Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710. DOI: 10.1056/NEJMoa1401731

Supplementary Appendix

Supplement to: DeBaun et al. Transfusion Trial for Silent Cerebral Infarcts in Sickle Cell Anemia

Contents:

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Supplement to Methods:

M. DeBaun (Chair, PI), designed the SIT Trial, after completion of a feasibility trial[11] and in conjunction with J. Casella (Vice Chair, co-PI) and other members of the Executive Committee (R. McKinstry, D. White, M. Noetzel, R. Ichord, D. Hirtz), and members of the initial Data Coordinating Center for the SIT Trial (M. Terrin and B. Barton of the Maryland Medical Research Institute). The data in the trial was gathered by the site investigators and research coordinators at each participating site. Data collected by the research coordinators at each site was overseen by the site Principal Investigators. At least one site visit was conducted by M. DeBaun, J. Casella, or J. Strouse and often a second site visit was conducted by M. DeBaun with research coordinators to review the quality of the data and research governance documents pertaining to the trial. Data was collected and entered into a REDCap database specifically designed for the SIT Trial and monitored for accuracy and completion by the Data and Statistical Coordinating Center of the SIT Trial located at Washington University School of Medicine in St. Louis and the Clinical Coordinating Center located at Vanderbilt University School of Medicine. M. DeBaun and M. Gordon, analyzed the data and vouch for the data and analyses. M. DeBaun wrote the first draft with statistical analysis input and review from M. Gordon and J. P. Miller. Review and editing of the manuscript was completed by members of the Executive Committee. Members of the Executive Committee and the site investigators made the decision to publish this paper.

Statistics

In 2010 the DSMB approved a reduction in sample size to 196, given a lower than predicted dropout rate and no expected loss in statistical power.

Supplemental Tables:

Table S1. Intention to treat analysis. - Comparison between randomization groups on changes in Wechsler Abbreviated Scale of Intelligence (WASI) performance, verbal, and full IQ score from baseline to interim and to exit visits with estimated least squares means (LSM) and based on two-way repeated measures analysis of variance.

WASI	Group	Time														
		Baseline					Interim					Exit				
		N	LSM	Std Err	95% CI		N	LSM	Std Err	95% CI		N	LSM	Std Err	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Performance IQ	Observation	86	92.6	1.4	89.9	95.3	71	93.7	1.4	90.9	96.5	80	94.9	1.4	92.2	97.7
	Transfusion	86	91.0	1.4	88.3	93.6	80	93.9	1.4	91.1	96.6	86	92.3	1.4	89.6	94.9
Verbal IQ	Observation	87	96.8	1.5	93.8	99.8	71	98.7	1.6	95.6	101.8	80	97.5	1.5	94.5	100.6
	Transfusion	85	93.2	1.5	90.2	96.1	80	94.3	1.5	91.3	97.3	87	92.0	1.5	89.1	95.0
Full IQ	Observation	86	94.1	1.4	91.4	96.8	71	95.7	1.4	92.9	98.4	80	95.7	1.4	93.0	98.4
	Transfusion	85	91.2	1.4	88.6	93.9	80	93.4	1.4	90.7	96.1	86	91.2	1.4	88.5	93.8

	Baseline to Interim				Baseline to Exit			
	Between Group (Transfusion vs. Observation) Difference in Change	95% CI		p-value	Between Group (Transfusion vs. Observation) Difference in Change	95% CI		p-value
		Lower	Upper			Lower	Upper	
Performance IQ	-1.8	-4.7	1.2	0.2	1.1	-1.9	4.0	0.5
Verbal IQ	0.7	-2.6	4.1	0.7	1.9	-1.4	5.1	0.3
Full IQ	-0.6	-3.4	2.2	0.7	1.7	-1.1	4.4	0.2

Note:

1. Non-significant interaction term suggested that there is no difference between observation and transfusion groups with respect to the IQ changes from baseline to interim and exit visits.
2. Data is analyzed by randomization assignment; cross-overs are ignored.
3. In total, 171 subjects at baseline, 151 subjects at interim, and 166 subjects at exit have Full IQ scores which are the sum of T scores of four subscale, Vocabulary, Similarities, Matrix, and Block. Full IQ score cannot be calculated if there is missing data in the subscales.

Intelligence Quotient (IQ)
Number (N)
Standard Error (Std Err)

Table S2. Intention to treat analysis. - Comparison between randomization groups on changes in Behavior Rating Inventory of Executive Functioning (BRIEF) subtests from baseline to interim and to exit visits with estimated least squares means (LSM) based on two-way repeated measures of analysis of variance.

		Time														
BRIEF Subtests	Group	Baseline					Interim					Exit				
		N	LSM	Std Err	95% CI		N	LSM	Std Err	95% CI		N	LSM	Std Err	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Inhibit	Observation	87	52.2	1.2	49.9	54.6	73	51.7	1.3	49.2	54.2	81	51.9	1.2	49.5	54.3
	Transfusion	88	51.9	1.2	49.6	54.3	79	52.1	1.2	49.6	54.5	86	52.4	1.2	50.0	54.7
Shift	Observation	87	53.2	1.2	50.9	55.5	73	54.0	1.3	51.5	56.4	78	53.7	1.2	51.3	56.1
	Transfusion	88	53.5	1.2	51.2	55.8	80	53.4	1.2	51.0	55.7	87	52.4	1.2	50.0	54.7
Control	Observation	87	53.8	1.3	51.3	56.2	73	53.2	1.3	50.6	55.8	81	52.0	1.3	49.4	54.5
	Transfusion	88	54.4	1.2	52.0	56.9	79	52.9	1.3	50.3	55.4	86	53.2	1.3	50.7	55.6
BR	Observation	87	53.4	1.2	51.0	55.9	73	53.2	1.3	50.6	55.8	80	52.7	1.3	50.2	55.2
	Transfusion	87	53.6	1.2	51.2	56.1	79	53.0	1.3	50.5	55.5	88	53.4	1.2	50.9	55.8
Initiate	Observation	87	53.6	1.1	51.4	55.8	73	53.2	1.2	50.8	55.5	81	53.0	1.2	50.7	55.3
	Transfusion	88	51.9	1.1	49.7	54.1	79	53.0	1.2	50.7	55.3	85	51.9	1.1	49.6	54.1
Memory	Observation	87	57.4	1.3	54.8	59.9	73	57.3	1.4	54.6	59.9	81	56.5	1.3	53.9	59.1
	Transfusion	88	57.0	1.3	54.5	59.6	80	56.9	1.3	54.3	59.5	87	56.7	1.3	54.2	59.3
Plan	Observation	87	54.9	1.2	52.6	57.3	73	54.3	1.3	51.8	56.8	81	53.0	1.2	50.6	55.5
	Transfusion	86	54.3	1.2	51.9	56.6	80	55.6	1.2	53.2	58.1	86	53.8	1.2	51.4	56.2
Organization	Observation	86	51.5	1.0	49.4	53.5	73	51.8	1.1	49.7	53.9	81	52.0	1.1	49.9	54.0
	Transfusion	88	51.2	1.0	49.2	53.2	79	50.6	1.1	48.6	52.7	85	50.7	1.0	48.7	52.8
Monitor	Observation	86	51.5	1.2	49.2	53.8	73	51.9	1.2	49.5	54.3	81	51.5	1.2	49.2	53.8
	Transfusion	87	51.0	1.2	48.8	53.3	80	51.8	1.2	49.5	54.2	87	52.1	1.2	49.8	54.3
MT	Observation	87	54.5	1.2	52.2	56.9	73	54.6	1.2	52.1	57.1	80	53.9	1.2	51.5	56.3
	Transfusion	87	53.7	1.2	51.4	56.1	80	54.5	1.2	52.1	56.9	88	53.4	1.2	51.1	55.8
GEC	Observation	87	54.5	1.2	52.1	56.9	73	54.3	1.3	51.8	56.8	81	53.6	1.2	51.1	56.0
	Transfusion	87	54.0	1.2	51.6	56.4	80	54.2	1.2	51.8	56.7	88	53.7	1.2	51.3	56.1

BRIEF Subtests	Baseline to Interim				Baseline to Exit			
	Between Group (Transfusion vs. Observation) Difference in Change	95% CI		p-value	Between Group (Transfusion vs. Observation) Difference in Change	95% CI		p-value
		Lower	Upper			Lower	Upper	
Inhibit	-0.6	-3.7	2.5	0.7	-0.7	-3.7	2.3	0.6
Shift	0.9	-2.4	4.1	0.6	1.6	-1.6	4.8	0.3
Control	1.0	-2.4	4.3	0.6	-0.6	-3.8	2.7	0.7
BR	0.4	-2.7	3.6	0.8	-0.5	-3.5	2.6	0.8
Initiate	-1.5	-4.4	1.4	0.3	-0.6	-3.4	2.3	0.7
Memory	0.0	-3.0	3.0	1.0	-0.5	-3.4	2.5	0.7
Plan	-2.0	-4.9	0.9	0.2	-1.4	-4.2	1.4	0.3
Organization	0.9	-1.8	3.6	0.5	1.0	-1.6	3.6	0.5
Monitor	-0.4	-3.5	2.6	0.8	-1.0	-4.0	2.0	0.5
MT	-0.7	-3.3	2.0	0.6	-0.3	-2.9	2.3	0.8

GEC	-0.4	-3.1	2.3	0.8	-0.6	-3.2	2.0	0.7

Note: Non-significant interaction term suggested that there is no difference between observation and transfusion groups with respect to the BRIEF changes from baseline to interim and to exit visits. Additionally, data is analyzed by randomization assignment; cross-overs are ignored.

Intelligence Quotient (IQ)
Number (N)
Standard Error (Std Err)
95% Confidence Interval (95% CI)
Behavioral Regulation (BR)
Metacognition (MT)
Global Executive Composite (GEC)

Table S3. Odds Ratio of Baseline Factors for Primary Endpoint (Stroke, New or Enlarged Silent Cerebral Infarction)					
	Primary Endpoint		**Unadjusted**	**Adjusted**	
	Yes (N=20) N (%)	**No (N=176) N (%)**	**OR (95% LCL, 95% UCL)**	**OR (95% LCL, 95% UCL)**	**P Value**
Randomization Group					
Observation (N=97)	14 (14.4)	83 (85.6)	ref		
Transfusion (N=99)	6 (6.1)	93 (93.9)	0.38 (0.14, 1.04)	0.31 (0.10, 0.93)	0.04
Characteristics					
Sex					
Male	11 (9.9)	100 (90.1)	0.93 (0.37, 2.35)		
Female	9 (10.6)	76 (89.4)	ref		
Parental report of recurring headaches					
Yes	13 (16.3)	67 (83.8)	3.02 (1.15, 7.95)	4.43 (1.50, 13.06)	0.007
No	7 (6.0)	109 (94.0)	ref		
	Median (IQR)**	**Median (IQR)**			
Age at Randomization – yr.	7.8 (6.8, 9.2)	10.2 (8.0, 12.1)	1.40 (1.12, 1.75)	1.41 (1.12, 1.78)	0.004
TCD Velocity during screening (cm/sec)*	153 (136.5, 164.5)	145 (128.0, 165.0)	1.01 (0.99, 1.03)		
Rate of Hospital Admissions for Pain† (per 100 person years)	33.3 (0.0, 100.0)	33.3 (0.0, 100.0)	1.00 (0.99, 1.01)		
Rate of Hospital Admissions for ACS† (per 100 person years)	0.0 (0.0, 16.7)	0.0 (0.0, 33.3)	0.99 (0.98, 1.01)		
Steady state hemoglobin (g/dl)	7.8 (7.1, 8.2)	7.8 (7.3, 8.6)	0.91 (0.58, 1.41)		
Hemoglobin F (%)‡	9.5 (4.0, 17.5)	9.0 (5.0, 14.5)	1.00 (0.94, 1.06)		
Steady state reticulocytes (%)	12.1 (10.7, 16.2)	10.8 (8.2, 14.8)	1.06 (0.98, 1.16)	1.11 (1.01, 1.22)	0.038
Steady state WBC (count/ microL) $\times 10^3$	13.1 (11.2, 17.8)	12.1 (10.0, 14.4)	1.01 (0.96, 1.05)		
Steady state platelets (K/ cu mm) 10^3§	455.0 (320.0, 520.0)	431.5 (370.0, 502.5)	1.01 (0.73, 1.40)		
Blood pressure – systolic (mmHg)	107.0 (100.5, 109.5)	108.5 (102.5, 116.0)	0.97 (0.93, 1.01)		
Oximetry reading (%)	96.0 (94.5, 98.0)	97.0 (94.0, 99.0)	0.99 (0.84, 1.17)		

Note: Odds ratios were computed using multiple imputations in stepwise logistic regression and a significance level of 0.1 was required to allow a variable into the model, and a significance level of 0.15 was required for a variable to stay in the model.

* Fifteen points were added to results of imaging TCD to standardize the unit to non-imaging TCD result.
** Interquartile range
† The mean for the rate for of hospital admissions for pain in the primary endpoint group is 71.7 vs. 64.8 in the non-endpoint group. The mean for the rate of hospital admissions for ACS was 15.0 in the primary endpoint group vs. 18.2 in the non-endpoint group.
‡ Type F % at baseline was set to missing if type F % was done prior to 3 years of age or the type F % date was missing and the age at the time of the test could not be computed.
§ Platelet count was divided by 1000.