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 |
| FVIII  n = 65 | r  p | - | -0.52  <.0001 | -0.60  <.0001 | -0.31  0.013 | -0.032  0.81 |
| VWF  n = 63 | r  p | - | -0.03  0.83 | -0.003  0.98 | -0.22  0.086 | -0.2  0.18 |
| Protein C  n=61 | r  p | + | 0.09  0.47 | 0.14  0.27 | 0.014  0.91 | 0.17  0.18 |
| Free PS  n=62 | r  p | + | -0.076  0.56 | -0.014  0.92 | -0.14  0.27 | -0.087  0.50 |
| Total PS  n=62 | r  p | + | 0.054  0.68 | 0.077  0.55 | 0.039  0.77 | -0.087  0.50 |
| Antihrombin  n=61 | r  p | + | 0.15  0.26 | 0.074  0.57 | 0.038  0.77 | 0.36  0.0046 |
| TAFI  n=63 | r  p | - | 0.054  0.67 | 0.060  0.64 | 0.093  0.47 | 0.051  0.69 |
| TFPI  n=62 | r  p | + | -0.20  0.12 | -0.17  0.18 | 0.030  0.81 | -0.080  0.56 |
| APC-R  n=65 | R  p | + | -0.11  0.38 | -0.09  0.49 | -0.04  0.76 | -0.02  0.88 |
| CAT Lagtime  n=56 | r  p | + | -0.34  0.010 | -0.30  0.025 | -0.13  0.32 | 0.03  0.83 |
| CAT ETP  n=56 | r  p | - | -0.22  0.096 | -0.28  0.038 | -0.034  0.81 | -0.29  0.031 |
| CAT Peak  n=56 | r  p | - | -0.31  0.021 | -0.37  0.0056 | -0.079  0.56 | -0.28  0.037 |
| CAT ttPeak  n=56 | r  p | + | -0.055  0.69 | -0.0029  0.98 | 0.027  0.84 | 0.11  0.40 |
| CloFAL CI  n=56 | r  p | - | 0.17  0.22 | 0.14  0.30 | -0.11  0.40 | 0.17  0.22 |
| CloFAL MA  n=56 | r  p | - | 0.017  0.90 | 0.025  0.85 | -0.17  0.20 | -0.24  0.076 |
| CloFAL T1  n=56 | r  p | + | -0.27  0.047 | -0.21  0.12 | 0.061  0.66 | -0.035  0.80 |
| TAT  n=61 | r  p | - | -0.12  0.35 | -0.056  0.67 | 0.16  0.21 | 0.15  0.26 |
| ELT  n=62 | r  p | - | -0.11  0.39 | -0.17  0.18 | 0.051  0.69 | 0.11  0.41 |
| FVIII Half-life  n=19 | r  p | - | 0.11  0.69 | -0.030  0.91 | -0.41  0.13 | -0.48  0.067 |

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 |
| FVIII  n = 37 | r  p | - | -0.70  <0.0001 | -0.48  0.0027 | -0.25  0.14 | -0.050  0.77 |
| VWF  n = 36 | r  p | - | -0.054  0.75 | 0.0082  0.96 | 0.023  0.90 | 0.11  0.53 |
| Protein C  n=36 | r  p | + | 0.091  0.60 | 0.041  0.81 | 0.084  0.63 | 0.14  0.40 |
| Free PS  n=36 | r  p | + | 0.11  0.52 | 0.17  0.31 | -0.16  0.35 | -0.31  0.067 |
| Total PS  n=36 | r  p | + | 0.033  0.85 | 0.11  0.51 | -0.15  0.37 | -0.023  0.89 |
| Antihrombin  n=36 | r  p | + | -0.19  0.26 | -0.072  0.68 | -0.043  0.81 | -0.021  0.90 |
| TAFI  n=36 | r  p | - | -0.0023  0.99 | 0.090  0.60 | -0.0038  0.98 | -0.032  0.85 |
| TFPI  n=35 | r  p | + | 0.033  0.85 | -0.0058  0.97 | -0.065  0.71 | -0.43  0.010 |
| APC-R  n=37 | R  p | + | -0.35  0.033 | -0.27  0.11 | -0.039  0.82 | 0.21  0.21 |
| CAT Lagtime  n=32 | r  p | + | -0.35  0.048 | -0.31  0.082 | -0.16  0.40 | -0.075  0.68 |
| CAT ETP  n=32 | r  p | - | -0.19  0.3 | 0.016  0.93 | -0.081  0.66 | 0.38  0.032 |
| CAT Peak  n=32 | r  p | - | -0.28  0.12 | -0.041  0.82 | -0.15  0.42 | 0.30  0.10 |
| CAT ttPeak  n=32 | r  p | + | -0.025  0.89 | -0.092  0.61 | 0.071  0.71 | -0.16  0.40 |
| CloFAL CI  n=30 | r  p | - | 0.0011  0.99 | 0.0098  0.96 | -0.077  0.69 | -0.042  0.83 |
| CloFAL MA  n=30 | r  p | - | 0.11  0.58 | 0.094  0.62 | -0.10  0.58 | 0.26  0.16 |
| CloFAL T1  n=30 | r  p | + | -0.11  0.58 | -0.14  0.48 | 0.031  0.87 | 0.19  0.31 |
| TAT  n=35 | r  p | - | 0.022  0.91 | -0.17  0.33 | -0.062  0.73 | 0.21  0.23 |
| ELT  n=35 | r  p | - | 0.033  0.85 | 0.10  0.57 | 0.22  0.21 | 0.082  0.64 |
| FVIII Half-life  n=11 | r  p | - | 0.11  0.74 | 0.10  0.77 | 0.18  0.60 | -0.39  0.23 |

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 |
| FVIII  n=18 | R  p | - | -0.57  0.013 | -0.23  0.35 | -0.34  0.19 | -0.12  0.63 | FVIII  n=19 | -0.06  0.81 | 0.019  0.94 | 0.19  0.43 | 0.22  0.36 |
| VWF  n=17 | R  p | - | 0.034  0.90 | 0.15  0.56 | 0.25  0.34 | -0.05  0.84 | VWF  n=32 | -0.08  0.75 | -0.11  0.64 | -0.13  0.60 | 0.23  0.35 |
| Protein C  n=17 | R  p | + | 0.19  0.48 | 0.41  0.10 | 0.11  0.69 | 0.37  0.14 | Protein C  n=33 | 0.011  0.96 | -0.41  0.081 | -0.056  0.82 | -0.04  0.86 |
| Free PS  n=17 | R  p | + | -0.29  0.25 | -0.11  0.68 | -0.21  0.44 | -0.19  0.47 | Free PS  n=33 | 0.36  0.13 | 0.27  0.25 | -0.19  0.43 | -0.43  0.068 |
| Total PS  n=17 | R  p | + | 0.038  0.88 | 0.12  0.63 | 0.025  0.93 | -0.10  0.70 | Total PS  n=33 | 0.21  0.40 | 0.11  0.65 | -0.25  0.31 | 0.072  0.77 |
| Antihrombin  n=17 | R  p | + | -0.13  0.62 | 0.022  0.93 | -0.17  0.53 | -0.22  0.41 | Antihrombin  n=33 | -0.24  0.33 | -0.27  0.26 | -0.006  0.98 | 0.13  0.59 |
| TAFI  n=17 | R  p | - | 0.058  0.83 | 0.15  0.55 | 0.21  0.44 | -0.22  0.40 | TAFI  n=33 | 0.27  0.27 | 0.17  0.47 | -0.13  0.59 | 0.17  0.49 |
| TFPI  n=16 | R  p | + | -0.25  0.34 | -0.38  0.14 | -0.27  0.33 | -0.44  0.086 | TFPI  n=33 | 0.16  0.52 | 0.15  0.54 | -0.045  0.86 | -0.42  0.075 |
| APC-R  n=18 | R  p | + | -0.28  0.26 | -0.18  0.46 | -0.35  0.17 | 0.23  0.35 | APC-R  n=33 | -0.55  0.014 | -0.23  0.34 | 0.36  0.13 | 0.21  0.39 |
| CAT Lagtime  n=28 | R  p | + | -0.03  0.90 | 0.13  0.63 | 0.15  0.57 | -0.02  0.94 | CAT Lagtime  n=28 | -0.10  0.71 | -0.40  0.14 | -0.32  0.25 | -0.02  0.95 |
| CAT ETP  n=28 | R  p | - | -0.26  0.31 | 0.20  0.44 | -0.09  0.74 | 0.29  0.26 | CAT ETP  n=28 | -0.27  0.33 | -0.15  0.60 | 0.029  0.92 | 0.52  0.046 |
| CAT Peak  n=28 | R  p | - | -0.30  0.25 | 0.20  0.45 | -0.07  0.79 | 0.19  0.46 | CAT Peak  n=28 | -0.25  0.36 | -0.10  0.72 | -0.036  0.90 | 0.47  0.08 |
| CAT ttPeak  n=28 | R  p | + | 0.069  0.79 | 0.022  0.93 | 0.16  0.56 | -0.12  0.64 | CAT ttPeak  n=28 | 0.13  0.64 | -0.05  0.85 | -0.038  0.89 | -0.23  0.41 |
| CloFAL CI  n=15 | R  p | - | 0.29  0.29 | 0.52  0.048 | 0.31  0.26 | 0.091  0.75 | CloFAL CI  n=29 | -0.06  0.82 | -0.29  0.29 | -0.38  0.16 | -0.13  0.66 |
| CloFAL MA  n=15 | R  p | - | 0.16  0.57 | 0.21  0.46 | 0.016  0.95 | 0.37  0.17 | CloFAL MA  n=29 | -0.11  0.69 | -0.09  0.76 | -0.21  0.45 | 0.15  0.61 |
| CloFAL T1  n=15 | R  p | + | -0.36  0.19 | -0.60  0.018 | -0.42  0.12 | 0.043  0.88 | CloFAL T1  n=29 | 0.046  0.87 | 0.18  0.51 | 0.37  0.18 | 0.30  0.27 |
| TAT  n=16 | R  p | - | -0.50  0.05 | -0.57  0.021 | -0.23  0.42 | 0.049  0.86 | TAT  n=32 | 0.040  0.87 | -0.32  0.18 | 0.078  0.75 | 0.26  0.29 |
| ELT  n=16 | R  p | - | -0.03  0.91 | 0.19  0.47 | 0.49  0.066 | 0.013  0.96 | ELT  n=33 | 0.025  0.92 | 0.25  0.31 | 0.086  0.72 | 0.11  0.66 |

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