i) **Title page**

Title:

Reliability of the submaximal iSTEP performance test in children with Haemophilia

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ii) Main text:

Ongoing advancements in medical treatment have vastly improved health outcomes in boys with Haemophilia over the past ten years. Prophylaxis has reduced the number of bleeding episodes, which is reflected in positive changes to their lifestyles and long-term outlook [1]. Physical activity is recognised as essential for maintaining health, and boys with Haemophilia are now encouraged to regularly participate in physical activities to improve their strength, fitness and endurance, and to enhance their quality of life. In recent years, the inclusion of physical performance testing at routine clinical follow-up, alongside the HJHS, has been advocated for boys with Haemophilia [2]. One such measure of physical performance is the iSTEP, which is a quick and simple sub-maximal incremental exercise step test, with good clinical utility. The test protocol is published in clinicaltrials.gov [3] and is also provided in Appendix 1.

A feasibility study by Thorpe et al. established feasibility, safety and acceptability in children and young people (CYP) with Haemophilia [4] and showed that CYP with Haemophilia are less likely to complete the iSTEP compared to typically developing children, with only 53.5% of boys (23/43) completing level 5 on the iSTEP, compared with 83.3% (20/24) of similarly aged unaffected boys [5,6]. However, the reliability of the iSTEP for evaluating exercise capacity in boys with Haemophilia has not yet been established in clinical or research settings. In accordance with the recommendations of COSMIN (Consensus based Standards for the selection of health status Measurement Instruments), this study aimed to determine the test-retest reliability of the iSTEP test in boys with Haemophilia in order to provide a more comprehensive evaluation of the test's psychometric properties for wider clinical use, patient benefit and future research [7]. Ethical approval was obtained

from the Health Research Authority - Central London Research Ethics Committee (ref: 17/LO/1192).

Boys aged 6-15 years with mild, moderate or severe Haemophilia A or B, with or without inhibitors, were identified from clinic lists at Great Ormond Street Hospital for Children NHS Foundation Trust UK (GOSH). Exclusion criteria included musculoskeletal or central nervous system problems, joint or muscle bleed in the lower limb in the past six weeks, lower limb pain or a diagnosis of severe uncontrolled asthma or exercise-induced bronchoconstriction. All boys who met the eligibility criteria during the study period (Feb 2019- August 2019) were invited to participate. Parents or legal guardians of the eligible participants were initially approached via telephone to provide a brief explanation of the study. The patient information sheet was sent (via post) to the families who expressed interest in the study.

Twenty-two boys and families consented to take part. Two participants reported recent calf muscle and ankle joint injuries reported on the day of testing and were not tested. Following screening and informed consent, all participants were tested on the iSTEP twice (T1 and T2) on the same day with an interval of one hour between the two tests. Two physiotherapists involved in testing were randomly allocated to administer T1 or T2 and were blinded to the results of the test performed by the other physiotherapist.

The primary outcome was the time taken to complete iSTEP in seconds, and the secondary outcomes were peak heart rate (PHR), Wong-Baker Pain Rating Scale (WBPRS), and OMNI perceived exertion scale measured immediately after completing the iSTEP. The Intraclass Correlation Coefficient (ICC) estimates and

their 95% confidence intervals (CI) were calculated (SPSS statistical package version 25) for test-retest reliability based on an absolute agreement, 2-way mixed-effects model. T-test and Wilcoxon tests were used to compare differences between the two tests.

Twenty boys participated in this study; 17 were diagnosed with Haemophilia A and 3 with Haemophilia B. There were 15 participants diagnosed with severe Haemophilia, 1 moderate, 3 mild, and 1 participant had an inhibitor. The mean age was 11.45 years (SD: 2.68), and no participant had radiological evidence of joint arthropathy. One participant also had a respiratory condition and three participants were diagnosed with Autistic Spectrum Disorder (ASD). Table 1 includes the disease and anthropometric characteristics for all participants, those who completed the iSTEP and those who were unable to complete the iSTEP. Individual participant's anthropometric measurements and time and levels completed on the iSTEP are provided in the supplementary information, Table SI-1.Thirteen of the twenty participants (65%) completed all five levels on the iSTEP on both occasions, and one participant completed on the second attempt only. Children as young as seven years were able to follow the instructions and were able to complete the test successfully.

The ICC for time to complete the test was 0.88 (95% CI =0.72, 0.95). The average time to complete iSTEP was 517.50 sec (SD: 120.26) for T1 and 511.35 sec (SD: 156.31) for T2. Times taken to complete T1 and T2 were not significantly different (p=0.7), with a mean difference of 6.15 seconds, 95% CI= -26.46, 38.76. The average PHR was 180.9 bpm (SD: 17.61) for T1 and 178.2 bpm (SD:17.75) for T2, with no significant difference between the two tests. Similarly, there were no significant differences in the WBPRS and OMNI scores reported by the participants

at the end of the first and second test. The results of all the participants are presented in Table 2.

Results suggest that the overall test-retest reliability of the iSTEP test was moderate to good in CYP with Haemophilia for time to complete the iSTEP [8]. The comparison of PHR in both tests (T1 and T2) indicated that boys performed near their maximal capacity on both occasions. Using Bongers et al. (2014) age and gender-matched predicted HRmax for children, we found that 95% (19/20) worked above 80% of their predicted maximal Heart Rate (HRmax) [9] showing that boys with Haemophilia made comparable cardiovascular effort to their unaffected peers.

The iSTEP completion rate in this reliability study was 65%, which is higher than 53.3 % reported by Thorpe et al. [6] but still considerably lower than unaffected peers (83.3%) [5]. However, the fact that two-thirds of boys with haemophilia did complete the iSTEP test suggests a ceiling effect in this cohort, which precludes discrimination of physical performance in CYP performing at a higher level. This further highlights the need for establishing psychometric properties for higher-level physical performance tests in boys with Haemophilia that are sensitive to sub-clinical joint problems and associated functional or endurance deficits.

Further exploration of data from participants who were unable to complete the iSTEP test revealed some interesting findings. Firstly, five of the seven non-completers had high BMI (four of whom were obese), and they all stopped on their own due to fatigue and breathlessness. One of the overweight (but not obese) participants managed to complete the test on the second occasion suggesting some learning effect. Secondly, all four participants with comorbidities (ASD and respiratory condition) were unable to complete the test. Of these four, two also had

a high BMI. Thirdly, two participants (one with ASD and the other with a respiratory condition) were unable to concentrate and focus on the task and had difficulty maintaining a coordinated stepping pattern; both were, for safety reasons, stopped by the investigators before completion during both tests. Finally, for only one participant, the step height was increased to 20 cm as per the test protocol, where the height of the step is standardised for each child and is set on approximately 50% of the length of the child's fibula. This increased step height could have potentially hindered his performance on the iSTEP due to the increased effort required when stepping. However, this participant was also on the 89th BMI centile, so it is difficult to assess whether either or both reasons contributed to his non-completion. These findings appear to indicate that the iSTEP test might be used as a screening tool to identify children who have suboptimal physical performance levels, whether or not this is directly related to their Haemophilia diagnosis.

No adverse events were observed by investigators or reported by the participants, indicating that the iSTEP test may be safe to use in boys with Haemophilia. However, for children presenting with reduced coordination or attention difficulties, close monitoring is required to reduce the risk of falling during testing. Additionally, none of the participants in this study had known joint arthropathy. Further testing will need to be conducted before using iSTEP on boys with joint damage.

The clinical utility of the iSTEP test is supported as it is low-cost, portable and easy to administer. The iSTEP test is a measure of exercise capacity that can identify sub-maximal physical performance in boys with Haemophilia. It provides objective and useful information about a child or young person's physical performance level, which can then be used to prescribe individualised training programmes and assist in the longitudinal medical management.

In conclusion, the test-retest reliability of the iSTEP appears good but is confounded by a ceiling effect. Given the ease of use and its good clinical utility iSTEP can potentially be used in clinics to identify and monitor children who are not functioning at their optimal level. Further work is needed to establish reliability with a larger sample and a wide age range of boys with Haemophilia.

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Deepti Chugh conducted research, analysed the data, interpreted the results, and wrote the paper. Nicola Thorpe designed and conducted the research. Dr Lucy Alderson and Professor Eleanor Main analysed the data, interpreted the results, and critically commented on draft manuscripts. Melanie Bladen designed the study, analysed the data, interpreted the results, and critically commented on draft manuscripts. All authors read and approved the final manuscript.

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iv) References

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v) Tables

Table 1. Participant disease and anthropometric characteristics

	All Participants N=20	**Completed iSTEP N=13**	**Did not complete iSTEP N=7**
Age mean (SD)	11.45 (2.68)	11.58 (2.63)	11.71 (2.98)
Diagnosis			
Haemophilia A	17	10	7
Haemophilia B	3	3	0
Severity			
Mild	3	1	2
Moderate	1	1	0
Severe	15	10	5
Inhibitor	1	1	0
Treatment			
Prophylaxis	17	12	5
On demand	2	0	2
Novel Treatment	1	1	0
Known joint arthropathy	0	0	0
Comorbidities			
Autistic Spectrum Disorder	3	0	3
Cystic Fibrosis	1	0	1
Height (cm) mean (SD)	152.31 (17.95)	149.18 (15.4)	159.93 (19.11)
Weight (kg) mean (SD)	49.24 (21.79)	41.51 (14.26)	64.36 (24.98)
BMI (Kg/m^2) mean (SD)	20.26 (4.91)	17.99 (2.66)	24.09 (5.76)
BMI centiles			
95th and above (Obese)	4	0	4
85th-94th (Overweight)	2	1	1
5th-84th (normal)	13	11	2
Below 5th (underweight)	0	0	0

Table 2. Results of the primary and secondary outcomes for all participants for Test 1 and Test 2

	iSTEP Test 1	iSTEP Test 2	Mean difference (SD) p value
iSTEP (seconds) Mean (SD)	517.50 (120.26)	511.35 (156.31)	6.15 (69.69); 0.7
Peak Heart Rate Mean (SD)	180.9 (17.61)	178.25 (17.75)	2.65 (8.05); 0.16
Pain immediately post Median (range)	0 (0,2)	0 (0, 3.75)	p= 0.12
OMNI RPE –immediately post Median (range)	6 (2.25, 7)	5.5 (3, 7.8)	p= 0.63

OMNI RPE- OMNI Rate of Perceived Exertion

Supplementary Information – Table SI-1

Participant number	Age (years)	BMI (centile)	Height (cm)	Weight (kg)	Level achieved iSTEP Test 1	Level achieved iSTEP Test 2	Time Completed (seconds) iSTEP Test 1	Time Completed (seconds) iSTEP Test 2
R01	13	30.5 (99)	162.2	80.35	3	3	393	361
R02*	13	17.4 (29)	156.3	42.4	2	1	321	128
R04	12	16.2 (14)	146	34.5	5	5	600	600
R05	10	18.7 (78)	142.1	37.7	5	5	600	600
R06	13	16.1 (10)	140	31.5	5	5	600	600
R07	15	21.2 (67)	164.8	57.5	5	5	600	600
R08	7	14.7 (24)	129	24.5	5	5	600	600
R09*	13	26.4 (96)	164.9	71.8	3	3	360	380
R11*	7	15.7 (55)	124	24.2	2	4	346	480
R12*	13	30.1 (98)	174.1	91.3	2	1	290	144
R13	8	23.5 (98)	153.3	55.2	4	5	480	600
R14	7	19 (92)	131.2	32.7	5	5	600	600
R15	14	22.6 (81)	172.9	67.5	5	5	600	600
R16	12	18.6 (62)	149.7	41.6	5	5	600	600
R17	11	15.3 (12)	148.4	33.8	5	5	600	600
R18	9	15.1 (21)	133.3	26.9	5	5	600	600
R19	14	21.2 (68)	172.7	63.3	5	5	600	600
R20	13	NA	NA	NA	5	5	600	600
R21	14	22.3 (79)	176.6	69.5	5	5	600	600
R22	15	25 (89)	184.7	85.3	3	2	360	334

*Participants with comorbidities; NA- Not available