Contemporary Clinical Trials 82 (2019) 46–52

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Phase II trial of web-based tailored asthma management intervention in adolescents at clinics

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1. Introduction

Clinical trials are critical for medical decision-making; however, conduct is costly and labor intensive. Traditionally, clinical trials are conducted in a controlled environment with a restricted patient population. In addition to the use of electronic initiatives (e-initiatives) such as the use of electronic medical records (EMR) for patient identification, recruitment and data collection, pragmatic clinical trials promote patient enrollment in a "real world" setting with fewer exclusion criteria and less need for research infrastructure. The pragmatic trial also uses comparative adaptive methods and approaches to ensure results provide real-world evidence, i.e., evidence that study execution and data analysis are translatable to practice. Puff City, a web-based, asthma management program for urban adolescents with asthma, has been evaluated in Detroit Public High Schools [1,2], and results of these school-based randomized trials were promising for potential dissemination beyond schools [1,2]. To demonstrate pragmatic approaches to conduct of a randomized trial, we extended the Puff City program to a clinical setting and conducted a seamless Phase II/III pragmatic trial of the program in a group of urban, primary care clinics.

In a previous publication, we described the design of a pragmatic randomized controlled trial to evaluate a behavioral intervention directed at urban teens with asthma [3] with a two-fold objective: (1) to study the efficacy of Puff City in a clinical setting and (2) to conduct a trial that is cost efficient. Briefly, we used the comparative adaptive approach to increase efficiency by first conducting a Phase II trial as an interim analysis with a pre- defined marker study to identify a group (an enriched population) that might benefit most from the intervention [3]. Pragmatic e-initiatives were used for trial conduct including application of HEDIS criteria to administrative data to identify patients with persistent asthma, a system-wide e-scheduling appointment system to identify the upcoming appointments of potential participants at our primary care locations, and e-tracking and EMR monitoring for patient follow-up. Our experience in using the EMR for trial recruitment and retention is detailed in a previous publication [4]. The purpose of this study is to report the Phase II trial results based on CONSORT guidelines [5] and to assess intervention benefit overall, as well as to describe the enriched population identified through the marker-positive analysis.

2. Methods

2.1. Trial design

This was an adaptive, seamless, randomized, controlled Phase III trial of Puff City with a Phase II trial as the interim analysis with inclusion of a pre-specified marker positive study. The marker positive study is part of the adaptive design and can be used to enroll patients in a subsequent trial with an enriched patient population. All methods were approved by the institutional review boards of Henry Ford Health System and Augusta University.

2.2. Participants

Using our EMR, we applied HEDIS criteria to our hospital databases to identify youth, aged 15–19 years with persistent asthma [3]. We accessed health system-wide appointment scheduling to identify upcoming appointments at participating primary care clinics for potentially eligible patients. Patients confirmed as eligible were recruited at the scheduled clinic visit upon providing consent (parent) and assent (teen). Upon completion of a baseline assessment, participants were randomized when they logged in for session 1. We used electronic patient-reported outcomes [ePROs] and EMR data (asthma medication dispensing, asthma-related ED visits, and asthma-related hospitalizations) collected at baseline prior to randomization, 6 months after study intervention completion, and at year 1 after randomization. Upon enrollment, youth in the treatment and control groups were given a packet containing information on how to access Puff City or the asthma

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https://doi.org/10.1016/j.cct.2019.04.011
Received 30 November 2018; Received in revised form 5 April 2019; Accepted 17 April 2019
Available online 04 May 2019
1551-7144/

websites on a computer with internet access, a letter asking permission for students to access websites from a school computer, and information on computer resources in the area.

2.3. Intervention and control arms

The study intervention arm, Puff City, and control arm, existing web-based asthma education, have been described in a previous publication [1,2]. In brief, Puff City is a web-based, asthma management tool that is theory-based and uses computer-tailoring. Targeted behavioral outcomes include controller medication adherence, keeping a rescue inhaler nearby, and smoking reduction or cessation. Patients randomized to the treatment group (tailored, web-based asthma education) received four online sessions designed to be accessed no < 1 week apart. A booster session at 6 months was created to sustain positive change and correct early stages of relapse.

Patients randomized to the control arm received four sessions of existing, online, asthma education from recognized US and Canadian organizations that had a history of providing evidence-based information on asthma management [6]. Sites were reviewed to ensure topics similar to that presented in Puff City was included (e.g., avoidance of environmental triggers, information on medication usage, and partnership with a healthcare provider). After login, control students were given access to links for the control websites. To regulate dosage, control teens received a 'time expired' message after 30 min of browsing, which corresponded to the 30 min maximum time needed to complete a tailored session by the intervention group [1,2].

2.4. Outcome measures

Outcomes were based on encounters documented in the EMR and ePROs. The Asthma Control Test (ACT) was the primary endpoint (P1) for testing the intervention effect at Year 1. The ACT is a patient self-reported survey tool consisting of 5 questions, with a total score ranging from 5 to 25 (where < 20 is uncontrolled, and ACT < 15 is poorly controlled). The tool is used to measure asthma control by assessing the frequency of asthma symptoms, use of rescue medications, and impact of asthma on daily functioning over the course of the previous 4 weeks. The tool has been evaluated and found to have high internal consistency and reliability [5]. The secondary endpoints for the study were (S1) asthma exacerbations occurring over the 12 month follow-up period, defined as asthma hospitalizations, emergency department (ED) visits, or oral corticosteroid dispensing, and ePROs, (S2) symptom-days, (S3) symptom-nights, (S4) days of restricted activity, and (S5) school/work days missed in the past 30 days at 1 year post randomization. The number of asthma-related ED visits and hospitalizations within a 12 month period has been used as a clinical measure of asthma control and, according to Expert Panel 3: Guidelines for the Diagnosis and Management of Asthma, is a measure of risk of a future acute event [7]. These secondary endpoints were selected based on their relevance to the healthcare decisions being made by patients, providers, and payers as part of adapting a pragmatic approach [8–10], and have been used in previous asthma studies [1,2]. Poorly controlled asthma, defined as ACT ≤ 15 and shared asthma medication were also collected at year 1 as exploratory endpoints.

Safety outcomes during study intervention (or up to 6 months after randomization) were also collected as a secondary outcome. Serious Adverse Events (SAE) are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a study intervention. All SAE was reviewed by an independent medical monitor, blinded to treatment-arm, for adjudication of possible relation to the study intervention. Chi-square test or fisher exact test was used to compare SAE differences between the two groups.

2.5. Sample size and power calculation

For this study, an adaptive design permits a first interim analysis after the first 142 patients have completed the year 1 endpoint, and a second interim analysis at completion of Phase II when endpoint data collection has occurred for a total of 250 patients. Targeted enrollment for the final phase (Phase III) was calculated to be 500 patients. This paper reports on the Phase II second interim analysis (n = 250 patients) as proposed to be enrolled under the NHLBI funding (1R01HL114981–01).

The sample size/power calculation was specified a priori based on published data [1,2]. The two interim analyses would allow 80% power to detect a significant intervention effect if the observed test statistic is ± 3.3569 or p-value < .0008 at first interim analysis, ± 2.4341 or p-value < .0149 at the second interim analysis, or ± 2.0017 or p-value < .0453 at the final analysis. We also incorporated an enrichment component of the trial and planned to conduct marker-positive analysis using primary endpoint of ACT at year 1 at the second interim analysis with the intention to only enroll marker-positive patients in the rest of Phase III trial (n = 250) [3] assuming that 80% of entire trial patients (n = 500) would be marker positive, in order to retain 80% power in the marker positive (enriched) population with effect size = 0.48. The trial would be stopped if no trend was observed toward intervention benefit on the primary endpoint (ACT at year 1) at the completion of the Phase II component of the trial. A marker positive ancillary study would be considered using asthma exacerbations (S1) occurring over the 12 months as outcome.

2.6. Randomization

Online randomization to the treatment (Puff City) or control group (existing, online asthma education) occurred when participants logged in for session 1 of the intervention/control program. For this trial, the unit of randomization was the patient. The 1:1 randomization schema was generated by University of Michigan Center for Health Communications Research using the urn design [10], an adaptive sampling approach that improves balance compared to blocked randomization. Randomization was stratified by gender, computer and internet access at home, and baseline ACT ≤ 15 (yes/no) where ≤15 is considered very poorly controlled. The randomization algorithm was validated prior to its application.

2.7. Statistical analysis

The planned analyses are detailed in a previous publication [3]. Briefly, data were evaluated for normality and data transformation or nonparametric tests were used if data were not normally distributed. We first compared baseline variable differences between the treated and control groups to evaluate the randomization. We used intention-to-treat (ITT) for the trial analysis. For the primary endpoint of ACT score at 12 months, 6-month survey data was used if ACT was missing at 12-month. If ACT was missing for both 6 and 12 months survey, the median ACT score calculated among patients with the same study arm was used, given ACT was not normally distributed. Wilcoxon test, was used to test Puff City effect on ACT score at year one (primary endpoint). Logistic regression was used to study the intervention effect for the secondary outcomes, including asthma-related hospitalizations, ED visits, or oral corticosteroid dispensing medications (S1), self-report of asthma-related functional status (daytime or nighttime symptoms, restricted activity, and missing school day or work, S2-S5), respectively at year one. The safety data, toxicity grades and SAE, were also described.

To further explore the intervention effect, we conducted two ancillary analyses: first, we tested the change of asthma symptom status at 12 months from baseline (where each patient served as his/her own control) using a paired t-test for continuous variables and McNemar test for proportional variable for all patients and patients in each arm

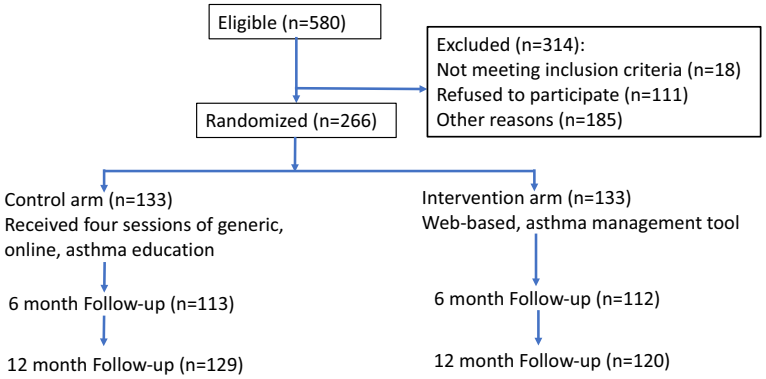

Fig. 1. Trial conduct at the completion of Phase II component.

respectively. Secondly, we performed the marker positive analysis using a multivariable model with baseline variables as covariates, YR1 asthma exacerbations (S1) as the outcome, and with the inclusion of a "baseline variable by treatment" interaction term. The analysis focused on moderating effects (e.g., baseline variable may influence Puff City effect) on YR1 asthma exacerbations (S1). Any moderating effects were further evaluated as quantitative effects (influencing the magnitude of the effect) or qualitative effects (influencing the direction of the effect) of study intervention. A marker would be identified if it qualitatively influenced Puff City effect at p-value $< .05$ in a sub group of the study population.

3. Phase II trial results

Of the 580 patients identified as having scheduled clinical visits within the study timeframe, $n = 314$ were excluded. Of the 314 excluded, $n = 18$ were ineligible, $n = 111$ refused to participate, and ($n = 185$) were excluded due to cancellation or "no show" for the clinic

Table 1
Baseline group comparisons.

Variable	Response	All ($N = 266$)	Puff city ($N = 133$)	Control ($N = 133$)	p-Value
Site	Clinic A	43 (16%)	22 (17%)	21 (16%)	.13
	Clinic B	2 (1%)	0 (0%)	2 (2%)	
	Clinic C	6 (2%)	2 (2%)	4 (3%)	
	Clinic D	1 (0%)	1 (1%)	0 (0%)	
	Clinic E	45 (17%)	28 (21%)	17 (13%)	
	Clinic F	3 (1%)	0 (0%)	3 (2%)	
	Clinic G	166 (62%)	80 (60%)	86 (65%)	
Sex	Male	139 (52%)	69 (52%)	70 (53%)	.902
	Female	127 (48%)	64 (48%)	63 (47%)	
Age	*N*, Mean ± Std Dev	266, 14.8 ± 1.6	133, 14.9 ± 1.6	133, 14.7 ± 1.5	.427
Hispanic/Latino	No	255 (96%)	127 (95%)	128 (96%)	> .999
	Yes	11 (4%)	6 (5%)	5 (4%)	
Race	Black or African American	186 (70%)	91 (68%)	95 (71%)	.386
	White or Caucasian	58 (22%)	29 (22%)	29 (22%)	
	American Indian or Alaskan Native	3 (1%)	3 (2%)	0 (0%)	
	Native Hawaiian or Pacific Islander	1 (0%)	0 (0%)	1 (1%)	
	Other/Unknown	18 (6%)	10 (8%)	8 (6%)	
Education	Below high school	78 (29%)	36 (27%)	42 (32%)	.67
	High school	174 (65%)	89 (67%)	85 (64%)	
	College or higher	14 (5%)	8 (6%)	6 (5%)	
Computer at home	No	17 (6%)	10 (8%)	7 (5%)	.617
	Yes	249 (94%)	123 (92%)	126 (95%)	
Medicaid	No	164 (62%)	78 (59%)	86 (65%)	.697
	Yes	93 (35%)	47 (35%)	46 (35%)	
	Unknown	9 (3%)	8 (6%)	1 (1%)	
ACT score	*N*, Median (Q1, Q3)	266, 20 (16, 22)	133, 20 (16, 22)	133, 19 (16, 22)	.951
ACT score ≤ 15	No	222 (83%)	111 (83%)	111 (83%)	> .999
	Yes	44 (17%)	22 (17%)	22 (17%)	
Having asthma symptom days (past-30-days) (S2D) %	No	41 (15%)	24 (18%)	17 (13%)	.308
	Yes	225 (85%)	109 (82%)	116 (87%)	
Nighttime symptoms/30 days (S3D) %	No	112 (42%)	58 (44%)	54 (41%)	.619
	Yes	154 (58%)	75 (56%)	79 (59%)	
Restricted activity/30 days (S4D)%	No	99 (37%)	49 (37%)	50 (38%)	.899
	Yes	167 (63%)	84 (63%)	83 (62%)	
Missed school or work/30 days (S5D)%	No	109 (64%)	63 (71%)	46 (57%)	.057
	Yes	61 (36%)	26 (29%)	35 (43%)	
Report sharing asthma medication	No	212 (80%)	106 (80%)	106 (80%)	1.000
	Yes	54 (20%)	27 (20%)	27 (20%)	
ER visit or hospitalization in past 12 months	No	175 (66%)	88 (66%)	87 (65%)	.897
	Yes	91 (34%)	45 (34%)	46 (35%)	
Pets at home	No	121 (45%)	61 (46%)	60 (45%)	.902
	Yes	145 (55%)	72 (54%)	73 (55%)	

appointment (Fig. 1). A total of 266 patients (targeted enrollment = 250 for the Phase II component of the trial) were recruited from 7 HFHS clinics and randomized to Puff City (n = 133) or the control group (n = 133).

3.1. Patient characteristics at baseline by randomization group (Table 1)

Patient baseline characteristics were well balanced between groups (Table 1). Among the 266 patients randomized, the mean age (STD) was 15 years (1.6) and 70% were attending school. Overall, 52% of participants were male, 70% African American, 35% Medicaid enrollees, and 93% of patients had a computer with internet access at home. The median baseline ACT score was 20. About 22% of teens had ACT scores ≤15. Self-reported asthma symptom (days, the past 30 days prior to the enrollment) were in the range of 4–5, and 34% of patients reported an ED visit/hospitalization in the 12 months prior to the index visit. At the time of the enrollment, 55% of patients had pets at home.

3.2. Outcomes and estimations

3.2.1. Primary endpoint

An imputation was performed for 21 patients (13 in treated and 8 in controls) who did not have ACT measurements at year 1 but had some information from the YR1 survey. The ACT median was 22 in the Puff City treated group, 21 in the control treated group, with no treatment benefit observed (p-value = 0.416) at the completion of Phase II component (interim analysis).

3.2.2. Secondary endpoints (S1–S5)

There was a 5% difference in asthma exacerbations between the treated (20%) and the control (25%) groups that did not reach statistical significance. Self-reported asthma morbidity and functional status variables are presented in Table 2. No significant difference was observed between the two groups, although teens randomized to Puff City reported more symptoms at night and school/work missed, compared to control group with p-value = .12 for symptoms at night on all teens and p-value .047 for missing schools based on 67% of teens who completed the questionnaire.

3.2.3. Exploratory endpoints

Teens in the Puff City treated group were less likely to share medicine at home, compared to patients in the control group (7% vs, 17%, p = .028). In the control group, fewer teens had ACT scores ≤15 than treatment patients (OR = 4.8, p = .0023). Differences in ED visits/hospitalizations were not significant.

3.2.4. Safety endpoints

A total of 137 patients experienced adverse events during the 6-month follow-up period after study intervention. Of these, 54% were abnormal laboratory results or grade 1 toxicity, 41.6% were grade 2 toxicity, and 6 (4.4%) were grade 3 or 4 toxicity. Four (4) SAE (2 from treated and 2 from control) were reported in which one patient had a gunshot injury induced complication and three patients experienced major depression. All grade 3 and 4 events, as well as SAEs, underwent central review by a medical monitor, who was blinded to randomization status. None were ruled as being a study-related events. Incidence of SAEs was similar for each treatment arm (Fishers Exact test p = 1.0).

3.3. Ancillary analysis of change at 12 months from baseline

We conducted an ancillary analysis examining overall changes in asthma control indicator baseline variables at the YR1 endpoint. Results of the analysis are presented in Table 3 for both treated and control combined. ACT score improved 2 points (to 22 at 12 months) in all participants from median value of 20 at baseline (p < .001) indicating a significant effect regardless of the study intervention arm. Rates of asthma symptoms days and nights were reduced at 12 months from baseline in a range of 7% to 21% (p-value < .05), as well as the reduction of sharing asthma medication (8%, with p = .01). When analyzed by treatment arm, a similar significant reduction was observed in the treated group, except for missing school/work days (p = .666) in the treated group (Table 3.1). In the control group, no change was observed for sharing asthma medication (p = .452, Table 3.2).

3.4. Ancillary analysis of the marker-positive

Three baseline variables, days of restricted activity, use of asthma medication, and pets at home, had a significant interaction with treatment (Puff City intervention) on YR1 asthma exacerbations. Multivariable modeling revealed that pets at home (pets n = 145 and no pets n = 121) moderated the effect of the Puff City intervention (Fig. 2).

Among teens with pets at home, Puff City treated patients had significantly fewer asthma exacerbations at YR1, compared to control treated patients (OR = 0.35, 95%CI 0.15–0.84). In contrast, among those without pets at home, the Puff City intervention was associated with increased risk although there was no significant difference detected, suggesting pets at home is a marker for possible intervention efficacy (OR = 1.55, 95% CI 0.67–3.60). Patient baseline characteristics in the enriched population (pets at home) are presented in Table 4. The enriched population had fewer AA, fewer males, and more poorly controlled asthma, as determined by ACT ≤ 15. An ad-hoc analysis was conducted by testing if AA moderated Puff City effect on

Table 2
Treatment comparisons 12 months after study intervention.

Primary endpoint at 12 months	Puff city (n = 133)	Control (n = 133)	OR (Puff City vs. Control)	95% CI	p-Value
ACT score (ITT) (N, Median, (Q1, Q3))	133, 22, (20, 24)	133, 21, (19, 24)			.4161
Secondary endpoints					
ER visit/hospitalization/oral prescription/injectable steroids at 12 month (S1), n %	133, 26 (20%)	133, 33 (25%)	0.736	0.412, 1.317	.3025
Symptom days/30 days (S2) %	124, 84 (68%)	130, 88 (68%)	1.002	0.592, 1.696	.9933
Symptom nights/30 days (S3) %	133, 56 (42%)	133, 44 (33%)	1.471	0.893, 2.423	.1295
Restricted activity/30 days (S4) at 12 m	133, 56 (42%)	133, 57 (43%)	0.970	0.596, 1.577	.9013
Missed school/work/30 days (S5) %	90, 29 (32%)	89, 17 (19%)	2.014	1.011, 4.010	.0465
Exploratory endpoint					
Sharing asthma medications (Y/N) at 12 m %	117, 8 (7%)	126, 21 (17%)	0.367	0.156, 0.865	.0219
ACT score < 15 (Y/N) at 12 m %	133, 21 (16%)	133, 5 (4%)	4.800	1.752, 13.149	.0023
ER visit or hospitalization in past 12 months[a]	133, 15 (11%)	133, 17 (13%)	0.867	0.414, 1.818	.7064

[a] Listed here as an exploratory endpoint to distinguish from the secondary endpoint which includes injectable steroids which was not collected at the 12-month timepoint.

Table 3
Comparison of change in asthma control indicators at 12 months from baseline.

Variable	Category	Baseline (N = 266)	12 month (N = 266)	Change from baseline to 12 month	p-Value
ACT score, Median (Q1, Q3)		20 (16, 22)	22 (20, 24)	2	< .001
ACT score less than or equal 15	No	222 (83%)	240 (90%)	7%	.021
	Yes	44 (17%)	26 (10%)	−7%	
Asthma symptom days (past-30-days)	No	41 (15%)	82 (32%)	17%	< .001
	Yes	225 (85%)	172 (68%)	−17%	
Asthma symptom nights (past-30-days)	No	112 (42%)	166 (62%)	20%	< .001
	Yes	154 (58%)	100 (38%)	−20%	
Restricted activity due to asthma (past-30-days)	No	99 (37%)	153 (58%)	21%	< .001
	Yes	167 (63%)	113 (42%)	−21%	
Missed school/work (past-30-days)	No	109 (64%)	133 (74%)	10%	.039
	Yes	61 (36%)	46 (26%)	−10%	
ER visit or hospitalization in past 12 months	No	175 (66%)	234 (88%)	22%	< .001
	Yes	91 (34%)	32 (12%)	−22%	
Sharing asthma medications (Y/N) at 12 m	No	212 (80%)	214 (88%)	8%	.011
	Yes	54 (20%)	29 (12%)	−8%	

Table 3.1
Comparison of asthma status change at 12 months from baseline (Puff City Treated group only).

Variables	Category	Baseline (N = 133)	12 month (N = 133)	Change from baseline to 12 month	p-Value
Intention to treat ACT score		18.9 ± 4.5	20.8 ± 4.2	1.9	< .001
ACT score less than or equal 15	No	111 (83%)	112 (84%)	1%	.868
	Yes	22 (17%)	21 (16%)	−1%	
Asthma symptom days (past-30-days)	No	24 (18%)	40 (32%)	14%	.008
	Yes	109 (82%)	84 (68%)	−14%	
Asthma symptom nights (past-30-days)	No	58 (44%)	77 (58%)	14%	.020
	Yes	75 (56%)	56 (42%)	−14%	
Restricted activity due to asthma (past-30-days)	No	49 (37%)	77 (58%)	21%	< .001
	Yes	84 (63%)	56 (42%)	−21%	
Missed school/work (past − 30-days)	No	63 (71%)	61 (68%)	-3%	.663
	Yes	26 (29%)	29 (32%)	3%	
ER visit or hospitalization in past 12 months	No	88 (66%)	118 (89%)	23%	< .001
	Yes	45 (34%)	15 (11%)	−23%	
Sharing asthma medications (Y/N)	No	106 (80%)	109 (93%)	13%	.002
	Yes	27 (20%)	8 (7%)	−13%	

Table 3.2
Comparison of asthma status change at 12 months from baseline (Puff City Control group only).

Control treated group	Category	Baseline (N = 133)	12 month (N = 133)	Change from baseline to 12 month	p-Value
Intention to treat ACT score		18.9 ± 4.3	21.4 ± 3.3	2.5	< .001
ACT score less than or equal 15	No	111 (83%)	128 (96%)	13%	< .001
	Yes	22 (17%)	5 (4%)	−13%	
Asthma symptom days (past-30-days)	No	17 (13%)	42 (32%)	19%	< .001
	Yes	116 (87%)	88 (68%)	−19%	
Asthma symptom nights (past-30-days)	No	54 (41%)	89 (67%)	26%	< .001
	Yes	79 (59%)	44 (33%)	−26%	
Restricted activity due to asthma (past-30-days)	No	50 (38%)	76 (57%)	19%	.001
	Yes	83 (62%)	57 (43%)	−19%	
Missed school/work (past-30-days)	No	46 (57%)	72 (81%)	24%	< .001
	Yes	35 (43%)	17 (19%)	−24%	
ER visit or hospitalization in past 12 months	No	87 (65%)	116 (87%)	22%	< .001
	Yes	46 (35%)	17 (13%)	−22%	
Sharing asthma medications (Y/N)	No	106 (80%)	105 (83%)	3%	.452
	Yes	27 (20%)	21 (17%)	−3%	

asthma exacerbations at YR1 and as the result, no interaction between treatment and AA was detected (p-value = .64).

4. Discussion

The purpose of this research was to use pragmatic approaches to evaluate a web-based, tailored intervention (Puff City) in a clinical setting. While successful in designing and conducting a seamless pragmatic Phase II/III trial, the interim analysis at the completion of the Phase II component of the trial showed no Puff City benefit for ACT score at 1 year. Although no safety concerns were raised based on results from an independent medical monitor blinded to treatment assignments, the trial was discontinued at Phase II due to lack of an indication of overall Puff City benefit.

Several results for these analyses were unexpected in that control patients reported greater benefit from participating in the trial than patients in the treatment arm. In the spirit of comparative effectiveness, patients randomized to the control arm of the trial had access to existing asthma education websites, as opposed to “standard care”. Control sites were selected if they covered topics similar to that of Puff City and may have provided targeted messaging or may have presented information in a manner superior to Puff City. Previous trials of Puff

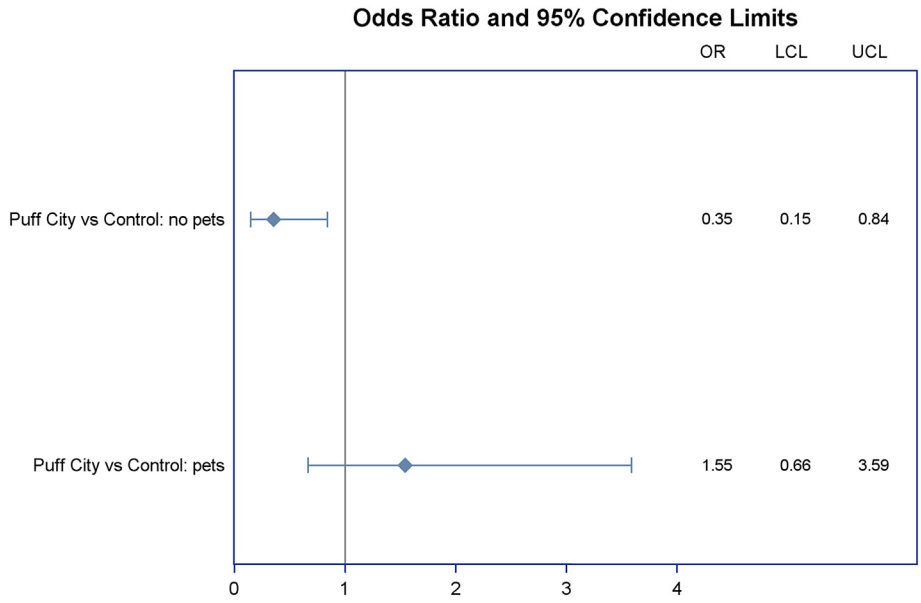

Fig. 2. Marker-positive study.
Puff City Innervation effects are dependent upon status of pets at home; an OR and 95% Confidence interval < 1 indicates a significant Puff City benefit on reduction of asthma exacerbations at 12 months.

Table 4
Patient baseline characteristics in the study population.

Variable	Response	All (*N* = 266)	No pets at home (*N* = 121)	Pets at home (*N* = 145)	*p*-Value
Site	Clinic A	43 (16%)	23 (19%)	20 (14%)	.518
	Clinic B	2 (1%)	1 (1%)	1 (1%)	
	Clinic C	6 (2%)	4 (3%)	2 (1%)	
	Clinic D	1 (0%)	0 (0%)	1 (1%)	
	Clinic E	45 (17%)	16 (13%)	29 (20%)	
	Clinic F	3 (1%)	1 (1%)	2 (1%)	
	Clinic G	166 (62%)	76 (63%)	90 (62%)	
Age	*N*, Mean ± Std Dev	266, 14.8 ± 1.6	121, 14.9 ± 1.7	145, 14.8 ± 1.5	.986
Sex	Male	139 (52%)	70 (58%)	69 (48%)	.095
	Female	127 (48%)	51 (42%)	76 (52%)	
Race	UnK	1 (0%)	0 (0%)	1 (1%)	< .001
	Black or African American	186 (70%)	96 (79%)	90 (62%)	
	White or Caucasian	58 (22%)	12 (10%)	46 (32%)	
	American Indian or Alaskan Native	3 (1%)	0 (0%)	3 (2%)	
	Native Hawaiian or Pacific Islander	1 (0%)	0 (0%)	1 (1%)	
	Other	17 (6%)	13 (11%)	4 (3%)	
Education	Below high school	78 (29%)	37 (31%)	41 (28%)	.567
	High school	174 (65%)	76 (63%)	98 (68%)	
	College/other	14 (5%)	8 (7%)	6 (4%)	
Hispanic/Latino	No	255 (96%)	117 (97%)	138 (95%)	.759
	Yes	11 (4%)	4 (3%)	7 (5%)	
Computer at home	No	17 (6%)	11 (9%)	6 (4%)	.131
	Yes	249 (94%)	110 (91%)	139 (96%)	
ACT score	*N*, Mean ± Std Dev	266, 18.9 ± 4.4	121, 19.4 ± 4.0	145, 18.5 ± 4.7	.195
ACT score ≤ 15	No	222 (83%)	106 (88%)	116 (80%)	.101
	Yes	44 (17%)	15 (12%)	29 (20%)	
Restricted Activity/30 days (S4D)%	No	99 (37%)	46 (38%)	53 (37%)	.806
	Yes	167 (63%)	75 (62%)	92 (63%)	
Symptom nights/30 days (S3D) %	No	112 (42%)	52 (43%)	60 (41%)	.793
	Yes	154 (58%)	69 (57%)	85 (59%)	
Symptom days/30 days (S2D) %	No	41 (15%)	23 (19%)	18 (12%)	.172
	Yes	225 (85%)	98 (81%)	127 (88%)	
Missed school or work/30 days(S5D)%	No	109 (41%)	50 (41%)	59 (41%)	.410
	Yes	61 (23%)	24 (20%)	37 (26%)	
Doctor visits for asthma/12 months	*N*, Mean ± Std Dev	266, 1.5 ± 2.6	121, 1.6 ± 3.1	145, 1.4 ± 2.1	.967
ER visit or hospitalization in past 12 months	No	175 (66%)	80 (66%)	95 (66%)	.918
	Yes	91 (34%)	41 (34%)	50 (34%)	
Sharing asthma medications	No	212 (80%)	94 (78%)	118 (81%)	.456
	Yes	54 (20%)	27 (22%)	27 (19%)	
Study arm	Puff City	133 (50%)	61 (50%)	72 (50%)	.902
	Control	133 (50%)	60 (50%)	73 (50%)	

City were conducted in populations that could be considered more vulnerable (urban high schools and emergency departments) than the present clinic population and consisted of a higher percentage of African-American patients (90%, 88.4%, and 69.9% for schools, ED, and clinic, respectively), of which fewer had access to a computer (74.1%, 71.1%, and 93.6%, for schools, ED, and clinic, respectively) [2,4,11]. Missing data (e.g., 30% of data missing for "missed school or work" variable) and extreme values for the ACT scores among controls (which are not taken into account when comparing medians) could also account for this trial's departure from results of the previous school-based Puff City trials, in which Puff City results were more positive.

As expected, both groups showed improvement from baseline. A rather serendipitous finding was the significant reduction in sharing medications in the treated group that was not observed in the control group. Because sharing asthma medications was something we heard, not infrequently, in conversations with youth and community members during program development, we included messaging related to this behavior. We are unaware of other teen asthma programs addressing this issue, and the behavior is not widely reported or measured in the literature. Valet et al. reported on the sharing of asthma medications among Medicaid enrollees and found 16% reported doing so [12], compared to our 20.3%. In their study, sharing medications was not associated with Emergency Department visits in the previous 6 months or use of rescue inhalers in the previous 14 days [12].

Although we are not able to detect an overall trend at Phase II for the Puff City intervention effect, the ancillary marker study was conducted with a focus on identifying a sub-group of patients who would most benefit from Puff City. This approach of identifying an enriched population is used to confirm the efficacy of an intervention with a much smaller sample size. We chose asthma exacerbations as the outcome for the marker study because this is an acceptable measure of asthma control [13]. The objective of a marker analysis, unlike studies of association, is to identify a subgroup of patients who would, in a Phase III trial, most likely derive benefit from the intervention. Despite a racial variation in pet ownership [14,15,16], our ad-hoc analysis showed that across race, teens with pets are more likely to derive benefit from the intervention in a Phase III trial.

Puff City messages about pets include keeping the pet out of the bedroom, washing hands/changing clothes after playing with pets, routinely vacuuming the pet's living area, and using an air filter in the teen's room. Having pets at home may complicate asthma control for teens, and perhaps this advice led to positive changes in other areas. Asthma management in this less vulnerable clinic population may largely involve pet ownership (white families are more likely to keep pets indoors [14,15,16]), while maintaining control in more vulnerable populations could involve more complex issues associated with social determinants.

Using pragmatic approaches to design and conduct a seamless phase II/III trial to disseminate Puff City asthma intervention to routine clinical care is feasible. The trial was stopped early at the completion of the Phase II component due to a lack of trend of Puff City benefit. Our post-hoc analysis showed significant and consistent asthma recovery at 12 months from the baseline regardless of randomization arm, suggesting that current online asthma education is beneficial to adolescents with asthma. Nevertheless, the post-hoc marker analysis showed significant Puff City benefit in reducing asthma exacerbations compared to controls for an enriched sub-cohort of teens with pets at home. The advantage of this analysis approach is the benefit of a smaller sample size, without loss of power, when conducting a Phase III trial with the enriched population.

Acknowledgement

This work was supported by the National Institutes of Health [grant number R01HL114981-02].

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