COVER PAGE	
Study Title	Interventions To Help Asthma Clinical Adherence (ITHACA)
NCT Number	NCT02999789
Document Description	Statistical Analysis Plan
Document Date	23 February 2021

This study was a quasi-experimental single-center pilot trial that used a staggered implementation design which measured the effect of an asthma medication reminder system device on asthma controller medication adherence during an initial run-in period and an intervention period. Because the intervention was a reminder system, it was not possible to 'blind' the participants.

For the pilot phase, we aimed to recruit children ages 5 to 17 years with a diagnosis of persistent asthma who required a daily inhaled corticosteroid metered dose inhaler and whose guardian was the person responsible for directly administering or supervising the administration of their daily asthma medication. Our target sample size at the study's onset was to recruit 30 children ages 5 to 17. The sample size was limited by the budget limitations. Based on cost-efficiency and limitations, 30 participants would give a general estimate of the effectiveness of this intervention. The study results could be used for the power calculations for a future, larger RCT. Assuming a positive effect of reminder systems and a baseline adherence rate of 60%, with 15 patients in each group, with a power of 0.80, an alpha of 0.05, there would be enough power to detect a 15% change in adherence which is within the range of improvement reported. This percentage change translated to a Number Needed to Treat (NNT) of 6 patients.

We only recruited from a University-affiliated clinic serving publicly insured children. We recruited children whose asthma subspecialist or health care provider practiced at the Children's Health Center (CHC) at Zuckerberg San Francisco General Hospital. We only recruited from the primary care clinics and the asthma clinic. We only recruited children whose guardian responsible for administering their daily asthma medication had Limited English Proficiency (LEP) and whose primary language was Spanish. Lastly, we only included children whose daily inhaled cortociosteroid was a metered dose inhaler (MDI) that was either Flovent (fluticasone proprionate) HFA (Hydrofluoroalkane) or Qvar (beclomethasone diproprionate) HFA. This was the case because the SmartInhaler device was only available for those two MDIs.

We excluded children whose guardian(s) had a low health literacy based on the Short-test of Functional Health Literacy in Adults in Spanish (S-SFHLA) and those who were unable to demonstrate correct medication technique based on standard evaluation after completion of a standard teaching protocol. Patients who were using a long acting beta-agonist as part of their asthma management plan were excluded. As a result, the study focused on children who fell into the mild persistent asthma classification. We excluded patients whose guardian responsible for administering their daily asthma medication did not have a Bluetooth enabled cell phone capable of receiving text messages, did not have an available reliable power outlet where they could recharge the battery of their SmartInhaler device, did not have an operating system of iOS or Android on their cell phone, or did not have a data plan with their cellular phone plan. We excluded patients with chronic lung disease. We excluded children whose guardian (s) did not directly administer their daily asthma medication or directly supervise the children self-administering their daily asthma medication. Lastly, we excluded patients whose asthma medication regimen was being managed by an asthma subspecialist or health care provider outside of the Children's Health Center at Zuckerberg San Francisco General Hospital.

There were three recruitment strategies. We posted advertisements about the study around the hospital with a study call back number. We also contacted potential subjects who had previously consented to being contacted for participation in research from earlier asthma studies via mail. Lastly, we identified prospective subjects through a chart review of future primary care and asthma clinic visits and asked the health care provider to ask patient's guardians during the visit if they were interested in being contacted by study staff regarding ITHACA. If the patient's guardians agreed to be contacted, we would call them and do the screening form over the phone to make sure they met the inclusion and exclusion criteria. The primary mentor for this study, Dr. Michael Cabana, is a Principal Investigator for one of the research sites for AsthmaNet, a nationwide clinical research network created by the National Heart Lung and Blood Institute. Aside from the principal investigator, a research assistant was hired. Their main duties would

be to lead recruitment and retention of patients, collect data, conduct follow-up visits and oversee day-to-day study tasks.

A summary of the different events at each visit is detailed in **Figure 2**. After consent was obtained from both the child and caregiver, we collected demographic data on the child (e.g., age, gender, age of asthma diagnosis, occupation, languages spoken at home, relatives with asthma, smoking exposure) and the characteristics of the patient's disease (e.g., severity, medications used, previous hospitalizations, current provider, subspecialty provider for asthma [if any], duration of use of current medications) which may affect adherence to their medication or asthma symptom control. The subject's guardian then completed a few surveys including the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), the Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ), the Parent Asthma Management Self-efficacy (PAMSE) scale and a survey that included self-described medication taking behavior and a decision-making survey(a modified Reported Adherence to Medication (RAM) Survey). The RAM Survey, is a 3 question instrument, which helps describe and predict potential types of nonadherence behavior. The PAQLQ is an asthma-specific quality of life scale that has been validated in children and adolescents aged seven to 17 years and it has officially been translated into Spanish (Juniper, 1996). The PACQLQ is an asthma-specific quality of life scale for caregivers of children with asthma. (Juniper, 1996).The PAMSE measures parental self-efficacy for the management and prevention of acute asthma exacerbations. (Bursch, 1996) Since the RAM survey and PAMSE scale are available in English only, they were translated into Spanish using a systematic approach (Brislin, Lonner & Thorndike, 1973). The child's guardian also completed the Childhood Asthma Control Test (C-ACT). Although the C-ACT is used only for patients ages 4 to 11, we used this for children older than 11 because this version is only to be filled out by the parent or guardian. The C-ACT is a 7 item scale, with scores ranging from 0 (poor asthma control) to 27 (complete asthma control). In general, a C-ACT score >19 indicates well-controlled asthma.

The final step prior to the end of the initial visit was giving the participant and guardian the SmartInhaler device. Participants received either a Flovent or a Qvar SmartInhaler device depending on which daily controller medication they were taking. The SmartInhaler device unobtrusively would record every time the asthma daily medication is taken and communicate this information to the study center.

If the activated reminder system was activated and the participant did not take their daily medication, the SmartInhaler would send a text message to the patient's cell phone in Spanish reminding them to take their daily medication. Only the Flovent SmartInhaler featured an additional audio-visual reminder on the device that could also remind study participants to take their missed medication. Due to the Flovent SmartInhaler's additional feature reminding patients, participants were stratified into two groups according to the type of SmartInhaler they were using. The aim was to recruit 15 participants to use the Flovent SmartInhaler and 15 participants to use the Qvar SmartInhaler.

Data regarding daily asthma medication adherence was obtained using the SmartInhaler. Medication adherence for each medication would be calculated as a percentage of total number of doses received during the study period divided by the total number of doses prescribed. As a result, the percentage ranged from 0 to 100. The activated reminder system was initially deactivated but the SmartInhaler was turned on since it was going to be measure baseline adherence. A power cord given to the participants and guardians so they could recharge the battery of the SmartInhaler when it became depleted. The guardians of the participants were compensated with a $20 gift card for their time. The ACT, RAM, PAQLQ, PACQLQ, and PAMSE were completed at every study visit.

The time interval between visit 1 and visit 2 was the run-in period. During the run-in period, we determined baseline daily asthma controller medication rates using the SmartInhaler system without the activated reminder system and we also assessed baseline asthma symptom control.

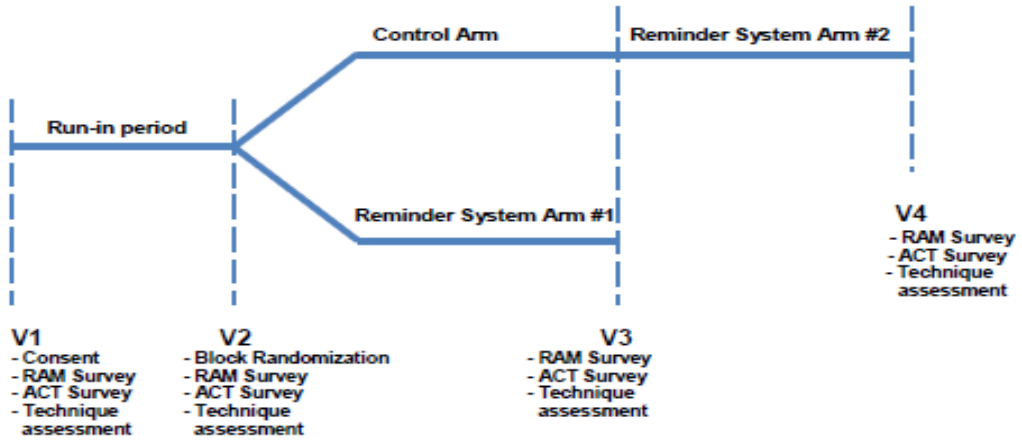

Figure 1: Study Design and Events for Each Visit (ACT = Asthma Control Test; RAM = Reported Adherence Medication Scale)

During visit 2, participants were randomized by a block design to ensure participants were equally distributed among both study groups. The University's Clinical and Translational Science Institute was consulted to assist in creating the randomization through computer generated random numbers. Once those numbers were generated, they were placed in envelopes by non-study personnel. A staggered implementation design was implemented in order to offer the intervention to all participants. Half the patients were randomly selected to have the reminder system activated during this 2nd visit. The reminder system was activated and data regarding daily asthma medication adherence was obtained using the SmartInhaler and sent to the data center. The other half did not have the reminder system activated in order to provide for a concurrent control group. That group had delayed activation until the 3rd visit.

During the 3rd visit, the rest of the participants had the reminder system activated. As for the group that had the SmartInhaler reminder system activated at the 2nd visit, we collected the SmartInhaler devices and administered a modified version of the Technology Acceptance Model (TAM) questionnaire which collects patient feedback about the device's usefulness. The TAM determines the user acceptance of any technology perceived usefulness and perceived ease of use factors. The TAM questionnaire, first developed by Davis (1993) and validated in different contexts by several researchers (Nair & Das, 2011), consisted of 17 questions, of which 13 were on a 5-point Likert-type scale questionnaire, with the scale ranging from 1 (strongly agree) to 5 (strongly disagree). A modified version of this questionnaire was used for this study. For the delayed activation group, their final visit was their 4th visit. At that final visit, we collected the SmartInhaler devices and obtain patient feedback on its usefulness by administering the TAM.

DATA ANALYSIS

In order to analyze the data, we consulted a statistician from the UCSF Clinical and Translational Science Institute (CTSI). The statistician analyzed the entire data set using statistical software. Demographic characteristics of each group were assessed to see if there were obvious disproportionate distributions of certain characteristics in the groups which may have affected the adherence. Medication adherence for each medication was calculated as a percentage of the total number of doses received during the study period divided by the total number of doses prescribed. As a result, this percentage ranged from 0 to 100. Medication adherence percentages and asthma symptom control scores during both the run-in and intervention periods were measured and the differences between the two time periods (Adherence Delta Δ and asthma symptom control Delta) was calculated for each patient. For objectives 1 & 2, we compared the mean "adherence delta" and "asthma symptom control delta" for each group using a student t-test.

Finally for the third objective, in order to assess if there were specific patient behavior characteristics which were associated with the success of a novel asthma medication reminder system, we identified those patients whose adherence rates increased from baseline. We compared the scores of the RAM Scale for those patients with a change in adherence compared to those patients with no improvement in adherence. We used a chi-squared test to assess if the RAM scores which suggest 'forgetful nonadherence' were associated with improved adherence rates during exposure to the reminder system. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).