Title: Findings from a Pilot Randomised trial of an Asthma Internet Self-management Intervention (RAISIN)

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## ABSTRACT

**Objective**

To evaluate the feasibility of a Phase 3 randomised controlled trial (RCT) of a web-site (Living Well with Asthma) to support self-management.

**Design and Setting**

Phase 2, parallel group, RCT, participants recruited from 20 general practices across Glasgow, UK. Randomisation through automated voice response, after baseline data collection, to website access for minimum 12 weeks or usual care.

**Participants**

Adults (age ≥ 16rs) with physician diagnosed, symptomatic asthma (asthma control questionnaire (ACQ) score ≥ 1). People with unstable asthma or other lung disease were excluded.

**Intervention**

‘Living Well with Asthma’ is a desktop/laptop compatible interactive website designed with input from asthma/ behaviour change specialists, and adults with asthma It aims to support optimal medication management, promote use of action plans, encourage attendance at asthma reviews and increase physical activity.

 **Outcome measures**

Primary outcomes were recruitment/retention, website use, ACQ and mini asthma quality of life questionnaire (AQLQ). Secondary outcomes included patient activation, prescribing, adherence, spirometry, lung inflammation, and health service contacts after 12 weeks. Blinding post-randomisation was not possible.

**Results** Recruitment target met. Fifty one participants randomised (25 intervention group). Age range 16-78 years; 75% female; 28% from most deprived quintile. 45/51 (88%) (20 intervention group) followed up. Nineteen (76% of the intervention group) used the website, for a mean of 18 minutes, (range 0,49). Seventeen went beyond the two ‘core’ modules. Median number of logins was 1 (interquartile range 1,2, range 0,7). No significant difference in the pre-specified primary efficacy measures of ACQ scores (-0.36; 95% confidence interval: -0.96, 0.23; p=0.225), and mini-AQLQ scores (0.38;-0.13, 0.89; p=0.136). No adverse events.

**Conclusions**

Recruitment and retention confirmed feasibility; trends to improved outcomes suggest use of Living Well with Asthma may improve self-management in adults with asthma and merits further development followed by investigation in a Phase 3 trial.

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Mesh Terms: Asthma, internet, primary health care, medication adherence

**Article summary of strengths and limitations**

* A recent UK review of asthma deaths showed many could have been avoided if medication management and other self-management strategies had been better, so finding optimum approaches to support self-management of asthma is critical and digital interventions show promise.
* The “Living Well with Asthma” website was iteratively designed with input from experts in asthma, self-management support, behaviour change and adults with asthma themselves; it aims to support optimal medication management, promote use of action plans, encourage attendance at asthma reviews and increase physical activity.
* We conducted a Phase 2 parallel group, randomised controlled trial; randomisation was through automated voice response, after baseline data collection but blinding of the researchers or participants at outcome, measurement was not possible.
* Our low response rate is a concern, however, we have described our population in detail (unlike previous reports of digital interventions for asthma self-management), and our baseline characteristics demonstrate that patients were recruited from a range of socio-economic backgrounds.

## INTRODUCTION

Asthma is a common condition affecting over 300 million people worldwide, with increasing global prevalence.[1] While there are newer pharmacological treatments for individuals with severe asthma,[2-5] improvements in outcomes for the majority with mild to moderate asthma have stalled.[6] A recent UK review of asthma deaths showed potentially avoidable factors in the majority, particularly relating to self-management and adherence to treatment.[7]

Despite clear evidence that self-management education, asthma action plan use and regular professional review improve outcomes,[8] translation into everyday practice has proven difficult,[6] and most patients still lack an action plan and sufficient understanding to self-manage effectively. Poor adherence to regular preventative medication (primarily with inhaled corticosteroids, ICS) is a particular problem. Using digital interventions to promote self-management behaviors shows promise, but uncertainty persists as to the most effective formulation of the intervention and the target population.[9]

In this Phase II, pilot randomised controlled trial (RCT) we evaluated the feasibility and effectiveness of using a low intensity online intervention aimed at promoting effective self-management (especially adherence to ICS) in adults with mild to moderate asthma, compared to usual care. We developed the intervention (‘Living Well with Asthma’) incorporating evidence from the literature and relevant theory. Several phases of user testing in alignment with the ‘person based approach’ to developing digital behaviour change interventions were undertaken.[10] Following the Medical Research Council (MRC) Guidance on Developing and Evaluating Complex Interventions,[11] our objective was to determine the feasibility of conducting a Phase 3 RCT, and obtained initial estimates of effects on outcomes.

## METHODS

Our trial protocol is described in detail elsewhere,[12] and received approval from the West of Scotland Research Ethics Committee (ref WS/13/004). A brief summary is provided here.

### Settings and participants

We recruited from 20 General Practices in Glasgow, UK, between 23/09/2013 to 21/02/2014, using clinical databases to identify potential participants who were invited by mail to participate and complete the Asthma Control Questionnaire (ACQ). We recruited adults aged 16 years or older, with a physician diagnosis of asthma and ACQ score ≥ 1, who provided written informed consent. For full inclusion and exclusion criteria see Table 1. Our search strategy is shown in the Supplementary Data file.

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| **Table 1 Inclusion and exclusion criteria** |
| **Inclusion criteria** |
| * Written informed consent
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| * Age 16 years or older
 |
| * Diagnosis of asthma by a health professional, and duration of asthma symptoms > 1 year
 |
| * Asthma Control Questionnaire score (ACQ) ( 6 questions version) ≥ 1 suggesting poorly controlled asthma
 |
| * Ability to access the internet via desktop or laptop (tablets and smartphones not sufficient)
 |
| **Exclusion Criteria** |
| * Unstable asthma as defined as the presence of 1 or more of the following events in the 4 weeks prior to randomisation:
	+ asthma related hospital admission
	+ Emergency department attendance for asthma
	+ ‘out of hours’ visit of patients to the GP for asthma
	+ GP visit to patient at home for asthma
 |
| * Presence of active lung disease other than asthma
 |
| * Mental impairment or language difficulties that make informed consent impossible
 |
| * frequent asthma exacerbations with > 4 courses of oral prednisolone in the 12 months prior to randomisation
 |
| * Cognitive impairment
 |
| * Terminal illness
 |

### Study design overview & intervention description

We conducted a non blinded pilot RCT of access to the ‘Living Well with Asthma’ website versus usual care for 51 participants. Participants were assessed in their own homes at baseline and at 12 weeks or as soon as possible after this date.

The intervention development is described elsewhere,[13] but in summary aimed to a) provide understanding of current level of asthma control and how to improve it, specifically by optimizing use of prescribed medication; b) challenge attitudes and concerns around medications; c) learn how to get the most out of their annual asthma review; d) prompt provision and use of a personal asthma action plan from a health professional; e) send timely reminders for influenza vaccination and reordering refill inhaler prescriptions. The website did not advise medication changes, but suggested contacting a health professional if inadequate control was identified, with clear advice for seeking help in an emergency. The website is interactive, aiming to engage the user in recognising that their asthma is uncontrolled, and illustrate the benefits via case vignettes (based on real life examples) of taking their medications as prescribed. The website is tailored based on their current use of preventer inhalers (never been prescribed; prescribed but don’t really use; use regularly). There is a ‘4 week challenge’ that users can sign up to, where they commit to taking their preventer regularly for 4 weeks, are guided through establishing their personal barriers to regular use (see screenshot in Supplementary Data file for further illustration)and developing potential solutions to these barriers.

The intervention group were given website login details and a computer link, and advised to use the website as much or as little as they wished (total time to visit all pages once approximately 90 minutes). We developed the website using an open source software package called LifeGuide.[14, 15]

### Randomisation & blinding

Randomisation occurred after baseline data collection, using a third party interactive voice response system (IVRS) ensuring allocation concealment. The randomisation schedule was generated in advance of the study by the Robertson Centre for Biostatistics, in a 1:1 ratio, using the method of randomised permuted blocks of length 4, without stratification. Access to the randomisation schedule was restricted to those within the Centre with responsibility for provision of the IVRS. The comparison group were offered access to the intervention after the follow up visit.

### Primary outcomes

The primary endpoints were: recruitment and retention rates at follow up, website use, and changes from baseline for ACQ [16] and mini-asthma quality of life questionnaire (AQLQ) scores.[17] Both the ACQ and mini-AQLQ have a minimal clinically important difference (MCID) of 0.5.[18] This pilot study was not powered to detect a difference in these two clinical outcomes, they were included in order to assess feasibility and inform sample size calculations for a future full scale RCT.

### Secondary outcomes

We evaluated a range of secondary outcomes in order to assess their feasibility for use in a future full scale RCT.

Individual domains of the mini-AQLQ were reported. These comprise of symptoms, activity limitation, emotional function, and environmental stimuli. Knowledge, skills and confidence to manage health was measured via the Patient Activation Measure (PAM).[19] Self-reported adherence was assessed by both enquiring what proportion of prescribed inhaled corticosteroids were actually taken, and via the Morisky Medication Adherence Scale (MMAS).[20] Airway inflammation is measured by fraction exhaled nitric oxide (FeNO).[21] Lung function was assessed (via pre-bronchodilator spirometry FEV1 (forced expiratory volume in 1 second); FEV1 percentage predicted, and FEV1/FVC (forced vital capacity). Lung function (spirometry) was performed to ATS (American Thoracic Society) standards,[21, 22] where possible, and the proportion of tests not meeting these standards recorded. As well as the asthma specific mini-AQLQ, generic quality of life (QOL) was measured using the EQ (EuroQol)-5D.[23] We collected changes to medication use, recorded numbers of health service contacts, and severe exacerbations were noted by recording the number of oral prednisolone courses. These data were self-reported. Those in the intervention group received the problematic experience of therapies scale (PETS) to facilitate understandings of barriers to using the website, and following its advice.

### Data analysis

Continuous data are summarized as mean and standard deviation (SD) or range, or as median and inter-quartile range (IQR), and categorical data as counts and percentages. Linear regression was used to estimate differences in continuous outcomes between groups at follow up, adjusting for baseline scores. Estimated between-group differences are reported with a 95% confidence interval (CI) and p-value. For continuous outcomes that were not normally distributed, changes from baseline were compared between groups using Wilcoxon Rank Sum Tests. Categorical variables were compared between groups using Fisher’s exact test. All analyses were carried out using SPSS Statistics 22 and Microsoft Office Excel. The primary analysis was intention-to-treat and involved all patients who were randomly assigned, except with spirometry where only those meeting ATS/ERS eligibility criteria will be analysed.[22]

## RESULTS

### Baseline characteristics (Table 2)

The groups were largely well matched. Participants were aged between 16 and 78 years, and 75% were female.

**Table 2 Baseline demographic characteristics of study population per group**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Overall****(n = 51)** | **Comparison****(n = 26 )** | **Intervention****(n = 25)** |
| **Age (years),mean (SD)** | 45.5 (15) | 46.4 (14) | 44.6 (17) |
| **Female, n (%)** | 38 (75) | 20 (77) | 18 (72) |
| **Ethnicity** |
|  White, n (%) | 48 (94) | 24 (92) | 24 (96) |
|  Other, n (%) | 3 (6) | 2 (8) | 1 (4) |
| **Smoking status:** |
|  Current, n (%) | 5 (10) | 2 (8) | 3 (12) |
|  Former smoker, n (%) | 18 (35) | 11 (42) | 7 (28) |
|  Never smoked, n (%) | 28 (55) | 13 (50) | 15 (60) |
| **SIMD quintile (1 = most deprived, 5 = least deprived):** |
|  SIMD 1, n (%) | 14 (28) | 7 (27) | 7 (28) |
|  SIMD 2, n (%) | 11 (22) | 6 (23) | 5 (20) |
|  SIMD 3, n (%) | 9 (18) | 4 (15) | 5 (20) |
|  SIMD 4, n (%) | 5 (10) | 3 (12) | 2 (8) |
|  SIMD 5, n (%) | 12 (24) | 6 (23) | 6 (24) |
| **Employment status:** |
|  Employed, n (%) | 25 (49) | 11 (42) | 14 (56) |
|  Unemployed, n (%) | 8 (16) | 3 (12) | 5 (20) |
|  Retired, n (%) | 9 (18) | 5 (19) | 4 (16) |
|  Student, n (%) | 2 (4) | 1 (4) | 1 (5) |
|  Other, n (%) | 7 (14) | 6 (23) | 1 (4) |
| **Education level:** |
|  Secondary education, n (%) | 18 (35) | 7 (27) | 11 (44) |
|  Tertiary/further education, n (%) | 33 (65) | 19 (73) | 14 (56) |
| **BMI (kg/m2)**, mean(SD) | 30.4 (6.8) | 31.3 (8.0) | 29.4 (5.2) |
| **Number of comorbidities** (over and above index condition), mean (SD) | 2.6 (1.7) | 2.6 (1.9) | 2.6 (1.4) |
| **Length of asthma diagnosis (yrs)**, median (IQR) | 18.5 (8.6 to 28.6) | 17.0 (8.6 to 27.8) | 20.3 (9.7 to 28.6) |
| BMI = body mass index. SIMD = Scottish Index of Multiple Deprivation.  |

### Primary outcomes

#### Recruitment and retention (Figure 1)

Recruitment target of 50 participants was met. Participating practices were mostly urban, and spread across deprivation categories. Response rate to the postal invitation was 4.6%, lower than anticipated, and only 27% of those screened were subsequently randomised, with the majority failing due to ACQ <1 (75%). Those randomised were younger (45.5 vs 51.5 years) and more likely to be female (75% vs 50%) than screen failures, but with similar socio-economic deprivation. The attrition rate (not completing follow up) was 12%: 20% in intervention group, 4% in the comparison group, (Fisher test p=0.10).

#### Website use

Nineteen of the 25 participants in the intervention group logged in at least once (76%) with 17 going beyond the initial ‘core’ section. The subsequent section was tailored depending on which of 3 options was chosen: 1) I have never been prescribed a preventer inhaler (n = 1); 2) I have been prescribed an inhaler but don’t really use it (n=6); or 3) I have a preventer and usually use it as prescribed (n = 10). The mean number of logins was 1.8 (range 0 to 7), median 1, (IQR 1,2), and the average time spent on the website during the study period was 18 minutes (range 0 to 48.9). More detail is shown in Figure A Supplementary File.

Beyond the core ‘introduction’ and ‘my asthma’ sections the most popular sections were ‘take the 4 week challenge’ (n = 13), and ‘common concerns and queries’ (n = 11). Further usage data are shown in Table A (Supplementary Data File). The majority (95%) of participants acknowledged that asthma was impacting on their life (Table B, Supplementary Data File).

#### ACQ score (table 2)

Our planned analysis was for the 7 question version of the ACQ, which includes spirometry, for which there was considerable missing data (n=23). There was no significant difference in the intervention compared to control group, (-0.42 (95% CI:-0.95, 0.11), p = 0.121). We also analyzed the equally valid 6 question version (without spirometry) [24] which was available for all (n=45), and demonstrated a similar result and it is this result which is presented in **Table 3**.

Fifty five percent of the intervention group and 48% of the comparison group achieved the MCID of an improvement of at least 0.5 points (p = 0.767).

#### AQLQ score (Table 3)

There was no significant difference in mini-AQLQ scores in the intervention group compared to the control group. Fifty percent of the intervention group and 36% in the comparison group achievied the MCID of improvement of at least 0.5 points (p = 0.379).

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| **Table 3 Primary Outcomes(ACQ and mini-AQLQ). Summaries of scores at baseline, follow up and change from baseline, with estimated between group difference from baseline-adjusted linear regression model with 95% CI and p-value. Summaries of achievement of an improvement by more than the minimum clinically important difference (MCID) at follow up, with Fisher Exact Test p-values to compare groups.** |
|  |  |  | **Intervention** | **Control** | **Estimated Difference****(95% CI)** | **p-value** |
| **ACQ Score 6 question version (continuous 0-6; 0 = totally controlled, 6 = severely uncontrolled)** |
|  | Baseline | Mean (SD) | 1.87 (0.59) | 1.97 (0.68) |  |  |
|  | Follow-up | Mean (SD) | 1.22 (0.91) | 1.65 (1.15) |  |  |
|  | Change | Mean (SD) | -0.65 (1.08) | -0.32 (0.94) | -0.36 (-0.96, 0.23) | 0.225 |
| **ACQ Score 6 question version (MCID improvement at follow up)** |
|  | Improvement ≥0.5 | n (%) | 11 (55%) | 12 (48%) |  | 0.767 |
| **Mini-AQLQ Score (continuous 1-7; 1 = severely impaired; 7 = not impaired at all)** |
|  | Baseline | Mean (SD) | 4.97 (1.03) | 4.65 (1.02) |  |  |
|  | Follow-up | Mean (SD) | 5.40 (1.01) | 4.76 (1.30) |  |  |
|  | Change | Mean (SD) | 0.43 (0.78) | 0.11 (0.88) | 0.38 (-0.13, 0.89) | 0.136 |
| **Mini-AQLQ Score (MCID improvement at follow up)** |
|  | Improvement ≥0.5 | n (%) | 10 (50%) | 9 (36%) |  | 0.379 |
|  | ACQ = Asthma Control Questionnaire (fall in score is desirable). AQLQ = Asthma Quality of Life Questionnaire (rise in score desirable). |

### Secondary outcomes

The rationale for including a range of secondary outcomes was to assess their feasibility for inclusion in any future full scale RCT. All outcomes were acceptable to participants and feasible to measure and analyze, apart from spirometry.

#### Mini-AQLQ domain scores (Table 4)

The ‘activity limitation’ domain of the mini-AQLQ showed a statistically significant improvement in scores in favour of the intervention group. The remaining individual domains of the mini-AQLQ showed numerical improvement in the intervention group, which was not statistically significant.

#### Other patient centred outcomes (Table 4 and Table 5)

There was a significant improvement in PAM scores (Table 4) in the intervention group compared to the control group, indicating that intervention patients were more highly activated in relation to managing their own health.

There was no significant difference in mean MMAS scores in the intervention group (**Table 4**) compared to the control group. However, more participants in the intervention group achieved the MCID ≥2 compared to usual care (30% vs 4%, p = 0.034), although the intervention group did have lower baseline scores.

The change in EQ-5D health utility score showed no significant between-group difference (**Table 5**), with median change in score of 0 in both groups.

#### Physiological and inflammatory outcomes.

Spirometry analysis included only those meeting ATS acceptability standards (22/45, 11 per group) [22]. Effect sizes were small, and none achieved statistical significance (Table 4).

FeNO levels (indicating airways eosinophilic inflammation) showed no significant between-group difference (Table 5).

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| **Table 4 Secondary outcomes – continous variables normally distributed. Summaries of scores at baseline, folllow up and change from baseline, with estimated between group difference from baseline-adjusted linear regression model with 95% CI and p-value. Summaries of achievement of an improvement by more than the minimum clinically important difference (MCID) at follow up, with Fisher Exact Test p-values to compare groups. N = 45 unless otherwise stated.** |
|  |  |  | **Intervention** | **Control** | **Estimated Difference****(95% CI)** | **p-value** |
| **mini-AQLQ Symptom Domain Score (continuous, 1 = severely impaired; 7 = not impaired at all)** |
|  | Baseline | Mean (SD) | 4.56 (1.10) | 4.30 (0.84) |  |  |
|  | Follow-up | Mean (SD) | 5.15 (1.20) | 4.38 (1.35) |  |  |
|  | Change | Mean (SD) | 0.59 (1.10) | 0.08 (1.05) | 0.56 (-0.08 to 1.22) | 0.084 |
| **mini-AQLQ Activity Limitation Domain Score (continuous, 1 = severely impaired; 7 = not impaired at all)** |
|  | Baseline | Mean (SD) | 5.30 (1.24) | 5.31 (1.33) |  |  |
|  | Follow-up | Mean (SD) | 5.98 (0.92) | 5.38 (1.33) |  |  |
|  | Change | Mean (SD) | 0.68 (1.01) | 0.07 (1.10) | **0.60 (0.05 to 1.15)** | **0.034** |
| **mini-AQLQ Emotional Function Domains Score (continuous, 1 = severely impaired; 7 = not impaired at all)** |
|  | Baseline | Mean (SD) | 5.48 (1.09) | 4.80 (1.48) |  |  |
|  | Follow-up | Mean (SD) | 5.75 (1.01) | 4.84 (1.82) |  |  |
|  | Change | Mean (SD) | 0.27 (0.78) | 0.04 (1.30) | 0.35 (-0.33 to 1.03) | 0.301 |
| **mini-AQLQ Environmental Domains Score (continuous, 1 = severely impaired; 7 = not impaired at all)** |
|  | Baseline | Mean (SD) | 4.75 (1.39) | 4.11 (1.54) |  |  |
|  | Follow-up | Mean (SD) | 4.85 (1.30) | 4.23 (1.67) |  |  |
|  | Change | Mean (SD) | 0.10 (0.89) | 0.12 (0.90) | 0.08 (-0.46 to 0.62) | 0.768 |
| **PAM (continuous, 0 = no activation; 100 = high activation)** |
|  | Baseline | Mean (SD) | 65.7 (10.0) | 66.2 (14.1) |  |  |
|  | Follow-up | Mean (SD) | 73.0 (13.9) | 65.7 (16.5) |  |  |
|  | Change | Mean (SD) | 7.3 (11.3) | -0.5 (12.5) | **7.72 (0.53 to 14.90)** | **0.036** |
| **MMAS (continuous, range 0-8, 0 = low adherence; 8 = high adherence)** |
|  | Baseline | Mean (SD) | 4.88 (1.97) | 5.59 (1.85) |  |  |
|  | Follow-up | Mean (SD) | 5.46 (1.80) | 5.82 (1.85) |  |  |
|  | Change | Mean (SD) | 0.58 (1.37) | 0.23 (1.03) | 0.19 (-0.50 to 0.88) | 0.586 |
| **MMAS (MCID improvement at follow up)** |
|  | Improvement ≥2.0 | n (%) | 6 (30) | 1 (4) |  | **0.034** |
| **FEV1 (L) (continuous) (n = 22)** |
|  | Baseline | Mean (SD) | 2.62 (0.56) | 2.66 (0.69) |  |  |
|  | Follow-up | Mean (SD) | 2.72 (0.58) | 2.68 (0.49) |  |  |
|  | Change | Mean (SD) | 0.10 (0.18) | 0.02 (0.31) | 0.08 (-0.12 to 0.27) | 0.428 |
| **FEV1 % predicted (continuous) (n = 22)** |
|  | Baseline | Mean (SD) | 87.4 (13.6) | 85.2 (17.1) |  |  |
|  | Follow-up | Mean (SD) | 90.6 (13.8) | 85.7 (11.8) |  |  |
|  | Change | Mean (SD) | 3.3 (6.3) | 0.6 (9.4) | 3.4 (-2.8 to 9.5) | 0.265  |
| **FEV1 /FVC (%) (continuous) (n = 22)** |
|  | Baseline | Mean (SD) | 76.7 (7.0) | 77.6 (10.9) |  |  |
|  | Follow-up | Mean (SD) | 79.1 (6.7) | 80.2 (9.5) |  |  |
|  | Change | Mean (SD) | 2.4 (5.3) | 2.6 (4.5) | - 0.4 (-3.9 to 3.1)  | 0.829 |
|  | ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire. FEV1 = forced expiration in 1 second. FVC = forced vital capacity. MMAS = Morisky Medication Adherence Score. PAM = Patient Activation Measure. P values in bold indicate significance < 0.05 |

#### Medication changes and health service contacts (Table 5)

The median weekly number of puffs of reliever inhaler used in the intervention group reduced from 11 to 5, but remained unchanged in the control group at 4 puffs per week at baseline and at follow-up (p = 0.022). Although this between-group change in bronchodilator use was statistically significant, the groups were imbalanced at baseline. There was no significant between-group difference in the percentage of recommended ICS doses self-reportedly taken, nor the equivalent beclometasone doses prescribed. There were no significant between-group differences in health service contacts or prednisolone courses prescribed.

#### Further feasibility outcomes

The PETS results are shown in Figure 2 (Supplementary Data File), illustrating barriers to using the website. The biggest barriers relate to time and opportunity, rather than content.

No serious adverse events were recorded.

The main source of missing data was from the spirometry results where 23 participants had results not suitable for analysis, due to not meeting ATS criteria. All questionnaires were completed sufficiently well to allow calculation of scores, with only one response missing from each of the mini-AQLQ, PAM, and MMAS all from different participants.

#### Sample size for a fully-powered subsequent study

Using baseline adjusted calculations of the change in ACQ score above assuming a standard deviation of 1.0, a sample size of 134 would be required to detect a between-group change of ≥ 0.5 (MCID) in ACQ with 90% power at 0.05 significance. Assuming a similar attrition rate of 12%, the total sample size required would be 154.

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| **Table 5 Secondary outcomes, not normally distributed. Summaries of scores at baseline, follow up and change from baseline, Summaries of prescribing and health service use over the study period, with Fisher Exact Test for categorical data, and Mann Whitney test to compare median differences between groups.** |
|  |  |  | **Intervention** | **Comparison** | **p-value** |
| **EQ-5D health utility (continuous, 0.000 = dead; 1.000 perfect health)** |
|  | Baseline | Median (IQR) | 0.848 (0.725 , 1.000) | 0.796 (0.620 , 1.000) |  |
|  | Follow-up | Median (IQR) | 1.000 (0.796, 1.000) | 0.796 (0.727, 1.000) |  |
|  | Change | Median (IQR) | 0.000 (0.000, 0.111) | 0.0000 (-0.052, 0.194) | 0.972 |
| **EQ-5D visual analogue scale (continuous, 0 worst health; 100 best health))** |
|  | Baseline | Median (IQR) | 75 (70, 84) | 80 (70, 90) |  |
|  | Follow-up | Median (IQR) | 80 (73, 88) | 80 (70, 90) |  |
|  | Change | Median (IQR) | 2.5 (-6.5, 13.0) | 1.0 (-10, 10) | 0.409 |
| **Fractional exhaled Nitric Oxide (FeNO) (continuous, low score indicates low inflammation)** |
|  | Baseline | Median (IQR) | 26.0 (16.0, 46.5) | 25.0 (11.0, 36.0) |  |
|  | Follow-up | Median (IQR) | 23.0 (12.0, 44.5) | 19.0 (10.0, 27.0) |  |
|  | Change | Median (IQR) | -2.5 (-11.5, 8.5) | -2.0 (-15.0, 2.0) | 0.615 |
| **Puffs reliever taken per average week(continuous)** |
|  | Baseline | Median (IQR) | 11 (7, 28) | 4 (2, 12) |  |
|  | Follow-up | Median (IQR) | 5 (0.5, 14) | 4 (0, 28) |  |
|  | Change | Median (IQR) | -7 (-14, 1 ) | 0 (-4, 4) | **0.022** |
| **Percentage prescribed ICS reportedly taken (continuous)** |
|  | Baseline | Median (IQR) | 85.7 (14.3, 100.0) | 100.0 (71.4, 100.0) |  |
|  | Follow-up | Median (IQR) | 92.9 (71.4, 100.0) | 100.0 (85.7, 100.0) |  |
|  | Change | Median (IQR) | 0.0 (0.0, 14.3) | 0.0 (0.0, 7.1) | 0.730 |
| **Equivalent beclometasone dose (mcg) (continuous)** |
|  | Baseline | Median (IQR) | 400(300, 1000) | 800 (400, 800) |  |
|  | Follow-up | Median (IQR) | 400(300, 1000) | 800 (400, 800) |  |
|  | Change | Median (IQR) | 0(0, 0) | 0 (0, 0) | 0.209 |
| **Prednisolone course** | n, % with at least one | 1 (5) | 3 (12) | 0.617 |
| **Hospital/ A&E visit** | n, % with at least one | 0 | 0 | - |
| **Non-routine GP/Nurse visit** | n, % with at least one | 3 (15) | 6 (24) | 0.710 |
| **Routine GP/Nurse visit (e.g. asthma review)** | n, % with at least one | 5 (25) | 8 (32) | 0.745 |
|  | A&E = accident & emergency. ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire. EQ5D = EuroQol, GP = general practitioner. ICS = inhaled corticosteroids. IQR = interquartile range. Mcg = micrograms. P values in bold indicate significance < 0.05 |

## DISCUSSION

### Principle findings

This Phase II pilot RCT of the Living well with Asthma resource demonstrates that this website merits further development, and that subsequent progression to a full scale Phase III RCT is feasible. Recruitment targets were achieved, and attrition rates were comparable to rates of other published digital interventions.[9] We had no upper age limit, unlike similar asthma digital intervention studies. This is important as our recent metareview only found one study that included participants over 50 years of age, and descriptions of participants’ characteristics were limited, with socio-economic status ignored.[9] This information is important to understand the ‘reach’ of the intervention.

In terms of primary efficacy outcomes, there were no significant between group differences in terms of ACQ and mini AQLQ, although it is important to note that this pilot trial was not powered to show such a differences. However there are some interesting findings in analysis, as both the ACQ and mini-AQLQ demonstrate encouraging and consistent trends in favour of the intervention group, with one sub-domain of the AQLQ (activity limitation) reaching the MCID and statistical significance. It is worth noting that for both primary efficacy outcomes, a proportion of those in the comparison group demonstrated an improvement in MCID scores as well as the intervention group. This is often the case in unblinded complex intervention trials, and validates our approach of making this a pilot RCT, and not just a feasibility study. In terms of website use, 76% of individuals logging in is comparable with other behaviour change websites,[25, 26] and it is encouraging that an average of only 18 minutes usage resulted in consistently positive trends across almost all outcomes. Asthma specific research indicates that users like to spend 5-8 minutes per online session.[27] Our exploration of usage patterns suggests that some users missed sections that they could potentially have benefited from. These two facts combined leads us to conclude that it would be preferable to provide the core modules initially and then ‘release’ further sections weekly or fortnightly, a strategy that has been used successfully for a weight loss intervention also developed using LifeGuide software.[26] Qualitative process evaluation interviews of those in the intervention group have been completed and will be reported separately. Findings from this qualitative work will inform the further development of this resource, prior to evaluation in a full-scale trial.

We assessed the feasibility of collecting a range of secondary outcomes in any future RCT, and in doing so demonstrated a significant improvement in the patient activation measure (PAM), which indicates that those in the intervention group had improved knowledge, confidence and skills to manage their asthma. Significant between group differences in the numbers of patients showing a MCID improvement in adherence and reliever use should be interpreted with caution due to baseline between-group imbalances. The feasibility of researchers undertaking spirometry in the participants’ own homes using a portable handheld device was found to be low, as reported in other studies [28]. Potential solutions include: more intensive training of research staff; use of a device providing test by test acceptability information; or undertaking trial visits in a dedicated clinical research facility by staff experienced in spirometry. However, this latter solution could have a negative effect on recruitment, as 21% of our study visits were undertaken in the evening and weekend, which facilitated recruitment of a population who can rarely make it into such RCTs (fulltime employed). There is a balance between precision of measurements versus encouraging a more representative sample. Whether spirometry is required at all in a study aimed at people with mild to moderate asthma is not clear, and there is precedence in the literature for not including these outcome measures in similar primary care based trials or for using simpler to perform lung function measures such as peak expiratory flow rate (PEFR).[29, 30]

Lack of time and opportunity were the biggest barriers to using the website and providing the contents on a smartphone app or tablet would be worth investigating. During the introduction questions at the start of the website 95% of users agreed to statements which showed that asthma was negatively impacting on their lives. However at the end of the trial 42% of users doubted the personal relevance of the website, anecdotally reporting that the website would be more useful for people with symptomatic asthma. To be in the trial in the first place all users were symptomatic (as defined by ACQ score), so challenging this mismatch between users’ perceptions and the reality would be warranted in future versions of a mobile friendly digital intervention..

### Strengths and limitations

Blinding to group allocation during analysis was not possible due to the different numbers in each group being known by the researcher undertaking the analysis. As with many digital interventions, the ‘reach’ is a potential issue and our low response rate is a concern, even taking into account our very broad recruitment strategy. Similar trials have described similar recruitment difficulties.[31] However given how common asthma is, improvements in even a small proportion of patients could lead to significant benefit overall , particularly with an intervention such as that trialled here which is entirely internet based and once developed is very economical to make available to large numbers of people. Therefore what seems like a low reach, can still improve outcomes for a large number of people. We have described our population in detail, and our baseline characteristics demonstrate that patients were recruited from a range of socio-economic backgrounds. Those excluded due to not having internet access were older than those who were excluded for other reasons (data not shown), but this is becoming less of an issue with year on year increases in the number of households with internet access (84% in 2014, United Kingdom).[32]

### Comparable studies in the literature

Our recently published metareview suggests digital interactive interventions to support asthma self-management show promise but there is no clear picture about the ‘active ingredients’ of the interventions.[9] In the development of this intervention, we have described its contents fully including an analysis of behaviour change techniques used,[13] allowing more meaningful future comparisons. When focussing on interventions aimed at those with mild to moderate asthma, most have included considerable health professional input as well as self-monitoring work on the part of the participants, and have not shown clinical improvements.[33] This evaluation of Living Well with Asthma adds to the literature on digital asthma self-management suggesting that an intervention not including regular user self-monitoring or costly health professional input may have positive results.

**Future research**

We have shown that evaluating the Living Well with Asthma intervention was feasible and resulted in encouraging trends in clinical outcomes. Further qualitative work to understand usage patterns with intervention group participants have been completed and will inform a future version of the resource. To overcome the ‘practical barriers’ to using the intervention future versions need to be mobile and tablet compatible, and will require further user testing . Following this development work on the resource, these findings suggest that a large scale Phase III RCT is merited, with some exploration of recruitment strategies and minor modification to outcome measurement methods. Low intensity digital interventions that are easier to deliver at scale may be a more successful strategy, particularly in those with mild to moderate asthma.

## Additional Information

### Abbreviations

A&E: Accident and emergency; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ATS/ERS: American Thoracic Society/European Respiratory Society; BMI: body mass index; BTS: British Thoracic Society;EQ-5D: EuroQol 5D; FeNO: Fractional Exhaled Nitric Oxide; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; GP: General Practitioner; ICS: inhaled corticosteroids; MCID minimal clinical important difference; MMAS: Morisky Medication Adherence Scale; MRC: Medical Research Council; PAM: Patient Activation Measure; PEFR: Peak Expiratory Flow Rate; PETS: Problems of Experienced Therapy Scale; RCT: Randomised Controlled Trial.

### Competing interests

This project (developing and evaluating the Living well with Asthma resource) was funded through a clinical academic fellowship awarded to DM by the Chief Scientist Office, Scottish Government <http://www.cso.scot.nhs.uk/> (ref CAF 11/08). The funders played no part in the design, data collection, data analysis/interpretation, the writing of the manuscript; or in the decision to submit the manuscript for publication. All other authors received no direct funding for their role in this project.

MT declares neither he nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker’s honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem, Novartis, GSK, Teva. He has received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to attend international scientific meetings from: GSK, Astra Zeneca, Mundipharma. He has received funding for research projects from: GSK, Almirall.

 All other authors declare that they have no competing interests.

### Authors’ contributions

DM, FM, SW led planning and development of the intervention with support from NCT, RC, LY and MT. DM, FM, SW, AM planned the evaluation, with support from NCT, RC, KA LY and MT. DM and KS were responsible for recruitment, and DM, KS and KA undertook data collection. DM led data analysis and interpretation with support from FM, SW, AM, NCT, MT, RC, KS and LY. DM drafted the manuscript with initial support from FM, SW and AM and additional input from MT, LY, NCT, RC, KS, and KA. All authors critically reviewed the manuscript, contributing important intellectual content, and approved the final manuscript.

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### Ethical Approvals

This study was approved by the West of Scotland Research Ethics Committee (ref 13/WOS/0004)

**Figure Legend**

**Figure 1. Flow of participants through study**

\*actual search terms refined iteratively through recruitment (see Supplementary Data file for detail).

ACQ = asthma control questionnaire score, FeNO = fractional exhaled nitric oxide.

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