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Delivering clinical trials at home: protocol, design and implementation of a direct-to-family paediatric lupus trial

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ABSTRACT

Introduction Direct-to-family clinical trials efficiently provide data while reducing the participation burden for children and their families. Although these trials can offer significant advantages over traditional clinical trials, the process of designing and implementing direct-to-family studies is poorly defined, especially in children with rheumatic disease. This paper provides lessons learnt from the design and implementation of a self-controlled, direct-to-family pilot trial aimed to evaluate the effects of a medication management device on adherence to hydroxychloroquine in paediatric SLE.

Methods Several design features accommodate a direct-to-family approach. Participants meeting eligibility criteria from across the USA were identified a priori through a disease registry, and all outcome data are collected remotely. The primary outcome (medication adherence) is evaluated using electronic medication event-monitoring, plasma drug levels, patient questionnaires and pill counts. Secondary and exploratory endpoints include (1) lupus disease activity measured by a remote SLE Disease Activity Index examination and the Systemic Lupus Activity Questionnaire; and (2) hydroxychloroquine pharmacokinetics and pharmacodynamics. Recruitment of the initial target of 20 participants was achieved within 10 days. Due to initial recruitment success, enrolment was increased to 26 participants. Additional participants who were interested were placed on a waiting list in case of dropouts during the study.

Discussion and dissemination Direct-to-family trials offer several advantages but present unique challenges. Lessons learnt from the protocol development, design, and implementation of this trial will inform future direct-to-family trials for children and adults with rheumatic diseases. Additionally, the data collected remotely in this trial will provide critical information regarding the accuracy of teleresearch in lupus, the impact of adherence to hydroxychloroquine on disease activity and a pharmacokinetic analysis to inform paediatric-specific dosing of hydroxychloroquine.

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INTRODUCTION

Clinical trials provide essential information to guide safe and effective interventions, but many fail to meet primary endpoint(s), terminate early due to operational difficulties or do not result in drug label changes. Reasons for failure include insufficient sample size, difficulties with recruitment and retention, flawed study design, inadequate outcome measures and high costs.[1] Paediatric clinical trials face these challenges and added barriers of less prevalent disease requiring smaller sample sizes, feasibility, ethical concerns, and general reluctance by parents and providers to enrol children.[2] Additionally, the current COVID-19 pandemic is disrupting healthcare and clinical research worldwide.[3] Collectively, these challenges threaten the success of clinical trials, particularly in paediatrics and rare diseases.

A new clinical trial approach has emerged over the past decade in which data collection and research activities are conducted remotely.[4–6] Rather than relying exclusively on brick-and-mortar research facilities, a clinical research organisation can distribute activities to remote locations, including the participant's home. Such trials are often referred to as 'virtual,' 'decentralised' or 'direct-to-family' trials, which better acknowledge the critical role of parents, caregivers and other family members in supporting research participation. Compared with traditional clinical trials, a direct-to-family design can improve participant recruitment and retention,[6–8] increase participant diversity,[9 10] improve efficiency and reduce costs.[8–10] Data from devices, survey responses, biospecimens and even teleresearch examinations can be collected at home.[7 9 11 12] Furthermore, a direct-to-family approach may increase the feasibility of conducting a trial during a pandemic. At least 1600 clinical trials have been terminated, suspended or withdrawn due to COVID-19,[13] making teleresearch an urgent, unmet need. Recognising the impact of COVID-19 on

clinical research, regulatory authorities have issued guidance supporting direct-to-family methods.[14 15]

Despite several potential benefits, the feasibility of conducting direct-to-family trials in children is largely unknown. Here, we describe the design and implementation of a successful, ongoing, direct-to-family pilot trial for paediatric lupus, which completed enrolment in 10 days, along with lessons learnt and guidance for future direct-to-family studies.

In designing our direct-to-family trial, we previously identified an important clinical question in a serious paediatric disease. SLE is a chronic, multisystem autoimmune disease that causes organ damage, early death, reduced quality of life and high healthcare costs.[16] Hydroxychloroquine (HCQ) prevents disease flares, reduces organ damage and improves survival, and therefore is used in nearly all patients with SLE.[17 18] Despite these benefits, up to 76% of patients are non-adherent,[19] and low HCQ levels are associated with increased disease activity.[20 21] Paediatric patients with SLE have more severe disease and worse outcomes than adults,[22] making them especially vulnerable to low HCQ levels due to added challenges with adherence[23] and the potential for underdosing due to a lack of pharmacokinetic data. Due to the lack of dosing information in paediatrics, HCQ is on the 2019 Best Pharmaceuticals for Children Act list for priority research.[24] Given the opportunity to improve outcomes by optimising adherence and the lack of pharmacokinetic data for HCQ in paediatric SLE, we selected this patient population and objective for our pilot, direct-to-family trial.

METHODS

Study synopsis

The Individual Patient Exposure and Response in Pediatric Lupus (iPERSONAL) trial is a single-arm, self-controlled, unblinded pilot trial aimed to evaluate the intervention of an electronic pill bottle cap with automated reminders on adherence to HCQ in 26 paediatric patients with SLE. Data are collected at four in-home visits over a 6-month period, including a physician-guided teleresearch examination conducted at the first visit. Eligibility criteria are noted in table 1 and the schedule of activities is shown in online supplemental table 1.

Intervention

The electronic pill bottle contains an electronic sensor in the cap that monitors and records date and time of bottle openings. The expected time of medication administration is programmed via a mobile application. If the bottle has not been opened 10 min after the dosage is due, the cap alerts the user with flashing lights and an audible chime. The participant can opt in to receive additional notifications including a text message 30 min after the programmed time or a phone call 60 min after the programmed time. We prospectively collect additional openings, including study visit pill counts, erroneous openings or refills. As a result, the study team is able to account for differences between pill counts and dispensed doses reported by the electronic pill bottle.

Outcomes

The primary outcome is HCQ adherence, defined as the proportion of dispensed doses measured using an electronic pill bottle that records the date and time of each bottle opening. Adherence is measured for a 14-day run-in period (baseline) before automated reminders are activated for the remainder of the study.

Secondary outcomes include (1) medication adherence measured using the Medication Adherence Self-Reported Inventory, plasma HCQ concentrations and manual pill counts; and (2) disease activity measured by the SLE Disease Activity Index-2K (SLEDAI) and the Systemic Lupus Activity Questionnaire. The remote physicians and in-home nurses conducting the disease activity assessment received training to conduct a virtual paediatric gait, arms, legs and spine musculoskeletal examination, as well as a teleresearch SLEDAI.

Exploratory outcomes include HCQ population pharmacokinetics and pharmacodynamics to relate HCQ plasma levels, dosing and response. The electronic pill bottle allows for precise recording of each HCQ dose dispensed, which facilitates the pharmacokinetic analysis. Operational metrics, including participant and caregiver satisfaction, are additional exploratory outcomes evaluating feasibility of the direct-to-family design.

Enrolment

By identifying eligible participants from the registry before recruitment calls, we met our initial enrolment target of 20 participants and completed the electronic

Table 1 Eligibility criteria

Main inclusion criteria*†	Exclusion criteria
► Age 5–17.5 years ► Enrolled in the CARRA Registry with a diagnosis of SLE ► Receiving hydroxychloroquine for ≥3 months ► Access to internet	► No predefined exclusion criteria

*Recruitment limited to states in which subinvestigators held medical licences.
†Full inclusion criteria available at ClinicalTrials.gov.
CARRA, Childhood Arthritis and Rheumatology Research Alliance.

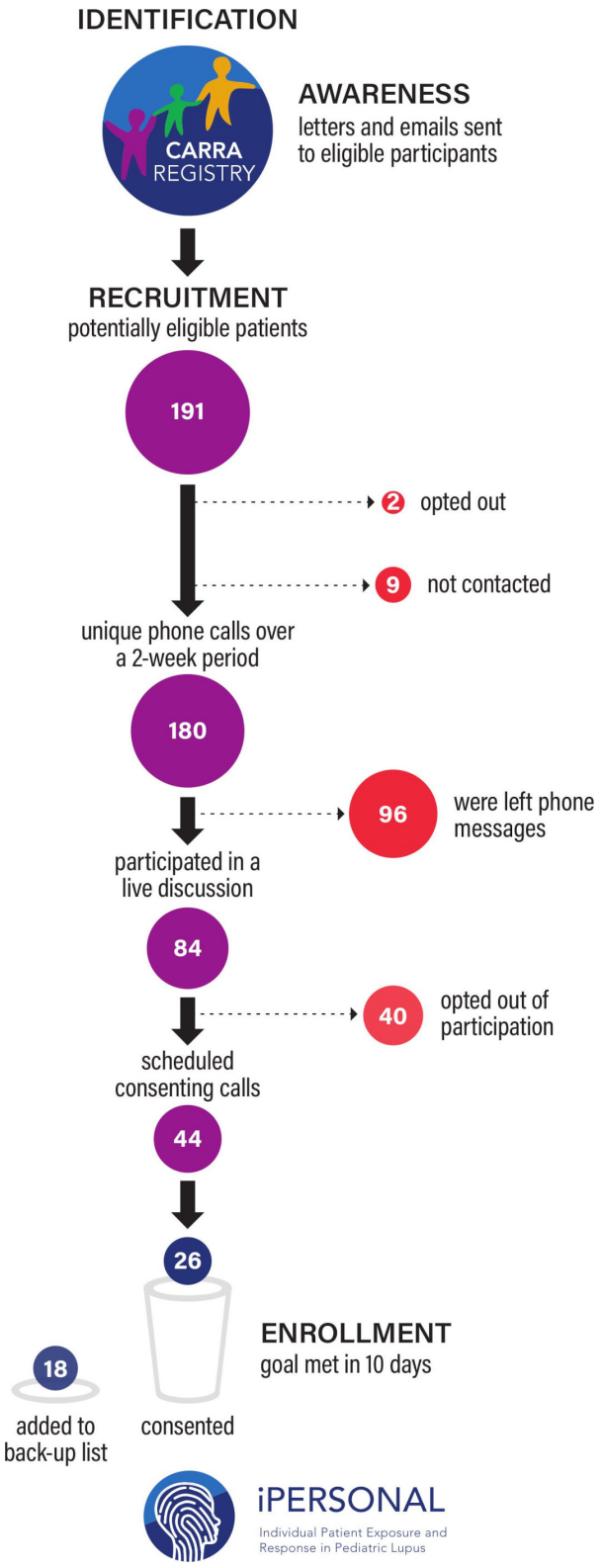

Figure 1 Participant recruitment and enrolment. CARRA, Childhood Arthritis and Rheumatology Research Alliance.

informed consent process within 10 days (figure 1). Because of high interest, we expanded enrolment to 26 participants and added additional interested participants to a waiting list.

Impact of COVID-19

One participant and family members of two participants developed COVID-19 infections during the course of the study to date, which required two visits to be rescheduled and one visit to be conducted entirely remotely. Nevertheless, we were able to continue to collect data remotely for all three participants. Data collection is expected to continue through July 2021.

TRIAL DESIGN AND IMPLEMENTATION CONSIDERATIONS

Appropriateness of direct-to-family approach

One challenge in direct-to-family trials is the logistics of prescribing and administering investigational medical products outside of a research facility, while ensuring appropriate safety monitoring. In iPERSONAL, we studied a drug already prescribed to participants as standard of care by their rheumatologists, meaning the study investigators did not prescribe the medication. Instead, the intervention is a minimal-risk, device-based, behavioural intervention. In addition, HCQ has an excellent safety profile in SLE[25 26] and is taken orally by study participants. Collectively, this approach reduced the risk of safety events during the study.

A second key consideration for direct-to-participant trials is the availability of outcome measures that can be assessed remotely. For the primary outcome of medication adherence, all measures were amenable to in-home assessment including electronic medication event monitoring, plasma drug levels, patient questionnaires and pill counts during an in-home study visit.

For the secondary outcomes related to disease activity, we selected several complementary measures including an in-home teleresearch examination, patient-reported disease activity questionnaires, and biomarkers from blood and urine samples. We developed the in-home teleresearch examination based on the commonly used SLEDAI,[27] which includes physical examination plus laboratory components. For the physical examination components, the in-home nurse conducted hands-on assessments (ie, auscultation of heart and lungs, tender and swollen joint count) under the real-time guidance of a remote physician via video; while the physician was able to directly visualise joint swelling and range of motion, visible skin, hair and mucosal changes, and general behaviour, body posture and movements. Skin, scalp and mucosal lesions were photographed for closer review by the physician when necessary. The physician also interviewed the participant via video for symptoms of active disease (eg, vision change, headache, stroke) and reviewed laboratory test results to complete the score for each SLEDAI component.

Optimised recruitment through a disease registry

A key challenge in recruiting trial participants outside a medical facility is ensuring participants actually have the disease of interest. To overcome this challenge, we recruited participants from the Childhood Arthritis and

Rheumatology Research Alliance (CARRA) Registry, which is the largest registry of paediatric rheumatic diseases in North America, providing robust data on over 10 000 participants across 71 sites. Through the CARRA Registry, we identified participants with a physician-confirmed diagnosis of SLE, as self-reported diagnoses may be unreliable.[28]

Secured funding

Under the 21st Century Cures Act, the US Food and Drug Administration (FDA) was tasked with creating a framework for evaluating the use of real-world evidence for regulatory decisions.[29] In addition, the FDA provided funding for the direct-to-family paediatric trial through the Global Pediatric Clinical Trials Network. Aligning our study with priorities of the FDA facilitated funding for this study.

Patient and public involvement

Direct-to-family trials are inherently intended to be family centred. Accordingly, patient and family engagement was critical early in the design process. We engaged patient communities from the Patients, Advocates and Rheumatology Teams Network for Research and Service, a Patient-Centered Outcomes Research Institute-funded Patient Powered Research Network (https://www.pcori.org/research-results/2019/partners-enabling-real-time-personalized-engagement-research-app-based), and the Lupus Foundation of America (LFA). We also involved leaders from CARRA's SLE Disease Research Group as a key stakeholder. Representatives from the organisations created an Advisory Group consisting of organisation representatives, patients and parents. The Advisory Group met monthly during the design phase to provide input related to the study protocol and recruitment; the committee will meet again at the end of the study to develop materials to share the results with the lupus community.

Engaging stakeholders early in the planning process resulted in several changes that shaped the final trial. For example, the Advisory Group helped develop study materials, including trial name and branding, informed consent form and recruitment materials. These changes were made prior to applying for institutional review board approval. Another key change was to involve the participant's paediatric rheumatologist after the Advisory Group clearly communicated the importance of involving the primary rheumatologist for management of safety or adverse events. After presenting the study generally to paediatric rheumatologists in the CARRA network, we contacted individual participant's primary rheumatologist as they joined the study to provide a study synopsis. After the primary rheumatologists opted in to receive study information, we then communicated laboratory results and any safety concerns via secure email or fax.

Navigated operational and technological challenges

To operationalise the direct-to-family trial, we needed a technology platform that could collect multiple different data streams (eg, continuous device data, laboratory data, patient-reported outcomes collected via mobile application, teleresearch examination), plus licensed study personnel to execute in-home study activities. We evaluated several vendors including traditional clinical research organisations, technology companies, niche virtual trial providers/start-ups and home healthcare delivery companies. Ultimately, we selected a vendor (Science 37, Los Angeles, California, USA) with the most experience in this type of trial design and a history of submitting data to FDA (the funding source for the study).

Importantly, we clearly delineated roles and responsibilities of the Duke Clinical Research Institute (DCRI) and Science 37. The DCRI team led study design, protocol development and overall project leadership. Recruitment and enrolment were managed by the DCRI's in-house call centre. Science 37 managed day-to-day operations, including assembling the in-home research team, packaging and shipping of study materials, collecting and shipping of biosamples, and creating a technology platform for consent, data elements, and surveys including patient-reported outcomes. We employed the DCRI informatics and data solutions team to integrate the Science 37 technology platform with data from patient-facing technologies, including the electronic pill bottle, laboratory results and the CARRA Registry.

Legal and regulatory requirements

We encountered several legal challenges related to conducting in-home clinical trial activities on a national scale.[30] First, we clearly delineated that we were conducting teleresearch, not telemedicine. Although we were studying a device-based intervention, and not a prescribed study drug, participants may nevertheless perceive in-home assessments as diagnosis and treatment. To mitigate the perception that the study was delivering medical care, we stated in the protocol and informed consent documents that the purpose of the study was not to diagnose or treat a medical condition. However, some states require in-state physician oversight for study procedures, including the activities of a home health nurse. Therefore, we selected a vendor (Science 37) with subinvestigators who held medical licences to practise in the states in which the participants lived.

Safety and security

We undertook several steps to ensure the privacy, security, and safety of study participants and their remotely collected health data, including an internal review of the Science 37 technology platform and independent verification that in-home research staff had undergone proper background and safety checks. We required a parent or designated adult to be present at the time of the in-home visit and to manage devices for children under the age of 13 years. To ensure health data security, we performed an

internal audit to determine compliance with regulatory guidances including Code of Federal Regulations Title 21, Part 50, Part 11, and International Conference on Harmonisation Good Clinical Practice E6; plus a review of data security and privacy, including Service Organization Control Type 2, HITRUST, or International Organization for Standardization 27001 compliance and single sign-on solution for user authentication.

Recruitment and enrolment

We obtained permission to use CARRA Registry and LFA logos on recruitment materials to help with recognition and credibility among potential participants. Additionally, the study was advertised through CARRA and LFA communications, such as email newsletters, to increase awareness of potential participants, providers and members of the community. Eligible participants in the CARRA Registry were contacted by mail and phone.

DISCUSSION

Direct-to-family trials have many potential advantages but present unique challenges, and accordingly must be carefully designed. In iPERSONAL, we identified that poor adherence to HCQ contributes to poor outcomes in paediatric SLE. To address this gap, we selected a low-risk intervention that could be assessed by measures collected in a participant's home. Our teleresearch clinical disease activity measure required several modifications and will need evaluation against objective measures and comparison with concurrent in-person assessments conducted outside of the trial.

When evaluating vendors to help operationalise the iPERSONAL trial, we discovered that direct-to-family trial design is still in its infancy. Most vendors had delivered fewer than five such trials, and many had not submitted data to the FDA. The majority of technology platforms we reviewed did not support integration of multiple data sources. Therefore, we relied on in-house informatics and data solutions teams to develop a complex data integration and data flow plan (online supplemental figure 1). It was also difficult to find a vendor with both a technology platform and in-home research team, including licensed physicians and nurses who could travel to the patient's home. Most vendors offered only the technology platform or research team. Using separate vendors for these activities would add complexity to operations and data integration.

From a legal standpoint, we realised that conducting in-home teleresearch on a national scale is largely uncharted. Telemedicine laws vary state by state, and many states require an in-person assessment for the prescribing of medication. Licensure of in-home research teams can be a significant barrier for national direct-to-family studies. Depending on the individual trial needs, there are several approaches, including (1) partnering with a network of licensed physicians in each participant's state, (2) having the principal investigator obtain licences in each state individually or through a multistate medical licence compact (https://www.imlcc.org/), or (3) carefully reviewing individual state requirements and managing trial procedures such that no in-state licensure is necessary. Telemedicine laws and FDA regulations are rapidly changing in the setting of COVID-19 and may have evolved since the writing of this article.[14]

Recruiting participants from a disease registry and engaging patient advocacy groups proved extremely useful for enrolment. Nearly half of all eligible patients who participated in a live discussion wanted to schedule a call for consent. Enrolment was so successful that we exceeded our initial enrolment goal and completed consenting all participants within 10 days. We believe leveraging a disease registry, using patient-facing technology, incorporating patient feedback into study design, and minimising participant burden contributed to quick and successful enrolment. Because these efforts were focused on a highly engaged patient population, additional studies are needed to evaluate the impact of the study design with different patient populations.

CONCLUSIONS

Direct-to-family trials may transform clinical research. These trials have many potential benefits related to enrolment, engagement, retention, cost-savings and feasibility. In designing and operationalising the first direct-to-family trial in paediatric SLE, we faced several challenges unique to this design. These challenges provide valuable insight into family-centred clinical research, which may ultimately provide more robust and meaningful research.

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