Australian Placental Transfusion Study (APTS): secondary analysis

Supplementary Appendix two

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eMethods

This section provides the reader with additional information on the methods used in the paper, as well as the code in order to reproduce the work.

Hypothetical scenarios

Firstly the true prevalence in the control group was set to 5%, for "assessment tools" of various sensitivities and specificities (80%, 85%, 90%, 95% and 100%) over three true relative risks (RR of 0.25, 0.5 and 0.75). This gave 15 proposed scenarios for the combinations of sensitivity/specificity/prevalence. Then the true prevalence was increased to 10%, and the 15 scenarios were rerun.

For example, at prevalence of 10% in the control arm and a relative risk of 0.5, with perfect sensitivity and specificity, you would expect the observed prevalence in the two arms of the trial to be 10% and 5%. However, with an assessment tool of 90% sensitivity and specificity, this gives a prevalence of 14% (140 = true positive cases * sensitivity + true negative cases * (1-specificity)) in the treatment group, and 18% (180) in the control group. Therefore the relative risk for treatment for this tool is 0.78. We can then calculate the sample size for this difference in proportions with 80% power and 5% significance using standard calculations. The code for this is given below.

```
library(pwr)

## Find sample size for a given true RR, assuming sensitivity and specificity of xx a
nd yy

RRsim_samplesize<- function(rr_true,     ## vector of true relative risks to look at
                            sensitivity, ## vector of sensitivities
                            specificity, ## vector of specificities
                            control_prev,## prevalence in control/placebo group
                            power=0.9    ## power, defaults to 0.9 (90% power)
){

  ##setup inputs
  sens<-rep(sensitivity,   times=length(rr_true)) ## sensitivities
```

```
  spec<-rep(specificity,   times=length(rr_true)) ## specificities
  r_pla<-rep(control_prev, times=length(sens))    ## baseline rate in control group
  n_each<-rep(1000,times=length(sens))  ## number of patients in each group,
                                        ## used to find proportions for inputs

  ## setup for loop
  rr<-vector()
  ss<-vector()
  r_trt<-vector()
  rr_scr<-vector()
  screen_pos_p<-vector()
  screen_pos_t<-vector()
  cases_t<-vector()
  cases_p<-vector()
  noncase_t<-vector()
  noncase_p<-vector()

  # loop thru each scenario
  for (i in 1:length(sens)){
    rr_true2<-rep(rr_true, times=(length(sens)/length(rr_true))) ##adjust length for
loop
    r_trt[i]<-rr_true2[i]*r_pla[i]
    cases_t[i]<-   r_trt[i]*n_each[i]     ## cases in treated
    noncase_t[i]<- n_each[i]-cases_t[i]   ## non cases in treated
    cases_p[i]<-   r_pla[i]*n_each[i]     ## cases in control
    noncase_p[i]<- n_each[i]-cases_p[i]   ## non cases in control
    screen_pos_t[i]<-sens[i]*cases_t[i]+(1-spec[i])*noncase_t[i]
                                          # found as '+' on new tool in trea
ted
    screen_pos_p[i]<-sens[i]*cases_p[i]+(1-spec[i])*noncase_p[i]
                                          # found as '+' on new tool in cont
rol
    rr[i]<-(cases_t[i]/n_each[i])/(cases_p[i]/n_each[i])  ## true RR (should match in
put value)
    rr_scr[i]<-(screen_pos_t[i]/n_each[i])/(screen_pos_p[i]/n_each[i])
                                          # RR given the sensitivity and spe
cificity
    samplesize<-pwr::pwr.2p.test(h=ES.h(p1=screen_pos_t[i]/n_each[i],
                                 p2=screen_pos_p[i]/n_each[i]), power=power)
    ss[i]<-samplesize$n*2                 # return overall samplesize
  }
  return(cbind(rr, rr_scr, sens, spec,ss))
}

scenario1<-RRsim_samplesize(rr_true = c(0.25, 0.5, 0.75),
                            sensitivity = c(1, 0.95, 0.9, 0.85, 0.8),
                            specificity = c(1, 0.95, 0.9, 0.85, 0.8),
                            control_prev = 0.1
                            )

scenario2<-RRsim_samplesize(rr_true = c(0.25, 0.5, 0.75),
                            sensitivity = c(1, 0.95, 0.9, 0.85, 0.8),
                            specificity = c(1, 0.95, 0.9, 0.85, 0.8),
                            control_prev = 0.15
                            )
```

Costings

Given the online system for ASQ-3 form completion, we assumed the following costs for the ASQ-3, as of April 2024:

- USD$850 per year for ASQ online subscription for assumed five years,
- USD$295 per site for the ASQ-3 kit, for assumed 20 sites,
- USD$0.50 per child for the questionnaire in the online system,
- USD$100 per child as site payment for ASQ completion

See https://brookespublishing.com/asq-product-packages/ for more details.

For the Bayley-III, we assumed a cost of AUD$1149 per child, based upon the Doyle et al paper. This was the cost in 2012 in Australia, so with CPI indexing, in 2024 this is equivalent to AUD$1529. Converting to USD$, this becomes USD$997 per child in 2024. We then assumed:

- USD$997 per child for the developmental assessment,
- USD$100 per child as site payment for completion

Reference: Doyle LW, Clucas L, Roberts G, Davis N, Duff J, Callanan C, McDonald M, Anderson PJ, Cheong JL. The cost of long-term follow-up of high-risk infants for research studies. J Paediatr Child Health. 2015 Oct;51(10):1012-6. doi: 10.1111/jpc.12892. Epub 2015 Apr 14.

The code to produce the comparison is given below.

```
sites<-20
years<-5

## for scenario one above:

bayley_200<- (996+200)*ceiling(scenario1[,5])
asq_200<-200.5*ceiling(scenario1[,5])+850*years+295*sites
```

eTables and eFigures

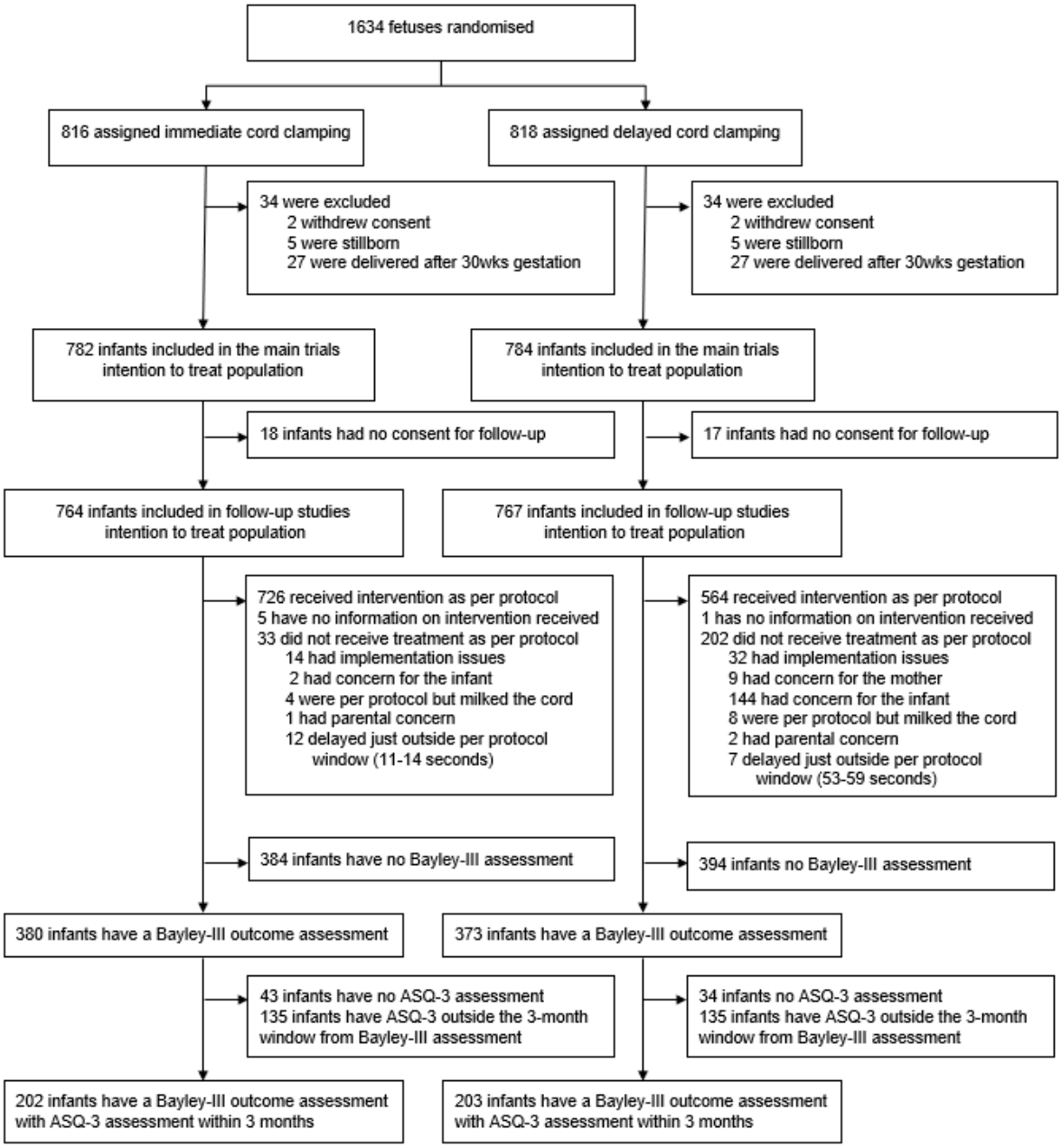

Figure S1: *Consort diagram for this secondary analysis*

Table S1: *ASQ-3 domains mapped to Bayley-III domains*

ASQ-3 domains	Bayley-III domains
Problem solving	Cognitive
Communication	Language
Gross motor	Motor scale – gross motor
Fine motor	Motor scale – fine motor
Personal-social	Social emotional
-	Adaptive behavior

Table S2: *Participant characteristics by treatment*

Characteristic	**Immediate cord clamping**, N = 202[1]	**Delayed cord clamping**, N = 203[1]
Country of randomization		
Australia	147 (73%)	140 (69%)
France	17 (8.4%)	21 (10%)
New Zealand	38 (19%)	42 (21%)
Gestational age at birth, weeks	27.9 (26.5, 28.9)	27.8 (26.4, 28.9)
Multiple birth status †		
Singleton	163 (81%)	154 (76%)
Twin	36 (18%)	45 (22%)
Triplet	3 (2%)	4 (2%)
Birth weight, grams	994 (814, 1,199)	1,000 (809, 1,185)
Mode of delivery		
Vaginal with instruments	14 (6.9%)	13 (6.4%)
Vaginal without instruments	72 (36%)	67 (33%)
Cesarean section in labor	34 (17%)	32 (16%)
Cesarean section not in labor	82 (41%)	90 (45%)
Gender of infant		
Female	75 (37%)	94 (47%)
Male	127 (63%)	108 (53%)
Age at assessment of ASQ-3*, months	24 (24, 27)	24 (24, 27)

[1]n (%); Median (IQR)
† Infants of multiple births underwent randomization independently
*Bayley-III assessment was performed within 3 months of this age

Table S3: Participant characteristics at birth and 2 years, comparing those in our cohort (n=405) to the remaining APTS infants with no matched ASQ-3 or Bayley-3 data (n=1161)

	Not in ASQ/Bayley cohort, N = 1,161[1]	**ASQ-Bayley cohort**, N = 405[1]
Characteristics around birth		
Randomized treatment		
Immediate cord clamping	580 (50%)	202 (50%)
Delayed cord clamping	581 (50%)	203 (50%)
Country of randomization		
Australia	749 (65%)	287 (71%)
Canada	6 (0.5%)	0 (0%)
France	14 (1.2%)	38 (9.4%)
New Zealand	224 (19%)	80 (20%)
Northern Ireland	81 (7.0%)	0 (0%)
Pakistan	68 (5.9%)	0 (0%)
USA	19 (1.6%)	0 (0%)
Gender of infant		
Female	513 (44%)	170 (42%)
Male	648 (56%)	235 (58%)
Calculated Gestational age at birth (weeks)	27.86 (26.29, 28.86)	27.86 (26.43, 28.86)
Gestation 27 weeks or older	763 (66%)	279 (69%)
Birth weight (grams)	980 (790, 1,204)	995 (810, 1,190)
Caesarean section	790 (68%)	239 (59%)
Mode of Delivery		
Vaginal with instruments	57 (4.9%)	27 (6.7%)
Vaginal without instruments	314 (27%)	139 (34%)
Cesarean section in labor	258 (22%)	67 (17%)
Cesarean section not in labor	532 (46%)	172 (42%)
Birth Presentation		
Cephalic	723 (62%)	241 (60%)
Breech	386 (33%)	145 (36%)
Other, including transverse	41 (3.5%)	19 (4.7%)
Unknown	11 (0.9%)	0 (0%)
Multiple birth status		
Singleton	858 (74%)	318 (79%)
Twin	264 (23%)	80 (20%)
Triplet	35 (3.0%)	7 (1.7%)
Quadruplet	4 (0.3%)	0 (0%)
Were uterotonics administered?	1,061 (91%)	368 (91%)
Did the mother receive a Blood Transfusion?	40 (3.4%)	11 (2.7%)

	Not in ASQ/Bayley cohort, N = 1,161[1]	**ASQ-Bayley cohort**, N = 405[1]
Ethnicity of the mother		
White	824 (71%)	319 (79%)
Aboriginal or Torres Strait Islander	52 (4.5%)	14 (3.5%)
Asian	200 (17%)	44 (11%)
Pacific Islander or Māori	72 (6.2%)	15 (3.7%)
Other	13 (1.1%)	13 (3.2%)
Outcomes at 2-years		
Died by 2 years	141 (14%)	0 (0%)
Unknown	121	0
Major disability at 2 years	203 (25%)	100 (25%)
Unknown	336	0
Disabilities at 2 years* (may be more than one per infant)		
Cerebral Palsy	16 (1.8%)	2 (0.5%)
Unknown	267	0
Severe visual loss	2 (0.2%)	0 (0%)
Unknown	270	0
Deafness	8 (0.9%)	3 (0.7%)
Unknown	274	2
Major problems with language or speech	165 (19%)	76 (19%)
Unknown	285	0
Cognitive delay	76 (9.4%)	52 (13%)
Unknown	349	0

[1]n (%); Median (IQR)

*according to definitions detailed in the APTS follow-up statistical plan (supplementary appendix one).

Table S4: *Sensitivity and Specificity for ASQ-3 traditional and optimal cut-points using Bayley domains less than 80*

	Traditional				Optimal			
Domain	Sensitivity	Specificity	Likelihood Ratio (positive)	Likelihood Ratio (negative)	Sensitivity	Specificity	Likelihood Ratio (positive)	Likelihood Ratio (negative)
Cognition	54% (33-73)	90% (86-93)	5.23 (3.29-8.32)	0.51 (0.34-0.78)	77% (56-91)	64% (59-69)	2.13 (1.66-2.73)	0.36 (0.18-0.73)
Language	50% (38-62)	92% (89-95)	6.63 (4.22-10.43)	0.54 (0.43-0.68)	79% (68-87)	75% (69-80)	3.13 (2.5-3.92)	0.28 (0.18-0.44)
Fine motor	50% (23-77)	89% (85-92)	4.51 (2.49-8.18)	0.56 (0.33-0.95)	64% (35-87)	87% (83-90)	4.89 (3.07-7.8)	0.41 (0.2-0.83)
Gross motor	52% (31-73)	90% (86-92)	4.98 (3.06-8.12)	0.53 (0.35-0.82)	70% (47-87)	84% (79-87)	4.22 (2.97-6)	0.36 (0.2-0.68)

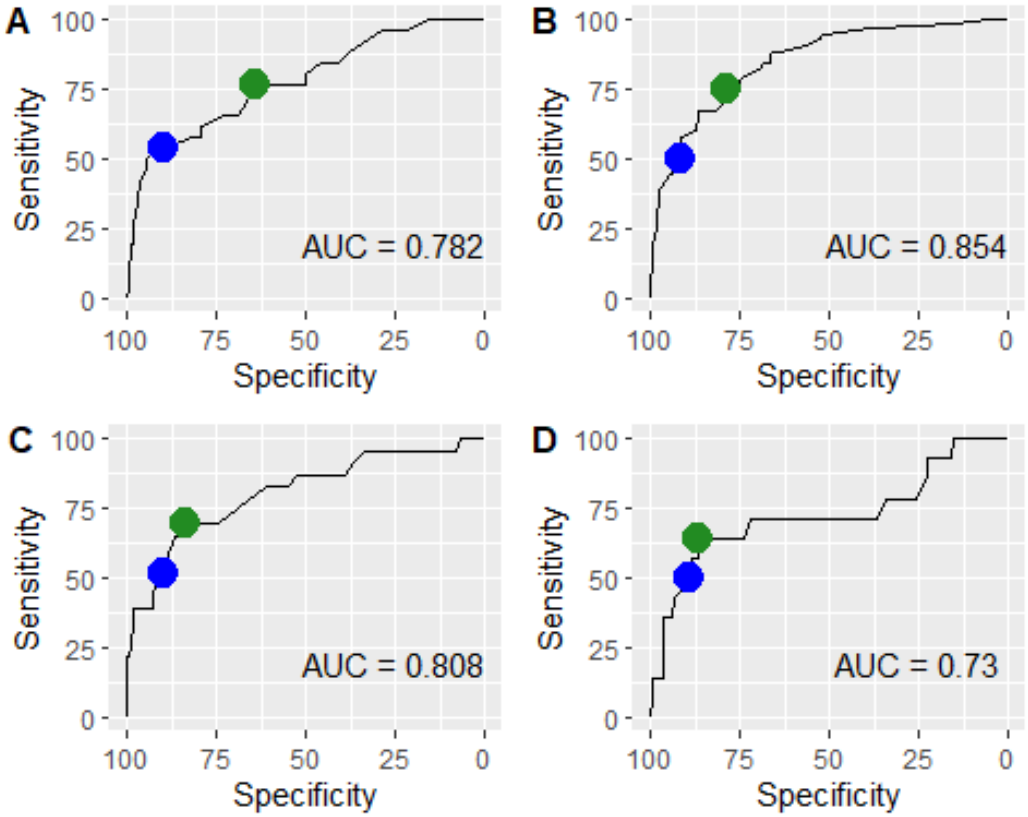

Figure S2: *ROC using delay <80 for ASQ-3 domains: (A) cognitive, (B) language, (C) gross motor and (D) fine motor. Blue indicates traditional cutpoints, and green indicates optimal cutpoints.*

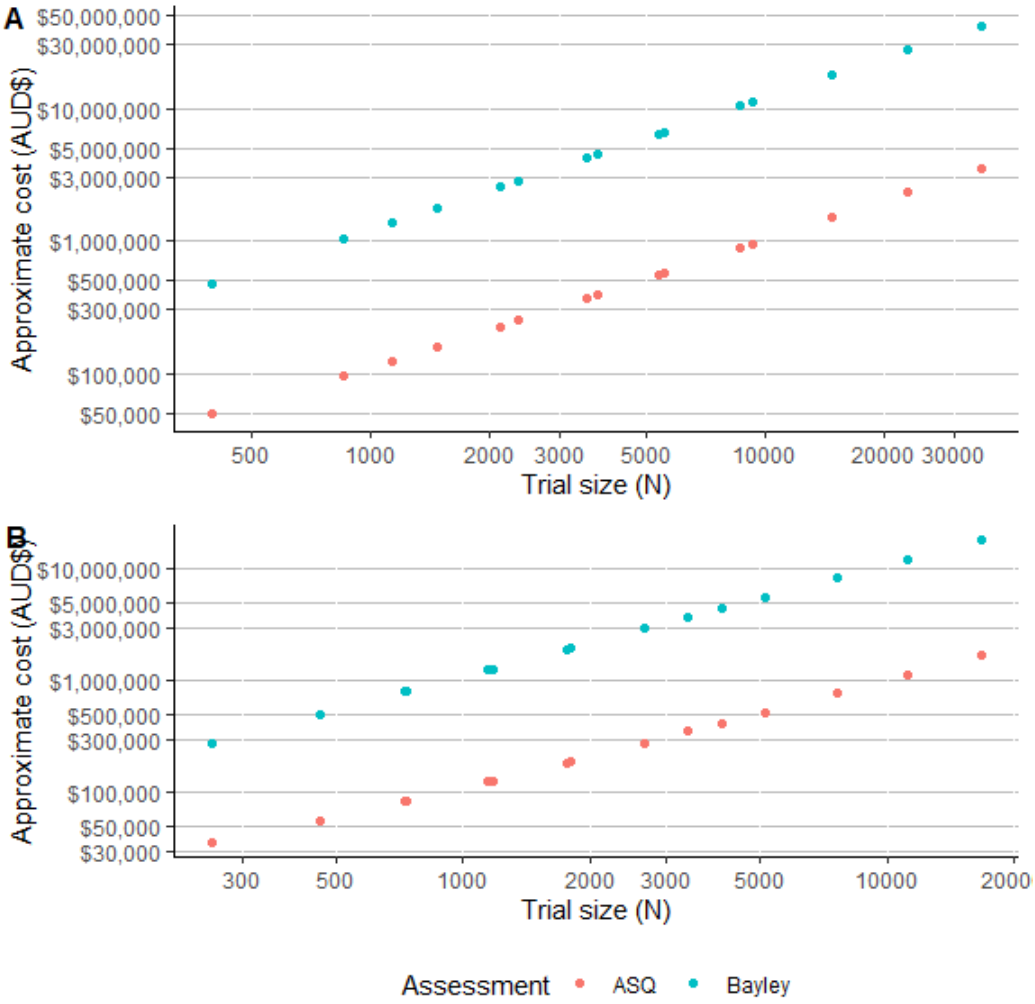

Figure S3: *Approximate cost of trial follow-up assessments using the ASQ-3 compared to the Bayley-III for scenarios with a control rate of 10% delay (A) and 15% delay (B). Assuming 20 sites performing follow-up over 5 years, with ASQ-3 costs of USD$850 per year for ASQ online subscription plus USD$0.50 per child, USD$295 per site for the ASQ-3 kit, and USD$100 per child as site payment for ASQ-3 completion. Bayley-III is assumed as USD$996 per child for the assessment, and USD$100 per child site payment for completion.*