PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
M. Samuels-Kalow

PROTOCOL TITLE

Medication Education for Dosing Safety (MEDS)

FUNDING

Shore Award

VERSION DATE
4/15/18

NCT NUMBER

2017P001482

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Hypothesis: A brief safety intervention, combining a pictorial handout, dosing demonstration with dispensed syringe, and teach-back for confirmation of understanding, will improve parental knowledge and implementation of appropriate weight-based dosing.

Specific aims

1. Determine the feasibility of a brief safety intervention delivered at ED discharge
2. Examine the effect of the brief safety intervention on parental knowledge and implementation of weight-based dosing

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Acetaminophen and ibuprofen are two of the most commonly used medication products among children <12 years old,[1] and these medications are frequently prescribed for patients leaving the emergency department (ED). Prior ED studies found that only 40% of parents knew the appropriate dose for their child, only 67% were able to measure out the amount they intended,[2] and that only 31% were aware of weight-based dosing.[3]

Our own work has shown that 32% of parents made an acetaminophen dosing error at ED discharge, despite provision of an instruction sheet.[4] After repeat teaching in the ED, parents remained at risk of error when called 5-10 days following their ED visit,[5] suggesting our existing teaching methods are inadequate and unsuccessful. Communication challenges, and resulting misunderstanding of dosing instructions, are particularly challenging for patients with limited health literacy[6] and limited English proficiency.[4]

Written instructions on commercially-available packages are insufficient to ensure comprehension and correct dosing. Over 98% of over-the-counter liquid medications are inconsistent with regard to dosing directions and markings on the dosing device.[7] Dosing cups, often dispensed with such medications, are associated with an increased risk of making a large dosing error when compared to an oral syringe.[8] Plain-language, pictogram-based interventions with teach-back have shown promise in improving dosing accuracy in the pediatric ED[9], but have not become a routine part of discharge teaching. In particular, a combination of improved teaching and provision of a dosing syringe is associated with a significantly decreased risk of error (adjusted OR 0.3, 95%CI 0.1-0.7).[10] Improved written materials may also have potential to improve provider counseling and teaching around medication use.[11] Our pilot work demonstrates that ED parents perceive a need for dosing demonstration,[12] and are open to teach-back techniques to confirm their understanding.[13]

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

We plan a randomized controlled trial of an intervention to improve ED discharge teaching. We plan to approach 400 parents, with a goal sample size of 200 parents. Parents will be approached for consent, and randomized after consent

We will enroll parents of children between ages of 90 days to 11.9 years, who are being discharged with a plan for use of liquid acetaminophen (any age) or ibuprofen (limited to those >6 months old). The clinical team will determine planned medication use.
Inclusion criteria include parental fluency in English or Spanish, ability to be reached by telephone over the next 7 days and planned discharge home.
Exclusion criteria include presence of a complex chronic condition[14] in the child and planned use of a non-standard weight-based medication dose. Adults who are not the parent or legal guardian of the child they are with in the ED will also be excluded.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

All participants will complete a demographic survey, including information about age, race/ethnicity, educational attainment, language fluency, and the Newest Vital Sign[15,16] for

assessment of health literacy/numeracy. The survey will also include questions about prior use of syringes to deliver medications in the past and comfort with mathematical calculations. All discharges will be observed by the RA using a standardized checklist developed for prior work. Teaching that occurs prior to discharge will not be observed. Data will be entered either onto paper forms or directly into REDCap.

The intervention will be delivered by a trained RA, separate from the treating team and will occur immediately after conclusion of the RN discharge. The intervention will include the following components:

1) Pictorial handout. We have developed simplified form of the existing dosing handouts from MGH that contain only the correct dose for each weight range (rather than the entirety of the dosing schedule).
2) Dosing demonstration. The RA will use a standardized syringe to demonstrate the safe dosing of APAP and motrin for the weight of the child.
3) Dispensed dosing syringe. The parent will receive the syringe (unmarked) from the RA. We have chosen not to mark the syringe because of concern of the parent using the marked dose for an incorrect medication or persisting with that dose as the child grows.
4) Teach back for confirmation of understanding. The parent will demonstrate the amount of liquid medication they would draw up using standard bottles. If the parent does not have the correct dose, they will clarify and expand the explanation and re-assess, until recall and comprehension is reached, thereby enabling adherence. RAs will have a final check for comprehension with the family to ensure that no unanswered questions or concerns remain.

RAs will be asked to document the number of teaching cycles required, their perceptions of the process and any elements that made the teaching easy or challenging.

Follow-up. Participants will be called at 48-72 hours to assess dosing knowledge (primary outcome), comfort with home care and encounters with other care providers; and at 5-7 days to assess persistence of knowledge. Participants will be asked during enrollment about their preferred time of day for follow-up calls. If they do not answer at the time of the follow-up call, they will sent a text message in their preferred language (Spanish or English) to arrange a time for follow-up. Parents will be allowed to refer to the information sheet at the time of assessment.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Participants will receive standard ED teaching or standard ED teaching + intervention, and so no participant will receive less than the existing standard of care.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The primary risks to subjects are minimized as below:

1. Confusion about Instructions: We feel this is less likely because the intervention is based on strategies, such as teach-back techniques, that confirm understanding

prior to discharge. All participating families will have the usual care discharge, and intervention families will have additional teaching. Fidelity of the RAs to the intervention will be monitored closely. Parents will be offered the opportunity to speak to their treating provider if they have any questions that the RA is unable to answer. Parental conversations with the treating provider following the intervention delivery will be observed and abstracted by the RA.

2. Privacy Breach: The risk of loss of confidentiality will be minimized by keeping all data in a locked cabinet in a locked office, on a secure research drive or in REDCap. All study staff will undergo CITI training in human subjects research and privacy protection. Demographic information collection and intervention delivery will be conducted in a private room. All privacy breaches will be reported to the IRB in accordance with MGH regulations.

3. Parental Distress: As with any ED study, we recognize the potential for parental distress when parents are approached for enrollment when their child is ill. We aim to minimize the potential for parental distress by approaching only parents of children deemed eligible for discharge home (not acutely ill or resolving illness) and by checking with the primary clinical team for appropriateness of enrollment prior to approaching the parent. As is standard for trial consent, parents will be told that their participation or lack of participation in the trial will not change the clinical care provided to their child. For parents in ongoing distress needing additional resources, the research staff will discuss with the primary clinical team and assist with consulting social work as necessary.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Additional protocols for subject safety are discussed in the detailed protocol and include:

4. Worsening illness in the ED. If a child's condition worsens such that s/he need to be admitted to the observation unit, inpatient floor or intensive care unit, all study procedures will cease, and the family will not be eligible for further study assessments. Hospitalization is such a significant intervention, with multiple levels of educational and clinical intervention, that any effect of the study intervention is likely to be lost. Therefore, hospitalized patients will be excluded from the primary intention-to-treat analysis. Exclusion based on hospitalization during the index ED visit should be randomly distributed across all groups and therefore should not significantly change the analysis.

5. Worsening illness at home. Approximately 2-2.5% of patients in our ED return within 72 hours, most often due to worsening of their ongoing illness. We will monitor the rate of return within 72 hours, the rate of return with admission to the hospital floor and the rate of admission to the ICU. These rates, and a brief summary of related events, will be provided to the independent safety monitors quarterly.

6. Worsening disease at home disclosed on phone call follow-up. Parents who report that their child is having worsening symptoms at home will be asked to follow-up with their primary care provider or asthma specialist. Parents who have concerns about their ability to follow-up will be referred to the PI.

7. Death. While we do not anticipate any deaths in this cohort of patients being discharged home, any deaths in any arm of the study will be reviewed by the independent safety monitor.

8. Disclosure of reportable condition. If a parent discloses child abuse or neglect as part of study enrollment or the interview process, study procedures will cease and the study staff will inform the treatment team and assist with contacting social work for further evaluation, which is the standard procedure in our institution for child protection concerns. No additional study procedures or assessments will be completed with that family. Parents will be informed in the consent that if reportable information is obtained during study procedures, that the study team is obligated and will report them in accordance with standard practice.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

There are major three categories of potential risks to participants from study participation: confusion about instructions, privacy breaches, and parental distress.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

The intervention teaching may improve parental understanding of safe medication dosing for their children at home. The overall study will add to our knowledge about how to safely communicate complex concepts to parents at the time of ED discharge.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

We will enroll parents of children between ages of 90 days to 11.9 years, who are being discharged with a plan for use of liquid acetaminophen (any age) or ibuprofen (limited to those >6 months old). This will include parents from all racial and ethnic groups who speak either English or Spanish.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

We will be enrolling parents who speak English and Spanish.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruitment methods Parents will be enrolled from the MGH ED by trained research assistants (RAs). RAs routinely screen for eligible patients for a variety of studies in our ED. Consenting participants will be randomized to intervention vs. usual care. The intervention will be delivered by RAs who have been trained by the PI (Samuels-Kalow) and the ED pharmacist (Hayes).

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

We plan to provide a single payment of $20 to the participant by mailed CVS gift card after completion of the first follow-up interview, and not to collect SSN/ITIN numbers. We are particularly interested in enrolling participants with limited health literacy and limited English proficiency, and therefore anticipate that many of our participants may be undocumented or be uncomfortable providing a social security number. This is a one-time acknowledgement of participant time and effort, not a repeating payment.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Parents will give informed consent for participation.

We are particularly interested in the effects of the intervention on parents with limited health literacy, and concerned that written consent could be a disproportionate barrier to enrollment for patients with limited health literacy. Therefore, we request permission to obtain a verbal consent from parents to reduce literacy related barriers to participation. RAs will consent eligible parents using a verbal consent process while individuals are in a private room. Parents will be given an information sheet in either English or Spanish.

We are requesting a waiver of written informed consent because the research meets the following criteria: The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. The study staff who explain the protocol and obtain consent are not part of the clinical team.

There will be no interview or survey participation by the child. We are asking only the parent, who will participate in the verbal consent process, to participate in the interview or survey. The RA will describe the key elements of consent to the parent including the potential risks and benefits of the study, protection of confidentiality of data and fact that their child's clinical care will be the same regardless of enrollment. Verbal informed consent will be documented by signature of the RA on the enrollment record.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:

Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

A Safety Monitoring Committee will be created as an independent body charged with ensuring that the safety of participants is protected and that the scientific goals of the study are being met. The SMC will be responsible for reviewing cases with potential adverse outcomes and will be empowered to terminate the trial based on evidence of substantial harm. To support those purposes, the Safety Monitoring Committee will perform expedited review of all serious adverse events, perform ongoing monitoring of non-serious adverse events, and determine whether study procedures should be changed or the study should be halted for reasons related to the safety of participants. The Safety Monitoring Committee will be Dr. Jean Klig, Assistant Professor of Emergency Medicine (pediatric emergency medicine) and Dr. Kevin Schwartz, Instructor of Emergency Medicine (pediatric emergency medicine).

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The full plan for review and response to adverse events is provided in the Detailed Protocol. All adverse events will be reported to the IRB in accordance with MGH regulations.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

RAs will be observed once each month for the first 3 months and then once a quarter to ensure intervention fidelity.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

The risk of loss of confidentiality will be minimized by keeping all data in a locked cabinet in a locked office, on a secure research drive or in REDCap. All study staff will undergo CITI training in human subjects research and privacy protection. Demographic information collection and intervention delivery will be conducted in a private room. All privacy breaches will be reported to the IRB in accordance with MGH regulations.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

N/A

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Biostatistical analysis

Primary analyses will be based on intention-to-treat. Data will be stored in REDCap and analyzed in STATA. We will evaluate:

- Study process variables Descriptive statistics will be used to delineate the number screened, eligible, approached, assented/consented and randomized. Reviewer checklists will be used to determine adherence. Duration of discharge process will be recorded for all participants to address questions about feasibility. We will also record number of teach-back cycles required. We will compare retention to follow-up call between intervention and control groups using a Mantel-Haenszel analysis.
- Outcomes The primary outcome is safe dosing (defined as within 20% range of the weight-based dose) at the 48-72 hour follow-up call. A 20% range has been used in prior studies,[9,10] and we have successfully completed telephone assessment of dose accuracy in previous work.[4,5] We will use logistic regression models to compare differences between study groups. The secondary outcomes (including parental comfort, encounters with other providers and persistence of dosing knowledge) will be used for hypothesis generation.
- Missing data. We will do a sensitivity analysis to test varied assumptions about missing data based on previously reported rates of dosing error following ED visits,[5,9] or multiple imputation depending on the number of patients with missing data.
- Exploratory subgroup analysis: We will examine: 1) intervention effect in English-speakers as compared to Spanish-speakers, 2) effect size by health literacy, and 3) the intervention efficacy in those receiving both acetaminophen and ibuprofen education as compared to those receiving single-medication education 4) differential risk of overdose error as compared to underdose error