

1 Effects at 3 Months Corrected Age of a Parent-Administered Exercise Program in the  
2 Neonatal Intensive Care Unit: A Randomized Controlled Clinical Trial

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34

35 **Abstract**

36 **Background.** Despite the risk of delayed motor development in infants born preterm,  
37 knowledge about interventions in the Neonatal Intensive Care Unit (NICU) and the effects of  
38 dosing is sparse.

39 **Objective.** To examine effectiveness of a parent-administered exercise program in the NICU  
40 on motor outcome at three months corrected age (CA) and the effect of dosing on motor  
41 performance.

42 **Design.** Randomized clinical trial.

43 **Setting.** University Hospitals in Tromsø, Trondheim and Oslo, Norway

44 **Participants.** 153 infants with gestational age  $\leq$  32 weeks at birth were randomly assigned to  
45 intervention or control groups.

46 **Intervention.** A 3-week parent-administered intervention designed to facilitate movements in  
47 preterm infants was performed in the NICU. Parents were asked to administer the intervention  
48 10 minutes twice a day.

49 **Measurements.** Test of Infant Motor Performance (TIMP) was used to assess short-term  
50 outcome at three months CA.

51 **Results.** No significant difference in the TIMP z-score was found between intervention and  
52 control groups at follow-up three months CA, but a significant positive relationship was found  
53 between total intervention dose and TIMP z-scores. The adjusted odds of having a clinical z-  
54 score  $<0$  at three months CA was about 6 times higher for infants with less than median  
55 intervention time than for infants with a longer intervention time.

56 **Limitations.** The number of infants born before 28 weeks was small. A spillover effect in  
57 favor of the control group was possible. We do not know if the infants received physical  
58 therapy after discharge from the hospital.

59 **Conclusions.** There was no difference in motor performance between the intervention group  
60 and the control group at three months CA. However, an increased intervention dose was  
61 positively associated with improved motor outcome.

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63 Words manuscript: **4317**

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85 **Introduction**

86 Despite increased survival rates for infants born preterm<sup>1,2</sup>, adverse neurological outcomes are  
87 associated with low birthweight preterm infants.<sup>1,3</sup> The last trimester of pregnancy is  
88 associated with rapid brain development.<sup>4</sup> The **presence of preterm birth may contribute to**  
89 **a disruption** of genetically programmed patterns of brain development associated with  
90 factors such as gestational age at birth, clinical stability, acquired brain injury,  
91 bronchopulmonary dysplasia, and non-optimal environmental influences.<sup>5-7</sup> There is growing  
92 evidence that neuroplasticity facilitates structural and functional reorganization of the brain  
93 through experience and active participation,<sup>8,9</sup> implying that early intervention may alter  
94 neurodevelopment in infants born preterm.<sup>6</sup>

95  
96 A number of early intervention programs aimed at improving outcomes for infants born  
97 preterm have been studied.<sup>10-13</sup> The most effective are those involving both the parent and the  
98 infant.<sup>6,13,14</sup> Many of these interventions have demonstrated significant and lasting effects on  
99 cognitive and behavioral outcomes in infants.<sup>15,16</sup> While the effects on motor outcomes are  
100 less robust,<sup>13</sup> interventions associated with improved motor outcomes specifically focused on  
101 motor skills.<sup>13,14</sup> These programs commonly involve both physical therapists (PTs) and  
102 parents<sup>6</sup> with the aim of moving the infant or **assisting the infant to move** into a variety of  
103 positions including facilitation of head and hands to midline.<sup>14</sup> Some studies have  
104 demonstrated intervention effects associated with positive motor outcome up to 24 months  
105 corrected age (CA),<sup>13,14</sup> but the duration and dosage of the activities vary.<sup>6</sup> Therefore, it  
106 remains unclear when to begin the interventions, and what dosages are most effective to  
107 improve motor skills.

108

109 The “Norwegian Physiotherapy Study in Preterm Infants” (NOPPI), a multicenter randomized

110 controlled clinical trial (RCT), evaluates whether a parent-administered intervention in the  
111 Neonatal Intensive Care Unit (NICU) improves motor outcomes of infants born preterm  
112 during the NICU stay and up to 24 months CA.<sup>17</sup> A 3-week individualized intervention  
113 program was designed to facilitate postural symmetry through balanced activation of ventral  
114 and dorsal postural muscles and incorporated activities as a basis for functional position  
115 changes. The authors previously reported improved motor outcomes on the Test of Infant  
116 Motor Performance (TIMP) from 34 to 37 weeks postmenstrual age (PMA), which favored  
117 the intervention group with an effect size of 0.4.<sup>18</sup> However, based on the General Movement  
118 Assessment, there was no difference between intervention and control groups in terms of  
119 fidgety movements<sup>19</sup> or movement quality at three months CA.<sup>20</sup> The present article reports  
120 on outcomes on the TIMP at three months CA and a post hoc analysis between intervention  
121 time and TIMP outcomes. Based on the positive findings **at 37 weeks PMA**, when the  
122 intervention ended, we hypothesized continued positive progress in overall motor  
123 development for infants in the intervention group compared with those in the control group.  
124 **The following** questions are addressed in this paper: 1) Does functional motor outcome at  
125 three months CA differ between groups? 2) Is there a relationship between the amount of  
126 intervention received and motor performance in the intervention group?

127

## 128 **Methods**

### 129 **Design Overview**

130 The study was a pragmatic, multicenter, single-blinded RCT assessing the effect of a  
131 preventive physical therapy program carried out in the NICU. In this study pragmatic implies  
132 that the RCT addresses the intervention as it occurs in routine clinical practice and not in an  
133 ideal setting. The study was conducted at three Norwegian hospitals (University Hospital of  
134 North Norway, Tromsø; St. Olav's University Hospital, Trondheim; and Oslo University

135 Hospital, Ullevål). Ethical approval was obtained from the Regional Ethics Committee (REC  
136 North: 2009/916-7). The data presented in this article comprise a part of the RCT. The  
137 analysis of the complete dataset is ongoing. The full study is registered at ClinicalTrials.gov  
138 NCT01089296.

139

## 140 **Setting and Participants**

141 **Study population and sample size.** Participants were recruited between March 2010 and  
142 October 2014. All infants born at gestational age (GA)  $\leq 32$  weeks, deemed medically stable at  
143 34 weeks PMA, and whose parents understood and spoke Norwegian, were eligible. Triplets  
144 and higher pluralities, infants with malformations or syndromes, and infants having  
145 undergone major surgery were excluded. Parents were invited to participate in the study one  
146 week prior to the planned initiation of the intervention at PMA 34 weeks. The study was  
147 explained, and parents who agreed to participate signed an informed consent.

148

149 Sample size was calculated based on the primary outcome of the NOPPI, Peabody  
150 Developmental Motor Scales-II scores<sup>21</sup> at 24 months CA and **those results will be**  
151 **presented in a separate paper.** A difference of 0.5 SD between the groups was considered to  
152 be clinically significant. To ensure a statistical power of 80% was achieved to detect this or a  
153 larger difference at 0.05 ( $\alpha$ ) significance level, 63 infants in each group were required. We  
154 planned to recruit 150 infants to account for dropouts and the impact of including twins.

155

## 156 **Randomization and Intervention**

157 **Randomization.** A web-based system developed and administered by the Unit of Applied  
158 Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian  
159 University of Science and Technology, Trondheim, Norway, was used for randomization.

160 Stratification was based on GA at birth (<28 week and  $\geq$ 28 weeks) and hospital. Twins were  
161 assigned to the same group because the intervention protocol made it impossible to withhold  
162 group assignment from the parents and the physical therapist who taught the intervention to  
163 the parents.

164

165 **Intervention.** The intervention has previously been described in detail<sup>17</sup> and was a modified  
166 version of Girolami's<sup>22</sup> handling and motor stimulation program for preterm infants. The  
167 intervention employed **guided** movement to improve postural control in prone, supine, side-  
168 lying and supported sitting. The primary aims were to improve head and trunk control and  
169 antigravity midline orientation of head, arms and legs in each position. The intervention in the  
170 positions mentioned above incorporated minute movements in all planes and intermittent  
171 adjusted compression over relevant muscle groups and joints. We added activities in which  
172 the infant was guided from supine to side-lying and from supine through side-lying to upright  
173 supported sitting. In the NOPPI study, the parent was trained by the PT to perform the  
174 intervention daily at the bedside. **Daily intervention was possible because the structure of**  
175 **the Norwegian maternity leave supports the opportunity for parents who come daily to**  
176 **the NICU to be with their infants.** The protocol also emphasized communication and social  
177 interaction between parent and infant.

178

179 The parent-administered intervention consisted of 15 different "play-exercises" that the PT  
180 could choose from based on each infant's tolerance for movement and level of development  
181 demonstrated on the NOPPI baseline assessment. One or more activities in each position of  
182 the four positions were always represented. The PT met with the parents for three sessions to  
183 teach, revise and support parent learning. During session one, the PT explained and  
184 demonstrated the play-exercises for the parent. The PT taught the parents about physiological

185 and behavior responses observed in preterm infants and strategies to appropriately respond to  
186 these cues. Emphasis was placed on awareness of the infant`s cues before, during and after the  
187 play-exercises. The parent received a “Play-Book” that contained photos and written  
188 instructions for each of the exercises. During the second session, the parent performed the  
189 intervention under the supervision of the PT. **The PT observed the parent’s performance of**  
190 **the exercises and provided input to enhance the delivery of each exercise in the protocol.**  
191 One week later, the PT scheduled a third consultation to answer questions and clarify delivery  
192 of the protocol. **Parents were invited to contact the PT if they were in need of additional**  
193 **support or clarification regarding the exercise protocol.**

194

195 Per the protocol, the parent was asked to administer the intervention up to 10 minutes, twice a  
196 day, for three consecutive weeks beginning at 34 weeks PMA and to **terminate the exercise**  
197 **protocol at 37 weeks PMA.** Parents were told that if the infant showed signs of stress, they  
198 could pause the intervention to calm the infant or terminate the session. A booklet containing  
199 boxes was provided for parents to record administration and duration of the intervention  
200 protocol twice daily. Parents were also asked to provide explanations when the intervention  
201 was not performed or if it was terminated. Regardless of adherence to the protocol, no actions  
202 were taken to alter compliance. Therefore, when fidelity was not being met, there were no  
203 actions taken.

204

205 All three NICUs applied principles from the Newborn Individualized Developmental Care  
206 and Assessment Program (NIDCAP)<sup>23</sup> as standard nursing care. If discharged from the  
207 hospital prior to 37 weeks PMA, the parents were asked to continue the intervention at home  
208 until their infant reached the termination age of the program. The infants in the control group



209 received no parental intervention, but parents were instructed in general information. Details  
210 of physical therapy provided after hospital discharge for either group are unknown.

211

## 212 **Outcome Measures**

213 **The primary aim of this analysis was to evaluate the difference in motor outcome**  
214 **between the intervention group and the control group on the TIMP at three months CA.**

215 A secondary outcome was the strength of the association between the total intervention time  
216 received and motor outcome on the TIMP.

217

## 218 **Procedure for baseline assessment at 34 weeks Post Menstrual Age**

### 219 *Test of Infant Motor Performance Screening Items*

220 Prior to randomization, a baseline assessment of motor development was performed at 34  
221 weeks PMA using the Test of Infant Motor Performance Screening Items (TIMPSI). The  
222 TIMPSI is a screening version of the TIMP (see below) and is valid for use from 34 weeks  
223 PMA until five months CA. To establish inter-rater reliability, the testing therapists attended a  
224 two-day training course on administration and scoring of the TIMP.<sup>24</sup> The therapists also met  
225 five times to discuss and reach consensus about the scoring based on videotaped TIMP  
226 assessments. **Moreover,** raters completed the researcher reliability protocol developed by the  
227 TIMP publisher. All NOPPI testers achieved a reliability level of  $>.90$ .

228

229 The TIMPSI, composed of three subsets of items from the TIMP, takes approximately 20  
230 minutes to administer. Depending on the infant`s score on the first set of 11 items, the  
231 examiner is directed to administer items identified as the “easy set” (ten items) or the “hard  
232 set” (eight items). Both the TIMP, and consequently the TIMPSI, address selective  
233 movements and postural control in supine, prone, supported sitting and standing, items which

234 aligned well with the main goals of the intervention. The TIMPSI test results were used to  
235 individualize the treatment protocol for each infant. At each hospital, the PT who  
236 administered the TIMPSI also taught the parent the intervention. Background factors at  
237 baseline were collected from interviews with the parents and from the medical records. Thus,  
238 the testing therapist was not blinded to knowledge of infant risk factors, baseline motor  
239 performance, or subsequent group assignment.

240

## 241 **Procedure for outcome assessment at three Months Corrected Age**

### 242 *Test of Infant Motor Performance*

243 **At three months corrected age**, a PT at each hospital blinded to baseline test scores and  
244 group assignment administered the TIMP. If the PT assigned to administer the post-  
245 intervention assessment inadvertently learned the group assignment but was the only person  
246 available, the test was video recorded and later scored by a PT unaware of group assignment.

247

248 The TIMP assesses postural control and selective movements and can be administered from  
249 34 weeks PMA until five months CA, and standards for two-week windows were identified  
250 when the test was normed. The TIMP has 13 Observed Items and 29 Elicited Items and takes  
251 on average 30 minutes to administer. Studies have demonstrated that the TIMP is responsive  
252 to intervention in preterm infants.<sup>18,25</sup> TIMP raw scores were transformed into z-scores based  
253 on the normative performance of 990 U.S. infants.<sup>26</sup> In the present study this z-score is  
254 referred to as the “clinical z-score”. A positive result indicates that the infant scores are above  
255 the mean of the normative group; a negative score indicates that the infant scores are below  
256 the mean.<sup>26</sup> It was intended that all post-testing be administered within the same two-week  
257 normative window; as close to the middle of the 12-13-week corrected age window as  
258 possible. Due to circumstances such as weather conditions and/or illness of the child or

259 parent, it was not always possible to perform the assessment during the preferred window.  
260 However, the infants' clinical z-scores were calculated for the appropriate CA at testing based  
261 on the normative table in the TIMP Manual.<sup>27</sup>

262

263 In a previous publication from the same trial,<sup>18</sup> the TIMP raw scores at 37 weeks PMA were  
264 calculated applying an alternative formula to calculate a statistical z-score, which results in a  
265 different mean and standard deviation. Using the infants' clinical z-scores does, however, give  
266 a more accurate measure of their functional motor development.

267

### 268 **Statistical Analysis**

269 A modified intention-to-treat analysis was performed; in case of missing values, the last  
270 measurement was carried forward for endpoint analysis. At baseline, differences between the  
271 intervention group and the control group were tested using chi-square-test or independent  
272 samples t-test. To examine whether the TIMP clinical z-score at 37 weeks PMA or at three  
273 months CA differed between groups, a linear mixed model was applied with adjustment for  
274 hospital as a fixed effect, taking into account the clustering effects of twin pairs by a random  
275 family effect.

276

277 The post hoc analyses were performed as follows: In the intervention group, the relationship  
278 between total intervention time in minutes logged by parents and the TIMP clinical z-scores at  
279 37 weeks PMA and at three months CA was evaluated in a linear model. Total intervention  
280 time was represented by a regression term, with other terms describing the effects of potential  
281 confounders (hospital, sex, birth weight, and mother's education). Correlation between time  
282 used on the intervention and baseline measures that might be related to the infant's health:

283 gestational age, birth weight, number of days on ventilation, number of days on continuous  
284 positive airway pressure was examined using Spearman's rho ( $r_s$ ).

285

286 Infants in the intervention group were further divided into two groups according to the median  
287 total time they received the intervention. For three children, the intervention time was by  
288 chance the median. Thus, there were not the same number of children in the two groups.

289

290 We estimated the odds ratios (OR) for having a clinical z-score below 0, vs. a z-score  $\geq 0$  if  
291 total time used on the intervention was  $<$  the median. Logistic regression analysis with  
292 adjustments for hospital, sex, birth weight, and mother's education was applied. Differences  
293 between groups that might be related to infant health were tested using a chi-square-test or  
294 independent samples t-test. Statistical analyses were performed with IBM SPSS Statistics  
295 version 24 (IBM Corp., Armonk, NY, USA).

296

### 297 **Role of Funding Source**

298 The Norwegian Fund for Postgraduate Training in Physiotherapy (grant number 1/370-00/09),  
299 Oslo, Norway funded this study. The funding source played no role in the design, conduct of  
300 the study or analysis and interpretation of the data.

301

### 302 **Results**

303 Figure 1 shows a flow chart of the 217 invited participants. Consent to participate was  
304 obtained for 153 (71%) children. After baseline assessment, 74 were randomized to the  
305 intervention group and 79 to the control group. Before start of the intervention period, 10 in  
306 the intervention group and three in the control group withdrew, leaving 64 and 76 in each  
307 group, respectively. Three of those who withdrew from the intervention group also withdrew

308 their consent for use of the baseline data. After the intervention was completed at 37 weeks  
309 PMA, but before the 3-months CA assessment, one participant in the control group withdrew  
310 and, for logistic reasons, one was not available for this assessment. Thus, 64 in the  
311 intervention group and 74 in the control group were assessed at three months CA, whereas  
312 baseline data was available for 71 children in the intervention group and 79 children in the  
313 control group.

314

315 Table 1 shows the characteristics of the infants at baseline. There were no significant  
316 differences between the intervention and the control group. With regard to twins, there were 5  
317 pairs in the intervention group and 11 pairs in the control group. However, as shown in Table  
318 1, the actual number of twins in each group is not consistent with the number of sets of twins  
319 because one infant died prior to recruitment and two infants were medically unstable and  
320 could not be recruited for the study. Fewer than 10% in the intervention and 15% in the  
321 control group had a diagnosis of intraventricular hemorrhage, periventricular leukomalacia,  
322 sepsis or bronchopulmonary dysplasia, and no significant group differences were found ( $p$   
323  $\geq 0.34$ ). Moreover, the groups did not differ regarding number of days on ventilation,  
324 continuous positive airway pressure or oxygen ( $p \geq 0.37$ ).

325

326 As shown in Figure 2, **when the baseline TIMPSI scores were recalculated using the**  
327 **clinical z-score calculation method, there was no significant difference between the**  
328 **intervention group and the control group** (estimated mean clinical z-scores = -0.32 (95%  
329 CI: -0.45 to -0.18) and -0.42 (95% CI: -0.54 to -0.30), respectively,  $p=0.43$ ). However, at 37  
330 weeks PMA the intervention group **had significantly** higher estimated **mean clinical z-scores**  
331 **than the control group on the TIMP** (0.03 (95% CI: -0.12 to 0.19) vs -0.24 (95% CI: -0.39  
332 to -0.08),  $p=0.014$ ). **At three months CA, with no intervention after 37 weeks PMA, there**

333 **was** no difference between the groups **on the TIMP** (estimated mean clinical z-scores = -0.04  
334 (95% CI: -0.20 to 0.12) and -0.08 (95% CI: -0.23 to 0.06),  $p=0.57$ ).

335

336 Among the 64 infants in the intervention group, parents of 59 (92%) maintained a record  
337 detailing the number and total time of each session. The mean as well as the median total time  
338 during the 3-week intervention period was 222 minutes or about half the recommended  
339 amount (420 minutes). Reasons for not performing the intervention or spending less than the  
340 intended time were consistently related to the infants' behavioral state (being sleepy, tired,  
341 hungry, or unwell).

342

343 Table 2 shows that there was no association between the intervention time and the TIMP  
344 clinical z-score at 37 weeks CA ( $p=0.42$ ) after multiple adjustments. In contrast, there was a  
345 statistically significant positive relationship between intervention time and the TIMP clinical  
346 z-score at three months CA ( $p=0.003$ ).

347

348 There was no significant correlation between intervention time and baseline measures related  
349 to the infants' health such as gestational age, birth weight, number of days on ventilation,  
350 number of days on continuous positive airway pressure, or number of days on oxygen ( $p$   
351  $\geq 0.26$ ).

352

353 At three months CA, 28 infants had TIMP clinical z-scores  $< 0$ . The adjusted odds of having a  
354 z-score below 0 was about 6 times higher for those whose parent had spent less than 222  
355 minutes on the intervention as compared to those who reported more time (Table 3). The  
356 groups did not differ with regard to a diagnosis of intraventricular hemorrhage, periventricular  
357 leukomalacia, sepsis or bronchopulmonary dysplasia ( $p \geq 0.24$ ).

358

## 359 **Discussion**

360 This study is the first pragmatic, randomized controlled clinical trial evaluating a parent-  
361 administered intervention performed before 37 weeks PMA. It **reconfirms** the results **of** the  
362 37 week follow-up,<sup>18</sup> which showed that at 37 weeks the intervention group had significantly  
363 higher motor scores than the control group. At three months CA, this difference was no longer  
364 significant. **However, we did find that in the intervention group, motor function assessed**  
365 **at three months CA showed a significant positive relationship between increased**  
366 **intervention dosage and improved motor outcome at three months, confirmed in a**  
367 **separate analysis dichotomizing both variables.**

368

369 A recent systematic review,<sup>14</sup> evaluating motor development interventions for infants born  
370 preterm commencing during or post-hospitalization, found that motor interventions focusing  
371 on the infants' active movements in a variety of positions were the most beneficial for  
372 enhancing motor skills from birth to 24 months CA. While the effect diminished over time, at  
373 three months CA the motor-specific interventions showed a large and significant effect size  
374 for motor skills. Most of these interventions included developmental support for the infant  
375 and parenting support and education.<sup>14</sup> Although similarities exist in the activities and  
376 underlying theoretical framework in the previous and present intervention, our findings were  
377 not consistent with a beneficial outcome at three months. Among the reviewed motor  
378 interventions, however, the ones that continued beyond the neonatal period had the strongest  
379 effects on motor development in the longer-term.<sup>14</sup> Therefore one might propose that the  
380 NOPPI intervention performed for three weeks in the NICU, was not long enough to diminish  
381 motor consequences in the long-term.

382

383 **However, an important finding in the present study is the significant linear relationship**  
384 **between increased intervention dosage and improved motor outcome at three months,**  
385 **confirmed in a separate analysis dichotomizing both variables.** There is substantial reason  
386 to attribute the statistical relationship to increased intervention dosage, given recent research  
387 regarding the capacity of the CNS to structurally and functionally change in response to  
388 experience.<sup>28,29</sup> It is well known that experience-dependent neuro-plasticity can cause re-  
389 organization of the developing brain.<sup>9,28,29</sup> Experience-dependent re-organization accentuates  
390 improved adaptive function and learning over time.<sup>4,28</sup> Therefore, it is likely that the improved  
391 motor outcome in the infants who received greater amounts of intervention supports the  
392 concept that dosage matters. An alternative explanation could be that the infants who received  
393 more intervention time were healthier. However, we did not find intervention time was related  
394 to the infants' diagnosis or other baseline health measures. The fact that the significant  
395 association between intervention time and motor outcome was only observed at three months  
396 CA but not at 37 weeks PMA when intervention ended may reflect a more pronounced  
397 tendency for the intervention effect to last longer in infants with a larger intervention dosage.  
398

399 A critical point to consider is that infants received only about half of the prescribed dosage of  
400 the intervention. Parents' reasons for spending less time on the intervention were solely  
401 related to the infants' behavioral state. In contrast, Girolami and Campbell<sup>22</sup> reported no such  
402 problems during treatment sessions for infants that had reached 34 weeks PMA, even though  
403 a comparable handling and motor stimulation program was administered twice daily for 12 to  
404 15 minutes. However, in Girolami and Campbell's study, the PT administered the  
405 intervention. The parents in this study took notice of infant stress cues, but because the  
406 NOPPI lacks data on physiological variables (such as heart-rate) during intervention, it is  
407 difficult to conclude whether the shorter duration of intervention minutes truly indicates the



408 infants couldn't tolerate handling more than once a day. As parents frequently report lower  
409 self-confidence in caring for their tiny infant and increased care-giving burdens after giving  
410 birth prematurely,<sup>6,14,30</sup> we speculate that perhaps parents were unable to comply with the  
411 requested amount of intervention. Therefore, one may argue that monitoring of physiological  
412 variables during administration of the program and examination of parent well-being and  
413 stress would have strengthened the study providing an understanding of reasons preventing  
414 parents from doing the intervention as requested.

415

416 A recent survey<sup>31</sup> of parents compliance with home-exercise programs for children with  
417 developmental disabilities suggests that adherence depends on factors such as self-efficacy,  
418 perception of barriers and ability to perform the program. For parents in the NICU, the  
419 environment presents a context that is often perceived as challenging, strange and scary,  
420 perhaps affecting caregiving activities.<sup>32</sup> Support and guidance provided by the health care  
421 workers is considered of great importance to empower the parents.<sup>32,33</sup> Thus, for parents to see  
422 the importance of preferred frequency and duration of the intervention, they may have  
423 benefited from more training to adjust the intervention protocol based on infant response. This  
424 might have been accomplished by having the PT attend the intervention sessions during the  
425 first week to provide guidance for parental decision-making. Alternatively, another approach  
426 to achieve optimal dosing might be parents performing the intervention once a day and PTs  
427 administering the second intervention. Finally, continuing a home-exercise program after  
428 discharge has also been shown to be effective.<sup>26</sup>

429

430 A strength of this research is that it was a pragmatic randomized multicenter controlled  
431 clinical trial, with blinded outcome assessors and long-term follow-up. The solid  
432 randomization procedures undertaken resulted in homogeneous groups. Moreover, GA was

433 used as an inclusion criterion rather than birth weight, avoiding inclusion of more mature  
434 growth-restricted infants, which would have made the results difficult to generalize. In  
435 addition, no important changes were introduced in the three NICUs during the inclusion  
436 period, with the exception of NOPPI-intervention program.

437

438 **There are several limitations that should be considered.** In this study, the sample size was  
439 based upon power for the test to be administered at 24 months (PDMS) and not the TIMP.  
440 Another possible weakness is the limited number of extremely preterm infants, (born <28  
441 weeks gestation (n=25)) available for recruitment during the study period. However, the  
442 extremely preterm infants enrolled were evenly distributed between the intervention and  
443 control groups diminishing bias related to group differences. Another weakness was a  
444 possible spillover effect in favor of the control group because of the lack of parent blinding.  
445 The potential spillover effect from the intervention group to the control group was reduced by  
446 instructing the parents in the intervention group not to disclose nor communicate the content  
447 of the intervention to other parents in their NICU. Finally, we do not know if the children  
448 received physical therapy after discharge from the hospital.

449

450 **Lastly, we acknowledge that there was an issue with fidelity that relates to the therapy**  
451 **dose received and the motor outcome at three months CA. Because the average**  
452 **intervention dosage was only about half of that intended, we recommend that future**  
453 **research should address whether** 1) infants born preterm are unable to tolerate the  
454 prescribed handling amount, 2) alterations in the parent education methods would increase  
455 compliance, or 3) a combined parent-and-therapist-administered intervention would improve  
456 the likelihood of obtaining the prescribed twice daily intervention dosage.

457

458 **Conclusions**

459 Although there was no significant difference on the TIMP between the two groups at three  
460 months CA, there was a statistically significant positive relationship between total  
461 intervention time and the TIMP clinical z-score. The odds of having a z-score below 0 was  
462 about six times higher for infants who had received less than 222 minutes intervention,  
463 indicating that a parent-administered individualized early motor intervention program in the  
464 NICU can produce a substantial effect on motor development in infants born preterm if the  
465 intervention dosage is at least as high as the median in our intervention group.

466

467 **Acknowledgements**

468 We extend our gratitude to the parents and their infants for their time and willingness to  
469 participate. The authors also gratefully acknowledge the University Hospital of North Norway  
470 HF, St. Olavs University Hospital Trondheim HF and Oslo University Hospital, Ullevål for  
471 their support through arrangements of personnel. Furthermore, we would like to express our  
472 gratitude to The Norwegian Fund for Post-Graduate Training in Physiotherapy for funding.

473

474 **REFERENCES**

475

- 476 1. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of  
477 extremely preterm neonates, 1993–2012. *JAMA*. 2015;314:1039–1051.
- 478 2. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term  
479 outcomes after extreme preterm birth in England: comparison of two birth cohorts in  
480 1995 and 2006 (the EPICure studies. *BMJ Open*. 2012;345:e7976.
- 481 3. Stensvold HJ, Klingenberg C, Stoen R, et al. Neonatal morbidity and 1-year survival of  
482 extremely preterm infants. *Pediatrics*. 2017;139:1-9.
- 483 4. Brodal P. *Central Nervous System: Structure and Function (4th Edition)*. USA: Oxford  
484 University Press; 2010.
- 485 5. Doyle LW, Anderson PJ, Battin M, et al. Long term follow up of high risk children:  
486 who, why and how? *BMC pediatrics*. 2014;14:279.
- 487 6. Spittle A, Treyvaud K. The role of early developmental intervention to influence  
488 neurobehavioral outcomes of children born preterm. *Seminars in Perinatology*.  
489 2016;40:542-548.
- 490 7. Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm  
491 infants. *Seminars in Perinatology*. 2016;40:497-509.
- 492 8. Merzenich MM, Van Vleet TM, Nahum M. Brain plasticity-based therapeutics.  
493 *Frontiers in Human Neuroscience*. 2014;8:1-16.
- 494 9. Mottahedin A, Ardalan M, Chumak T, Riebe I, Ek J, Mallard C. Effect of  
495 neuroinflammation on synaptic organization and function in the developing brain:  
496 Implications for neurodevelopmental and neurodegenerative disorders. *Frontiers in  
497 cellular neuroscience*. 2017;11:190.
- 498 10. Orton J, Anderson Peter J, Ferretti C, et al. Improving the outcome of infants born at  
499 <30 weeks' gestation - a randomized controlled trial of preventative care at home.  
500 *BMC pediatrics*. 2009;9:73.
- 501 11. Kaaresen PI, Rønning JA, Tunby J, Nordhov SM, Ulvund SE, Dahl LB. A randomized  
502 controlled trial of an early intervention program in low birth weight children:  
503 outcome at 2 years. *Early human development*. 2008;84:201-209.
- 504 12. Moore G, Lemyre B, Barrowman N, Daboval T, Moore G. Neurodevelopmental  
505 outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: A meta-  
506 analysis. *Archives of Pediatrics & Adolescent Medicine*. 2013;167:967-974.
- 507 13. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention  
508 programmes provided post hospital discharge to prevent motor and cognitive  
509 impairment in preterm infants. *Cochrane Database of Systematic Reviews*. 2015:1-  
510 107.
- 511 14. Hughes A, Redsell SA, Glazebrook C. Motor development interventions for preterm  
512 infants: A systematic review and meta-analysis. *Pediatrics*. 2016;138:e20160147.
- 513 15. Landsem IP, Handegård BH, Ulvund SE, Tunby J, Kaaresen PI, Rønning JA. Does an  
514 early intervention influence behavioral development until age 9 in children born  
515 prematurely? *Child Development*. 2015;86:1063-1079.
- 516 16. Vanderveen J, Bassler D, Robertson C, Kirpalani H. Early interventions involving  
517 parents to improve neurodevelopmental outcomes of premature infants: a meta-  
518 analysis. *Journal of Perinatology*. 2009;29:343-351.

- 519 17. Øberg GK, Campbell SK, Girolami GL, Ustad T, Jørgensen L, Kaaresen P. Study  
520 protocol: an early intervention program to improve motor outcome in preterm  
521 infants: a randomized controlled trial and a qualitative study of physiotherapy  
522 performance and parental experiences. *BMC pediatrics*. 2012;12:15.
- 523 18. Ustad T, Evensen KAI, Campbell SK, et al. Early parent-administered physical therapy  
524 for preterm infants: A randomized controlled trial. *Pediatrics*. 2016:e20160271.
- 525 19. Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G, Hart HM. *Prechtl's method on the*  
526 *qualitative assessment of general movements in preterm, term and young infants*.  
527 Cambridge: Cambridge University Press; 2004.
- 528 20. Fjørtoft T, Ustad T, Follestad T, Kaaresen PI, Øberg GK. Does a parent-administrated  
529 early motor intervention influence general movements and movement character at  
530 3months of age in infants born preterm? *Early Human Development*. 2017;112:20-24.
- 531 21. Folio M, Fewell R. *Peabody Developmental Motor Scales, Examiner's Manual*. 2 ed.  
532 Austin, Texas: Pro-ed; 2000.
- 533 22. Girolami GL, Campbell SK. Efficacy of a neuro-developmental treatment program to  
534 improve motor control in infants born prematurely. *Pediatric Physical Therapy*.  
535 1994;6:175-184.
- 536 23. Als H, Duffy FH, McAnulty G, et al. NIDCAP improves brain function and structure in  
537 preterm infants with severe intrauterine growth restriction. *Journal of Perinatology*.  
538 2012;32:797-803.
- 539 24. IMPS I. Workshop in the test of infant motor performance. From research to practice.  
540 In. Tromsø, Norway: Girolami, GL; 2011.
- 541 25. Lekskulchai R, Cole J. Effect of a developmental program on motor performance in  
542 infants born preterm. *Australian Journal of Physiotherapy*. 2001;47:169-176.
- 543 26. Campbell SK, Levy KP, Zawacki KL, Liao KP-J. Population-based age standards for  
544 interpreting results on the test of motor infant performance. *Pediatric Physical*  
545 *Therapy*. 2006;18:119-125.
- 546 27. Campbell SK. The test of infant motor performance. Test user's manual version 3.0  
547 for the TIMP version 5. In. Chicago, IL 2012.
- 548 28. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the  
549 developing brain. *European Journal of Paediatric Neurology*. 2017;21:23-48.
- 550 29. Belsky J, de Haan M. Annual research review: Parenting and children's brain  
551 development: The end of the beginning. *Journal of Child Psychology and Psychiatry*.  
552 2011;52:409-428.
- 553 30. Treyvaud K. Parent and family outcomes following very preterm or very low birth  
554 weight birth: A review. *Seminars in Fetal and Neonatal Medicine*. 2014;19:131-135.
- 555 31. Medina-Mirapeix F, Lillo-Navarro C, Montilla-Herrador J, Gacto-Sánchez M, Franco-  
556 Sierra M, Escolar-Reina P. Predictors of parents' adherence to home exercise  
557 programs for children with developmental disabilities, regarding both exercise  
558 frequency and duration: a survey design. *European journal of physical and*  
559 *rehabilitation medicine*. 2017;53:545-555.
- 560 32. Lutz KF, Anderson LS, Riesch SK, Pridham KA, Becker PT. Furthering the  
561 understanding of parent-child relationships: A nursing scholarship review series. part  
562 2: Grasping the early parenting experience—the insider view. *Journal for Specialists*  
563 *in Pediatric Nursing*. 2009;14:262-283.

- 564 33. Nordhov SM. *A randomised clinical trial on the impact of early intervention on*  
565 *parental child-rearing attitudes and cognitive, motor and behavioral outcomes in*  
566 *preterm infants* [PhD]. Institute of Clinical Medicine University of Tromsø 2011.  
567

**TABLE 1.** Baseline characteristics of the infants in the Intervention Group and the Control Group (“usual care”).

	Intervention Group (n=71)	Control Group (n=79)	p-value
Gestational age <28 weeks, n (%)	10 (14)	15 (19)	0.42
Boys, n (%)	36 (51)	44 (56)	0.54
Twins, n (%)	12 (17)	23 (29)	0.08
Has no older siblings, n (%)	41 (58)	54 (68)	0.18
Birth weight, gram, mean (SD)	1417 (417)	1385 (368)	0.62
Social background factors			
Mother’s age, years, mean (SD)	32.1 (5.5)	30.5 (4.9)	0.07
Mother’s education, years, mean (SD)	15.6 (2.7)	14.9 (2.8)	0.15
Father’s education, years, mean (SD)	14.5 (3.0)	14.6 (2.7)	0.83

**Table 2.** Relationship ( $\beta$ -coefficient) between total intervention time and motor performance (TIMP clinical z-score) 37 weeks postmenstrual age, PMA, and 3-months corrected age, CA (n=59)

	37 weeks PMA			3 months CA		
	$\beta$	95% CI	p	$\beta$	95% CI	p
*Total intervention time, hours	0.03	-0.06 to 0.11	0.50	0.14	0.06 to 0.22	0.001
†Total intervention time, hours	0.04	-0.05 to 0.12	0.42	0.14	0.05 to 0.22	0.003

TIMP; Test of Infant Motor Performance

CI, confidence interval

\*Adjusted for hospital

†Additional adjustments for sex, birth weight, mother's education



**TABLE 3.** Odds ratio for a low TIMP clinical z-score by 3 month corrected age (z-score <0) according to intervention-time-categories

	Total		Odds ratio for a clinical z-score < 0			
	z-score < 0	z-score ≥ 0	OR*	95% CI	OR†	95% CI
Intervention time	n=28	n=31				
Low (< 222 min)	19	8	5.9	1.8 to 18.8	5.7	1.7 to 19.1
High (≥ 222 min)	9	23	1.0		1.0	

TIMP; Test of Infant Motor Performance

CI, confidence interval

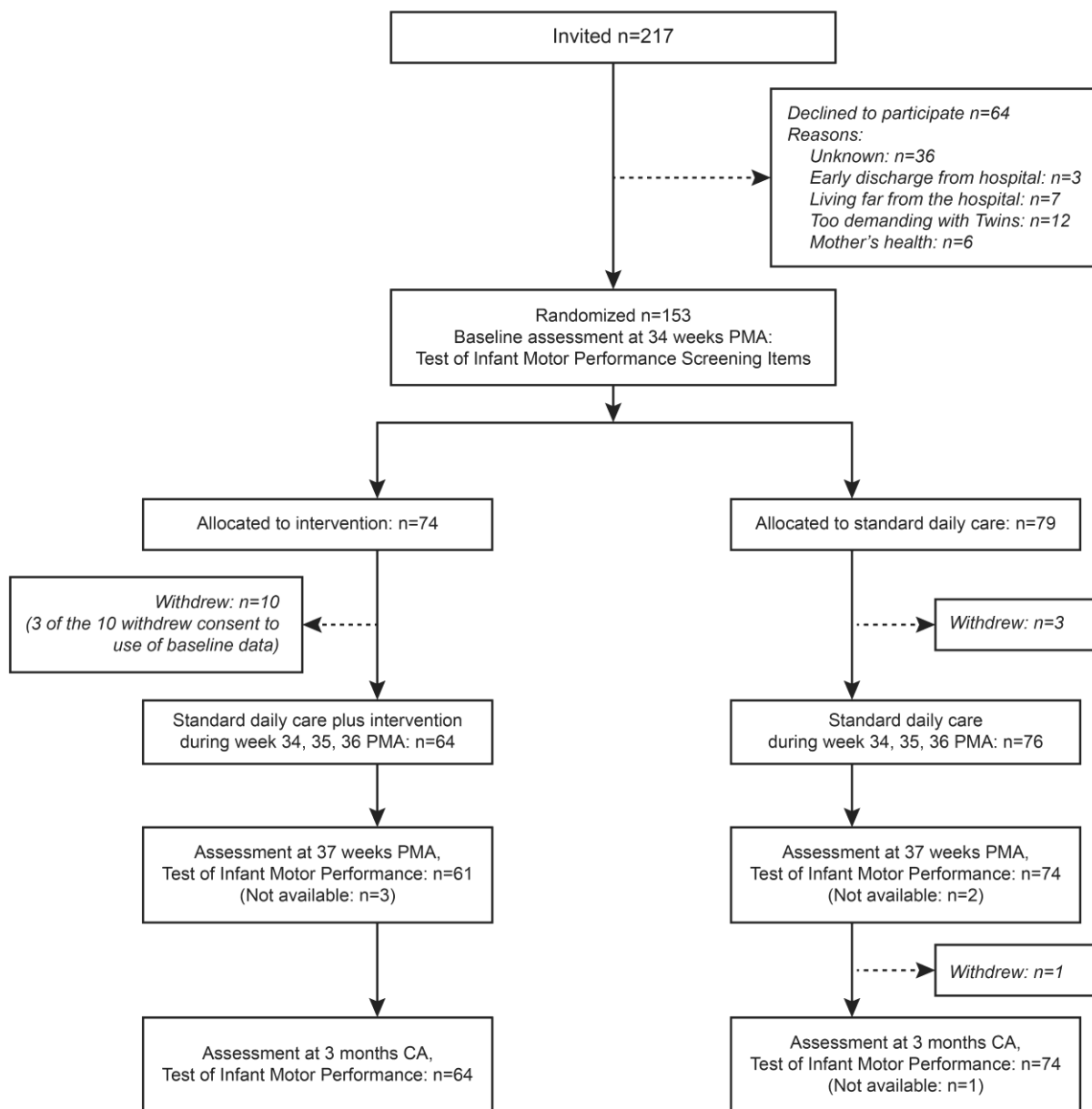
\*Adjusted for hospital

†Additional adjustment for sex, birth weight and mother's education

## **LEGENDS:**

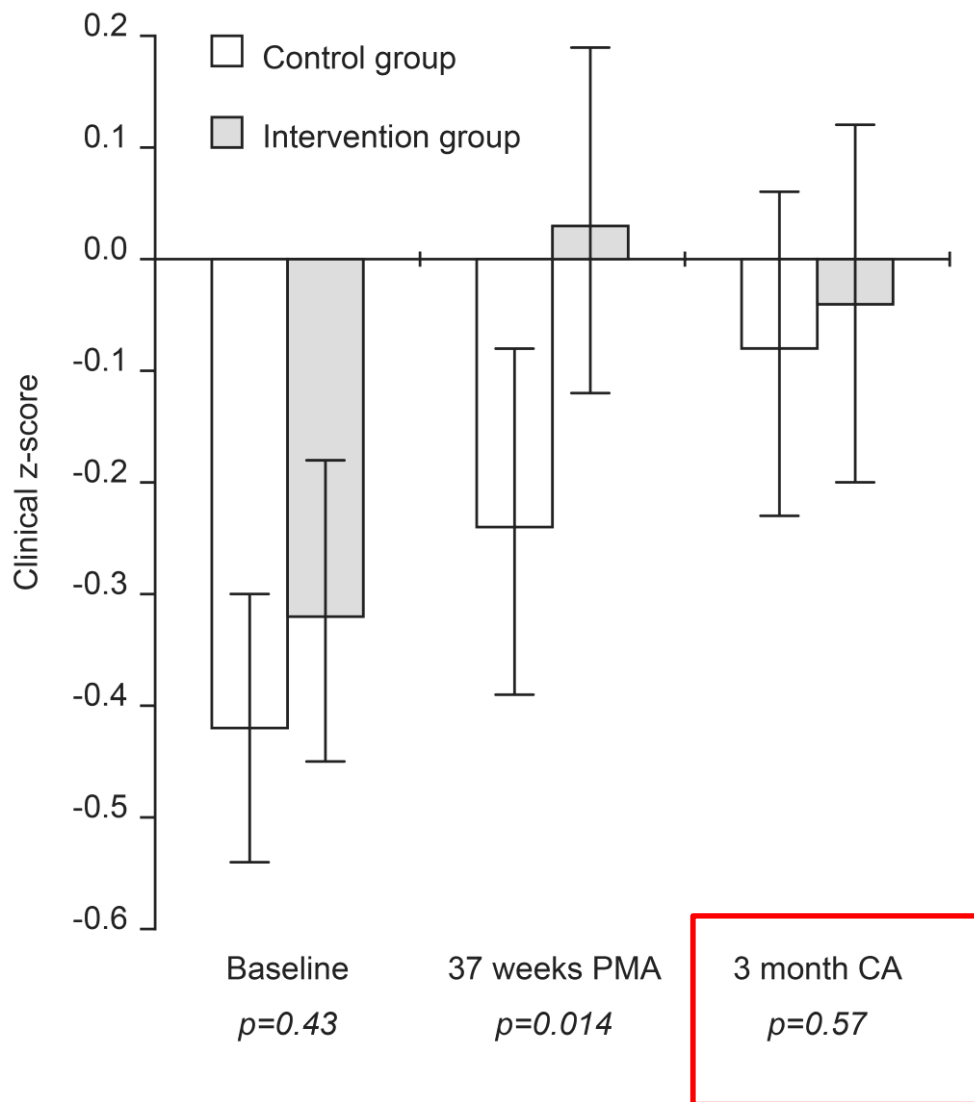
**FIGURE 1.** Flow of the participants through the study

**FIGURE 2.** Motor performance (estimated mean clinical z-score (95 % CI)) in the intervention group and the control group at baseline 34 weeks postmenstrual age, at follow up 37 weeks postmenstrual age (PMA) and at 3-months corrected age (CA) adjusted for clustering effects of twin pairs and hospital.



PMA; Postmenstrual age  
CA; Corrected age

**FIGURE 1.** Flow of the participants through the study



**FIGURE 2.** Motor performance (estimated mean clinical z-score (95 % CI)) in the intervention group and the control group at baseline 34 weeks postmenstrual age, at follow up 37 weeks postmenstrual age (PMA) and at 3-months corrected age (CA) adjusted for clustering effects of twin pairs and hospital.