

Online supplement

Appendix A1: Classification of groups

The children recruited were classified into three groups based on treatment levels and previous assessments:

1. Severe therapy resistant asthma (STRA): children in whom potentially modifiable factors had previously been addressed and have either or both of ongoing poor control and acute asthma attacks despite high dose ICS ($\geq 800\text{mcg}$ Budesonide equivalent) plus add on therapies (stage 4/5 BTS/SIGN guidelines)(13).
2. Difficult asthma (DA): children previously or currently prescribed high dose ICS who had been found to have modifiable factors (such as poor adherence) as a cause for ongoing poor asthma control
3. Mild-moderate asthma: well or partly controlled according to GINA guidelines(14) with a prescribed dose of ICS of $\leq 250\text{mcg}$ FP or $\leq 400\text{mcg}$ BUD (or equivalent) per day with the need for none or no more than one controller medication (long acting beta agonists, leukotriene receptor antagonists or theophylline).

Appendix A2: REFERRAL CRITERIA FOR RBH DIFFICULT ASTHMA PROTOCOL

1. Age ≥ 5 years
2. Children with difficult asthma under consideration for maintenance oral steroids, other biological agent such as omalizumab, other monoclonal antibody or immunosuppressive treatment

Those children who do not fulfil criteria 2 should fulfil each of the following criteria:

3. **Diagnosis of asthma** - evidence of one or more of:
 - Documented wheeze by healthcare professional
 - Airway hyper-responsiveness confirmed by direct or indirect challenge
 - Documented bronchodilator reversibility ($\geq 12\%$)
 - Recorded evidence of spontaneous variation in FEV_1 ($\geq 12\%$) or peak flow ($\geq 12\%$) in the past year
4. **Documented evidence of poor asthma control** – one or more of :
 - Persistent chronic symptoms (*most days for >3 months*) or an Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT) score of < 20
 - Persistent airflow obstruction ($\text{FEV}_1 < 80\%$ post bronchodilator)
 - Recurrent severe exacerbations in the past year (≥ 2 per year requiring hospital admission or ≥ 3 per year requiring high dose OCS for at least 3 days)
 - A single PICU admission in the past year
5. **Treatment thresholds**

Ongoing poor control (as defined above) despite the following treatment:

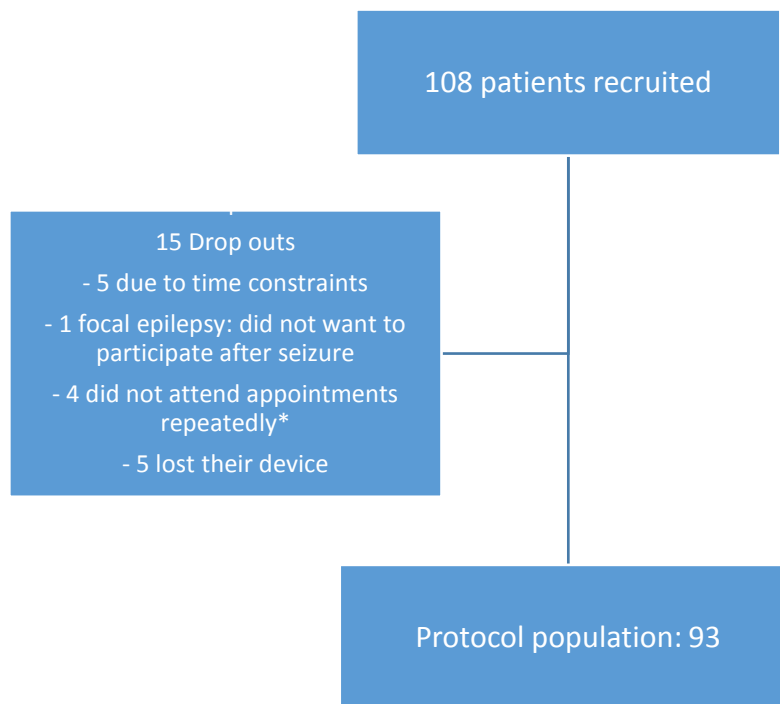
- High dose inhaled corticosteroids (budesonide $> 800\mu\text{g/day}$ or fluticasone $> 500\mu\text{g/day}$) plus a long acting β_2 agonist plus montelukast (or previous failed trial) or trial of other add on therapy such as theophylline

The following treatment whatever the level of asthma control

- Maintenance daily or alternate day corticosteroids or other biological agent such as omalizumab, other monoclonal antibody or immunosuppressive treatment

Figure S1

Patient population



** If patients did not come to their follow up visit they were called and offered a new appointment for follow up a few days later.*

Table S1: Comparison asthma control at the beginning and end of the monitoring period for the whole cohort

	Baseline visit (start of monitoring period): n=93	Follow Up visit (end of monitoring period): n=93	p-value
FeNO, ppb	34 (5-175)	21 (5-193)	0.0015*
Mean FVC, % predicted	96.3 ± 16.1	99.6 ± 14.2	0.0025*
Mean FVC, z-score	-0.52 ± 1.37	0.003 ± 1.25	< 0.0001*
Mean FEV₁, % predicted	86.4 ± 18.7	92.9 ± 15.9	<0.0001*
Mean FEV₁, z-score	-1.50 ± 1.56	-0.77 ± 1.39	< 0.0001*
FEF25-75, % pred	60 (16-189)	68 (20-243)	<0.0001*
BDR %	8.5 (0-123)	4.1 (0-42)	<0.0001*
ACT	15 (5-25)	18 (7-24)	0.0038*
cACT	20 (6-27)	22 (5-27)	0.0041*
ACT/cACT ≥ 20 controlled, n (%)	35/91 (38)	46/93 (49)	0.1406
mPAQLQ	4.9 (2-7)	5.9 (1.9-7)	<0.0001*
Exacerbations, n	1 (0-10)	0 (0-4)	0.0021*
OCS courses, n	0 (0-12)	0 (0-4)	0.0005*

Data are presented as medians (range) unless stated otherwise. *Value significant after adjusting for Bonferroni multiple comparison test <0.0063. FEV₁: forced expiratory volume in 1s, FVC: forced vital capacity, FEF25-75: forced expiratory flow at FVC 25 and 75%, FeNO: fractional exhaled nitric oxide: normal ≤20ppb, BDR: Bronchodilator reversibility, normal: ≤12%, (c)ACT: (childhood) asthma control test: controlled ≥20, mPAQLQ: median pediatric quality of life questionnaire score: 7: not bothered by asthma, OCS courses: oral corticosteroid courses

Table S2: Comparison adherence groups at baseline (beginning of monitoring period) and follow up (end of monitoring period)

	Visit	Good adherence $\geq 80\%$ (n=39)	Medium adherence 60-79% (n=25)	Poor adherence $<60\%$ (n=29)
FEV1, % pred	Baseline	92 (45-122)	85 (37-119)	88 (53-112)
	Follow up	96 (60-126)	91 (65-125)	91 (64-125)
	p-value	$<0.0001^*$	0.02	0.14
BDR, %	Baseline	7.0 (0-59)	9.1 (0-123)	8.1 (0-77)
	Follow up	4.1 (0-18)	3.7 (0-16)	4.7 (0-42.3)
	p-value	0.0080*	0.0043*	0.1919
FEF25-75 % pred	Baseline	62 (17-189)	85 (37-119)	61 (22-115)
	Follow up	74 (25-243)	91 (65-125)	68 (29-113)
	p-value	0.0081*	0.0206	0.0613
FeNO, ppb	Baseline	23 (5-175)	35 (10-99)	41 (6-122)
	Follow up	13 (5-155)	19 (8-65)	45 (8-193)
	p-value	0.0266	0.0016*	0.9772
ACT	Baseline	12.5 (6-22)	13.5 (5-24)	18 (8-25)
	Follow up	18 (7-24)	19 (7-24)	18 (8-24)
	p-value	0.01*	0.03	0.8966
PAQLQ	Baseline	5.2 (2-7)	3.9 (2.2-6.9)	5.1 (3-7)
	Follow up	6.2 (1.9-7)	5.5 (2.8-7)	5.6 (2.6-7)
	p-value	$<0.0001^*$	0.004*	0.13
Exacerbations	Baseline	1 (0-10)	1 (0-6)	0 (0-10)
	Follow up	0 (0-3)	0 (0-4)	1 (0-4)
	p-value	0.001*	0.10	0.81
OCS courses	Baseline	1 (0-12)	1 (0-5)	0 (0-10)
	Follow up	0 (0-2)	0 (0-4)	0 (0-4)
	p-value	0.002*	0.049	0.52

Data are presented as medians (range) unless stated otherwise. *Value significant after adjusting for Bonferroni multiple comparison test <0.0063 . FU: follow up visit, BDR: bronchodilator reversibility, FEF25-75: forced

expiratory flow at FVC 25 and 75%, FeNO: fractional exhaled nitric oxide, cACT: childhood asthma control test, mPAQLQ: median pediatric quality of life questionnaire score, OCS courses: oral corticosteroid courses

Table S3: Questionnaire results

	All patients (n=93)	Adherence ≥80% (n=39)	Adherence 60-79% (n=25)	Adherence <60% (n=29)	p-value
Median MARS-5 Score	23 (15-25)	24 (15-25)	23 (16-25)	23 (15-25)	0.0325*
*Not significant in post test analysis using Dunn's Multiple Comparison Test					
Median BMQ Necessity	4.4 (1-5)	4.4 (2.8-5)	4.4 (2.6-5)	4.2 (1-5)	0.9107
Median BMQ Concern	2.8 (1-5)	2.8 (1-4.4)	2.6 (1.4-4.6)	2.9 (1.6-5)	0.4222
Median BMQ Harm	2.5 (1-4.75)	2.3 (1-3.8)	2.5 (1-4.8)	2.7 (1.5-4.5)	0.0842
Median BMQ Overuse	2 (1-3.8)	2 (1-3.3)	2 (1-3.8)	2.2 (1.3-3.5)	0.0341*
*Significant difference between ≥80% and <60% adherence group in post Dunn's Multiple Comparison Test					

Data are presented as medians (range) unless stated otherwise. Adjusted for multiple comparison with Dunn's multiple comparison test. MARS-5: Medicine adherence rating scale; BMQ: belief in medicine questionnaire

Figure S2: Correlation between adherence and prescription uptake rate

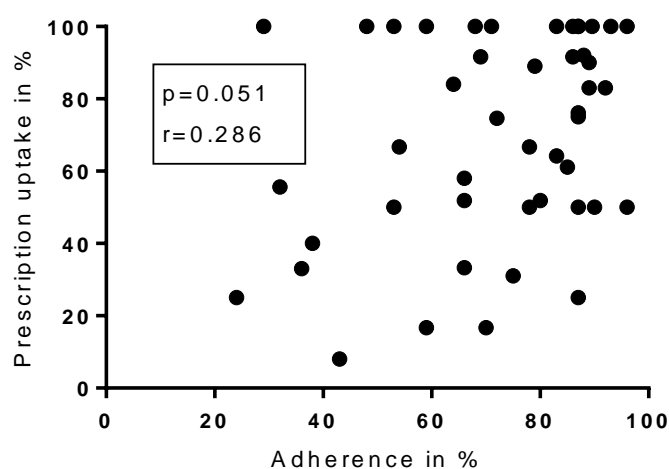


Figure S3: Correlation between adherence and MARS

