

Original Investigation

Pragmatic Trial of Health Care Technologies to Improve Adherence to Pediatric Asthma Treatment

A Randomized Clinical Trial

Bruce G. Bender, PhD; Peter J. Cvietusa, MD; Glenn K. Goodrich, MS; Ryan Lowe, PharmD; Heather A. Nuanes, BA; Cynthia Rand, PhD; Susan Shetterly, MS; Cathy Tacinas, RN; William M. Vollmer, PhD; Nicole Wagner, MPH; Frederick S. Wamboldt, MD; Stanley Xu, PhD; David J. Magid, MD, MPH

IMPORTANCE Most patients with asthma take fewer than half of prescribed doses of controller medication. Interventions to improve adherence have typically been costly, impractical, and at best only minimally successful.

OBJECTIVE To test a speech recognition (SR) intervention to improve adherence to pediatric asthma controller medication.

DESIGN, SETTING, AND PARTICIPANTS The Breathe Well study was a 24-month pragmatic randomized clinical trial. The study was conducted within Kaiser Permanente Colorado, a large, group-model health maintenance organization. A total of 1187 children aged 3 to 12 years with a persistent asthma diagnosis and prescription for an inhaled corticosteroid were randomized to the computerized SR intervention or usual care condition and followed up for 24 months between October 2009 and February 2013.

INTERVENTIONS Speech recognition telephone calls to parents in the intervention condition were triggered when an inhaled corticosteroid refill was due or overdue. Calls were automatically tailored with medical and demographic information from the electronic health record and from parent answers to questions in the call regarding recent refills or a desire to receive help refilling, learn more about asthma control, or speak with an asthma nurse or pharmacy staff member.

MAIN OUTCOMES AND MEASURES Adherence to pediatric asthma controller medication, measured as the medication possession ratio over 24 months.

RESULTS In the intention-to-treat analysis, inhaled corticosteroid adherence was 25.4% higher in the intervention group than in the usual care group (24-month mean [SE] adherence, 44.5% [1.2%] vs 35.5% [1.1%], respectively; $P < .001$). Asthma-related urgent care events did not differ between the 2 groups. The intervention effect was consistent in subgroups stratified by age, sex, race/ethnicity, body mass index, and disease-related characteristics.

CONCLUSIONS AND RELEVANCE The intervention's significant impact on adherence demonstrates strong potential for low-cost SR adherence programs integrated with an electronic health record. The absence of change in urgent care visits may be attributable to the already low number of asthma urgent care visits within Kaiser Permanente Colorado. Application of electronic health record-leveraged SR interventions may reduce health care utilization when applied in a population with less-controlled asthma.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00958932

JAMA Pediatr. doi:10.1001/jamapediatrics.2014.3280
Published online February 9, 2015.

← Editorial

+ Supplemental content at
jamapediatrics.com

Author Affiliations: Division of Pediatric Behavioral Health, National Jewish Health, Denver, Colorado (Bender, Wamboldt); University of Colorado, Denver (Bender, Wamboldt, Magid); Kaiser Permanente Colorado Institute for Health Research, Denver (Cvietusa, Goodrich, Lowe, Nuanes, Shetterly, Tacinas, Wagner, Xu, Magid); Johns Hopkins Medical School, Baltimore, Maryland (Rand); Kaiser Permanente Center for Health Research Northwest, Portland, Oregon (Vollmer).

Corresponding Author: Bruce G. Bender, PhD, Division of Pediatric Behavioral Health, National Jewish Health, 1400 Jackson St, Denver, CO 80206 (benderb@njhealth.org).

Current evidence-based guidelines from the National Heart, Lung, and Blood Institute recommend that patients with persistent asthma receive daily controller medication, most often an inhaled corticosteroid (ICS).¹ However, most patients are markedly nonadherent with their prescribed ICS^{2,3} and half of patients fill an ICS prescription only once in 12 months.⁴ Improving ICS adherence therefore could improve the health status of children with asthma and potentially reduce costly health care utilization including asthma-related emergency department (ED) visits and hospitalizations.^{5,6}

Although numerous adherence interventions have been developed, many are costly, labor intensive, of short duration, minimally effective, or not easily translated to large clinical settings.² To broadly improve asthma medication adherence, new interventions must lend themselves to adoption by health care delivery systems without adding a significant workload onto already overburdened clinicians. The objective of this pragmatic randomized clinical trial was to evaluate the effectiveness of a program that brings together communication and health information technology, including speech recognition (SR) software and electronic health records (EHRs), to improve pediatric asthma medication adherence.

Methods

Setting

This study was conducted at Kaiser Permanente Colorado (KPCO), a group-model health maintenance organization serving the Denver-Boulder-Longmont region in Colorado, between October 2009 and February 2013. At the time of the study, KPCO included 18 primary care and 2 specialty care medical offices, 2 contract hospitals, and more than 800 physicians and 500 000 enrollees. Kaiser Permanente Colorado uses a commercially available EpicCare EHR in routine care delivery. The institutional review boards of both National Jewish Health and KPCO approved this study. There is no requirement for informed consent because this is a low-risk study.

Study Design

The Breathe Well study was designed as a pragmatic randomized clinical trial. Pragmatic trials are typically large trials conducted in multiple settings with interventions delivered by existing clinical staff to a heterogeneous population of patients to answer clinically relevant questions.^{7,8} Enrollment occurred over 16 months; each participant remained in the study for 24 months. All standard clinical services, including telephone availability of asthma nurses and pharmacy staff, consultation with an allergist, and access to educational information, were available to both families in the intervention group and those in the usual care group. The trial protocol can be found in Supplement 1.

Patient Population

Eligible children were aged 3 to 12 years, were diagnosed as having persistent asthma, and filled 1 or more ICS prescriptions in the prior 6 months. Participants were limited to those en-

rolled in KPCO for at least 1 year to ensure that patients were consistently diagnosed as having persistent asthma and to establish a baseline ICS adherence rate. Participants were excluded if they (1) were identified by their physician as having a life-threatening comorbid condition; (2) had a sibling already included in the study; (3) had a parent who declined to participate; (4) were instructed to take an ICS only intermittently or as needed; or (5) obtained medication from a non-KPCO pharmacy.

Recruitment and Enrollment

Parents of eligible patients received an introductory letter explaining the Breathe Well study. Parents wishing not to participate could opt out by calling a telephone number or returning an enclosed postage-paid postcard. Children of parents who did not decline participation were then randomized to the intervention or usual care group (Figure 1). No participant incentives were provided.

Development of the SR Intervention

Speech recognition uses software that creates computer-generated telephone conversations. Creation of the intervention proceeded through a sequence of steps that included parent focus groups, script development, and beta testing. The final program contained the capacity to tailor each call with medical and demographic information from the EHR databases, for example, the name of the medication and prescribing physician. Throughout the SR call, referencing was made using the child's name and "his" or "her" depending on sex. The SR program responded to parent answers to questions in the call regarding a desire for help with medication refills or a callback from a clinician. Reminders were included about the importance of the ICS in the face of increasing allergen or cold seasons in the spring and late summer and about the importance of a flu shot in the fall. Eliza Corp delivered the SR intervention.

EHR Database

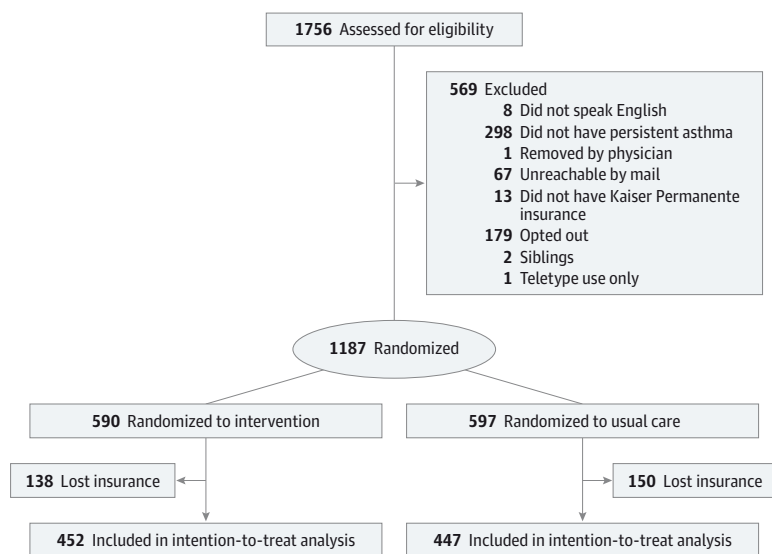
A study database was created to allow exchange of information between the EHR and the SR program. This information included the name of the child, home telephone number, name of the ICS, refill history, name of the prescribing physician, and the last 4 digits of the credit card used previously for mail-order medication refills if one was used.

Delivery of the Intervention

Families randomized to the intervention group received 1 of 3 SR call types: the welcome call, the basic refill call, and the tardy refill call. Calls were randomly placed between 9 AM and 8 PM until a parent or answering machine was reached. If the system reached a parent, subsequent calls were initiated at the time at which the successful connection with the parent had occurred previously. Each call lasted 2 to 5 minutes.

The initial parent call, the welcome call, was placed the first time the child's ICS prescription was overdue by 14 days. The call was designed to allow the parent to control the call by asking for the parent's permission to proceed at each step of the call, inquiring about whether the parent wanted additional or

Figure 1. Recruitment and Randomization



repeated information, and providing multiple options for refilling the child's medication or speaking with an asthma care nurse or pharmacist (eFigure in Supplement 2). If the call was received by an answering machine, the SR program left a medication refill reminder message and provided a callback number. Parents calling into the SR program were identified by their telephone number and then entered into the welcome call.

The basic refill call occurred 10 days before the child was due to run out of medication and after the family had received a welcome call. Content included a reminder of the need to refill the ICS, help refilling the medication, and the option for assistance through a callback from a pharmacy staff member or asthma care nurse.

Parents received the tardy refill call if the child was greater than 30 days past due for the ICS medication. Call content was similar to the basic refill call and provided the same options. However, the tardy refill call increased emphasis on the importance of medication adherence on the child's health.

When parents indicated a desire to speak with an asthma nurse, a message was transmitted through the EHR to the asthma nurse group. Nurses returned calls to parents the following business day. Requests to speak to pharmacy staff were handled by the SR program in 1 of 2 ways. During business hours, the call was transferred to a pharmacy staff member. If the SR call was completed outside business hours, parents were given the option of receiving a callback on the following business day. Families who had registered for mail-order pharmacy were given the option of charging their medication co-payment to the credit card on record and receiving the child's medication through the mail. In all 3 call types, a reminder was included instructing the parent with immediate concerns or questions about the child's asthma to call the child's physician. Calls were discontinued if an ICS prescription was canceled, and they were reinitiated if the ICS prescription was renewed.

The timing of the calls was based on an assessment of days remaining in a current fill or days overdue for a refill. To accurately estimate when an adherent patient would run out of ICS medication, the program automatically cross-referenced the medication dosing in the EHR electronic prescription record with the prescribed medication stock quantity to calculate the number of days of medication available to the patient.

Usual Care

All standard asthma resources remained available to both the intervention and usual care groups throughout the duration of the study. Pediatric asthma care at KPCO is provided by pediatricians, family physicians, and allergists, all of whom receive training in National Heart, Lung, and Blood Institute guidelines for asthma care. Patients at KPCO can request allergist care at any time without referral from their primary care physician.

Outcome Measures

The primary outcome of this study, adherence, was expressed as a proportion of days covered (PDC) over 24 months.⁹ The PDC was calculated as the total number of ICS days supplied divided by the period for which the medication was prescribed. Calculation of the PDC was adjusted to account for the supply that would extend beyond the end of the study period. Comparisons were adjusted for baseline PDC, which was calculated as the ratio of number of days a patient had possession of medication divided by the number of days enrolled 1 year prior to randomization. Once randomized to the intervention, all children were included in the intention-to-treat analysis even if the parents did not respond to a message left on an answering machine. In addition, all children remained in the analysis regardless of whether their ICS prescription was canceled. A sensitivity analysis that cen-

Table 1. Demographic and Illness-Related Characteristics at Randomization

Characteristic	Usual Care (n = 447)	Intervention (n = 452)
Age, mean (SE), y	8.1 (0.13)	8.2 (0.13)
Female, %	38.9	32.7
Low socioeconomic status, % ^a	10.6	11.4
Race/ethnicity, %		
White	55.9	56.7
African American	14.3	12.8
Hispanic	24.8	24.5
Asian	3.0	3.9
Native American	1.5	1.5
Hawaiian	0.5	0.7
BMI, mean (SE)	18.2 (0.20)	18.3 (0.22)
Eczema, %	9.4	10.8
Food allergy, %	1.3	1.3
Inpatient visits/person-year, mean (SE), No.	0.04 (0.01)	0.04 (0.01)
ED visits/person-year, mean (SE), No.	0.09 (0.02)	0.09 (0.02)
After-hours visits/person-year, mean (SE), No.	0.03 (0.01)	0.02 (0.01)
Oral steroid bursts/person-year, mean (SE), No.	0.383 (0.04)	0.469 (0.04)
Proportion of days covered, mean (SE), %	41.2 (1.15)	41.9 (1.13)
Primary care visits/person-year, mean (SE), No.	2.4 (0.10)	2.3 (0.08)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ED, emergency department.

^a Socioeconomic status was estimated using a geocoded database on home address mapped onto census poverty and education data. In cases where the census tract included 20% of citizens living below the US poverty level or 25% of adult citizens with less than a high school education, the patient was considered to reside in a neighborhood of low socioeconomic status.

sored patients when an ICS prescription was canceled was conducted. Means and standard deviations for both groups during follow-up were estimated and tested in a generalized linear model using a negative binomial distribution, an offset to account for person-years, and baseline PDC as a covariate. Patients who lost KPCO insurance coverage during the 2-year study period were included in a secondary analysis to evaluate potential sample attrition bias. In additional subgroup analyses, adherence was assessed for families who were contacted by the live SR call or through an answering machine message or for those who were never reached by the SR calls.

Secondary outcomes included β_2 -agonist use, oral steroid use, and asthma-related primary health care visits, ED visits, hospitalizations, and after-hours visits on weekends or weekdays after 6 PM based on visits with *International Classification of Diseases, Ninth Revision* codes associated with an asthma diagnosis (493.0, 493.1, 493.8, or 493.9). Potential effect modifiers included the demographic (eg, age, sex) and medical (eg, comorbidities, previous medication use, and health care use) variables shown in **Table 1**.

Parent satisfaction with the intervention was assessed through surveys completed by parents from the intervention

group at the completion of 12 months. Parents were asked to rate their agreement, from strongly agree to strongly disagree, with a series of statements about their satisfaction with the Breathe Well intervention (eg, “The Breathe Well phone calls were helpful”) and its impact on their child’s asthma (eg, “Because of the Breathe Well program, my child’s asthma is now under better control”).

Statistical Analysis

After randomization, intention-to-treat analysis was performed to determine adherence to pediatric asthma controller medication. The main outcome measures were tested in a generalized linear model using a negative binomial distribution with baseline PDC as a covariate. A secondary analysis including patients who lost insurance coverage evaluated potential sample attrition bias. Subgroup analyses determined adherence by families contacted through the live SR call or through an answering machine message as well as those who were not reached by the SR calls. SAS version 9.2 (SAS Institute, Inc) was used for statistical analysis.

Results

Enrollment

Of the 1756 patients with persistent asthma prescribed an ICS, 569 were excluded owing to a variety of factors but most commonly opting out or not meeting criteria for a persistent asthma diagnosis. The remaining 1187 patients were randomized to 1 of the 2 study conditions. Of these, 899 remained KPCO members at 24 months, 452 in the intervention group and 447 in the usual care group (**Figure 1**). Baseline characteristics of those who declined participation did not differ from those included in the study.

Baseline Characteristics

Baseline characteristics are presented for descriptive purposes only (**Table 1**). Few variables had missing data; exceptions included absence of race/ethnicity data for 23.9% of participants and socioeconomic status data for 2.2% of participants. The relatively higher incidence of boys than girls in both groups is consistent with population data for children with asthma.¹⁰ The mean (SE) baseline PDC, based on the 6-month period prior to randomization, was 41.9% (1.13%) for the intervention group and 41.2% (1.15%) for the usual care group.

Primary Outcome

The primary outcome analysis tested the hypothesis that families in the intervention group were more adherent to their ICS medication over 24 months than those in the usual care group. Adherence in the intervention group was 25.4% higher than that in the usual care group during the study interval (24-month mean [SE] PDC, 44.5% [1.2%] vs 35.5% [1.1%], respectively; $P < .001$) (**Table 2** and **Figure 2**). The magnitude of the superiority in adherence of the intervention group compared with the usual care group was 25.8% in year 1 and 25.3% in year 2 ($P < .001$ for both years), indicating that the intervention ef-

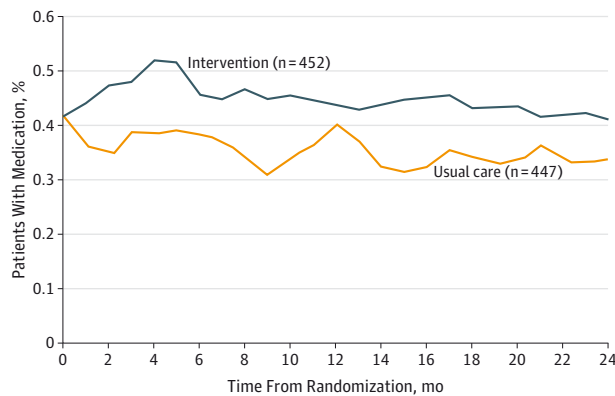
Table 2. Adherence Over 24 Months by Patient Group

Patient Group	No. (N = 899)	Adherence, Mean (SE), % ^a	P Value ^b
Usual care	447	35.5 (1.1)	<.001
Intervention	452	44.5 (1.2)	
No contact	28	33.3 (6.7)	.001
Contact	424	45.2 (1.2)	
Answering machine	140	40.5 (2.3)	.06
Live	284	47.6 (1.4)	

^a Assessed as proportion of days with medication over 24 months.

^b Significance tested through Poisson regression.

Figure 2. Medication Possession Ratio



fect persisted beyond the first year. Additionally, the intervention effect was consistent in subgroups stratified by age, sex, race/ethnicity, body mass index, or disease-related characteristics. The ICS prescriptions were canceled by fewer than 10% of participants, with rates equal between the 2 groups. A sensitivity analysis in which patients were censored at the time of ICS discontinuation produced results that were very similar to those of the primary analysis. Secondary analyses conducted within the intervention group allowed comparison of families reached by the intervention (n = 424) vs those not successfully contacted (n = 28). Adherence was 36% higher among the 424 families who were successfully contacted by the intervention calls, either live or through an answering machine, than among the 28 who were never contacted (24-month mean [SE] PDC, 45.2% [1.2%] vs 33.3% [6.7%], respectively; $P = .001$). Parents from the intervention group who were ever contacted in a live SR conversation (n = 284) did not have statistically significant greater adherence than parents from the intervention group who were only contacted via an answering machine message (n = 140) (24-month mean [SE] PDC, 47.6% [1.4%] vs 40.5% [2.3%], respectively; $P = .06$) (Table 2). In an analysis that included the 288 patients who disenrolled from KPCO during the 2-year study period (138 in the intervention group, 150 in the usual care group) (Figure 1), adherence in the intervention group was 24.6% higher than that in the usual care group (mean [SE] PDC, 43.1% [1.1%] vs 34.6% [1.1%], respectively; $P < .001$). This was similar to outcomes for the intervention and usual care groups with full 24-month participation, indicating that outcome bias did not result from loss of insurance plan enrollment.

Secondary Outcomes

Health Care Utilization

Asthma-related health care events were estimated as counts for 24 months as a ratio to eligible person-years. No between-group differences emerged for hospitalizations, ED visits, after-hours visits, β_2 -agonist use, or primary care visits (Table 3). After controlling for baseline oral steroid use, there was no difference in oral steroid bursts between the 2 groups.

Parent Satisfaction

A total of 181 families, or 42.8% of the intervention group, completed the 12-month survey. Parents were highly satisfied with the intervention program; more than 90% of parents agreed or agreed strongly with these statements: “The Breathe Well program has improved the care my child receives for asthma at Kaiser”; “The Breathe Well phone calls were helpful”; and “Getting help refilling my child’s asthma medication through the Breathe Well program was helpful.” Also among these parents, 84% agreed with the statement “Because of the Breathe Well program, my child’s asthma is now under better control.”

Discussion

Relative to usual care, the Breathe Well SR intervention produced improvement in ICS medication adherence that was greater by degree and duration than in any previous pediatric asthma adherence intervention study to our knowledge. Adherence to ICS as measured by the 24-month PDC was 44.5% in the intervention group and 35.5% in the usual care group. The intervention group adherence rate leaves room for improvement but nonetheless stands in striking contrast to adherence rates in population studies, which are typically below 30% and decline over time.^{4,11-13} The large improvements in adherence in this pragmatic randomized clinical trial emerged despite the fact that families who were not reached by the intervention or discontinued participation were included in the intention-to-treat analysis. Most parents in the intervention group indicated that the program had improved their child’s asthma control, and fewer than 10% dropped out during the 2-year study period. Breathe Well is distinguished from other adherence interventions by its use of the EHR, personalized communication, and large scale. In addition, to determine whether the intervention had a lasting impact, adherence was evaluated during a longer period (2 years) than in prior studies. The program was the first to fully integrate

Table 3. Health Care Utilization Over 24 Months

Outcome Variable	Mean (SE), No./Person-Year		P Value ^a
	Usual Care (n = 447)	Intervention (n = 452)	
Inpatient visits	0.02 (0.01)	0.01 (0.004)	.37
ED visits	0.04 (0.01)	0.06 (0.01)	.23
After-hours visits	0.03 (0.01)	0.01 (0.01)	.12
Oral steroid bursts	0.21 (0.18)	0.27 (0.23)	.05
β ₂ -Agonist canisters	3.2 (0.15)	3.3 (0.13)	.10
Primary care visits	1.5 (0.05)	1.6 (0.06)	.15

Abbreviation: ED, emergency department.

^a Significance tested through Poisson regression.

interactive communication technology into an EHR system to contact parents of children with asthma. In contrast to smaller studies executed manually by research staff,^{14,15} this trial tested an automated program initiating thousands of SR telephone calls that were individualized to each family, with impact consistent across patient age, sex, socioeconomic status, and race/ethnicity.

Higher adherence in the intervention group was not accompanied by lower asthma-related care utilization. A likely reason for the absence of change in health care utilization is reflected in already low exacerbation rates in KPCO compared with other patient populations. For example, in the 12 months prior to randomization, only 0.09% and 0.03% of study cohort patients went to an ED or were hospitalized for asthma, respectively; consequently, room for improvement in inpatient or ED visits in this well-controlled population was limited. An alternative explanation for the absence of change in health care outcomes might be that pharmacy refill data do not accurately reflect actual adherence. However, this explanation appears unlikely to account for the absence of change in health care outcomes. Adherence measurement was based on ICS refills obtained by families during a long period. Although individual plans vary, copays were required from all families to receive a refill. Refill rates in the intervention group did not decline over time, and no evidence suggested that families were stockpiling but not using medications. While refill data are not a direct measure of adherence behavior, pharmacy refill data correlate well with adherence measured by other ob-

jective means including electronic devices attached to inhalers or pill containers.¹⁶⁻¹⁹ Furthermore, accuracy of refill adherence measurement increases with longer study intervals.²⁰

A potential limitation to this study is that the most poorly adherent patients may have been excluded from the study since eligible patients were required to have made at least 1 ICS fill in the 6 months prior to enrollment. An additional limitation may be nonapplicability of the intervention to practices without an EHR or with an EHR that is different from the one used at KPCO. However, more than half of physicians use an EHR and current projections indicate that more than 90% of clinicians will be using an EHR within the decade.²¹ Further, the intervention in this study leveraged EpicCare, the most widely used ambulatory care EHR in the United States. The capacity to identify and sort patients by EHR indicators in this project is standard in all EHR systems, including eClinicalWorks, McKesson, Cerner, Allscripts, and GE Healthcare.

Conclusions

The significant improvement in adherence demonstrates strong potential for automated adherence interventions integrated within an EHR. Future research should focus on testing the intervention's impact on clinical outcomes and costs in other settings and patient groups including adolescents and vulnerable populations.

ARTICLE INFORMATION

Accepted for Publication: October 14, 2014.

Published Online: February 9, 2015.
doi:10.1001/jamapediatrics.2014.3280.

Author Contributions: Drs Bender and Magid had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bender, Cvietusa, Lowe, Rand, Tacinas, Vollmer, Wagner, Wamboldt, Magid.
Acquisition, analysis, or interpretation of data: Bender, Cvietusa, Goodrich, Lowe, Nuanes, Rand, Shetterly, Wamboldt, Xu, Magid.

Drafting of the manuscript: Bender, Cvietusa, Goodrich, Lowe, Wagner, Wamboldt, Xu.

Critical revision of the manuscript for important intellectual content: Bender, Goodrich, Nuanes, Rand, Shetterly, Tacinas, Vollmer, Wamboldt, Magid.

Statistical analysis: Bender, Goodrich, Shetterly, Xu.

Obtained funding: Bender, Wamboldt, Magid.

Administrative, technical, or material support: Bender, Goodrich, Lowe, Nuanes, Rand, Tacinas, Vollmer, Wagner, Wamboldt.

Study supervision: Bender, Cvietusa.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grant 1R01HL084067-01A2 from the National Institutes of Health.

Role of the Funder/Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program*

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma: Summary Report 2007. Bethesda, MD: National Heart, Lung & Blood Institute; 2007. NIH publication 08-5846.

2. Apter A, Bender B, Rand C. Adherence. In: Adkinson NF Jr, Bochner BS, Burks AW, et al, eds. *Middleton's Allergy: Principles and Practice.* 8th ed. New York, NY: Elsevier; 2014:1471-1479.

3. Kajioka EH, Itoman EM, Li ML, Taira DA, Li GG, Yamamoto LG. Pediatric prescription pick-up rates after ED visits. *Am J Emerg Med.* 2005;23(4):454-458.

4. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol.* 2006;118(4):899-904.

5. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma

- exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol*. 2011;128(6):1185-1191.e2.
6. Bender BG, Rankin A, Tran ZV, Wamboldt FS. Brief-interval telephone surveys of medication adherence and asthma symptoms in the Childhood Asthma Management Program Continuation Study. *Ann Allergy Asthma Immunol*. 2008;101(4):382-386.
7. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290(12):1624-1632.
8. Sullivan P, Goldmann D. The promise of comparative effectiveness research. *JAMA*. 2011;305(4):400-401.
9. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574.
10. Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001-2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(17):547-552.
11. Sloan CD, Gebretsadik T, Wu P, Mitchel EF, Hartert TV. Reactive versus proactive patterns of inhaled corticosteroid use. *Ann Am Thorac Soc*. 2013;10(2):131-134.
12. Vanelli M, Pedan A, Liu N, Hoar J, Messier D, Kiarsis K. The role of patient inexperience in medication discontinuation: a retrospective analysis of medication nonpersistence in seven chronic illnesses. *Clin Ther*. 2009;31(11):2628-2652.
13. Vaidya V, Gupte R, Balkrishnan R. Failure to refill essential prescription medications for asthma among pediatric Medicaid beneficiaries with persistent asthma. *Patient Prefer Adherence*. 2013;7:21-26.
14. Oake N, Jennings A, van Walraven C, Forster AJ. Interactive voice response systems for improving delivery of ambulatory care. *Am J Manag Care*. 2009;15(6):383-391.
15. Marcano Belisario JS, Huckvale K, Greenfield G, Car J, Gunn LH. Smartphone and tablet self management apps for asthma. *Cochrane Database Syst Rev*. 2013;11:CD010013.
16. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care*. 1999;37(9):846-857.
17. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. *Ann Pharmacother*. 2009;43(3):413-422.
18. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. *Med Care*. 2006;44(5):471-477.
19. Ndubuka NO, Ehlers VJ. Adult patients' adherence to anti-retroviral treatment: a survey correlating pharmacy refill records and pill counts with immunological and virological indices. *Int J Nurs Stud*. 2011;48(11):1323-1329.
20. Vollmer WM, Xu M, Feldstein A, Smith D, Waterbury A, Rand C. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv Res*. 2012;12:155-162.
21. American Academy of Family Physicians; American Academy of Pediatrics; American College of Physicians; American Osteopathic Association. Joint principles of the patient-centered medical home, March 2007. <http://www.medicalhomeinfo.org/downloads/pdfs/jointstatement.pdf>. Accessed June 1, 2014.