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Use of Mobile Devices and the Internet for Multimedia Informed Consent Delivery and Data Entry in a Pediatric Asthma Trial: Study Design and Rationale

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Abstract

Introduction—Phase III / IV clinical trials are expensive and time consuming and often suffer from poor enrollment and retention rates. Pediatric trials are particularly difficult because scheduling around the parent, participant and potentially other sibling schedules can be burdensome. We are evaluating using the internet and mobile devices to conduct the consent

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process and study visits in a streamlined pediatric asthma trial. Our hypothesis is that these study processes will be noninferior and will be less expensive compared to a traditional pediatric asthma trial.

Materials/Methods—Parents and participants, aged 12 through 17 years, complete the informed consent process by viewing a multi-media website containing a consent video and study material in the streamlined trial. Participants are provided an iPad with WiFi and EasyOne spirometer for use during FaceTime visits and online twice daily symptom reporting during an 8-week run-in followed by 12-week study period. Outcomes are compared with participants completing a similarly designed traditional trial comparing the same treatments within the same pediatric health-system. After 8 weeks of open-label Advair 250/50 twice daily, participants in both trial types are randomized to Advair 250/50, Flovent 250, or Advair 100/50 given 1 inhalation twice daily. Study staff track time spent to determine study costs.

Results—Participants have been enrolled in the streamlined and traditional trials and recruitment is ongoing.

Conclusions—This project will provide important information on both clinical and economic outcomes for a novel method of conducting clinical trials. The results will be broadly applicable to trials of other diseases.

Keywords

Clinical Trial; Informed Consent; Internet; Mobile Devices; Multimedia; Pediatric

INTRODUCTION

Clinical trials are the cornerstone of research evaluating drug efficacy and safety. Participation in most clinical research studies involves three primary components: providing informed consent; attending visits at the study center; and completing some procedures at home. However, increases in the numbers of procedures, study staff work burden, and longer trial duration coupled with reduced enrollment and retention rate of patient volunteers are increasing the cost and decreasing the value of clinical trials [1]. The cost of Phase III/IV trials was estimated at \$47,000 per participant in 2011, an 83% increase from the previous 3 years [2, 3] suggesting that the current model for clinical research is fiscally unsustainable.

Current methods of obtaining informed consent using a written document are insufficient [4–11]. Data show that research participants have a poor understanding of the basic elements of informed consent whether provided in oral or written format [4, 8, 12–17]. Multimedia formats can enhance comprehension in the research informed consent process [5, 18] and participants, including children, prefer multimedia to written formats [18, 19].

The number of clinic visit procedures, including the number of extraneous procedures, and length of trials have increased while enrollment and retention rates have decreased substantially in recent years [20, 21]. Participants often perceive joining a trial as inconvenient and time-consuming [22–25]. Telemedicine has been incorporated into asthma trials since 2001 and well-designed studies indicate mostly positive effects of the

intervention [26]. However, no telemedicine trials in asthma have evaluated whether these strategies reduce clinical trials costs [27].

Health information technologies have been used since the early 2000s to collect data from participants at home and the most common uses in asthma include symptom data, spirometry or peak flow data, and monitoring medication adherence [28–41]. Patients with asthma are enthusiastic about using mobile, internet or electronic means for recording data [39, 41–44]. Several studies have evaluated the quality and reliability of the data entered electronically and suggest that information may be more complete and accurate than data entered on written questionnaires [35, 36, 39].

In 2011, the National Institutes of Health (NIH) issued a Funding Opportunity Announcement entitled “Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials (RFA-HL-12-019)”. The goals for the application were to test new and innovative designs that have not been previously studied but that hold potential for increased efficiency and reduced cost of conducting clinical trials. Emphasis was to be placed on exploring novel methods for obtaining consent, reducing specialized infrastructure, minimizing visits, developing low-cost methods for monitoring study conduct, and testing the feasibility in a clinical trial.

These features have been incorporated into the Use of Mobile Devices and the Internet to Streamline an Asthma Clinical Trial (MICT) grant that will compare a *streamlined* design with a *traditional* clinical trial for pediatric asthma funded by the NIH (R01HL114899) and be conducted at outpatient clinics in the Nemours Children’s Health System located in Florida and the Delaware Valley. The purpose of this manuscript is to describe the methods and rationale for the *streamlined* trial.

MATERIAL AND METHODS

Trial Design

The *traditional* trial is a multi-center, double-blinded, placebo-controlled study designed to determine the optimal way to de-escalate therapy in patients with moderate persistent asthma that is well controlled on a fixed-dose combination of inhaled corticosteroid plus a long-acting beta₂-agonist (Long-acting Beta Agonist Step Down Study [LASST, NCT01437995]). The trial is being conducted at 18 academic asthma research centers that are part of the American Lung Association Asthma Clinical Research Centers (ALA-ACRC) network. GlaxoSmithKline (GSK) provided funding and blinded drug for the trial but did not have input into the scientific design. The trial was conceived and designed by academic researchers of the ALA-ACRC.

The *streamlined* trial [MICT, NCT02061280] is modeled after the *traditional* trial. While the *traditional* is being conducted at all of the 18 ALA-ACRC academic sites including the Nemours Children’s Health System sites in Jacksonville FL, Orlando FL, and Wilmington DE, the *streamlined* trial is being conducted only at Nemours Children’s Health System sites (Jacksonville FL, Orlando FL, Pensacola FL, Wilmington DE, and Philadelphia PA). GSK had no input into the concept, design, or implementation of the *streamlined* trial.

Researchers from the Nemours Children's Health System and the ALA-ACRC Data Coordinating Center were responsible for the design of the *streamlined* trial.

The relationship between the trial designs for the *streamlined* and *traditional* trials is shown in Figures 1 and 2.

The specific aims of MICT are: to measure and compare consent comprehension using web-based delivery of informed consent material via a dynamic interactive multimedia platform (Aim 1); to compare timeliness and completeness of study questionnaire and diary data completed electronically using an iPad with wireless internet access, and quality of spirometry performed during FaceTime visits with study staff observing participants who are using an EasyOne Plus meter from their home (Aim 2); and to compare Asthma Control Test scores between the *streamlined* and *traditional* trial design in order to test whether employing the novel internet and mobile device methods in the *streamlined* approach alter the clinical trial's clinically based outcomes (Aim 3). The outcomes for each aim will be compared with a concurrently conducted *traditional* clinical trial (LASST) also performed within the Nemours Children's Health System.

The primary differences between the *traditional* trial and the *streamlined* trial are listed in Table 1.

The shortened duration and smaller sample size of the *streamlined* study are due to the pilot nature of the grant. The *streamlined* trial is performed only in adolescents because the study is being conducted within a pediatric health-system that is only enrolling adolescents into the *traditional* trial. The consent processes differ because Aim 1 is to evaluate a novel method for obtaining informed consent (described below). Study treatments are open-label in the *streamlined* trial due to the unavailability of blinded drug from GSK. The Asthma Control Test (ACT) was selected as an alternative primary endpoint as the *streamlined* trial duration was not sufficiently long to evaluate episodes of poor asthma control in this pilot project with the NIH budget limits and proposed sample size. A one-year of follow-up period is typically required to capture episodes of poor asthma control, which is the duration of follow-up in the *traditional* trial. The ACT is being conducted at the same intervals in the *streamlined* and *traditional* trial. Furthermore, the Asthma Control Test is a patient reported outcome that is easier to assess than the primary outcome for the *traditional* trial, treatment failure. The Asthma Control Test is a 5-question Likert scale questionnaire that generates a score; a cut point has been validated to distinguish poor from well-controlled asthma [45]. The Nemours Children's Health System locations are the only sites conducting the *streamlined* trial because of the need for a single electronic health record system and secure patient portal access for participants to have communication with the study coordinators. Certain procedures are conducted only in the *traditional* trial for practical reasons: Measurement of exhaled nitric oxide requires expensive equipment and supply costs and could not be purchased for all sites; the Asthma Symptom Utility Index questionnaire must be administered in person by a study coordinator whereas a goal of the *streamlined* trial is to have the questionnaires and forms self-administered and completed electronically off-site from the clinic; and the Asthma in Females questionnaire was expected to apply to only a small number of female participants.

Development of the multi-media Informed Consent Video for the *Streamlined* Trial

The RFA included a request to explore novel methods for obtaining consent. Therefore, we created a multi-media web-based informed consent video that provides study information including all the basic elements, as well as, additional elements of informed consent [14]. The intent was to translate complex study information into an understandable and visually appealing video format that is suitable for low health literacy participants and their family. The video is viewed online by potential study participants followed by informed consent discussion via telephone with the study coordinator; informed consent is documented electronically. The development of the video and website materials occurred with considerable input from Nemours ethics experts. Due to the non-standard nature of the proposed consent process, and the need to have ongoing IRB input into the design of the electronic consent and website content, IRB review and approval in this instance could best be described as an ongoing collaboration between the research team and Nemours IRB leadership. Co-authors Wysocki (IRB Chair) and Garfinkel (Director of Nemours Office of Human Subjects Protection) recused themselves from all official IRB deliberations about this study. The design and content of the video and supplementary materials were developed using theory and principles to facilitate electronic learning [46, 47].

The narrator script for video content was adapted from the 13-page single-spaced parental permission form used for the *traditional* trial. The Nemours web team and principal investigator developed a script for the proposed video images. IRB approval for the video script was sought prior to any video recording because changes to the video after shooting would have been excessively expensive. A professional video director and local actor talent was used to create the video. The video content is divided into five sections each 3- to 4-minutes in length: About this Study, Participating in the Study, Possible Benefits and Risks, Payment for Participating, and Protecting your Privacy. The 3- to 4-minute section duration was recommended by the Nemours web team as the length of time that most people are willing to watch a segment in one sitting (which is also about the average length of a YouTube video).

In addition, each video section has content-related sidebar information with a tab that changes color when the video reaches a point that is described in the sidebar. The participant can select a sidebar tab to read additional study details (Figure 3). A segment of the video may be viewed in the Supplementary Material.

Creating the sidebar enabled us to keep the video length to about 15 minutes while providing additional information that the IRB required to be included for the informed consent process. For example, sidebar tabs “What is required for participation” and “What will the participants be asked to do” were created for the video section 2, “Participating in the Study”.

The 5 video sections must be viewed in sequence before the programming built into the video allows the viewer to progress to the next section. The participant can pause the video at anytime and resume where they left off. At the end of each video section, participants are required to answer 2 to 3 multiple-choice questions before the next video section becomes available. All responses, whether incorrect or correct, are provided with the correct answer

to reinforce learning. Upon completing viewing of the final video section, participants are provided a button to select if they are ready to enroll. An automatic email is generated to viewers thanking them for their interest and an email is sent to the study staff indicating that the video has been viewed in its entirety. Data from video views are captured in one of several Research Electronic Data Capture (REDCap) [48] instruments designed for the study and include the date and time watched, who watched the video (parent, child, or other), which sections were viewed, responses to the quizzes, which sidebar tabs were selected, and the duration that the video was watched.

The Informed Consent Process

Aim 1 of the project is to measure and compare parent and adolescent comprehension of the study information provided during the informed consent process between the *streamlined* and *traditional* trials. The study team psychologists and principal investigator developed a 17-item open-ended question consent questionnaire designed to assess knowledge and comprehension of the consent material. The interview questions were derived from questionnaires previously developed by co-investigators of this grant (NCI R03CA133442, NCI R03CA133419). The study coordinators are trained by the psychology staff to ask each interview question and to use non-leading prompts to elicit further knowledge when appropriate. Each consent interview question is scored by two coders as incorrect, partially correct, or correct.

To assess health literacy, each parent and adolescent is administered the Newest Vital Sign tool and results will be used as a covariate in analyses [49–51] [52–54]. The Newest Vital Sign (based on a nutrition label from an ice cream container) was selected over other measures of health literacy because it is a valid and reliable screening tool in both parents and caregivers of adolescents, and in adolescents; requires only 3 to 4 minutes to complete; and it has no ceiling effect [50, 52–55].

Streamlined Trial Informed Consent Process

After viewing the consent video and website materials, the parent and adolescent are scheduled for a one-on-one telephone call with the study coordinator to conduct the informed consent interview and the Newest Vital Sign. The telephone interaction is audio recorded (with consent from the parent and participant) using Cisco Webex™ for later analysis by the coders. The consent interview questions are administered separately to the parent and adolescent in order to measure comprehension for each independently. The parent is instructed to have the adolescent away from the phone during the interview and to not provide cues to the adolescent during their interview. After the consent interview is complete, the coordinator reviews study understanding and answers any remaining questions.

To obtain electronic documentation of informed consent, a short single-page parental permission form was adapted from the signature page of Nemours parental permission and assent IRB template forms. The forms are sent to MyNemours accounts (MyChart®, Epic®), secure online patient portals for Nemours patients and families, that have been set up separately for the parent and adolescent [56]. The parental permission is sent to the

parent's MyNemours account and the assent is sent to the adolescent's MyNemours account. The parental permission form has radio buttons to capture discrete responses for willingness to participate, relationship to the adolescent (parent or legal guardian), sending pulmonary function testing results to their primary care physician, and DNA storage. A short form was developed for pediatric assent. The parent and adolescent type their names onto the parental permission form and assent forms, respectively, and submit the document. The submitted document (with the date and time submitted) is stored in Epic® as part of the participant's electronic health record.

Documentation of legal guardianship is determined prior to any MyNemours account being created within the Nemours Children's Health System. Because Epic already meets 21 CFR [57] requirements, legal guardianship is verified through Nemours standard processes, and tracking of who sent the form and who submitted the form (an audit trail can be followed), this consent process was determined to meet the standards for electronic documentation of informed consent.

Traditional Trial Informed Consent Process

Informed consent consisting of parental permission and adolescent assent is obtained in a conventional face-to-face manner between the parent and adolescent and the study coordinator. The parent and adolescent are provided the consent documents upon arrival at their initial visit (or the documents may have been emailed/mailed to the family at their request ahead of the appointment) and allowed as much time as needed, usually about 20 to 30 minutes, to review the document (13 single-spaced pages including the signature page). The coordinator conducts the consent comprehension interview and Newest Vital Sign separately with the parent and then invites the adolescent into the room for an interview and Newest Vital Sign assessment. Because the parent is still in the room with the child, the coordinator instructs the parent not to cue the adolescent with answers to the interview questions. After the consent interview questions are completed, the coordinator reviews any incorrect responses and answers any remaining questions before obtaining parent and adolescent signatures on the parental permission form and assent documents, respectively. The entire interaction is audio recorded using the Audacity program [58] for later analysis by the coders; written informed consent from the parent and assent from the adolescent is obtained prior to audio recording.

Development of the Study Website

The study website is made available to *streamlined* trial participants who have provided consent and completed Visit 1. The study website was developed by the Nemours Bioinformatics Core Facility with the input from Nemours Web Development Team to be intuitively easy to use and visually appealing (Figure 4). The website is accessed by any device with internet connection using a unique username and password for each participant. Each participant is provided with an iPad with Wi-Fi at Visit 1. The iPad has been pre-configured with iPad passcodes and study Gmail accounts for use by each individual participant. The iPad is used to complete the Morning Report and Evening Report by simply tapping an icon (Figure 5) or can be accessed by any device with an internet connection by going to the study website and logging in.

The study website is the primary access point for entering peak expiratory flow and symptom data every morning and evening. A unique feature of the study website is that the Morning and Evening Reports section is open for data entry only during specific time intervals (morning: 3AM to 3PM and evening: 3PM to 3AM) which prevents back filling of diary data often seen with paper forms [41]. Peak expiratory flows are entered on the Morning Report and the participant's personalized Asthma Action Plan will open up automatically if the day's value is in the yellow or red zone. Once the user has logged into the study website for the first time on their iPad, a cookie is stored on the device and subsequent access to the Morning or Evening Report can be done by simply tapping the icon. Data from each entry is stored in the REDCap system and can be accessed by the study staff 24/7 [48]. Features in REDCap that are advantageous for this project include: (1) user authentication and role-based security, (2) intuitive case report forms, (3) real-time data validation and data integrity checks, (3) audit capabilities, (4) central data storage and backups, and (5) data export to commonly used statistical packages [48].

Because the data are captured in real-time in REDCap, several safety features are incorporated into the study for the Morning and Evening Reports. Automatic emails are sent to the study coordinator when the participant enters:

- A peak expiratory flow value in the red zone for two consecutive days;
- New or increased use of asthma medications;
- An urgent or unscheduled visit for medical care (Figure 6 and Figure 7);
- Study Diskus counter numbers that indicate adherence is below 75%, or ProAir counter numbers that indicate 10 or more puffs of albuterol (one nebulizer treatment = 2 puffs) are used two days in a row;
- No morning or evening report submissions for 3 days in a row.

For each morning or evening entry submitted, the participant earns \$1 (\$2/day); the total potential amount that can be earned for twice daily reporting is approximately \$300. The study website can be accessed 24/7 and has links including their personalized asthma action plan, instructional videos on how to use the study medications, and national websites for asthma information.

Randomization and Trial Procedures

Participants undergo two randomizations, the first to trial (MIST or LASST) and the second to treatment assignment. The study staff log into a website created by the ALA-ACRC data coordinating center (Johns Hopkins University) to generate randomizations that are stratified by site to minimize biases due to site variability. The trial randomizations are stratified for the Jacksonville FL, Orlando FL, and Wilmington DE sites as these are the sites participating in both the *streamlined* and *traditional* trials. The trial randomization uses a modified Zelen design in which potential participants are randomized to be approached about enrolling in the *traditional* or *streamlined* trial prior to obtaining consent to participate in the trial [59, 60]. Random treatment assignments are assigned at Visit 3 after ensuring that participants meet all criteria for study continuation, primarily that the participant has stable

asthma and is suitable for de-escalation of asthma therapy. The *streamlined* trial is also randomized by site for treatment assignment at the participating sites Jacksonville FL, Orlando FL, Pensacola, FL, Wilmington DE, and Philadelphia PA. The *traditional* trial treatment allocation is generated by the ALA-ACRC data coordinating center for the 18 academic sites participating, for which the Nemours Pediatric Health System is considered a single site. Primary inclusion and exclusion criteria are shown in Table 2. The time and events schedule for the *streamlined* trial are shown in Table 3.

Participant identification and recruitment

Participants for the *streamlined* and *traditional* trial are identified and recruited in the same manner. Nemours implemented an electronic health record (EHR) (Epic Systems, Verona, WI) in 1998 with rollout to all Nemours campuses completed by 2005. Thus, Nemours has an extensive database of children with asthma from which to identify potentially suitable participants. An EPIC data warehouse query is generated using the inclusion criteria for age, diagnosis of asthma (ICD-9 code, 493.x), and medication prescribed on the most recent clinic visit. The recruiting staff reviews the EHR record for any information that would indicate the participant has unstable asthma or is otherwise unsuitable for participation. Any medical questions about a potential participant are resolved by discussions with the principal investigator, study physician, and study coordinator prior to initiating contact with the family. Once a suitable participant is identified, the recruiter performs the trial assignment and contacts the family by telephone and leaves a voice message if needed. Second and third attempts to reach families for unreturned calls are initiated two and three weeks later, and if still no response a flyer is sent with study information. In addition, “patient lists”, a feature of EPIC, are created for potential participants we have attempted to reach. These lists alert the study staff when the patient is coming to Nemours for a clinic appointment for any subspecialty. The staff contacts the family to let them know we will attempt to speak with them while at the clinic. In addition, we distribute flyers at health fairs, non-Nemours physician offices, and other locations; have information on Nemours Facebook page; and conduct interviews with local TV stations. Potential participants who have been randomized to the *streamlined* trial and who indicate preliminary interest in the study have data entered into REDCap, which will trigger an email contact with a unique link inviting the participant to view the consent video.

Study Visits for the *Streamlined* Trial

Only the first and last study visits are conducted onsite at the clinic in the *streamlined* trial; all other visits are conducted by FaceTime using the iPad. Prior to the onsite or FaceTime appointments (including Visit 1), participants are sent secure links from REDCap or via php code to their study email account to complete questionnaires including Asthma Control Test, Clinic Visit Assessment form, Quality of Life, and EuroQol-5 Dimensions (EQ-5D). These links are participant specific and once completed and submitted, the data are stored on the REDCap server in that participant’s data record. If eligibility is confirmed at Visit 1, the participant receives their iPad, which has been pre-loaded with icons for the study Gmail account; FaceTime contacts; videos for how to perform spirometry and do the FaceTime visits, and use the EasyOne handheld Spirometer; the study website; and morning and evening reports. The participant is trained on use of the EasyOne and baseline PFTs are

obtained. The EasyOne device was selected because of its accurate and reliable measures of lung function in pediatric patients [65] and suitability for collection of longitudinal data [66]. Data values that indicate worsening of asthma control trigger alert emails sent to the study coordinators to prompt further review. During the FaceTime appointments, the study coordinator reviews unresolved email alerts, morning and evening report adherence, medication issues; and conducts spirometry. At the final visit, the EasyOne is returned and spirometry data is downloaded. The iPad is configured for personal use and returned to the participant to keep.

Payment for Study Participation

In the *streamlined* trial, participants are paid using the CT Payer system. CT Payer is an online payment operation system that allows for HIPAA safe payments using reloadable prepaid MasterCards to clinical trial participants [67]. When participants complete study responsibilities, research staff pay them immediately for onsite or FaceTime appointments and bi-weekly for Morning and Evening Report submissions, by loading payment onto their card via the CT Payer online utility. Payments to *traditional* trial participants are made through generating stipend requests by the coordinator that are routed through the Nemours Research Administration office, and then to Nemours Accounting Department. A paper cheque is generated which is then mailed to the participant's home address. Participants are paid following each clinic visit.

Tracking Study Costs

Determining study costs is an essential component of the *streamlined* and *traditional* trials. Nemours has had an online effort reporting system for over 10 years in which research staff record time spent on each research project individually on a daily basis. In order to obtain more granular data for this project, the study staff keep stopwatches with them at all times to record the time for both the *traditional* and *streamlined* trial. Data collection for tracked effort is divided into discrete sections and subsections:

Preparing participant information for visit (chart reviews, paperwork preparation)

- Pre-visit procedures
- Onsite or FaceTime visit procedures
- Post-visit procedures
- Consenting procedures
- Charting and interim visit procedures

We will use salary data to determine the staff costs for conducting the *traditional* and *streamlined* clinical trials. Study infrastructure (study website and consent video) start-up costs including IRB submission will be included for the *streamlined* trial. Because of its novel design, the *streamlined* trial required considerable interaction with the IRB prior to submission which differs from typical clinical trial submissions to the IRB. We will also include the costs required at our institution for processing stipend cheques to trial participants for the *traditional* trial and the CT Payer payments for the *streamlined* trial.

Satisfaction Survey for the Consent Process

A satisfaction survey was developed specifically to evaluate the parent's satisfaction with the consent process for both the *streamlined* and *traditional* trials. The electronic survey is sent to parents of participants through REDCap after Visit 1 in the *streamlined* and *traditional* trials. On each survey, parents are asked about their satisfaction on the amount of and the way information was provided as well as key questions to determine if the consent process provided them with the necessary information to make a well-informed decision about participation. In addition, a slider scale is provided to determine their preference for the video website and phone call at one extreme and written consent with in-person meeting with the study staff at the other extreme.

Data Analysis

The sample size was determined for Specific Aim 1 (comprehension and retention following the consent interview between participants enrolled in the *streamlined* and *traditional* trial), with subsequent assessment of detectable differences for Specific Aims 2 and 3 using that sample size. Because our hypothesis is that our novel web-based consent process will be at least as good as the *traditional* process, we have elected to use a non-inferiority design. We used the preliminary data from two R03 grants on consent comprehension, assumed normalcy of the data, and defined the non-inferiority margin as 2.4, which corresponds to 0.5 standard deviation units to calculate the power for a range of sample sizes.

Based on these calculations and other considerations discussed below, we propose to randomize 120 participants: 60 participants into the *streamlined* trial and 60 participants into the *traditional* trial. This will give us greater than 80% power to reject the hypothesis that the web-based consent process yields significantly lower scores than the traditional process at a threshold of 2.4 units on the consent interview scale, after allowing for approximately 10% loss to follow-up.

For Aim 2, because we are unaware of meaningful measures to establish non-inferiority margins for completeness and quality of data collection, we will use 0.5 SD as a qualitative measure of non-inferiority. We anticipate this sample size will allow us to estimate the proportion of study days with diary data with a 95% confidence interval width of 15%. For example, in a recently completed ALA-ACRC pediatric trial, the proportion of days with a diary card entry was 90%, the corresponding 95% confidence interval would be 82.5% to 97.5%. The second objective of Aim 2 is to evaluate the comparability of the quality of spirometry from the *streamlined* and *traditional* trials. We will employ the spirometry review system currently used in an ALA-ACRC trial, which grades each spirometry session with a letter grade (A to F). For initial spirometry sessions, the current overall Grade Point Average (GPA) is 3.68, with a standard deviation of 0.67. Using these values, with a sample size of 60 in each of the *traditional* and *streamlined* trials, we expect to be able to estimate spirometry quality using a similar review system with a 95% confidence interval ranging from approximately 3.51 to 3.85, which should be adequate to allow us to compare spirometry quality in the two groups.

For Aim 3, we will have greater than 90% power to detect a clinically meaningful difference of 3 in the ACT score [61, 68] between one of the treatment arms in the *traditional* trial and the corresponding treatment arm in the *streamlined* trial, assuming a mean score of 19 with a standard deviation of 4 (data from a ALA-ACRC trial).

We will compare the consent interview scores of those participating in the *streamlined* trial with those participating in the *traditional* trial (Specific Aim 1) and data completeness and quality GPA (Specific Aim 2) using t-tests without adjustment to estimate the differences in scores. We will consider the novel interactive consent process to be non-inferior to the *traditional* process if the upper bound of the 95% confidence interval for the difference (*traditional* minus *streamlined*) is less than 2.4, our a priori margin of non-inferiority as determined from pilot data using the assessment. We will use a similar approach for the evaluating non-inferiority of data quality.

For Aim 3, we will compare ACT scores within each treatment group between the *traditional* and *streamlined* groups, using a multivariate regression model that incorporates both trial and treatment group. We will evaluate the contrast for each treatment group and determine if there is evidence to support an interaction between treatment group and trial. If there is not sufficient evidence to support an interaction, we will perform the test of the trial effect on the change in ACT score without including an interaction term. In all cases, primary analyses will use crude (unadjusted) comparisons, although we will also report analyses that include adjustments for possible differences between the *streamlined* and *traditional* groups in important demographic characteristics.

Progress and Challenges

The primary challenge for the project has been participant recruitment. Identification of suitable participants is predicated on the *traditional* trial inclusion and exclusion criteria, which are used for the *streamlined* trial. Because Nemours is a pediatric institution, we are limited to enrollment of adolescents 12 through 17 years old whereas other sites within the ALA-ACRC are able to enroll adults. However, Nemours has recruited very successfully for ALA-ACRC trials for the past 15 years by enrolling participants from the organization's subspecialty pulmonary and allergy clinics. To bolster recruitment, we have added sites within the Nemours primary care network to refer patients to the trial. Nemours has over 30 primary care sites in the Delaware Valley and 12 surrounding the Nemours Children's Hospital in Orlando. Adding the primary care sites will also increase the robustness of the data.

Because enrollment for the *traditional* trial was competitive across the 18 ALA-ACRC sites, the *streamlined* trial was faced with matching the *traditional* trial enrollment deadline which ended in July 2014. Enrollment for the *traditional* trial began in the summer of 2012 and the *streamlined* study website was ready in June 2013. Therefore, we began collecting data in January 2013 for the consent comprehension portion of the project in *traditional* trial participants before the trial randomization process began to ensure adequate data were collected for Aim 1. To date, we have enrolled 31 participants in the *streamlined* trial and 37 in the *traditional* trial.

In addition, early in the trial we found that sending emails with the study questionnaire links far in advance of the clinic or FaceTime appointment resulted in participants not completing the questionnaires in a timely manner. Thus, we changed our process such that the questionnaires are sent 4 days and 3 nights before the scheduled appointment. The study staff monitor for questionnaire completion in REDCap as the visit approaches but at times follow-up text messages and phone calls are required.

DISCUSSION

This grant was funded through NHLBI in response to RFA-HL-12-019 “Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials” for 4-years starting in August 2012. The project received IRB approval in June 2012 to develop the study processes including the novel consenting component. The consent video script and the electronic consenting process were approved by the IRB in May 2013. The study website was completed in June 2013.

Phase III/IV trials are often complex and involve considerable staff time and numerous study procedures. Over the 1999 to 2005 period, Phase III staff work burden increased by nearly 70% and median number of study procedures by 65% according to one report [21]. Thus, the typical Phase III/IV trial design provided an opportunity to create a study which could focus on reducing the number of procedures performed by study staff and reduce the amount of time the study staff spend at clinic visit appointments with study participants. To optimally compare two study designs, it is important that the trials run concurrently by the same study staff that have all received the same training for each of the projects. At the time the RFA was posted, we were fortunate that the ALA-ACRC network was finalizing LASST, a large Phase IV comparative effectiveness trial, of traditional proportions in both sample size and number of procedures. Our *streamlined* trial was designed to shorten the consent process from the study staff perspective, and eliminate as much of the pre-study visit, onsite study visit, and immediate post-study visit procedures for the study staff. One other area we chose to focus on was eliminating the tedious process for requisitioning paper cheques for participant stipends that involves multiple steps, individuals, and departments before they are mailed to participants. Each step in the stipend process is another opportunity for problems and delays so we chose to work with CT Payer for online payments. CT Payer had reasonable start-up fees and easy setup process.

There are few recently published data on costs for conducting clinical trials [69–71]. Therefore, we developed a process for capturing granular data on the time taken to conduct each study step by the study staff for both the *traditional* and *streamlined* trial. Having the same staff conduct both the *traditional* and *streamlined* trials will allow for accurate comparison of study expenses. Data are recorded in real-time by having all study staff use stopwatches to record the time spent.

At the time the study was developed, there were fewer tablet devices on the market than are available currently. The intent was to have a device the participants could use to complete study questionnaires from home with an integrated email program for sending/receiving the questionnaires. In addition, in order to assess participant effort when performing spirometry

for scheduled appointments, we needed a device that would allow us to view their spirometry technique in real time. While we could have used a video conferencing program such as Skype for most any device, it would have meant setting up additional accounts and passwords whereas the Apple iPad had FaceTime integrated into the system. We also debated about including a security program, Mobile Iron Sentry, on the iPad to allow study staff to track the device should it be lost or stolen. However, the iPad 2 iOS (the device we purchased for the project) would not prevent the device from being wiped even with Mobile Iron and could be set up for a new user should it be stolen. With each iPad we provided the participants with a Defender case to minimize the chance for damage should the iPad be dropped. So far no iPads have been lost or stolen and only one iPad developed a crack on the screen but was not replaced.

We also debated whether to use iPads with Wi-Fi only or cellular service. The intent was to allow participants to have 24/7 internet access for the purpose of completing questionnaires and morning and evening reports without service interruption. However, there was concern that the cellular data plan could be easily used up by adolescents before the service month ended and then there might be difficulty completing the study procedures. Therefore, we decided to purchase iPads with Wi-Fi capability. We purchased a limited number of Sprint hotspots for families without Wi-Fi to borrow for the study period or if they were travelling and would not have Wi-Fi at their destination. Thus far, only 20% of participants have required hotspot use.

REDCap has been very functional for the study purpose. We selected using REDCap to house the data because we had a bioinformatics team that is highly experienced in its use and it is available to institutions worldwide. In addition, our intent is to have our data system be freely available to other investigators after the trial is complete. Currently, REDCap is used in over 1300 institutions in 86 countries by 134,000 projects [48, 72].

Conclusion

We have developed a multi-media informed consent process that allows for electronic documentation of consent that families can complete from home. The process meets both federal and ethical requirements for electronic signature and engaging in a consent process with families, respectively. In addition, we used REDCap, a database system widely available at academic centers around the world, to send participant specific questionnaires by email and receive completed responses without the need for external data entry. This approach was developed to improve the efficiency of and reduce the costs of conducting large clinical trials. These processes will be applicable to clinical trials in most therapeutic areas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Trial design for *streamlined* and *traditional* trials

The relationship between the study design for the *streamlined* (MIST) and *traditional* (LASST) clinical trials. MIST, Mobile Devices and the Internet to Streamline an Asthma Clinical Trial; LASST, Long-acting Beta Agonist Step Down Study. Participants are randomized to either the *streamlined* or *traditional* trial design.

Figure 2.

Details of visit type for *streamlined* trial design

Sequence of onsite and FaceTime virtual study visits in the streamlined trial design. Only the first and final study visits occur at the study site.

Figure 3.
Screenshot of consent video navigation page
Streamlined trial consent web page demonstrating the 5 parts of the consent video. The sidebar material on the left side of the video image provides additional detail on the study and the tabs highlight as relevant parts of the video are played.

Figure 4.
Screenshot of study webpage for morning and evening data entry
Streamlined trial study site webpage for entering symptom report data each morning and evening. Additional information can be accessed by selecting the links on the left.

Figure 5.

Screenshot of iPad dock icons

The iPad dock icons including (left to right) study Gmail account, preloaded contact information for FaceTime appointments, video for using the EasyOne and conducting FaceTime appointments, login screen for the consent and study websites, Morning Report for entering PEF and medication use, Evening Report for entering symptoms and unscheduled medication use. PEF, peak expiratory flow.

Did you need urgent unscheduled medical attention last night or today? ☒ Yes ☐ No

Why did you need urgent medical attention?
(check all that apply)

- ☐ This was a phone contact with the study site about my asthma
- ☐ This was a phone contact with my doctor's office about my asthma
- ☐ This was a clinic visit to the study site about my asthma
- ☐ This was a visit to my doctor's office about my asthma
- ☒ This was an emergency department visit

Shortness of breath and wheezing all day.

Tell us about this event

Figure 6.
Screenshot of evening report data entry screen
Example of drop down questions that appear if the participant selects that they required unscheduled medical care on the Evening Report.

Figure 7.

Screenshot of alert email to study coordinators

Example of an email received by the study coordinator when a participant submits an Evening Report indicating unscheduled medical care. Any text that the participant includes in the Evening Report submission is included in the email.

Table 1

Design differences between *streamlined* and *traditional* clinical trial.

	<i>Streamlined</i> (MICT)	<i>Traditional</i> (LASST)
Study Duration	20 weeks	56 weeks
Sample Size	120	450
Ages	12 to 17 years	12 years and older
Informed Consent Process	Web-based delivery of informed consent material via a dynamic interactive multimedia platform and electronic informed consent documentation	Conventional face-to-face interaction with study staff and written documentation of informed consent
Study treatments	Open-label	Double-blinded
Primary clinical endpoints	Asthma Control Test	Episode of poor asthma control; Asthma Control Test is a secondary endpoint
Study site locations	Nemours Children's Health System in Florida and the Delaware Valley	18 academic asthma research centers located in the United States that are part of the ALA-ACRC (including Nemours Children's Health System in Florida and the Delaware Valley)
Procedures being done in <i>Traditional</i> but not in <i>Streamlined</i> Trial		Exhaled nitric oxide measurement Asthma Symptom Utility Index questionnaire Asthma in Females questionnaire

Table 2**Primary Inclusion and Exclusion Criteria**

Inclusion Criteria	
Age	<ul style="list-style-type: none"> 12–80 years for LASST 12–17 years for MICT and LASST at Nemours Children’s Health System
Diagnosis	Physician diagnosed asthma (without any other co-morbid pulmonary disease)
Required Daily Medication at Baseline (any combination of medium-dose inhaled corticosteroid plus long-acting beta agonist given twice daily)	<ul style="list-style-type: none"> Advair Diskus – 250/50 mcg, 1 puff 2× daily Advair HFA – 115/21 mcg, 2 puffs 2× daily Symbicort – 160/4.5 mcg, 2 puffs 2× daily Dulera – 100/5 mcg, 2 puffs 2× daily <p>Or a combination of medium dose ICS + long-acting beta agonist:</p> <ul style="list-style-type: none"> Flovent (fluticasone)HFA – greater than 264 mcg and up to 480 mcg/day Flovent (fluticasone) Diskus – greater than 300 mcg and up to 500 mcg/day Asmanex (mometasone) – 400 mcg/day Qvar (beclomethasone) – greater than 240 mcg and up to 480 mcg/day Alvesco (ciclesonide) – 320 mcg/day Pulmicort Flexhaler (budesonide) – greater than 600 mcg and up to 1200 mcg/day <p>PLUS Long-acting beta agonist</p> <ul style="list-style-type: none"> Serevent (salmeterol) Diskus – 50 mcg every 12 hours Foradil (formoterol) Aerolizer – 12 mcg every 12 hour
Asthma Control	Asthma Control Test score 20, and the absence of unscheduled visits or use of rescue prednisone for 4 weeks prior to enrollment ^{45, 60}
FEV1	Pre-bronchodilator FEV ₁ 70% predicted
Smoking History	< 10 pack/year history of tobacco use and abstinence for at least 1 year
Exclusion Criteria	
	Chronic oral steroid therapy
	Hospitalization or urgent care visit within 4 weeks of the screening visit
	Near fatal asthma within 2 years of enrollment or high risk of near fatal or fatal asthma ^{61–63}
	Women who are pregnant or lactating

Table 3**Time and Events Schedule**

Visit	V0	V1 Part 1 ^a	V1 Part 2 ^b	V2	V3	V4	V5	V6 Part 1 ^a	V6 Part 2 ^b
Time Window (weeks)		-12 to -10	-10 to -6	-6 to -2		2-4	5-7	11-13	
Target (week)		-11	-8	-4	0	3	6	12	
Type of visit ¹	Pre V1 Eligibility	Phone	Clinic	iPad/ FaceTime	iPad FaceTime	iPad FaceTime	iPad FaceTime	iPad FaceTime	Clinic
Trial Randomization	x								
Consent		x							
Eligibility evaluation ²	x	x	x		x				
Procedures									
Pregnancy test			x						
Blood (DNA, allergy)									x
Height and Weight ³			x	x	x		x	x	x
Vital Signs			x						x
Physical Exam			x						x
Treatment Randomization ⁵					x				
Consent Interview		x						x	
Exhaled nitric oxide (selected sites)			x						x
Spirometry Pre and Post 6			x	x	x	x	x		
Questionnaires^c									
Screening Form		x			x				
Baseline asthma and medical history			x						
Asthma Control Test			x	x	x	x	x	x	
Children's Health Survey for Asthma			x		x		x	x	
Clinic Visit Form				x	x	x	x	x	
EQ-5D			x					x	
Quality of Life			x		x		x	x	
Complete Morning and Evening reports on iPad				x	x	x	x	x	

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Visit	V0	V1 Part I ^a	V1 Part 2 ^b	V2	V3	V4	V5	V6 Part I ^a	V6 Part 2 ^b
Medication and device distribution									
Treatment medication distribution ⁴	x	x	x	x	x	x	x		
iPad Daily Report/PEF/AAP review	x	x	x	x	x	x			
Receive/Return iPad and EasyOne ⁸	x						X		

^aConducted during FaceTime visit

^bConducted at clinic site

^cQuestionnaires are completed online prior to each iPad/FaceTime visit