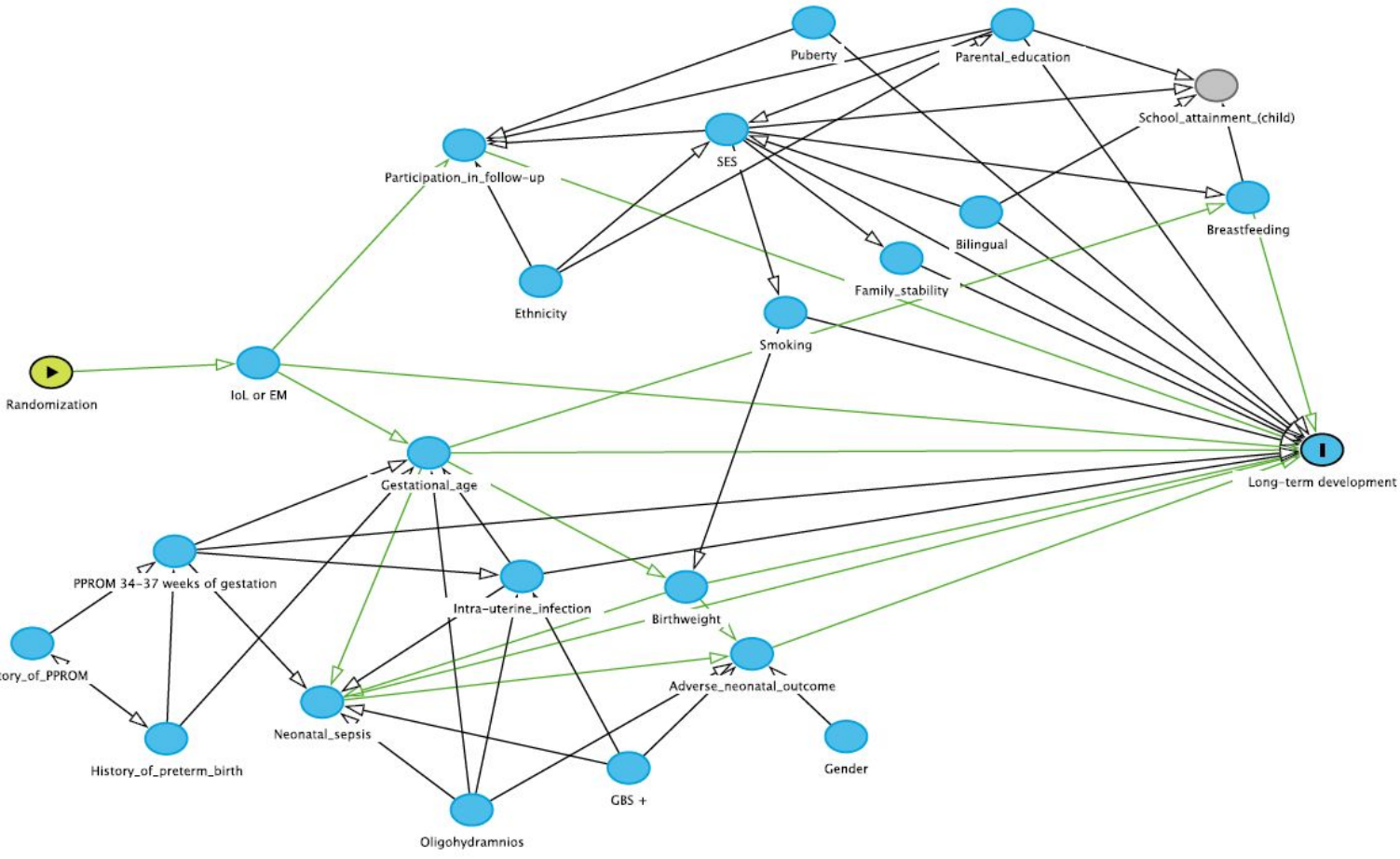
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Pajkrt, Martijn A. Oudijk, Bas Nij Bijvank, Caroline J. Bax, Janneke van 't Hooft.

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**Additional file 4.** Direct Acyclic Graph (DAG) identifying potential confounding measures



**Additional file 5.** GRIPP2 short form

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	8, 20-21
2: Methods	Provide a clear description of the methods used for PPI in the study	8, 20-21
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	8
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	NA
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	NA

# BMJ Open

**Child outcomes after induction of labour or expectant management in women with preterm prelabour rupture of membranes between 34-37 weeks of gestation: Study protocol of the PPROMEXIL Follow-up trial.  
A long-term follow-up study of the randomised controlled trials PPROMEXIL and PPROMEXIL-2.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046046.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Mar-2021
Complete List of Authors:	de Ruigh, Annemijn; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology, Amsterdam Reproduction & Development Simons, Noor; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology, Amsterdam Reproduction & Development Van 't Hooft, Janneke; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology, Amsterdam Reproduction & Development van Wassenaer-Leemhuis, Aleid; Amsterdam UMC Location AMC, Department of Neonatology and Paediatrics, Emma Children's Hospital, Amsterdam Reproduction & Development Aarnoudse-Moens, Cornielieke; Amsterdam UMC Location AMC, Department of Neonatology and Paediatrics, Emma Children's Hospital, Amsterdam Reproduction & Development van Wely, Madelon; Amsterdam University Medical Centres, Netherlands Satellite of the Cochrane Gynaecology and Fertility Group van Baaren, Gert-Jan; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology Vlemmix, Floortje; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology van der Ham, D.P.; Martini Hospital, Department of Obstetrics and Gynaecology van Teeffelen, Augustinus; Maastricht UMC+, Department of Obstetrics and Gynaecology Mol, Ben; Monash University, Department of Obstetrics and Gynaecology Roseboom, Tessa; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology, Amsterdam Reproduction & Development; Amsterdam UMC Locatie AMC, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Pajkrt, Eva; Amsterdam UMC Location AMC, Department of Obstetrics and Gynaecology, Amsterdam Reproduction & Development
<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Paediatrics
Keywords:	Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS,

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	Prenatal diagnosis < OBSTETRICS, Developmental neurology & neurodisability < PAEDIATRICS

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3 1 **Child outcomes after induction of labour or expectant**  
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6 2 **management in women with preterm prelabour rupture of**  
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8  
9 3 **membranes between 34-37 weeks of gestation: Study protocol**  
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11  
12 4 **of the PPROMEXIL Follow-up trial**

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14 5 *A long-term follow-up study of the randomised controlled trials PPROMEXIL and*  
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16 6 *PPROMEXIL-2.*

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3 71 **ABSTRACT**  
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6 72 **Introduction:** Late preterm prelabour rupture of membranes (PROM between 34<sup>+0</sup> and 36<sup>+6</sup>  
7  
8 73 weeks gestational age) is an important clinical dilemma. Previously, two large Dutch  
9  
10 74 randomised controlled trials (RCTs) compared induction of labour (IoL) to expectant  
11  
12 75 management (EM). Both trials showed that early delivery does not reduce the risk of  
13  
14 76 neonatal sepsis as compared to EM, although prematurity related risks might increase. An  
15  
16 77 extensive, structured long-term follow-up of these children has never been performed.

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19 78 **Methods and analysis:** The PPROMEXIL Follow-up trial aims to assess long-term  
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21 79 childhood outcomes of the PPROMEXIL (ISRCTN29313500) and PPROMEXIL-2 trial  
22  
23 80 (ISRCTN05689407), two multicentre RCTs using the same protocol, conducted between  
24  
25 81 2007-2010 evaluating IoL versus EM in women with late preterm PROM. The PPROMEXIL  
26  
27 82 Follow-up will analyse children of mothers with a singleton pregnancy (PPROMEXIL trial n=  
28  
29 83 520, PPROMEXIL-2 trial n=191, total IoL n=359; total EM n=352). At 10-12 years of age all  
30  
31 84 surviving children will be invited for a neurodevelopmental assessment using the Wechsler  
32  
33 85 Intelligence Scale for Children-V, Color-Word Interference Test and the Movement  
34  
35 86 Assessment Battery for Children-2. Parents will be asked to fill out questionnaires assessing  
36  
37 87 behaviour, motor function, sensory processing, respiratory problems, general health and  
38  
39 88 need for health care services. Teachers will fill out the Teacher Report Form and answer  
40  
41 89 questions regarding school attainment. For all tests means with SD's will be compared, as  
42  
43 90 well as predefined cut-off scores for abnormal outcome. Sensitivity analyses consisting of  
44  
45 91 different imputation techniques will be used to deal with loss-to-follow-up.

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48  
49 92 **Ethics and dissemination:** The study has been granted approval by the MEC of the  
50  
51 93 AmsterdamUMC (MEC2016\_217). Results will be disseminated through peer-reviewed  
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53 94 journals and summaries shared with stakeholders. This protocol is published before analysis  
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55 95 of the results.  
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96 **Registration:** Dutch Trial registration number: NTR6953 (registration December 28<sup>th</sup>, 2017).

97 The study has been peer reviewed, approved and funded by ZonMW (843002826).

98

99 **Key words:** Late preterm prelabour rupture of membranes, induction of labour, expectant

100 management, long-term outcome, child development, child health

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3 104 **ARTICLE SUMMARY**  
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5 105 **Strengths and limitations of this study**  
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- 8 106 • This long-term follow-up study will be the first study to evaluate long-term  
9  
10 107 developmental outcomes (cognitive, motor, and behavioural development, sensory  
11  
12 108 processing, respiratory problems, general health, children's need for health-care  
13  
14 109 services, and school attainment) in the offspring of women who have been treated  
15  
16 110 during pregnancy with induction of labour or expectant management for late preterm  
17  
18 111 prelabour rupture of membranes.  
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20  
21 112 • Children will be evaluated at 10-12 years of age with internationally validated  
22  
23 113 neurodevelopmental tests by a trained team consisting of a (neuro)psychologist and  
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25 114 physician masked to the study group, and with questionnaires, translated for Dutch  
26  
27 115 children, using norm scores for Dutch children.  
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31 116 • The study will be performed within the Dutch Consortium for Healthcare Evaluation  
32  
33 117 and Research in Obstetrics and Gynecology - NVOG Consortium 2.0, a collaboration  
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35 118 of approximately 70 obstetric hospitals (academic and non-academic hospitals) in the  
36  
37 119 Netherlands.  
38  
39  
40 120 • Alongside this long-term follow-up study a separately reported economic evaluation  
41  
42 121 study will be planned to investigate cost-effectiveness of both treatments taking long-  
43  
44 122 term developmental outcomes into account.  
45  
46  
47 123 • The main limitation is that we expect to have an incomplete follow-up rate due to a  
48  
49 124 high loss to follow-up, which we estimate to be 60 to 70%. Baseline characteristics of  
50  
51 125 children participating in follow-up versus lost to follow-up will be compared, to assess  
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53 126 whether selection or attrition bias may be present in our study.  
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## 128 INTRODUCTION

### 129 Background and rationale

130 Late preterm prelabour rupture of membranes (late preterm PROM) between 34<sup>+0</sup> and 36<sup>+6</sup>  
131 weeks gestation, is an important clinical problem occurring in 1.5% of pregnant women, of  
132 which 25% will deliver within 24 hours.(1) After PROM, the risk of infection increases for both  
133 mother and foetus. Recently, three large randomised controlled trials (RCTs) compared  
134 induction of labour to expectant management for women whose pregnancy was complicated  
135 by late preterm PROM.(2-4) The Dutch PPROMEXIL and PPROMEXIL-2 trial, and the  
136 Australian PPROMT trial showed that induction of labour does not reduce the risk of neonatal  
137 sepsis as compared to expectant management, while increasing prematurity related risks,  
138 such as hypoglycaemia and hyperbilirubinemia. Furthermore, an Individual Participant Data  
139 Meta-analysis (IPD-MA) investigating participant data of all three RCTs also concluded that  
140 expectant management is an acceptable alternative to induction of labour, as both  
141 treatments resulted in comparable rates of a composite of adverse neonatal outcomes.(5)  
142 Moreover, an economic analysis of the PPROMEXIL trial, showed that health care costs for  
143 induction of labour are slightly higher, although not statistically significant, with a mean  
144 difference of €754 (€8,094 for induction of labour versus €7,340 for expectant management,  
145 95% confidence interval (CI) -€335 to €1,802).(6) Therefore, currently most national  
146 guidelines advocate expectant management for late preterm PROM.(1, 7, 8)

147  
148 In 2015 our research team performed a follow-up study of children at two years of age, born  
149 to women who participated in the PPROMEXIL trial.(9) This follow-up study was performed  
150 with limited budget and used internationally validated screening questionnaires. Even though  
151 this study had a follow-up rate of 44% and no extensive neurodevelopmental assessments  
152 were used, an increase in neurodevelopmental impairment was found in the expectant  
153 management group as compared to the induction of labour group (abnormal score (-2  
154 standard deviation (SD)) in  $\geq 1$  domains of the Ages and Stages Questionnaire: 14%



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3 155 induction of labour group versus 26% expectant management group, difference in  
4  
5 156 percentage -11.4; 95% CI -21.9 to -0.98).(9) Hypothetically, a prolonged stay of the foetus in  
6  
7 157 an environment at risk for (subclinical) infections such as maternal placental inflammation  
8  
9 158 (histological or clinical chorioamnionitis) and foetal side placental inflammation (funisitis and  
10  
11 159 chorionic plate vasculitis) in case of expectant management could affect brain development  
12  
13 160 (i.e. neurological outcome) and therefore explain the neurodevelopmental impairment seen  
14  
15 161 at 2 years of age.(10) The developmental effects of induction of labour or expectant  
16  
17 162 management after late preterm PROM in children after 2 years are still unknown.  
18  
19 163 Furthermore, understanding the long-term effects on women's offspring of either treatment is  
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21 164 important for both clinicians and pregnant women when deciding how to manage late  
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23 165 preterm PROM.  
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28 167 Until now, no other study has performed or planned a comprehensive long-term follow-up of  
29  
30 168 children born after late preterm PROM. Study feasibility was investigated by an online  
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32 169 questionnaire filled out by parents and members of a Dutch patient organization representing  
33  
34 170 patients affected by preterm birth due to complications in pregnancy. Results showed that  
35  
36 171 89% of parents were willing to participate in an extensive follow-up study. Parents rated the  
37  
38 172 outcomes general health, behaviour, school attainment and respiratory problems as most  
39  
40 173 important outcomes (data not published). A systematic review on neurodevelopment in  
41  
42 174 preterm children showed a strong relationship between gestational age at delivery and  
43  
44 175 cognitive abilities (i.e. academic attainment, emotional and behavioural needs) in very,  
45  
46 176 moderately and late preterm infants. These deficits persist beyond primary school for all  
47  
48 177 neurodevelopmental domains. They stress the importance of knowledge on these long-term  
49  
50 178 domains and advise trials to plan long-term follow-up to gain insight on possible  
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52 179 neurodevelopmental delay in children.(11)  
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## 58 181 **Objectives**

59 182 Therefore, the aim of this study is to conduct a structured follow-up of all children born to

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3 183 women with late preterm PROM who were randomised to induction of labour or expectant  
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5 184 management in the PPROMEXIL and PPROMEXL-2 trial. Long-term cognitive, motor, and  
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7 185 behavioural development, sensory processing, respiratory problems, general health,  
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9 186 children's need for health-care services, and school attainment will be assessed at 10-12  
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11 187 years of age using internationally validated measurements and questionnaires, translated  
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13  
14 188 and using norm scores for Dutch children.  
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## 190 **METHODS AND ANALYSIS**

### 191 **Study setting**

192 We will perform an extensive long-term follow-up study of two previously executed RCTs  
193 (PPROMEXIL Follow-up trial, NTR 6953, METC 2016\_217, NL58494.018.16) investigating  
194 long-term developmental outcomes (cognitive, motor, behavioural development), sensory  
195 processing, respiratory problems, general health, children's need for health-care services,  
196 and school attainment. This will be assessed at 10-12 years of corrected age in children born  
197 to women with a singleton pregnancy complicated by late preterm PROM (between 34+0 and  
198 36+6 weeks gestation), who participated in the RCTs PPROMEXIL, and PPROMEXIL-2 trial.  
199 Details of the PPROMEXIL (ISRCTN29313500) and PPROMEXIL-2 trial (amendment of the  
200 PPROMEXIL trial (MEC 05-240, ISRCTN05689407) have been published elsewhere.(2, 3)  
201 These two large RCTs, using the same study protocol and conducted between 2007 and  
202 2011 in 61 academic and non-academic hospitals in The Netherlands, assessed whether  
203 induction of labour versus expectant management would reduce the incidence of neonatal  
204 sepsis in women with late preterm PROM. In the induction of labour group, patients were  
205 induced within 24 hours after randomization. Patients in the expectant management group  
206 were monitored until the onset of spontaneous delivery or induced after 37+0 weeks  
207 according to national guidelines.(1)

### 209 **Participants and eligibility criteria**

210 All children born to women with a singleton pregnancy who participated in the PPROMEXIL  
211 trials will be invited for this long-term follow-up assessment. Children will be evaluated at 10-  
212 12 years of age. As the total number of multiple pregnancies in the PPROMEXIL- and  
213 PPROMEXIL-2 trials was very low (14/727 (1.9%) and equally distributed among treatment  
214 groups), only singleton pregnancies will be included in the analysis. See Figure 1. for the  
215 overview of PPROMEXIL follow-up participants.

216

## 217 **Procedures and recruitment**

218 The study protocol is designed, constructed and reported according to the recommendations  
219 given in the Standard Protocol Items: Recommendations for Interventional Trials (See  
220 Additional file 1. SPIRIT checklist for reporting randomised trials, Additional file 2. SPIRIT  
221 schematic diagram of enrolment PPROMEXIL follow-up participants., and Additional file 3.  
222 GRIPP2 short form.)(12) The study will be performed within the Dutch Consortium for  
223 Healthcare Evaluation and Research in Obstetrics and Gynecology - NVOG Consortium 2.0,  
224 a collaboration of approximately 70 obstetric hospitals (academic and non-academic  
225 hospitals) in the Netherlands (<https://zorgevaluatienederland.nl/nvog>). Research nurses will  
226 be asked to crosscheck medical records for possible occurrence of death of women's  
227 offspring before contacting parents and their child for participating in this follow-up study. All  
228 parents will be contacted by post to announce this follow-up study, and if they give consent  
229 to be approached by the research team, they will be contacted by telephone or email to  
230 explain study details. Parents will be informed that participation is voluntary and that they  
231 may withdraw consent to participate at any time (see Additional file 4). They will be informed  
232 that declining participation will not affect their or their child's care. Parents will be given  
233 sufficient time to read the patient information and they will be given the opportunity to ask  
234 questions by telephone or email prior to signing the informed consent form. Written study  
235 information at children's reading level will be available for all children (specified for children  
236 <12 years of age and ≥12 years of age. An independent physician (i.e. not a member of the  
237 research team) will be available to answer any questions patients may have. Written  
238 informed consent will be obtained from both parents prior to the examination. Children ≥12  
239 years of age have to sign their own informed consent, in addition to the informed consent of  
240 their parents, at the day of the assessment. A copy of the informed consent form(s) will be  
241 given to the parents/child. All study documents will be available through the study website.

242 Concealment of treatment allocation at time of the PPROMEXIL and PPROMEXIL-2 trials  
243 (i.e. induction of labour or expectant management) was not possible due to the type of

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3 244 intervention, and therefore parents and children entered in this follow-up study will be aware  
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5 245 of treatment allocation. The research team performing the follow-up examinations and all  
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7 246 members of the research team performing data entry and data analyses will be masked to  
8  
9 247 treatment allocation.

10  
11 248 All data will be collected, captured, and coded in accordance with existing polices to ensure  
12  
13 249 patient confidentiality. Data will be recorded using an electronic case record form and will be  
14  
15 250 stored in a web-secured database (available through the study website).(13) The  
16  
17 251 investigators will publish the results of this trial in a peer reviewed medical journal as soon as  
18  
19 252 appropriate. The Clinical Research Unit (CRU) of the Amsterdam UMC will monitor data  
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21 253 collection.

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### 26 27 255 **Follow-up assessment and outcomes**

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29 256 During a single visit in an outpatient clinic of a local hospital close to the family's  
30  
31 257 neighbourhood, children will be assessed on long-term neurodevelopmental outcomes using  
32  
33 258 standardized and validated neurodevelopmental tests and questionnaires. A trained team  
34  
35 259 consisting of a (neuro)psychologist and physician, masked to the study group, will perform all  
36  
37 260 neurodevelopmental tests. Neurodevelopmental assessment of children has a structured  
38  
39 261 approach, is enjoyable for most children and is not invasive. During neurodevelopmental  
40  
41 262 assessment of the child, parents will be asked to fill out questionnaires on sensory  
42  
43 263 processing, behaviour, respiratory problems, and child's health. If necessary, parents will be  
44  
45 264 assisted with filling out questionnaires. All, but one, questionnaires are digital and can be  
46  
47 265 filled out on a tablet during the assessment or at any other time at home.

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51  
52 267 After completing all examinations, parents receive a short report on their child's test results.  
53  
54 268 This short report will give information on total test scores and tell parents whether their child's  
55  
56 269 scores are above, on or below average. If test scores indicate that children would benefit  
57  
58 270 from supportive (health, developmental or educational) care, parents are advised to contact

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3 271 their general practitioner for referral to a paediatrician or psychologist.  
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8 273 *Main study outcomes*

9  
10 274 - Cognitive development (Wechsler Intelligence Scale for Children -V)

11  
12 275 - Motor skills (Movement-ABC-2)

13  
14 276 - Behaviour (Child Behaviour Checklist)

15  
16  
17 277 *Secondary study outcomes*

18  
19 278 - School attainment (Teacher's Report Form and additional questions)

20  
21 279 - Sensory processing (Short Sensory Profile-NL)

22  
23 280 - Respiratory problems (International Study of Asthma and Allergies in Childhood  
24  
25 questionnaire)

26  
27 281  
28 282 - Pubertal status (Puberty Developmental Scale)

29  
30 283 - General health (questionnaire)

31  
32 284  
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34

35 285 *Assessment of cognitive development*

36  
37 286 Cognitive Development will be assessment using the Dutch version of the Wechsler

38  
39 287 Intelligence Scale for Children (WISC-V).(14) The WISC-V is used worldwide to assess

40  
41 288 cognition in children aged six to 16 years and consists of 10 subtests that are combined into

42  
43 289 a Full Scale IQ score (FSIQ) and five primary indexes: verbal comprehension, visual spatial,

44  
45 290 fluid reasoning, working memory and processing speed. Besides these primary indexes, an

46  
47 291 additional mathematics subtest will be obtained to provide an objective measurement of this

48  
49 292 area of academic attainment. The WISC-V total intelligence quotient (IQ) score and primary

50  
51 293 indexes have a mean score of 100 points with a SD of 15 points. We will compare mean

52  
53 294 (SD) between treatment groups. Furthermore, an index score  $\leq 70$  ( $\geq -2$  SD below the mean

54  
55 295 score) will be considered as a severe cognitive delay and will be compared between groups.

56  
57 296 An index score  $>70$  and  $\leq 84$  ( $\geq -1$  SD and  $< -2$ SD below the mean score) will indicate a mild

1  
2  
3 297 cognitive delay. Normal cognitive outcome is defined as no severe or mild  
4  
5 298 neurodevelopmental delay. A difference between the two treatment groups of 7.5 points (0.5  
6  
7 299 SD) could indicate a potential clinical relevant difference.

9 300 Child's executive functioning will be tested using subtests of the WISC-V and the Color-Word  
10  
11 301 Interference Test (CWIT). The CWIT measures cognitive set shifting and the ability to inhibit  
12  
13 302 a dominant and automatic verbal response by separate and combined Color Naming and  
14  
15 303 Color Reading items. The CWIT subtests have a mean of 10 points with a SD of 2 points. An  
16  
17 304 CWIT index score of  $\leq 4$  (i.e. more than -2 SD below the mean score) is considered a severe  
18  
19 305 delay in executive functioning and will be analysed.

### 22 306 *Assessment of motor skills*

23  
24 307 Child's motor function will be measured by the Movement Assessment Battery for Children-2  
25  
26 308 (M-ABC-2).<sup>(15)</sup> The M-ABC-2 is the most commonly used tool used to examine fine and  
27  
28 309 gross motor skills. The M-ABC-2 provides data about a child's performance of age-  
29  
30 310 appropriate tasks within three domains; manual dexterity, aiming and catching, and balance.  
31  
32 311 M-ABC-2 scores will be calculated as standard scores and percentiles for each domain, and  
33  
34 312 as a total test score. The mean standard score for all domains and the total score is 10  
35  
36 313 points, with a SD of 3 points. We will compare mean (SD) between treatment groups. The  
37  
38 314 age band two (7-10 years of age) and three (11-16 years of age) of the M-ABC-2 will be  
39  
40 315 used, as appropriate according to the child's age. Percentiles as defined by the M-ABC-2  
41  
42 316 testing manual and used in daily practice for testing motor skills in children will be applied. In  
43  
44 317 short, a standard score of  $\leq 5$  points, representing  $\leq 5^{\text{th}}$  percentile will be defined as a  
45  
46 318 significant movement difficulty and a severe delay in motor skills and will be compared  
47  
48 319 between treatment groups. A standard score of 6 or 7 points, representing  $> 5^{\text{th}}$  to  $\leq 16^{\text{th}}$   
49  
50 320 percentile will indicate that the child is at risk of having a movement difficulty and therefore  
51  
52 321 will be classified as mild delay in motor skills. A standard score of  $\geq 8$  points,  
53  
54 322 representing  $> 16^{\text{th}}$  percentile will be defined as no movement difficulty and normal  
55  
56 323 development of motor skills.  
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3 324 Additionally, parents will fill out the M-ABC-2 checklist, a questionnaire that consists of three  
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5 325 sections on movement in static and/or predictable environment, movement in a dynamic  
6  
7 326 and/or unpredictable environment and non-motor factors that may affect the child's  
8  
9 327 movement. The sections on static and dynamic movements are summed up to a total score,  
10  
11 328 with a higher score indicating a worse motor function. A total score of  $\geq 95^{\text{th}}$  percentile ( $\geq 9$   
12  
13 329 points) indicates severe motor impairment and will be compared between both treatment  
14  
15 330 groups.

### 18 331 *Assessment of behavioural development*

20 332 Child's behaviour will be measured by the Child Behaviour Checklist (CBCL), a parental  
21  
22 333 questionnaire used to screen for behaviour problems in children.(16) It informs on eight  
23  
24 334 narrow syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints,  
25  
26 335 social problems, thought problems, attention problems, rule-breaking behaviour, and  
27  
28 336 aggressive behavior) and three broadband scales (internalizing, externalizing behavioural  
29  
30 337 problems and a total problems score) which are composed out of the narrow-band syndrome  
31  
32 338 scales. The CBCL broadband scales T scores have a mean of 50 points with a SD of 10  
33  
34 339 points. We will compare mean (SD) between treatment groups. Furthermore, a score  $> 90^{\text{th}}$   
35  
36 340 percentile ( $> 63$  points) on one of the two broad dimensions scales (internalizing problems or  
37  
38 341 externalizing problems), or the total problem score (sum of all scores) of the CBCL will be  
39  
40 342 defined as abnormal and clinically relevant for indicating behavioural problems. Scores  $\geq 84^{\text{st}}$   
41  
42 343 and  $\leq 90^{\text{th}}$  percentile ( $\geq 60$  and  $\leq 63$  points) are considered borderline and scores  $< 84^{\text{th}}$   
43  
44 344 percentile ( $< 60$  points) are defined as normal.

### 48 345 *Assessment of school attainment*

50 346 Child's academic attainment and behaviour will be assessed using the Teacher's Report  
51  
52 347 Form (TRF).(17) The TRF assesses problem behaviour in the last two months and identifies  
53  
54 348 the same eight syndromes as the CBCL, and also inquires on academic attainment  
55  
56 349 (Academic Performance). With parental permission, the TRF will be filled out by the child's  
57  
58 350 school teacher (the teacher who has known the child in the school setting for more than two  
59  
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3 351 months can complete the TRF). Accompanying the TRF, teachers will be asked some  
4  
5 352 additional questions regarding the child's need for additional educational support in- or  
6  
7 353 outside the classroom. For the TRF the cut-off percentiles of the broad band and total scores  
8  
9 354 as used in the CBCL will be applied. For Academic Performance a cut-off score of <10<sup>th</sup>  
10  
11 355 percentile ( $\leq 36$  points) will be defined as abnormal. Scores between 10<sup>th</sup> and 16<sup>th</sup> percentile  
12  
13 356 are classified as borderline and  $\geq 17^{\text{th}}$  percentile are considered normal outcome.

### 16 357 *Assessment of sensory processing*

18 358 Sensory processing will be determined using the Short Sensory Profile questionnaire (SSP-  
19 359 NL).(18) The Short Sensory Profile contains sections corresponding to each sensory system,  
20  
21 360 sections that indicate the modulation of sensory input across sensory systems, and sections  
22  
23 361 that indicate behavioural and emotional responses that are associated with sensory  
24  
25 362 processing. This questionnaire consists of 38 items, classified into seven subscales (Tactile  
26  
27 363 Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Underresponsive/Seeks  
28  
29 364 Sensation, Auditory Filtering, Low Energy/Weak, and Visual/Auditory Sensitivity). For every  
30  
31 365 subscale parents will be asked how frequently their children respond in the way described by  
32  
33 366 each item using a 5 point Likert scale (nearly never, seldom, occasionally, frequently, almost  
34  
35 367 always). Lower scores on the total score and subscales indicate more sensory symptoms.  
36  
37 368 Subscales and the total scores will be used to classify as "definite difference" (cut off scores  
38  
39 369  $\geq -2$  SD below the mean) and will be compared between groups. "Typical performance" will  
40  
41 370 be defined as  $< -1$  SD below the mean, "probable difference" will be defined as  $\geq -1$  SD and  
42  
43 371  $< -2$  SD below the mean.

### 48 372 *Assessment of respiratory problems*

50 373 Respiratory problems, such as asthma or other lung problems will be assessed using the  
51 374 International Study of Asthma and Allergies in Childhood questionnaire (ISAAC  
52  
53 375 questionnaire) which informs on asthma, rhinitis and eczema.(19) The diagnosis of asthma  
54  
55 376 will be defined as a positive answers to the question: "In the last 12 (twelve) months, has  
56  
57 377 your child had wheezing?", as this question has a sensitivity of 100%, specificity of 78%,  
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3 378 positive predictive value of 73%, and negative predictive value of 100% for the diagnosis of  
4  
5 379 asthma.(20)

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7  
8 380 *Assessment of anthropometry and pubertal status*

9  
10 381 Children will be asked to fill out the Puberty Developmental Scale (PDS), a self-report  
11  
12 382 measure of pubertal status.(21) Children will be asked questions regarding on e.g. growth in  
13  
14 383 height, skin changes, body or facial hair, deepening of the voice (for boys), and starting to  
15  
16 384 menstruate or developing breasts (for girls). Physical examination will be restricted to  
17  
18 385 measurement of height/weight and blood pressure. Results of physical examination  
19  
20 386 (height/weight, body mass index) will be used for baseline characteristics. Puberty status will  
21  
22 387 be used for baseline characteristics and subgroup analysis.

23  
24  
25 388 *Assessment of child's health and need for health care services*

26  
27 389 A general questionnaire consisting of 61 items, will be used to assess demographic  
28  
29 390 characteristics and will ask questions regarding the present (last 12 months) and the past  
30  
31 391 health and health care use (from discharge after delivery until date of assessment) (also  
32  
33 392 used in previous follow-up studies such as ProTWINkids study at three and four years,  
34  
35 393 TripleP study(22-24)). Questions address child's health, need for health care services,  
36  
37 394 hospital visits, hospital submission, need for surgery, use of medication, psychological  
38  
39 395 problems, need for developmental therapies (such as physical therapists, remedial teaching,  
40  
41 396 speech therapist, occupational therapist). Health care use and (health) related problems will  
42  
43 397 be clustered into different clinically relevant groups (e.g. need for medical specialist and/or  
44  
45 398 developmental care, medication use in the past and present, hospital admissions and  
46  
47 399 surgery to give insight in the range of health related problems).

48  
49 400 Parents will be asked to give permission to gather medical information on the child's health  
50  
51 401 via the general practitioner and the preventive youth healthcare services if needed.

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54 402 *Economic analysis*

55  
56 403 Alongside this long-term follow-up study, an economic evaluation study will be planned to  
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3 404 investigate cost-effectiveness of both treatments taking long-term developmental outcomes  
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5 405 into account. Results of this economic evaluation will be reported separately from trial  
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7 406 results.  
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11 408 At present, no additional long-term follow-up in later life (>12 years of age) is planned.

13 409 Permission to approach parents and children for additional follow-up research in later life will  
14  
15 410 be obtained with informed consent form during the current follow-up study. If additional long-  
16  
17 411 term follow-up of children at an adolescence age will be planned in the future, additional  
18  
19 412 approval of the Medical Research Ethics Committee will be sought.  
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#### 25 414 **Sample size**

27 415 Since this is a follow up study, the maximum number of study participants is already defined  
28  
29 416 by the two PPROMEXIL trials, excluding multiple pregnancies and deceased children (Figure  
30  
31 417 1 and Additional file 2.). Consequently, 711 children are eligible for inclusion, 359 born in the  
32  
33 418 induction of labour group and 352 born in the expectant management group (PPROMEXIL  
34  
35 419 trial n=520, PPROMEXIL-2 trial n=191). As we will not be able to adjust the number of  
36  
37 420 recruited children, a power calculation will not be of any use to calculate a study sample size.  
38  
39 421 However, this calculation can indicate the minimum number of children that need to be tested  
40  
41 422 in order to find a clinically significant difference for the three main study outcomes: cognitive  
42  
43 423 development, motor skills and behavioural development. All sample size calculations are with  
44  
45 424 a power of 90%, a two-sided  $\alpha$  of 0.05 and  $\beta$  of 0.20. To be able to detect a clinically relevant  
46  
47 425 difference in mean scores of 0.5 SD in the main outcomes, minimally 86 children per group  
48  
49 426 are needed (total 172 children). This 0.5 SD equals a difference of 7.5 IQ points in the mean  
50  
51 427 score of the WISC-V test (cognitive development), a difference of 1.5 points on the mean  
52  
53 428 total standard scores of the M-ABC-2 (motor skills) and a difference of 5 points on the mean  
54  
55 429 T scores in any of the broadband problem scales of the CBCL (behavioral development)  
56  
57 430 between both groups. Thus, since 172 children comprise 24% of our total, also in case of  
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3 431 limited follow up, differences of 0.5 SD can be picked up. Based on previous experience in  
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5 432 our research team with follow-up trials and based of existing literature, we expect to have a  
6  
7 433 follow-up rate of 30 to 40% of the children.(25)  
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9 434

### 11 435 **Statistical methods**

13 436 Differences in background characteristics and the maternal, pregnancy, delivery and  
14  
15 437 neonatal outcomes between the induction of labour group and expectant management group  
16  
17 438 will be compared using unpaired T-test, Mann-Whitney U test, Chi-square test or Fisher's  
18  
19 439 exact test when appropriate. The same characteristics will be compared in children assessed  
20  
21 440 at follow-up and for the original participants of the PPROMEXIL trials. This will allow us to  
22  
23 441 assess whether selection or attrition bias may be present in our study (e.g. due to drop-out of  
24  
25 442 healthy or unhealthy children). To compare the long-term developmental outcomes between  
26  
27 443 both treatment groups mean differences and the corresponding 95% CI will be calculated.  
28  
29 444 For dichotomous outcomes relative risk (RR) with corresponding 95% CI will be calculated.  
30  
31 445 Our main analyses shall be based upon the results from the children assessed in follow-up  
32  
33 446 (complete case analysis).(25)  
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36 447

38 448 The relatively simple statistical analysis described above can be justified by the fact that our  
39  
40 449 study is a follow-up of two RCTs and consequently no confounding measures are expectant  
41  
42 450 (See Additional file 5. Direct Acyclic Graph (DAG)). The DAG confirms that there are no  
43  
44 451 variables susceptible to have influenced the likelihood of receiving the intervention and  
45  
46 452 subsequently have influenced long-term outcome of the child. On the other hand, selection  
47  
48 453 bias may occur as a consequence of incomplete follow-up. We will evaluate the effect of  
49  
50 454 differences in background characteristics (such as maternal smoking, social-economic  
51  
52 455 status) and if applicable, report unadjusted and adjusted odds ratios for dichotomous  
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54 456 outcomes using logistic models and adjusted mean differences and the corresponding 95%  
55  
56 457 CI for continuous outcomes using general linear models.  
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3 459 *Sensitivity analyses*

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5 460 Our pre-planned sensitivity analyses will only be performed for the WISC-V, the Movement-  
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7 461 ABC and the CBCL total scores to minimize the effect of multiple testing.

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9 462 Imputation missing data: A sensitivity analysis using imputation techniques will be performed  
10  
11 463 to impute missing data for children that are lost to follow-up. Imputation techniques will only  
12  
13 464 be applied when it can be assumed that data is (mostly) missing at random and the follow-up  
14  
15 465 rate is follow-up rate  $\geq 70\%$  (the group agreed on an arbitrary). If the loss to follow-up rate is  
16  
17 466 higher a best- and worst-case scenario will be performed. In these two scenarios the missing  
18  
19 467 cases are imputed either all as 'normal' (best case) or as 'abnormal' (worst case) outcomes.  
20  
21 468 These scenarios will provide some insight on the robustness of the complete case follow-up  
22  
23 469 results.

24  
25  
26 470 Age and puberty adjusted scores: Despite the fact that most children are born late  
27  
28 471 premature/near term or full term, a sensitivity analyses will be performed using age-adjusted  
29  
30 472 scores (corrected for prematurity). Finally, a sensitivity analysis using results of the PDS  
31  
32 473 indicating child's puberty status will be performed.

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37 475 *Subgroup analyses exploring the potential impact of effect modification*

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39 476 Dealing with the effect of 'down-stream' factors: During time to follow-up (due to loss to  
40  
41 477 follow-up) a substantial difference in the prevalence 'down-stream' factors could potentially  
42  
43 478 appear ('down-stream' factors are defined as potential effect modifiers appearing after  
44  
45 479 randomization, such as sepsis at birth, positive GBS). In sensitivity analysis the potential  
46  
47 480 interaction of the following 'down-stream' factors will be explored: gestational age at PROM,  
48  
49 481 receiving antibiotics, receiving steroids for fetal maturation, receiving tocolysis, group B  
50  
51 482 streptococci (GBS) positivity, a positive vaginal culture (including GBS and other pathogens  
52  
53 483 not consistent with normal flora), neonatal sepsis, and for women who participated in the  
54  
55 484 former follow-up study of children at 2 years of age.(9) The analysis will be stratified by these  
56  
57 485 different factors and the potential differences in long term outcomes between the different  
58  
59 486 strata will be explored.

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3 487  
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5 488 A P-value of <0.05 was considered to indicate statistical significance. All analyses will be  
6  
7 489 performed according to the intention-to-treat principle using IBM SPSS (NY, USA) or in  
8  
9 490 RStudio (Boston, MA).

10  
11 491  
12  
13 492 A statistical analysis plan (SAP), reporting a more detailed description of the statistical  
14  
15 493 methods and analyses, will be published separately from the PPROMEXIL follow-up  
16  
17 494 protocol.

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### 21 496 **Patient and public involvement**

22  
23  
24 497 The Dutch association for parents of incubator children and the Dutch Collaboration of  
25  
26 498 parent- and patient organisations endorsed the study and provided input on the study  
27  
28 499 proposal. Parents from the Dutch association for parents of incubator children participated in  
29  
30 500 an online survey. Additionally, mothers of prematurely born children participated in a focus  
31  
32 501 group meeting organized by our research team, to discuss the different aspects of child's  
33  
34 502 long-term development to incorporate in long-term follow-up research.

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### 39 40 504 **DISCUSSION**

41  
42 505 Long-term follow-up of all children born to mothers participating in obstetric intervention trials  
43  
44 506 is of crucial importance.(26) The outcome late neurodevelopmental morbidity has been  
45  
46 507 identified and selected by parents as one of 13 core outcomes for studies evaluating  
47  
48 508 preventive interventions for preterm birth.(27) Furthermore, previous studies have stressed  
49  
50 509 the importance of long-term follow-up by demonstrating that interventions performed during  
51  
52 510 pregnancy can have unexpected long-term effects on children which may not be apparent at  
53  
54 511 birth or during neonatal assessment.(28) By assessing cognition, motor function, behaviour,  
55  
56 512 respiratory problems, general health and school attainment in an extensive and structured  
57  
58 513 follow-up, this study will have the unique opportunity to help understanding the long-term

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3 514 effects of our current treatment regimen for late preterm PROM on women's offspring.  
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5 515 Results from our study should be validated in other follow-up studies comparing induction of  
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7 516 labour to expectant management.  
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For peer review only

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3 521 **ETHICS AND DISSEMINATION**

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5 522 **Ethics approval and consent to participate**

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7 523 The PPROMEXIL Follow-up trial aims to assess long-term childhood outcomes of the  
8  
9 524 PPROMEXIL trial (ISRCTN29313500) and PPROMEXIL-2 trial (MEC 05-240,  
10  
11 525 ISRCTN05689407), two multicentre RCTs using the same study protocol. The Medical Ethics  
12  
13 526 Committee of the Academic Medical Centre Amsterdam (MEC) has approved the  
14  
15 527 PPROMEXIL Follow-up trial (MEC2016\_217, NL58494.018.16). Table 1 describes the  
16  
17 528 chronology of submission and amendments to the MEC.  
18  
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20  
21 529 **Table 1.**

22 530 **Chronology submission and revisions PPROMEXIL follow-up study**

Version no.	Date (DD-MM-YYYY)	Main reasons for change
1	29-09-2016	N/A, first submission to MEC
2	20-12-2017	MEC2016_217#C20161752 Modifications requested by MEC d.d. 05-09-2016
3	04-01-2018	Modifications requested by MEC d.d. 04-01-2018 Additional information on informed consent about saving data (mother and child) up to 15 years after trial
3	10-01-2018	Approval MEC d.d. 10-01-2018
4	31-05-2018	Amendment 1: <ul style="list-style-type: none"><li>- Administrative modifications</li><li>- Change of acronym to PPROMEXIL follow-up</li><li>- Addition of two questionnaires (ISAAC and Puberty developmental scale)</li></ul>
4	04-07-2018	Approval amendment version 4 d.d. 04-07-2018
5	10-08-2018	Amendment 2: <ul style="list-style-type: none"><li>- Modification in protocol on how to recruit participants</li></ul>



		(via research nurses and PhD student) - Modification in Patient Information Files on recruitment
5	23-08-2018	Approval amendment version 5 d.d. 23-08-2018
6	06-11-2018	Amendment 3:  - Clarification on informed consent procedure, parents and participants will be counseled through the telephone and sign informed consent at home  - Minor modifications in the general health questionnaire
6	23-11-2018	Approval amendment version 6 d.d. 23-11-2018
7	03-04-2019	Amendment 4:  - Addition of patient information files for children age 12-15
7	12-04-2019	Approval amendment version 7 d.d. 12-04-2019

531

532 See <https://www.zorgevaluatienederland.nl/evaluations/ppromexil-follow-up> for the full study  
533 protocol and electronic case record form. Written informed consent will be obtained from both  
534 parents prior to the examination. Children  $\geq 12$  years of age have to sign their own informed  
535 consent, in addition to the informed consent of their parents, at the day of the assessment. A  
536 copy of the informed consent form(s) will be given to the parents/child.

537

### 538 **Dissemination**

539 No arrangements have been made concerning public disclosure. The trial is registered in the  
540 Dutch Trial register (Trial registration number: NTR6953. Date of registration December 28th  
541 2017). An overview of the WHO trial registration data set is described in Table 2.

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546 **Table 2.**547 **WHO trial registration data set**

Primary Registry and Trial Identifying Number	Trial NL6623 (NTR6953)
Date of Registration in Primary Registry	December 28 <sup>th</sup> , 2017
Secondary Identifying Numbers	n/a
Source(s) of Monetary or Material Support	ZonMW Dutch Healthcare efficacy program
Primary Sponsor	Academical Medical Center (AMC), Amsterdam, The Netherland
Secondary Sponsor(s)	n/a
Contact for Public Queries	Drs. Noor Simons Followup.ppromexil@amsterdamumc.nl
Contact for Scientific Queries	Prof. dr. Eva Pajkrt e.pajkrt@amsterdamumc.nl
Public Title	PPROMEXIL follow-up
Scientific Title	Child outcomes after induction of labour or expectant management in women with preterm prelabour rupture of membranes between 34-37 weeks of gestation: the PPRMEXIL Follow-up trial, a long-term follow-up study of the randomised controlled trials PPRMEXIL and PPRMEXIL-2.
Countries of Recruitment	The Netherlands
Health Condition(s) or Problem(s) Studied	Late preterm prelabour rupture of membranes (PROM between 34 <sup>+0</sup> and 36 <sup>+6</sup> weeks gestational age). Long-term effects of induction of labour versus expected management.
Intervention(s)	n/a
Key Inclusion and Exclusion Criteria	The PPRMEXIL Follow-up trial will analyse children of mothers with a singleton pregnancy (induction of labour n=359; expectant management n=352). At 10-12 years of (corrected) age all surviving children will be invited for follow-up.
Study Type	Follow-up of a randomized controlled trial
Date of First Enrollment	August 3 <sup>rd</sup> , 2018

Sample Size	All sample size calculations are with a power of 90%, a two-sided $\alpha$ of 0.05 and $\beta$ of 0.20. To be able to detect a clinically relevant difference in mean scores of 0.5 SD in all tests, 86 children per group will be sufficient (total 172 children). This 0.5 SD equals a difference of 7.5 IQ points in the mean score of the WISC-V test (cognitive development), a difference of 1.5 points on the mean total standard scores of the M-ABC-2 (motor skills) and a difference of 5 points on the mean T scores in any of the broadband problem scales of the CBCL (behavioral development) between both groups. Thus, since 172 children comprise 24% of our total, also in case of limited follow up, differences of 0.5 SD can be picked up.
Recruitment Status	Open for patient inclusion
Primary Outcome(s)	Cognitive development (Wechsler Intelligence Scale for Children, WISC-V) Motor skills (Movement-ABC-2) Behaviour (Child Behavior Checklist, CBCL).
Key Secondary Outcomes	Academic attainment and behavior (Teacher Report Form, TRF) Sensory processing (Short Sensory Profile, SSP) Respiratory problems (International Study of Asthma and Allergies in Childhood questionnaire, ISAAC questionnaire) Pubertal status (Puberty Developmental Scale, PDS) Height, weight, bloodpressure General health and demographics (questionnaires)
Ethics Review	The Medical Ethics Committee of the Academic Medical Centre Amsterdam (METC) has approved the PPROMEXIL Follow-up trial (METC 2016_217, NL58494.018.16).
Completion date	n/a
Summary Results	n/a
IPD sharing statement	n/a

548

549 Trial results will be submitted to a peer-reviewed journal, regardless of the outcome and  
550 made open access available in accordance with the Netherlands Organisation for Health  
551 Research and Innovation (ZonMW) policy. Results will be incorporated in national guidelines  
552 and patient information leaflets. Co-authorship will be based on the international committee

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3 553 of medical journal editor's guidelines. Contributors that not fulfil these criteria will be listed as  
4  
5 554 collaborators. The order of authors will be based on scientific input.  
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9 556 **Availability of data and materials**

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11 557 The datasets used and/or analysed during the current study will be available from the  
12  
13 558 corresponding author on reasonable request.  
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22 561 **FOOTNOTES**

23  
24  
25 562 **Author's contributions**

26  
27 563 AdR, NS, JvtH, AvWL, CAM, MvW, GJvB, FV, DvdH, ASPvT, BWM, TR, EP are member of  
28  
29 564 the PPRMEXIL Follow-up trial study group and were involved in conception and design of  
30  
31 565 the study. AdR, NS, JvtH drafted the manuscript which follows the SPIRIT checklist for  
32  
33 566 reporting randomised trials. AdR, NS, JvtH, AvWL, CAM, MvW, GJvB, FV, DvdH, ASPvT,  
34  
35 567 TR, BWM, EP discussed and fine-tuned the final design of the study. All authors edited the  
36  
37 568 manuscript and read and approved the final version of the manuscript.  
38  
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40 569

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42 570 **Funding statement**

43  
44 571 The study group received funding by ZonMW, the Netherlands Organization for Health  
45  
46 572 Research and Development (governmental funding), grant number: 843002826. ZonMW  
47  
48 573 peer reviewed the primary study protocol, they had no other involvement in study design.  
49  
50 574 ZonMw will not have any involvement in data collection, nor in analysis or writing of the  
51  
52 575 manuscript.  
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57 577 **Competing interest statement**

58  
59 578 Dr. Ben Willem Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548). Dr.  
60

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3 579 Ben Willem Mol reports consultancy for ObsEva, Merck Merck KGaA and Guerbet. All other  
4  
5 580 authors did not report any conflicts of interest.  
6

7 581

8  
9 582 **Acknowledgements**

10  
11 583 We would like to thank the research nurses and research midwives from the Dutch  
12  
13 584 Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology - NVOG  
14  
15 585 Consortium 2.0 as well as the Dutch Consortium Trialbureau for their efforts. The authors  
16  
17 586 thank the contributors of PPROMEXIL and PPROMEXIL-2 trial. For a list of contributors to  
18  
19 587 the PPROMEXIL and PPROMEXIL-2 trials see Additional file 6.  
20  
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22 588

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25 589 **List of abbreviations**

26  
27 590 CBCL; Child Behavior Checklist, CI; confidence interval, CWIT; Color-Word Interference  
28  
29 591 Test, DCD; Developmental Coordination Disorder, FSIQ; Full Scale IQ score, GA; gestational  
30  
31 592 age, GBS; group B streptococci, IPDMA; Individual Participant Data Meta-analysis, IQ;  
32  
33 593 intelligence quotient, ISAAC questionnaire; International Study of Asthma and Allergies in  
34  
35 594 Childhood questionnaire, ISRCTN; International Standard Randomised Controlled Trial  
36  
37 595 Number, M-ABC-2; Movement Assessment Battery for Children-2, M.D.; Doctor of Medicine,  
38  
39 596 MEC; Medical ethics committee; in Dutch: medisch ethische toetsingscommissie (METC),  
40  
41 597 NTR; Trial registration number, NVOG; the Dutch college of Obstetricians and  
42  
43 598 Gynecologists, in Dutch: Nederlandse Vereniging voor Gynaecologie en Obstetrie (NVOG),  
44  
45 599 PDS; Puberty Developmental Scale, PROM; prelabour rupture of membranes, PPROMEXIL  
46  
47 600 trial; Preterm Prelabour Rupture Of Membranes EXpectant management vs Induction of  
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49 601 Labour trial, PPROMT; the Preterm Pre-labour Rupture of Membranes close to Term Trial,  
50  
51 602 RCT; randomised controlled trial, RR; relative risk, SD; standard deviation, SSP-NL; Short  
52  
53 603 Sensory Profile, TRF; Teacher Report Form, WISC-V-NL; Wechsler Intelligence Scale for  
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55 604 Children-V.  
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3 606 **Figures and Tables**  
4

5 607 **Figure 1.** Overview of PPROMEXIL follow-up participants  
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7 608 **Table 1.** Chronology submission and revisions PPROMEXIL follow-up study  
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9 609 **Table 2.** WHO trial registration data set  
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11 610 **Additional file 1.** SPIRIT checklist for reporting randomised trials  
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13 611 **Additional file 2.** SPIRIT Schematic diagram of enrolment PPROMEXIL follow-up  
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15 participants.  
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17 613 **Additional file 3.** GRIPP2 short checklist PPROMEXIL follow-up  
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19 614 **Additional file 4.** Patient information PPROMEXIL Follow-up (English version)  
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21 615 **Additional file 5.** Direct Acyclic Graph (DAG) figure  
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23 616 **Additional file 6.** Authors PPROMEXIL randomised controlled trials.  
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Figure 1. Overview of PPROMEXIL follow-up participants

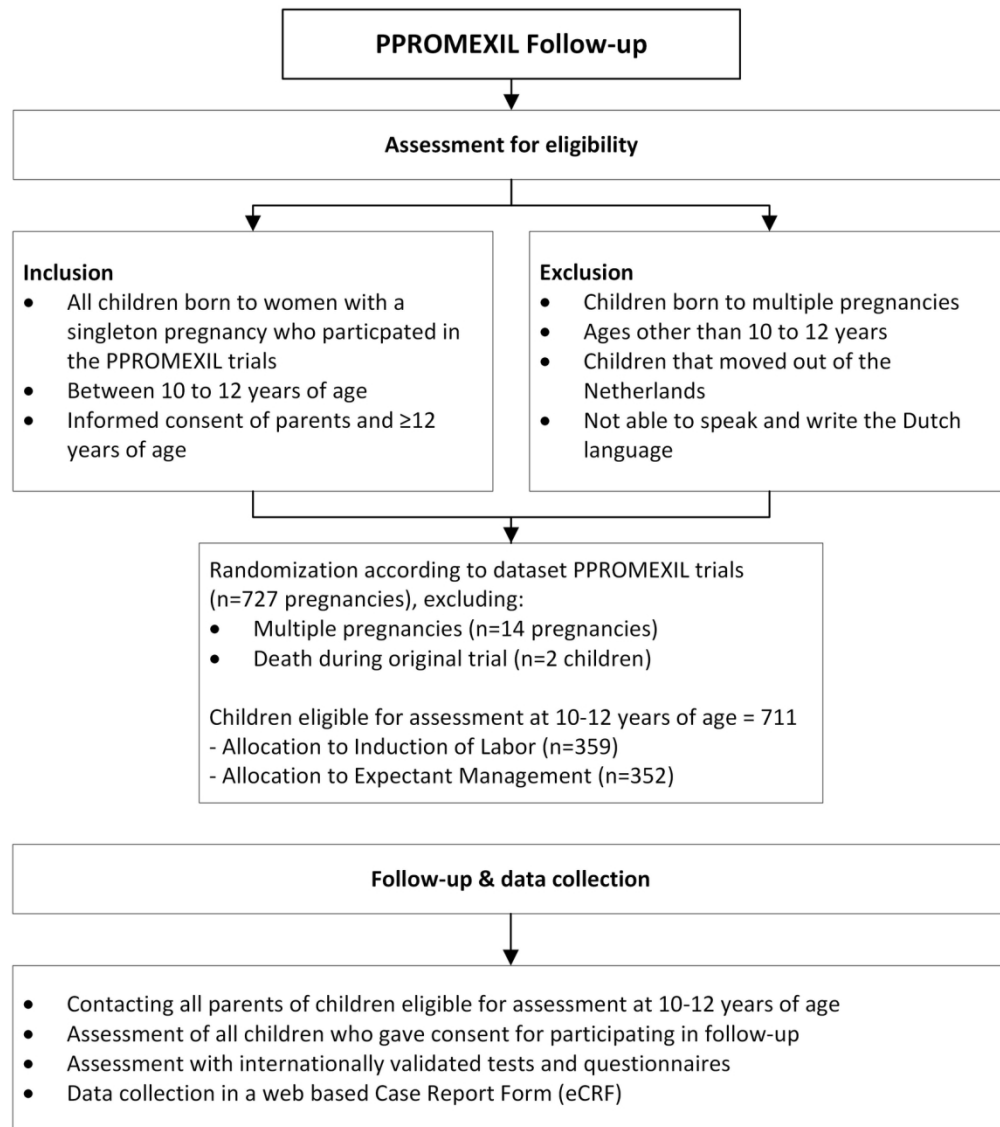


Figure 1. Overview of PPROMEXIL follow-up participants

144x170mm (300 x 300 DPI)

**Additional file 1. SPIRIT checklist for reporting randomized trials**

Section/item	Item No	Description	Adressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 10, 25-26
	2b	All items from the World Health Organization Trial Registration Data Set	5, 10, 25-26 Table 2
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	5, 25-27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 27
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10, 11

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

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4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-17
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13	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10, 17, Figure1, Additional file 2
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20	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18, 19
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26	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11, 12
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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36	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-12
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46	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-12
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52	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-12
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4	Blinding	17a	Who will be blinded after assignment to interventions
5	(masking)		(eg, trial participants, care providers, outcome
6			assessors, data analysts), and how
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9		17b	If blinded, circumstances under which unblinding is
10			permissible, and procedure for revealing a participant's
11			allocated intervention during the trial
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#### Methods: Data collection, management, and analysis

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16	Data collection	18a	Plans for assessment and collection of outcome,
17	methods		baseline, and other trial data, including any related
18			processes to promote data quality (eg, duplicate
19			measurements, training of assessors) and a
20			description of study instruments (eg, questionnaires,
21			laboratory tests) along with their reliability and validity,
22			if known. Reference to where data collection forms can
23			be found, if not in the protocol
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28		18b	Plans to promote participant retention and complete
29			follow-up, including list of any outcome data to be
30			collected for participants who discontinue or deviate
31			from intervention protocols
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34	Data	19	Plans for data entry, coding, security, and storage,
35	management		including any related processes to promote data
36			quality (eg, double data entry; range checks for data
37			values). Reference to where details of data
38			management procedures can be found, if not in the
39			protocol
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43	Statistical	20a	Statistical methods for analysing primary and
44	methods		secondary outcomes. Reference to where other details
45			of the statistical analysis plan can be found, if not in
46			the protocol
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49		20b	Methods for any additional analyses (eg, subgroup and
50			adjusted analyses)
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53		20c	Definition of analysis population relating to protocol
54			non-adherence (eg, as randomised analysis), and any
55			statistical methods to handle missing data (eg, multiple
56			imputation)
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3 **Methods: Monitoring**  
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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10, 23-25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11, 24
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA

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4	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24-28
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
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19	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
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24	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11, 26, 27
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33		31b	Authorship eligibility guidelines and any intended use of professional writers	27
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37		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	27
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41	<b>Appendices</b>			
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43	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10, 11, 23, 29 additional file 4
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48	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license

**Additional file 2.** SPIRIT schematic diagram of schedule of enrolment, interventions, and assessments of the women participating in PPROMEXIL trials and children participating in PPROMEXIL follow-up

	STUDY PERIOD			STUDY PERIOD		
	Original PPROMEXIL trials - women			PPROMEXIL Follow-up - children		
	Enrolment original trials	Allocation original trials	Outcomes original trials	Enrolment follow-up study	Assessment follow-up study	Close-out
TIMEPOINT	<i>Women with PPROM between 34 and 36+6 weeks of gestation</i>	t = 0	<i>Pregnancy, childbirth and neonatal period</i>	<i>After 10 – 12 years</i>	<i>Age 10-12 years</i>	<i>Age 10-12 years</i>
ENROLMENT:						
Eligibility screen	X			X		
Informed consent	X			X	X	
Allocation		X				
INTERVENTIONS:						
Induction of Labor		X				
Expectant Management		X				
ASSESSMENTS:						
Baseline variables	X	X		X		
Outcome variables			X		X	X



**Additional file 3. GRIPP2 short form**

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	8, 20-21
2: Methods	Provide a clear description of the methods used for PPI in the study	8, 20-21
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	8
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	NA
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	NA

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3 **Additional file 4.** Patient information PPROMEXIL Follow-up (English version)  
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## 8 **Patient information** 9 **PPROMEXIL Follow-up trial**

### 10 11 12 **Child outcomes after induction of labour or expectant** 13 **management in women with preterm prelabour rupture of** 14 **membranes between 34-37 weeks of gestation: the PPROMEXIL** 15 **Follow-up trial, a long-term follow-up study of the randomised** 16 **controlled trials PPROMEXIL and PPROMEXIL-2.** 17 18 19 20 21 22 23 24

25 Dear Sir/Madame,  
26

27 We would like to inform you on this research project called: 'Child outcomes after induction of  
28 labour or expectant management in women with preterm prelabour rupture of membranes  
29 between 34-37 weeks of gestation: the PPROMEXIL Follow-up trial, a long-term follow-up  
30 study of the randomised controlled trials PPROMEXIL and PPROMEXIL-2.'. You and your  
31 child have been asked to take part in a medical-scientific study. Participation requires your  
32 written consent. In this letter we would like to inform you on the purpose of this research  
33 project and any advantages or disadvantages that it may hold for you. Please read this  
34 information carefully and do not hesitate to ask the investigator for an explanation if you have  
35 any questions. You can also ask the independent expert, who is mentioned at the end of this  
36 document, for additional information regarding the study protocol (page 4). And you may also  
37 discuss it with your partner, friends or family. Additional (general) information about  
38 participating in a study can be found in the enclosed general brochure on medical research.  
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#### 43 **Introduction**

44 In the past you have participated in a trial called: PPROMEXIL or PPROMEXIL-2. You have  
45 participated in this trial because during your (last) pregnancy you have been diagnosed with  
46 premature preterm rupture of the fetal membranes (PPROM) at 34-37 weeks' gestational  
47 age. You have been treated with either expectant management or induction of labor. Short-  
48 term outcomes of your pregnancy and your child have been assessed at that time. In the  
49 proposed follow-up trial we would like to investigate offspring's long-term outcomes of  
50 women who participated in the PPROMEXIL trial; such as offspring's cognitive- and  
51 neurodevelopment, motor skills, behavioral development and general health.  
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#### 55 **Purpose of the research protocol**

56 The goal of this study is to assess the long-term effects on children born to mothers whose  
57 pregnancy was complicated by PPROM between 34-37 weeks and who were treated with  
58 either induction of labor or expected management (PPROMEXIL and PPROMEXIL-2 trial).  
59 We would like to investigate child's cognitive development (intelligence), neurodevelopment  
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3 (fine and gross motor skills), academic attainment (school results), behavioral development  
4 and general health (diseases, hospital admissions, respiratory problems, but also length,  
5 weight, growth).  
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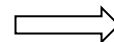
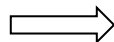
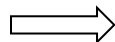
### 8 **What participation involves**

9 If you decide to participate in our research protocol we will contact you by phone. All data will  
10 be collected during one visit in a local or academic hospital in the neighborhood. During this  
11 visit children will be assessed on cognitive- and neurodevelopment and general health. Also  
12 physical examination will be obtained. Assessment of children has a playful approach, is  
13 enjoyable for most children and is not invasive. Furthermore, we will ask you to fill out  
14 questionnaires. Filling out these questionnaires will cost approximately 35 minutes. If  
15 necessary we would like to ask your permission to look up details on your (last) pregnancy  
16 and delivery in your medical chart. Furthermore, we would like to ask permission to obtain  
17 data from your child's consultation bureau or general practitioner.  
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21 Also, we would like to assess your child's academic attainment and school performance.  
22 Therefore we would like to ask the teacher at school to fill out a short questionnaire. We will  
23 ask the teacher whether your child needs any special education or additional support  
24 teaching.  
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27 If appreciated you can receive a short report on your child's cognitive, motor and behaviour  
28 development as measured by the different neurodevelopmental tests (WISC-V-NL, M-ABC-2,  
29 and CBCL). This short report will give information on total test scores and will tell you  
30 whether the test results of your child are above, on or below average. If the test results are  
31 below average, we will be advise you to contact your general practioner or a psychologist (in  
32 Dutch: 'GZ psycholoog of klinisch praktiserend psycholoog') for further help and  
33 interpretation of the different test scores.  
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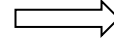
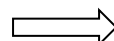
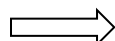
**Summary of study protocol**



During your (last) pregnancy you have participated in the PPRMEXIL trial

Short term outcomes of your child have been assessed shortly after birth

Years passed by and we would like to know how your son or daughter is developing. How is he/she doing at school? And is he/she good at sports?



We would like to investigate your son or daughter in a local hospital in your neighborhood during a single visit

Together we will make some tests. Some of these tests may be easy, while others could be a little bit more difficult

Also, we would like to investigate whether he or she is good at sports. And a physical examination will be obtained.



We would like to ask you to fill out four questionnaires about your son or daughter

### **Possible advantages and disadvantages**

If you and your child participate in this research project it will cost time. Assessment of children has a playful approach, is enjoyable for most children and is not invasive. Participation in this trial is not associated with any risks.

You will not experience any personal benefit from participation in this study. However, your participation may contribute to more knowledge on the long-term (treatment) effects of induction of labour or expectant management on women's offspring after preterm prelabor rupture of the fetal membranes (PPROM) at a gestational age of 34-37 weeks.

### **Voluntary participation**

It is up to you to decide whether or not you and your child will participate in the study. Participation is voluntary. If you do participate in the study, you can always change your mind and decide to stop, at any time during this study, without stating a reason. The data collected until that time will still be used for the study. Your participation in this research will not change any decision making and quality of care that would be normally given to you or your child.

### **Confidential information**

We assure that all data collected during the study will remain confidential. Data will be obtained in a coded manner. The investigator is the only person who will know which code you have. The key to the code will stay with the investigator. In the reports about the study only use this code will be used. You will not find your name in scientific papers.

Some people may access your medical and personal data. This is to check whether the study has been conducted in a good and reliable manner. General information about this policy can be found in the general brochure on medical research. People who may access your and your child's data are: the study team, a monitor of the study and the Healthcare Inspectorate. They will keep the data a secret. If you sign the consent form, you consent to your medical and personal data being collected, stored and accessed. The investigator will store your data for 15 years.

### **Study subject insurance**

This study is not associated with any risks for you or your child. Therefore, the Academic Medical Center (AMC) does not need to take out additional insurance.

### **Compensation for participation**

You and your child will not be paid for your participation in this study. You will be reimbursed for your travel costs.

### **Signing the consent form**

When you have had sufficient time for reflection, you will be asked to decide on participation in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participation in the study. The signature sheet is kept by your attending physician. You will get a copy or a second copy of this consent form.

**Finally**

If you have any questions, please contact the research team. You can contact one of the investigators (Noor Simons, PhD student, number; 020 – 5661470) or with the principal investigator in the AMC (Prof. dr. E. Pajkrt, gynecologist-perinatologist, number: 020 – 5661279). If you would like any independent advice about participation in this study, you may contact Dr. J.W. Ganzevoort, gynaecologist. He knows about the study but is not involved in it. Contact details: Dr. J.W. Ganzevoort, gynaecologist, department of Obstetrics and Gynaecology, Academic Medical Center (tel: 020-56 63769).

Thank you for your attention.

Kind Regards,

Prof. dr. E. Pajkrt,  
Principal investigator  
Professor Fetal and Maternal Medicine  
Department of Gynecology and Obstetrics  
Academic Medical Center, Amsterdam

Prof. dr. T. Roseboom  
Professor of Early Development and Health  
Department of Clinical Epidemiology, Biostatistics and Bioinformatics  
Department of Gynecology and Obstetrics  
Academic Medical Center, Amsterdam



**Informed consent PPROMEXIL Follow-up - parents**

- ✓ I have read the information sheet. I was also able to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether me and my child will participate in this study.
- ✓ I know that participation is voluntary. I know that me and my child may decide at any time not to participate after all or to withdraw from the study.
- ✓ I know that some people will be able to access this person's personal data. These people are listed in this information sheet.
- ✓ I give permission for information to be requested from my gynaecologist about my pregnancy and delivery.
- ✓ I give permission to fill out questionnaires about my child, and I agree with one physical exam and one neurodevelopmental exam with my child (WISC-V and M-ABC-2).
- ✓ I give permission for information (regarding myself or my child) to be requested from my general practitioner or the GGD ('consultatiebureau').
- ✓ I know that it's possible to be contacted in the future (by post or telephone) after this study for another follow-up research project, if I give consent for this.
- ✓ I consent to my data and data regarding my child being stored at the research location for another 15 years after this study.

**I agree to participation in this study**

Date: \_\_\_\_ - \_\_\_\_ - \_\_\_\_\_

First and last name child: .....

Child's date of birth: .....

First and last name child's parent/guardian: .....

Signature child's parent/guardian:

First and last name child's second parent/guardian: .....

Not applicable, because:.....

Signature child's second parent/guardian:



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**Additional:**

I give consent for being contacted again (by post or by telephone) after this study for a follow-up study

I do                       I do not

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To be signed by the AMC investigator:

I declare that I have fully informed this/these person(s) about this study.

Name of investigator (or his/her representative):.....

Date: \_\_\_\_ - \_\_\_\_ - \_\_\_\_

Signature:

*The study subject will receive the full information sheet, together with a copy of the signed consent form.*

For peer review only





**Informed consent PPRMEXIL Follow-up – child 12 year and older**

- I have read the information sheet. I was also able to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether I will participate in this study.
- I know that participation is voluntary. I know that me and my child may decide at any time not to participate after all or to withdraw from the study.
- I know that some people will be able to access this person’s personal data. These people are listed in this information sheet.
- I give permission to fill out one questionnaire, and I agree with one physical exam and one neurodevelopmental exam (WISC-V and M-ABC-2).
- I know that it’s possible to be contacted in the future (by post or telephone) after this study for another follow-up research project, if I give consent for this.
- I consent to my data being stored at the research location for another 15 years after this study.

I have read all above and the information letter and want to participate with this research.

Date: \_\_\_\_ - \_\_\_\_ - \_\_\_\_\_

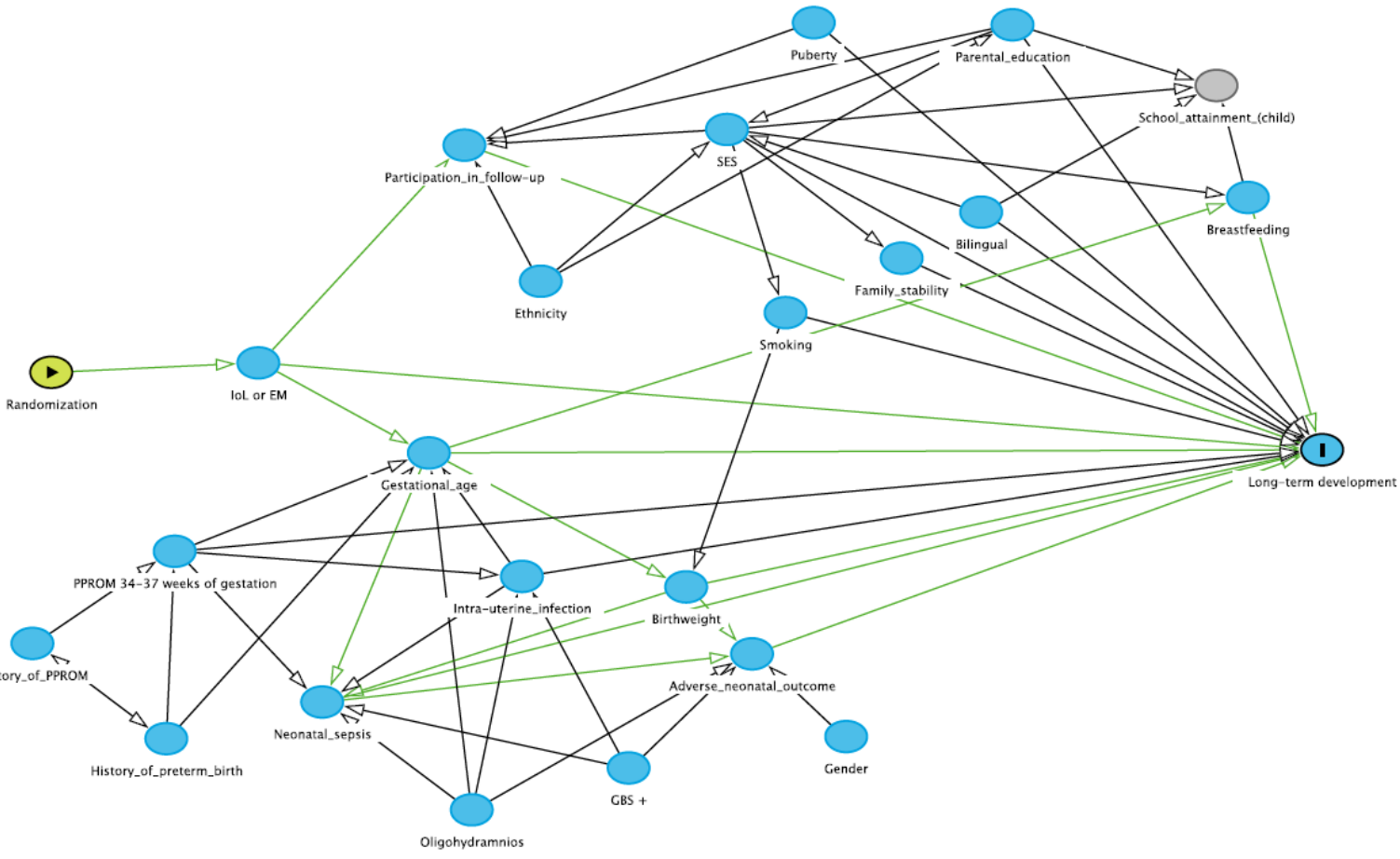
First and last name child:.....

Date of birth child: .....

Signature child: .....

My parent(s)/guardian(s) also agree with participation in this study and sign informed consent on a separate form.

Additional file 5. Direct Acyclic Graph (DAG) identifying potential confounding measures



view only

**Additional file 6.**

Contributors to the PPROMEXIL and PPROMEXIL-2 trials

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