COVER PAGE

Study Title	Interventions To Help Asthma Clinical Adherence (ITHACA)
NCT Number	NCT02999789
Document Description	Study Protocol
Document Date	28 January 2019

Study Application (Version 1.10)

1.0 General Information

***Enter the full title of your study:**

Interventions To Help Asthma Clinical Adherence

***Enter the study number or study alias**

ITHACA
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
◆	**UCSF** - *136261* - M_PEDS-ZSFG

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Cruz, Edward S, M.D., M.P.H.

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Cabana, Michael D, MD, MPH
Other Investigator

B) Research Support Staff

Arteaga, Vanessa M
Study Coordinator
Valenzuela, Miriam B

Research Assistant

3.3 *Please add a Study Contact:

Cruz, Edward S, M.D., M.P.H.

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

Cabana, Michael D, MD, MPH

3.5 If applicable, please select the Designated Department Approval(s):

Fuentes-Afflick, Elena MD, MPH, MD, MPH
Scientific Reviewer

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Cruz, Edward S, M.D., M.P.H.	Principal Investigator, Project Director, Subject Contact Study: Oversees all aspects of the proposed study, including design, data collection, analysis, recruitment, informed consent, and reporting of results.	Dr. Cruz is a MD and Assistant Clinical Professor at UCSF Department of Pediatrics. He has a Masters in Public Health and completed a primary care research fellowship prior to his faculty appointment where he was trained in conducting studies like this one.
Dr. Cabana, Michael D MD, MPH, MD, MPH	Co-Investigator, Faculty Advisor, Subject Contact Study: Oversees management of entire project, data collection, data management, protocol adherence, and	Dr. Cabana is a MD and Professor at UCSF Department of Pediatrics. He has over 10 years of research and clinical experience in conducting studies like this one.

		dissemination of findings. Will help with study design, interpretation of results, and editing the manuscript.	
	Valenzuela, Miriam B	Research Assistant: Will assist in recruitment for this study, informed consent, data collection and entry, following up with study participants, troubleshooting patient reminder device.	Miriam Valenzuela was hired to be the Research Assistant on this study. She has experience doing research with the Health Advocates Program at UCSF.
	Arteaga, Vanessa M	Clinical Research Coordinator: Will assist in recruitment for this study, informed consent, data collection and entry, following up with study participants, troubleshooting patient reminder device.	Vanessa Arteaga was hired to be the Research Coordinator on this study. She has experience doing research with the Health Advocates Program at UCSF.

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed). If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

5.2 * Risk level (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

5.3 * Subject contact:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- (•) Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ( ) Unfunded (no specific funds earmarked for this project)
- ( ) Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

( ) Yes (•) No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

(●) Yes ( ) No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

( ) Yes (●) No

5.8 * This is a clinical trial:

(●) Yes ( ) No

Clinical Trial Registration
"NCT" number for this trial:

5.9 * This is a multicenter study:

( ) Yes (●) No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

(●) Yes ( ) No

5.11 * This application involves a Humanitarian Use Device:

(●) No
( ) Yes, and it includes a research component
( ) Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

(●) No
( ) Yes, and requires CHR and GESCR review
( ) Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

( ) Yes (●) No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

( ) Yes (●) No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Funding

6.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation:**

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	Academic Pediatric Association, Inc.	05	UCSF	Grant	P0508095	

Sponsor Name:	Academic Pediatric Association, Inc.
Sponsor Type:	05
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	P0508095
Awardee Institution:	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	P0508095
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Interventions To Help Asthma Clinical Adherence (ITHACA)
PI Name: (If PI is not the same as identified on the study.)	Edward Cruz
Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

6.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.**
- **If your sponsor is not yet in the list, enter it in the box below.**

○ Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

6.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

○ Yes ◉ No

If **yes**, indicate which portion of your grant you will be attaching:

- ☐ The Research Plan, including the Human Subjects Section of your NIH grant or subcontract
- ☐ For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- ☐ The section of your progress report if it provides the most current information about your human subjects work
- ☐ The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

7.0 Sites

7.1 Institutions (check all that apply):

- ☐ UCSF
- ☐ China Basin
- ☐ Helen Diller Family Comprehensive Cancer Center
- ☐ Mission Bay
- ☐ Mount Zion
- ☑ San Francisco General Hospital (SFGH)
- ☐ SF VA Medical Center (SF VAMC)
- ☐ Blood Centers of the Pacific (BCP)
- ☐ Blood Systems Research Institute (BSRI)
- ☐ Fresno (Community Medical Center)
- ☐ Gallo
- ☐ Gladstone
- ☐ Institute on Aging (IOA)
- ☐ Jewish Home
- ☐ SF Dept of Public Health (DPH)

7.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or

collaborating on this project (Help Text updated 9/13):

- ☐ Other UC Campus
- ☐ Other institution
- ☐ Other community-based site
- ☐ Foreign Country

List the foreign country/ies:

7.3 Check any research programs this study is associated with:

- ☐ Cancer Center
- ☐ Center for AIDS Prevention Sciences (CAPS)
- ☐ Global Health Sciences
- ☐ Immune Tolerance Network (ITN)
- ☐ Neurosciences Clinical Research Unit (NCRU)
- ☐ Osher Center
- ☐ Positive Health Program

8.0 Study Design

8.1 * Study design (Help Text updated 9/13):

For this pilot phase, I plan to recruit 20 children ages 5 to 17 years with a diagnosis of persistent asthma who require a daily inhaled corticosteroid metered dose inhaler and whose primary caregiver has limited English Proficiency (LEP), whose primary language is Spanish, and whose parent is the person responsible for administering their daily asthma medication. Newer literature has cited that measuring Parental LEP was superior to primary language spoken at home in terms of measuring the impact of language barriers on children's health and health care (Flores et al.).
Initially, the sample size was increased to 30 because after the SmartInhalers were purchased, it was noted that the Flovent-compatible device had an additional feature of a visual reminder that the Qvar-compatible device did not have. Both have an audio reminder built in. This visual reminder can also remind study participants to take their missed medication. Due to the Flovent SmartInhaler's additional feature reminding patients, I stratified the participants into two groups according to the type of SmartInhaler they were using. I was aiming to recruit 15 participants to use the Flovent SmartInhaler and 15 participants to use the Qvar SmartInhaler. After consented, participants received a SmartInhaler device (either Qvar or Flovent) and it was attached to the asthma medication device. A participant's parent /guardian may have been asked to approve a change of medication from Qvar to Flovent or vice-versa in order to be eligible for each arm if the arm they wished to enroll in was already filled. The participant's primary care provider or asthma care provider was asked to approve the switch also. After the study was completed, the parent/guardian, primary care provider, and/or asthma care provider can switch the medication back to the original medication they were on if they wish.

On February 16, 2018, Teva Pharmaceutical Industries Ltd. announced that production of Qvar was being discontinued and instead the QVAR® RediHaler™ (beclomethasone dipropionate HFA) Inhalation Aerosol was now being launched on the market. As a result of that change and because the dimensions of the new device were incompatable with the Qvar SmartInhaler, I can no longer recruit participants on Qvar RediHaler. Only participants on Flovent can participate in the study. The alternate option is to change the patient's daily medication from Qvar RediHaler to Flovent to be compatable with the SmartInhaler. The sample size will naturally decrease to 20 as only 7 total Flovent SmartInhalers remain. A participant's parent/guardian may be asked to approve a change of medication from Qvar to Flovent in order to be initially eligible for the study or continue being in the study. The participant's primary care provider or asthma care provider will be asked to approve the switch also.

During the first six-weeks of the study, I will determine baseline daily asthma medication rates using the Smart-Inhaler device with the reminder system inactivated and also assess baseline asthma symptom control. During the subsequent six-week period, I will turn on the reminder system for half of the study participants and continue to keep the reminder system off for the other half. Once the reminder system is on, data regarding daily asthma medication adherence can be obtained using the SmartInhaler and sent to

our data center. During the final six-weeks of the intervention period, I will turn on the reminder system for the remaining fifteen participants. During the final visit for all participants, I will assess asthma symptom control, collect the SmartInhaler devices and obtain patient feedback on its usefulness.

Flores, G., Abreu, M., & Tomany-Korman, S. C. (2005). Limited english proficiency, primary language at home, and disparities in children's health care: how language barriers are measured matters. *Public health reports*,*120*(4), 418.

8.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

- [ ] Phase I
- [ ] Phase II
- [ ] Phase III
- [x] Phase IV

9.0 Scientific Considerations

9.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

(•) Yes ( ) No

If yes, state the hypothesis or hypotheses:

1. The reminder system intervention will increase daily asthma medication adherence for children with persistent asthma whose parents have Limited English proficiency (LEP) and whose primary language spoken at home is Spanish compared to baseline medication adherence rates.
2. The reminder system intervention will help improve adherence, affect self-management, asthma symptom control, parental self-efficacy, and improve parental and child quality of life (QOL) in children with persistent asthma whose parents have Limited English Proficiency (LEP) and whose primary language spoken at home is Spanish compared to baseline.
3. The reminder system device will be most useful for those patients are characterized as 'forgetful' and who do not unilaterally manipulate their own medication regimen.

9.2 * List the specific aims:

The overall aim is to conduct a pilot test to estimate the effect of a novel reminder system in improving daily asthma medication adherence rates in children whose parents have Limited English Proficiency (LEP) and whose primary language spoken at home is Spanish. The first aim is to determine if a novel reminder system can improve daily asthma medication adherence during a six-week evaluation period when compared to baseline medication adherence rates during a six-week period in the same group. The second aim is to determine whether a novel reminder system can improve asthma symptom control during a short-term, six-week evaluation period. The third aim is to assess if there are specific, patient behavior characteristics which are associated with the success of a novel asthma medication reminder system.

9.3 Statistical analysis:

For Aim 1, we recognize that some patients may already have high levels of adherence and it may be difficult to improve levels that are already close to 100%. As a result, we will use the run-in adherence percentage as the 'baseline' adherence for each patient. We will compare the medication adherence percentage during the study period with the medication adherence during the run-in period. The difference between the medication adherence percentages during the two time periods (Adherence Delta) will be calculated for each patient. Assuming a normal distribution, we will compare the mean "adherence delta" for each group using a student t-test.

For Aim 2, we will use the run-in asthma symptom control measure and the run-in asthma QOL measures as the 'baselines' for each patient. We will compare the asthma symptom control measure and QOL measures during the study period and the run-in period. We will use the Childhood Asthma Control Test (C- ACT) which is for patients 4 to 11. We will not be using the regular Asthma Control Test (ACT) because this is geared for adolescents who self-administer their daily asthma medication and this study is only recruiting patients whose parents or guardians administer their daily asthma medication. 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 difference between the asthma control during the two time periods (asthma symptom control Delta) will be calculated for each patient. We will compare the mean C-ACT differences for each group using a student t-test.
In regards to QOL, we will use the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), an asthma-specific quality of life scale that has been validated in children and adolescents aged seven to 17 years. We will also use the Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ). It measures issues that caregivers may be experiencing as a result of their child's asthma. The PAQLQ measures overall quality of life with asthma using 23 questions (Juniper et al.). Each answer is evaluated on a seven-point Likert scale, resulting in a total score that could range from 23 (lowest quality of life) to 161 (highest quality of life). The scale includes measurement of the impact of asthma in three areas: activity limitation (five questions, score range 5–35), symptoms (10 questions, score range 10–70), and emotional function (8 questions, score range 8–56). The PACQLQ contains 13 questions with a seven-point Likert scale resulting in a total score of 13 (lowest) to 91 (highest). Both the PACQLQ and the PAQLQ have good validity and a change in score greater than 0.5 on the seven-point Likert scale can be considered clinically important. Overall PAQLQ/PACQLQ domain scores will be calculated for each participant during the study period and the run-in periods. Overall and domain-specific PAQLQ/PACQLQ scores will be compared using general linear model repeated measures ANOVA.
In regards to measuring parental self-efficacy, we will use the Parent Asthma Management Self-efficacy (PAMSE) scale. The questionnaire measures parental self-efficacy for the management and prevention of acute asthma exacerbations. (Bursch et al.) This scale consists of 13 questions. Each answer is evaluated on a five-point Likert scale, resulting in a total score of 65 with the higher score indicating higher parental self-efficacy. The scale has reliability and validity. PAMSE scores will be calculated for each parent during the study period and the run-in periods. Overall scores will be compared using general linear model repeated measures ANOVA.

For Aim 3, to assess if there are specific, patient behavior characteristics which are associated with the success of a novel asthma medication reminder system, we will identify those patients whose adherence rates increased by at least 20%. We will compare the scores of the Reported Adherence Medication (RAM) Scale for those patients with a change in adherence compared to those patients with no improvement in adherence (Wroe, 2002). We will use a chi-squared test to assess if the RAM scores which suggest 'forgetful nonadherence' are associated with improved adherence rates during exposure to the reminder system.

9.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

- ☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- ☐ CTSI Clinical Research Center (CRC) advisory committee
- ☑ Departmental scientific review
- ☐ Other:

Specify **Other**:

10.0 Background

10.1 Background:

Asthma, a chronic inflammatory disease of the lungs, contributes to significant child morbidity through decreased quality of life, school absenteeism, emergency room visits, exercise limitation, hospitalizations and death. Medicaid-enrolled children have disparities in asthma care and increased adverse events secondary to asthma as compared to children with private insurance. (Vila, 2010; Liu, 2009; Lin, 2007;

Chabra, 1998) Enhancing patient medication adherence is a key component of successful asthma management and treatment (NAEPP, 2007). Adherence is the final common pathway by which all innovations are translated into improved patient outcomes (Osterberg, 2005). However, current patient medication adherence rates are only 40-70% in practice (Bozek, 2010; Latry, 2008; vanDellen, 2008; Clerisme-Beaty, 2011). These low rates of patient adherence lead to poor asthma control (Lasmar, 2009, Krishnan, 2004), preventable morbidity, and unnecessary health care utilization (Williams, 2004; Bender, 2004).

Methods to improve patient asthma medication adherence could enhance current therapies and impact disease morbidity (Cabana, 2011). Overall, there are a dearth of methods to improve medication adherence that have been rigorously evaluated. If successful, these techniques can be translated into practical strategies to influence everyday asthma management. There are several small studies of different adherence interventions, such as: supportive accountability (Burgess, 2010), altered expectation (Wise, 2009) reminder systems (Strandbygaard, 2010), tailoring treatment schedules (Chappuy, 2010) and motivational interviewing (Riekert, 2009). Selection of a specific adherence intervention depends on a 'match' with the (a) study population, (b) intervention, (c) context or reason for non-adherence, as well as (d) the importance and novelty of the intervention for asthma care.

There are different reasons for non-adherence which may be more amenable to specific types of interventions. For example, **'**Deliberate' or 'Intelligent' nonadherence is associated with patient lack of agreement or motivation. In this case, motivational interviewing may be an appropriate intervention. 'Unintentional' or 'Unwitting' nonadherence occurs when a patient incorrectly interprets medication instructions, which then leads to non-adherence. In this case, enhanced asthma education may be the most appropriate intervention. 'Forgetful' or 'Erratic' nonadherence is associated with patient intent to take the medication, but the inability to remember to use the medication. In this case, a reminder system may be the most appropriate intervention. 'Forgetful' nonadherence is reported to be the most common cause of nonadherence (Weinstein, 2005).

One potential intervention to address the most common reason for nonadherence ('forgetful' nonadherence) is a 'smart' reminder system device that monitors medication use and can send messages to patients to remind them to take their medications**.** With the ubiquitous nature of text-messaging capabilities in cell phones, short-text messaging (STM) systems coupled with a medication device monitor can potentially be used to remind patients about daily medication adherence (Strandbygaard, 2010).

The proposed pilot study in digital health represents a new area of investigation for our team. Our team has developed, evaluated and published successful interventions to help improve physician counseling about asthma, as well as patient medication adherence. The effect of new technologies to track patient symptoms and medication use may have positive or negative effects on the provider-patient relationship. Devices that unobtrusively collect adherence data can help providers assess the effects of prescribed medications and frequency of use, which can make patient management and communication more clear and efficient; however, patient feedback about adherence needs to be provided in a constructive manner. This new monitoring information creates a new dimension in the provider-patient relationship. The proposed study represents the first pilot study by our team to develop experience using these digital health interventions. Overall, this study is the first step in developing interventions that combine physician counseling and the use of digital health tools to track and measure adherence.

Due to language and cultural barriers, Latino patients have had little access to new technologies such as patient reminder systems. We have developed a partnership with Adherium (formerly called Nexus6 from Auckland, New Zealand) to modify a medication monitoring system to send reminder messages in Spanish. There are no studies that have used a novel monitoring system to transmit reminder messages to Spanish-speaking guardians of children with persistent asthma.

As a result, we are proposing a pilot trial to assess the effectiveness of a novel digital health patient reminder system (SmartInhaler) in improving asthma medication adherence in children whose parents have LEP and are monolingual Spanish-speaking. The proposed **I**nterventions **T**o **H**elp **A**sthma **C**linical **A**dherence (ITHACA) pilot study is a key step in evaluating asthma medication reminder systems, assessing which patients benefit from such interventions, and understanding the potential magnitude of such effects.

10.2 Preliminary studies:

The promising nature of the reminder system intervention for asthma was confirmed by a recent systematic review. The systematic review was conducted by using all titles of published clinical trials in the National Library of Medicine focused on reminder systems and asthma medication adherence. 894 potential articles were reviewed and 7 patient-level intervention studies were found for medication adherence (as opposed to immunization reminders or physician-oriented reminders). The studies used outmoded systems with reminders that were 'infrequent' and/or 'non adaptable' and would send reminders regardless of patient adherence. Despite the use of outdated technology in these studies, all studies suggested higher patient medication adherence for those patients randomized to the 'reminder' group, compared to the control group. The mean difference in adherence between groups was 18% in the follow-up periods. None of the studies routed reminders to cell phones/e-mail and the inhaler. New advances in

cell phone technology and routing systems, offer an opportunity to improve adherence rates and tailor systems to patient preferences. New systems offer the ability to deliver reminders to patients only when necessary, as well as to multiple settings (cell phone call, text message, e-mail, etc.) based on patient preferences.

Members of our team has experience in asthma care, health education and the development and evaluation of interventions to improve physician management of asthma. For example, One member of our team developed the Physician Asthma Care Education (PACE) program (Cabana, 2006). The PACE intervention consists of interactive physician seminars sessions to review asthma guidelines, specific communication techniques and key asthma educational messages. We conducted a national, cluster-randomized controlled trial with 101 primary care providers and a random sample of 870 of their asthma patients in 10 regions in the US. At each site, we recruited a local instructional team and standardized the PACE curriculum. As part of the evaluation, we interviewed a random sample of each of the asthma patients of the 101 providers. One year after the intervention, compared to controls, parents reported that physicians in the intervention group were more likely to inquire about patients' asthma concerns (OR 1.73; 95% CI: 1.17, 2.58); encourage patients to be active (OR: 1.71; 95% CI: 1.13, 2.59); and set treatment goals (OR: 1.50; 95% CI: 1.02, 2.24). Patients of physicians that attended the PACE program had a greater decrease in days limited by asthma symptoms (8.5 vs. 15.6 days; $p< 0.05$), and decreased ED asthma visits (0.30 vs. 0.55 visits/year; $p< 0.05$). (Cabana, '06) During the PACE evaluation, we developed data collection tools which include a parent telephone survey, and a self-administered physician survey.

Although the patient reminder system's effect on asthma medication adherence has not been studied in Spanish-speaking patients, preliminary studies in children and adolescents have found increased adherence when using a patient reminder system. (Chan, 2015) The effect of new digital health technologies to track patient symptoms and medication use may have positive or negative effects on the provider-patient relationship. Overall, the proposed ITHACA study represents our team's systematic approach to the incorporation, development and evaluation of digital health technology to complement asthma patient education and counseling.

10.3 References:

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Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. *J Asthma*. 2010; 47: 162-165.

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Liu SY, Pearlman DN. Hospital readmissions for childhood asthma: the role of individual and neighborhood factors. *Public Health Rep.* Jan-Feb 2009;124(1):65-78.

Lin RY, Pitt TJ, Lou WY, Yi Q. Asthma hospitalization patterns in young children relating to admission age, infection presence, sex, and race. *Ann Allergy Asthma Immunol.* Feb 2007;98(2):139-145.

National Asthma Education and Prevention Program: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2007.
Osterberg L, Blaschke T. Adherence to medication. *New Engl J Med*. 2005; 353:487-497.
Riekert KA, Borrelli B, Bilderback A, Rand CS. The development of a motivational interviewing intervention to promote adherence among inner-city, African-American adolescents with asthma. *Patient Educ Coun*. 2011; 82: 117-122.
Strandbygaard U, Tomsen SF, Backer V. A daily SMS reminder increases adherence to asthma treatment: a three-month follow-up study. *Resp Med*. 2010; 104: 166-171.
Van Dellen QM, et al. Adherence to inhaled corticosteoroids in children with asthma and their parents. *Resp Med*. 2008; 102: 755-763.
Vila D, Rand CS, Cabana MD, et al. Disparities in asthma medication dispensing patterns: the case of pediatric asthma in Puerto Rico. *The Journal of asthma : official journal of the Association for the Care of Asthma.* Dec 2010;47(10):1136-1141.
Weinstein AG. Should patients with persistent severe asthma be monitored for medication adherence? *Ann Allergy Asthma Immunol.* 2005; 94:251-7.
Williams LK, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *JACI*. 2004; 114: 1288-93.
Wise RA, Bartlett SJ, Brown ED, et al. Randomized trial of the effect of drug presentation on asthma outcomes: the American Lung Association Asthma Clinical Research Centers. *JACI.* 2009; 124: 436-444.
Wroe AL, et al. Intentional and unintentional nonadherence: a study in decision making. J. Behavioral Medicine. 2002; 25:355-372.

If you have a separate bibliography, attach it to the submission with your other study documents.

11.0 Sample Size and Eligibility

11.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

20

11.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

20

11.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

270

11.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

The sample size is limited by budget limitations. Based on cost-efficiency and limitations, we will recruit 20 patients to give us a general estimate of the effectiveness of this intervention (Bacchetti, 2008). These results will be used for the power calculations for a future, larger randomized controlled trial, which will be proposed through an R01 mechanism. Assuming a positive effect of reminder systems and a baseline adherence rate of 60%, with 20 patients, with a power of 0.80, an alpha of 0.05, there be enough power to detect a 15% change in adherence. This percentage change translates to a Number Needed to Treat (NNT) of 6 patients.

Bacchetti P, McCulloch CE, Segal MR. Simple, defensible sample sizes based on cost efficiency. Biometrics. 2008; 64: 557-85.

11.5 * Eligible age range(s):

- [x] 0-6 years
- [x] 7-12 years
- [x] 13-17 years
- [ ] 18+ years

11.6 Inclusion criteria:

1. We will recruit 20 children ages 5 to 17 years with a diagnosis of persistent asthma who require a daily inhaled corticosteroid metered dose inhaler and whose guardian is the person responsible for administering their daily asthma medication during the study period.
2. We will recruit only patients who have received or receive care at San Francisco General Hospital's 6M Children's Health Center.
3. We will recruit patients whose daily inhaled corticosteroid are Flovent (fluticasone propionate) HFA (Hydrofluoroalkane) metered dose inhalers (MDI) only. A participant's parent/guardian may be asked to approve a change of medication from Qvar to Flovent in order to be eligible for the study. The participant's primary care provider or asthma care provider will be asked to approve the switch.
4. We will also recruit only patients whose guardian responsible for administering their daily asthma medication has Limited English Proficiency (LEP) and whose primary language is Spanish.

11.7 Exclusion criteria:

1. We will exclude patients whose guardian responsible for administering their daily asthma medication does not have a Bluetooth enabled cell phone capable of receiving text messages.
2. We will exclude patients whose guardian responsible for administering their daily asthma medication does not have an available reliable power outlet where they can recharge the battery of their SmartInhaler.
3. We will exclude patients whose guardian responsible for administering their daily asthma medication is unable to demonstrate correct medication technique based on standard evaluation (Press, 2011) after completion of a standard teaching protocol. In the case that the guardian always supervises the child but the child is the one who administers the medication, the child may be excluded if he/she is unable to demonstrate correct medication technique.
5. We will exclude patients with chronic lung disease.
6. We will exclude patients who do not have an operating system of iOS or Android on their cell phone and who have no data plan with their cellular phone plan.
7. We will exclude patients whose asthma medication regimen is being managed by an asthma subspecialist or health provider outside of the 6M Children's Health Center at San Francisco General Hospital.
8. We will exclude patients who are using an inhaled long acting beta-agonist (LABA) as part of their asthma management plan.

Press VG, et al. Misuse of respiratory inhalers in hospitalized patients with asthma or COPD. *J Gen Int Med.* 2011; 26: 635-642.

11.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

(•) Yes ( ) No

If **yes**, please explain the nature and rationale for the restrictions:

Latino patients have had little access to digital technologies due to cultural and language barriers. There are no studies that have used a novel monitoring system to transmit reminder messages to Spanish-speaking guardians of children with persistent asthma. We are restricting our inclusion criteria in order to study whether the SmartInhaler can improve daily asthma medication adherence in children with persistent asthma whose parents have Limited English Proficiency (LEP) and are monolingual Spanish-speaking.

12.0 Drugs and Devices

12.1 * Investigational drugs or biologics will be used OR approved drugs or biologics will be studied under this application:

○ Yes ◉ No

12.2 * Investigational medical devices or in vitro diagnostics will be used OR approved medical devices or in vitro diagnostics will be studied under this application:

◉ Yes ○ No

12.3 * A Non-Significant Risk (NSR) determination is being requested for an investigational device:

○ Yes ◉ No

12.4 Verification of IND/IDE numbers: If the sponsor's protocol does not list the IND/IDE number, you must submit documentation from the sponsor or FDA identifying the IND/IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

13.0 Study Device Details

13.1 List the medical devices or in vitro diagnostics to be studied or used and attach any FDA or sponsor correspondence relating to the device to the application in the Study Documents section: (Note: Device category descriptions added to the Help link December, 2014)

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	SmartInhaler	Yes	No	

Manufacturer/Supplier of Device	Nexus6
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

⊟	SmartTouch Qvar	Yes	No	

Manufacturer/Supplier of Device	Adherium (Formerly called Nexus6 Limited)

Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	Principal Investigator's locked private office
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

⊟	SMARTTOUCH AV FLOVENT	Yes	No	

Manufacturer/Supplier of Device	Adherium (Formerly called Nexus6 Limited)
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	Principal Investigator's locked private office
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

14.0 Other Approvals and Registrations

14.1 * Do any study activities take place on patient care units:

◉ Yes ○ No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

14.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

○ Yes ◉ No

14.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

○ Yes ◉ No

14.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

○ Yes ◉ No

14.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

○ Yes ◉ No

14.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

15.0 Procedures

15.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

This will be a pilot trial on the effect of a novel asthma medication reminder system device on patient daily asthma medication adherence. Because the intervention is a reminder system, it will not be possible to 'blind' the participants. After consent, participants will receive a SmartInhaler device and it will attach to the asthma medication device. The SmartInhaler Reminder System (Adherium) can be attached to the asthma medication device. It features an audiovisual reminder, which can also route messages or reminders to a patient's cellular phone or e-mail in English and Spanish. The user interface includes LED technology and a 4-button menu system with a built-in clock. The screen can be used for reminders or questionnaires. The audio ring tone reminder is modifiable to include different ring tones and various volumes. The system can be modified for any type of dosing regimen (e.g., bid, tid).
The Smartinhaler can be attached to all the commonly used asthma medication devices, including the traditional multi-dose inhaler, the discus and the turbohaler. The SmartInhaler can unobtrusively record every time the asthma daily medication is taken by the study participant. The SmartInhaler then communicates this information to patient's cell phone via BlueTooth which in turn relays the information to

the study center. The SmartInhaler then communicates this information to study center. This information can also be downloaded via a USB cord at the study visits. The Smartinhaler battery needs to be recharged when depleted so an electric power cord can recharge the battery when plugged into an electrical outlet.
If the patient does not take their daily asthma medication, the SmartInhaler provides a reminder for missed medications to the study participant via an audio-visual reminder on the device, or via a text message to the study participant's cell phone or e-mail account. The way the reminder is sent (via e-mail, cell phone or through audiovisual function on the inhaler) can be tailored to a study participant's preference. If the patient does take their daily medication, a 'congratulations' message can also be sent to the patient.
For the proposed study, the primary outcome is daily asthma medication adherence. Data regarding daily asthma medication adherence can also be obtained using a SmartInhaler, which can unobtrusively collect medication adherence data and send data back to the study center. Medication adherence for each medication will 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, this percentage can range from 0 to 100.
Patients will be recruited at the 6M Children's Health Center at San Francisco General Hospital. If the patient requires a change of their daily asthma medication from Qvar to Flovent to participate in the study, we will need both the primary care provider and/or asthma care provider and patient's guardian/parent to agree with the switch prior to proceeding with the study. Once the change is approved, we can proceed with the consent process. Once consented, we will collect demographic data on the patient's (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 the medication or asthma symptom control. The subject's guardian will then complete a few baseline 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 includes self-described medication taking behavior and decision-making (a modified Reported Adherence to Medication (RAM) Survey). The RAM Survey, is a 3 question instrument, which will help describe and predict potential types of nonadherence behavior (Wroe, 2002; Horne, 1999). 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 will be translated into Spanish using a systematic approach (Brislin, Lonner & Thorndike, 1973). Subject's guardian will also complete the Childhood Asthma Control Test (C-ACT). Although the C-ACT is used for only patients 4 to 11, we will use this for children older than 11 because this version is only to be filled out by the parent or guardian. This study will only recruit patients whose parents or guardians are the ones administering the daily asthma medication. 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 end of the initial visit will be giving the participant and guardian the SmartInhaler device. The activated reminder system will initially be deactivated but the SmartInhaler must still be turned on. A power cord will be given to the participants and guardians so they can recharge the battery of the SmartInhaler when it is depleted. The guardians of the participants will be compensated with a $20 gift card for their time.
During the run-in period of 6 weeks, baseline daily asthma medication rates will be determined using the SmartInhaler system without the activated reminder system. Baseline asthma symptom control will also be assessed. A visit will be scheduled prior to the intervention period to have the subject's guardian repeat the PAMSE, PAQLQ, PACQLQ, and RAM surveys in Spanish and the C-ACT instrument. At the end of the run-in visit, the participants will be randomized by a block design to ensure participants are equally distributed among both study groups. The CTSI 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. I have chosen a staggered implementation design in order to offer the intervention to all participants. Half the patients will be randomly selected to have the reminder system activated during this visit. The reminder system will be activated and data regarding daily asthma medication adherence can be obtained using the SmartInhaler and sent to our data center. The other half will NOT have the reminder system activated in order to provide for a concurrent control group. They will have delayed activation at their next visit. All the guardians of the participants will be compensated with a $20 gift card for their time.
During the intervention period of 6 weeks, the reminder system will be activated and data regarding daily asthma medication adherence can be obtained using the SmartInhaler and send it to our data center. At the third visit, the subject's guardian will once again complete the PAMSE, PAQLQ, PACQLQ, and RAM Surveys in Spanish. We will also assess asthma symptom control, based on the C-ACT instrument. For the group that had the SmartInhaler reminder system activated, we will collect the SmartInhaler devices and collect patient feedback about their usefulness. For the group who did not have it the reminder system on, it will be activated. The guardians of all the participants will be compensated with a $20 gift card for their time.
During the delayed activation group's intervention period of 6 weeks, data regarding daily asthma medication adherence can be obtained using the SmartInhaler and send it to our data center. At the conclusion of the 6 weeks, the subject's guardian will once again complete the PAMSE, PAQLQ, PACQLQ,

and RAM Surveys in Spanish. We will also assess asthma symptom control, based on the C-ACT instrument. For the group that had the SmartInhaler reminder system activated, we will collect the SmartInhaler devices and collect patient feedback about their usefulness. The guardians of the participants will be compensated with a $20 gift card for their time. We will use all this pilot data as preliminary results for a larger randomized controlled trial in this population.
At the end of the study, the parent/guardian, primary care provider, and/or asthma care provider can switch back to original asthma daily medication they were on originally if they were switched.

Any participant who had previously enrolled in the study in the Qvar arm may continue in the study if switched to the Flovent arm. For that to occur, we will need both the primary care provider and/or asthma care provider and patient's guardian/parent to agree with the switch prior to proceeding in the study.

Brislin RW, Lonner WJ, Thorndike RM. Cross-cultural research methods. 1973.
Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 2999; 47: 555-567.
Juniper, E. F., Guyatt, G. H., Feeny, D. H., Ferrie, P. J., Griffith, L. E., & Townsend, M. (1996). Measuring quality of life in children with asthma.*Quality of life research*, *5*(1), 35-46.
Juniper, E. F., Guyatt, G. H., Feeny, D. H., Ferrie, P. J., Griffith, L. E., & Townsend, M. (1996). Measuring quality of life in the parents of children with asthma. *Quality of Life Research*, *5*(1), 27-34.
Bursch, B., Schwankovsky, L., Gilbert, J., & Zeiger, R. (1999). Construction and validation of four childhood asthma self-management scales: parent barriers, child and parent self-efficacy, and parent belief in treatment efficacy. *Journal of Asthma*, *36*(1), 115-128.
Wroe AL, et al. Intentional and unintentional nonadherence: a study in decision making. J. Behavioral Medicne. 2002; 25:355-372.

If you have a procedure table, attach it to the submission with your other study documents.

15.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

(•) Yes ( ) No

List any standard instruments used for this study:

1. Reported Adherence to Medication (RAM) Survey: A 3 item survey instrument, which can help determine the likelihood of behavior due to forgetful medication non-adherence versus intentional non-adherence.
2. Childhood Asthma Control Test (c-ACT): 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 C-ACT is used for patients 4 to 11 years of age.
3. Short-Test of Functional Health Literacy in Adults in Spanish (S-TOFHLA): A 36 item instrument to measure parents' ability to read and understand health-related materials. The score can range from 0 to 36. A score of 0-16 means the patient's functional health literacy is inadequate. A score of 17-22 means the patient's functional health literacy is marginal. A score of 23-36 means the patient's functional health literacy is adequate.
4. Pediatric Asthma Quality of Life Questionnaire (PAQLQ): A 23 item, 7-point Likert scale covering three domains: symptoms, emotional function, and activity limitation. A total score can range from 23 (lowest quality of life) to 161 (highest quality of life).
5. Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ): A 13 item, 7-point Likert scale with a total score ranging from 13 (lowest quality of life) to 91 (highest quality of life).
6. Parent Asthma Management Self-efficacy (PAMSE): A 13 item, 5-point Likert scale that measures parental self-efficacy for the management and prevention of their child's asthma attacks. A total score can range from 13 (lowest self-efficacy) to 65 (highest self-efficacy).
7. Medication Technique Assessment: A standardized approach to assess asthma medication device technique utilizing detailed checklists by an observer.

Attach any non-standard instruments at the end of the application.

15.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

( ) Yes (•) No

If yes, explain:

15.4 Sharing of experimental research test results with subjects or their care providers:

(•) Yes ( ) No

If yes, explain:

The patient's primary care provider or asthma subspecialist may be informed of results of their patient's daily asthma medication adherence. They may also be informed of other information obtained during the screening or study such as poor health literacy, purposeful non-adherence, and poor asthma medication delivery technique. All of this information may be pertinent in improving the management of their asthma. The patient and their guardians may be informed of the results of their daily asthma medication adherence as it may serve to modify and improve their nonadherence behavior. If a change in medication is necessary for the trial the child's primary care physician or asthma care provider will be contacted to ensure they are in agreement with that change before consent and enrollment.

15.5 * Specimen collection for future research and/or specimen repository/bank administration:

( ) Yes (•) No

15.6 Time commitment (per visit and in total):

The visits after the run-in period for both groups would take 1 hour in order to fill out questionnaires, review inhaler technique, and upload data to the study computer.
An approximation of total time commitment would be 5 to 7 hours.

15.7 Locations:

The study locations will be mainly at San Francisco General Hospital and may include the investigators' private offices, conference rooms assigned to the General Pediatrics department and/or patient/provider rooms at the 6M Children's Health Center. On occasions, the study visits could occur at the participants' home or residence or at a nearby café only if this is easier for the participant.

15.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

All study data will be directly labelled/recorded with the personal identifying information when acquired. The database with all personal identifying information will reside on REDCap. REDCap is a way to provide medical researchers with a professionally managed, secure, web based, HIPAA compliant environment for building and managing web-based projects. Only study personnel will have access to this REDCap database including the principal investigator, co-investigator, and research assistant.
On occasions, a study visit could occur at a participant's residence or at a nearby café. On these occasions, a secure encrypted laptop will be used to record all necessary data. The data would be de-identified on this laptop. All asthma medication adherence data will be uploaded using a USB cable to the SmartInhalerLive software via the internet. The SmartInhalerLive program would not contain personal identifying information only data with a numerical code. All personal identifying information will reside exclusively on REDCap.

16.0 Alternatives

16.1 Study drug or treatment is available off-study:

- ○ Yes
- ◉ No
- ○ Not applicable

16.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

◉ Yes ○ No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

All participation in research studies is voluntary. If a patient and his/her guardian decide not to participate, that will not impact their ability to receive medical care at the 6M Children's Health Center or San Francisco General Hospital.

16.3 Describe other alternatives to study participation that are available to prospective subjects:

17.0 Risks and Benefits

17.1 * Risks and discomforts:

Participation in research will mean a loss of privacy. Subjects and their guardians will be asked personal information that may be uncomfortable talking about, including information about their daily asthma medication adherence. Subjects and their guardians will be asked to keep in touch with study personnel both via phone and in person at 3-4 scheduled visits depending on the group they are assigned to.
Other risks of participating in the study could occur from malfunction of the SmartInhaler. The SmartInhaler will have an audiovisual reminder that will be activated a maximum of twice daily reminding the subject's parent/guardian to administer their daily medication. The reminder system will be set up to alarm twice daily as chosen by the subject's parent/guardian. The reminder system will alert the parent /guardian every minute for 15 minutes at the time the medication is due and then stop. If the device malfunctions, the audiovisual reminder does not activate at all or the audiovisual reminder activates more than twice, the parent/guardian should let the study investigators know as soon as possible. Although there may be a risk of the subject not receiving their daily asthma medication because of the audiovisual reminder malfunctioning or the 15 minutes passing and the alarm stopping, parents/guardians of the subjects will be instructed to administer the medication only twice daily regardless of whether a reminder is given or not.
If the subject's parent/guardian's cellular phone malfunctions, the parent/guardian will not be able to receive a text message reminder. Nontheless, the SmartInhaler itself will still provide an audiovisual reminder.
If the subject is asked to switch medication from Qvar to Flovent, there are no risks in this change as both are approved, equally therapeutic, and their dosages and concentrations are equivalent.

17.2 Steps taken to minimize risks to subjects:

Subjects and their guardians will not have to answer any questions that make them feel uncomfortable. All study questionnaires will be done on paper only and will be identifiable via a study ID number. All subjects' information and study data will be on REDCap which is a secure, web-

based, HIPAA compliant server on the UCSF website. Subjects' personal names will not be used in any published reports about the study. All subjects and their guardians will be given copies of the study consent form and the Experimental Subject's Bill of Rights to keep for their records. Study subjects can terminate their participation in the study at any point in time. Once the study has ended, data has been analyzed and results approved for publication, all personal identifiers will be deleted from the data.

If we meet a Subject and their guardian at a cafe for study purposes, confidentiality will be maintained. Patient identifiers will not be displayed on any device or paper questionnaire and they will only be identified by an ID code. All patient identifiers will be securely stored on REDCap only. All computers used in a cafe will be securely encrypted according to UCSF guidelines to protect the data and also protect against loss/theft of device. Strong passwords will be used on the encrypted device to protect against unauthorized access. Any devices used will be routinely and regularly reviewed and updated according to UCSF data security procedures. If paper questionnaires are used, no patient identifiers will be on them and only a numerical ID code will be used on the questionnaire. At the cafe, no data transmission involving patient identifiers will occur. Since all SmartInhaler data is relayed to the SmartInhaler website via the participant's guardian's own cell phone bluetooth connection, no other bluetooth connection will be used to do this. If data needs to be uploaded directly from the SmartInhaler to the SmartInhaler Live website because the guardian's cell phone was unable to do this, data will be uploaded via a USB cable onto a secure encrypted device to the SmartInhaler website. If a wireless connection is used at the cafe, it would only be to transmit coded date from the SmartInhaler itself to the SmartInhaler live website through a USB cord that connects to the encrypted secure laptop. As mentioned before, the SmartInhaler website has no patient identifiers and only coded data. All patient identifiers are only on REDCap and would only be accessed using a secure transmission process such as the UCSF internet servers.

17.3 Benefits to subjects:

(•) Yes ( ) No

If yes, describe:

The SmartInhaler device may directly benefit study subjects by improving their asthma medication adherence and their overall symptom control.

17.4 Benefits to society:

Asthma, a chronic inflammatory disease of the lungs, contributes to significant child morbidity through decreased quality of life, school absenteeism, emergency room visits, exercise limitation, hospitalizations and death. The proposed pilot study in digital health represents a new area of investigation. Our goal is to develop interventions that combine data from digital health technologies, (such as asthma reminder systems) with programs that improve how providers effectively discuss, counsel and manage patients with poor medication adherence for Spanish-speaking patients who do not have easy access to these devices. The proposed pilot study will provide general estimates of the effectiveness of the reminder system device in improving asthma adherence. In addition, the proposed pilot study will deliver new technologies to a monolingual Spanish-speaking population that has traditionally not had access to due to language and cultural barriers.

17.5 Explain why the risks to subjects are reasonable:

Although participation in research will mean a loss of privacy; however, all subjects' personal information and records will be handled as confidentially as possible. The information obtained in this study may greatly benefit the management and treatment of asthma and reduce morbidity to asthma thus outweighing study risks.

18.0 Data and Safety Monitoring Plan

18.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

Study personnel will monitor study progress and any negative implications it may be having. Personnel will be monitoring data in 2 week intervals and at all scheduled visits.

18.2 This study requires a Data and Safety Monitoring Board:

- ○ Yes
- ◉ No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

18.3 If No, provide rationale:

- ○ Social/Behavioral research
- ○ Phase I trial
- ○ Treatment IND/Compassionate Use Trial
- ◉ Other (explain below)

If **Other,** explain:

This study will involve use of a FDA-approved medical device that provides a patient reminder to take their daily asthma medication. It does not involve the trial of a new medication or device. The device will be used according to the manufacturer's recommendations only.

19.0 Confidentiality and Privacy

19.1 Plans for maintaining privacy in the research setting:

All study questionnaires will be done on paper identifying them with a participant ID number only. All subject's record and study data will be entered and kept on REDCap which is a secure, web-based, HIPAA compliant server on the UCSF website. Subjects' personal names will not be used in any published reports about the study.

19.2 Possible consequences to subjects resulting from a loss of privacy:

No personal information can be shared with anyone without written consent by the subjects' guardian's permission. No personal names will be used in any published study results.

19.3 Study data are:

- ☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- ☑ Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- ☐ Added to the hospital or clinical medical record
- ☑ Created or collected as part of health care
- ☐ Used to make health care decisions
- ☑ Obtained from the subject, including interviews, questionnaires
- ☐ Obtained from a foreign country or countries only

☐ Obtained from records open to the public
☐ Obtained from existing research records
☐ None of the above

If **derived from a medical record**, identify source:

Electronic Clinical Works, LCR

19.4 Identifiers may be included in research records:

◉ Yes ○ No

If **yes**, check all the identifiers that may be included:

☑ Names
☑ Dates
☑ Postal addresses
☑ Phone numbers
☐ Fax numbers
☑ Email addresses
☐ Social Security Numbers*
☑ Medical record numbers
☐ Health plan numbers
☐ Account numbers
☐ License or certificate numbers
☐ Vehicle ID numbers
☐ Device identifiers or serial numbers
☐ Web URLs
☐ IP address numbers
☐ Biometric identifiers
☐ Facial photos or other identifiable images
☐ Any other unique identifier

* Required for studies conducted at the VAMC

19.5 Identifiable information might be disclosed as part of study activities:

○ Yes ◉ No

If **yes**, indicate to whom identifiable information may be disclosed:

☐ The subject's medical record
☐ The study sponsor
☐ Collaborators
☐ The US Food & Drug Administration (FDA)
☐ Others (specify below)
☐ A Foreign Country or Countries (specify below)

If **Others**, specify:

19.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

☑ Data are stored securely in My Research

- [x] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [ ] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [x] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

19.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

19.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

○ Yes ◉ No

Explain:

19.9 This study will be issued a Certificate of Confidentiality:

○ Yes ◉ No

20.0 Subjects

20.1 Check all types of subjects that may be enrolled:

- [ ] Inpatients
- [x] Outpatients
- [ ] Healthy volunteers
- [ ] Staff of UCSF or affiliated institutions

20.2 Additional vulnerable populations:

- [x] Children
- [x] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [x] Subjects with diminished capacity to consent
- [x] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [x] Economically or educationally disadvantaged persons
- [ ] Investigators' staff
- [ ] Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

Asthma is a chronic inflammatory disease of the lungs affecting nearly 10.1 million children causing significant morbidity. Medicaid-enrolled children have disparities in asthma care and increased adverse events secondary to asthma as compared to children with private insurance. Research including children

with public insurance is crucial to decreasing adverse outcomes due to asthma especially in disadvantaged populations. Due to language and cultural barriers, monolingual Spanish-speaking patients have had little access to new technologies such as patient reminder systems. The proposed study will deliver new technologies to a population that has traditionally not had access to due to language and cultural barriers.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

All participants will be given the Subject's Bill of Rights for participating in a research study in Spanish.

21.0 Inclusion of Children in Research

21.1 This study will enroll children who can legally consent for themselves:

○ Yes ◉ No

If **yes,** explain why they can consent for themselves in the research setting:

If you will **ONLY** be enrolling children who can legally consent for themselves, press **SAVE and CONTINUE** to skip the rest of this section.

21.2 Select all the regulatory categories that apply:

- ☐ No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- ☑ Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- ☐ Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- ☐ Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

There is a dearth of research regarding patient reminder systems in children and adolescents with asthma. Due to the significant morbidity due to asthma in children, research attempting to decrease asthma morbidity and increase quality of life is imperative. Direct benefits to the subjects include increasing asthma control due to the device's reminder system. Study results may also benefit the treatment and management of childhood asthma overall.

21.3 Parental permission or waiver:

- ☑ Parental permission will be obtained
- ☐ Waiver of parental permission is requested: Parental permission is not a reasonable requirement
- ☐ Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of parental permission**, explain why the study meets the regulatory criteria for this waiver:

21.4 Assent of children or waiver:

- ☑ Assent of children old enough to provide assent will be obtained
- ☑ Waiver of assent is requested: Children cannot be consulted or the research has prospect of direct benefit only available in the study
- ☐ Waiver of assent is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of child's assent**, explain why the study meets the regulatory criteria for this waiver:

Children younger than 7 years old eligible for the study cannot assent. Since we are also looking to recruit 5 and 6 year olds, we request a waiver of assent for them however their parent/guardian will sign and consent for them.

21.5 Documentation of permission and assent (select all that will be used):

- [x] Permission form addressed to the parents
- [x] Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
- [x] Assent form addressed to the child, 13 years and older (for subjects and parents)
- [ ] Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

- (•) One parent's signature will be obtained
- ( ) Two parents' signatures will be obtained

If this study is approvable under .404 or .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

21.6 This study may enroll wards of the state:

( ) Yes (•) No

22.0 Inclusion of Non-English Speaking Subjects

22.1 Indicate which method(s) you will use to consent non-English speaking subjects:

- [x] Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- [ ] Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

22.2 Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study:

The principal investigator and research assistant are native fluent Spanish speakers. Whenever the co-investigator communicates with the subjects, he will use a qualified Spanish interpretor.

23.0 Recruitment

23.1 * Methods (check all that apply):

- [x] Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
- [x] Study investigators recruit their own patients by letter. Attach the letter for review.
- [x] Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.

- [x] Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
- [x] Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.
- [x] Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [x] Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [x] Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- [ ] Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.
- [x] Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.
- [ ] Other

If **Other**, explain:

23.2 * How, when, and by whom eligibility will be determined:

Once a potential subject is identified, the investigators will screen the patient and primary guardian for eligibility using inclusion and exclusion criteria as determined by the study team. The patient will also be excluded if they are unable to demonstrate correct medication technique based on standard evaluation (Press, 2011) after completion of a standard teaching protocol.

Press VG, et al. Misuse of respiratory inhalers in hospitalized patients with asthma or COPD. *J Gen Int Med.* 2011; 26: 635-642.

23.3 * How, when, where and by whom potential subjects will be approached:

Subjects who are patients of 6M clinic will be screened initially utilizing electronic clinical works (eCW) or LCR at SFGH. Children with asthma are frequently seen in the 6M clinic and as such, we will work with nursing/clinician assistance to identify families who may meet the study criteria and approach them to discuss the study while they are waiting for their physician. Study staff will identify potential subjects in the clinic schedules via a brief screen of the electronic medical record for wheezing/asthma symptoms and medication history. The potential subject will be approached for screening during clinic visits with the permission of the physician in direct care with the patient. If the patient agrees to be screened, they will be asked about the child's wheezing/asthma history and given more information about the study and study personnel will follow up with the patient via telephone. If the patient is not eligible, they will be asked if they would like to be contacted for future research studies. Letters will also be sent to potential subjects who have previously given consent to be contacted for participation in research or who have been identified through medical records as potential subjects.

23.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

(•) Yes ( ) No

24.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

24.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

24.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

24.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

24.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [x] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

24.5 * Describe any health information that will be collected prior to obtaining informed consent:

Prior to informed consent, the patient's medical record may be reviewed to screen if eligible per inclusion and exclusion criteria. Demographic information, medication lists, problem lists, medical history, and progress notes may all be reviewed for eligibility purposes.

Note: HIPAA requires that you collect the minimum necessary.

24.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the

research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

Once the study has concluded, the data will be analyzed and results will be submitted for publication. Once a research paper has been approved for publication, the identifiers will be destroyed and only unique codes will be retained.

25.0 Informed Consent

25.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [ ] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [ ] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

25.2 * Process for obtaining informed consent:

Once potential eligible participants for the study have been identified and they meet inclusion criteria, the process of informed consent will begin. The process of consenting the patient's guardian will occur in Spanish in designated study areas at San Francisco General Hospital. Designated areas will include the Children's Health Center, Investigators' offices or private conference rooms. Once consented, all participants and their guardian will receive a copy of the consent form in Spanish along with the Experimental Subject's Bill of Rights in Spanish.ights to keep.

25.3 * How investigators will make sure subjects understand the information provided to them:

Investigators will consent all participants and their guardians in Spanish and provide all study materials in Spanish. Materials in English will be translated into Spanish using a systematic approach.

26.0 Financial Considerations

26.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [ ] Subjects will not be paid
- [ ] Cash
- [ ] Check
- [ ] Debit card
- [x] Gift card
- [x] Reimbursement for parking and other expenses
- [ ] Other:

Specify **Other**:

26.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

Gift Cards of $20 will be given to each participant after completion of a study visit. Study subjects can receive up to $80 if they complete 4 visits.

26.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

○ Yes ◉ No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

27.0 CTSI Screening Questions

27.1 * This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites:

- **SFGH Clinical Research Center**
- **Moffitt Adult Clinical Research Center**
- **Moffitt Hospital Pediatrics & NCRC**
- **Mount Zion Hospital Clinical Research Center**
- **Tenderloin Center**
- **CHORI Children's Hospital Pediatrics & Adult Clinical Research Center**
- **Kaiser Oakland Research Unit**
- **SF VA Medical Center Clinical Research Unit**

Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

◉ Yes ○ No

27.2 This project involves community-based research:

○ Yes ◉ No

27.3 This project involves practice-based research:

○ Yes ◉ No

28.0 End of Study Application

28.1 End of Study Application Form **To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.**