

Supplementary Appendix 1

Baseline characteristics of cohort with follow-up data; patient demographic data, healthcare utilisation and medication – group data (mean \pm SD or median [inter-quartile range]) for all subjects is presented in column 1 followed by data for individual Centres. All patients satisfied the American Thoracic Society definition of refractory asthma (Proceedings of the ATS workshop on refractory asthma:current understanding, recommendations and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 2000 Dec;162(6):2341-2351). Comparisons were made using one-way analysis of variance or a Kruskal-Wallis analysis of variance of ranks - significance was taken as $p < 0.05$

	All (349)	Belfast (89)	Brompton (92)	Leicester (73)	Manchester (95)	
Female (%)	222 (64)	55 (62)	59 (64)	41 (56)	67 (71)	P=0.28
Race White (%)	315 (90.3)	89 (100)	75 (81.5)	60 (82.2)	91 (95.8)	P<0.001
Age (y) First Assessed at Difficult Asthma Service	44.8 \pm 13.6	43.2 \pm 14.2	43.0 \pm 12.6	45.2 \pm 13.2	47.7 \pm 13.9	P=0.07
Age (y) asthma diagnosed	16 [3 – 35]	20 [2 – 38]	10 [2 -27]	24 [5 – 42]	18 [5 – 33]	P=0.04
Height (m)	1.66 \pm 0.10	1.65 \pm 0.08	1.68 \pm 0.10	1.66 \pm 0.11	1.65 \pm 0.09	P=0.08
Weight (kg)	81.5 \pm 20.0	81.1 \pm 19.5	84.8 \pm 18.4	82.4 \pm 23.6	78.0 \pm 18.7	P=0.13
BMI (kg/m²)	29.1 \pm 6.4	29.3 \pm 6.3	29.6 \pm 6.0	29.7 \pm 7.1	28.1 \pm 6.2	P=0.32
Smoking status						
Never (%)	210 (60.2)	55(61.8)	63(68.5)	45 (61.6)	47 (49.5)	P=0.13
Ex-smoker (%)	108 (30.9)	26 (29.2)	24 (26.1)	23 (31.5)	35 (36.8)	
(years since stopped)	(9.4 \pm 8.0)	(10.3 \pm 9.0)	(10.6 \pm 7.2)	(11.0 \pm 8.1)	(6.2 \pm 6.8)	
Current smoker (%)	19 (5.4)	6 (6.7)	2 (2.2)	5 (6.8)	6 (6.3)	
(pack years)	(14.6 \pm 14.9)	(23.9 \pm 24.8)	(10.2 \pm 8.4)	(11.9 \pm 10.2)	(13.8 \pm 11.0)	
Unknown	12 (3.4)	2 (2.2)	3 (3.3)	0	7 (7.4)	
Unscheduled visits in preceding 12 months (n)	4 [2 – 6] (339)	5 [2 – 9] (86)	4 [1.5 – 6] (89)	4 [2 – 6] (73)	3 [2 – 5] (91)	P=0.01
Rescue Steroid Courses	4 [2 – 6]	4 [1 – 6]	5 [2 – 7.5]	5 [2.5 – 6]	2 [0 – 4]	P<0.001

In The Previous Year (n)	(322)	(78)	(81)	(73)	(90)	
Hospital admissions in preceding 12 months (n)	0 [0 – 2] (344)	0 [0 – 1] (87)	1 [0 – 3] (92)	0 [0 – 1] (73)	0 [0 – 1] (92)	P<0.001
Total number of ITU admission (n)	0 [0 – 0] (345)	0 [0 – 0] (87)	0[0 – 1] (92)	0 [0 – 0] (73)	0[0 – 0] (93)	P=0.004
Maintenance Oral Steroids (%)	143 / 348 (41%)	32 / 89 (36%)	51 / 91 (56%)	28 / 73 (38%)	32 / 95 (34%)	P=0.008
Oral Steroid Dose (mg) (n)	15 [10 – 20] (140)	15 [6 – 20] (31)	19 [10 – 20] (52)	10 [8 – 15] (28)	15 [10 – 30] (29)	P=0.06
BDP Equivalent Dose (ug) (n)	2000 [1000 – 2000] (333)	1600 [1000 – 2000] (87)	2000 [2000 – 2000] (88)	2000 [1600 – 2000] (73)	1200 [1000 – 2000] (85)	P<0.001
SABA use per day	6 [4 – 8] (238)	8 [4 – 9] (29)	6 [4 – 8] (68)	4 [2 – 9] (57)	8 [5.25 – 10] (84)	P=0.003
LABA use(%)	324/330 (98%)	87/88 (99%)	89/90 (99%)	66/70 (94%)	82/82 (100%)	P=0.047
Theophylline n (%)	132 / 345 (38%)	36 / 89 (40%)	48 / 90 (53%)	24 / 73 (33%)	24 / 93 (26%)	P=0.001
Nebuliser Use (%)	149 / 344 (43%)	42 / 88 (48%)	58 / 90 (64%)	18 / 73 (25%)	31 / 93 (33%)	P<0.001
Any Steroid Sparing Medications	4 / 344 (1%)	1 / 86 (1%)	0 / 89 (0%)	1 / 73 (1%)	2 / 90 (2%)	P=0.514
Anti-IgE Treatment n (%)	3 / 346 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	P=0.044
PPI (%)	99 / 346 (29%)	25 / 89 (28%)	30 / 90 (33%)	17 / 73 (23%)	27 / 94 (29%)	P=0.571
Aspirin / NSAID Sensitivity n (%)	32/334 (10%)	7/87 (8%)	6/85 (7%)	9/70 (13%)	10/92 (11%)	P=0.59
Anti-histamine n (%)	80/342 (23%)	15/88 (17%)	24/89 (27%)	14/72 (19%)	27/93 (29%)	P=0.18
Nasal Steroids n (%)	84/342 (25%)	26/88 (30%)	21/89 (24%)	13/72 (18%)	24/93 (26%)	P=0.40
Leukotriene Receptor Antagonists n (%)	125/343 (36%)	48/88 (55%)	38/89 (43%)	21/73 (29%)	18/93 (19%)	P<0.001

Pre-bronchodilator spirometry (n)	(338)	(89)	(89)	(71)	(89)	
FEV₁ (L)	1.95 ± 0.82	1.94 ± 0.70	1.85 ± .079	2.20 ± 0.87	1.86 ± 0.90	P=0.03
% predicted	66.0 ± 23.7	66.8 ± 23.9	59.9 ± 20.6	74.1 ± 22.8	65.5 ± 25.7	P=0.004
FVC (L)	3.09 ± 1.04	3.08 ± 0.89	3.25 ± 1.09	3.13 ± 1.12	2.91 ± 1.05	P=0.19
% predicted	82.1 ± 20.0	82.9 ± 20.1	83.0 ± 18.3	82.6 ± 21.6	79.9 ± 20.5	P=0.70
FEV₁ / FVC ratio %	63.0 ± 15.1	63.4 ± 14.9	55.7 ± 14.5	70.6 ± 13.2	63.5 ± 14.4	P<0.001
Subjects with baseline post-bronchodilator study (n)	(239)	(57)	(44)	(69)	(69)	
PreBronchodilatorFEV₁ (L)	1.91 ± 0.84	1.69 ± 0.63	1.83 ± 0.81	2.20 ± 0.87	1.84 ± 0.91	P=0.004
(% predicted)	(64.3± 23.2)	(58.0 ± 18.6)	(58.8 ± 20.9)	(74.1 ± 23.1)	(64.0 ± 25.3)	P<0.001
Pre-Bronchodilator FVC (L)	3.07 ± 1.09	2.99 ± 0.96	3.34 ± 1.18	3.13 ± 1.13	2.92 ± 1.08	P=0.24
(% predicted)	(81.1 ± 20.2)	(80.1 ± 19.5)	(83.9 ± 18.5)	(82.8 ± 21.9)	(79.0± 20.4)	P=0.57
Post-bronchodilator FEV₁ (L)	2.19 ± 0.89	1.94 ± 0.68	2.29 ± 1.04	2.37 ± 0.87	2.15 ± 0.91	P=0.04
(% predicted)	(74.1 ± 24.0)	(66.7 ± 20.9)	(74.1 ± 26.6)	(80.0± 22.8)	(75.1 ± 24.7)	P=0.03
Post-Bronchodilator FVC (L)	3.32 ± 1.09	3.21 ± 0.93	3.64 ± 1.29	3.30 ± 1.13	3.24 ± 1.02	P=0.22
(% predicted)	(88.1± 19.2)	(86.5 ± 18.8)	(91.2 ± 21.3)	(87.7 ± 20.8)	(87.8 ± 17.0)	P=0.70
Post-bronchodilator FEV₁/FVC ratio (%)	65.6 ± 14.3	61.1 ± 12.6	61.6 ± 15.6	71.7 ± 12.1	65.4 ± 14.9	P<0.001

Supplementary appendix 2- Lung function and healthcare outcomes of cohort with follow-up data by Clinical Centre – group data (mean \pm SD or median [inter-quartile range]) for all subjects is presented in column 1 followed by data for individual Centres. Comparisons were made using paired analysis (paired t-test or Wilcoxon test as appropriate) - significance was taken as $P < 0.05$.

	All (349)	Belfast (89)	Brompton (92)	Leicester (73)	Manchester (95)	
Pre- bronchodilator FEV1 %predicted (n)	72.7 \pm 27.7 (273)	81.8 \pm 22.5 (83)	62.8 \pm 23.5 (67)	76.1 \pm 25.5 (70)	66.4 \pm 36.6 (53)	P<0.001
FVC % predicted(n)	86.3 \pm 21.6 (263)	95 \pm 18.5 (83)	78.7 \pm 20.8 (66)	83.2 \pm 22 (69)	85.9 \pm 22.8 (45)	P<0.001
Post bronchodilator FEV1 % predicted (n)	73.8 \pm 32.5 (110)	88.8 \pm 38.5 (6)	57.8 \pm 39.7 (23)	79.4 \pm 26.7 (69)	65.1 \pm 35.8 (12)	P<0.05
Post bronchodilator FVC %predicted (n)	83.8 \pm 26.6 (101)	80.5 \pm 42.1 (6)	81.4 \pm 26.7 (17)	83 \pm 26.3 (68)	95.3 \pm 16.3 (10)	P=0.543
Unscheduled visits in preceding 12 months (n)	2 [0 – 6] (324)	1 [0 – 3] (86)	1 [0–4.25] (86)	0 [0 – 1] (70)	10 [6 – 13] (82)	P<0.001
Rescue Steroid Courses in the preceding 12 months (n)	2[0 - 4] (326)	2 [0 – 4] (85)	2 [1 – 5] (88)	2 [1 – 4] (71)	2 [0 – 4] (82)	P=0.507
Hospital admissions in preceding 12	0 [0 – 1]	0 [0 – 1]	0 [0 – 1.5]	0 [0 – 0]	0 [0 – 1]	P<0.01

months (n)	(329)	(87)	(89)	(71)	(82)	
BDP Equivalent Dose, ug (n)	2000 [1000-2000] (341)	1600 [800 – 2000] (88)	2000 [2000 -2000] (90)	1600 [1600 – 2000] (69)	2000 [1000 – 2000] (94)	P<0.001
SABA use per day	7 [4 – 10] (242)	7[4 – 9] (21)	4 [2 – 8] (71)	6 [2 – 10] (59)	8 [6 – 10] (91)	P<0.001

Supplementary Appendix 3

Steroid sparing strategies by Centre – the denominator for steroid sparing strategies is 224 (patients who were on maintenance oral steroids either at baseline or follow-up).

	All (n=224)	Belfast (n= 55)	Brompton (n=67)	Leicester (n=47)	Manchester (n=55)	
Methotrexate						
Tried	47 (31%)	8 (15%)	3 (5%)	22 (47)	14 (25%)	P<0.001
Success	12 (26%)	0 (0%)	2 (67%)	4 (18%)	6 (43%)	
Cyclosporin						
Tried	23 (10%)	9 (14%)	7 (10%)	2 (4%)	5 (9%)	P=0.27
Success	7 (30%)	3 (33%)	2 (29%)	0 (0%)	2 (40%)	
Mycophenolate						
Tried	3 (1%)	2 (4%)	0 (0%)	0 (0%)	1 (2%)	-
Success	2 (67%)	2 (100%)	-	-	0 (0%)	
Azathioprine						
Tried	11 (5%)	1 (2%)	2 (3%)	3 (6%)	5 (9%)	P=0.27
Success	3 (27%)	0 (0%)	1 (50%)	2 (67%)	0 (0%)	
Any steroid sparing strategy						
Tried	64 (29%)	15 (27%)	10 (15%)	23 (49%)	16 (29%)	P=0.001

Supplementary Appendix 4

Additional therapeutic options by centre- the denominator for other strategies is 349 (all subjects).

	All (n=349)	Belfast (n= 89)	Brompton (n=92)	Leicester (n=73)	Manchester (n=95)	
Itraconazole						
Tried	18 (5%)	1 (1%)	1 (1%)	2 (3%)	14 (15%)	P<0.001
Success	14 (78%)	0 (0%)	0 (0%)	1 (50%)	12 (86%)	
Subcutaneous Bricanyl						
Tried	15 (4%)	1 (1%)	12 (13%)	0 (0%)	2 (2%)	P<0.001
Success	6 (40%)	1 (100%)	5 (42%)	-	0 (0%)	
IV Aminophylline						
Tried	28 (8%)	1 (1%)	21 (23%)	1 (1%)	5 (5%)	P<0.001
Success	22 (79%)	0 (0%)	16 (76%)	1 (100%)	5 (100%)	
SMART						
Tried	85 (24%)	21 (24%)	3 (3%)	15 (21%)	46 (48%)	P<0.001
Success	75 (88%)	18 (86%)	3 (100%)	8 (53%)	44 (96%)	
Omalizumab						
Tried	59 (17%)	12 (13%)	35 (38%)	1 (1%)	11 (12%)	P<0.001
Success	37 (63%)	7 (58%)	23 (66%)	0 (0%)	7 (64%)	