I. Background and Significance

Many patients with asthma are not adherent with asthma treatment. The average medication adherence rate of children with asthma was found to be 48% in a review of ten studies (10); similar findings have been reported for adult patients (11, 12). A recent publication demonstrated that, in a cohort of 405 adults with asthma from a large HMO, overall adherence to ICS was approximately 50%. Even after a severe asthma exacerbation, adherence often does not improve. Patients with a visit to the emergency department for exacerbation of asthma only temporarily increased ICS adherence before quickly returning to baseline rates (13). Similarly, less than half of ICS prescriptions were filled after children were hospitalized for asthma (14). Poor adherence leads to inadequate asthma control. Under-utilization of ICS has been repeatedly linked to poor asthma control, reflected in increased symptoms, hospitalization, and asthma-related death (7-9).

Interventions to improve adherence have been at best only partially successful. Although numerous psychoeducational interventions have been designed to improve ICS adherence and treatment outcomes, few have been successful in changing patient behavior when tested in randomized trials. We reviewed 16 individual and group asthma management interventions ranging from one to many sessions over periods up to one year (15). In one, families were required to attend three separate educational workshops, and a “Family Coordinator” conducted two home visits, made a series of telephone contacts with families, and accompanied families to the physician’s office (16). Families reported improved asthma management but no objective adherence data.
were collected. In a second study, the intervention—consisting of three 1-hour sessions with an asthma nurse educator—did not alter electronically monitored ICS adherence (17).

Most prior adherence interventions were time-, labor-, and cost-intensive. For example, 221 adults with asthma were randomized into one of three groups: High intervention, Low intervention, or usual care (18). Despite receiving educational materials, a one-hour individualized asthma education session, monthly support groups, and follow-up telephone calls from a health educator, the High intervention group was undifferentiated from the Low intervention or usual care groups in medication use or on measures of respiratory illness, health care use, or functional status. A similar lack of treatment effect was seen in two additional studies with relatively high-level interventions involving at least 6 hours of education (19, 20). Two studies reported improvement in ICS adherence but not asthma control (21, 22). Hence, we propose a different approach to solving this important clinical problem.

We propose a practical, randomized clinical trial to test the impact of a health communication intervention designed to improve inhaled asthma controller medication adherence in 3-12 year old children with asthma in Kaiser Permanente of Colorado (KPCO), the largest health maintenance organization in the state. The Telecommunication Enhanced Adherence Management (TEAM) intervention is designed to increase communication with and support of pediatric patients and their parents by using automated telecommunication technology to: 1) allow parents more easy access to caregivers, 2) provide an immediate opportunity to request refills and inquire about their child’s symptoms, and 3) provide educational and motivating messages about the importance of the child’s daily asthma medication. This health-communication intervention will be delivered through state-of-the-art speech recognition (SR) technology. Advances in SR technology have made computer-generated conversation easier and more acceptable to respondents, and allow for correct interpretation of parents’ spoken responses that in turn can lead to a range of appropriate SR responses. The investigative team has extensive experience using automated telecommunication technology to promote health-enhancing behavior change. The Benefit-Risk Model and Social Marketing Theory continue to guide both the objective and process of the intervention. Prospect Theory complements these and will guide development of the motivating messages to be contained in the SR intervention. This will be a Practical Clinical Trial aimed at the entire population of KPCO parents of a child receiving an inhaled corticosteroid (ICS) for asthma. It is expected that a minimum of 12-month participation in the TEAM intervention will increase ICS refill persistence and medication adherence (primary outcome) sufficient to produce significant improvement, relative to the usual-care control group, in asthma-related health outcomes as reflected in frequency of urgent care visits, prednisone use, beta2-agonist use, and parent-reported symptom control and quality of life (secondary outcomes). A sub-study will randomly sample 200 families, both before and after participation in the TEAM intervention, to gather information about variables that may moderate the effectiveness of the intervention including race, socioeconomic status, illness severity, family structure, and benefit-risk perception. The presumption that
prescription refilling is an accurate measure of adherence will be tested in a second sub-study that will use electronic devices to track ICS adherence. This system-based intervention has been designed using the RE-AIM framework so that it should have high reach and be consistently implemented at modest cost, and if effective, it can be maintained within KPCO as well as readily exported to other clinical healthcare settings.

The intervention is expected to change parents’ benefits-risk perception and to increase ICS refills and adherence. It is not expected that this intervention will resolve the problem of poor adherence for all families, but that it will effectively increase ICS adherence in enough of the patient population of KPCO to produce clinically significant and measurable improvement, relative to the usual-care control group, in asthma-related health outcomes. Consistent with the RE-AIM model, if found to be effective this system-based intervention can be maintained within KPCO and can be adapted and introduced into other clinical settings.

Advisory Committee/Safety Monitoring. An Advisory Committee co-chaired by Dr. Cvietusa (Chief of Allergy) and including Dr. Ruby Kadota (Chief of Pediatrics) with at least 3 other KPCO care providers, will help oversee development of the TEAM intervention, scripting of core messages, and troubleshooting problems that may arise. The first responsibility of this committee will be to assure that patient safety and well-being are considered at every point of the program. The committee will be fully informed about results from focus groups, and will help to determine that this information is adequately considered in intervention development and implementation. They will also review any parent concerns or complaints that are registered through any communication mechanism including SR, phone calls, and comments relayed to caregivers, pharmacists, or other KPCO staff. The committee will review recruitment numbers, including number of refusals, and help to generate solutions to any problems that may arise through the course of the study. Finally, the committee will gather input from pediatricians and allergists to foster a positive relationship between study personnel and physicians.

Staff orientation and training. KPCO pharmacists, nurses, asthma care managers, call center and administrative staff will receive a general communication informing them about the TEAM study. The asthma care managers will additionally attend a minimum of 6 hours of orientation, training, feedback, and problem solving sessions during the development phase. KPCO adopts new programs on a continuing basis to improve patient care, and hence innovations to existing patient management procedures are generally well accepted.

Physician involvement. All KPCO pediatricians and allergists will receive information about the TEAM intervention during regularly scheduled department meetings. Physicians will co-sign the initial introductory letter, and a second letter to parents 12 months after randomization. Finally, physicians will be informed about the information that will appear in each patient’s EMR following an SR intervention.

The TEAM staff represents a broad interdisciplinary mix of researchers with expertise in medication adherence, asthma care, behavioral science, health services research, internal medicine, health care delivery systems, pharmacology, qualitative methods, and biostatistics. As the proposed study builds logically on their prior research, they are particularly well-suited to carry out this investigation. The KPCO and NJMRC researchers have met regularly to plan this project and have forged an excellent working relationship. Drs. Bender, Wamboldt, Rand, and Vollmer have all worked...
together on different projects in the past and have established a productive relationship as well. Drs. Russ Glasgow, Sarah Hampson, and Debra Ritzwoller have also joined this project, each bringing new expertise. Finally, Drs. Vollmer and Rand have worked with Eliza Corporation in a previous project using SR technology to communicate with adult patients with asthma. Dr. Magid and colleagues at KPCO have been at the forefront of the conduct of system-level practical clinical trials.

Phase 1 focus groups will be conducted by Corona Research. They were selected because of their highly qualified facilitators and staff, excellent recommendations from CDPHE and established successful records in conducting health-related focus group research. Contracts, Business Associates Agreements, and any other required agreements will be completed before focus group activity is started. Phase 2 focus groups will be conducted by staff at NJMRC.

The 1 year completion surveys will be administered by Anderson, Niebuhr & Associates, Inc. Anderson-Niebuhr has over 25 years experience in survey administration and is a preferred Kaiser vendor working with Kaiser Permanente on over 125 different projects across all regions. In addition, they take great efforts in protecting the security and privacy of our patients’ information.

Eliza Corporation Applications of SR in Health Care Settings. Eliza Corporation has extensive SR experience and works exclusively in the area of patient communication within healthcare systems. In the past six years, Eliza has had over 100 million health-related “conversations” with members and healthcare consumers and currently works with healthcare consumers in all 50 states, the District of Columbia, and Puerto Rico. Eliza is currently engaged and successfully interacts with diverse populations including regional and ethnic groups, young and healthy adults, and aging seniors challenged with co-morbid conditions. Eliza has conducted SR programs that have included Medicare and Medicaid populations, seniors, parents of children needing immunizations, patients with chronic diseases, and low-income, uninsured communities. In one program, Eliza reached out to over 86,600 health plan members nationwide, with a concentration in the Southeast, to promote follow-up diabetes care. SR calls resulted in a member making a follow-up appointment (50%) significantly more frequently that when members were contacted by live phone calls (33%). In another project, flu vaccination calls were markedly more successful when conducted by SR. In this program, Eliza reached out to over 8,000 households in Newark, New Jersey as part of a State of New Jersey sponsored effort. The outreach, which included many Medicaid beneficiaries, demonstrated a significant increase in immunization rates among children 19-36 months old, over a one year period. Further, significantly more patients obtained flu shots when contacted by SR (58%) than by mail (50%) or by live call (50%).

This project was submitted to NHLBI of the NIH for a five year funding grant, and the project will be a collaboration between National Jewish Medical and Research Center and KPCO.

2. Hypothesis and Objectives
We will conduct a randomized practical clinical trial to test a theory-driven, system-based (as opposed to clinician-based) intervention designed to improve adherence to daily asthma medications and thereby improve asthma outcomes.

As the activities in Phases 1 and 2 focus on information gathering, there are no hypotheses directly related to these efforts. The information gathered will be used towards the Phase 3 intervention, and will relate to the intervention hypotheses below.

Primary Hypothesis:
1. Adherence with ICS medications in the TEAM intervention group will be greater than in the usual care group.

Secondary Hypotheses:
2. The TEAM intervention will result in a decrease in asthma symptoms as reflected in reduced beta<sub>2</sub>agonist use, and a decrease in non-routine, asthma-related health care visits when compared to the usual care group.
3. Parents in the TEAM intervention group will report greater improvement in symptom control, quality of life, and satisfaction with their child’s asthma care than parents in the usual care group.
4. Parents in the TEAM intervention group will report a larger positive change in perception of medication benefit than parents in the usual care group.
5. Characteristics of the patients and their families, including illness severity, duration of illness, age, race, language preference, socioeconomic status, and benefit-risk perception, will act as moderating variables influencing response to the intervention.
6. Adherence with ICS medication in the TEAM intervention group will continue to be greater than in the usual care group over a 2 year time period.

3. Study Methods:
   3.A. Study Description

We propose to conduct a randomized, practical clinical trial to test the impact of a communication enhancement program for parents of 3-12 year old children with asthma in the largest health maintenance organization (HMO) within Colorado. Research in this setting has the significant advantage of not only establishing the utility of a behavior-changing strategy, but at the same time demonstrating that the strategy can be applied in a large healthcare system and sustained over time. The proposed intervention will be referred to here as the Telecommunication Enhanced Adherence Management (TEAM) program. This proposal builds upon ongoing efforts within Kaiser Permanente of Colorado (KPCO), the participating HMO, to use automated telecommunication technology to prevent diabetes, reduce cardiac risk, reduce calorie consumption, and increase exercise adherence, with the introduction of an intervention to increase adherence with daily ICS therapy. Speech Recognition (SR), the telecommunication technology used in this trial, has not previously been employed to promote adherence in a population of children treated for asthma within a large HMO. TEAM creates a theory-based enhanced communication program using SR with support from asthma care manager nurses. The Asthma Care Manager program already exists within KPCO, but with SR the frequency and quality of communication with parents is expected to improve significantly, resulting in more ICS medication refills, better persistence in ICS use, and improved asthma outcomes. Through SR calls, parents will be reminded and motivated about the importance of continued daily use of ICS medications, asked about their child’s recent asthma symptoms, and given the opportunity to receive a call back from an asthma care manager or to place a request for a medication refill.
Telecommunication Enhanced Adherence Management (TEAM) is a five-year project that will plan, execute, and evaluate the impact of an innovative approach to improving medication refilling and consequently treatment outcomes for children with asthma in a large healthcare system. It draws on Benefit-Risk Perception, Prospect, and Social Marketing theories to create tailored and targeted health communication messages.

All parents of 3 to 12 year old children who are KPCO members, diagnosed with asthma, and for whom a daily ICS has been prescribed, are eligible to participate, for all three study phases. The TEAM intervention is aimed at parents because they have the primary responsibility of filling prescriptions and supervising medication administration to their children of these ages. Quality improvement efforts at KPCO have documented that over 99% of pediatric patients with persistent asthma are prescribed an ICS. Parents will be randomized to receive either usual care or the TEAM intervention to increase ICS adherence in their children. Randomization will be at the level of individual children. The Intervention group will receive SR communication directed to the parents, linking them as needed to asthma care managers or the medication refill system at KPCO. Those parents in the Usual Care group will receive the existing asthma care program at KPCO including access to the full complement of existing disease management resources, e.g., asthma care managers, but without the SR intervention. Since asthma often runs in families and the potential increased number of telephone calls resulting from enrollment of multiple children may be annoying to families and prevent accurate assessment of the impact of the SR intervention as designed, only one child from any household will be enrolled. Home address and subscriber ID will be the data fields used to define family membership. We estimate that only 4.6% of the available KPCO pool of potential participants reside in the same household; excluding half of these (2.3%) will have little impact on data analyses.

During phase 1 and 2 of this study, efforts will be focused on developing the SR system to have maximal utility and usability. Utility means that users can get what they desire out of the system. Usability refers to the ease-of-use of the system. For optimal results both are key as most users will not keep using a system that does not meet their needs, no matter how easy to use the system is, and conversely, most users will not persist with a system that is too complex and frustrating, even if great results are promised at the end of the struggle. Two complementary methods will be employed during the SR refinement stage: focus groups and user testing.

Parent focus groups will be conducted at two time points in development, first before any intervention is scripted (Phase 1), and second to review the intervention as it is developed (Phase 2). Focus groups are an important tool for investigating how people conceptualize, experience, and talk about health issues, and for exploring barriers to performing health protective behaviors. Focus groups capitalize on group dynamics and allow a small group of respondents to be guided by a skilled moderator into increasing levels of focus and depth on the key issues of the research topic. The use of focus groups allows the researcher to observe first-hand the reaction of respondents representing the target group to receive the intervention. Focus groups will be conducted by Corona Research in partnership with National Jewish and KPCO.

Phase 1. Development of SR messages to change a parent’s perception of the benefits of ICS medication and risk of the illness.

The first phase of the project will be devoted to defining the health communication messages and developing components of the intervention and measurement capabilities. Following guidelines drawn from the aforementioned health communication
theories, initial steps will include evaluating the knowledge, attitudes, and behaviors we wish to change, with particular emphasis on using gain-framed messages to change parental benefit-risk perceptions in relationship to ICS. KPCO pediatricians, allergists, and asthma care managers will be engaged for insights into parent understanding and attitude based on their patient interactions. The advisory committee, comprised of KPCO asthma caregivers, will also provide essential input in this phase (see description of advisory committee below). Additionally, our experiences from conducting the related studies will help to design the intervention.

The purpose of the two to five focus groups in Phase 1 will be to explore (a) the parents’ illness representations for their child’s asthma, (b) their beliefs about the use of controller medication, and (c) parental reactions to some preliminary gain-framed, affectively positive message content developed by the research team from leading health communication theories. These topics will be addressed by guided group discussion. We will consult frequently with our consultants Drs. Hampson, Glasgow, Rand, and Vollmer to help create the theory-driven health communication messages and the SR design during this process. Also in this phase, we will collaborate with the KPCO asthma care managers to develop systems of communication between them and the SR system. The asthma care managers will be the primary link between the SR outreach and parents who request or require additional assistance or information. Orientation, training, and practice sessions will occur primarily with these asthma case managers. Other caregiver groups, including physicians, nurses, and pharmacists, will receive one hour of orientation to the TEAM program in order to help them to understand the program. Finally, we will be working with the Eliza Corporation, a firm with extensive SR experience, to develop a HIPAA-compliant SR system addressing the specific requirements of the KPCO population and objectives of this study.

At the conclusion of phase 1 focus groups, a round of user-testing will be implemented using an existing SR intervention currently being utilized in other Kaiser Permanente regions. This will allow the study team to gather feedback about the call’s ease of use, flow logic, efficiency, and helpfulness before the initial SR intervention is designed.

Script content will be written following the Phase 1 focus groups and user-testing, as described above. One advantage of this intervention program is that it is almost entirely over the telephone and therefore reading skill is not an issue. Nonetheless, vocabulary content for the SR calls will target a 6th grade level, and caution will be exercised to assure that we employ "plain language" (see www.plainlanguage.gov) that does not requires a higher level of health literacy.

Phase 2. Testing and refining the intervention to be implemented.
A second set of parent focus groups will be conducted to gather responses to the scripted messages, and to determine whether parents believe these gain-framed messages will change perceptions and ICS adherence behavior. Once the SR intervention is further refined, in the user-testing phase it will be piloted on a sample of up to 50-100 consecutive parents of patients receiving an ICS prescription, responses will be evaluated, and adjustments consequently will be made to the intervention.
Regular meetings with the asthma care managers and teleconferences with Eliza representatives will be used to review experiences during the pilot phase, to examine any problems that may have occurred, and to seek input about refinement of the TEAM intervention. Final changes to the intervention will be completed during the second year of the study, following which in Phase 3 recruitment, randomization, and implementation of the intervention will begin.

In Phase 2, numerous SR messages developed on the basis of both theory and feedback from Phase 1 focus groups and user testing will be presented to two to five focus groups for their reactions. In Phase 2, parents will first rate the messages independently for how motivating and how affectively positive they are perceived to be, followed by a group discussion about how the messages could be improved. These focus groups will also provide an opportunity for parents to give feedback on other intervention materials and procedures.

Once the SR scripts have been modified based on feedback from the focus groups, we will begin user testing activities in Phase 2 to get detailed information about how successfully end-users can navigate and get the results they desire from the SR system (75, 80). An iterative process will be employed during user testing (77). In brief, for each new “version” of the system, up to 15 users will be asked to “think aloud” as they use the SR system. The key issue here is to observe and listen to the users without helping them in the process. Based on the one-on-one observations of and feedback from these users, the SR design team will modify the system versions until a panel of 5 users suggests that we have “gotten it right.” We expect that user testing will require from 2-6 iterative testing and refinement cycles.

**Phase 3. Randomization, recruitment, and data collection** will begin in the third year. Two sub-studies (Intervention Moderators and ICS Adherence) will also be initiated at this time. Parents will be enrolled up until month 42 in order to be able to complete a minimum of 12 months participation and outcome measurement for all patients. The fifth and final year will include completion of the intervention at the 54-month point followed by compilation and assessment of data. The cost analysis data, collected throughout the trial, will begin in this phase. The primary outcomes will be the continuous measure of medication acquisition (CMA) and the continuous measure of medication gaps (CMG) (75). Other outcomes will include assessment of beta_2_agonist use and emergency department visits, hospitalizations, and oral steroid bursts.

The first 6 months of Phase 3 will consist of field live testing with up to 300 parents. This means that up to 150 families will be randomized to receive the intervention. As part of the phase 2 user testing protocol, a random selection of these parents will be called by research staff to gather feedback about the call’s ease of use, flow logic, efficiency, and helpfulness before the full SR intervention is implemented. This field live test is a standard procedure which has been used in similar research studies using SR technology.
Parents randomized to the intervention will receive a welcome letter and brochure prior to their first SR call or message. The letter and brochure will let the parent know they have been randomly assigned to the SR intervention, confirm we have their correct phone number, further explain the SR intervention and provide study staff contact information in case they have questions or do not wish to participate. Three SR call types will be used for the intervention: (1) Welcome call, (2) Basic refill reminder, and (3) Tardy refill reminder. In total participants will receive 3-12 SR phone calls or phone messages lasting approximately 1-3 minutes each during a 12 month period. The goal of the calls and messages is: (1) remind parents to refill their child’s ICS prescription, (2) assist parents in refilling their child’s ICS prescription, (3) Help answer parent questions about their child’s asthma medicine by offering a call back from an ACM, and (4) Provide tips to parents on what controlled asthma looks like and how they can keep their child breathing as freely as possible. In addition to the SR calls, new users to ICS and patients who are past due in refilling current ICS prescriptions will also receive a call from an ACM. Furthermore, those patients who have requested a refill of their ICS prescription as a result of the intervention but have not picked it up within 7 days will receive a reminder call to do so at the pharmacy of their choosing.

Upon completion of one year in the study, intervention participants will receive a survey administered by Anderson, Neibuhr and Associates, Inc. The survey will look at:

1. the patient’s opinion about the program (i.e., did they like it, why or why not, what suggestions for changes do they have)
2. life circumstances that predict response to the intervention (beliefs about medications, social support, life stress, and personal demographics)

To measure the sustainability of the program, data will be collected on participants for an additional year, making enrollment in the study last for 2 years. Intervention participants will be re-consented for an additional year to allow them an opportunity to opt-out if they no longer desire to participate. Control patients’ lack of active involvement in the study and minimal risk for the data to be collected will not be re-consented for the additional year of data collection. See section 3E for more details on the consenting process.

Phase 4. Data analysis and preparation of the final report will be completed in the final 6 months of this proposed study. This phase will include evaluation of the program and recommendations for future refinement. Evaluation of the program will include assessment of refill behavior, disease control, quality of life, and parent satisfaction. Information learned about variable response to the intervention based on patient and family characteristics will guide future refinements of the SR intervention. Also included will be an assessment of whether baseline benefit-risk perception influenced receptiveness to the intervention, and whether the intervention altered parents’ benefit-risk differential score. Dr. Glasgow will help to evaluate the reach, adoption, and system impact of this public-health oriented, system-based program using the RE-AIM model.

Sub Studies
Two sub-studies (Intervention Moderators and ICS Adherence) are planned and will be elucidated when the sub studies protocol is submitted and reviewed by the IRB. No sub study activities will begin before IRB approval.

Assessment of generalizability and translatability to other health care systems. Glasgow’s framework (RE-AIM) (46) to evaluate interventions to determine the translatability of health promotion interventions includes five dimensions that will be employed here. First, Reach – the absolute number, proportion, and representativeness of those who participated in the intervention compared to the target population. Reach is also an evaluation component of SMT and will be assessed here as the degree to which eligible parents agree to participate in the project. We will also compare the characteristics of eligible persons who agree to participate to those who do not agree to participate. Second, Effectiveness – the success in promoting the study goal. Effectiveness will be assessed by evaluating study outcomes as described above. Third, Adoption – the absolute number, proportion, and representativeness of settings from organizations that subsequently use the intervention. Because KPCO physician and health plan leaders have already indicated their broad support of this project, we anticipate that eligible parents of all KPCO clinics and physicians will participate – that is, we expect adoption to be 100%. However, we will confirm whether this occurs and to the degree that it does not we will compare the characteristics of the clinics and or physicians who do and do not have parents participating. Fourth, Implementation – the practitioners' fidelity to the intervention’s protocol. We will assess both technical performance and asthma care manager performance. Measures of the technical performance include the SR system reliability and acceptance by participants. Measures of asthma care manager and pharmacist performance including completeness of documentation in the electronic medical record and ability to respond to requests from intervention participants in a timely manner (e.g. for advice or medication refills). Finally, Maintenance – the level of sustained individual behavior and organizational use of the intervention over time. To assess the maintenance or decay of the intervention we will track the measures of implementation at 3, 6, 9, and 12 months after intervention onset, including system reliability and asthma care manager and pharmacist performance.

3.B. Target Population

**Inclusion criteria for Phases 1, 2 and 3:**

- Parents of children 3-12 years old
- Diagnosis of asthma for child by a KPCO physician
- Children receiving a new or renewed prescription for an ICS
- Parents do not actively opt-out during an offer to participate in activities
- Parent of child speaks fluent English

All parents of 3 to 12 year old children who are KPCO members, and have been diagnosed with asthma, and for whom a daily ICS has been prescribed, are eligible to participate, for all three study phases.
This proposed study will include children and their parents/guardians (both male and female adults). The intervention is directed to the parent, while the consequence of the intervention is directed to the child.

We cannot include Spanish-speaking participants. Although KPCO provides Spanish-speaking physicians, in 2005 less than 1% of adult members (0.7%) required a Spanish-speaking provider or translation services. All KPCO members who are identified as needing translation services will be excluded from the study in order to prevent any non-English speakers from receiving recruitment letters and any subsequent intervention phone calls.

We have chosen not to include adolescent-age children in this study largely because we believe that any intervention with this age group should include the adolescents as well as parents. SR with adolescents will require careful development and testing that may need to include age-specific branching. Therefore, we view such intervention as a future but not a present possibility. Similarly, SR may be used directly with younger children in the future, but we believe further development and careful piloting will be needed first.

Presently, approximately 3000 children with asthma, 3-12 years old, are eligible to participate. The TEAM intervention is aimed at parents because they have the primary responsibility of filling prescriptions and supervising medication administration to their children of these ages. In phase 3, participants will be randomized to receive either usual care or the TEAM intervention at equal levels to increase ICS adherence. Randomization will be at the level of individual patients.

The intervention is directed to the parent, while the consequence of the intervention is directed to the child. We anticipate that the gender distribution of the study sample will be proportional to that of the health plan region as a whole. Previous studies at KPCO have succeeded in including race and gender groups reflecting the overall KPCO population. We expect a random distribution of SR patients among providers and anticipate that the gender characteristics of the participants will closely mirror those of the KPCO population. Thus, the proportion of men and women in the sample should be fairly comparable. Based upon our preliminary studies approximately 24% of those patients who will be eligible to participate are from minority racial or ethnic groups.

3.C. Identification and Screening Methods

We request a waiver of HIPAA privacy rule authorization to allow for the use of PHI for identification of potential study participants. All parents of 3 to 12 year old children who are KPCO members, and have been diagnosed with asthma, and for whom a daily ICS has been prescribed, are eligible to participate, for all three study phases.
For each phase of the study, eligible KPCO members will be identified through query of KPCO databases (clinical, pharmacy, administrative) by IHR programmers and analysts. No further screening is required to determine eligibility, and no clinic tests are required as a part of the baseline data collection. Therefore, all eligible individuals who are identified by this review and do not decline the invitation to participate will be enrolled in the study and analyzed on an intention-to-treat basis, i.e., outcome data on patients whose parents drop out of the program will be included in the analyses.

3.D. Recruitment Methods

Focus groups in Phase 1: In-person focus group participants will be KPCO parents or guardians of a child with asthma prescribed a daily inhaled corticosteroid, who will be recruited by a letter signed by their child’s primary care physician or allergist. The KPCO Principal Investigator will contact providers with eligible parents of patients by phone or in person to inform them of the project. Each provider contacted will be given a list of names of parents of their patients identified through the registry who are potential focus group subjects. They will also be given recruitment letters for each individual on the list. Study team staff will ask each provider to approve parents from the list would be appropriate for recruitment for the focus groups by signing the letters to those individuals. The medical providers have been asked to sign these letters to add credibility to them and address any HIPAA requirements for presence of a treatment relationship to the child. The KPCO study team will send out this recruitment letter in waves according to focus group dates to all the subjects deemed appropriate by the medical providers. The recruitment letter will contain a postage paid postcard that the subjects can send back if they do not wish to be contacted for recruitment. Corona Research and/or KPCO staff will conduct follow-up phone calls to recruit and schedule those subjects who are interested in participating. Contracts, Business Associates Agreements, and any other required agreements will be completed before focus group activity is started. The sample, letters and conference room scheduling will be under the control of KPCO project staff.

Two to five groups will be conducted in Phase 1, dependent on the overall quality and amount of input. Up to fifteen participants will be recruited for each group, anticipating that 6 to 12 people will attend a focus group. Written informed consent, including permission to videotape the session, will be obtained from all participants, and the groups will be held at KPCO facilities. Participants will be given a $50 grocery gift certificate for their time and expense. The groups will last no more than 90 minutes and will be led by a moderator assisted by an observer. The moderator will use a topic guide and probe questions to direct discussion and ensure all issues are covered.

User-testing in Phase 1: Phase1 focus group attendees who expressed interest in participating in future TEAM study focus groups and/or user-testing will be recruited by phone and asked for their verbal consent to participate. Those who agree will to listen to a PEANUT study phone call while on the phone with a KPCO staff member and asked for their feedback. The PEANUT phone call is part of an SR intervention currently being
used in KP-NW and KP-Hawaii and is aimed at increasing medication adherence in adults diagnosed with persistent asthma. Participants will be asked to imagine that the call is referring to their child's asthma. After they listen to the call they will be asked questions about the call's ease of use, efficiency, flow logic and helpfulness. The total length of the call will last approximately 10-15 minutes. The participant feedback obtained from these calls will give project staff at NJMRC, KPCO and Eliza valuable input from parents before the initial phone intervention is designed and tested in phase 2.

**Focus groups in Phase 2:** In-person focus group participants will be KPCO parents or guardians of a child with asthma prescribed a daily inhaled corticosteroid, who will be recruited by a letter signed by their child's primary care physician or allergist. The KPCO Principal Investigator will contact providers with eligible parents of patients by phone or in person to inform them of the project. Each provider contacted will be given a list of names of parents of their patients identified through the registry and/or pharmacy records who are potential focus group subjects. They will also be given recruitment letters for each individual on the list. Study team staff will ask each provider to approve parents from the list who would be appropriate for recruitment for the focus groups by signing the letters to those individuals. The medical providers have been asked to sign these letters to add credibility to them and address any HIPAA requirements for presence of a treatment relationship to the child. The KPCO study team will send out this recruitment letter in waves according to focus group dates to all the subjects deemed appropriate by the medical providers. The recruitment letter will contain a postage paid postcard that the subjects can send back if they do not wish to be contacted for recruitment. Corona Research and/or KPCO staff will conduct follow-up phone calls to recruit and schedule those subjects who are interested in participating. Contracts, Business Associates Agreements, and any other required agreements will be completed before focus group activity is started. The sample, letters and conference room scheduling will be under the control of KPCO project staff.

Two to five groups will be conducted in Phase 2, dependent on the overall quality and amount of input. Up to fifteen participants will be recruited for each group, anticipating that 6 to 12 people will attend a focus group. Written informed consent, including permission to videotape the session, will be obtained from all participants, and the groups will be held at KPCO facilities. Participants will be given a $50 grocery gift certificate for their time and expense. The groups will last no more than 90 minutes and will be led by a moderator assisted by an observer. The moderator will use a topic guide and probe questions to direct discussion and ensure all issues are covered.

**Phase 2 user-testing activities:** Once the SR scripts have been modified based on feedback from the focus groups, we will begin a user testing phase. Participants in this stage will be randomly selected among eligible parents who will receive an invitation letter signed by their child’s primary care physician or allergist. The KPCO Principal Investigator will contact providers with eligible patients by phone or in person to inform them of the project. Each provider contacted will be given a list of names of parents of their patients identified through the registry who are potential focus group subjects.
They will also be given recruitment letters for each individual on the list. Study team staff will ask each provider to approve parents from the list would be appropriate for recruitment for the focus groups by signing the letters to those individuals. The KPCO study team will send out this recruitment letter in waves according to focus group dates to all the subjects deemed appropriate by the medical providers. The medical providers have been asked to sign these letters to add credibility to them and address any HIPAA requirements for presence of a treatment relationship to the child. The recruitment letter will contain a postage paid postcard that the subjects can send back if they do not wish to be contacted for recruitment. A member of the KPCO study team will then conduct follow-up phone calls to recruit those subjects interested in participating.

If interested, participants will call study staff or will express interest in participating when called by study staff, and receive an incentive of a $25 grocery gift certificate to listen to calls over the phone and provide feedback. An iterative process will be employed during user testing (77). In brief, for each new “version” of the system, up to 15 participants will be asked to “think aloud” as they use the SR system. The key issue here is to observe and listen to the users without helping them in the process. Based on the one-on-one observations and feedback from these users, the SR design team will modify the system versions until a panel of 5 users within a cycle suggests that we have “gotten it right.” We expect that user testing will require from 2-6 iterative testing and refinement cycles.

**Phase 3:** Eligible KPCO members will be identified through query of KPCO databases. No further screening is required to determine eligibility, and no clinic tests are required as a part of the baseline data collection. Therefore, all eligible individuals who are identified by this review and do not decline the invitation to participate will be enrolled in the study and analyzed on an intention-to-treat basis, i.e., outcome data on patients whose parents drop out of the program will be included in the analyses. Home address and primary subscriber ID will be used to ensure that no more than one child per family will be included in this project.

Parents will be recruited by a letter signed by their child’s primary care physician, allergist, or another KPCO physician such as the department heads of family medicine and pediatrics. Study staff will contact providers of eligible patients to inform them of the project. Each provider contacted will be given a list of patient names identified through the registry and/or pharmacy records whose parents are potential study participants. Study team staff will ask each provider to approve patients from the list who’s parents they feel would be appropriate to recruit for the study. The approval of this is designed to address any HIPAA requirements for presence of a treatment relationship to the child.

The KPCO study team will send out this recruitment letter in waves as subjects become eligible and are deemed appropriate by the medical providers for participation in the study. The letter will indicate that the parent have a 50% chance of receiving 3-12 computerized phone calls or messages in the coming year. The recruitment letter will contain a postage paid postcard that the subjects can send back if they do not wish to
participate. There will also be a phone number listed for parents to contact study staff with questions or to indicate that they do not wish to participate.

Lack of a receipt of an opt-out phone call or postcard will be taken as evidence of implicit consent to participate in the study and will result in random assignment to the intervention or the usual care group. Any parent indicating that they do not wish to participate will not be re-contacted and will not receive any SR calls.

The recruitment strategy for the Phase 3 sub-studies will be elucidated when the full Phase 3 activities protocol is reviewed by the IRB.

Intervention participants will be contacted at completion of their original consent agreement of one year participation. They will be sent a newsletter with a study update and a request to continue participation in the study for an additional year. They will be given a phone number to call with questions or to opt-out of continued participation as well as an opt-out postcard to send back to the study team to be removed from continued participation in the study.

Survey: After completion of 1 year in the study, all intervention participants will be contacted to complete a survey administered by Anderson-Niebuhr. The survey will be sent with a letter explaining the survey questions and procedures. Participants will have an opt-out option and will be removed from the recruitment list if they send the postcard back. Anderson Niebuhr will mail reminder postcard to participants who have not sent back the survey after 10-14 days. After another 10-14 days a second mailed survey will be sent to participants. If the mailed surveys are still not returned phone contact will be made with participants to encourage them to return the mail survey or complete the survey over the telephone. After all 8 attempts have been exhausted, or the participant declines to participate, the participant will no longer be contacted.

3.E. Informed Consent Process and HIPAA Authorization

Focus groups in Phases 1 and 2:
For the in-person focus groups in Phases 1 and 2, written consent will be obtained from each participant. This written consent will include permission to videotape the session and the groups will be held at KPCO facilities. Consent will be required of all in-person focus group participants in Phases 1 and 2. Study team members will complete the informed consent process with each participant upon arrival at the focus group session. The study purpose will be explained in detail in an unhurried, non-coercive manner. Once study staff has reviewed the consent form with the participant, they will ask the participant to explain the purpose of the focus groups in their own words and answer any questions a participant has. At the conclusion of the session, participants will be given the option to sign-up to receive another invitation to participate in a later focus group and/or user testing call. It will be explained that this is their choice and they will only be invited back if needed. As with the initial focus group invitation, they will be given the option to opt-out when they receive the recruitment letter and phone call.
All signed hard copies of the consent forms will be kept in a locked cabinet by study staff at KPCO IHR. All study staff responsible for obtaining consent are IRB certified. KPCO staff will reserve and physically prepare the focus group locations for each session, and will remain outside the room during the session to answer any questions. Within a phase, all focus groups or one-on-one sessions will have the same content. Changes to focus group topics will be made only when progressing from Phase 1 to Phase 2.

New and repeated participants may take part in each phase of the feedback process. A single participant may participate in more than one feedback session (focus groups or user testing.) if they express interest in doing so.

**User testing in Phase 1 and 2:**
For the telephone-based user testing activities in Phase 1 and 2, verbal consent will be obtained from each participant over the phone.

**Intervention in Phase 3:**
The initial recruitment letter to parents will cover all of the elements of consent, including the fact that participation is voluntary and that refusal to participate will not affect their health plan eligibility or the care that they receive from KPCO. Additionally, a study brochure and introduction letter will be sent to all parents randomly assigned to the intervention before any SR calls are made. These documents will re-enforce the voluntary nature of the study, further explain the intervention and provide another opportunity for parents to opt-out of the intervention by contacting study staff. Parents electing not to participate in the calls at that point will still be included in the analysis on an intention-to-treat basis. Indeed, unwillingness to participate in the calls is an important measure of reach and impact.

This system-based intervention employs a consent process different from that used in most clinical trial research. Individual recruitment and signed consent is not possible, and the effect of a system-wide intervention cannot be tested on a small subset of volunteers. Nonetheless, we believe the informed consent process does give parent ample opportunity to decline participation; after receiving the initial recruitment letter, introductory intervention and brochure, and during every SR telephone call. This informed consent process has been employed previously in research at Kaiser Permanente. On the issue of child assent, assent is not warranted as this project does not have any intended direct contact with any child, only the child’s parents. The SR system will simply reinforce the prescribed therapies that the child is expected to follow, under their parent’s direction and the care of the child’s physician. During the process of preparing this application, the investigative team has held meetings with the IRB/HRPPP administrators at both KPCO and NJMRC. The two administrators have met for discussion.

To continue participation in the study for an additional year, the intervention group will be sent a newsletter with a study update and a consent agreement. This second consent will use the same language and elements of the originally approved IRB
consent form for this study. It will remind participants what the study entails and allow participants to opt-out of continued participation in the study by sending back an opt-out postcard or calling the study phone line where they can also ask any questions about the study. Like the original consent, if they do not opt-out, their enrollment will continue for up to one additional year.

Since control participants had no active participation in the study during the year they were enrolled, and since the original recruitment letter indicated that if the participant would be randomized to the control group they would not be contacted by us again, we request a waiver of HIPAA authorization for the control group’s continued participation of up to one additional year. Due to the low level of risk, lack of active participation, and their initial consent showing willingness to participate, we feel this continued collection of data will not put any burden on the control participants, whereas contacting this group may. We feel contacting the control group to consent them for an additional year will cause confusion and create an undo burden.

The consent process for the Phase 3 sub-studies will be elucidated when the full Phase 3 activities protocol is reviewed by the IRB.

Survey:
Similarly to the approved consent above, the letter sent to all intervention participants after 1 year in the study will cover all of the elements of consent, including the fact that participation is voluntary and that refusal to participate will not affect their health plan eligibility or the care that they receive from KPCO. Similarly to the letter covering all elements of a consent form, the phone contacts to complete the survey will also include all elements of consent which are outlines in the phone script. The caller will make sure the participant understands and agrees to participate before continuing with questions. Returning the survey or agreeing to respond to the survey questions on the call will indicate a participant’s consent. The participant will have an opportunity to opt-out of the survey if they do not want to participate. Since there is a very low level of risk, participants have already agreed to participate in the study, and the survey is getting feedback on the intervention they are part of, we don’t feel any additional consent is necessary.

HIPAA Authorization
We request a waiver of HIPAA privacy rule authorization to allow for the use of PHI for identification of potential study participants. All parents of 3 to 12 year old children who are KPCO members, and have been diagnosed with asthma, and for whom a daily ICS has been prescribed, are eligible to participate, for all three study phases. Additionally, the initial recruitment letter will indicate which PHI will be used during the SR phone calls and messages, namely patient asthma diagnosis and ICS medication name.

The proposed project will be overseen by both the National Jewish and KPCO IRBs. Discussions have been held conjointly with both IRBs, and an initial plan established. The KPCO IRB will serve as the primary IRB since all participants are from KPCO, with the NJMRC IRB ceding to the KPCO IRB. With the input of KPCO staff, the Eliza
Corporation and various consultants, NJMRC will take what is learned from Phases 1 and 2 to design core health messages and the phone system for the speech recognition program. Due to the high level of collaboration between NJMRC and KPCO study staff, KPCO study staff will coordinate communication with the KPCO IRB on issues pertinent to the study and NJMRC. All direct patient contact will occur at KPCO. Confidentiality agreements will be in place for all study staff between the NJMRC and KPCO once IRB approval is obtained.

3.F. Participant Compensation

Focus groups in Phases 1 and 2: Focus group participants in each phase will be given a $50 grocery gift certificate for their time and expense. The groups will last no more than 90 minutes and will be led by a moderator assisted by an observer.

Phase 1 User-testing: The total length of the user-testing call will last approximately 10-15 minutes and participants will be compensated with a $25 gift certificate for their time.

Phase 2 user testing:
The total length of each user-testing call will last approximately 10-15 minutes and participants will be compensated with a $25 gift certificate for their time.

Phase 3 Intervention:
There will be no participant compensation for phase 3 intervention activities. Participant compensation for sub studies will be elucidated when the sub studies protocol is submitted and reviewed by the IRB.

4. Study Procedures

4.A. Treatment, Intervention, or Observation
Telecommunication Enhanced Adherence Management (TEAM) is a five-year project that will plan, execute, and evaluate the impact of an innovative approach to improving medication refilling and consequently treatment outcomes for children with asthma in a large healthcare system. It draws on Benefit-Risk Perception, Prospect, and Social Marketing theories to create tailored and targeted health communication messages.

Intervention overview: The goal of the SR-based TEAM intervention is to increase adherence to ICS and consequently improve health outcomes. This represents a low-intensity, public health-oriented intervention consistent with the RE-AIM framework. It is designed for maximum generalizability, high patient adoption, and rapid implementation in the clinical setting. Because this is a system-based intervention, it is tested at the system level and all KPCO children meeting inclusion criteria are eligible to participate.
The TEAM intervention is a program to increase communication with families, provide feedback to families about their refill adherence, assess asthma symptoms, deliver health communication messages, encourage parents to ask questions of asthma care managers, and facilitate refilling ICS prescription. SR calls will be tailored to specific situations including new or re-issued ICS prescriptions, failure to fill an initial prescription, failure to refill, or failure to refill following an ED visit, hospitalization, or oral steroid burst resulting from an asthma exacerbation.

All parents of 3 to 12 year old children who are KPCO members, diagnosed with asthma, and for whom a daily ICS has been prescribed, are eligible to participate. The TEAM intervention is aimed at parents because they have the primary responsibility of filling prescriptions and supervising medication administration to their children of these ages. Quality improvements efforts at KPCO have documented that over 99% of pediatric patients with persistent asthma are prescribed an ICS. Participants will be randomized to receive either usual care or the TEAM intervention to increase ICS adherence. Randomization will be at the level of individual patients. The Intervention group will receive SR communication directed to parents, linking them as needed to asthma care managers or the medication refill system at KPCO. Those in the Usual Care group will receive the existing asthma care program at KPCO including access to the full complement of existing disease management resources, e.g., asthma care managers, but without the SR intervention. Since asthma often runs in families and the potential increased number of telephone calls resulting from enrollment of multiple children may be annoying to families and prevent accurate assessment of the impact of the SR intervention as designed, only one child from any household will be enrolled. Home address and subscriber ID will be the data fields used to define family membership. We estimate that only 4.6% of the available KPCO pool of potential participants reside in the same household; excluding half of these (2.3%) will have little impact on data analyses.

Parent focus groups will be conducted at two time points in development, first before any intervention is scripted, and second to review the intervention as it is developed.

**Phase 1. Development of SR messages to change a parent’s perception of the benefits of ICS medication and risk of the illness.** The first phase of the project will be devoted to defining the health communication messages and developing components of the intervention and measurement capabilities. Following guidelines drawn from the aforementioned health communication theories, initial steps will include evaluating the knowledge, attitudes, and behaviors we wish to change, with particular emphasis on using gain-framed messages to change parental benefit-risk perceptions in relationship to ICS. KPCO pediatricians, allergists, and asthma care managers will be involved to capture insights into parent understanding and attitude based on their patient interactions. The advisory committee, comprised of KPCO asthma caregivers, will also provide essential input in this phase and will review the content for the focus groups and provide input during script development. Additionally, our experiences from conducting the related studies will help to design the intervention. Following SMT guidelines, the focus groups will help us understand parents’ perceptions of their child’s
asthma and medications and what messages are likely to change attitudes and behavior. More specifically, the focus groups will allow an opportunity to test whether the gain-framed messages invoke a positive affective response to the potential gain from ICS. At the conclusion of phase 1 focus groups, a round of user-testing will be implemented using an existing SR intervention currently being utilized in other Kaiser Permanente regions. This will allow the study team to gather feedback about the call’s ease of use, flow logic, efficiency, and helpfulness before the initial SR intervention is designed. We will consult frequently with our consultants Drs. Hampson, Glasgow, Rand, and Vollmer to help create the theory-driven health communication messages and the SR design during this process. Also in this phase, we will collaborate with the KPCO asthma care managers to develop systems of communication between them and the SR system. The asthma care managers will be the primary link between the SR outreach and parents who request or require additional assistance or information. Orientation, training, and practice sessions will occur primarily with these asthma case managers. Other caregiver groups, including physicians, nurses, and pharmacists, will receive one hour of orientation to the TEAM program in order to help them to understand the program. Finally, we will be working with the Eliza Corporation, a firm with extensive SR experience, to develop a HIPAA-compliant SR system addressing the specific requirements of the KPCO population and objectives of this study.

The focus group content areas are provided in Appendix A.

Phase 2. Testing and refining the intervention to be implemented. A second set of parent focus groups will be conducted to gather responses to the scripted messages, and to determine whether parents believe these gain-framed messages will change perceptions and ICS adherence behavior. Following SMT guidelines, once the SR intervention is further refined, in the user testing phase it will be piloted by phone on a sample of parents of patients receiving an ICS prescription, responses will be evaluated, and adjustments consequently will be made to the intervention. Regular meetings with the asthma care managers and teleconferences with Eliza representatives will be used to review experiences during the pilot phase, to examine any problems that may have occurred, and to seek input about refinement of the TEAM intervention. Final changes to the intervention will be completed during the second year of the study, following which recruitment, randomization, and implementation of the intervention will begin.

Focus groups for Phases 1 and 2 will be held at the Arapahoe, Westminster, East, Skyline, Lakewood, and Aurora Centepointe clinics. For both the focus groups and user testing, each participant may participate in more than one feedback session if they express interest in doing so and is needed for the project. The KPCO Principal Investigator will contact providers with eligible patients by phone or in person to inform them of the project. Each provider contacted will be given a list of names of parents of their patients identified through the registry who are potential focus group subjects. They will also be given recruitment letters for each individual on the list. Study team staff will ask each provider to approve parents from the list would be appropriate for recruitment for the focus groups by signing the letters to those individuals. The KPCO
study team will send out this recruitment letter in waves according to focus group dates to all the subjects deemed appropriate by the medical providers. The medical providers have been asked to sign these letters to add credibility to them and address any HIPAA requirements for presence of a treatment relationship to the child. The recruitment letter will contain a postage paid postcard that the subjects can send back if they do not wish to be contacted for recruitment.

**Phase 3. Randomization, recruitment, and data collection** will begin in the third year. Two sub-studies (described below) will also be initiated at this time. Parents will be enrolled up until month 42 in order to be able to complete 12 months participation and outcome measurement for all patients.

The first 6 months of Phase 3 will consist of field live testing with up to 300 parents. This means that up to 150 families will be randomized to receive the intervention. As part of the phase 2 user testing protocol, a random selection of these parents will be called by research staff to gather feedback about the call’s ease of use, flow logic, efficiency, and helpfulness before the full SR intervention is implemented. This field live test is a standard procedure which has been used in similar research studies using SR technology.

Parents randomized to the intervention will receive a welcome letter and brochure prior to their first SR call or message. The letter and brochure will let the parent know they have been randomly assigned to the SR intervention, confirm we have their correct phone number, further explain the SR intervention and provide study staff contact information in case they have questions or do no wish participate. Three SR call types will be used for the intervention: (1) Welcome call, (2) Basic refill reminder, and (3) Tardy refill reminder. In total participants will receive 3-12 SR phone calls or phone messages lasting approximately 1-3 minutes each during a 12 month period. The goal of the calls and messages is: (1) remind parents to refill their child’s ICS prescription, (2) assist parents in refilling their child’s ICS prescription, (3) Help answer parent questions about their child’s asthma medicine by offering a call back from an ACM, and (4) Provide tips to parents on what controlled asthma looks like and how they can keep their child breathing as freely as possible. The Welcome call will be the first call to all “new users” to the SR intervention. The Basic refill call will be used when participants ICS prescription is due to be refilled and the Tardy refill call will used when a participant is past due for refilling their child’s ICS prescription. In addition to the SR calls, new users to ICS and patients who are past due in refilling current ICS prescriptions will also receive a call from an ACM. Furthermore, those patients who have requested a refill of their ICS prescription as a result of the intervention but have not picked it up within 7 days will receive a reminder call to do so at the pharmacy of their choosing.

In order to obtain sustainability measures, in the fourth and fifth year participants enrolled and still eligible for the study will be asked to continue participation for an additional year. Data will be collected in the same way for the additional year of participation for both intervention and control groups. Consenting information for continued participation is described in more detail in section 3E.
The fifth and final year will include completion of the intervention at the 54-month point followed by compilation and assessment of data. The cost analysis data, collected throughout the trial, will begin in this phase. The primary outcomes will be the continuous measure of medication acquisition (CMA) and the continuous measure of medication gaps (CMG) (75). Other outcomes will include assessment of beta₂ agonist use and emergency department visits, hospitalizations, and oral steroid bursts.

Phase 4. Data analysis and preparation of the final report will be completed in the final 6 months of this proposed study. In accord with the SMT model, this phase will include evaluation of the program and recommendations for future refinement. Evaluation of the program will include assessment of refill behavior, disease control, quality of life, and parent satisfaction. Information learned about variable response to the intervention based on patient and family characteristics will guide future refinements of the SR intervention. Also included will be an assessment of whether baseline benefit-risk perception influenced receptiveness to the intervention, and whether the intervention altered parents’ benefit-risk differential score. Dr. Glasgow will help to evaluate the reach, adoption, and system impact of this public-health oriented, system-based program using the RE-AIM model.

4.B. Participant Contact

Focus groups in Phases 1 and 2: For call development, feedback will be gathered both through in-person focus groups and one-on-one discussion of almost finalized calls. Focus groups for Phases 1 and 2 will be held at the Arapahoe, Westminster, East, Skyline, Lakewood, and Aurora Centrepointe clinics. New and repeated participants may take part in each phase of the feedback process. A single participant may participate in more than one feedback session (focus groups or user testing) if they express interest in doing so.

Corona Research and/or KPCO staff will conduct follow-up phone calls to recruit and schedule those subjects who are interested in participating. Corona Research and/or NJMRC staff will moderate the focus groups. Corona research or Production Transcriptions will transcribe the results. Contracts, Business Associates Agreements, and any other required agreements will be completed before focus group activity is started. The sample, letters and conference room scheduling will be under the control of KPCO project staff.

For in-person focus groups and user testing activities, participants will be KPCO parents or guardians of a child with asthma, who will be recruited by a letter signed by their child’s primary care physician or allergist.
Corona Research and/or KPCO staff will contact eligible focus group participants via telephone to schedule a focus group. They will attempt to contact each potential participant up to 12 times. Messages will be left on the first attempt and on subsequent attempts that are at least 3 days after a prior message. If an attempt is made prior to 3 days after a message, the attempt will be documented, but no message will be left. The call to schedule a focus group with a potential attendee should last no more than five minutes.

Two to five groups will be conducted in Phase 1 and two to five for Phase 2, with 6 to 12 people in a focus group (120 maximum focus group participants). Up to fifteen participants will be recruited for each group to be sure that at least 6-12 attend. Within a phase, all focus groups or one-on-one sessions will have the same content. Changes to focus group topics will be made only when progressing from Phase 1 to Phase 2. Written informed consent, including permission to videotape the session, will be obtained from all participants, and the groups will be held at KPCO facilities. The groups will last no more than 90 minutes and will be led by a moderator assisted by an observer. The discussions will center on knowledge and opinion, and not personal health issues. However, if any medical event occurs during the focus group or user testing activities, medical resources will be available as appropriate to the situation (calling 911, contacting KPCO After Hours care, or calling the Asthma Care Managers.) Focus group staff will be provided the information and training to handle these events appropriately.

**Phase 1 User-testing:** Phase 1 focus group attendees who expressed interest in participating in future TEAM study focus groups and/or user-testing will be recruited by phone and asked for their verbal consent to participate (approximately 20 people). Those who agree will to listen to a PEANUT study phone call while on the phone with a KPCO staff member and asked questions about the call's ease of use, efficiency, flow logic and helpfulness. The total length of the call will last approximately 10-15 minutes.

**Phase 2 user testing:** Once the SR scripts have been modified based on feedback from the focus groups, we will begin a telephone-based user testing phase to get detailed information about how successfully end-users can navigate and get the results they desire from the SR system (75, 80). An iterative process will be employed during user testing (77). Each user testing episode should last 10-15 minutes, on the telephone. In brief, for each new “version” of the system, up to 15 users will be asked to “think aloud” as they use the SR system. The key issue here is to observe and listen to the users without helping them in the process. Based on the one-on-one observations of and feedback from these users, the SR design team will modify the system versions until a panel of 5 users within a cycle suggests that we have “gotten it right.” We expect that user testing will require from 2-6 iterative testing and refinement cycles.

**Phase 3:** The TEAM program integrates SR into the existing clinical infrastructure at KPCO. The TEAM intervention will complement the asthma care manager program already in place in KPCO. The SR calls will provide an intervention that is expected to lead to greater use of ICS among children with asthma. For those parents who request
or require personal contact, the existing asthma care managers program can provide easy access to answer questions about asthma and its treatment. Asthma care managers will receive daily, automated reports from the SR program indicating which families have requested a return call. Parents will be informed that these return calls will occur within 24 hours, but only on weekdays between the hours of 7am and 7pm... Additionally, KPCO pharmacists will be fully informed about the TEAM program. In this way, pharmacists encountering parents requesting information or who call the pharmacy refill line will understand how the SR system works and the purpose of the SR encounter, and will be prepared to answer further questions or to place a refill order. The mail order pharmacy will also receive daily, automated reports from the SR program indicating which families have requested an automated refill or return call to refill and/or answer questions about their ICS prescription.

4.C. Drugs, Devices or Instruments

Not applicable. The medications of interest in this study are part of the KPCO formulary, with administration as prescribed and concordant with usual care practices.

4.D. Tissue Samples (pathology specimens, blood, hair, saliva, etc.) and Banking

Not applicable

4.E. Genetic Testing

Not applicable

4.F. Data Collection and Management

NJMRC and KPCO each have experience with the design, implementation, operation, and maintenance of many large-scale clinical trials. Drs. Bender and Magid will supervise all data collection procedures, coding and storage. A smooth and efficient process for data management and quality control is important to the success of this study. This will be facilitated by the existing close linkages between the KPCO and Eliza data and communication systems.

All data transmitted to the NJMRC from KPCO will be identified only with a unique artificial patient identification number and no protected health information (PHI) data will be kept in the database. Only the KPCO analyst will have access to the linkage code and file to link patient HRNs and the artificial ID. This linkage code and file will be destroyed once the analytical dataset is finalized. Datasets will be limited datasets, containing dates and no direct personal identifiers, and will require passwords for access. We will comply with all NJMRC and KPCO procedures for
maintaining the security and confidentiality of patient data. These standards are in accordance with federal regulations for handling this type of data. All KPCO and NJ computers used by study staff require password sign-on to gain access. Confidentiality agreements will be established between National Jewish project staff and KPCO before any data are shared. A Business Associate Agreement will be established between KPCO and Eliza Corporation will be finalized prior to the start of call development using the focus groups. Eliza Corporation will be active in the call development activities of Phases 1 and 2, but no PHI will be shared with Eliza during those phases.

Business Associates agreements will be established with Anderson-Niebuhr before any data are shared. Anderson-Niebuhr takes multiple steps to protect the privacy of participants (see risks to participant’s privacy with explanation of patient protection below). Name, mailing address, and phone number will be provided to Anderson-Niebuhr. This information is necessary in order for Anderson-Niebuhr to contact participants for the survey. If a participant sends back an opt-out postcard, Anderson-Niebuhr will remove the participant from their database and will no longer contact the participant. Likewise, if a participant indicates they are not interested in participating and would not like to be contacted again, Anderson-Niebuhr will remove the participant from the database and will no longer contact the participant.

**Focus groups in Phases 1 and 2:** For call development, feedback will be gathered both through in-person focus groups and one-on-one discussion of almost finalized calls. In-person focus group activities will be conducted by project staff from Corona Research in partnership with National Jewish and KPCO. For the in-person focus groups, written informed consent, including permission to videotape the session, will be obtained from all participants, and the in-person groups will be held at KPCO facilities. The groups will last no more than 90 minutes and will be led by a moderator assisted by an observer. The moderator will use a topic guide (see Appendix A) and probe questions to direct discussion and ensure all issues are covered. There will be no sensitive or highly personal questions asked during these focus groups. The use of videotaping will allow for more accurate transcription, and participant comments will be attributed using seating or assigned codes (e.g. seat 1, seat 5, or, participant 3, participant 7). Corona Research or Production Transcriptions will transcribe and select staff from NJMRC will qualitatively analyze the Phase 1 and 2 focus group sessions. Select staff from NJMRC and KPCO may view and listen to the video and/or audio recordings of the focus group sessions. However, only de-identified results will be shared with the rest of the project staff. Focus group videotapes will be stored in locked cabinets at National Jewish, with no identifying documentation on participants in the proximity (such as consent forms or recruitment information). All focus group videotapes will be demagnetized and shredded within a year of the conduct of the focus groups.
**Phase 1 and 2 user-testing activities:** Verbal consent will be attained over the phone. All information from these calls will not be linked to an individual, the notes will be in both hard copy for individual calls and electronic copy for the summary files, and will be stored in locked cabinets and/or on password protected computers accessible only to KPCO project staff. There will be no sensitive or highly personal questions asked during these sessions.

**4.G. Data Analysis**

**Phase 1 and 2:**
Focus groups: The blocks of focus groups are progressive in nature, such that the findings from Phase 1 will be used in Phase 2, and the findings from the Phase 2 focus groups will be used in the Phase 2 user testing activities. All information collected in Phases 1 and 2 will be discussed and analyzed qualitatively, to provide themes to direct the development of the call system. Only select Corona Research, NJMRC, and KPCO staff will transcribe and analyze the results, while the other study staff from NJMRC and KPCO will review and respond to de-identified, summary information on the focus groups. Within a phase, all focus groups or one-on-one sessions will have the same content. Changes to focus group topics will be made only when progressing from Phase 1 to Phase 2. This review will be regular and cumulative, as the call development process will build on itself over time. Themes and issues that arise will be tracked and addressed in subsequent phases.

**Phase 3:**
Evaluation of the comparability of the TEAM intervention and usual care control groups. Demographic and relevant clinical data and from the medical records of all subjects who randomized into the TEAM intervention group will be further examined for differences between those who drop out after the first SR call and those who continue with the study. Similarly, the subjects who agree to participate during TEAM intervention will be compared to the subjects randomized into the usual care control group. Any variables found to be even marginally different (p<0.10) across groups at baseline will be used as covariates in all subsequent analyses.

**Outcome Measures:** Outcome measures consist of data obtained through the KPCO databases, including information on ICS persistence, beta2 agonist refills, and urgent care visits. In this way, comparisons can be made between the usual care and intervention groups.

**Cost Analyses**
A detailed economic analysis will be conducted in the last year of the project to examine the economic and cost effects of the intervention, namely if the outcomes for the intervention condition are significantly better than those in the control condition. The primary goals of this analysis will be: 1) to comprehensively determine intervention costs from the perspective of a sponsoring organization, and
2) to estimate the costs per incremental improvement in the primary outcome of medication adherence. Two areas of cost will be considered in this analysis: costs associated with the intervention program, and changes in the cost of medical care utilization attributable to the intervention.

Further data analysis will be conducted to discover predictors of emergent health care utilization in KPCO children with asthma, ages 3-17, with emphasis on patterns of medication use. Key predictors will include one-year refilling of inhaled corticosteroids, oral steroids, and beta2agonists. Outcomes to be examined include hospitalizations, ED visits, urgent care visits, regular office visits, and oral steroids usage. Variables that may modify the relationship between refills and health care utilization that we propose to examine include age, gender, race, body mass index, and history of hospitalization, ED use, and medication use. These data analyses are expected to help identify strategies to effectively analyze the TEAM intervention as well as identify behavioral risk patterns that invite further intervention.

4.H. Duration of Study
This is a five year study starting September 2007 and ending May 2012. Phase 1 and 2 activities will take place in the first two years of the study. For both the focus groups and user testing, each participant may participate in more than one feedback session, if they express interested in doing so and is needed for the project. Phase 3: Randomization, recruitment, and data collection will begin in the third year. Two sub-studies will also be initiated at this time. Parents will complete a minimum of 12 months participation. Parents will be enrolled up until month 42 in order to be able to complete a minimum of 12 months participation and outcome measurement for all patients. The fifth and final year will include completion of the intervention at the 54-month point followed by compilation and assessment of data.

5. Risks and Benefits
5.A. Risks to Subjects
(Must be addressed for all studies as applicable)

5.A.1 Physical Risks:
In sum, no meaningful physical or mental health risk is directly associated with participating in Phase 1 and 2 activities of the study. If any medical event occurs during the focus group or user testing activities, medical resources will be available as appropriate (calling 911, contacting After Hours care, or calling the Asthma Care Managers.) It is also expected that no meaningful physical or mental health risk will be directly associated with participating in Phase 3 activities of the study.

5.A.2 Psychological, social, economic, and legal risks:
It is expected that no meaningful psychological, social, economic, and legal risk is directly associated with participating in Phase 1 and 2 activities of the study.
It is also expected that no meaningful psychological, social, economic, and legal risk will be directly associated with participating in Phase 3 activities of the study.

5.A.3 Vulnerable subjects:

This proposed study will include children and their parents/guardians (both male and female adults). The intervention is directed to the parent, while the consequence of the intervention is directed to the child. We anticipate that the gender distribution of the study sample will be proportional to that of the health plan region as a whole. Previous studies at KPCO have succeeded in including race and gender groups reflecting the overall KPCO population. We expect a random distribution of SR patients among providers and anticipate that the gender characteristics of the participants will closely mirror those of the KPCO population. Thus, the proportion of men and women in the sample should be fairly comparable (see table below).

All eligible individuals of any race or ethnic group who are members of KPCO, are parents of children with asthma, and who agree to participate will be enrolled in this research study. Demographic information collected from previous KPCO research was used to predict the racial and ethnic representation in the proposed research, as shown in the table below. Based upon our preliminary studies approximately 24% of those patients who will be eligible to participate are from minority racial or ethnic groups.

The KPCO IRB will serve as the primary IRB since all participants are from KPCO. The initial letter to parents on the focus groups, user testing and intervention will cover all of the elements of consent, including the fact that participation is voluntary and that refusal to participate will not affect their health plan eligibility or the care that they receive from KPCO.

On the issue of child assent, assent is not warranted as this project does not have any intended direct contact with any child, only the child’s parents. The reminder system will simply reinforce the prescribed therapies that the child is expected to follow, under their parent’s direction and the care of the child’s physician.

5.A.4 Risks to patient privacy and confidentiality:
(Must be addressed, as there are always risks to confidentiality.)

The primary risk associated with the study is a breach of confidentiality. This could happen in one of several ways. While being contacted to participate in focus groups or in the study, or as part of one of the intervention calls, someone other than the participant may learn of the participant’s or participant’s child’s health condition and/or medication use. Additionally, in Phase 3 we will be
routinely exchanging protected health information (PHI) with the Eliza Corporation as part of the study. This is necessary in order for Eliza to be able to make the calls. Specifically, Eliza must know each participant’s name, phone number, gender, medication name, doctor name, and last 4 digits of credit card (if on file from mail order pharmacy records). The Eliza Corporation could use this information in inappropriate ways, such as sharing it with another commercial vendor, or the information could be accessed by unauthorized parties if the data transmissions are not secure. KPCO, NJMRC, and Eliza will follow strict procedures to assure the security and integrity of all study data. Our procedures for transmitting data to and from Eliza will meet HIPAA requirements for security. We will use a secure FTP site to transfer information back and forth with Eliza. No information transferred from KPCO to NJMRC for analysis will contain PHI such as name, date of birth, or street address. Patients will be identified solely by their study ID number with the translation key being held at KPCO and not accessible by NJMRC personnel.

Like necessary exchange of PHI with Eliza, it is also necessary to exchange PHI with Anderson-Niebuhr who will be conducting the survey administered to all intervention participants upon completion of one year in the study. Data including participant name, address, and phone number will be shared with Anderson-Niebuhr. This information is necessary in order to conduct the mail and phone completion of the survey. Anderson-Niebuhr is a preferred Kaiser vendor and has been working with Kaiser Permanente on over 125 projects. Anderson Niebuhr has excellent policies and procedures in place to ensure confidentiality and data security and has an outstanding track record of conducting research on health-related issues for over 35 years. Anderson Niebuhr adheres to HIPAA standards for protecting health data and has stringent standards of confidentiality and data security that include the following:

a. Anderson Niebuhr staff have extensive experience conducting surveys and all staff members are CITI (Collaborative Institutional Training Initiative) certified through Emory University program in human subjects research protection.

b. Anderson Nieburn staff receive HIPAA-specific training which includes knowledge testing and certification.

c. All project data will be stored in our highly secure computer system. They take the following data measures:

- A unique identification number is assigned to each person in the sample to help protect respondent confidentiality. Survey responses are stored separately from sample information.

- Anderson Neibuh will use HIPAA-compliant, secure file transfer protocols to transmit protected data to and from KP. Data files are transferred electronically via our password protected, secure FTP site. All files are
automatically encrypted during the upload and download processes, and all files are stored “at rest” in a tamper-evident encrypted state. Tracking logs verify file integrity and access.

- Anderson Niebuhr has firewalls in place and their file server is password protected to help prevent remote access.

- Anderson Niebuhr adheres to strict practices regarding confidentiality. All electronic linking information and electronic sample lists are deleted 30 days after project completion. Paper copies of sample lists, linking information, and completed questionnaires are shredded 30 days after project completion.

- At the end of the project period, paper documents are shredded and electronic documents are deleted.

- Currently, all telephone interviewing data are maintained in the CATI program. However, only a select group of Anderson-Niebuhr employees have access to this information through use of passwords and limited installation of software. The CATI software also has multiple levels of password protection that can be utilized to further restrict persons from accessing data files.

- CATI interviewing stations are only able to access the specific drive delegated to CATI in the LAN file server; they are not mapped to access the main drive where project information is stored. This also prevents the workstations from accessing any printers. In addition, when interviewers are working on a CATI project, they have access to only the individual records on which they are working, and address information is never displayed. Once the data are collected, they cannot access the record or data.

Finally, as we have done in the past we will establish a Business Associates Agreement (BAA) with Anderson Niebuhr that establishes through a formal contract requirements for confidentiality and data security.

Drs. Bender and Magid will be responsible for monitoring the integrity of the data as well as patient safety. This plan will define adverse events (AE) for this study and include a plan for unanticipated AE reporting. We will develop a tracking system to keep track of participant and provider complaints about the study that come to our attention. We will track any breaches of confidentiality. In addition, the advisory board, chaired by Dr. Peter Cvietusa, will monitor any AE, patient complaint, or KPCO staff concerns that might arise related the study. The board will also review our intervention protocols while they are being developed in order
to assure that they are medically appropriate and that they conform to KPCO policies regarding the confidentiality of medical record information. Specifically, we will make sure that the scripts for dealing with family members and other non-participants who may answer the phone, do not disclose any protected health information. Because the scripts are all automated, we have virtual assurance that once the scripts are finalized, all calls will conform exactly to protocol.

5.B. Study Alternatives

The alternative to the participant is to not participate in the study and continue to receive normal care through Kaiser Permanente. If potential participants choose not to participate, the usual health care they receive will not be affected and will still be available to them. The purpose of this study is to encourage adherence to already-prescribed medical therapy. No additional therapy will be recommended or provided, no adjustments to prescribed usage will be made, and no clinical measurements will be taken as part of this study. The intervention is simply designed to encourage and assist members to use their medications as directed by their doctors.

5.C. Risks to Investigators or Kaiser Permanente

There are no known risks to KP investigators or staff. This study is not likely to be detrimental to KPCO, as it demonstrates KPCO’s commitment to patient care and favorable outcomes, and the information gained will identify areas for quality improvement in the management of children with asthma. There are no conflicts of interest for the investigators or project staff.

For participants and members of Kaiser Permanente, no meaningful physical or mental health risk is directly associated with participation in the study.

The primary risk associated with the study is a breach of confidentiality. This could happen in one of several ways. While being contacted to participate in the study, or as part of one of the intervention calls, someone other than the participant may learn of the participant’s health condition and/or medication use. KPCO, NJMRC, Corona Research, and Eliza will follow strict procedures to assure the security and integrity of all study data. Our procedures for transmitting data to and from Eliza will meet HIPAA requirements for security. We will use a secure FTP site to transfer information back and forth with Eliza. No information transferred from KPCO to NJMRC for analysis will contain PHI such as name, date of birth, or street address. Patients will be identified solely by their study ID number with the translation key being held at KPCO and not accessible by NJMRC personnel.
Staff orientation and training. KPCO pharmacists, nurses, asthma care managers, call center and administrative staff will receive a general communication informing them about the TEAM study. The asthma care managers will additionally attend a minimum of 6 hours of orientation, training, feedback, and problem solving sessions during the development phase. KPCO adopts new programs on a continuing basis to improve patient care, and hence innovations to existing patient management procedures are generally well accepted.

Physician involvement. All KPCO pediatricians and allergists will receive information about the TEAM intervention during regularly scheduled department meetings. Physicians will co-sign the initial introductory letter, and a second letter to parents 12 months after randomization. Finally, physicians will be informed about the information that will appear in each patient's EMR following an SR intervention.

5.D. Benefits of the Study

**Phase 1 and 2 focus groups:** Participants in both phases will continue to have access to the full range of services to which their health plan benefits entitle them. Focus group participants may benefit from information discussed on asthma issues relevant to their child, being made aware of available KPCO resources, and other information voluntarily shared by other participants.

**Phase 1 and 2 user testing activities:** User testing participants will continue to have access to the full range of services to which their health plan benefits entitle them. They may also benefit from information mentioned during the call on asthma issues relevant to their child and being made aware of available KPCO resources.

**Phase 3:** Participants in both groups will continue to have access to the full range of services to which their health plan benefits entitle them. A few SR participants may view the calls as a nuisance, and some may be annoyed at being contacted by a computer to ask about their medication usage. In sum, however, no meaningful physical or mental health risk is directly associated with being in the study.

It is our hope and expectation that this study will accomplish the following:

A. Increase adherence with ICS medications in the TEAM intervention group, versus the usual care group.
B. The TEAM intervention will result in a decrease in asthma symptoms as reflected in reduced beta₂-agonist use, and a decrease in non-routine, asthma-related health care visits when compared to the usual care group.
C. Parents in the TEAM intervention group will report greater improvement in symptom control, quality of life, and satisfaction with their child's asthma care than parents in the usual care group.
D. Parents in the TEAM intervention group will report a larger positive change in perception of medication benefit than parents in the usual care group.

E. Characteristics of the patients and their families, including illness severity, duration of illness, age, race, language preference, socioeconomic status, and benefit-risk perception, will act as moderating variables influencing response to the intervention.

5.E. Risk-Benefit Justification
(Must be addressed for all studies)

All phases of the study involve minimal risks. The study reinforces the usual care already provided to patients, and does not alter care. The potential benefits to participation are moderate to high, as improved medication adherence will likely lead to better asthma control and health outcomes in children with asthma.

The knowledge gained from this study will help to improve the quality of care for children with asthma taking inhaled corticosteroids. In the investigator’s opinion, the risks, discomforts, and inconvenience to study participants are reasonable to the potential benefits of participation.