Aim: Identify and evaluate exercise tests for children and adults with CF

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The following exercise tests are reviewed below:

Incremental cycle ergometry (VO_{2peak}/W_{peak})
6 Minute Walk Test
Modified Shuttle Test – *(adults only as no data found in children)*

For each test, data on reliability, validity (concurrent, predictive, convergent, discriminate) and responsiveness were extracted. For ease of interpretation of the clinimetric property table, a summary has been presented (Table 1). Full data is presented separately for children and adults in Tables 2 to 6. An assessment of feasibility was undertaken for all tests (Table 7). Consensus within the team was reached on answers to four key questions relating to the use of exercise tests in research.

Table 1:
Summary of clinimetric properties of exercise tests in children and adults with CF

		Children		Adults	
Measurement tool	**Cycle ergometry (VO_{2peak}/W_{peak})**	**6 Minute Walk Test**	**Cycle ergometry (VO_{2peak}/W_{peak})**	**6 Minute Walk Test**	**Modified Shuttle Test**
Reliability	I/E	Yes	Yes	N/D	I/E
Validity	Yes	To be discussed *?Accurate for what?*	Yes	To be discussed *?Accurate for what?*	I/E
Responsiveness	Yes (physical training) N/D (IVAB)	Yes (physical training) N/D (IVAB)	Yes	N/D	Yes
Is the measurement biologically plausible	Yes	Yes	Yes	Yes	Yes
Reflection of the clinical severity	Yes	Yes	Yes	Yes	Yes
Correlation with the true outcome	Yes	N/D	Yes	N/D	Yes
Reference values	Yes	Yes	Yes	Reference equations from age 40+ years only Some data from young healthy adults	No

Table 2:
Clinimetric properties of incremental cycle ergometry (VO_{2peak}/W_{peak}) in children with CF

RELIBILITY	<u>Kent et al (unpublished data)</u> Sample: N=16 (9M:7F); mean age: 9.1 (1.6)y mean (SD) FEV_1 %predicted: 88 (17)% W_{peak}: no significant bias (p=0.988); CV=8.9W W_{peak}%predicted: no significant bias (p=0.438); CV=10.0%predicted
VALIDITY	**Concurrent validity:** <u>Gulmans et al 1997a</u> Sample: N=14 (8M:6F) Mean age 14.8 (1.7)y Mean FEV_1% pred. (SD) [range]: 59 (16) Results: vs. $\dot{V}_{O_{2peak}}$ r=0.91 (p<0.001) <u>Pianosi et al 2005a</u> Sample: N=28, mean [range] initial age: 10 [7 to 16]y, mean [range] initial FEV_1%pred: 81 [33 to 137]% Results: Mixed-effects model: significant correlation between FEV_1 and VO_{2peak} over time (p=0.0001). Downward inflection of VO_{2peak} at an FEV_1 of 80% predicted **Predictive validity:** <u>Pianosi et al 2005b</u> Sample: N=28, mean [range] initial age: 10 [7 to 16]y, mean [range] initial FEV_1%pred: 81 [33 to 137]% Results: The hazard ratios indicate a lower risk of death in the follow-up period in patients with higher VO_{2peak}. Final but not initial VO_{2peak} was highly predictive of mortality in the following 8 years (assessed by Kaplan-Meier plot) **Discriminate validity:** <u>Wideman et al 2009</u> Sample: N=10 children with CF, mean [range] age: 15 [10 to 22] years, FEV_1%pred: 78 [45 to 123]. N=10 matched controls Results: VO_{2peak} (L/min): Sig. difference between CF and controls. Mean [range] CF: 1.33 [0.43 to 2.37] vs. control: 2.09 [1.15 to 3.96] (p=0.004) VO_{2peak} (ml/kg/min): Sig. difference between CF and controls. Mean [range] CF: 31 [9 to 45] vs. control: 41 [29 to 65] (p=0.027)

	<u>Selvadurai et al 2004</u> Sample: N=148 children with CF, range age: 9 to 17 years, mild to severe lung disease (categorised by FEV_1%pred) Results: Sig. difference mild vs. moderate to severe in VO_{2peak} (prepubescent girls: 42(8) vs. 41(7) ml/kg/min, $p<0.05$; pubescent girls: 45(9) vs. 36(6) ml/kg/min, $p<0.05$; prepubescent boys: 44(9) vs. 39(6) ml/kg/min, $p<0.05$; pubescent boys: 52(8) vs. 38(7) ml/kg/min, $p<0.05$) Sig. difference mild vs. moderate to severe in W_{peak} (prepubescent girls: 10(2) vs. 9(2) W/kg, $p<0.05$; pubescent girls: 10(2) vs. 9(2) W/kg, $p<0.05$; prepubescent boys: 10(2) vs. 9(2) W/kg, $p<0.05$; pubescent boys: 12(2) vs. 11(2) W/kg, $p<0.05$) <u>Selvadurai et al 2003</u> Sample: N=16 girls with CF, mean (SD) age: 15 (2)years, mean (SD) FEV_1%pred: 96(9), N=16 matched controls Results: VO_{2peak}: No significant difference (CF 36(7) vs. control 39(8) ml/kgLBM/min <u>Selvadurai et al 2002a</u> Sample: N=97, mean (SD) [range] age: 14 (8) [8 to 16] years, FEV_1%pred not significantly different between classes of mutations Results: VO_{2peak} (ml/kg/min): Class I: 30(4), sig. different to classes III, IV and V ($p<0.05$) Class II: 32(5), sig. different to classes III, IV and V ($p<0.05$) Class III: 44(6), sig. different to classes I, II, IV and V ($p<0.05$) Class IV: 54(7), sig. different to classes I, II and III ($p<0.05$) Class V: 54(7), sig. different to classes I, II and III ($p<0.05$) <u>Klijn et al 2003b</u> Sample: N=39, mean (SD) age: 13(2) years, FEV_1%pred: 82(22) Results VO_{2peak} (ml/min): No sig. difference between mild and moderate disease. Mild 1,666(365) vs. moderate 1,605(474) $p>0.05$ VO_{2peak} (%pred): Sig. difference between mild and moderate disease. Mild 87(15) vs. moderate 74(13) $p<0.001$ W_{peak} (W): No sig. difference between mild and moderate disease. Mild 137(31) vs. moderate 129(38) $p>0.05$ <u>Nixon et al 2001</u> Sample: N=30 children with CF, mean (SD) age: 11(3)years, FEV_1%pred: 96(24) [39 to 129], N=30 matched controls

	Results VO_{2peak} (ml/kg/min): sig. difference between CF and control. CF 37(8) vs. control 41(9), p=0.036 W_{peak} (%pred): sig. difference between CF and control. CF 85(26) vs. control 99(16), p=0.012 <u>de Meer et al 1999</u> Sample: N=41 (moderate CF: n=15; mild CF: n=13; healthy: n=13) (moderate CF: 9M:6F; mild CF: 8M:5F; healthy: 8M:5F) Mean age: moderate CF: 14.8 (1.9); mild CF: 15.3 (1.8); healthy: 15.2 (1.9) Mean FEV_1% pred. (SD) [range]: moderate CF: 56 (12); mild CF: 100 (11); healthy: 111 (12) Population: CF children Results: Sig. difference in W_{max} between children with moderate CF and healthy children ($p<0.05$) Moderate CF: 122 (45)W vs. healthy: 201 (38)W mean difference [95%CI]: -79 [-111 to -46]W Sig. difference in W_{max} between children with mild CF and healthy children ($p<0.05$) Mild CF: 166 (37) W vs. healthy: 201 (38) W mean difference [95%CI]: -35 [-56 to -14]W Sig. difference in W_{max}/FFM between children with moderate CF and healthy children ($p<0.05$) Moderate CF: 3.3 (0.8) W/kg vs. healthy: 4.6 (0.3) W/kg mean difference [95%CI]: -1.3 [-1.8 to -0.8]W/kg Sig. difference in W_{max}/FFM between children with mild CF and healthy children ($p<0.05$) Mild CF: 3.9 (0.5) W/kg vs. healthy: 4.6 (0.3) W/kg mean difference [95%CI]: -0.7 [-1.2 to -0.3]W/kg **Convergent validity: No data**
RESPONSIVENESS	<u>IVAB</u> <u>Robinson et al 2009</u> Sample: N=28, mean [range] age: 14 [8 to 17]y, mean [range] FEV_1%pred (on admission): 61 [28 to 92] Results: VO_{2peak} (ml/kg/min): sig. improvement Time 1 to Time 2. Mean [range] on admission: 31 [23 to 45], on discharge: 33 [24 to 52], actual change: 2 [-7.9 to 7.4] FEV_1 (L): sig. improvement Time 1 to Time 2. Mean [range] on admission: 1.74 [0.76 to 3.0], on discharge: 1.85 [0.87 to 3.16], actual change: 0.11 [-0.28 to 0.66] <u>Physical training</u> <u>Orenstein et al 2004</u> Sample: N=62 (32 aerobic group, 30 strength group), mean age: 12 years, FEV_1%pred: aerobic group 92(18)%, strength group 90(18)%

	Results: Aerobic group: W_{peak} (W): Start 4.6(0.3) vs. end 4.7(0.3) p=0.003 VO_{2peak} (ml/kg/min): Start 35(5) vs. end 34(7) p=0.329 Strength group: W_{peak} (W): Start 4.6(0.4) vs. end 4.6(0.3) p=0.032 VO_{2peak} (ml/kg/min): Start 33(6) vs. end 31(7) p=0.065 <u>Klijn et al 2004</u> Sample: N=20 (11 training group, 9 control group), mean (SD) age: training group 14(1), control group 14(2), mean (SD) FEV_1%pred: training group 75(21), control group 82(19) Results: (change from baseline) VO_{2peak} (ml/min): Training group 88(106) p<0.05, control group -48(63) p>0.05 VO_{2peak} (ml/kg/min): Training group 1.5(2.6) p>0.05, control group -0.6(1.9) p<0.05 VO_{2peak} (ml/kgFFM/min): Training group 1.3(4.6) p>0.05, control group -3.2(2.5) p<0.01 VO_{2peak} (%pred): Training group 4.7(5.6) p<0.05, control group -2.1(2.8) p>0.05 W_{peak} (W): Training group 11(14) p<0.05, control group -2(5) p>0.05 <u>Selvadurai et al 2002b</u> Sample: *(NB: Children recruited at start of admission for treatment of acute exacerbation)* N=22 aerobic training, mean (SD) age: 13(2) years, mean (SD) FEV_1%pred: 57(18) N=22 resistance training, mean (SD) age: 13(2) years, mean (SD) FEV_1%pred: 58(17) N=22 control group, mean (SD) age: 13(2) years, mean (SD) FEV_1%pred: 57(17) Results: Aerobic training: FEV_1%pred: at discharge 7(8) p<0.05, 1mth later 6(8) p<0.05; VO_{2peak} (ml/kg/min): at discharge 7(6) p<0.01, 1mth later 8(7) p<0.01 Resistance training: FEV_1%pred: at discharge 10(7) p<0.01, 1mth later 10(8) p<0.01; VO_{2peak} (ml/kg/min): at discharge 1(6) p>0.05, 1mth later 2(6) p>0.05 Control: FEV_1%pred: at discharge 5(7) p<0.05, 1mth later 5(7) p<0.05; VO_{2peak} (ml/kg/min): at discharge -1(6) p>0.05, 1mth later 3(6) p>0.05 <u>Gulmans et al 1999 (3)</u> Sample: N=14 (9M:5F) Mean age: 14.1 (20) [10.2 to 16.4] Mean FEV_1% pred. (SD) [range]: 58.3 (16.3) [28.8 to 84.9] Population: CF children Results: Start to end physical training (6 months)

	W_{max}: no significant difference, Time 1: 127(42) vs. Time 2: 138(47) W W_{max}/BM: no significant difference, Time 1: 2.94(0.61) vs. Time 2: 2.99(0.66) $W \cdot kg^{-1}$ W_{max}/FFM: no significant difference, Time 1: 3.47(0.58) vs. Time 2: 3.60(0.59) $W \cdot kg^{-1}$
Biological Plausibility	There is progression as disease severity increases and accepted as an independent predictor of mortality.
Reflection of Clinical Severity	?
Correlation with "True" Outcome	Independent predictor of mortality and correlates lung function (Pianosi et al, 2005a and b)
NORM VALUES	Godfrey et al 1971

Table 3:
Clinimetric properties of 6 Minute Walk Test in children with CF

RELIABILITY	<u>Balfour-Lynn et al 1998</u> Sample: N=12 (4M:8F) Mean age: 13.6 Mean FEV_1%pred: 64% Population: CF Results: Limits of agreement for difference: SpO_2: -1.7 to +1.0% HR: -34 to +39% Borg: -1.1 to +1.9 (absolute value) <u>Cunha et al 2006</u> Sample: N=16 (5M:11F) Mean age: 11.0 [8 to 16] Mean FEV_1%pred: N/R Disease: CF Results: No sig. difference between tests (p=0.31) <u>Gulmans et al 1996</u> Sample: N=23 (12M:11F) Age range: [8 to 16] Mean FEV_1%pred: 94 [61 to 130] Population: CF Results: No sig. difference between tests 1&2. (p=0.56) Mean(SD): trial 1: 737(85)m; trial 2: 742(90)m R=0.90 (p<0.001)
VALIDITY	**Concurrent validity** <u>Gulmans et al 1996</u> Sample: N=15 (9M:6F) Age range: 10.2 to 16.9 Mean FEV_1%pred: 58.0 [41.1 to 89.4] Population: CF Results: vs. $\dot{V}_{O_{2peak}}$ r=0.76 (p<0.001) vs W_{max} r=0.76 (p<0.001) **Predictive Validity** No data **Convergent Validity** 3 Minute Step Test vs. 6 Minute Walk Test <u>Aurora et al 2001</u> Sample: N=28 (12M:16F) Mean age: 13.7 [7.2 to 17.8] Mean FEV_1%pred: 34 [17 to 67] Population: CF Results: Rise in HR significantly greater in 3MST (p<0.0005) Mean difference: 8% 95%CI [-10.7 to 29.3]% Fall in SpO_2 significantly greater in 3MST (p<0.0005) Mean difference: 1.1% 95%CI [-2.1 to 4.6]%

	Balfour-Lynn 1998 Sample: N=54 (22M:32F) Mean age: 12.5 [6 to 18] Mean FEV_1%pred: 75 [51 to 99] Population: CF Results: Rise in HR significantly greater in 3MST ($p<0.0001$) Mean difference: 14% 95%CI [10 to 18]% Rise in Borg score significantly greater in 3MST ($p<0.0001$) Mean difference: 1.5 95%CI [1.1 to 1.9] Fall in SpO_2 comparable Mean difference: -0.4% 95%CI [-3.2 to 4.0]% Prasad et al 2000 Sample: N=54 (22M:32F) Mean age: 12.5 [6 to 18] Mean FEV_1%pred: 61 [14 to 103] Population: CF Results: Rise in 15 Count Score significantly greater in 3MST ($p<0.0001$) Difference in medians: 1.5 Rise in Borg score significantly greater in 3MST Difference in medians: 2.5 **Discriminate Validity** Swisher et al 2005 Sample: CF: n=21 healthy: n=21 (CF: 9M:12F healthy: 9M:12F) Mean age: 10.5 [5-17] Mean FEV_1%pred: 65% Population: CF Results: Sig. difference in distance walked between children with CF vs. healthy children ($p<0.05$) CF: 490.4 (77.1)m vs. healthy: 556.9 (93.9)m
RESPONSIVENESS	Gruber et al 2008 Sample: N=286 (n/s) Mean age: 11.5 (3.4) Mean FEV_1%pred: 82.7 (22.3) Population: CF Results: Start to end inpatient rehabilitation (physical training, intense airway clearance, high calorie diet) Sig. Improvement in walking distance ($p<0.05$), Time 1: 675.5(74)m vs Time 2: 701.9(83.9)m
Biological Plausibility	It is a submaximal test- may be more related to functional capacity
Reflection of Clinical Severity	Shows progression with increased severity
Correlation with "True" Outcome	?
NORM VALUES	Lammers AE, Hislop AA, Flynn Y, Haworth SG. The 6-minute walk test: normal values for children of 4-11 years of age. Arch Dis Child. 2008; 93:464-468 Li AM, Yin J, Yu CC et al. The six-minute walk test in healthy children: reliability and validity. Eur Respir J 2005;

	25: 1057-60

Table 4:
Clinimetric properties of incremental cycle ergometry (VO_{2peak} W_{peak}) in adults with CF

RELIABILITY	<u>McKone et al 1999</u> Sample: n=9, 6M:3F, mean (SD) age: 26 (8)y, mean [range] FEV_1 %predicted: 56 [30 to 82]%. Completed tests over 28 days (at least 7 days apart). No significant difference between tests in performance or physiological variables: Results: W_{peak} (W): Trial 1: 129 (33), Trial 2: 139 (39), Trial 3: 140 (39); CV=6.0% VO_{2peak} (L/min): Trial 1: 1.48(0.53), Trial 2: 1.52(0.37), Trial 3: 1.57(0.47), CV=6.9%
VALIDITY	**Concurrent validity: No data** **Predictive validity: No data** **Convergent validity: No data** **Discriminate validity:** <u>Troosters et al 2009</u> Sample: n=64 adults with CF, 35M:29F, mean (SD) age: males: 25(6)y, females: 27(9)y, mean (SD) FEV_1(%pred): males: 64(19)%, females: 66(20)% n=20 healthy adults, 11M: 9F, mean (SD) age: males: 24(3)y, females: 26(6)y, mean (SD) FEV_1(%pred): males: 101(16)%, females: 108(5)% Results: W_{peak} (W): CF: 155 (57) vs. healthy: 259 (60) ($p<0.001$), mean diff [95%CI]: 104 [74 to 134] VO_{2peak} (ml/min/kg): CF: 30 (9.7) vs. healthy: 48 (8.1) ($p<0.001$), mean diff [95%CI]: 18 [13 to 23] VO_{2peak} (%pred): CF: 71 (18) vs. healthy: 112 (16) ($p<0.001$), mean diff [95%CI]: 41 [32 to 50] <u>Sahlberg et al 2008</u> Sample: n=19 adults with CF, 12M:7F, mean (SD) age: males: 24.7 (6.6)y, females: 23.2 (6.1)y; FEV_1%predicted: 88(21), males: 92(19), females: 92(19) N=19 healthy adults, 12M:7F, mean (SD) age: males: 26.7 (5.8)y, females: 26.9 (6.6)y Results: No significant difference between adults with CF and healthy adults VO_{2peak} (L/min): females with CF: 1.9(0.6) vs. healthy females: 2.4(0.3) (p=ns) VO_{2peak} (L/min): males with CF: 3.1(0.6) vs. healthy males: 3.5(0.5) (p=ns) VO_{2peak} (ml/kg/min): females with CF: 32.2(8.9) vs. healthy females: 40.4(7.9) (p=ns)

	VO_{2peak} (ml/kg/min): males with CF: 43.4(5.8) vs. healthy males: 48.2(7.2) (p=ns) <u>Alison et al 1997</u> Sample: n=24 adults with CF, 18M:6F, mean (SD) age: 26 (7.7)y, FEV_1 (%pred) Mild: 98.3(3.2)%, Moderate: 58.4(2.8)%, Severe: 24.9(3.2)%. n= 10 healthy adults, 5M:5F, mean (SD) age: 24.6(2.4)y, FEV_1 (%pred): 108.0(3.0) Results: W_{peak} (W): CF: 146 (90) vs. healthy : 211(72) ($p<0.05$) VO_{2peak} (L/min): CF: 1.97 (1.14) vs. healthy : 2.83 (0.93) ($p<0.05$) <u>Moorcroft et al 2005</u> Sample: n=104 adults with CF, mean (SD) age: 25 (7)y, mean (SD) FEV_1%pred: 54 (21)% n=27 healthy adults, mean (SD) age: 26 (5)y, mean (SD) FEV_1%pred: 102 (11)% Significant difference between CF and healthy adults Results: VO_{2peak} (%pred): CF: 64 (16) vs. Healthy: 95 (13) ($p<0.001$) Significant difference between all groups (control vs. mild vs. moderate vs. severe) ($p<0.001$) VO_{2peak} (%pred): Severe: 49 (12)%; Moderate: 66 (10)%; Mild: 76 (13)%; Healthy: 95 (13)% <u>Shah et al 1998</u> n=17 adults with CF, 9M:8F, mean (SD) age: 25(10)y, FEV_1 %pred: 62(21)% Sample: n=17 healthy adults, 10M:7F, mean (SD) age: 25(8)y, FEV_1 %pred: 112(15)% Significant difference between CF and healthy adults Results: W_{peak} (kpm/min): CF: 715 (200) vs. Healthy: 1,185 (360) ($p<0.001$) VO_{2peak} (ml/min/kg): CF: 24.6 (6) vs. Healthy: 35.5 (8.5) ($p<0.001$) <u>Alison et al 1998</u> Sample: n=22 adults with CF, 16M:6F, mean (SD) age: 24(2)y, FEV_1 (%pred): Mild: 101(4)%, Moderate: 68(3)%, Severe: 27(3)% n= 9 healthy adults, 5M:4F, mean (SD) age 25(1)y, FEV_1 (%pred) 108(3)%. Results: W_{peak}(W) Mild CF: 242(51) vs. healthy: 219(24) (p=ns) Moderate CF 149(18) vs. healthy: 219(24) ($p<0.05$) Severe: 72(10) vs. healthy: 219(24) ($p<0.05$)

	VO_{2peak} ($L.min^{-1}$) Mild CF: 3.28(0.59) vs. healthy: 2.92(0.31) (p=ns) Moderate CF: 1.99(0.27) vs. healthy: 2.92(0.31) (p<0.05) Severe CF: 1.06(0.13) vs. healthy: 2.92(0.31)(p<0.05)
RESPONSIVENESS	**IVAB therapy** Alison et al 1994 Sample: n=14, 7M:7F, mean (SD) [range] age: 20 (3) [16 to 28]y Results: Significant improvement in FEV_1%pred: Start IVAB: 46(18)%, End IVAB: 55(22)% (p<0.005) Significant improvement in W_{peak} (W): Start IVAV: 80(36), End IVAB: 95(38) (p<0.001) **Exercise training** Sahlberg et al 2008 Sample: n=47 adults with CF, 25M:22F, mean (SD) age: males: 24.7 (6.6)y, females: 23.2 (6.1)y; FEV_1%predicted: 88(21), males: 92(19), females: 92(19) Results: VO_{2peak} (L/min): Endurance training: 0.11(0.18) vs. Resistance training: -0.17(0.23) (p<0.05) VO_{2peak} (ml/kg/min): Endurance training: 1.55(2.89) vs. Resistance training: -3.15(2.46) (p<0.01) W_{peak} (W): Endurance training: 4.8(11.0) vs. Resistance training: -4.7(13.3) (p<0.05)
Biological Plausibility	There is progression as disease severity increases and accepted as an independent predictor of mortality.
Reflection of Clinical Severity	Dodd et al 2006 Sample: N=22, 13M:9F, mean (SD) [range] age: 22(5.9) [17 to 41]y, mean (SD) [range] FEV_1 %pred: 61(20)[29 to 93]% Results: Correlations W_{peak} (W) vs. FEV_1%pred: r=0.49 (p<0.05) VO_{2peak} (L/min) vs. FEV_1%pred: r=0.39 (p=ns) W_{peak} (W) vs. CT-score (total): r=-0.46 (p<0.05) VO_{2peak} (L/min) vs. CT-score (total): r=-0.45 (p<0.05) W_{peak} (W) vs. CT-score (components): range r= -0.1 (p=ns) to -0.62 (p<0.01) VO_{2peak} (L/min) vs. CT-score (components): range r= -0.09 (p=ns) to -0.58 (p<0.01) FEV_1%pred vs. CT-score (total): r=-0.40 (p<0.05) FEV_1%pred vs. CT-score (components): range r=-0.07 (p=ns) to -0.46 (p<0.05)
Correlation with	Correlates with measures of respiratory structure and lung

"True" Outcome	function (see above)
NORM VALUES	Jones NL. Clinical Exercise Testing. 3rd Edn. Philadelphia, W.B. Saunders, 1988 Wasserman K Principles of Exercise Testing and Interpretation Lippincott Williams & Wilkins; Fourth Edition edition (October 1, 2004)

Table 5:
Clinimetric properties of 6 Minute Walk Test in adults with CF

RELIABILITY	No Data
VALIDITY	**Concurrent validity:** No data **Predictive validity:** No data **Convergent validity:** No data **Discriminate validity:** <u>Chetta et al 2001</u> Sample : n=25 adults with CF, 10M :15F, mean (SD) age: 25(5)y, mean (SD) FEV_1 %pred: 69 (23)%. n= 22 healthy adults, 8M : 14F, mean (SD) age: 26(6)y, mean (SD) FEV_1 %pred: 121(16)% Results: Walk distance: CF: 626(49) vs. healthy: 652(46)m (p=NS) Mean HR : 121(21) vs. healthy: 114(18)bpm (p=NS) Max HR : 143(18) vs. healthy: 136(17)bpm (p=NS) Mean SpO_2 : 92(4) vs. healthy: 97(1)% (p<0.001) VAS: 64(24) vs. healthy: 27(19)mm (p<0.001) <u>Troosters et al 2009</u> Sample: n=64 adults with CF, 35M:29F, mean (SD) age: males: 25(6)y, females: 27(9)y, mean (SD) FEV_1(%pred): males: 64(19)%, females: 66(20)% n=20 healthy adults, 11M: 9F, mean (SD) age: males: 24(3)y, females: 26(6)y, mean (SD) FEV_1(%pred): males: 101(16)%, females: 108(5)% 6MWD (m): CF: 702(82) vs. healthy: 833 (93) (p<0.001), mean diff [95%CI]: 131 [87-174] 6MWD (%pred): CF:91(9) vs. healthy: 107(11) (p<0.001), mean diff [95%CI]: 16[12-21]
RESPONSIVENESS	No Data
Biological Plausibility	It is a submaximal test- may be more related to functional capacity
Reflection of Clinical Severity	Shows progression with increased severity Some correlation with FEV_1
Correlation with "True" Outcome	No Data
NORM VALUES	Some data available in young adults: Troosters et al 2009 Chetta et al 2001 Reference equations developed in healthy adults aged 40y+ Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*

	1998;158:1384–1387. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;14:270–274.

Table 6:
Clinimetric properties of Modified Shuttle Test in adults with CF

RELIABILITY	Bradley et al 2000 Sample: N=12 adults with CF, 9M:3F, mean (SD) [range] age: 30 (15) [15 to 69]y, FEV_1 mean (SD) [range]: 40 (20) [14 to 72]%pred Results: Distance completed: r=0.99 (p<0.01), no significant difference between trials: Trial 1: 754 (361)m vs. Trial 2: 754 (362)m (p=0.98) Mean difference [LA]: 0 [-40 to 40]m
VALIDITY	**Predictive validity:** No data **Convergent validity:** No data **Discriminate validity:** No data **Concurrent validity:** Bradley et al 1999 Sample: N=20 adults with CF, 14M:6F, mean (SD) age: 25 (7)y, FEV_1: 49 (23)%pred Results: No significant difference between tests in physiological response to exercise HR_{peak}: MST: 169(24) beats/min; Treadmill: 171(23) beats/min (p=0.90) Peak rate of perceived breathlessness: MST: 6(1); Treadmill: 6(1) (p=0.90) End SaO_2: MST: 88(7)%; Treadmill: 89(7)% (p=0.10) Correlation MST vs. VO_{2peak}: r=0.95 (p<0.001)
RESPONSIVENESS	Bradley et al 2000 Sample: N=24 adults with CF, 17M:7F, mean (SD) age: 31(10)y, FEV_1 mean (SD): Start of IVAB: 42(20); End of IVAB: 50(26)%pred Results: Distance completed: significant difference between trials: Trial 1: 692(289)m vs. Trial 2: 867(336)m (p<0.01) Mean difference [95%CI]: 175[112 to 237]m Standardised response mean: MST distance: 1.18; FEV_1: 0.96; FEV_1%pred: 0.88 Bradley et al 2001 Sample: N=18 adults with CF, mean (SD) age: 23(5)y, FEV_1 mean (SD): Start of IVAB: 49(17); End of IVAB: 60(25)%pred Results: Distance completed: significant difference between trials: Trial 1: 860(366)m Vs.. Trial 2: 1024(333)m (p<0.01) Mean difference [95%CI]: 164[92 to 236]m Standardised response mean: MST distance: 1.12; FEV_1%pred: 1.03
Biological Plausibility	There is progression as disease severity increases
Reflection of	Bradley et al 1999

Clinical Severity	Sample: N=20 adults with CF, 14M:6F, mean (SD) age: 25 (7)y, FEV_1: 49 (23)%pred Results: MST vs. $FEV_{1\%pred}$: r=0.70 (p=0.001) VO_{2peak} vs. $FEV_{1\%pred}$: r=0.78 (p<0.001)
Correlation with "True" Outcome	Correlates with VO2peak and $FEV_{1\%pred}$
NORM VALUES	No

Table 7:
Summary of feasibility and acceptability of exercise tests

	Children		**Adults**		
Measurement tool	**Cycle ergometry (VO_{2peak}/W_{peak})**	**6 minutes Walk Test**	**Cycle ergometry (VO_{2peak}/W_{peak})**	**6 minutes Walk Test**	**Modified Shuttle Test**
1. Risk involved, safety	To be discussed *ECG systematically done before test. Need at least two persons and medical supervision.*	Safe. Submaximal test	To be discussed *ECG systematically done before test. Need at least two persons and medical supervision.*	Safe. Submaximal test	To be discussed *ECG systematically done before test. Need at least two persons and medical supervision.*
2. Cost (just ongoing costs)	Ongoing cost of consumables and calibration of equipment	No specific equipment required.	Ongoing cost of consumables and calibration of equipment	No specific equipment required.	No specific ongoing costs
3. Ease of performance	Acceptable. Patient motivation	Acceptable. Patients motivation	Acceptable. Patient motivation	Acceptable. Patients motivation	Acceptable. Patients motivation
4. Ease of administration	Acceptable. Follow set protocol	Acceptable.	Acceptable. Follow set protocol	Acceptable.	Acceptable. Follow set protocol
5. Time to administer	Varies. Test <15min	6 minutes plus set-up time	Varies. Test <15min	6 minutes plus set-up time	Varies. (15min)
6. Equipment and space needed, availability	Cycle ergometer Metabolic cart *(resuscitation trolley?)*	30 meters course plus turning space	Cycle ergometer Metabolic cart *(resuscitation trolley?)*	30 meters course plus turning space	CD
7. Applicable age group (suitable for FU after NB screening)	6+ years	4+ years	All	All	All
8. Specific advantages or limitations	<u>Advantages:</u> Linked to survival and FEV1 <u>Limitations</u>: Requires maximal subject motivation Measurement of VO2 etc requires costly gas analysers Gas analysers require calibration.	<u>Advantages:</u> Minimal equipment Can be used across disease severity Safe to use <u>Limitations</u>: Self paced Require a lot of space Very dependent on patient motivation	<u>Advantages:</u> Linked to survival and FEV1 <u>Limitations</u>: Requires maximal subject motivation Measurement of VO2 etc requires costly gas analysers Gas analysers require calibration.	<u>Advantages:</u> Minimal equipment Can be used across disease severity Safe to use <u>Limitations</u>: Self paced Require a lot of space Very dependent on patient motivation	<u>Advantages:</u> Minimal equipment Can be used across disease severity <u>Limitations</u>: Requires maximal subject motivation

Exercise Tests in children and adults with CF
Answers to 4 key questions

1. **Does this outcome have the potential to become a surrogate outcome?**

Incremental Cycle Ergometry VO_{2peak} W_{peak} Yes. This is the "gold standard" measure of metabolic capacity, is a predictor of true outcome measure (survival) and correlates with primary outcome measure (FEV1). It is potentially very valuable across all disease severities.

MST: When incremental cycle ergometry is unavailable it is potentially useful. However it is subject to a ceiling effect in patients with mild disease.

6MWT: Effort dependant so less reliable and useful than externally paced tests

2. **What are the most needed studies to further define this outcome parameter in CF patients and its potential to be a surrogate marker?**

Incremental Cycle Ergometry VO_{2peak} W_{peak} Further validity and Reliability and responsiveness studies across different severities. Standardisation of incremental protocol which will allow for standardisation for anthropometric differences (for longitudinal monitoring). Updated normal values for children throughout all feasible ages (?6y+)

MST: Further information in children and normal values throughout the age range is needed

6MWT: Further validity, reliability and responsiveness

3. **For what kind of therapeutic trial (therapeutic aim; phase of trial, target population, trial duration, number of patients involved, number of sites involved) is this outcome appropriate?**

Incremental Cycle Ergometry VO_{2peak} W_{peak}
therapeutic aim: Ascertaining changes in abnormal responses to exercise ascertaining treatment effects on dynamic lung function and gas exchange; Improvements in exercise capacity
phase of trial: 3-4
target population: All groups- can be difficult in patients with severe disease
trial duration: Long-term (i.e. >6 months) – (depends on what the study is assessing the efficacy of. EMEA CHMP recommendation of 6 months for FEV_1)
number of patients involved: Time consuming – can take up to 1 hour (statisticians to comment on sample size calculations?).
number of sites: For Wpeak – only with sites with access to a bike. For VO2- metabolic cart with online-gas analysis required.

MST:
therapeutic aim: Ascertaining improvements in functional exercise capacity

phase of trial: 3-4
target population: All groups- however is less useful in patients with better exercise capacity as it exhibits a ceiling effect in patients with better exercise capacity.
trial duration: Long-term (i.e. >6 months) – (depends on what the study is assessing the efficacy of. EMEA CHMP recommendation of 6 months for FEV_1)
number of patients involved: Easy to perform so can be done in large numbers
number of sites: need access to a 10m course

6MWT
therapeutic aim: Ascertaining improvements in functional exercise capacity
phase of trial: 3-4
target population: All groups- however is less useful in patients with better exercise capacity.
trial duration:
number of patients involved: Easy to perform so can be done in large numbers
number of sites: need access to a 30m course

4. Within what timeline can change be expected? What treatment effect can be considered clinically significant?
Incremental Cycle Ergometry VO_{2peak} W_{peak} There is no established timeline for change or MCID in children or adults with CF.

MST: There is no established timeline for change or MCID in children or adults with CF.

6MWT: There is no established timeline for change or MCID in children or adults with CF.

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