Supplemental Table 1: Spearman correlations between each parameter and each outcome at age 6 by treatment group.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   |   | Expected Correlation | Joint Bleeds | Other Bleeds | MRI Score | Joint Exam Score |
| FVIIIn = 65 | rp  | - | -0.52<.0001 | -0.60<.0001 | -0.310.013 | -0.0320.81 |
| VWFn = 63 | rp  | - | -0.030.83 | -0.0030.98 | -0.220.086 | -0.20.18 |
| Protein Cn=61 | rp  | + | 0.090.47 | 0.140.27 | 0.0140.91 | 0.170.18 |
| Free PSn=62 | rp  | + | -0.0760.56 | -0.0140.92 | -0.140.27 | -0.0870.50 |
| Total PSn=62 | rp  | + | 0.0540.68 | 0.0770.55 | 0.0390.77 | -0.0870.50 |
| Antihrombinn=61 | rp  | + | 0.150.26 | 0.0740.57 | 0.0380.77 | 0.360.0046 |
| TAFIn=63 | rp  | - | 0.0540.67 | 0.0600.64 | 0.0930.47 | 0.0510.69 |
| TFPIn=62 | rp  | + | -0.200.12 | -0.170.18 | 0.0300.81 | -0.0800.56 |
| APC-Rn=65 | Rp  | + | -0.110.38 | -0.090.49 | -0.040.76 | -0.020.88 |
| CAT Lagtimen=56 | rp  | + | -0.340.010 | -0.300.025 | -0.130.32 | 0.030.83 |
| CAT ETPn=56 | rp  | - | -0.220.096 | -0.280.038 | -0.0340.81 | -0.290.031 |
| CAT Peakn=56 | rp  | - | -0.310.021 | -0.370.0056 | -0.0790.56 | -0.280.037 |
| CAT ttPeakn=56 | rp  | + | -0.0550.69 | -0.00290.98 | 0.0270.84 | 0.110.40 |
| CloFAL CIn=56 | rp  | - | 0.170.22 | 0.140.30 | -0.110.40 | 0.170.22 |
| CloFAL MAn=56 | rp  | - | 0.0170.90 | 0.0250.85 | -0.170.20 | -0.240.076 |
| CloFAL T1n=56 | rp  | + | -0.270.047 | -0.210.12 | 0.0610.66 | -0.0350.80 |
| TATn=61 | rp  | - | -0.120.35 | -0.0560.67 | 0.160.21 | 0.150.26 |
| ELTn=62 | rp  | - | -0.110.39 | -0.170.18 | 0.0510.69 | 0.110.41 |
| FVIII Half-lifen=19 | rp  | - | 0.110.69 | -0.0300.91 | -0.410.13 | -0.480.067 |

Supplemental Table 2: Spearman correlations between each parameter and each outcome at age 6 by treatment group. JE = joint exam score

|  |  |  |
| --- | --- | --- |
| **Prophylaxis Treatment Group** |  | **Episodic Treatment Group** |
|  |  | **Expected Correlation** | **Joint Bleeds** | **Other Bleeds** | **MRI Score** | **JE Score** |  |  | **Joint Bleeds** | **Other Bleeds** | **MRI Score** | **JE Score** |
| FVIII | R | - | -0.32 | -0.36 | -0.14 | 0.10 |  | FVIII | 0.17 | 0.03 | -0.27 | 0.01 |
| n=32 | p  |   | 0.08 | 0.04 | 0.46 | 0.59 |  | n=33 | 0.36 | 0.88 | 0.13 | 0.97 |
| VWF | R | - | -0.15 | -0.06 | -0.09 | -0.17 |  | VWF | -0.04 | -0.09 | -0.32 | -0.14 |
| n=31 | p  |   | 0.43 | 0.77 | 0.61 | 0.36 |  | n=32 | 0.83 | 0.63 | 0.07 | 0.43 |
| Protein C | R | + | 0.02 | 0.10 | 0.22 | 0.15 |  | Protein C | -0.04 | 0.14 | -0.17 | 0.19 |
| n=28 | p  |  | 0.91 | 0.60 | 0.25 | 0.46 |  | n=33 | 0.84 | 0.43 | 0.33 | 0.30 |
| Free PS | R | + | -0.44 | -0.22 | -0.23 | 0.04 |  | Free PS | 0.21 | 0.17 | -0.12 | -0.16 |
| n=29 | p  |   | 0.02 | 0.26 | 0.24 | 0.85 |  | n=33 | 0.24 | 0.35 | 0.51 | 0.37 |
| Total PS | R | + | 0.01 | 0.16 | 0.004 | 0.06 |  | Total PS | -0.004 | 0.004 | -0.01 | -0.20 |
| n=29 | p  |   | 0.98 | 0.41 | 0.98 | 0.75 |  | n=33 | 0.98 | 0.98 | 0.97 | 0.26 |
| Antihrombin | R | + | 0.30 | 0.21 | -0.32 | 0.43 |  | Antihrombin | 0.07 | -0.03 | 0.20 | 0.26 |
| n=28 | p  |  | 0.12 | 0.27 | 0.10 | 0.02 |  | n=33 | 0.69 | 0.88 | 0.26 | 0.15 |
| TAFI | R | - | -0.05 | 0.13 | -0.01 | 0.15 |  | TAFI | 0.06 | -0.06 | 0.10 | -0.04 |
| n=30 | p  |   | 0.77 | 0.50 | 0.95 | 0.43 |  | n=33 | 0.72 | 0.73 | 0.56 | 0.84 |
| TFPI | R | + | -0.43 | -0.27 | -0.14 | -0.28 |  | TFPI | 0.05 | -0.04 | 0.19 | 0.07 |
| n=29 | p  |   | 0.02 | 0.15 | 0.46 | 0.14 |  | n=33 | 0.79 | 0.83 | 0.28 | 0.69 |
| APC-R | R | + | -0.28 | -0.24 | -0.01 | -0.25 |  | APC-R | -0.05 | -0.13 | -0.01 | 0.28 |
| n=32 | p  |  | 0.12 | 0.19 | 0.98 | 0.17 |  | n=33 | 0.77 | 0.47 | 0.96 | 0.11 |
| CAT Lagtime | R | + | -0.08 | -0.16 | -0.04 | -0.18 |  | CAT Lagtime | -0.26 | -0.05 | -0.02 | 0.30 |
| n=28 | p  |   | 0.67 | 0.41 | 0.84 | 0.36 |  | n=28 | 0.18 | 0.79 | 0.94 | 0.12 |
| CAT ETP | R | - | -0.33 | -0.42 | 0.20 | -0.19 |  | CAT ETP | -0.06 | -0.05 | -0.14 | -0.42 |
| n=28 | p  |  | 0.09 | 0.03 | 0.31 | 0.33 |  | n=28 | 0.75 | 0.78 | 0.49 | 0.03 |
| CAT Peak | R | - | -0.43 | -0.45 | 0.11 | -0.22 |  | CAT Peak | -0.05 | -0.12 | -0.12 | -0.39 |
| n=28 | p  |   | 0.02 | 0.02 | 0.58 | 0.25 |  | n=28 | 0.81 | 0.55 | 0.54 | 0.04 |
| CAT ttPeak | R | + | 0.12 | 0.04 | 0.08 | -0.09 |  | CAT ttPeak | -0.07 | 0.10 | 0.09 | 0.30 |
| n=28 | p  |  | 0.54 | 0.86 | 0.70 | 0.64 |  | n=28 | 0.72 | 0.60 | 0.67 | 0.12 |
| CloFAL CI | R | - | 0.23 | 0.14 | -0.24 | 0.20 |  | CloFAL CI | 0.14 | 0.13 | -0.05 | 0.16 |
| n=27 | p  |   | 0.26 | 0.49 | 0.24 | 0.33 |  | n=29 | 0.46 | 0.50 | 0.78 | 0.41 |
| CloFAL MA | R | - | 0.05 | 0.10 | -0.27 | 0.09 |  | CloFAL MA | -0.05 | -0.01 | -0.15 | -0.44 |
| n=27 | p  |  | 0.82 | 0.61 | 0.17 | 0.65 |  | n=29 | 0.81 | 0.95 | 0.43 | 0.02 |
| CloFAL T1 | R | + | -0.40 | -0.23 | 0.02 | -0.18 |  | CloFAL T1 | -0.08 | -0.11 | 0.11 | 0.07 |
| n=27 | p  |   | 0.04 | 0.25 | 0.94 | 0.37 |  | n=29 | 0.67 | 0.59 | 0.58 | 0.72 |
| TAT | R | - | -0.04 | -0.28 | 0.24 | 0.08 |  | TAT | -0.45 | -0.14 | 0.06 | 0.16 |
| n=29 | p  |   | 0.85 | 0.14 | 0.22 | 0.69 |  | n=32 | 0.01 | 0.45 | 0.73 | 0.37 |
| ELT | R | - | -0.09 | -0.22 | -0.12 | 0.19 |  | ELT | 0.22 | -0.02 | 0.35 | 0.05 |
| n=29 | p  |  | 0.65 | 0.25 | 0.53 | 0.32 |  | n=33 | 0.22 | 0.90 | 0.05 | 0.79 |
| FVIII Half-life | R | - | -0.02 | 0.15 | -0.24 | -0.62 |  | FVIII Half-life | -0.12 | -0.18 | -0.54 | -0.45 |
| n=8 | p  |   | 0.95 | 0.72 | 0.56 | 0.10 |  | n=11 | 0.72 | 0.59 | 0.080 | 0.16 |
| Adherence | R | - | 0.21 | 0.29 | -0.09 | 0.27 |   | Adherence | 0.00 | 0.11 | -0.26 | 0.19 |
| n=29 | p  |   | 0.25 | 0.11 | 0.610 | 0.13 |   | n=33 | 0.98 | 0.55 | 0.15 | 0.28 |

Supplemental Table 3: Results of Univariate Logistic Regression for the influence of each parameter on MRI joint failure at age 18.

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Odds Ratio Estimate (95% CI)** | **p-value** |
| FVIII Trough | 0.41 (0.20,0.87) | 0.019 |
| VWF | 0.99 (0.97,1.02) | 0.79 |
| Protein C | 1.02 (0.96,1.08) | 0.58 |
| Free Protein S | 1.01 (0.97,1.05) | 0.64 |
| Total Protein S | 1.01 (0.96,1.05) | 0.93 |
| Antithrombin | 1.02 (0.96,1.08) | 0.50 |
| TAFI | 1.11 (0.79,1.55) | 0.56 |
| TFPI | 1.20 (0.12,11.73) | 0.88 |
| APC-R | 0.067 (<0.001,221.27) | 0.51 |
| CAT Lagtime | 1.01 (0.87,1.16) | 0.92 |
| CAT ETP | 0.99 (0.99,1.00) | 0.23 |
| CAT Peak | 0.94 (0.86,1.02) | 0.15 |
| CAT ttPeak | 1.06 (0.92,1.22) | 0.44 |
| CloFAL CI | 1.00 (0.96,1.04) | 0.99 |
| CloFAL T1 | 1.01 (0.98,1.05) | 0.43 |
| CloFAL MA | 0.18 (<0.001,>999.999) | 0.72 |
| TAT | 0.89 (0.72,1.12) | 0.29 |
| ELT | 1.01 (0.99,1.01) | 0.28 |
| Treatment Group (Prophy vs Episodic) | 0.16 (0.033,0.75) | 0.021 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   |   | Expected Correlation | ABR | J-ABR | MRI Score | JE Score |
| FVIIIn = 37 | rp  | - | -0.70<0.0001 | -0.480.0027 | -0.250.14 | -0.0500.77 |
| VWFn = 36 | rp  | - | -0.0540.75 | 0.00820.96 | 0.0230.90 | 0.110.53 |
| Protein Cn=36 | rp  | + | 0.0910.60 | 0.0410.81 | 0.0840.63 | 0.140.40 |
| Free PSn=36 | rp  | + | 0.110.52 | 0.170.31 | -0.160.35 | -0.310.067 |
| Total PSn=36 | rp  | + | 0.0330.85 | 0.110.51 | -0.150.37 | -0.0230.89 |
| Antihrombinn=36 | rp  | + | -0.190.26 | -0.0720.68 | -0.0430.81 | -0.0210.90 |
| TAFIn=36 | rp  | - | -0.00230.99 | 0.0900.60 | -0.00380.98 | -0.0320.85 |
| TFPIn=35 | rp  | + | 0.0330.85 | -0.00580.97 | -0.0650.71 | -0.430.010 |
| APC-Rn=37 | Rp  | + | -0.350.033 | -0.270.11 | -0.0390.82 | 0.210.21 |
| CAT Lagtimen=32 | rp  | + | -0.350.048 | -0.310.082 | -0.160.40 | -0.0750.68 |
| CAT ETPn=32 | rp  | - | -0.190.3 | 0.0160.93 | -0.0810.66 | 0.380.032 |
| CAT Peakn=32 | rp  | - | -0.280.12 | -0.0410.82 | -0.150.42 | 0.300.10 |
| CAT ttPeakn=32 | rp  | + | -0.0250.89 | -0.0920.61 | 0.0710.71 | -0.160.40 |
| CloFAL CIn=30 | rp  | - | 0.00110.99 | 0.00980.96 | -0.0770.69 | -0.0420.83 |
| CloFAL MAn=30 | rp  | - | 0.110.58 | 0.0940.62 | -0.100.58 | 0.260.16 |
| CloFAL T1n=30 | rp  | + | -0.110.58 | -0.140.48 | 0.0310.87 | 0.190.31 |
| TATn=35 | rp  | - | 0.0220.91 | -0.170.33 | -0.0620.73 | 0.210.23 |
| ELTn=35 | rp  | - | 0.0330.85 | 0.100.57 | 0.220.21 | 0.0820.64 |
| FVIII Half-lifen=11 | rp  | - | 0.110.74 | 0.100.77 | 0.180.60 | -0.390.23 |

Supplemental Table 4: Spearman Correlations with Each Outcome at age 18. ABR = annualized bleeding rate from birth to age 18. J-ABR = annualized joint bleeding rate from birth to age 18. MRI score for this analysis was using the 45-point eMRI scale. Joint exam (JE) score here was the Colorado Pediatric Joint Assessment Scale score.

|  |  |  |
| --- | --- | --- |
| **Prophylaxis Treatment Group** |  | **Episodic Treatment Group** |
|  |  | **Expected Correlation** | ABR | J-ABR | MRI Score | JE Score |  | ABR | J-ABR | MRI Score | JE Score |
| FVIIIn=18 | Rp | - | -0.570.013 | -0.230.35 | -0.340.19 | -0.120.63 | FVIIIn=19 | -0.060.81 | 0.0190.94 | 0.190.43 | 0.220.36 |
| VWFn=17 | Rp | - | 0.0340.90 | 0.150.56 | 0.250.34 | -0.050.84 | VWFn=32 | -0.080.75 | -0.110.64 | -0.130.60 | 0.230.35 |
| Protein Cn=17 | Rp | + | 0.190.48 | 0.410.10 | 0.110.69 | 0.370.14 | Protein Cn=33 | 0.0110.96 | -0.410.081 | -0.0560.82 | -0.040.86 |
| Free PSn=17 | Rp | + | -0.290.25 | -0.110.68 | -0.210.44 | -0.190.47 | Free PSn=33 | 0.360.13 | 0.270.25 | -0.190.43 | -0.430.068 |
| Total PSn=17 | Rp | + | 0.0380.88 | 0.120.63 | 0.0250.93 | -0.100.70 | Total PSn=33 | 0.210.40 | 0.110.65 | -0.250.31 | 0.0720.77 |
| Antihrombinn=17 | Rp | + | -0.130.62 | 0.0220.93 | -0.170.53 | -0.220.41 | Antihrombinn=33 | -0.240.33 | -0.270.26 | -0.0060.98 | 0.130.59 |
| TAFIn=17 | Rp | - | 0.0580.83 | 0.150.55 | 0.210.44 | -0.220.40 | TAFIn=33 | 0.270.27 | 0.170.47 | -0.130.59 | 0.170.49 |
| TFPIn=16 | Rp | + | -0.250.34 | -0.380.14 | -0.270.33 | -0.440.086 | TFPIn=33 | 0.160.52 | 0.150.54 | -0.0450.86 | -0.420.075 |
| APC-Rn=18 | Rp | + | -0.280.26 | -0.180.46 | -0.350.17 | 0.230.35 | APC-Rn=33 | -0.550.014 | -0.230.34 | 0.360.13 | 0.210.39 |
| CAT Lagtimen=28 | Rp | + | -0.030.90 | 0.130.63 | 0.150.57 | -0.020.94 | CAT Lagtimen=28 | -0.100.71 | -0.400.14 | -0.320.25 | -0.020.95 |
| CAT ETPn=28 | Rp | - | -0.260.31 | 0.200.44 | -0.090.74 | 0.290.26 | CAT ETPn=28 | -0.270.33 | -0.150.60 | 0.0290.92 | 0.520.046 |
| CAT Peakn=28 | Rp | - | -0.300.25 | 0.200.45 | -0.070.79 | 0.190.46 | CAT Peakn=28 | -0.250.36 | -0.100.72 | -0.0360.90 | 0.470.08 |
| CAT ttPeakn=28 | Rp | + | 0.0690.79 | 0.0220.93 | 0.160.56 | -0.120.64 | CAT ttPeakn=28 | 0.130.64 | -0.050.85 | -0.0380.89 | -0.230.41 |
| CloFAL CIn=15 | Rp | - | 0.290.29 | 0.520.048 | 0.310.26 | 0.0910.75 | CloFAL CIn=29 | -0.060.82 | -0.290.29 | -0.380.16 | -0.130.66 |
| CloFAL MAn=15 | Rp | - | 0.160.57 | 0.210.46 | 0.0160.95 | 0.370.17 | CloFAL MAn=29 | -0.110.69 | -0.090.76 | -0.210.45 | 0.150.61 |
| CloFAL T1n=15 | Rp | + | -0.360.19 | -0.600.018 | -0.420.12 | 0.0430.88 | CloFAL T1n=29 | 0.0460.87 | 0.180.51 | 0.370.18 | 0.300.27 |
| TATn=16 | Rp | - | -0.500.05 | -0.570.021 | -0.230.42 | 0.0490.86 | TATn=32 | 0.0400.87 | -0.320.18 | 0.0780.75 | 0.260.29 |
| ELTn=16 | Rp | - | -0.030.91 | 0.190.47 | 0.490.066 | 0.0130.96 | ELTn=33 | 0.0250.92 | 0.250.31 | 0.0860.72 | 0.110.66 |

Supplemental Table 5: Spearman Correlations with Each Outcome at age 18 by treatment group.