

**Supplemental Data**

Supplemental Table 1: eMRI Scoring Sheet, from Hong W, Raunig D, Lundin B. Haemophilia. 2016;22(6):e519-e526. MRIs from the original JOS were rescored using this scoring system.

**JOINT:** Elbow R ( ) L ( ); Knee R ( ) L ( ); Ankle R ( ) L ( )

**SOFT-TISSUE CHANGES**

	Effusion/hemarthrosis	Synovial hypertrophy	Hemosiderin
Small	_____	_____	_____
Moderate	_____	_____	_____
Large	_____	_____	_____

**OSTEOCHONDRAL CHANGES**

	Humerus Femur Tibia	Ulna Tibia Talus	Radius Patella Fibula
<b>Erosions of joint surface or joint margins:</b>			
Any surface erosion	_____	_____	_____
Half or more of the articular surface eroded	_____	_____	_____
<b>Subchondral cysts:</b>			
At least one subchondral cyst	_____	_____	_____
More than one subchondral cyst	_____	_____	_____
Subchondral cysts involving more than one third of the articular surface	_____	_____	_____
<b>Cartilage degradation:</b>			
Any cartilage damage	_____	_____	_____
Any loss of joint cartilage height involving more than one third of the articular surface	_____	_____	_____
Loss of half or more of the total volume of joint cartilage	_____	_____	_____
Full-thickness loss of joint cartilage in at least some area	_____	_____	_____
Full-thickness loss of joint cartilage involves at least one third of the articular surface	_____	_____	_____
Full-thickness loss of joint cartilage involves at least half of the articular surface	_____	_____	_____
Full-thickness loss of joint cartilage involves at least two thirds of the articular surface	_____	_____	_____

x = positive; (x) = probable; (-) = probably negative; - = negative; 0 = not able to evaluate

**Total (max 45:9/36) \_\_\_\_\_:\_\_\_\_\_/\_\_\_\_\_**

Comparison of Joint Assessment Physical Exam Scales

Supplemental Table 2: Colorado Pediatric Joint Assessment Scale (CPJAS) used in the JOS-C. From Hacker MR, Funk SM, Manco-Johnson MJ. Haemophilia. 2007;13(1):71-78.

Appendix A. Modified Colorado Haemophilia Paediatric Joint Physical Examination Scale.\*

Scale component	Score	Physical findings
Swelling	0	No swelling
	1	Mild: joint looks slightly puffy; slight palpable swelling is present; may not be any measurable difference between the joints; bony landmarks clearly visible
	2	Moderate: joint looks swollen; swollen area feels firm on palpation; may feel boggy; there is a measurable difference between the joints; bony landmarks are palpable but not visible
	3	Severe: swollen and tense to palpation; there is measurable difference between the joints, and the bony landmarks are difficult to palpate
Muscle atrophy	0	No muscle atrophy
	1	Mild: muscle has slightly less contour than the contralateral side
	2	Moderate: flattening of the muscle belly
	3	Severe: severe muscle wasting and depression
Axial alignment	0	Normal: 0–8° valgus and 0° varus
	1	9–15° valgus or 1–5° varus
	2	>15° valgus or >5° varus
Range of motion	0	Normal: no loss
	1	Mild loss: loss of <10% of total range of motion (ROM)
	2	Moderate loss: loss of 10–33% of total ROM
	3	Severe loss: loss of >33% of total ROM
Contracture	0	No contracture
	1	Mild: 1–7°
	2	Moderate: 8–15°
	3	Severe: >15°
Crepitus	0	No crepitus
	1	Mild: barely detectable, audible or palpable sensation during motion
	2	Moderate: more pronounced crackling and/or rough sound or sensation during motion
	3	Severe: very audible and palpable grinding and crunching during motion
Strength (Break Test)	0	Normal: moves easily through full ROM against gravity without observable/measurable atrophy and can take additional resistance
	1	Moves through full or available ROM easily against gravity; may have observable/measurable atrophy and can take some additional resistance
	2	Moves through full or available ROM against gravity; cannot take additional resistance
	3	Unable to move through full or available ROM against gravity owing to weakness <i>Children under 4 years cannot perform a strength break test. Refer to instruction manual for age-appropriate skills and scoring criteria</i>
Gait	0	Normal walking, running, skipping, galloping, stairs
	1	Normal walking and at least one gait abnormality
	2	Abnormal walking and abnormal higher level skills <i>Refer to instruction manual for a list of normal gait components</i>
Splinting/orthotics	0	None
	1	Used as needed after an acute haemarthrosis or for occasional support
	2	Used regularly for high activity sports or to prevent recurrent hermarthrosis
	3	Used constantly
Pain with activity	0	Wong-Baker Face 0
	1	Wong-Baker Faces 1 or 2: hurts a little bit or a little bit more
	2	Wong-Baker Face 3: hurts even more
	3	Wong-Baker Faces 4 and 5: hurts a whole lot and as much as you can imagine
Pain without activity	0	Wong-Baker Face 0
	1	Wong-Baker Faces 1 or 2: hurts a little bit or a little bit more
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\*Refer to the instruction manual for the information necessary to conduct a physical joint examination.

The CPJAS differs from the original JOS scale in the following ways: (A) The axial alignment score delineations in the JOS were [0] no deformity, [1] 10° valgus to 5° varus, [2] >10° valgus or >5° varus, (B) The original JOS score did not include crepitus. After determining that 38% of severe hemophilia A patients under age 6 in our local database exhibit crepitus, the crepitus aspect of the score was subtracted from the JOS-C score when comparing scores longitudinally.

The CPJAS measures the same physical exam features but differs in scoring from the HJHS 2.1 (Feldman BM, Funk SM, Bergstrom BM, et al. Arthritis Care Res (Hoboken). 2011;63(2):223-230.), which is more commonly used today, in the following ways:

(A) HJHS 2.1 includes an additional point for swelling present  $\geq 6$  months. Recent analyses (unpublished data) show that this question is patient-reported and not objective, and future versions of HJHS will remove this (paper submitted).

(B) For muscle atrophy and crepitus measurements, HJHS combines moderate and severe measurements (so both 2 and 3 on CPJAS would score a 2 on HJHS).

(C) Range of motion loss for CPJAS is separated on HJHS into extension and flexion loss, and score cutoffs are different for HJHS [0] <5° loss, [1] 5-10° loss, [2] 11-20° loss, [3] >20° loss.

(D) Joint pain in HJHS is only scored if pain during range of motion, whereas CPJAS includes pain with and without activity.

(E) HJHS has 4 categories for strength instead of 3.

(F) HJHS has 4 possible scores for gait instead of 2.

(G) HJHS includes a joint laxity score but the CPJAS does not.

Supplemental Factor Product Information:

Sixteen (43%) participants were primarily treated with Kogenate® in the JOS-C, although only 7 (19%) were treated exclusively with Kogenate®. Many participants used multiple FVIII products: 27% used one other FVIII product, 24% used 2 other FVIII products, and 22% used 3 other FVIII products. One participant used a plasma-derived product. Six participants used long-acting factor products, including Adynovate® and Eloctate®, for up to 2 years of the JOS-C study period.

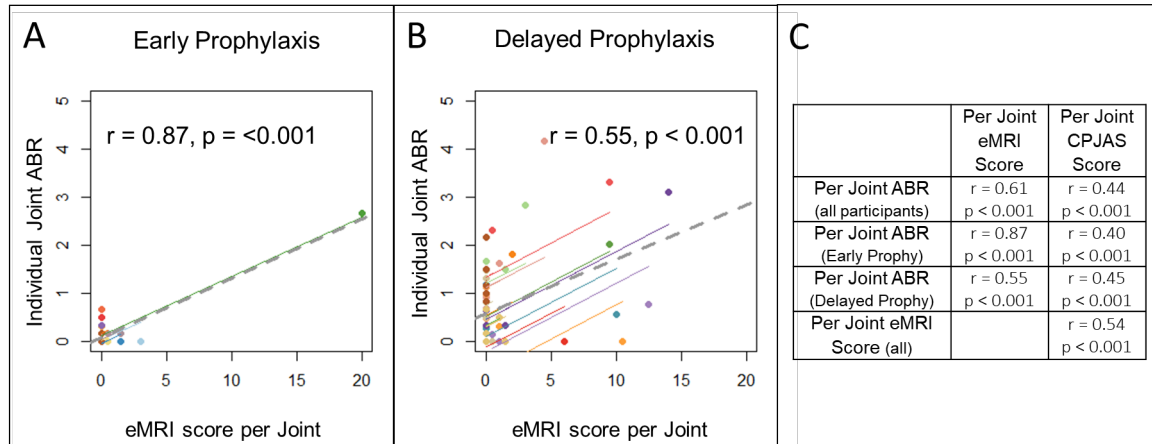
Adverse Events

There were no participant deaths. There were no differences in frequency of adverse events between the early and delayed prophylaxis groups (table 4). Participants underwent a total of 36 surgeries related to hemophilia, including 30 (16 early prophylaxis, 14 delayed prophylaxis) surgeries related to venous access (e.g. mediport replacement or removal). There were 3 joint surgeries: 1 ankle fusion and 1 knee synovectomy on the delayed prophylaxis arm, and 1 ankle fusion on the early prophylaxis arm.

**Supplemental Table 3:** JOS-C Adverse Events. Hemophilia-related illnesses and surgeries included predominantly central line surgeries, central line-associated bacterial infections, with a few hospitalizations for bleeding episodes and one episode of anaphylaxis to a new factor product. Mean and median numbers refer to number of events per person during the study period.

	<b>Early Prophylaxis</b>	<b>Delayed Prophylaxis</b>
Participants in Analysis	15	18
Life-Threatening Bleeds	1 (epistaxis requiring transfusion)	1 (subdural hematoma)
Hemophilia-related Illnesses and Surgeries	Mean: 1.7±2.1 Median: 1	Mean: 1.7±2.4 Median: 1
Non-hemophilia related illnesses and surgeries	Mean: 1.1±1.4 Median: 1	Mean: 1.4±1.6 Median: 1

**Supplemental figure 1:** Repeated measures correlation between individual joint ABR and eMRI scores at age 6 for (A) early prophylaxis and (B) delayed prophylaxis groups. Each color represents a participant, each dot represents an index joint, and each line represents the relationship correlation between the variables listed on the axes. Additional repeated measures correlations are shown in panel C.



**Supplemental figure 2:** Summary of factor VIII inhibitor development during the JOS and JOS-C. High titer inhibitors are defined as inhibitors > 5 Bethesda units. Low titer inhibitors are defined as > 0.6 Bethesda units.

