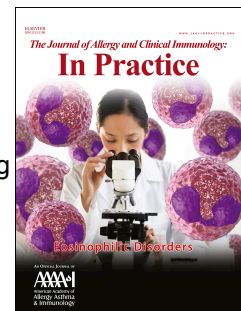


Journal Pre-proof

Clinical outcomes in people with difficult-to-control asthma using electronic monitoring to support medication adherence

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Clinical outcomes in people with difficult-to-control asthma using electronic monitoring to support medication adherence

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RESULTS

Additional clinical information

Prednisolone usage in fluticasone/salmeterol+INCA 28-day FeNO suppressors

Nine of the fluticasone/salmeterol+INCA 28-day FeNO suppressors were taking prednisolone. All had prednisolone and cortisol levels by HPLC prior to the test. Eight had a suppressed cortisol value (≤ 82 nmol/L), and 6 had detectable prednisolone, suggesting that the majority were adherent to this treatment, and up to 3 partially adherent. It is therefore unlikely that a change in prednisolone usage influenced the results of the 28-day test. This is in keeping with our previous data showing that the fluticasone+INCA 7-day test FeNO suppression results are similar irrespective of whether the patient is taking prednisolone or not¹, and in keeping with prescription refill data showing that people with severe asthma adhere better to prednisolone than ICS/LABA².

FeNO non suppressors not progressing to biological therapy

There were 8 FeNO non suppressors who remained engaged with the clinical service who did not progress to biological therapy. It can be seen from the graphs showing the individual patient data for the non suppressors (the right hand panels in the sub-parts of figures 2 and 3), that there were some patients who had relatively large improvements in ACQ and/or FEV1 during monitoring. Six of the 8 patients were not using prednisolone, and with the improved control they reported there was no indication for biologic therapy. One patient reduced prednisolone from 10 to 3 mg daily, with further reductions limited by adrenal suppression. Asthma control remained good and so there was no indication for a biologic. The remaining patient was on prednisolone 5 mg daily for both inflammatory bowel disease and asthma. Asthma control was good, but they would not have been able to taper or stop the prednisolone due to the inflammatory bowel disease, and so there was no indication for a biologic.

41

Supplementary References

- E1. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma. *Am J Respir Crit Care Med* 2019; 199:454-64.
- E2. Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012; 67:751-3.

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Table E1: Baseline patient characteristics of the 103 subjects with FeNO ≥ 45 ppb included in the INCA monitoring service evaluation. Data are shown as median (IQR), mean $\pm$ SD or n (%) as appropriate. Where data are missing, the number of subjects is provided in brackets.

Female - n (%)	56 (54.4)
Age - years	48 (27-59)
BMI – kg/m² (n=102)	28.4 (25.2-32.9)
Atopic, n (%)^a (n=100)	60 (60.0)
Time since asthma diagnosis – years (n=100)	17.5 (9-26)
ACQ-6	2.52 $\pm$ 1.38
FeNO - ppb	76 (60-118)
Blood eosinophils - cellsx10⁹/L (n=79)	0.4 (0.19-0.69)
Inhaled steroid - BDP equivalent μg^b	2000 (2000-2000)
On maintenance prednisolone - n (%)	63 (61.2)
Prednisolone dose - mg	10 (6.6-14.4)
FEV₁ - % predicted (n=90)	77.4 $\pm$ 19.8
FEV1 - L (n=90)	2.35 (1.85-2.99)
FEV₁/FVC - %	71.7 (64.1-78.6)

IgE - kU/L (n=101)

193 (64.6-527)

46

47 *a* = atopy defined with immunology test; skin prick or RAST positive to inhaled aeroallergen (cat,
48 dog, house dust mite, mixed grasses, *Aspergillus fumigatus*). *b* = baseline dose of inhaled steroid as
49 prescribed expressed as equivalent dose of beclomethasone dipropionate (BDP).

50

51 **Figure Legend:**

52 **Figure E1:** FeNO measurements at baseline, after 28 days of treatment with
53 fluticasone/salmeterol+INCA in place of usual ICS/LABA, and then at a median (range) 4.75 (1-14)
54 months post INCA monitoring.

Figure 1

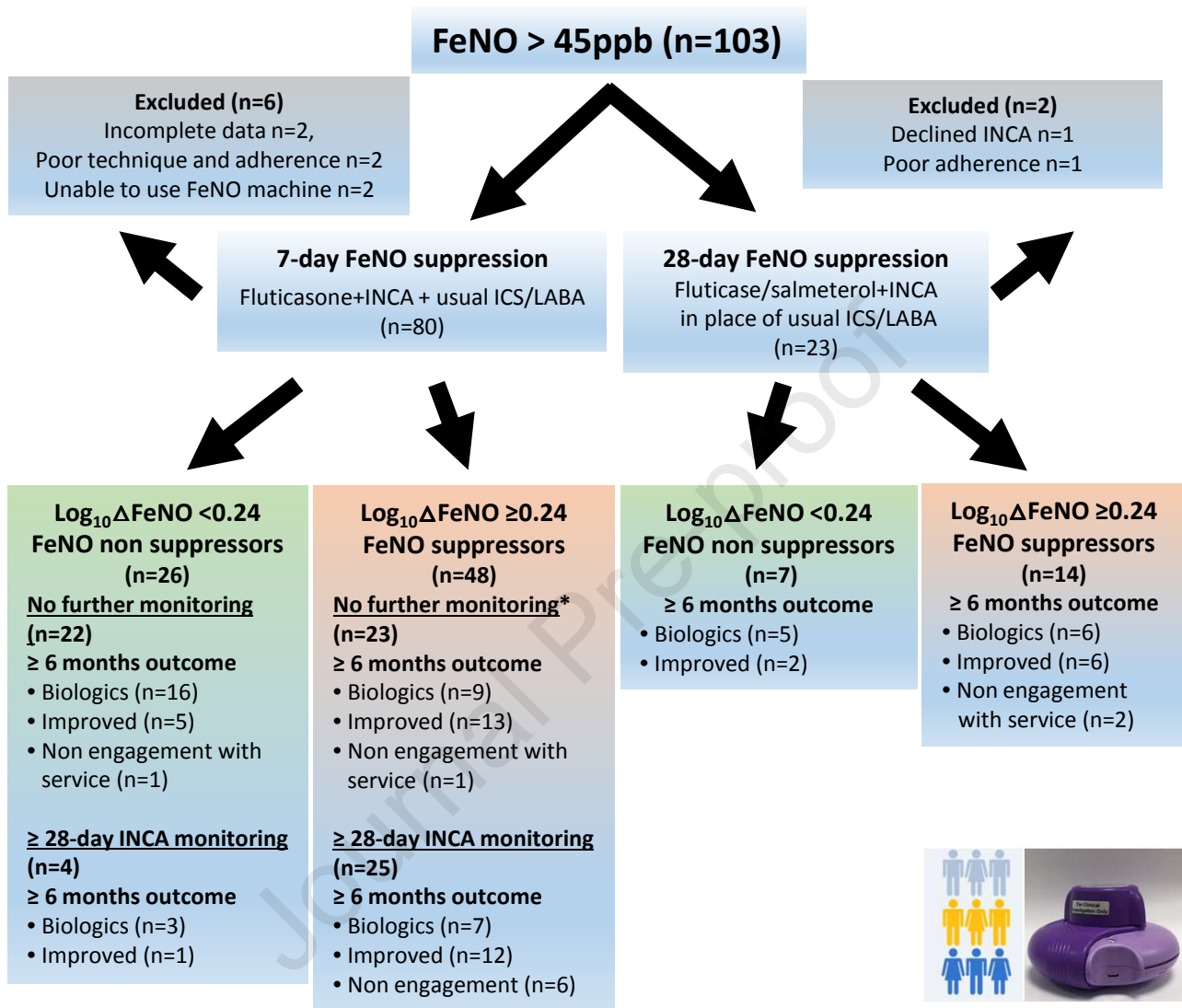


Figure 2

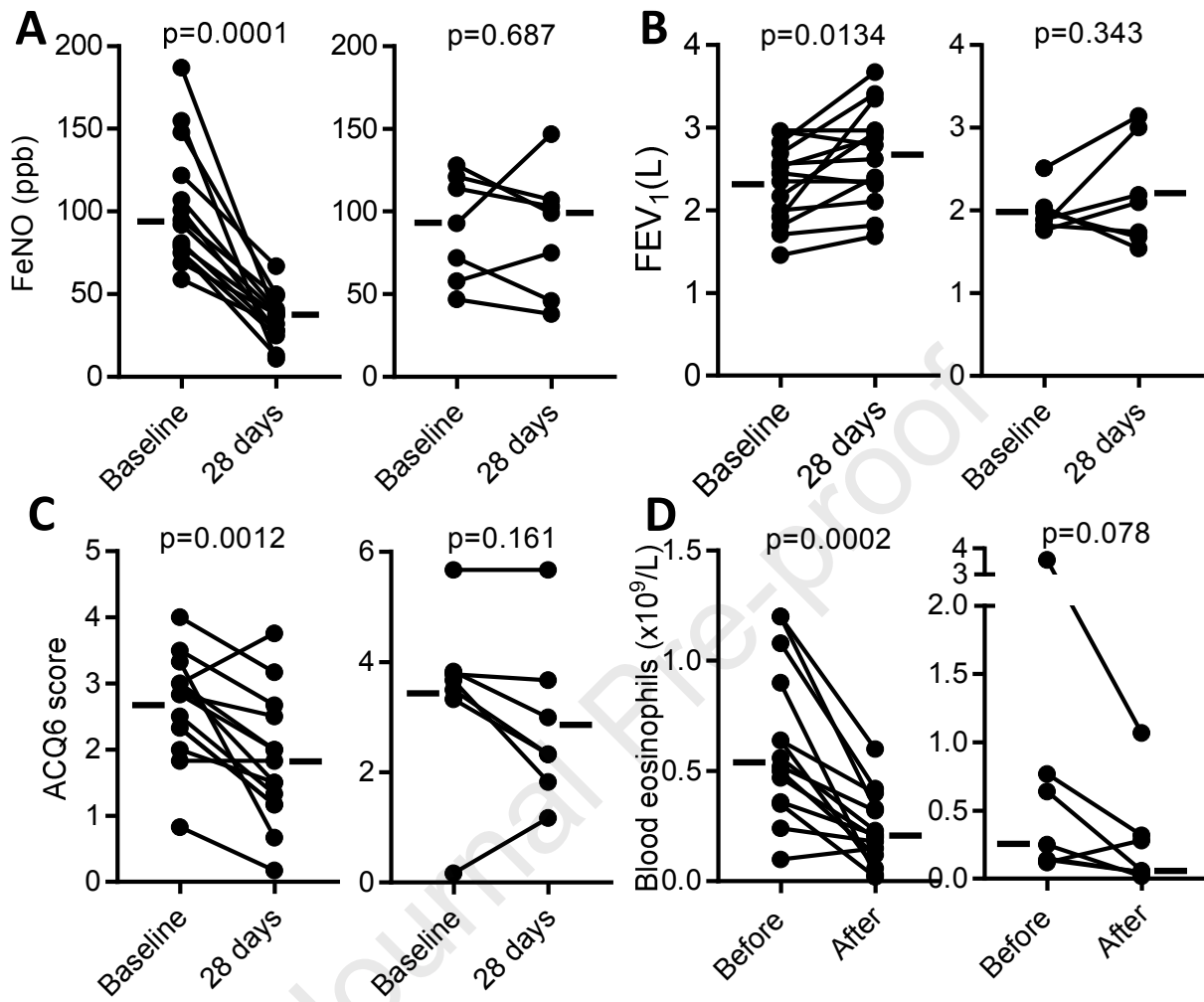


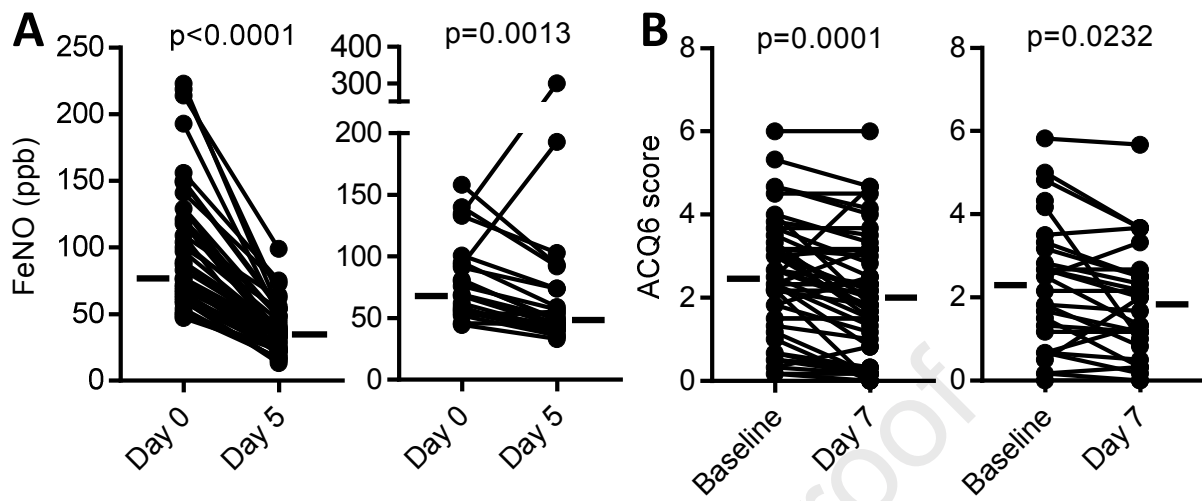
Figure 3

Figure 4

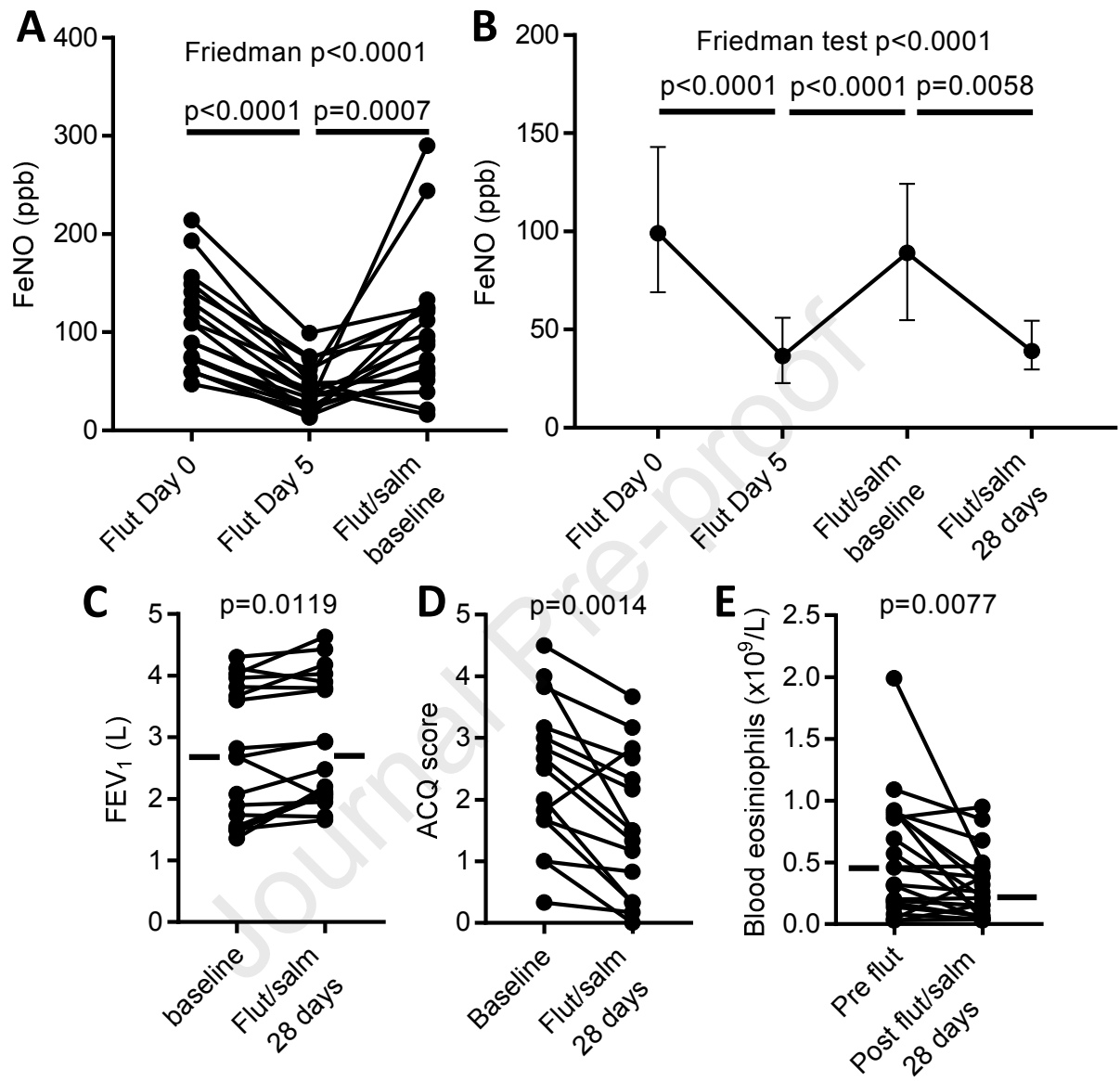


Figure 5

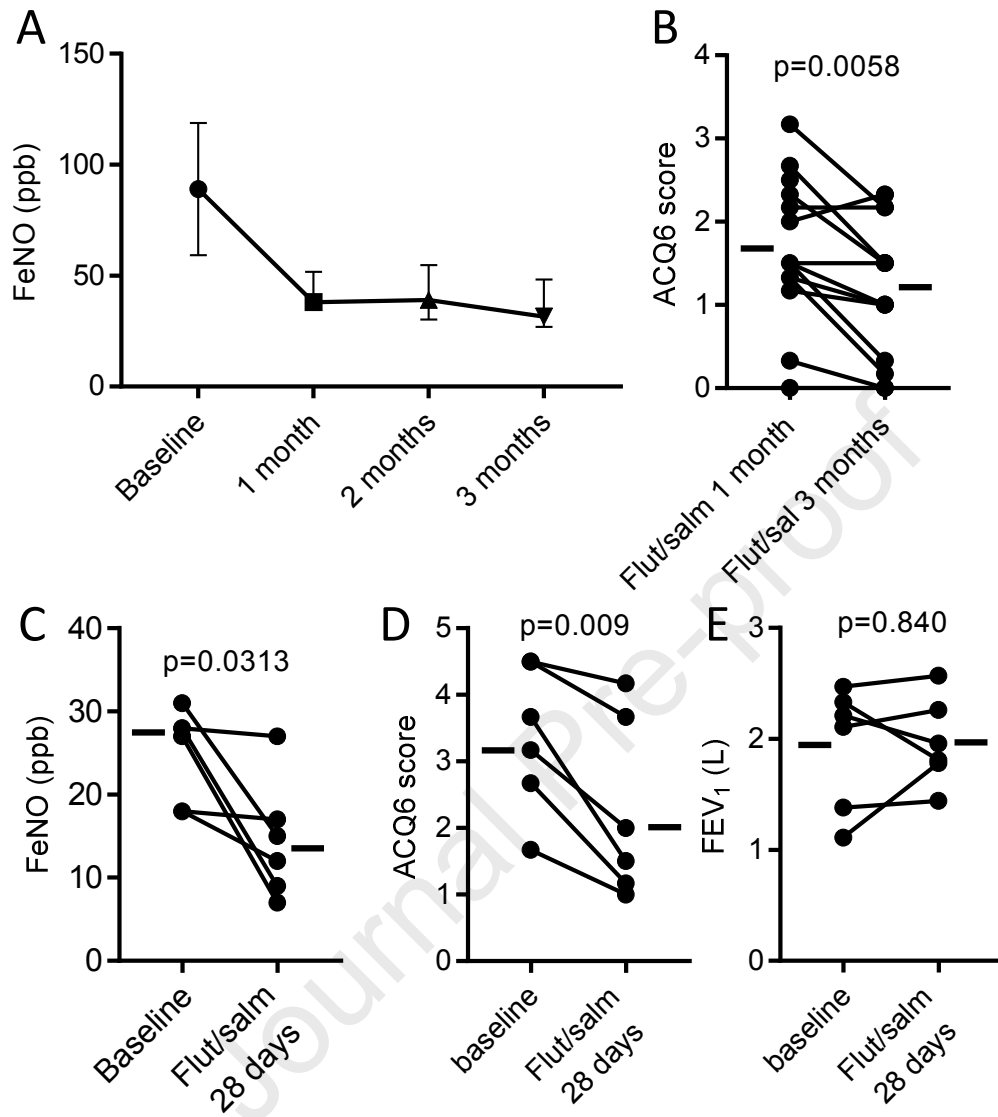
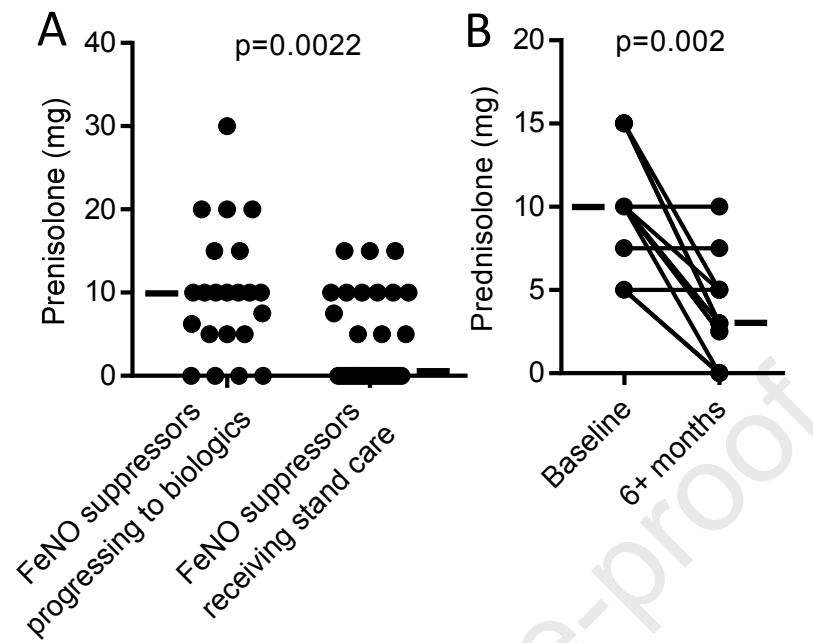
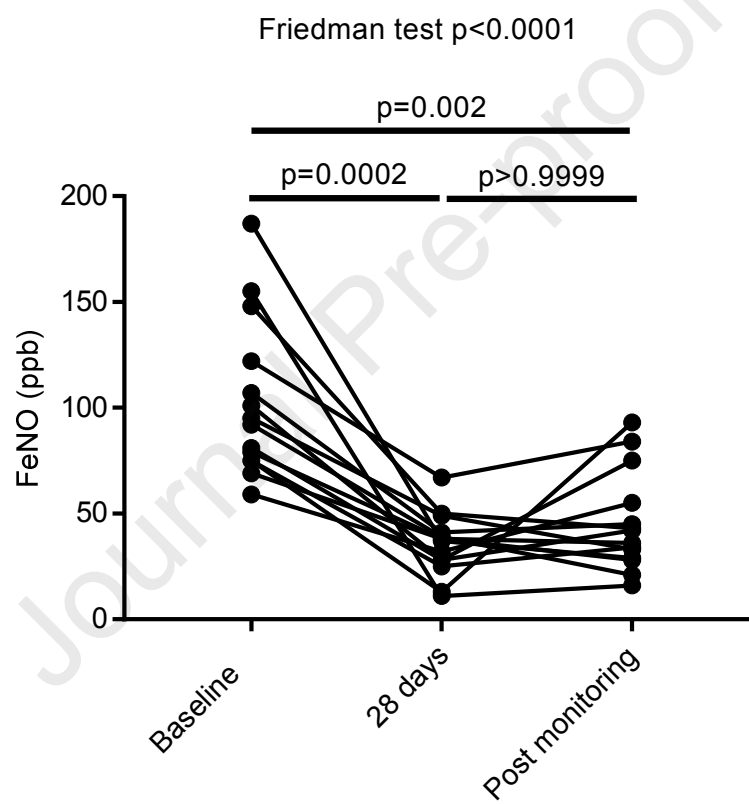


Figure 6



Supplementary Figure E1



Clinical outcomes in people with difficult-to-control asthma using electronic monitoring to support medication adherence

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Contributions: All authors contributed to the design of the service evaluation. CEB and MC undertook the clinical assessments and collated the data. PB and SN analysed the data. PB drafted the manuscript. All authors re-drafted the manuscript and approved the final version.

Source of support: INCATM devices were provided by Vitalograph. FeNO meters were provided at negotiated rate by Circassia.

Conflicts of Interest:

INCATM devices were provided by Vitalograph. FeNO meters were provided at negotiated rate by Circassia. SN, and MC have no conflicts of interest. CEB has received funds for TEVA for attending specialist nurse meetings. AM has delivered lectures organised by GlaxoSmithKline, AstraZeneca, Orion, Boehringer Ingelheim, Chiesi, Napp and Roche, and has received support to attend scientific meetings from Chiesi and Roche. SS has received consultancy fees and/or speaker fees from the following outside the submitted work: GlaxoSmithKline, Astra Zeneca, Chiesi, Napp, Boehringer Ingelheim, Roche, Owlstone Medical, ERT medical and Mundipharma. SS reports grants from the EPSRC/MRC (molecular pathology node), MRC confidence in concept scheme, NIHR-EME program linked to asthma/severe asthma outside of the submitted work. PB has received the following outside the submitted work: i) consultancy fees from Genentech-Roche and Boehringer-Ingelheim via the University of Leicester, ii) support to attend scientific meetings from Chiesi and Napp, iii) grant funding from Genentech.

Running title: Electronic monitoring to support medication adherence in difficult asthma

Online supplement: This article has an online data supplement.

39 ABSTRACT

40 Background

41 Non-adherence in difficult-to-control asthma can be identified using 7-day FeNO suppression
42 testing where patients take additional fluticasone via Diskus™ with an INCA™ acoustic monitoring
43 device attached, and self-measure FeNO at home. However, this is inconvenient for patients
44 attending a tertiary centre and limited by FeNO meter availability. It is not known if this approach
45 alters clinical outcomes.

46 Objectives

47 To examine patient acceptability and the effectiveness of replacing usual combination inhaled
48 corticosteroid (ICS)/long-acting β 2-agonist (LABA) therapy with a fluticasone/salmeterol Diskus
49 500+INCA for 28 days as the initial intervention, compared to the 7-day FeNO suppression test.
50 Secondly, to explore clinical outcomes following INCA monitoring.

51 Methods

52 A service evaluation of FeNO suppression testing in clinical practice.

53 Results

54 21/23 subjects offered replacement of their usual ICS/LABA with fluticasone/salmeterol+INCA as
55 the initial intervention accepted and completed 28 days of monitoring. Fourteen (66.6%) patients
56 reduced their FeNO by >42% (FeNO suppressors), accompanied by improvements in FEV1, ACQ
57 and blood eosinophils, similar to the 7-day test (n=74). 22/62 (35.5%) FeNO suppressors
58 progressed to biologic therapy, compared to 24/33 (72.7%) non suppressors (p=0.0006). FeNO
59 suppressors taking maintenance prednisolone (n=13) who did not receive biological therapy
60 reduced the median baseline dose from 10 to 3 mg, with further reductions limited by adrenal
61 suppression.

62 Conclusion

63 Replacing existing inhaled therapy with fluticasone/salmeterol+INCA for 28 days is acceptable to
64 the majority of people with difficult-to-control asthma, and identifies prior medication non-
65 adherence. INCA monitoring coupled with clinical support potentially improves patient adherence
66 and asthma control, preventing unnecessary progression to biological therapy.

HIGHLIGHTS BOX**What is already known about this topic?**

7-day FeNO suppression testing with fluticasone+INCA™ electronic monitoring added to usual therapy, coupled with home FeNO monitoring identifies medication non-adherence in difficult-to-control asthma. Long term clinical outcomes are not known.

What does this article add to our knowledge?

A simplified approach where usual ICS/LABA is replaced with fluticasone/salmeterol+INCA™ for 28 days with repeat assessments in clinic provides similar results to the 7-day test. Clinical outcomes improved for many previously non adherent patients.

How does this study impact current management guidelines

Use of the 28 day fluticasone/salmeterol+INCA protocol as a pre-step/stratification tool for biological therapy in patients with a high baseline FeNO may reduce unnecessary biologic prescribing and OCS exposure, whilst optimising treatment with ICS/LABA therapy.

KEY WORDS

Asthma, difficult-to-control asthma, severe asthma, adherence, biologic therapy, electronic inhaler monitoring, FeNO, FeNO suppression testing

ABBREVIATIONS

ACQ – asthma control questionnaire

INCA – inhaler compliance assessment

ICS – inhaled corticosteroid

LABA – long-acting β_2 -agonist

ppb – parts per billion

89 INTRODUCTION

90 Non-adherence with inhaled corticosteroids (ICS) in difficult-to-control “severe” asthma is
 91 common^{1, 2}. Identifying non-adherence is important as it is associated with poorer asthma
 92 outcomes^{1, 2}, and potentially inappropriate treatment escalation to high cost therapies. Changing
 93 long term adherence behaviour remains challenging as there are multiple factors underlying this³,
 94 and whilst interventions consistently improve adherence, translating this into better clinical
 95 outcomes has been inconsistent⁴⁻⁶.

96 Directly observed ICS treatment over 7 days in people with asthma who have a FeNO ≥ 45 parts per
 97 billion (ppb) identifies non adherent patients with difficult-to-control asthma who are responsive to
 98 ICS⁷. Monitoring of both inhaler use and technique is possible using the Inhaler Compliance
 99 Assessment (INCATM) device. This device attaches to the DiskusTM (AccuhalerTM) dry powder
 100 inhaler and records audio from inhaler priming through the exhalation, inhalation and breath hold
 101 sequence of inhaler use. Analysis of the digital audio recordings from the INCA provides
 102 information on both the time of use and the quality of inhaler technique⁸. We demonstrated that
 103 monitoring of ICS use and inhalation technique using the INCATM device attached to a fluticasone
 104 DiskusTM (AccuhalerTM) dry powder inhaler (fluticasone+INCA), in addition to the patient’s usual
 105 medication, coupled with patient home FeNO measurements, similarly identifies an ICS-responsive
 106 non adherent group of asthma patients⁸. Subsequent replacement of the patients usual ICS/LABA
 107 with fluticasone/salmeterol Diskus+INCA (fluticasone/salmeterol+INCA) for 28 days maintained
 108 the fall in FeNO, and was accompanied by significant improvements in lung function, ACQ, and
 109 blood eosinophil counts⁸.

110 While identifying ICS non-adherence in FeNO-high people with asthma over 7 days is now
 111 achievable, for people travelling long distances to a tertiary centre this is inconvenient as they must
 112 return to clinic after 7 days, and the cost and availability of home FeNO meters may create a
 113 bottleneck when planning assessments. In view of the logistical issues of performing the 7-day

114 FeNO suppression test and home FeNO monitoring, we have explored the feasibility of foregoing
115 this, by offering difficult-to-control asthma patients replacement of their usual daily ICS/LABA
116 combination therapy with fluticasone/salmeterol+INCA, with objective measurements repeated in
117 the clinic after 28 days, without home FeNO measurements. Patients were then offered monitoring
118 for a further 2 months, with objective clinic measurements at monthly intervals. We have compared
119 the outcome of this approach with the 7-day FeNO suppression test and assessed the long term
120 clinical outcomes at >6 months for all patients undergoing 7-day or 28-day monitoring, to
121 understand whether asthma control has improved or whether the patients have progressed to
122 biological therapies.

123

124 METHODS

125 This was a prospective service evaluation of fluticasone+INCA and fluticasone/salmeterol+INCA
126 use in patients attending the NHS England-commissioned Glenfield Hospital Difficult Asthma
127 Clinic (DAC), Leicester, UK. The asthma service lead and Leicester National Research Ethics
128 Committee - East Midlands approved the study as a clinical service evaluation. Data were analysed
129 for patients receiving these interventions from January 2015 to October 2019, with outcome data
130 analysed up to March 2020.

131 The inhaler monitoring technology used was the INCA™ device, designed to work with the
132 Diskus™ (also known as Accuhaler™) inhaler⁸. This acoustic monitoring technology provides a
133 time-stamped sound file that can be analysed using an automated validated algorithm providing
134 information on the timing and the technique of inhaler usage⁸.

135 Patients attending the Glenfield DAC were considered for INCA monitoring if they presented with
136 a FeNO of ≥ 45 ppb. Patients undertook either of the following: i) 7-day fluticasone+INCA
137 monitoring in addition to their usual ICS/LABA medication as described previously⁸, followed in
138 some patients by replacement of their usual ICS/LABA with fluticasone/salmeterol 500
139 (Seretide™) Diskus+INCA, one inhalation twice daily; or ii) replacement of their usual ICS/LABA
140 with fluticasone/salmeterol 500 (Seretide™) Diskus+INCA, one inhalation twice daily as the initial
141 intervention. Before starting, specialist nurses educated the patient about their asthma and inhaled
142 medication, and inhaler technique was assessed. If there was any concern about inhaler technique
143 or inhaler use due to a lack of understanding, the test was delayed. If at next review FeNO remained
144 elevated, INCA monitoring was commenced. Subjects were trained to use the Diskus and they were
145 informed that the INCA device would record both timing and quality of inhalation. Baseline
146 measurements of FeNO, FEV₁, and ACQ6 were made, and these were repeated post monitoring.
147 Blood eosinophil measurements from up to 3 months prior to monitoring, and up to 3 months post
148 monitoring, were also assessed. Patients who suppressed their FeNO following 7-days

149 fluticasone+INCA or 28-days fluticasone/salmeterol+INCA were offered further
 150 fluticasone/salmeterol+INCA monitoring.

151 On return to the clinic after 7 or 28 days, results from the INCA™ device were uploaded to a server
 152 using the Vitalograph IC Data Compression Utility application and analysed using the embedded
 153 sound analysis algorithm⁸. Good adherence during INCA monitoring for 7 or 28 days was defined
 154 as $\geq 80\%$ adherence based on outcomes identified previously studying prescription refills². A fall in
 155 FeNO with $\Delta \log_{10} \text{FeNO}$ value of ≥ 0.24 was accepted as a positive test and an indicator of
 156 intentional or non intentional non-adherence to ICS as described previously⁷. This equates to an
 157 approximate $\geq 42\%$ fall in FeNO between the start of monitoring and the post monitoring value⁷. For
 158 those undergoing extended monitoring, at the end of each month, repeat measurements were made
 159 in the clinic for FEV₁, ACQ6, FeNO, and blood eosinophils. At each appointment, the specialist
 160 nurse would review these results with the patient and use the graphs produced from the INCA
 161 analysis to discuss adherence and technique issues. Education about ICS use and technique was
 162 provided at each appointment specific to the patient's needs. Motivation for change was also
 163 assessed and lifestyle discussed in order to help the patient identify how behaviour could be
 164 modified to improve inhaler adherence.

165 The relationship between the fall in FeNO and long term outcome in terms of asthma control and
 166 progression to biological therapy was analysed using the latest clinical data available up to March
 167 2020.

168 **Statistical analysis**

169 Data were link-anonymised and collected in a systematic manner to allow reporting of the utility of
 170 the testing in routine clinical care. Normally distributed variables were presented using the mean $\pm$
 171 standard deviation, and unpaired/paired t-tests and repeated measures ANOVA were used to
 172 compare across groups. Non-normally distributed variables were presented using the median and
 173 interquartile range, and the Friedman, Mann-Whitney U, Wilcoxon signed-rank and tests were used

174 to compare across groups. Chi-squared tests were used to test for differences between groups for
175 categorical variables. All statistical analyses were performed using GraphPad Prism v7 (GraphPad
176 Software, San Diego, California)
177

178 RESULTS

179 The pathway of assessment for all patients and the number in each arm in this service evaluation is
 180 summarised in **figure 1**. The demographic details of the patients with FeNO ≥ 45 ppb are
 181 summarised in **Table E1**.

182 The acceptability and clinical response to 28 days replacement of usual care ICS/LABA with 183 fluticasone/salmeterol+INCA

184 Of 23 patients with FeNO ≥ 45 ppb offered fluticasone/salmeterol+INCA as a replacement for their
 185 usual ICS/LABA inhaler, 22 (95.6%) accepted. One however did not engage with the process. In
 186 those who completed 28 days monitoring, 14/21 (66.6%) of patients demonstrated a fall in the
 187 $\Delta \log_{10} \text{FeNO} \geq 0.24$ (described from here as FeNO suppressors), indicative of prior intentional or
 188 unintentional non-adherence (**Fig.2A**). The number of patients taking $<80\%$ of the prescribed doses
 189 was 2/21 (9.5%); both were in the suppressor group. There were significant improvements in FEV₁
 190 and ACQ6 in the FeNO suppressor group (n=14) but not the non suppressor group (n=7) (**Figs.2B**
 191 **and C**). Blood eosinophils measured up to 3 months pre fluticasone/salmeterol+INCA and up to 3
 192 months post fluticasone/salmeterol+INCA also fell significantly in the FeNO suppressor group
 193 (**Fig.2D**). FeNO levels at a median 4.75 months post monitoring (range 1-14 months) were not
 194 significantly different to the 28-day value (**Figure E1**), although it is evident that 2 patients had
 195 notable relapses.

196 Nine FeNO suppressors were using prednisolone and further details are provided in the online
 197 repository under “Additional clinical information”.

198 The clinical response to 28 days replacement of usual care ICS/LABA with 199 fluticasone/salmeterol+INCA following the 7-day FeNO suppression test

200 There were 80 patients who underwent 7-day FeNO suppression testing where fluticasone 1000 μg
 201 + INCA was added to existing ICS/LABA treatment as described previously⁸. A subset of these

202 data from the first 30 patients undergoing the 7-day fluticasone+INCA FeNO suppression test have
 203 been published previously⁸. Six patients were excluded from analysis due to failure to engage in the
 204 process (n=2), inability to use the FeNO machine (n=2) or technical faults with the INCA device (n-
 205 2), leaving 74 patients for analysis. There was a fall in $\Delta\log_{10}\text{FeNO} \geq 0.24$ in 48/74 (64.9%) patients
 206 (FeNO suppressors)(**Fig.3A**). There was also a smaller but statistically significant fall in FeNO in
 207 the group defined as FeNO non suppressors ($\Delta\log_{10}\text{FeNO} < 0.24$)(**Fig.3A**), and small but significant
 208 improvements in ACQ(6) in both groups (**Fig.3B**).

209 Twenty five of the 48 patients who suppressed their FeNO during the 7-day fluticasone+INCA test
 210 were offered monitoring for a further 28 days using fluticasone/salmeterol+INCA in place of the
 211 usual ICS/LABA (23 patients were not offered this because we did not commence 28-day
 212 monitoring for 12 months after starting 7-day FeNO suppression testing, and INCA supplies were
 213 also limited for a period). Three did not engage with the process, leaving 22 for analysis. Of note,
 214 when there was a period of a week or more before returning to start treatment with
 215 fluticasone/salmeterol+INCA after the 7-day fluticasone+INCA test (18 patients), the FeNO had
 216 relapsed to the baseline value in 14/18 patients, suggesting that non adherent behaviour is rarely
 217 altered by the 7-day test alone (**Fig.4A**). After 28 days of treatment with
 218 fluticasone/salmeterol+INCA, FeNO had again fallen to values similar to those observed at the end
 219 of the 7-day test (**Fig.4B**), demonstrating that the FeNO response to “observed” ICS treatment is
 220 reproducible, and also, not just the result of adding extra ICS to maintenance treatment during the 7-
 221 day test. There were also significant improvements in FEV₁ (data for n=18) and ACQ-6 (data for
 222 n=15) in the FeNO suppressor group after the fluticasone/salmeterol+INCA period (**Fig.4C and D**).
 223 Blood eosinophils (data for n=21) measured up to 3 months pre the 7-day fluticasone test and then
 224 up to 3 months post the period of fluticasone/salmeterol+INCA monitoring, also fell significantly
 225 (**Fig.4E**).

FeNO remains suppressed and adherence remains >80% with 3-months

fluticasone/salmeterol+INCA monitoring

There were 16 FeNO suppressors from the initial 7-day and 28-day monitoring periods, who continued the use of fluticasone/salmeterol+INCA treatment for 3 months. During this time, adherence was >80% of prescribed doses at month 2 in all 16 patients, and remained >80% in 14/16 (87.5%) of patients at month 3. The FeNO level remained suppressed (**Fig.5A**). There were further improvements in ACQ between month 1 and month 3 (data available for n=13) (**Fig.5B**).

Effects of fluticasone/salmeterol+INCA in patients with low baseline FeNO

Fluticasone/salmeterol+INCA was also offered to 6 people with a baseline FENO of <45 ppb where a degree of non-adherence was volunteered by the patient during clinic consultations. Interestingly, there was still a statistically significant fall in FeNO after 28 days of treatment, from a median 27.5 ppb to 13.5 ppb (**Fig.5C**) and a significant improvement in ACQ (**Fig.5D**), but no change in FEV1 (**Fig.5E**).

6+ month clinical outcomes following INCA adherence monitoring

Outcomes at 6+ months after INCA monitoring were analysed in the all patients defined as FeNO suppressors (non adherent) versus non suppressors (adherent), taking the fluticasone+INCA 7-day-only group, fluticasone+INCA followed by fluticasone/salmeterol INCA group, and fluticasone/salmeterol+INCA alone groups together. Patients were managed using standard clinical care, including multi-disciplinary team discussion regarding treatment approaches and progression to biological therapies, with the results of INCA monitoring available to inform treatment decisions. Their clinical characteristics are summarised in **table 1**.

At the time of analysis, data were available for 95 patients. One out of 33 FeNO non suppressors was non adherent and not engaged with the clinical service. 24/33 (72.7%) of the FeNO non suppressors were adherent had been started on or were awaiting treatment with biological therapy,

250 compared to 22/62 (35.5%) of the FeNO suppressors ($p=0.0006$). Eight out of 33 (24.2%) FeNO
251 non suppressors had improved asthma control and did not need treatment with biologics compared
252 to 31/62 (50.0%) patients in the FeNO suppressor group ($p=0.0172$). Further clinical information
253 explaining why some FeNO non suppressors did not progress to biologic therapy is provided in the
254 online repository under “additional clinical information”.

255 The baseline maintenance oral steroid dose was significantly higher in FeNO suppressors who
256 progressed to biologic therapy (median 10 mg versus 0 mg respectively, $p=0.0015$, **Fig.6A**). There
257 were 13 FeNO suppressors who were receiving oral prednisolone at baseline and who did not
258 receive biologic therapy. Overall, the prednisolone dose in this group was reduced from a median
259 baseline dose of 10 mg to 3 mg ($p=0.002$)(**Fig 6B**) with standard care. The predominant reason for
260 not stopping prednisolone completely was adrenal suppression. One of the 13 patients in this group,
261 who was receiving 10 mg maintenance prednisolone, was unable to reduce the dose due to arthritis.
262 In the FeNO suppressors who received biologic therapy, 18 were receiving maintenance
263 prednisolone, but only one patient managed to reduce this by >50% before starting biologic therapy
264 ($p<0.0001$ compared to those who did not receive biologic therapy).

265 We also treated 6 patients with fluticasone/salmeterol+INCA whose baseline FeNO was <45 ppb.
266 Their FeNO and ACQ fell significantly, but FEV1 was unchanged after 28 days of treatment. One
267 of these patients subsequently stopped maintenance triamcinolone treatment, but the other 5
268 progressed to biological therapy.

269

270 **DISCUSSION**

271 In this service evaluation we have shown that electronic monitoring of inhaler use and technique is
 272 acceptable to >90% of people attending a specialist severe asthma clinic. We have demonstrated
 273 that replacing usual ICS/LABA treatment with fluticasone/salmeterol+INCA for 28 days identifies
 274 a similar proportion of patients who suppress their FeNO as the previously described 7-day test
 275 where fluticasone is added to existing treatment. Identification of intentional or non intentional non-
 276 adherence through this approach is associated with improved clinical outcomes without the need to
 277 progress to biological therapies.

278 The 7-day FeNO suppression test we described previously involves adding 1000 µg once daily of
 279 fluticasone delivered via Diskus (Accuhaler) to the patient's usual treatment, and the provision of a
 280 portable FeNO meter so that the patient can record their FeNO at home⁸. An INCA device attached
 281 to the Diskus records both the time of inhalation but also the quality of inhalation from priming the
 282 device, exhalation, inhalation and breath hold via an embedded microphone⁸. The patient then needs
 283 to re-attend the clinic for the FeNO data and INCA data to be downloaded, and to return the FeNO
 284 meter so that other patients can be tested. We showed previously that approximately 65% of
 285 patients with a baseline FENO ≥ 45 ppb were classified as non adherent due to a subsequent fall in
 286 FeNO with a $\Delta \log_{10}$ FENO value of ≥ 0.24 FeNO. On subsequent replacement of their usual therapy
 287 with fluticasone/salmeterol Diskus 500+INCA, we demonstrated that the improvement in FeNO
 288 was maintained, and therefore not just a reflection of the excess fluticasone delivered during the 7-
 289 day test. In our extended Leicester cohort reviewed here, data from 74 patients undergoing the 7-
 290 day fluticasone+INCA test showed that 64.9% of people with severe asthma achieved a fall in
 291 FeNO with a $\Delta \log_{10}$ FENO value of ≥ 0.24 , in keeping with our previous study from multiple
 292 centres⁸. This is also remarkably similar to the 65% non-adherence rate identified previously from
 293 prescription refills where non-adherence was defined as <80% prescription collection².

294 When patients had an unmonitored period between finishing the 7-day fluticasone+INCA test and
295 returning to replace their usual ICS/LABA with fluticasone/salmeterol+INCA, in 14 of 18 cases the
296 FeNO value had relapsed. This suggests that knowledge of the results of the 7-day test alone may
297 improve non adherent behaviour in approximately 20% of people with difficult-to-control asthma.
298 In the patients where the FeNO had relapsed after the 7-day test, replacement of their usual
299 treatment with fluticasone/salmeterol+INCA reduced FeNO again to levels similar to those post the
300 7-day test, demonstrating that the FeNO response to monitored ICS is reproducible and consistent.

301 The 7-day test is resource intensive, and the availability of FeNO meters was limiting the rate at
302 which we could assess patients, leading to a long waiting list. Furthermore, for people who were
303 tertiary referrals living out of area, attending the clinic twice within 7-days was often difficult. We
304 were also aware that the 7 day test alone did not alter adherence behaviour in approximately 80% of
305 patients. We therefore explored the utility of foregoing the 7-day fluticasone+INCA FeNO
306 suppression test by simply replacing existing ICS/LABA treatment with fluticasone/salmeterol
307 Diskus 500 + INCA as the initial intervention, with the patient then returning to clinic
308 approximately 28 days later for repeat measurements of FeNO, ACQ, and spirometry. This
309 management approach was acceptable to 21/23 patients. Our data show that 14/21 (66.6%) of these
310 patients demonstrated a fall in the FeNO level with a $\Delta\log_{10}\text{FeNO}$ value of ≥ 0.24 , an almost
311 identical rate to that observed with the 7-day test. This fall in FeNO was accompanied by significant
312 improvements in FEV_1 and ACQ, and many patients asked to continue with the
313 fluticasone/salmeterol Diskus. Overall adherence was $>80\%$ in 91.3% of patients during this
314 monthly monitoring.

315 From the perspective of service delivery, moving straight to fluticasone/salmeterol+INCA
316 monitoring in place of the 7-day test with home FeNO monitoring involved less nurse input as
317 patients did not require training on home FeNO monitoring, and patients who could not measure
318 their own FeNO were also eligible. This approach also eliminated the bottleneck created by the

319 availability of home FeNO meters. Furthermore, it was felt that 28 days of adherence monitoring
 320 gave more useful information on patient adherence and inhaler technique over time, allowing a
 321 more informed discussion with the patient when the data were next reviewed.

322 The group of patients who did not achieve a fall in FeNO with a $\Delta\log_{10}\text{FeNO}$ value of ≥ 0.24 during
 323 the 7-day fluticasone+INCA test or the 28-day fluticasone/salmeterol+INCA test nevertheless
 324 demonstrated a significant fall in FeNO, and improvements in ACQ and FEV₁, albeit less marked
 325 than the changes in FeNO suppressors. While a $\Delta\log_{10}\text{FeNO} \geq 0.24$ is a good discriminator of non-
 326 adherence supported by prescription refill data⁷, adherence is clearly a continuous rather than a
 327 categorical variable. These data suggest that there is also an element of suboptimal adherence to
 328 ICS/LABA in some people with severe asthma and a raised FeNO, who do not reach the
 329 $\Delta\log_{10}\text{FeNO} \geq 0.24$ threshold with electronically monitored therapy.

330 A key question that we have examined for the first time is whether knowledge of adherence through
 331 electronic monitoring alters longer term clinical outcomes. We assessed the outcomes for patients
 332 from 6 months after a period of electronic monitoring, with data for some patients available up to
 333 4.75 years. Patients were managed through a severe asthma multi-disciplinary team with knowledge
 334 of the outcome of INCA adherence monitoring. Demonstration of good adherence is one of the
 335 requirements for progression to biological therapy and subsequent re-imburement for the costs in
 336 the UK National Health Service. It is therefore not surprising that we found a significantly higher
 337 proportion of people who were FeNO non suppressors, and thus deemed adherent, progressed to
 338 biological therapy than FeNO suppressors who were deemed non adherent. Nevertheless, FeNO
 339 suppressors in about 35% of cases still progressed to biological therapy, often because they
 340 demonstrated poor asthma control or failure to reduce oral steroids with further
 341 fluticasone/salmeterol+INCA monitoring coupled with improved adherence, or if they were
 342 considered high risk from asthma. However, a substantial proportion of FeNO suppressors
 343 demonstrated improved asthma control following the period of INCA monitoring. This was

344 manifest in particular by the demonstration that 77% of FeNO suppressors were able to
345 substantially reduce the dose of maintenance oral prednisolone, with failure to stop completely
346 usually due to adrenal suppression rather than loss of asthma control. Prior to this, these patients
347 were under consideration for biological therapy. In contrast, meaningful prednisolone reduction was
348 rarely achieved in those FeNO suppressors who progressed to biological therapy.

349 With our experience using this INCA technology, it is our opinion that this greatly informs the
350 identification and management of medication non-adherence in difficult-to-control asthma. The
351 INCA monitoring of ICS/LABA is not the only factor at play, because patients also receive monthly
352 appointments with the nurse specialist team who provide education and support to help the patient
353 understand the impact of ICS non-adherence on their asthma symptoms and control. However, in
354 our view, the data from the INCA technology with confirmation that the ICS/LABA has been
355 inhaled regularly and correctly rather than the device primed but not used or used incorrectly,
356 coupled with objective measurements of FeNO that are fed back directly to the patients, greatly
357 facilitates an informed and objective discussion. This helps to identify both intentional and non
358 intentional non-adherence. With this in place, we have observed improved asthma control for many
359 in the longer term, with avoidance of progression to biological therapy with the potential costs, side
360 effects and inconvenience that entails. We have not undertaken a formal cost-effectiveness analysis,
361 but if one nurse was employed full time to supervise INCA monitoring, in the UK we would only
362 need to prevent 4 people progressing to biological therapy to fund this salary annually.

363 It has been argued by some that non adherent patients at high risk of asthma death should be started
364 on biological therapies as a priority to reduce risk⁹. Whether this is an effective strategy is unknown
365 as there is no evidence that biological therapies reduce asthma deaths. We agree that this should be
366 considered, but suggest that tackling non-adherence to ICS use remains mandatory in this situation
367 as ICS are the only drugs clearly associated with protection from asthma death¹⁰. Furthermore,
368 phase 3 trials of biological therapies in severe asthma have only included patients using ICS, and it

369 cannot be assumed that biologics are effective when inadequate doses of ICS are taken. In fact,
370 there is emerging evidence that patients receiving biological therapies who are non adherent to ICS
371 do poorly¹¹. Thus, monitoring adherence through FeNO monitoring and with an electronic device
372 such as INCA that confirms that the drug has been inhaled, may help identify and tackle non-
373 adherence in patients responding poorly to biological therapy.

374 In summary, our experience suggests that a period of nurse-led electronic monitoring of ICS/LABA
375 using a device that records when and how a dose is taken, can identify non adherent patients with
376 difficult-to-control asthma, and with nurse support, can modify patient behaviour leading to
377 improved clinical outcomes without need to progress to biological therapies.

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REFERENCES

1. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180:817-22.
2. Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012; 67:751-3.
3. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am* 2005; 25:107-30.
4. Bender BG. Nonadherence to Asthma Treatment: Getting Unstuck. *J Allergy Clin Immunol Pract* 2016; 4:849-51.
5. De Keyser HEH, Kaye L, Anderson WC, Gondalia R, Theye B, Szeffler SJ, et al. Electronic medication monitors help determine adherence subgroups in asthma. *Respir Med* 2020; 164:105914.
6. Merchant R, Szeffler SJ, Bender BG, Tuffli M, Barrett MA, Gondalia R, et al. Impact of a digital health intervention on asthma resource utilization. *World Allergy Organ J* 2018; 11:28.
7. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2012; 186:1102-8.
8. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma. *Am J Respir Crit Care Med* 2019; 199:454-64.
9. Green RH, Shaw D. Strict adherence rules to obtain monoclonal therapy might cost lives. *Lancet Respir Med* 2017; 5:678-9.
10. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343:332-6.
11. d'Ancona G, Kavanagh J, Roxas C, Green L, Fernandes M, Thomson L, et al. Adherence to corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. *Eur Respir J* 2020; 55.

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Table 1. Baseline patient characteristics of the 95 subjects with baseline FeNO ≥ 45 ppb included in the analysis of clinical outcomes who completed 7-day fluticasone+INCA or 28-day fluticasone/salmeterol+INCA monitored treatment, dichotomised by a $\Delta\log_{10}$ FeNO reduction at 7-days or 28 days respectively of $\geq$ or <0.24 compared to baseline. Data are shown as median (IQR), mean $\pm$ SD or n (%) as appropriate.

	$\Delta\log_{10}$ FeNO reduced ≥ 0.24 (FeNO suppressors) (n=62)	$\Delta\log_{10}$ FeNO reduced <0.24 (FeNO non suppressors) (n=33)	P value
Female - n (%)	36 (58.1)	16 (48.5)	0.395
Age - years	45 (23.8-56.5)	51 (31.0-60.0)	0.181
BMI – kg/m ²	28.4 (25.0-32.2)	28.4 (25.1-33.8)	0.778
Atopic – n (%) ^a (n=59 suppressors)	35 (56.4)	21 (63.6)	0.521
Time since asthma diagnosis – years (N=60 suppressors)	18 (9.0-24.8)	18 (8-30)	0.653
ACQ-6	2.54 $\pm$ 1.27	2.48 $\pm$ 1.65	0.846
FeNO - ppb	82 (66-121.3)	69 (55.5-98.0)	0.045

Eosinophils – cells x 10⁹/L			
(N=51 suppressors, N=22 non suppressors)	0.47 (0.2-0.79)	0.36 (0.15-0.64)	0.319
Inhaled steroid -BDP equivalent µg^b	2000 (2000-2000)	2000 (2000-2000)	0.788
On maintenance prednisolone^c - n (%)	36 (58.1)	23 (69.7)	0.375
Prednisolone dose^c - mg	10 (7.5-15)	10 (5.0-15)	0.637
FEV₁ – L (N=58 suppressors, N=27 non suppressors)	2.51 (1.84-3.23)	2.25 (1.89-2.69)	0.385
FEV₁ - % predicted	78.1 ± 19.4	78.3 ± 21.3	0.966
FEV₁/FVC - %			
IgE - kU/L	200.5 (64.0-528.0)	180 (68.4-535.5)	0.843

a = atopy defined with immunology test; skin prick or RAST positive to inhaled aeroallergen (cat, dog, house dust mite, mixed grasses, Aspergillus fumigatus). b = baseline dose of inhaled steroid as prescribed expressed as equivalent dose of beclomethasone dipropionate (BDP). c = one patient on maintenance intramuscular triamcinolone, allocated as 10 mg oral prednisolone daily

394

395 **FIGURE LEGENDS**

396

397 **FIGURE 1.**

398 A summary of the patient assessments and outcomes. * Further 28-day monitoring was not
 399 undertaken in n=23 7-day FeNO suppressors as we did not commence this for 12 months after
 400 starting 7-day FeNO suppression testing, and INCA supplies were limited for a period.

401 **FIGURE 2.**

402 Clinical responses in FeNO-high patients with difficult-to-control asthma when usual ICS/LABA
 403 therapy is replaced with fluticasone/salmeterol+INCA electronic monitoring. **A)** FeNO, **B)** FEV₁,
 404 **C)** ACQ6, **D)** blood eosinophils. FeNO suppressors are shown in the left panel of each figure,
 405 FeNO non suppressors on the right panel of each figure. Horizontal bars represent medians (FeNO,
 406 blood eosinophils), or means (FEV₁, ACQ6).

407 **FIGURE 3.**

408 Changes in FeNO (**A**) and ACQ6 (**B**) in FeNO-high patients undergoing the 7-day FeNO
 409 suppression test with fluticasone+INCA added to usual therapy. FeNO suppressors are shown in the
 410 left panel of each figure, FeNO non suppressors on the right panel of each figure. Horizontal bars
 411 represent medians (FeNO) or means (ACQ6).

412 **FIGURE 4.**

413 Clinical responses in FeNO-suppressors identified from the 7-day fluticasone+INCA suppression
 414 test, subsequently treated with fluticasone/salmeterol+INCA in place of usual ICS/LABA treatment.
 415 **A)** In the majority of patients returning to start fluticasone/salmeterol+INCA after a previous 7-day
 416 suppression test, the FeNO had relapsed to the pre-suppression test level. **B-D)** With replacement of
 417 usual ICS/LABA with fluticasone/salameterol+INCA, **B)** FeNO falls again, to similar levels

418 observed after the 7-day fluticasone suppression test (median [IQR]), **C**) FEV₁ increases, and **D**)
 419 ACQ6 falls. **E**) Blood eosinophils numbers recorded up to 3 months after
 420 fluticasone/salmeterol+INCA were significantly lower than the values recorded up to 3 months
 421 before the 7-day fluticasone suppression test. Horizontal bars represent medians (FeNO, blood
 422 eosinophils), or means (FEV₁, ACQ6)

423 **FIGURE 5.**

424 **A-B)** The clinical response is sustained with prolonged fluticasone+INCA use. **A**) FeNO remains
 425 suppressed with 3 months of fluticasone/salmeterol+INCA treatment (n=16, median [IQR]). **B**) ACQ
 426 improves further from 28 days to month 3 with extended fluticasone/salmeterol+INCA treatment.
 427 **C-E)** Clinical responses in patients with FeNO <45 ppb treated with fluticasone/salmeterol+INCA
 428 in place of usual ICS/LABA. **C**) FeNO, **D**) ACQ, **E**) FEV₁. Horizontal bars represent medians
 429 (FeNO), or means (FEV₁, ACQ6).

430 **FIGURE 6.**

431 **A)** Baseline oral steroid use in FeNO suppressors who progressed to biological therapy versus those
 432 who continued to receive standard care. **B)** Oral steroid dose reduction in the 13 FeNO suppressors
 433 taking oral steroids who received standard care. One patient receiving monthly intramuscular
 434 triamcinolone was allocated a 10 mg equivalent dose of oral prednisolone at baseline. Horizontal
 435 bars represent medians.