

## Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS)

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1 **Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional**  
2 **anaesthesia in infancy (GAS): an international, multicentre, randomised controlled**  
3 **equivalence trial.**

4

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88 The corresponding author attests that all authors have seen and approved the final text.  
89

90

91 | **Summary:** [\(Word count: 365\)](#)

92 | Background: In laboratory animals, exposure to most general anaesthetics leads to neurotoxicity  
93 | manifested by neuronal cell death, and abnormal behaviour and cognition. ~~-Some, everal~~ large  
94 | human cohort studies demonstrate an association between general anaesthesia at a young age and  
95 | subsequent neurodevelopmental deficits, but are prone to bias. [Others have found no evidence](#)  
96 | [for an association.](#) We aimed to establish whether general anaesthesia in early infancy has an  
97 | effect on neurodevelopmental outcomes in a randomised controlled trial (RCT).

98 | Methods: In this international assessor-masked equivalence RCT, infants less than 60 weeks'  
99 | postmenstrual age and born at greater than 26 weeks gestation undergoing inguinal  
100 | herniorrhaphies without prior exposure to general anaesthesia or risk factors for neurologic injury  
101 | were recruited. They were randomly assigned to receive either an awake-regional or sevoflurane-  
102 | based general anaesthetic. The primary outcome measure was the Wechsler Preschool and  
103 | Primary Scale of Intelligence-Third Edition (WPPSI-III) Full Scale Intelligence Quotient (FSIQ)  
104 | at 5 years of age. The [primary](#) analysis was as-per-protocol adjusted for gestational age at birth  
105 | and country using multiple imputation to deal with missing data. [An intention-to-treat analysis](#)  
106 | [was also performed.](#) A difference in means of five points was predefined as the clinical  
107 | equivalence margin. This trial is registered with ANZCTR, number ACTRN12606000441516  
108 | and ClinicalTrials.gov, number NCT007566000.

109 | Findings: Between Feb 2007 and Jan 2013, 722 infants were randomised, 363 to the awake-  
110 | regional and 359 to general anaesthesia. The median duration of anaesthesia in the general  
111 | anaesthetic group was 54 minutes. [There were 74 protocol violations in the awake-regional](#)  
112 | [group and 2 in the general anaesthesia group.](#) -Primary outcome data for the as-per-protocol  
113 | analysis were obtained from 205 children in the awake-regional group and 242 in the general  
114 | anaesthesia group. The FSIQ score (mean [standard deviation (SD)]) was 99.08 (18.35) in the  
115 | awake-regional group and 98.97 (19.66) in the general anaesthesia group, with a difference in  
116 | means (awake-regional minus general anaesthesia) of 0.23, 95% Confidence Intervals -2.59 to  
117 | 3.06) showing strong evidence of equivalence. [The results with the intention-to-treat analysis](#)  
118 | [were similar to the as-per-protocol analysis.](#)

119 Interpretation: We found strong evidence that just under an hour of general anaesthesia in early  
120 infancy does not alter neurodevelopmental outcome compared to awake-regional anaesthesia in a  
121 predominantly male study population.

122 Funding: National Institutes of Health (NIH) USA, Food and Drug Administration USA,  
123 Thrasher Research Fund, Australia National Health and Medical Research Council (NHMRC),  
124 Health Technologies Assessment-National Institute for Health Research UK. Australian and  
125 New Zealand College of Anaesthetists, Murdoch Children’s Research Institute, Canadian  
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129 Children’s Hospital Foundation, the Stan Perron Charitable Trust, and the Callahan Estate.

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131

132 **Research in context**

133 **Evidence before this study**

134 We searched Medline and Cochrane controlled trials register (May 20, 2018) for original  
135 research and meta-analyses describing the association between anaesthetic exposure during  
136 childhood and neurodevelopmental outcome.

137 The search terms used were “anesthesia” and “child development” or “anesthesia” and “learning  
138 disorders”. No randomised trials were found except for the interim analysis of this trial published  
139 in the Lancet in 2016 which found equivalence in Bayley-III scores between infants exposed to  
140 either regional or general anaesthesia. The majority of large cohort studies report an association  
141 between surgery before the age of four years and an increased risk for a later diagnosis of a  
142 behavioural problem or poorer academic attainment. In some of the studies the size of the  
143 increased risk is very small, in others it is only seen after multiple exposures. Several, but not all,  
144 of the cohort studies did not find an association with neurocognitive outcome as assessed by  
145 formal IQ testing. Weaknesses in these cohort studies include confounding, bias, heterogeneous  
146 populations at the time of exposure and heterogeneous outcome measures making interpretation  
147 and generalisation problematic.

148 **Added value of this study**

149 We report the 5 year neurodevelopmental outcome results for the GAS trial, the first randomised  
150 controlled trial designed to assess the effect of general anaesthesia in infancy on  
151 neurodevelopmental outcome. We used the most reliable and validated measure of general  
152 intellectual ability, the Wechsler Preschool and Primary Scale of Intelligence-Third Edition Full  
153 Scale IQ score and *found strong evidence for equivalence between awake-regional and just less*  
154 *than one hour of general anaesthesia.* No significant differences were seen in a range of other  
155 neurocognitive and behavioural measures.

156 **Implications of all the available evidence**

157 This randomised controlled trial provides strong evidence that an hour of exposure to a general  
158 anaesthetic during early infancy does not cause measureable neurocognitive or behavioural  
159 deficits at 5 years of age. These results are consistent with the MASK and PANDA cohort



160 | studies. Nearly half the general anaesthetics in infancy are under an hour in duration and thus  
161 | this study should allay some of the concerns generated by the preclinical data and previous  
162 | cohort studies. This trial does not address the possibility that longer or repeated anaesthesia  
163 | exposures in early childhood are detrimental. The trial was also conducted in a predominantly  
164 | male population, and thus further research is needed which is directed specifically towards  
165 | answering these questions relating to female sex, and multiple and prologed expsoures.

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167

168

169 **Introduction**

170 There are ongoing concerns about anaesthesia induced neurotoxicity for the developing brain.<sup>1-2</sup>  
171 In animal models, exposure to most general anaesthetics at a young age results in a range of  
172 morphologic changes.<sup>3</sup> These exposed animals, including non-human primates, exhibit neuronal  
173 cell death, impaired neurogenesis, glial death and abnormal axon formation.<sup>4-7</sup> Some animal  
174 models have also found that anaesthesia exposure in infancy is associated with altered  
175 behaviours including heightened emotional reactivity to threats, and impaired learning and  
176 memory formation persisting into early adulthood.<sup>8,9</sup> Given the greater complexity of human  
177 development, it is unclear how these animal model findings translate to humans.

178 In human cohort studies there is mixed and conflicting evidence for an association between  
179 exposure to anaesthesia in early childhood and a range of adverse neurodevelopmental  
180 outcomes.<sup>10</sup> In light of the preclinical and clinical findings, ~~anaesthesia societies in several~~  
181 ~~countries have issued statements advising practitioners to consider delaying non-urgent surgery~~  
182 ~~and to be prepared to discuss the issue with parents and~~ the United States Food and Drug  
183 Administration has mandated warning labels on most general anaesthetics used in children.<sup>11,12</sup>  
184 There have also been numerous calls for more definitive research to determine if anaesthetic  
185 exposure in early childhood has a clinically relevant impact on neurodevelopment in humans.<sup>13,14</sup>

186 There are inherent difficulties in drawing any conclusions about causation from these cohort  
187 studies due to likely confounding, hence a randomised controlled trial would provide the  
188 strongest evidence for or against general anaesthesia causing adverse neurodevelopmental  
189 outcome.

190 The neurodevelopmental outcome after general anaesthesia or awake-regional anaesthesia in  
191 infancy (GAS) trial was designed to answer the question of whether an exposure to general  
192 anaesthesia ~~exposure~~ in infants leads to clinically significant long term neurodevelopmental  
193 changes. A randomised trial to answer this question could only be performed on children  
194 undergoing a surgery for which either a volatile anaesthetic (which has been shown to cause  
195 injury and neurobehavioural deficits in animal models) or an awake-regional technique (which  
196 does not cause neuronal injury in animal models) can be used.<sup>15</sup> Inguinal herniorrhaphy is one  
197 such surgery. An equivalence design was chosen as the primary aim was to determine if we

198 could exclude general anaesthesia causing clinically relevant neurotoxicity. Our hypothesis was  
199 that there would be no clinically important differences in neurodevelopmental outcome between  
200 general anaesthesia and regional anaesthesia. Such a finding of equivalence would result in: a)  
201 clinicians no longer subjecting children to the various risks of delaying surgery, and b)  
202 anaesthetists not avoiding general anaesthesia by using alternative, and potentially less well  
203 established anaesthetic techniques.

204 The primary outcome for this trial (reported in this paper) is the Wechsler Preschool and Primary  
205 Scale of Intelligence (WPPSI-III) Full Scale Intelligent Quotient (FSIQ) measured at 5 years of  
206 age. A range of other secondary neurodevelopmental outcomes were also assessed at 5 years of  
207 age and are reported in this paper. Neurodevelopmental outcome at 2 years of age for the GAS  
208 trial was assessed using the Bayley Scales of Infant and Toddler Development III and has been  
209 previously published.<sup>16</sup> There was no evidence for a difference in the scores between awake-  
210 regional and general anaesthesia groups. An assessment at two years was regarded as an interim  
211 or secondary outcome as neurodevelopmental delays can be measured more accurately by  
212 assessments conducted at five years of age. Data relating to apnoea in the immediate post-  
213 operative period, intra-operative blood pressure, regional anaesthesia and surgical outcomes have  
214 been published previously.<sup>17-20</sup>

215

## 216 **Methods**

### 217 **Study design**

218 This was a multicentre, international, parallel group, randomised, assessor masked, controlled  
219 equivalence trial comparing neurodevelopmental outcome at 5 years of age after infants were  
220 randomised to receive awake-regional anaesthesia or general anaesthesia for inguinal  
221 herniorrhaphy. The trial was done in 28 hospitals in Australia, Italy, the US, the UK, Canada, the  
222 Netherlands and New Zealand. Institutional Review Board or Human Research Ethics  
223 Committee approval was obtained at each site and written informed consent was obtained from  
224 the infant's parents or guardians. A summary of the protocol is available online.<sup>21</sup>

225 The GAS trial is registered in Australia and New Zealand at ANZCTR: ID#  
226 ACTRN12606000441516 first registered on 16th October 2006; in the United States (US) at  
227 ClinicalTrials.gov: ID#: NCT00756600 first registered on 18th September 2008; and in the  
228 United Kingdom (UK) at UK Clinical Research Network (UKCRN) ID#: 6635 (ISRCTN ID#:  
229 12437565; MREC No: 07/S0709/20).

230 | The statistical analysis plan is available at ANZCTR (ID# ACTRN12606000441516):  
231 | <http://www.anzctr.org.au/AnzctrAttachments/1422-GAS%20SAP%205%20years.pdf>.

### 232 **Participants**

233 Inclusion criteria were infants up to 60 weeks' postmenstrual age, born at greater than 26 weeks'  
234 gestation and scheduled for inguinal herniorrhaphy. Exclusion criteria were any contraindication  
235 for either anaesthetic technique, a history of congenital heart disease requiring surgery or  
236 pharmacotherapy, mechanical ventilation immediately before surgery, known chromosomal  
237 abnormalities or other known acquired or congenital abnormalities that might affect  
238 neurodevelopment, previous exposure to volatile general anaesthesia or benzodiazepines as a  
239 neonate or in the third trimester in utero, any known neurological injury such as cystic  
240 periventricular leukomalacia or grade three or four intraventricular haemorrhage, any social or  
241 geographical factor that might make follow-up difficult or having a primary language at home in  
242 a region where neurodevelopmental tests were not available in that language. We identified  
243 eligible infants from operating room schedules or at preadmission clinics and recruited in the  
244 clinic or in the preadmission areas of the operating floor.

## 245 **Randomisation and Masking**

246 Infants were randomly assigned (1:1) to receive either general anaesthesia or awake-regional  
247 anaesthesia using a 24 hour web-based randomisation service managed by the Data Management  
248 and Analysis Centre, Department of Public Health, University of Adelaide, Australia.

249 Randomisation was done in blocks of two or four [in a computer generated random allocation](#)  
250 [sequence](#) and stratified by site and gestational age at birth: 26-29 weeks and 6 days, 30-36 weeks  
251 and 6 days and greater than 37 weeks. The anaesthetist was aware of group allocation but  
252 individuals who administered neurodevelopmental assessments were not. Parents who asked  
253 about their infant's group allocation were informed and told to mask this information from  
254 assessors. After assessments were completed, parents and assessors were asked if they were  
255 aware of group allocation.

## 256 **Procedures**

257 The awake-regional group received a spinal, caudal or combined caudal/spinal anaesthetic  
258 according to institutional preferences. Bupivacaine or levobupivacaine at a dose of 0.75 -1mg/kg  
259 was administered for spinal anaesthesia. Caudal anaesthesia was with 0.25% bupivacaine or  
260 levobupivacaine up to a total dose of 2.5 mg/kg. Several patients in the US in whom it was  
261 known that the surgery would take longer than one hour were also administered 3%  
262 chloroprocaine via a caudal catheter (loading bolus of 3% chloroprocaine 1 ml/kg over several  
263 minutes and then an infusion at 1-2 ml/kg/hr). Additional ilioinguinal and field blocks were  
264 performed according to surgical preference. Oral sucrose was given if the child was unsettled but  
265 no other pharmacological sedation was permitted. Infants who demonstrated agitation that was  
266 not resolved by oral sucrose or in whom the awake-regional anaesthetic was inadequate were  
267 treated with sevoflurane. The administration of sevoflurane, nitrous oxide or any other general  
268 anaesthetic in this group was considered a protocol violation.

269 The general anaesthesia group received sevoflurane for induction and maintenance in a mix of  
270 air and oxygen. The concentration of sevoflurane, choice of airway device, ventilation technique  
271 and use of neuromuscular blocking agents were left to the preference of the anaesthetist.  
272 Supplemental opioids and nitrous oxide were not allowed but caudal, ilioinguinal-iliohypogastric  
273 or field block with bupivacaine were permitted to provide postoperative analgesia.

274 Both groups could also be given oral, rectal or intravenous paracetamol. Monitoring and  
275 recording were identical in both groups with heart rate, blood pressure, oxygen saturation, and  
276 expired sevoflurane concentrations (where applicable) every 5 minutes. In both groups  
277 intraoperative serum glucose values were measured after induction; rescue protocols for  
278 hypoglycaemia, hypotension and hypoxaemia were applied as appropriate.

## 279 **Outcome assessments**

280 Neuropsychological assessments were to be undertaken within 4 months of the child turning 5  
281 years of age. The total assessment time was estimated to take approximately 3 hours to complete  
282 and assessments were performed at each site by a child psychologist certified to conduct the  
283 tests. Quality control was maintained by a national coordinating psychologist. The primary  
284 outcome measure was that the Wechsler Preschool and Primary Scale of Intelligence-Third  
285 Edition Full Scale Intelligence Quotient WPPSI-III FSIQ score. Other ~~The~~ secondary outcome  
286 measures tests used were ~~the Wechsler Preschool and Primary Scale of Intelligence-Third~~  
287 ~~Edition (WPPSI-III)~~, selected NEPSY-II subtests to assess attention and executive function, the  
288 Wechsler Individual Achievement Test Second Edition (WIAT-II) or the BVN (the Italian  
289 equivalent of the WIAT-II), selected subtests of the Children's Memory Scale (CMS), the Global  
290 Executive Composite (GEC) of the Behavior Rating of Executive Function – Preschool Version  
291 (BRIEF-P), the Adaptive Behavioral Assessment System Second Edition (ABAS-II) and the  
292 Child Behaviour Checklist Caregiver Questionnaire (CBCL). Participatory tests were  
293 administered by the psychologist and a parent/caregiver completed the informant report  
294 questionnaires. Parents were asked if their child had been diagnosed with cerebral palsy (CP),  
295 Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), or had  
296 any other neurodevelopmental issues. They were also asked if the child had received any  
297 neurodevelopmental interventions. Hearing or vision problems were also noted. Demographic  
298 data, family structure and medical history since randomisation were recorded, and a brief  
299 physical and neurologic examination was done for each patient. All these outcome measures  
300 were listed a priori in the protocol.

301 All study data were sent to the Murdoch Children's Research Institute in Melbourne, Australia.  
302 All data forms were checked by a research assistant not involved in primary data collection or

303 entry. Data on test forms that were not completed according to test manual instructions were  
304 rejected.

305 An independent Data Safety Monitoring Committee met approximately every 6 months during  
306 recruitment. Site visits were performed by the national coordinating teams for each country  
307 annually or biennially, and site visits at the national coordinating sites were done by principal  
308 investigators from other nations to check the validity of data. Summary data by allocation were  
309 presented to this committee.

### 310 **Statistical Analysis**

311 The study hypothesis was that the primary outcome, WPPSI-III FSIQ score at 5 years of age, is  
312 equivalent in infants who are anaesthetised for inguinal herniorrhaphy using awake-regional  
313 anaesthesia or general anaesthesia. Because this was an equivalence study, the outcome was  
314 analysed on an as-per-protocol basis to ensure a conservative estimate of the treatment effect in  
315 the direction of non-equivalence. In general it is best practice to analyse outcomes on an  
316 intention-to-treat (ITT) basis where all participants are included according to their randomised  
317 allocation and issues of selection bias are avoided. In this study there were unavoidable protocol  
318 violations, the majority of which were in babies allocated to regional anaesthesia who had some  
319 exposure to general anaesthesia particularly if the awake-regional anaesthesia failed. If all infants  
320 were analysed according to their randomised allocation in an ITT analysis, this switching from  
321 one randomised treatment to the other could dilute the potential effect of general anaesthesia and  
322 thus bias the trial towards equivalence.<sup>22</sup>

323 Equivalence was defined *a priori* as the 95% confidence interval (CI) of the difference in means  
324 of the FSIQ lying within minus five and plus five IQ points. Intention-to-treat analyses were also  
325 planned. All confidence intervals are two-sided

326 The sample size was based on the primary outcome; the 5-year follow-up WPPSI-III FSIQ score.  
327 Assuming an expected difference of one standardised score point, a standard deviation of 15,  
328 and a 90% chance that a 95% CI will exclude a difference of more than five points (the largest  
329 difference acceptable to show equivalence), the trial would need 598 infants. The sample size  
330 formula used was based on approximations to the normal distribution, and used a two one-sided

331 | test (TOST) procedure. Enrolling roughly 720 participants would allow for 10% loss to follow-  
332 up and 10% with a major protocol violation.

333 We used multiple imputation under a multivariate normal distribution to impute missing outcome  
334 data in the primary analysis of all outcomes, with a sensitivity analysis on complete cases only.

335 | The mi impute mvn statement in Stata was used to do the multiple imputations. The variables  
336 used in the multiple imputation models included baseline, post-randomisation, 2 year cognitive  
337 variables and 5 year outcome variables. The following prespecified variables were used as  
338 possible predictor variables within the imputation approach (since most of these variables also  
339 have missingness, they were also imputed where necessary): Baseline: anaesthesia group,  
340 country, sex, gestational age at birth, birth weight, mother received antenatal steroids, mother's  
341 education, maternal age < 21; Surgery: need for fluid bolus for hypotension, duration of surgery,  
342 significant postoperative apnoea, age at surgery; 2 years: composite cognitive, language, motor  
343 and social-emotional score of the Bayley scales of Infant and Toddler Development-Third  
344 Edition, any additional anaesthetic exposures since the inguinal herniorrhaphy, any interventions  
345 for neurodevelopmental problems, any other neurological abnormality; 5 years: WPPSI-III FSIQ,  
346 any chronic illness, any additional anaesthetic exposures since the inguinal herniorrhaphy, total  
347 length of any readmission to hospital, cerebral palsy, any interventions for neurodevelopmental  
348 problems, any other neurological abnormality. With many missing observations these multiple  
349 imputation models did not always converge, in which case applicable variables were not  
350 included in order to ensure convergence of models. The variables used in the analysis model  
351 were always included in the imputation models.

352 For all continuous outcomes, linear regression was used with the factor variables anaesthesia arm  
353 (factor levels: awake regional and general anaesthesia), gestational age at birth and country as  
354 fixed effects. Adjusted mean differences are presented with 95% CIs.

355 All binary outcomes were analysed using generalised linear models (GLM) with binomial link  
356 function in order to enable estimation of risk ratios, adjusting for the same factors as for the  
357 linear regression. Risk ratios are presented with 95% CIs.

358 All following subgroup analyses were pre-specified in the statistical analysis plan: country,  
359 duration of surgery greater or less than 120 minutes, and age at surgery (greater or less than 70  
360 days). A subgroup analysis by ex-term versus ex-preterm (born at <37 weeks gestation) was also



361 performed post hoc. P-values for the interactions are presented along with subgroup treatment  
362 effect estimates and 95% CIs. All analyses were carried out in Stata (version 14.2).

363 **Role of the funders**

364 The funders of this study had no role in data collection, analysis, interpretation, writing this  
365 manuscript or the decision to submit this manuscript. AG has complete access to the data. All  
366 other authors have access to the data on request. All authors were responsible for the decision to  
367 submit this manuscript.

368

## 369 Results

370 Between 9<sup>th</sup> February 2007 and 31<sup>st</sup> January 2013, 722 infants were recruited and randomised at  
371 28 centres in 7 countries (table 1). There were two misrandomisations and one family withdrew  
372 consent after randomisation and before surgery. This left 361 children in the intention-to-treat  
373 analysis for the awake-regional group and 358 children in the general anaesthesia group [Figure  
374 1]. Table 2 summarises baseline data for each group and Table 3 summarises demographic data  
375 at the 5 year assessment. There were 74 protocol violations in the awake-regional group (the  
376 surgeries for 5 children were cancelled and 69 children received some sevoflurane or other  
377 general anaesthetic agent) and two protocol violations in the general anaesthesia group (surgery  
378 cancelled). The only adverse events during the anaesthesia were related to respiratory  
379 complications. These have been previously described in full in a separate publication. <sup>17</sup> There  
380 were no other adverse events in either group. The frequency of hypotension has also been  
381 described elsewhere. <sup>18</sup>

382 The 5 year follow up assessments were conducted from 13<sup>th</sup> March 2012 to 27<sup>th</sup> April 2018. In  
383 total 91 families were lost to follow up in the awake-regional group and 97 in the general  
384 anaesthesia group; a follow up rate of 74%. Of those that attended for assessment the WPPSI-III  
385 FSIQ was complete for 205 in the awake-regional group and 242 in the general anaesthesia  
386 group. Numbers lost to follow up and numbers of complete case assessments are listed for each  
387 sit in table 1.

388 Table 4 summarises the results for the individually administered tests for each group and the  
389 differences in means between groups. There was strong evidence for equivalence of the WPPSI-  
390 III FSIQ means between awake-regional and general anaesthesia groups in both the as-per-  
391 protocol and intention-to-treat analyses using multiple imputation to account for missing data  
392 (adjusted mean difference for awake-regional minus general anaesthesia 0.23, 95% CI -2.59 to  
393 3.06 for as-per-protocol analysis; and 0.16, -2.45 to 2.78 for intention-to-treat analyses). There  
394 was also evidence for equivalence in the complete cases analyses (adjusted mean difference for  
395 awake-regional minus general anaesthesia 0.628, 95% CI -2.093 to 3.349 for as-per-protocol  
396 analysis; and 0.266, -2.268 to 2.799 for intention-to-treat analyses). In all these analyses the  
397 upper and lower bounds of the 95% confidence intervals were well within the prespecified 5  
398 point equivalence margin. There was also evidence for equivalence of the verbal, performance

399 and processing speed composite scores of the WPPSI-III, with the 95% confidence intervals  
400 around the differences in means again within 5 points in as-per-protocol, intention-to-treat,  
401 multiple imputation and complete case analyses. For all the other individually administered  
402 secondary outcomes (Table 4) and parent or caregiver reported outcomes (Table 5) none of the  
403 95% confidence intervals around the differences in means were either entirely above or below  
404 zero in any of the analyses. Although an equivalence margin was not prespecified for these  
405 secondary outcomes a reasonable assumption of equivalence could be made, as the upper and  
406 lower bounds of all 95% confidence intervals were within a third of a standard deviation for all  
407 analyses (the equivalence limit prespecified for the primary outcome).

408 Some of the NEPSY-II subscales had large numbers of missing data and the standard deviations  
409 were very large with the multiple imputation models. This is because the correlations of the  
410 variables included in the multiple imputation model with the outcome variable were low, leading  
411 to not much information being recovered using the multiple imputations, while additional noise  
412 was added.

413 Table 6 gives the proportion of children in each group that were reported by a parent to have  
414 been diagnosed with a neurodevelopmental disorder and the risk ratio for both as-per-protocol  
415 and intention-to-treat analyses. No evidence for any differences was found, with the 95%  
416 confidence intervals of all risk ratios crossing 1. However the low event rates limit the inferences  
417 that can be drawn regarding equivalence.

418 The subgroup analyses for the primary outcome are reported in Table 7. These analyses suggest  
419 that the differences between groups were similar by age of exposure, and prematurity. Small  
420 sample sizes in some of the countries made it inconclusive to interpret country differences in the  
421 results. Duration of exposure was not analysed as no children had exposures longer than 120  
422 minutes. The p-value evaluating treatment by country interaction was 0.0496 for the complete  
423 case analysis and 0.0643 for the multiple imputation analysis; providing evidence of  
424 heterogeneity of the results by country.

425 In Table 8, the characteristics of children who attended the 5 year follow up are compared to the  
426 baseline data of the randomised population and the 2 year outcome data for those who attended

427 the 2 year follow up. Table 9 demonstrates the unmasking of group allocation for children who  
428 attended the 5 year follow up.

429

430

431

432 **Discussion:**

433 In this randomised trial we found strong evidence for equivalence in full scale IQ measured at  
434 five years of age between children anaesthetised with awake-regional and general anaesthesia for  
435 inguinal herniorrhaphy in infancy. In a range of other neuropsychological tests evidence of  
436 equivalence may also be reasonably assumed as the 95% CI around the differences in means fell  
437 within one third of a standard deviation. These results are consistent with the previously reported  
438 2 year outcomes of the GAS trial using the Bayley-III.<sup>16</sup>

439 The primary outcome was determined at 5 years of age as there is robust evidence for the  
440 emergence of the unitary construct of ‘general intelligence’ and for the individual stability of that  
441 construct from middle childhood until adulthood. - IQ testing in children around the age 5-6 years  
442 has a strong correlation with adult IQ.<sup>23</sup> It has also been shown that IQ aged 5 years is highly  
443 predictive of later Maths ability, and that higher IQ in childhood positively predicts a range of  
444 benefits in academic, economic and health outcomes across the lifespan.<sup>24</sup> The WPPSI-III is a  
445 well-validated, standardised, reliable test for assessing IQ in young children.

446 ~~The IQ, as a measure of intelligence, has significant implications for social-emotional,~~  
447 ~~educational and vocational outcomes throughout the lifespan. The WPPSI-III is an~~  
448 ~~individualised, standardised, reliable and valid test for assessing IQ in young children.~~ The

449 WPPSI-III FSIQ was set as the primary outcome not only due to its strong psychometric  
450 properties and predictive potential, but also due to the preclinical data. The widespread cortical  
451 damage seen in preclinical models would most likely result in a global decline in function. This  
452 would be best identified by a measure of general intellectual function such as the WPPSI-III.

453 Secondary outcome measures were selected to assess a broad range of cognitive domains that  
454 could potentially be impacted based on known vulnerabilities of the developing brain and in  
455 response to early animal and human studies. In choosing the tests a number of factors were  
456 considered: previous studies found deficits in both hippocampal and non-hippocampal memory;  
457 deficits that arise from damage to systems that subservise specific skills are spread through various  
458 regions of the brain and are particularly vulnerable to neurological insult (i.e. attention,  
459 information processing and executive function); there is a possibility of a cumulative effect of  
460 subtle individual or multiple deficits on skill development such as visuo-motor integration,

461 reading, spelling and arithmetic; and there is previous evidence for social and emotional deficits.  
462 Specific individually administered tests and informant report measures were selected from  
463 readily available standardised tests in common clinical use with documented reliability and  
464 validity statistics for use in this age group.

465 Several previous cohort studies have sought to identify associations between anaesthesia  
466 exposure in early childhood and a range of neurodevelopmental outcomes. The PANDA study  
467 was an ambidirectional cohort study that compared neurodevelopmental outcome between  
468 children that had previous inguinal herniorrhaphy and their unexposed siblings using a range of  
469 neuropsychological tests performed at 8-15 years of age.<sup>25</sup> This study found no evidence of  
470 group differences in IQ scores, or scores on a range of other tests of neurocognitive function and  
471 behaviour. Similarly, the MASK cohort study found no evidence for differences between test  
472 scores between children that had a single anaesthetic compared to those that had no previous  
473 anaesthetics, although children that had multiple anaesthetics did have an increased risk of  
474 deficits in processing speed and fine motor outcomes, and parents reported increased problems  
475 related to executive function, behaviour and reading.<sup>26</sup> Other cohort studies have found evidence  
476 for an association between anaesthesia exposure and cognitive, memory, listening  
477 comprehension and language deficits.<sup>27-30</sup>

478 Several other large population-based data linkage studies have found evidence for an association  
479 between anaesthesia in early childhood and a very small decrease in performance in school  
480 grades or school readiness tests.<sup>31-34</sup> There is mixed evidence in cohort studies for an association  
481 between anaesthesia in early childhood and a subsequent diagnosis of ADHD or other learning  
482 disability.<sup>35-42</sup> It is plausible that there may be an increased ~~the~~ risk of these diagnoses without  
483 an increased ~~the~~ risk of worse outcomes in neurocognitive testing, however other confounding  
484 factors are also a possible explanation for these observed associations. The GAS trial found no  
485 evidence for an increased risk of behavioural disorders such as ASD or ADHD, however the  
486 diagnosis of ADHD and learning disability is typically made in older children, and the low event  
487 rate and hence limited power reduced our ability to draw a definitive conclusion.

488 In all these cohort studies any association found between exposure and poor outcome may be  
489 explained by confounding. Children have anaesthesia because they are having surgery or  
490 invasive investigations. The condition warranting the procedure may itself be associated with

491 increased risk of adverse neurodevelopmental outcome. Similarly children with pre-existing but  
492 as yet undiagnosed behavioural problems may be at greater risk of needing the procedure. Lastly  
493 perioperative factors other than anaesthesia may also increase the risk of poor  
494 neurodevelopmental outcome. In most studies, attempts are made to limit the effects of known  
495 confounders through patient selection, matching and adjustments in the analysis but the potential  
496 influence of confounding can never be eliminated. The GAS trial is the only randomised trial so  
497 far that assesses the impact of anaesthesia on neurodevelopment and thus provides the strongest  
498 human evidence.

499 Several previous cohort studies have found more evidence for a detrimental effect after multiple  
500 exposures compared to a single exposure. In the GAS trial a substantial number of children had  
501 subsequent anaesthetics. The number of children having subsequent anaesthetics was well  
502 balanced between arms and thus the occurrence of subsequent anaesthetics is unlikely to  
503 influence or bias the results of this trial.

504 There was weak evidence for an interaction between country and treatment. The reason for this is  
505 not immediately apparent and given the marginal level of evidence this finding should be  
506 interpreted with caution.

507 Despite careful selection of patients, an awake-regional technique is not always adequate for  
508 herniorrhaphy. Thus a substantial number of children in the awake-regional group had some  
509 exposure to general anaesthetics. These children were excluded in the as-per-protocol analysis.  
510 The lack of any substantive difference between the as-per-protocol and intention-to-treat  
511 analyses implies that this did not introduce a bias to the trial. In addition, some children were lost  
512 to follow up. Multiple imputation was used to reduce the impact of these missing data under the  
513 missing at random assumption. However even with multiple imputation the results could be  
514 influenced by the selective follow-up of participants. Children who performed poorly at 2 years  
515 were more likely to be lost to follow up at 5 years. The reason for this is unclear however this is  
516 unlikely to lead to a bias as the 2 year outcome was included in the multiple imputation model.  
517 Overall, the loss to follow up was greater than anticipated in the protocol, however the  
518 boundaries of the 95% confidence intervals fell within the predefined bounds of equivalence  
519 indicating that the precision of the results was adequate in spite of this greater than expected loss  
520 to follow up.

521 Given the nature of the interventions it was impossible to mask the treating surgeons or  
522 anaesthetists to group allocation. It was also impractical to completely mask inquisitive parents  
523 as adhesives used to secure the airway usually leave signs of skin irritation in the general  
524 anaesthesia group, and there would be a puncture mark in the back from the spinal needle in the  
525 spinal group. Clinicians making the 5-year assessment were masked successfully in the great  
526 majority of cases. It is unlikely that unmasking surgeons, anaesthetists or parents would bias the  
527 outcome for the individually administered tests. However, when interpreting parent reported  
528 outcomes this potential bias should be considered.

529 There are considerations to make when assessing the generalisability of the GAS trial. Firstly,  
530 the population was predominantly male, which was expected given the surgical pathology  
531 selected to create homogeneity within the study sample. Secondly, the infants were exposed over  
532 a narrow period of development (early infancy); this period being chosen as the period of high  
533 cerebral vulnerability and because this is when both awake regional anaesthesia and general  
534 anaesthesia are commonly used for herniorrhaphy. When determining at which age children might  
535 be at greatest risk, it is difficult to translate the animal data to humans.<sup>13,43</sup> In general, younger  
536 animals have been found to be at greater risk and thus it would be expected that in humans,  
537 infants and the foetus would be most at risk. Some cohort studies have found children exposed at  
538 2-4 years of age to be at greater risk, but this may also be explained by confounding factors, and  
539 is less consistent with the preclinical data.<sup>31,32</sup> Thirdly it could be argued that 5 years of age is  
540 too early to detect long term neurocognitive outcomes as there are a number of executive  
541 functions and social-emotional skills that do not develop until later in life. However these results  
542 on individually administered, standardized tests and parent reports indicate that children who  
543 undergo anaesthesia in infancy start school life with no neurodevelopmental risk factors.  
544 Exploration of executive function and social emotional functions later in development could be  
545 an area of future study. Fifthly, in this trial the children received only one general anaesthetic  
546 (sevoflurane) in the general anaesthesia group. There are several other general anaesthetics that  
547 are used in childhood such as isoflurane, desflurane and propofol. At this stage there are no  
548 preclinical data to suggest that any effects seen with sevoflurane would be different to the effects  
549 seen with these other agents and thus it is reasonable to assume that the GAS trial results would  
550 translate to other general anaesthetic agents. There are also some preclinical data that suggest the  
551 effect may be greater if multiple agents are given concurrently. The GAS trial results cannot be



552 | generalized to situations where multiple general anaesthetic agents are given concurrently.

553 | Lastly, the length of exposure was on average just under an hour and less than 2 hours for all  
554 | children. Animal data suggest longer exposures are more likely to cause neurotoxicity, although  
555 | there is no clear “cut off” for length of exposure that does or does not have an effect. While an  
556 | hour of anaesthesia was shorter than the exposure used in many of the animal experiments, the  
557 | equivalence of animal exposure time to that in humans is unknown. Furthermore the median  
558 | duration of general anaesthesia for children in the 1.5 million procedures in the National  
559 | Anesthesia Clinical Outcomes Registry (USA) was 57 minutes with infants having a median  
560 | duration of 79 minutes.<sup>44</sup> Thus the duration of exposure in the GAS trial is longer than nearly  
561 | half the anaesthetics given to small children.

562 | The number of children potentially affected by national safety warnings about the neurotoxic  
563 | potential of general anaesthesia such as the FDA warning is significant. During the first 3 years  
564 | of life approximately 10 percent of children from developed countries will undergo a general  
565 | anaesthetic for a variety of surgical, diagnostic and medical procedures which translates to  
566 | millions of children/year.<sup>27,45</sup> Most of these children are healthy and will be exposed to a single  
567 | short or intermediate length anaesthetic during their childhood.<sup>40</sup> Given the high prevalence of  
568 | exposure in early childhood, even small effects on brain development due to general anaesthesia  
569 | could have very large public health consequences. There is also the very real potential that  
570 | parents and providers will delay necessary procedures in children in an effort to limit exposure at  
571 | a time of cerebral vulnerability, putting some children at risk for both medical and  
572 | developmental impairments. The GAS trial, being consistent with data from ~~in addition to~~  
573 | several previous cohort studies, provides strong evidence that just under one hour of general  
574 | anaesthesia in infancy does not cause significant neurocognitive or behavioural deficits.

575 | (Word count 5451)

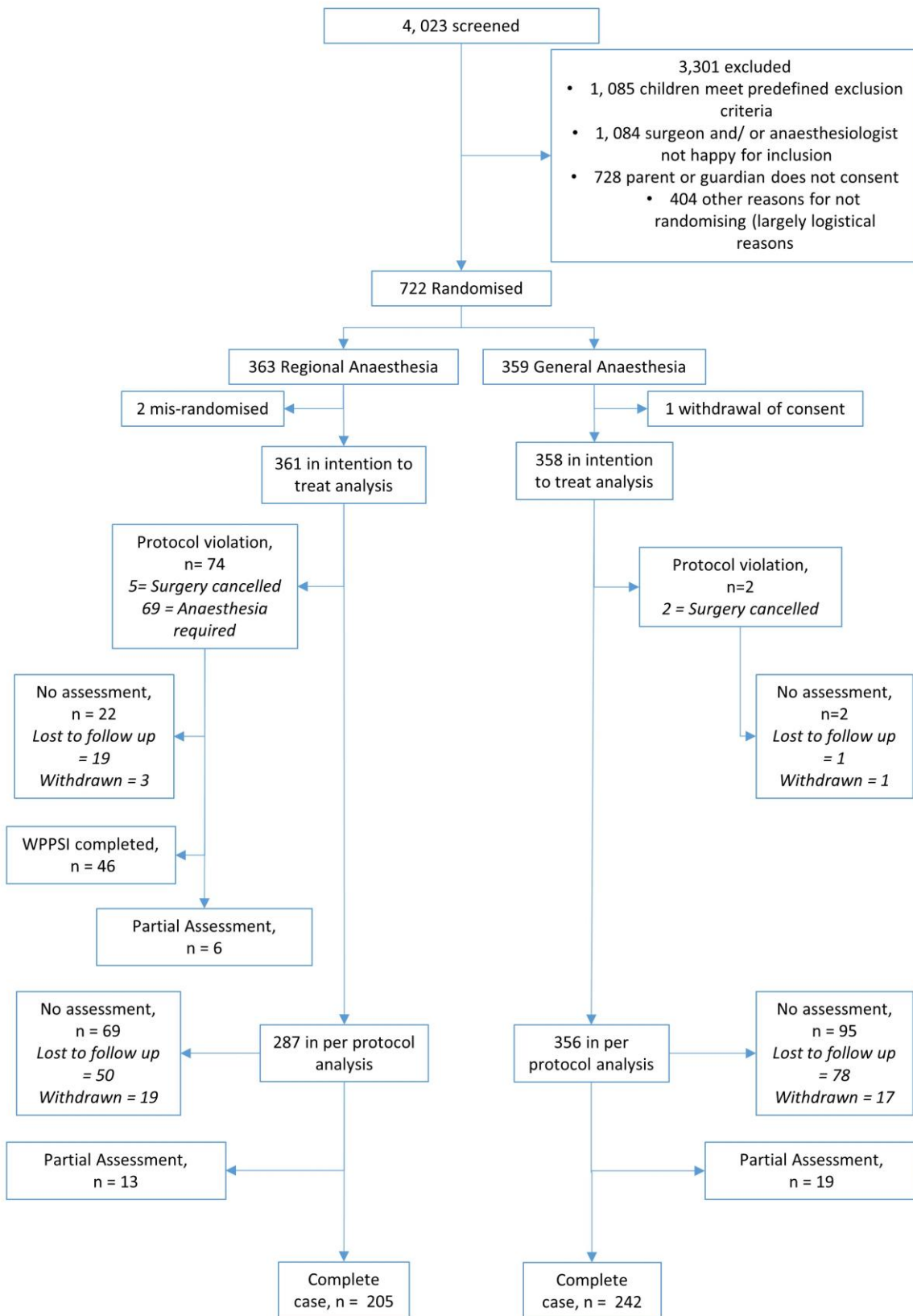
576 |

577 **Data sharing statement**

578 The de-identified data set collected for this analysis of the GAS trial will be available six months  
579 after publication of this manuscript. The study protocol, analysis plan and consent forms will  
580 also be available. The data may be obtained from the Murdoch Children’s Research Institute by  
581 emailing [andrew.davidson@rch.org.au](mailto:andrew.davidson@rch.org.au). Prior to releasing any data the following are required: a  
582 data access agreement must be signed between relevant parties, the GAS Trial Steering  
583 Committee must see and approve the analysis plan describing how the data will be analysed ,  
584 there must be an agreement around appropriate acknowledgement and any additional costs  
585 involved must be covered. Data will only be shared with a recognised research institution which  
586 has approved the proposed analysis plan.

587

589 **Figure 1:** Trial Profile



Site	Randomisation		Follow-up - complete case*			
	RA, N = 361	GA, N = 358	PP - RA, N = 205	PP - GA, N = 242	ITT - RA, N = 251	ITT - GA, N = 242
<b>Australia</b>						
Royal Children's Hospital, Melbourne	57	28	39	44	46	44
Monash Medical Centre, Melbourne	26	25	15	15	16	15
Women's and Children's Hospital, Adelaide	6	5	2	3	4	3
Princess Margaret Hospital for Children, Perth	16	15	7	10	8	10
<b>New Zealand</b>						
Starship Children's Hospital, Auckland	13	12	7	9	8	9
<b>USA</b>						
Children's Hospital, Boston	29	31	18	21	22	21
Children's Memorial Hospital, Chicago	2	3	0	0	0	0
Dartmouth Hitchcock Medical Centre, Lebanon	2	2	2	1	2	1
Vanderbilt Children's Hospital, Nashville	1	2	0	1	0	1
The University of Iowa Hospital, Iowa	8	8	4	4	6	4
Children's Medical Centre, Dallas	7	7	0	7	2	7
Children's Hospital of Philadelphia, Philadelphia	1	1	0	1	0	1
Seattle Children's Hospital, Seattle	11	14	5	13	8	13
The Children's Hospital, Colorado	9	9	4	4	5	4
The University of Vermont/ Fletcher Allen Health Care, Burlington	1	0	1	0	1	0
<b>Canada</b>						
Montreal Children's Hospital, Montreal	21	20	9	15	11	15
Centre de Recherche CHU Sainte-Justine, Montreal	3	5	1	5	3	5
<b>United Kingdom</b>						
Bristol Royal Hospital for Children, Bristol	2	2	1	1	1	1
Royal Hospital for Children, Glasgow	27	25	20	16	21	16
Birmingham Children's Hospital NHS trust, Birmingham	7	6	5	3	6	3
Royal Belfast Hospital for Sick Children, Belfast	2	2	1	0	1	0
Royal Liverpool Children's Hospital, Liverpool	1	1	0	1	0	1
Sheffield Children's Hospital, Sheffield	5	4	0	1	3	1
<b>Italy</b>						
Gaslini Hospital for Children, Genoa	42	39	23	26	30	26
Buzzi Children's Hospital, Milan	25	23	16	15	20	15
Ospedali Riunti, Bergamo	16	20	6	9	7	9
<b>The Netherlands</b>						
Wilhelmina Children's Hospital, University Medical Centre, Utrecht	15	14	14	13	14	13
Universitair Medisch Centrum, Groningen	6	5	5	4	6	4

RA = awake-regional anaesthesia. GA = general anaesthesia. PP = per protocol. ITT = intention to treat. \*Complete case includes a full WPPSI-III assessed at 5 year follow-up. Results do not include partial assessments.

**Table 1: Enrolment and complete case follow-up by site**

	As per protocol		Intention to treat	
	RA group, N = 287	GA group, N = 356	RA group, N = 361	GA group, N = 358
<b>Baseline demographics</b>				
Gender, Male	232 (287, 81%)	304 (356, 85%)	294 (360, 82%)	306 (358, 86%)
Chronological age at surgery (days)	287, 68.9 (31)	356, 71.1 (32)	358, 70.1 (32)	357, 71.0 (32)
Post menstrual age at surgery (days)	287, 317.2 (32)	356, 319.7 (32)	357, 318.3 (33)	357, 319.5 (32)
Weight of child at surgery (kg)	287, 4.2 (1.1)	356, 4.3 (1.1)	359, 4.2 (1.1)	357, 4.3 (1.1)
<b>Pregnancy and birth details</b>				
Mean (SD) Post menstrual age at birth (days)	287, 248.2 (29)	356, 248.6 (27)	360, 248.3 (29)	358, 248.6 (27)
Prematurity (Born < 37 weeks gestation)	160 (287, 56%)	195 (356, 55%)	198 (361, 55%)	196 (358, 55%)
Birth Weight (kg)	287, 2.3 (0.9)	355, 2.3 (0.9)	359, 2.4 (0.9)	357, 2.3 (0.9)
Z score for birth weight	287, -0.7 (1.3)	355, 0.7 (1.3)	359, -0.7 (1.2)	357, -0.7 (1.3)
N, Median (IQR) Apgar score at 1 minute	237, 9 (7-9)	282, 8.5 (7-9)	292, 9 (7-9)	284, 9 (7-9)
N, Median (IQR) Apgar score at 5 minutes	237, 9 (9-10)	282, 9 (9-10)	292, 9 (9-10)	284, 9 (9-10)
One of a multiple pregnancy	52 (284, 18%)	61 (356, 17%)	62 (360, 17%)	62 (358, 17%)
Mother received partial course antenatal steroids	16 (287, 6%)	19 (356, 5%)	20 (360, 6%)	19 (358, 5%)
Mother received complete course antenatal steroids	95 (287, 33%)	98 (356, 28%)	114 (360, 32%)	98 (358, 28%)
Mother diagnosed with chorioamnionitis	10 (287, 4%)	12 (356, 3%)	11 (360, 3%)	12 (358, 3%)
Prolonged rupture of the membranes (>24 hours)	28 (287, 10%)	34 (356, 10%)	32 (360, 9%)	34 (358, 10%)
Mother diagnosed with pre-eclampsia	50 (287, 17%)	68 (356, 19%)	60 (360, 17%)	68 (358, 19%)
Sepsis during pregnancy	36 (286, 13%)	50 (356, 14%)	43 (358, 12%)	50 (358, 14%)
Mode of delivery of birth				
Cephalic vaginal	135 (287, 47%)	157 (356, 44%)	169 (360, 47%)	157 (358, 44%)
Breech vaginal	1 (287, <1%)	6 (356, 2%)	3 (360, 1%)	6 (358, 2%)
Compound vaginal	2 (287, 1%)	4 (356, 1%)	3 (360, 1%)	4 (358, 1%)
Caesarean section	149 (287, 52%)	189 (356, 53%)	185 (360, 51%)	191 (358, 53%)
Caesarean section and mother went into labour	42 (287, 15%)	58 (356, 16%)	52 (360, 14%)	59 (358, 16%)
Mother exposed to nitrous oxide during delivery	48 (275, 18%)	62 (344, 18%)	61 (344, 18%)	62 (346, 18%)
IVH				
IVH Grade 1	5 (286, 2%)	6 (356, 2%)	5 (359, 2%)	6 (358, 2%)
IVH Grade 2	2 (286, 1%)	0 (356)	2 (359, 1%)	0 (358)
Retinopathy of prematurity	17 (198, 9%)	16 (256, 6%)	20 (246, 8%)	16 (257, 6%)
Hearing defects detected by perinatal screening	7 (253, 3%)	10 (356, 3%)	8 (316, 3%)	10 (325, 3%)
PDA diagnosed				
PDA never treated	9 (286, 3%)	9 (355, 3%)	11 (359, 3%)	9 (357, 3%)

PDA treated with non-steroidal anti-inflammatory drugs	14 (286, 5%)	10 (355, 3%)	16 (359, 4%)	10 (357, 3%)
<b>Familial Demographics:</b>				
Primary language(s) only spoken*	252 (287, 88%)	305 (356, 86%)	311 (360, 86%)	307 (358, 86%)
Maternal Age at Birth >21	273 (286, 96%)	339 (356, 95%)	339 (358, 95%)	341 (358, 95%)
Family structure two caregivers together, at birth	261 (286, 91%)	324 (356, 91%)	328 (359, 91%)	326 (358, 91%)
Maternal education				
Completed tertiary studies	150 (286, 52%)	171 (354, 48%)	181 (359, 51%)	171 (358, 48%)
Continuing tertiary studies	50 (286, 17%)	67 (354, 19%)	68 (359, 19%)	67 (358, 19%)
Completed year 11 or 12	62 (286, 22%)	83 (354, 23%)	77 (359, 22%)	84 (358, 24%)
Did not complete year 11	25 (286, 9%)	33 (354, 9%)	32 (359, 9%)	34 (358, 10%)
<b>Anaesthesia Details:</b>				
N, Median (IQR) Blood glucose level (mmol/L)	255, 5.4 (4.7-6.1)	314, 5.5 (4.8-6.4)	312, 5.4 (4.7-6.2)	314, 5.5 (4.8-6.4)
Rescue glucose given IV	2 (282, 1%)	4 (356, 1%)	2 (350, 1%)	4 (356, 1%)
Haemoglobin (g/100 ml)	250, 10.3 (2.1)	307, 10.2 (2.0)	305, 10.3 (2.1)	307, 10.2 (2.0)
Need for fluid bolus for hypotension	15 (287, 5%)	59 (356, 17%)	21 (355, 6%)	59 (356, 17%)
Vasoactive drugs given (including atropine)	4 (287, 1%)	17 (356, 5%)	6 (355, 2%)	17 (356, 5%)
N, Median (IQR) Duration of surgery (mins)	286, 26.0 (19.0-35.0)	355, 28.0 (20.0-40.0)	353, 28.0 (20.0-38.0)	355, 28.0 (20.0-40.0)
N, Median (IQR) Duration of sevoflurane exposure (mins)	NA	356, 54.0 (41.0-70.0)	67, 42.0 (31.0-62.5)**	356, 54.0 (41.0-70.0)
Mean end tidal sevoflurane concentration (%)	NA	356, 2.6 (0.7)	67, 2.3 (0.8)**	356, 2.6 (0.7)
Total concentration x hours of exposure	NA	356, 2.6 (1.1)	67, 1.9 (1.0)**	356, 2.6 (1.1)
Any significant apnoea to 12hrs postop***	6 (287, 2%)	15 (356, 4%)	10 (360, 3%)	15 (358, 4%)

Data are n (N, % of non-missing data) or n, mean (SD), unless otherwise stated. APP= As Per Protocol; GA= General Anaesthesia; ITT= Intention to treat; IV= Intra-venously; IVH= Intra ventricular haemorrhage; IQR= Interquartile Range; PDA = Patent ductus arteriosus; RA= Awake Regional Anaesthesia.

\* The primary language spoken at home, is the primary language in each country that the Bayley was conducted eg. in Italy it was conducted in Italian

\*\* For those cases that received sevoflurane

\*\*\* significant apnoea defined as a pause in breathing for more than 15 seconds or more than 10 seconds if associated with oxygen saturation less than 80% or bradycardia (20% decrease in heart rate)

**Table 2: Baseline descriptive statistics demographic data**

591

	As per protocol		Intention to treat	
	RA group, N = 287	GA group, N = 356	RA group, N = 361	GA group, N = 358
<b>Assessment Details</b>				
Location of 5-year assessment at hospital	198 (216, 91.7%)	228 (257, 88.7%)	246 (268, 91.8%)	228 (257, 88.7%)
<b>Family Demographics at 5 years</b>				

Paid Employment is the main family income	201 (214, 93.9%)	237 (256, 92.6%)	243 (266, 91.4%)	237 (256, 92.6%)
Family Structure, two caregivers living together	194 (214, 90.7%)	223 (257, 86.8%)	230 (266, 86.5%)	223 (257, 86.8%)
Number of children at home				
1	50 (214, 23.4%)	53 (257, 20.6%)	63 (266, 23.7%)	53 (257, 20.6%)
2	95 (214, 44.4%)	133 (257, 51.8%)	120 (266, 45.1%)	133 (257, 51.8%)
3	56 (214, 26.2%)	48 (257, 18.7%)	67 (266, 25.2%)	48 (257, 18.7%)
> 3	13 (214, 6.1%)	23 (257, 8.9%)	16 (266, 6.0%)	23 (257, 8.9%)
Birth order				
1	113 (211, 53.6%)	137 (257, 53.3%)	137 (261, 52.5%)	137 (257, 53.3%)
2	69 (211, 32.7%)	81 (257, 31.5%)	87 (261, 33.3%)	81 (257, 31.5%)
> 2	29 (211, 13.7%)	39 (257, 15.2%)	37 (261, 14.2%)	39 (257, 15.2%)
Age at follow-up assessment	217, 5.2 (0.2)	258, 5.3 (0.3)	269, 5.2 (0.2)	258, 5.3 (0.3)
<b>Events since original anaesthesia</b>				
Any hospitalisation	101 (199, 50.8%)	129 (250, 51.6%)	131 (249, 52.6%)	129 (250, 51.6%)
Number of days hospitalised				
0	105 (169, 62.1%)	127 (213, 59.6%)	125 (213, 58.7%)	127 (213, 59.6%)
1	22 (169, 13.0%)	30 (213, 14.1%)	34 (213, 16.0%)	30 (213, 14.1%)
2	11 (169, 6.5%)	13 (213, 6.1%)	13 (213, 6.1%)	13 (213, 6.1%)
>=3	31 (169, 18.3%)	43 (213, 20.2%)	41 (213, 19.2%)	43 (213, 20.2%)
Any anaesthesia	71 (102, 69.6%)	71 (111, 64.0%)	89 (133, 66.9%)	71 (111, 64.0%)
Number of anaesthetics				
0	104 (156, 66.7%)	132 (181, 72.9%)	131 (197, 66.5%)	134 (183, 73.2%)
1	28 (156, 17.9%)	27 (181, 14.9%)	37 (197, 18.8%)	27 (183, 14.8%)
2	11 (156, 7.1%)	11 (181, 6.1%)	14 (197, 7.1%)	11 (183, 6.0%)
>=3	13 (156, 8.3%)	11 (181, 6.1%)	15 (197, 7.6%)	11 (183, 6.0%)
Any seizures	14 (173, 8.1%)	17 (217, 7.8%)	17 (217, 7.8%)	17 (217, 7.8%)
<b>Events since 2 year assessment</b>				
Child had a head injury that involved loss of consciousness	2 (213, 0.9%)	2 (266, 0.8%)	3 (265, 1.1%)	2 (257, 0.8%)
Child has any chronic illness	38 (213, 17.8%)	43 (258, 16.7%)	48 (265, 18.1%)	43 (258, 16.7%)
Child had any prescribed medication for two months or longer	37 (214, 17.3%)	44 (257, 17.1%)	44 (266, 16.5%)	44 (257, 17.1%)
Child has had an intervention for neurodevelopmental issues	49 (213, 23.0%)	60 (257, 23.3%)	64 (264, 24.2%)	60 (257, 23.3%)
Speech Therapy	36 (217, 16.6%)	48 (259, 18.5%)	50 (269, 18.6%)	48 (259, 18.5%)
Physiotherapy	11 (217, 5.1%)	17 (259, 6.6%)	12 (269, 4.5%)	17 (259, 6.6%)
Occupational Therapy	18 (217, 8.3%)	20 (259, 7.7%)	21 (269, 7.8%)	20 (259, 7.7%)
Psychology	7 (217, 3.2%)	6 (259, 2.3%)	8 (269, 3.0%)	6 (259, 2.3%)
Other interventions	9 (217, 4.1%)	16 (259, 6.2%)	12 (269, 4.5%)	16 (259, 6.2%)
Child attends play group/child care on a regular basis	186 (213, 87.3%)	231 (257, 89.9%)	234 (265, 88.3%)	231 (257, 89.9%)
<b>Physical examination</b>				
Height (cm)	207, 110.8 (5.5)	237, 110.8 (5.5)	254, 110.8 (5.4)	237, 110.8 (5.5)

Weight (kg)	206, 19.3 (3.3)	236, 19.4 (2.8)	253, 19.4 (3.2)	236, 19.4 (2.8)
Head circumference (cm)	194, 51.6 (1.8)	224, 51.2 (2.6)	241, 51.6 (1.8)	224, 51.2 (2.6)
Arm circumference (cm)	191, 17.6 (1.9)	219, 17.4 (1.7)	233, 17.6 (1.9)	219, 17.4 (1.7)

Data are n (N, % of non-missing data) or n, mean (SD). RA = awake-regional anaesthesia. GA = general anaesthesia.

**Table 3: 5-year descriptive statistics data**

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	APP multiple imputation			APP complete case			ITT multiple imputation			ITT complete case		
	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*
<b>Global function</b>												
WPPSI III - FSIQ composite score	287, 99.1 (18.4)	356, 99.0 (19.7)	0.2 (-2.6; 3.1)	205, 100.5 (14.3)	242, 100.1 (15.3)	0.6 (-2.1; 3.3)	361, 98.9 (18.0)	358, 98.8 (19.2)	0.2 (-2.5; 2.8)	251, 100.4 (14.1)	242, 100.1 (15.3)	-266 (-2.3; 2.8)
<b>Verbal/language</b>												
WPPSI-III Verbal IQ composite score	287, 100.6 (18.3)	356, 99.7 (20.4)	0.8 (-2.1; 3.8)	206, 101.8 (14.7)	240, 100.9 (15.4)	0.7 (-2.1; 3.4)	361, 99.6 (18.6)	358, 99.6 (19.1)	0.0 (-2.6; 2.7)	251, 101.2 (14.8)	240, 100.9 (15.4)	0.0 (-2.6; 2.5)
NEPSY-II Word Generation scaled score	287, 9.1 (4.7)	356, 9.0 (4.8)	0.1 (-0.6; 0.9)	182, 9.4 (3.4)	199, 9.3 (3.3)	0.1 (-0.6; 0.8)	361, 9.1 (5.5)	358, 9.1 (4.7)	-0.1 (0.6; 0.5)	220, 9.3 (3.5)	199, 9.3 (3.3)	0.1 (-0.6; 0.7)
NEPSY-II Speeded Naming combined scaled score	287, 10.6 (19.6)	356, 7.4 (23.9)	3.3 (-1.1; 7.7)	132, 9.7 (3.0)	142, 9.8 (3.2)	0.0 (-0.7; 0.8)	361, 8.7 (10.3)	358, 9.2 (15.0)	-0.5 (-4.9; 3.9)	162, 9.8 (3.0)	142, 9.8 (3.2)	0.1 (-0.6; 0.8)
<b>Perceptual/visuo-spatial</b>												
WPPSI-III Performance IQ composite score	287, 99.6 (19.3)	356, 100.0 (20.3)	-0.2 (-3.1; 2.8)	206, 100.7 (15.2)	241, 101.2 (15.9)	0.0 (-2.9; 2.8)	361, 100.1 (18.2)	358, 99.8 (19.6)	0.4 (-2.3; 3.1)	252, 101.1 (14.7)	241, 101.2 (15.2)	0.199 (-2.4; 2.8)
NEPSY-II Design Copy scaled score	287, 9.4 (23.8)	356, 6.7 (45.1)	3.1 (-2.7; 8.9)	172, 9.6 (3.4)	207, 9.9 (3.1)	-0.2 (-0.8; 0.5)	361, 13.7 (44.8)	358, 9.6 (26.1)	3.9 (-2.6; 10.4)	212, 9.6 (3.3)	207, 9.9 (3.1)	-0.2 (-0.8; 0.4)
<b>Processing speed</b>												
WPPSI-III Processing Speed Q composite score	287, 95.2 (20.8)	356, 94.7 (21.3)	0.8 (-2.5; 4.0)	196, 95.8 (14.5)	220, 96.3 (15.4)	0.0 (-2.8; 2.9)	361, 95.8 (20.5)	358, 94.6 (21.1)	1.31 (-1.7; 4.3)	241, 96.3 (14.4)	220, 96.3 (15.4)	0.3 (-2.4; 2.9)
<b>Attention/executive function</b>												
NEPSY-II Sentence Repetition scaled score	287, 6.4 (29.7)	356, 8.3 (24.2)	-1.4 (-5.4; 2.7)	175, 9.7 (2.9)	202, 9.7 (2.8)	0.0 (-0.6; 0.6)	361, 13.5 (55.3)	358, 10.8 (23.3)	2.4 (-1.0; 5.8)	214, 9.7 (3.0)	202, 9.7 (2.8)	-0.1 (-0.6; 0.5)
NEPSY-II Auditory Attention combined scaled score	287, 8.7 (4.3)	356, 8.8 (4.6)	-0.1 (-0.8; 0.6)	167, 9.0 (2.7)	183, 9.3 (3.0)	-0.3 (-0.8; 0.3)	361, 8.7 (4.2)	358, 8.8 (5.1)	-0.1 (-0.8; 0.6)	207, 8.9 (3.0)	183, 9.3 (3.0)	-0.3 (-0.8; 0.3)
NEPSY-II Inhibition combined scaled score	287, 7.9 (6.0)	356, 8.4 (5.5)	-0.5 (-1.3; 0.3)	150, 8.3 (3.1)	160, 8.9 (3.0)	-0.6 (-1.3; 0.1)	361, 7.8 (7.2)	358, 8.4 (5.1)	-0.6 (-1.5; 0.4)	179, 8.4 (3.1)	160, 8.9 (3.0)	-0.5 (-1.1; 0.2)
NEPSY-II Statue scaled score	287, 8.6 (33.0)	356, 10.8 (32.1)	-2.6 (-8.9; 3.8)	160, 8.8 (3.5)	182, 8.6 (3.6)	0.2 (-0.5; 1.0)	361, 7.1 (19.3)	358, 8.1 (14.0)	-0.9 (-1.7; 0.2)	192, 8.8 (3.5)	182, 8.6 (3.6)	0.2 (-0.5; 0.9)
CMS Numbers scaled score	287, 8.0 (4.6)	356, 7.8 (4.6)	0.2 (-0.5; 0.9)	194, 8.3 (3.2)	229, 8.1 (3.4)	0.1 (-0.5; 0.7)	361, 7.9 (3.9)	358, 7.7 (4.3)	0.1 (-0.5; 0.8)	236, 8.2 (3.2)	229, 8.1 (3.4)	0.0 (-0.6; 0.6)
<b>Memory &amp; learning</b>												
NEPSY-II Memory for Names combined scaled score	287, 8.1 (4.6)	356, 8.0 (4.6)	0.2 (-0.5; 0.9)	180, 8.1 (3.2)	208, 8.1 (3.2)	0.2 (-0.5; 0.8)	361, 8.2 (4.4)	358, 8.0 (4.6)	0.2 (-0.5; 0.9)	218, 8.2 (3.2)	208, 8.1 (3.2)	0.2 (-0.4; 0.8)
CMS Word Lists I Learning scaled score	287, 8 (4.8)	356, 8.3 (4.9)	-0.4 (-1.1; 0.4)	186, 8.3 (3.4)	224, 8.6 (3.5)	-0.4 (-1.0; 0.3)	361, 8.1 (4.9)	358, 8.3 (5.3)	-0.3 (-1.0; 0.5)	227, 8.3 (3.4)	224, 8.6 (3.5)	-0.3 (-1.0; 0.3)
CMS Word Lists II Delayed scaled score	287, 9.5 (4.0)	356, 9.4 (4.4)	0.1 (-0.5; 0.8)	178, 9.7 (2.8)	209, 9.6 (2.9)	0.0 (-0.5; 0.6)	361, 9.5 (3.9)	358, 9.3 (4.7)	0.1 (-0.5; 0.7)	216, 9.6 (2.9)	209, 9.6 (2.9)	0.0 (-0.6; 0.5)
<b>Social perception</b>												
NEPSY-II Affect Recognition scaled score	287, 10.1 (28.6)	356, 8.9 (18.1)	1.5 (-1.7; 4.6)	174, 10.6 (2.8)	208, 10.4 (3.2)	0.3 (-0.4; 0.9)	361, 11.6 (15.4)	358, 7.4 (74.2)	4.3 (-5.0; 13.5)	215, 10.6 (2.8)	208, 10.4 (3.2)	0.2 (-0.3; 0.8)
NEPSY-II Theory of Mind scaled score	287, 9.3 (4.1)	356, 9.6 (4.6)	-0.3 (-0.9; 0.4)	163, 9.8 (2.9)	178, 9.8 (3.0)	-0.1 (-0.7; 0.5)	361, 9.2 (4.6)	358, 9.6 (4.3)	-0.4 (-1.1; 0.3)	197, 9.7 (3.1)	178, 9.8 (3.1)	-0.2 (-0.8; 0.4)
<b>Sensorimotor</b>												
NEPSY-II Fingertip Tapping Repetitions combined scaled score	287, 9.5 (5.4)	356, 9.4 (5.2)	0.0 (-0.8; 0.8)	180, 9.8 (3.4)	195, 9.7 (3.4)	-0.1 (-0.8; 0.5)	361, 9.6 (4.7)	358, 9.5 (5.3)	0.1 (-0.6; 0.9)	217, 9.8 (3.4)	195, 9.7 (3.4)	0.0 (-0.6; 0.6)
NEPSY-II Fingertip Tapping	287, 7.6	356, 7.1	0.5 (-0.4;	173, 8.1	183, 7.7	0.4 (-0.3;	361, 7.8	358, 7.2	0.6 (-0.4;	204, 8.1	183, 7.7	0.5 (-0.2;

Sequences combined scaled score	(5·3)	(6·6)	1·4)	(3·4)	(3·6)	1·1)	(6·2)	(6·2)	1·6)	(3·4)	(3·6)	1·1)
<b>Academic</b>												
WIAT-II Word Reading composite score	220, 92·1 (20·5)	275, 93·3 (25·9)	-1 (-4·5; 2·5)	147, 92·3 (18·1)	167, 92·8 (21·1)	-1·5 (-4·7; 1·8)	278, 92·1 (23·7)	276, 93·3 (26·6)	-1·2 (-4·6; 2·3)	175, 92·8 (18·8)	167, 92·8 (21·1)	-1·3 (-4·4; 1·8)
WIAT-II Spelling composite score	220, 90·2 (16·3)	275, 91·1 (20·6)	-1·2 (-3·6; 1·2)	141, 90·1 (13·2)	152, 90·8 (16·5)	-1·7 (-4·3; 0·9)	278, 89·9 (17·8)	276, 91·3 (19·2)	-1·6 (-4·2; 1·1)	166, 90·6 (13·7)	152, 90·8 (16·5)	-1·5 (-4·0; 1·0)
WIAT-II Numerical Operations composite score	220, 98·0 (21·3)	275, 96·1 (26·5)	0·8 (-2·8; 4·5)	146, 98·8 (16·2)	161, 96·2 (20·8)	0·3 (-3·1; 3·7)	278, 97·1 (20·8)	276, 96·3 (26·4)	0·5 (-2·9; 3·9)	172, 98·7 (16·6)	161, 96·2 (20·8)	0·2 (-3·0; 3·5)

Data are n, mean (SD). \*Difference (95%CI). RA = awake-regional anaesthesia. GA = general anaesthesia. SE = standard error. APP = as per protocol. ITT = intention to treat.

**Table 4: Descriptive statistics WPPSI-III and other individually administered tests for each group**

	APP multiple imputation			APP complete case			ITT multiple imputation			ITT complete case		
	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*	RA group	GA group	Difference in RA-GA*
<b>Executive function</b>												
BRIEF-P (Global Executive composite, T score)	287, 49·2 (16·0)	356, 51·9 (17·6)	-2·7 (-5·2; -0·1)	198, 48·4 (12·5)	232, 51·5 (13·4)	-2·9 (-5·4; -0·4)	361, 49·6 (15·5)	358, 51·9 (17·5)	-2·4 (-4·8; 0·1)	246, 48·9 (12·7)	232, 51·5 (13·4)	-2·4 (-4·7; 0·0)
<b>Adaptive Behaviour</b>												
ABAS-2 (Global Adaptive Behaviour composite score)	287, 94·4 (20·9)	356, 92·6 (23·3)	2·0 (-1·2; 5·2)	168, 95·9 (16·3)	200, 94·1 (16·5)	1·5 (-1·7; 4·8)	361, 94·3 (23·3)	358, 92·5 (23·9)	1·9 (-1·3; 5·1)	205, 95·5 (16·8)	200, 94·1 (16·5)	1·0 (-2·1; 4·2)
<b>Maladaptive Behaviour</b>												
CBCL (Total problems, T score)	287, 45·2 (13·8)	356, 47·1 (16·6)	-2·0 (-4·3; 0·4)	215, 44·6 (11·7)	254, 46·7 (12·5)	-1·9 (-4·1; 0·3)	361, 45·7 (15·0)	358, 47·1 (15·6)	-1·4 (-3·6; 0·8)	265, 45 (12·1)	254, 46·7 (12·5)	-1·5 (-3·6; 0·6)
CBCL (Internalising problems T score)	287, 46·6 (14·4)	356, 48·5 (17·4)	-1·9 (-4·3; 0·6)	215, 46·1 (12·5)	254, 48·0 (12·5)	-1·8 (-4·1; 0·4)	361, 46·8 (15·2)	358, 48·5 (16·0)	-1·6 (-3·9; 0·6)	265, 46·2 (12·5)	254, 48·0 (12·5)	-1·7 (-3·9; 0·4)
CBCL (Externalising problems T score)	287, 44·5 (13·2)	356, 46·1 (15·0)	-1·6 (-3·7; 0·5)	215, 44·0 (10·7)	254, 45·8 (11·9)	-1·7 (-3·7; 0·4)	361, 45·1 (13·9)	358, 46·1 (15·0)	-1·1 (-3·1; 1·0)	265, 44·4 (11·3)	254, 45·8 (11·9)	-1·2 (-3·2; 0·8)

Data are n, mean (SD). \*Difference (95%CI). RA = awake-regional anaesthesia. GA = general anaesthesia. SE = standard error. APP = as per protocol. ITT = intention to treat.

**Table 5: Descriptive statistics parent-rated behavioural outcome measures by group**

	As per protocol			Intention to treat		
	RA group, N = 287	GA group, N = 356	RR (95% CI)	RA group, N = 361	GA group, N = 358	RR (95% CI)
Any developmental issues	25 (12.3)	21 (8.8)	1.4 (0.8; 2.4)	33 (12.9)	21 (8.8)	1.5 (0.9; 2.5)
Speech or language issues / interventions	18 (8.4)	17 (6.6)		24 (9)	17 (6.6)	
Psychomotor issues / interventions	8 (3.7)	6 (2.3)		9 (3.4)	6 (2.3)	
Global developmental delay	2 (1)	0 (0)		4 (1.6)	0 (0)	
Behavioural disorders (ADHD, ASD or ODD)	8 (3.8)	15 (6)	0.7 (0.3; 1.7)	13 (4.9)	15 (6)	0.99 (0.5; 2.0)
Diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)	3 (1.4)	4 (1.6)		7 (2.6)	4 (1.6)	
Diagnosed with Autism Spectrum Disorder (ASD)	5 (2.4)	11 (4.4)		7 (2.7)	11 (4.4)	
Hearing abnormality	8 (3.8)	11 (4.4)	0.9 (0.4; 2.2)	12 (4.5)	11 (4.4)	1.1 (0.5; 2.4)
Child has a hearing aid	0 (0)	3 (1.2)		0 (0)	3 (1.2)	
Visual defect of any type in either eye	21 (9.9)	31 (12.2)	0.8 (0.5; 1.3)	28 (10.6)	31 (12.1)	0.8 (0.5; 1.4)
Legally blind (<6/60 in both eyes)	0 (0)	0 (0)		0 (0)	0 (0)	
Cerebral palsy	1 (0.5)	3 (1.2)	0.6 (0.1; 5.5)	1 (0.4)	3 (1.2)	0.4 (0.0; 3.8)

Data are n (% of non-missing data). RR = Risk Ratio. RA = awake-regional anaesthesia. GA = general anaesthesia.

**Table 6: 5-year non-psychometric outcome data**

	RA group*	GA group*	Difference in RA-GA	95% CI for difference in RA-GA
<b>Age at surgery (&lt;=70 days)</b>				
APP multiple imputation	111, 98.7 (20.3)	155, 98.2 (19.7)	0.6	-4.1 to 5.3
APP complete case	77, 100.2 (15.1)	107, 99.6 (15.8)	1.0	-3.5 to 5.6
ITT multiple imputation	145, 97.9 (18.6)	155, 98.2 (19.6)	-0.4	-4.8 to 3.9
ITT complete case	97, 99.6 (14.9)	107, 99.6 (15.8)	0.0	-4.2 to 4.2
<b>Age at surgery (&gt;70 days)</b>				
APP multiple imputation	176, 99.7 (17.0)	201, 99.6 (21.0)	0.3	-3.4 to 4.1
APP complete case	128, 100.7 (13.9)	135, 100.5 (14.9)	0.5	-2.9 to 4.0
ITT multiple imputation	213, 100.0 (17.1)	202, 99.6 (18.7)	0.7	-2.7 to 4.1
ITT complete case	152, 100.9 (13.5)	135, 100.5 (14.9)	0.5	-2.7 to 3.8
<b>Australia</b>				
APP multiple imputation	87, 96.0 (16.7)	103, 97.2 (18.4)	-1.2	-6.2 to 3.9
APP complete case	63, 97.7 (13)	72, 98.6 (15.1)	-0.6	-5.4 to 4.3
ITT multiple imputation	105, 96.9 (18.3)	103, 96.8 (18.6)	0.1	-5.2 to 5.3
ITT complete case	74, 98.4 (12.9)	72, 98.6 (15.1)	0.1	-4.5 to 4.6
<b>USA</b>				
APP multiple imputation	49, 99.3 (18.9)	77, 99.6 (19.9)	-0.6	-7.7 to 6.6
APP complete case	34, 101.2 (13.7)	52, 100.2 (16.0)	0.8	-5.6 to 7.2

ITT multiple imputation	71, 98.1 (18.3)	77, 99.5 (18.9)	-1.5	-7.7 to 4.7
ITT complete case	46, 100.2 (13.5)	52, 100.2 (16.0)	-0.5	-6.3 to 5.3
<b>Canada</b>				
APP multiple imputation	16, 93.4 (19.2)	25, 99.1 (19.2)	-5.9	-19.7 to 8.0
APP complete case	10, 97 (12.5)	20, 100.1 (16.9)	-3.8	-17.0 to 9.4
ITT multiple imputation	24, 94.7 (17.1)	25, 99.3 (18.6)	-5.0	-15.4 to 5.5
ITT complete case	14, 95.9 (12.4)	20, 100.1 (16.9)	-4.5	-15.5 to 6.4
<b>New Zealand</b>				
APP multiple imputation	12, 89.5 (19.4)	12, 95.4 (18.5)	-5.9	-23.3 to 11.5
APP complete case	7, 89.6 (13.2)	9, 96.8 (12.9)	-9.9	-24.5 to 4.7
ITT multiple imputation	13, 90.5 (18.2)	12, 96.0 (17.6)	-5.3	20.0 to 9.4
ITT complete case	8, 90.3 (12.4)	9, 96.8 (12.9)	-8.5	-22.5 to 5.4
<b>United Kingdom</b>				
APP multiple imputation	36, 97.8 (19.9)	39, 97.9 (20.1)	1.3	-7.3 to 10.0
APP complete case	27, 98.7 (18.4)	22, 100.1 (15.3)	2.8	-6.5 to 12.0
ITT multiple imputation	44, 96.9 (20.4)	40, 97.6 (20.9)	-0.2	-8.6 to 8.3
ITT complete case	32, 97.8 (18.6)	22, 100.1 (15.3)	0.2	-8.8 to 9.2
<b>Italy</b>				
APP multiple imputation	67, 107.3 (19.0)	81, 101.5 (21.4)	5.6	-1.0 to 12.3
APP complete case	45, 107.8 (12.5)	50, 103.1 (16.2)	4.7	-1.3 to 10.6
ITT multiple imputation	83, 106.5 (17.0)	82, 102.2 (20.9)	4.1	-1.7 to 9.9
ITT complete case	57, 107.2 (11.7)	50, 103.1 (16.2)	4.0	-1.4 to 9.4
<b>The Netherlands</b>				
APP multiple imputation	20, 100.4 (13.4)	19, 99.1 (14.1)	1.3	-7.6 to 10.2
APP complete case	19, 100.3 (12.9)	17, 99.4 (10.3)	1.0	-6.9 to 9.0
ITT multiple imputation	21, 100.9 (13.2)	19, 98.9 (13.1)	2.0	-6.5 to 10.6
ITT complete case	20, 100.7 (12.7)	17, 99.4 (10.3)	1.5	-6.3 to 9.3
*Data are n, M (SD). RA = awake-regional anaesthesia. GA = general anaesthesia. APP = as per protocol. ITT = intention to treat. Note: duration of surgery (< 2 hours vs >= 2 hours) subgroups were not done because all participants had surgery duration < 2 hours				
<b>Table 7: Subgroup analyses for the primary outcome (WPPSI III)</b>				

	Attended 5 year visit			Did not attend 5 year visit		
	RA group, N = 271	GA group, N = 259	Total, N = 530	RA group, N = 90	GA group, N = 99	Total, N = 189
<b>Sex of child</b>						
Female	54 (19.9%)	36 (13.9%)	90 (17.0%)	12 (13.5%)	16 (16.2%)	28 (14.9%)
Male	217 (80.1%)	223 (86.1%)	440 (83.0%)	77 (86.5%)	83 (83.8%)	160 (85.1%)
Age (days) at surgery	67.1 (30.2)	71.9 (31.3)	69.5 (30.8)	79.1 (35.0)	68.7 (32.7)	73.6 (34.1)
Birth weight (kg)	2.4 (0.9)	2.3 (0.9)	2.4 (0.9)	2.2 (0.9)	2.3 (0.9)	2.3 (0.9)

Maternal age at birth						
>21	258 (95.2%)	252 (97.3%)	510 (96.2%)	81 (93.1%)	89 (89.9%)	170 (91.4%)
18-21	9 (3.3%)	6 (2.3%)	15 (2.8%)	2 (2.3%)	8 (8.1%)	10 (5.4%)
<18	4 (1.5%)	1 (0.4%)	5 (0.9%)	4 (4.6%)	2 (2.0%)	6 (3.2%)
PMA (days) at birth	249.5 (27.6)	248.4 (27.2)	249.0 (27.4)	244.6 (31.1)	249.0 (27.2)	246.9 (29.1)
Prematurity						
>=37	121 (44.6%)	115 (44.4%)	236 (44.5%)	42 (46.7%)	47 (47.5%)	89 (47.1%)
<37	150 (55.4%)	144 (55.6%)	294 (55.5%)	48 (53.3%)	52 (52.5%)	100 (52.9%)
2-year Bayley-III scores						
Cognitive scaled score	9.9 (2.7)	9.8 (3.0)	9.9 (2.8)	9.2 (3.4)	8.9 (2.6)	9.0 (3.0)
Language composite score	96.2 (14.7)	95.1 (16.0)	95.7 (15.3)	87.8 (17.0)	89.5 (13.3)	88.7 (15.1)
Motor composite score	98.5 (14.2)	97.2 (13.7)	97.9 (13.9)	94.1 (18.4)	96.0 (13.1)	95.1 (15.7)
Social-emotional scaled score	9.8 (3.8)	9.1 (3.6)	9.5 (3.8)	7.9 (3.5)	8.8 (3.7)	8.4 (3.6)
Attended the 2 year visit						
No	55 (20.3%)	45 (17.4%)	100 (18.9%)	44 (48.9%)	43 (43.4%)	87 (46.0%)
Yes	216 (79.7%)	214 (82.6%)	430 (81.1%)	46 (51.1%)	56 (56.6%)	102 (54.0%)

Data are n (%) unless otherwise specified. RA = awake-regional anaesthesia. GA = general anaesthesia. PMA = postmenstrual age

**Table 8: Characteristics of children that attended the 5 year follow up are compared to the baseline data of the randomised population and the 2 year outcome data for those that attended the 2 year follow up.**

	As per protocol		Intention to treat	
	RA group, N = 287	GA group, N = 356	RA group, N = 361	GA group, N = 358
Psychologist discovered arm of the study the child was randomised to	7 (3.4%)	7 (2.9%)	11 (4.3%)	7 (2.9%)
Paediatrician discovered arm of the study the child was randomised to	13 (8.0%)	13 (6.7%)	16 (7.9%)	13 (6.7%)
Caregiver knew which arm of the study the child was randomised to	105 (51.2%)	118 (47.2%)	131 (51.4%)	118 (47.2%)

Data are n (% of non-missing data). GA= General Anaesthesia; RA= Awake Regional Anaesthesia.

**Table 9: Details of unmasking at 5 year assessment**

## Contributors:

MEMcC was involved in study design, concept and conduct, data coordination, data interpretation, writing the manuscript and revising it critically.

JCdeG was involved in the coordination and supervision of data collection, data analyses and interpretation, revised the manuscript and approved the final manuscript as submitted.

LD contributed to protocol development, data collection, statistical plan, statistical analysis, data interpretation and writing of the manuscript.

ND, DW and GB were involved in study design and conduct, data acquisition and coordination, data interpretation and writing the manuscript.

AG contributed to statistical analyses, statistical analysis plan, data interpretation, and revising the manuscript critically.

RS, RWH, DCB, NM and SS were involved in study design, protocol development, data interpretation and writing the manuscript.

SJS was involved in study conduct, data acquisition and coordination, revising the manuscript and submission of paper.

JM coordinated study conduct in the US including data acquisition and follow-up.

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PLH was involved in study conduct, data acquisition, assistance with statistical analysis plan and editing the manuscript critically.

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GF was involved in study design, data acquisition and contribution to writing the manuscript.

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**Declaration of Interests:**

We declare no competing interests.

**Disclaimer:**

The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health UK.

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