Oral Iron Versus Oral Iron Plus a Web-based Behavioral Intervention in Young Children (IRONCHILD)

BCM IRB# H-45869

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1. STUDY OVERVIEW

1.1. TITLE: A single-center, open-label, randomized feasibility trial of standard oral iron therapy versus oral iron plus a web-based behavioral intervention in young children with nutritional iron deficiency anemia

1.2. TRIAL REGISTRATION: Clinicaltrials.gov No. NCT04371536

1.3. PROTOCOL VERSION

Issue date: May, 27, 2020

Protocol Version number: 2

1.4. FUNDING: NHLBI K23 HL132001

1.5. ROLES AND RESPONSIBILITIES:

Principal Investigator:

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All co-investigators contributed to refinement of the study protocol and will approve the final manuscript.

2. INTRODUCTION

2.1. BACKGROUND AND RATIONALE

Iron deficiency anemia (IDA) is a major health problem, affecting 2 billion persons worldwide including nearly half a million young children in the U.S. For young children in the US, the primary etiology is nutritional, often resulting from excessive cow milk intake and limited iron rich foods in the diet. Peak incidence is 1 to 4 years of age, a period of rapid and critical neurodevelopment. Children from low socioeconomic status homes are disproportionately affected by IDA. Low-income children who are at risk for food insecurity as well as underserved racial/ethnic minority groups, specifically Latinos, have higher rates of iron deficiency and IDA.

IDA is associated with inferior neurodevelopmental outcomes, poorer executive functioning, and decreased visual and auditory processing time. The World Health Organization evaluated key studies examining the association of IDA with neurocognitive outcome and estimated that a decrement in hemoglobin of 1 g/dL due to iron deficiency results in approximately 1.73 IQ points lost. More severe and chronic IDA is associated with worse outcomes, and therefore incomplete therapy prolongs the extent and severity of such consequences. The cumulative effect, especially on children from socially disadvantaged groups disproportionately affected by IDA, is yet another setback that contributes to suboptimal outcomes in quality of life, educational achievement, and overall contribution to society.

Successful treatment of nutritional IDA will directly address the US Department of Health and Human Services' Healthy People 2020 objective of reducing iron deficiency among young children. Yet, research on therapeutic approaches that directly address a key health condition within this group is lacking. Standard therapy is oral iron therapy for a minimum of 3 months. Yet, non-adherence often

results in treatment failure, prolonging the negative consequences of IDA. Its unpleasant effects, including abdominal discomfort, nausea, constipation, and bad taste often result in medication refusal. Poor understanding by caregivers of its long-term impact, lack of motivating factors to promote adherence, and the need for a prolonged treatment course also contribute to non-adherence.

We propose that an alternative approach to standard oral iron therapy exists. This alternative approach is an intervention that promotes oral iron adherence by increasing caregiver motivation. Previous successful pediatric adherence interventions include educational and behavioral components with or without a technology-based component. The majority target caregivers of older children with chronic medical conditions that require long-term therapy. We conducted formative research with caregivers of children with nutritional IDA to characterize barriers and facilitators to adherence. Utilizing that data, we developed a self-determination theory-based web intervention, *IRONCHILD*, to increase parental motivation to adhere to oral iron therapy.

Well-designed randomized trials that compare different IDA treatment approaches in young children are sorely needed and would result in significant benefit to short-term clinical and long-term developmental outcomes. However, it is unknown whether families of young children with IDA are willing to be randomized to this different treatment approach (standard delivery of oral iron and oral iron with a web-based adherence intervention). The results of this feasibility study will assess the ability to successfully conduct such important comparative RCTs.

2.2. OBJECTIVE

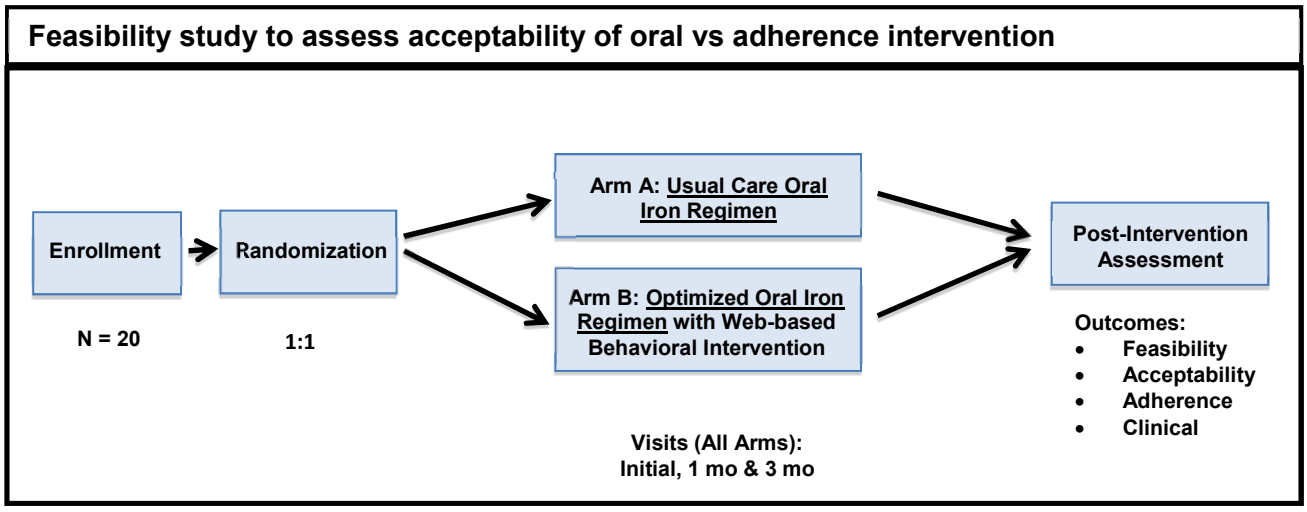
To determine the feasibility of conducting a randomized controlled trial comparing standard care oral iron to oral iron with a web-based intervention in young children with nutritional IDA.

2.3. Hypotheses:

- Enrollment will be feasible (≥50% enrollment of eligible patients).
- The interventions will be viewed as acceptable.
    - Subjects will be willing to receive the treatment intervention as assigned (≥80% agreement with randomization per Arm).
    - The IRONCHILD (Arm B) intervention will be viewed as acceptable (≥70% retention per Arm).

2.4. TRIAL DESIGN

This study is a randomized, open-label single center, two-arm feasibility trial to evaluate the feasibility of randomizing young children with nutritional iron deficiency anemia to (a) usual care with oral or (b) oral iron with a web-based behavioral intervention.



This pilot trial of 20 subjects will test the (1) feasibility of randomization to oral versus oral iron with a behavioral intervention, (2) acceptability of the optimized adherence intervention versus standard delivery of oral iron, (3) oral iron adherence rates in arms A and B, and (4) clinical efficacy in all arms as measured by change in hemoglobin concentration at 1- and 3-month clinic visits.

3. METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

3.1. STUDY SETTING

- This study will be conducted at a single academic hospital. Subjects will be evaluated in the Texas Children's Cancer and Hematology Center.

3.2. ELIGIBILITY CRITERIA

INCLUSION CRITERIA	RATIONALE
1. Age ≥ 12 months to < 48 months	Nutritional iron deficiency rarely seen at other ages
2. IDA confirmed by hematologic indices and iron laboratory parameters[1]* • Hgb between ≥6 g/dL AND ≤10 g/dL • MCV ≤70 fl • Ferritin ≤15 ng/mL OR TIBC ≥425 μg/dL	Iron deficiency without anemia but depleted iron stores is extremely common, but only children with frank, moderate anemia will be enrolled. This will allow for conclusive assessment of treatment efficacy in patients in whom outpatient oral iron therapy is considered safe (i.e. pRBC transfusion is not indicated for severe anemia).
3. Clinical history consistent with nutritional IDA such as prolonged breastfeeding without adequate iron supplementation or excessive milk intake (cow milk, almond milk, soy milk, goat milk or other milk, excluding breastmilk), defined as ≥3 cups (24 ounces)/day	Low iron diet is the most common etiology of IDA in this age group.
4. Primary language of English or Spanish	Behavioral Intervention (IRONCHILD, Arm B) available in English or Spanish
5. Access to a smartphone with data plan and/or other internet access (i.e. home computer)	Randomization to Arm B would require internet access to view content from home
*CBC indices must be performed with 7 days of study enrollment. Iron indices must be performed within 30 days of study enrollment.	

EXCLUSION CRITERIA	RATIONALE
1. Iron deficiency likely or definitely due to blood loss from the intestine or other sites.	Ongoing gastrointestinal or other blood loss would confound the effects of oral iron treatment.

2. Administration of a blood transfusion	The goal of this study is to enroll with IDA who are clinically stable that may be managed in an outpatient setting.
3. History or evidence of intestinal malabsorption	Oral iron cannot be expected to be effective in malabsorption states
4. History of prior intravenous iron therapy	Effects of intravenous iron would confound treatment responses
5. Major co-morbidity such as a serious chronic medical condition unrelated to iron deficiency apparent on history, physical examination, or laboratory tests	Other medical conditions may result in malabsorption, bleeding, renal disease, inflammation or other confounders that would affect observed changes in the primary outcome independent of the intervention
6. Other cause of anemia (sickle cell disease, thalassemia, bone marrow failure, etc.) apparent by history, physical examination, and/or laboratory tests.	Children with anemia due to other causes would not be expected to respond to iron
7. Inability to tolerate oral medications	Some children with feeding or swallowing disorders, severe neurological problems and/or inability to easily take liquids are unsuitable candidates
8. Other medical or social factors at discretion of treating physician	Unforeseen circumstances that will undermine the ability to determine the relative efficacy of the two study medications

3.3. INTERVENTIONS

3.3.1. Dietary recommendations

- Both arms will receive the same dietary counseling: limitation of cow milk to $\leq$16 ounces/day and information sheet on iron-rich foods.

3.3.2. Arm A: Usual care oral iron regimen

- **Oral iron therapy:** All subjects receiving oral iron therapy will receive ferrous sulfate 3 mg/kg elemental iron once daily in liquid formulation.
    - This dose is chosen because it is within the standard recommended dosing range[2,3], has demonstrated efficacy in previous IDA studies[4,5], and is recommended by the Centers for Disease Control as a simplified treatment dosing regimen with the goal of improved adherence rates.[6]
    - Further, it has demonstrated efficacy in a RCT of 80 children with nutritional IDA.[7]
    - Families will be instructed not to give the iron with milk as it will limit iron absorption.

3.3.3. Arm B: Optimized oral iron regimen with adherence intervention (IRONCHILD)

- **Oral iron therapy** as per Arm A
- **IRONCHILD web-based intervention** aimed at promoting oral iron adherence. This web-based intervention was developed specifically for caregivers of young children with nutritional IDA to promote oral iron adherence (Appendix).

- Information will be delivered in the clinic setting via a tablet device concurrent with clinical visits. Incorporating the intervention at standard visits will test the ability of the intervention to effect change in a real-world setting.
- Caregivers will be provided tablet computer in clinic and oriented to website
- Caregivers will be given a unique log-in and password with instructions on how to access the site between visits
- Delivery of the intervention at each visit should take 15 minutes or less.
    - Baseline visit (Session 1) content will be viewed
    - At 1-month follow-up visit, additional (Session 2) content will be viewed
    - At 3-month final visit, subjects will view final (Session 3) content

3.4. ADVERSE EVENT REPORTING AND RISKS

3.4.1. Definitions: Adverse Events

- An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sig (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.
- An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Drug Label or of greater severity or frequency than expected based on the information in the Drug Label.
- Information regarding occurrence of AEs will be captured throughout the study. The collection period for all AEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed, or thirty days after the subject takes the last dose of study drug, whichever is later.
- The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. AEs will be recorded in the patient CRF and will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or other support), or require changes in study medication(s).
- AEs that begin or worsen after first dose of study drug should be recorded in the AE CRF. AE monitoring should be continued until the date of the last dose of study treatment.
- Once an AE is detected, it must be followed until its resolution or until judged to be permanent, and an assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.
- If an AE occurs more than once in a course of therapy, only the most severe grade of the event is reported. If an AE progresses through several grades during the course of therapy, only the most severe grade is reported.
- For reporting purposes, the duration of the AE should be the duration of the highest (most severe) grade of the toxicity. The resolution date of the AE is defined as the date at which the AE returns to baseline (note that the resolution date may therefore be different from the date at

which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date is recorded as “ongoing”. Dates used in AE reporting for laboratory test abnormalities should be the date the sample was collected (not the date the sample was processed or the date the results were reported).

- The completed CRF summarizing the non-serious AE should be reviewed and signed by the PI or their designee.

AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines.

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject’s clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization[++]
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)

An UPIRSO is defined as incident, experience or outcome that is unexpected (in terms of the nature, severity or frequency) given

(a) the description of the likely harms in the protocol, the consent form or the other materials submitted to the IRB and

(b) the characteristics of the subject population; related to a subject's participation in the research; and suggests that the research places subjects or others at greater risk of harm - physical, psychological, economic or social harms - than was previously known or recognized.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB) the site investigator will report SAEs/UPIRSOs to the IRB and regulatory agencies as required.

3.4.2. RISKS: ARMS A and B

- All enrolled subjects will be treated with an oral iron preparation in the standard dose. Oral iron medications, labelled as “supplements’ by the FDA, are approved for this purpose, and when used appropriately, are without significant risks. The AEs of special interest and SAEs that will be captured are listed below.
- AEs of special interest (assessed at Weeks 4 and 12):
    - Staining of teeth
    - Constipation
    - Nausea
    - Vomiting
    - Abdominal Pain
    - Diarrhea
- SAE:
    - Accidental ingestion of a large amount of an oral iron preparation by the patient may result in acute iron poisoning which can manifest as severe diarrhea, acidosis, shock, and death. Iron ingestion is one of the most common causes of accidental drug related death in children. Therefore, study medications will be administered in a child-proof container, and parents will be given strict instructions to keep the study medicine in a safe location out of the child’s reach.
    - Study subjects will be asked to report accidental ingestion immediately to the study team but will be specifically asked about this complication at the Weeks 4 and 12.

3.5. SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

- See definitions of AEs and SAEs in section 3.4.

- This protocol has a category 1 risk, research involving minimal risk with the prospect of direct benefit to the individual subjects. Monitoring and reporting of adverse events will comply with the BCM Institutional Review Board requirements.
- AE capture (Study database)
    - All **AEs of special interest** described in section 3.4, will be captured.
    - All **SAEs** will be captured (expected and unexpected).
    - Other expected childhood ailments, unrelated to the study treatment, including but not limited to upper respiratory infections and other non-specific viral infections, asthma, ear infections and environmental allergies may occur, unrelated to study, and will not be captured.
    - All captured AEs will be scored utilizing criteria listed in the Common Terminology Criteria for Adverse Events (CTCAE) version 5, and will be included in the visit data collection.
- The PI will provide a Continuing Review Report to the Baylor College of Medicine IRB at least annually.
- In addition, all SAEs and any unanticipated problems involving risk to subjects or others (UPIRSOs) that meet reporting criteria as defined by the BCM IRB will be submitted to the BCM IRB per their policy.
- All safety data collected on study participants will be reviewed by the Texas Children's Cancer and Hematology Centers Data Review Committee.

AEs of special interest and SAEs will be captured from start of treatment to Week 12 unless otherwise indicated above.

3.6. BENEFITS

Study subjects may discontinue their participation at any time. However, information regarding the benefits to continued iron therapy, with or without additional interventions, will be made explicitly clear prior to their discontinuation.

- Whichever Arm the subject is randomized to, he or she will be receiving therapeutic iron, regular structured follow-up, and careful monitoring of hematologic parameters consistent with standard of care.
- Successful treatment of the subjects' iron deficiency is expected to improve their overall wellbeing, energy level and color, and possibly correct or mitigate any impaired cognitive and behavioral outcomes resulting from iron deficiency.
- Alternative care will be offered to the subjects, which might include less or longer follow-up and fewer laboratory studies.
- Every effort will be made to retain study subjects in the trial for the entire 12 weeks to enable complete follow-up data collection.

3.7. ASSESSMENTS OF MEDICATION ADHERENCE

- Study visit attendance (All Arms)
- Volume of unused medication returned at each visit (All Arms)

3.8. TREATMENT FAILURE

- At the 4 week visit, a lack of response in hemoglobin concentration (Hgb rise <1 gm/dL) will be addressed with increased emphasis on adherence and dietary recommendations.

3.9. WITHDRAWAL/TERMINATION

- Subjects that 'No Show' for 4 or 12-week visits and are unable to be contacted/rescheduled. Data already collected will be used in the analysis.
- Alternative diagnosis discovered
- In the investigator's medical opinion, it is best to withdraw the subject from the protocol

3.10. STOPPING RULES

- If more than one subject has the serious AE of iron poisoning (Arms A or B), the study will be suspended while an assessment of the child-proof containers and safety is performed.
- The study will be discontinued if one of the products is recalled by the manufacturer or Food and Drug Administration (FDA).

3.11. CONCOMITANT CARE

- Follow-up visits occur at 1- and 3-months but may occur more frequently depending on the severity of the anemia.
- Patients are ineligible for study if they have received a pRBC transfusion prior to enrollment. Enrolled subjects whose clinical course worsen and in whom a hematologist elects to treat with pRBC transfusion will be taken off study.
- Subjects enrolled on Arms A and B may not receive IV iron therapy during the 12 week study.
- Subjects who continue to have iron deficiency or IDA upon study completion will receive treatment at discretion of their attending hematologist.

3.12. OUTCOMES

The primary endpoints for this study are the feasibility outcomes.

- **Primary:** Enrollment
- **Secondary**
    - Agreement with randomization (willingness to receive the treatment arm assigned)
    - Retention (visit follow-up attendance)

Data on the following outcomes will also be collected to inform future clinical trial design.

- **Oral iron adherence**
    - Returned medication volume
- **Clinical**
    - Change in hemoglobin concentration at the 1 month visit
    - Resolution of IDA at the 3 month clinic visit, defined as:
        - Hgb >11 g/dL, MCV >70 fl, ferritin >15 ng/mL, and TIBC <425 μg/dL.
- **Adverse events** (All Arms, see section 3.4 and 3.5)

3.13. PARTICIPANT TIMELINE

	STUDY VISITS			
STUDY PROCEDURES	Wk 0 (Baseline)	#Wk 4	$Wk 8	#Wk 12
Eligibility screening	x			
Consent/Enrollment	x			
Randomization	x			
*Laboratory Studies, standard of care (SOC)	x	x		x
&Laboratory Studies (Research)	x	x		x
**Comprehensive History	x			x
+Comprehensive Exam	x			
+Focused Physical Exam		x		x
Iron Medication	x	x	x	
AE Review		x		x

#Week 4 and 12 visit windows are ±3 days of treatment initiation date.

*Laboratory studies (SOC) include: CBC, Retic, Iron Panel

&Research laboratory studies: serum hepcidin (0.5-1 mL) to be drawn at the same time of SOC laboratory studies (All Arms) Serum hepcidin will be collected to characterize changes in iron laboratory parameters in patients with IDA enrolled on this study that are not routinely performed as standard of care. Week 4 and 12 research labs will include: serum iron, ferritin, transferrin, total iron binding capacity.

**Medical history: prior hospitalizations, laboratory results, medications, dietary and review of systems; social and family history.

+Physical exam: Comprehensive PE consists of vital signs, general, HEENT, cardio-respiratory, abdominal, extremities and skin; Focused PE consists of vital signs, general, cardio-respiratory, abdominal and skin

3.14. SAMPLE SIZE

The sample size of 20 patients is determined primarily by consideration of feasibility. We expect that this study will provide compelling preliminary data to demonstrate the ability to conduct a fully powered randomized clinical trial. Collecting data on clinical response will allow us to estimate standard deviation for the design of future studies. Suppose the true standard deviation of hemoglobin change is 1.7, a sample size of 20 patients allows us to estimate the standard deviation with a margin of error $<\pm 0.47$.

3.15. RECRUITMENT

Information regarding the trial will be available at clinicaltrials.gov. The PI will inform all hematology providers of the study and eligibility criteria prior to study implementation. Information about the clinical trial will be provided via direct communication by the PI and co-investigators with physicians at Texas Children's Hospital including Emergency Department (ED) physicians, hospitalists, house staff and community practice providers.

Potential subjects will be identified through review of new patient referrals to Texas Children's Hospital Cancer and Hematology Center, inpatient admissions and/or consultations for iron deficiency anemia. The outpatient hematology clinic schedule will be pre-screened daily by the data manager, who will notify the PI of potential patients. The PI will assess eligibility and notify the primary hematology provider about those subjects who are potentially eligible. After confirmation of eligibility, the PI or a Co-I will describe the study to eligible patients' families. If interested, informed consent will be obtained and the subject enrolled. Parents must provide written, informed consent before any study procedures occur.

All research related costs, including drug, will be covered by the study. In addition, each subject will receive financial compensation for participation. Payment will be made at completion of the study visits at week 4 ($50), and 12 ($50) based on attendance for a total of $100 in compensation.

Expected recruitment rate will be 1-2 participants per week. Duration of recruitment period is expected to be approximately 6 to 9 months. Assessment of study recruitment and retention will be performed when 5 participants have been enrolled on the study, or at approximately 2 months.

3.16. SCREENING AND ENROLLMENT LOG

A secure study screening and enrollment log will be kept for IRONCHILD. Each screened patient will be categorized as either: ineligible, eligible but not approached, eligible and enrolled, eligible and declined. If the latter (eligible and declined), the reason for declining will also be obtained and noted in the study log. Information on all enrolled subjects will include: date of consent, date of randomization, agreement with randomization (yes/no), and follow-up visits within study windows (scheduled and actual). After the 12 week study period, subjects will be noted to have either completed all visits, removed from the study, or to have been lost-to-follow-up. For any subjects who do not complete the study, the time point at which they were removed or lost-to-follow-up will also be noted.

4. METHODS: RANDOMIZATION / ASSIGNMENT OF INTERVENTIONS

4.1. RANDOMIZATION

- Subjects will be randomly assigned to one of two groups with a 1:1 allocation by a utilizing a randomization generator program.

4.2. SEQUENCE GENERATION

- Participants will be randomly assigned to an experimental arm with a 1:1 allocation by a computer generated randomization schedule using permuted blocks of 2 and 4.

4.3. ALLOCATION CONCEALMENT MECHANISM / BLINDING

- Not applicable - this is an open-label study

4.4. IMPLEMENTATION

- An investigational pharmacist will perform the sequence generation. Trial investigators will perform enrollment and implementation of study group assignments and will not be involved in the allocation process.

5. METHODS: DATA COLLECTION, MANAGEMENT, & ANALYSIS

5.1. DATA COLLECTION METHODS

Clinical information for all patients will be collected from each patient's electronic medical record at all visits while on study on electronic Case Report Forms (eCRF). This information will include the following: name, gender, race, ethnicity, primary language spoken in the home, socioeconomic status (annual income and number of persons living in the home), number of caregivers in home, date of birth, current medications, medical history, physical exam, and laboratory results.

Data specific to subjects randomized to Arm B (web intervention) will also be automatically collected and stored as participants navigate the website. The database and website will be hosted on a secure, password protected website, and the database will be further protected by a password set by the study team. Parents will be assigned a unique password by the study team, and this password will be used to login to the secure website. Rather than their actual name, the data collected as a family navigates the website (e.g., logins, goals, etc.) will be stored in the database by a unique identifier accessible only to the study team.

5.2. DATA MANAGEMENT

The eCRF will be housed in Texas Children's Hospital REDCap. REDCap is a self-managed, secure, web-based data support system. The data is backed up offsite nightly and hosted in a secure environment maintained by Information Resources. This password protected study database will include a subject's personal identifiers and all Protected Health Information (PHI) such as medical history. All personnel who will be accessing the data will be trained in REDCap and have individual user ID and passwords. Subjects will have a study ID number that will be utilized in lieu of personally identifiable information for all research data provided to statisticians.

5.3. STATISTICAL METHODS

All planned analyses are descriptive in nature. Summary statistics such as mean, standard deviation, and 95% confidence intervals will be reported. No formal hypothesis testing will be performed.

6. METHODS: MONITORING

6.1. DATA MONITORING

All health information collected by which subjects can be identified will be coded for research purposes. Each participant will be assigned a unique study identification number. Directly identifying information will not be kept with the data. All research results will be presented/published in a manner which ensures that no individual can be identified.

All paper records will be stored in a locked cabinet behind a locked door in a co-investigator's office at Texas Children's Hospital. All electronic records will be secured under a password protected file on the TCH server in which only members of the study protocol will have access. All data will be maintained on a server managed and maintained by institutional IT staff. PHI will be destroyed at the earliest possible opportunity and kept for no longer than 5 years after the end of the study.

The study will be monitored by the Texas Children's Cancer and Hematology Centers (TXCH) Data Review Committee according to the Data Safety Monitoring Plan set forth.

6.2. AUDITING

Quality assurance and audits will be conducted in accordance with the TXCH clinical research quality assurance plan.

7. ETHICS AND DISSEMINATION

7.1. RESEARCH ETHICS APPROVAL

This protocol and template informed consent forms will be reviewed and approved by Baylor College of Medicine IRB with respect to scientific content and compliance with applicable research and human subjects regulations. Subsequent to initial review and approval, the investigators will make safety and progress reports to the IRB at least annually and within three months of study completion.

7.2. PROTOCOL AMENDMENTS

Any modifications to the protocol, which impact the conduct of the study, or potential risk/benefit of the participants, will require a formal amendment to the protocol with IRB approval.

7.3. CONSENT OR ASSENT

Informed consent will be obtained after information has been provided to patients' families along with a discussion of the risks and benefits along with opportunity for questions. Consent forms will be provided for all parents involved in the trial. Due to the young age of the patient population and short study participation assent will not be required.

7.4. CONFIDENTIALITY

Records of each patient's participation in this study, including the original informed consent document, will be kept in a locked file cabinet in the Texas Children's Cancer and Hematology Center by Clinical

Research staff. Access to local research files is limited to data management personnel, study team members, and the Institutional Review Board. These entities may need to view data for quality assurance and data management purposes. Confidentiality of all medical records would be maintained by correct identification of the appropriate person before viewing the medical record and ascertaining the reason for the viewing of the medical records.

8. DECLARATION OF INTERESTS

Jacquelyn Powers, MD, No financial or other competing interests.

8.1. ACCESS TO DATA

The PI and data manager will be given direct access to the data sets. Additional study team members will be given access to portions of the data as needed for study analysis and manuscript preparation.

8.2. ANCILLARY AND POST TRIAL CARE

Participants who continue to have iron deficiency upon study completion will receive treatment at discretion of their provider.

8.3. DISSEMINATION POLICY

Every attempt will be made to reduce the interval between completion of data collection and the release of the study results. After completion of the trial by all participants we expect to take about 3 to 4 months to compile the final results and submit them for presentation at a prominent society meeting and publication in a high profile peer reviewed journal.

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APPENDIX. IRONCHILD Intervention

Development of IRONCHILD

IRONCHILD is a theoretically-based intervention designed to be delivered via an interactive website (www.iron-child.com) at standard clinical visits over a three month period with an overall objective of improving adherence to oral iron therapy in caregivers of young children with nutritional IDA. Its development involved both stakeholder input and incorporation of behavioral theory. Formative research was conducted via a mixed-methods study of children with nutritional IDA and their primary caretaker, which included demographic and clinical information and semi-structured interviews with caregivers to characterize barriers to and facilitators of iron therapy.

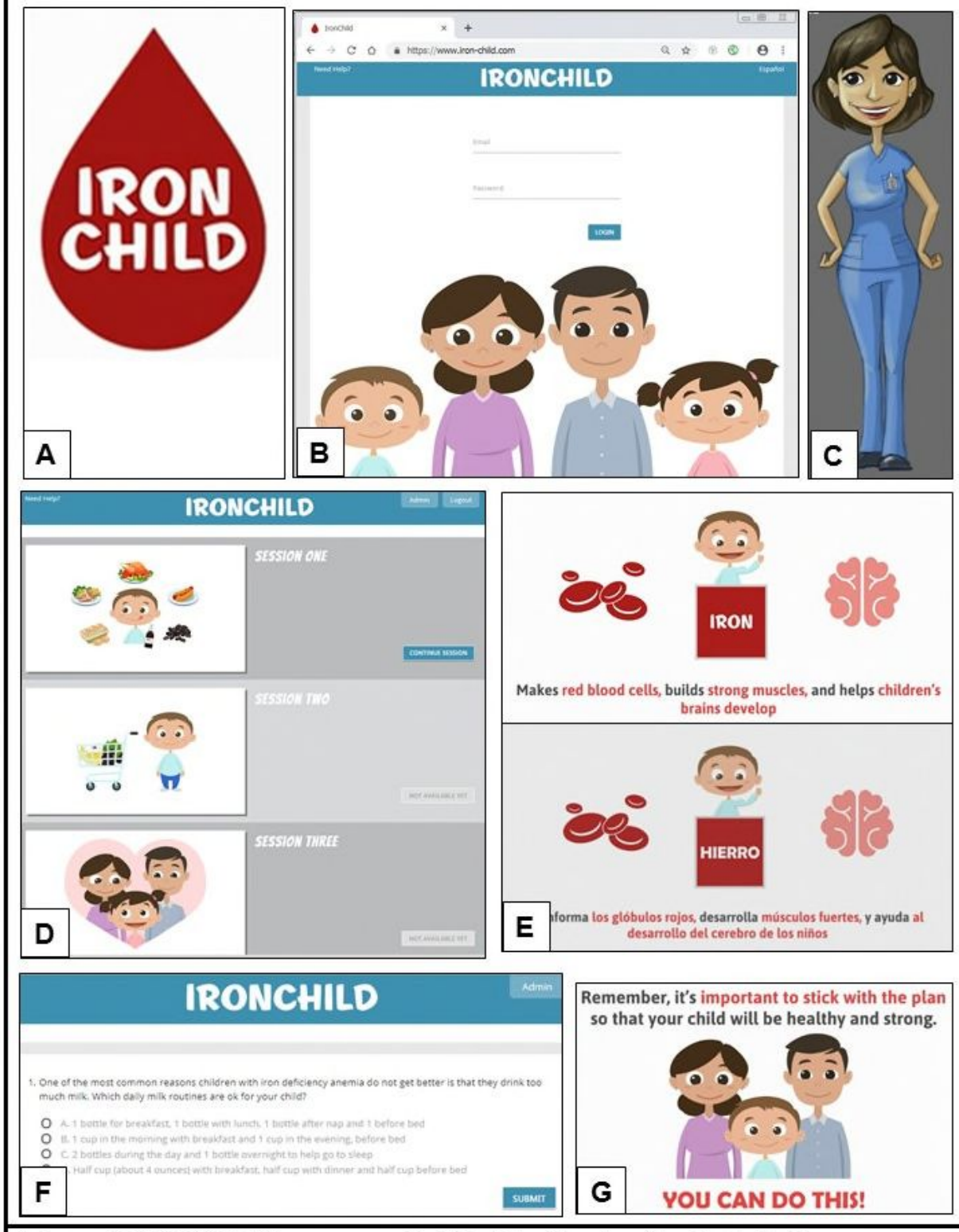
Results from the formative research, along with constructs from the self-determination theory of motivation (autonomy, competence, relatedness), informed message content for IRONCHILD. This theory was selected because the degree to which its three principle constructs (basic psychology needs) are met drives levels of motivation to perform a specific behavior such as medication adherence. Three scripted online intervention sessions were developed, professionally translated into Spanish, and then animated by a professional animation and web design studio. Audio recording with a professional bilingual voice actor provided the narration.

Session Content (Figure)

At the initial visit, participants are introduced to a relational agent or virtual health educator, Maria, who is a pediatric nurse and mother of a child formerly treated for IDA. Maria provides an introduction to the overall program format and content and guides each session. Participants next view a Topic Introduction animation that provides an overview of the diagnosis of IDA, its clinical consequences, and a typical treatment course with oral iron therapy. This is followed by two unique content segments that provide information on (1) dietary counseling and (2) administration of oral iron therapy. Following each segment, participants view question/response options, make a selection, and receive feedback. At the end of the session, participants select goal(s) related to therapy adherence for the interval between clinical visits.

The second session provides two additional content segments that focus on (1) problem-solving for difficulties related to medication administration and (2) identifying motivating factors to adhere to therapy (Figure 3). The third session allows users to access all previous content and provides closing information about adhering to any ongoing treatment recommendations from their child's provider. Between visits, access to the website occurs via a unique username and password caregivers can use to logon to the website and view previous sessions. All aspects of IRONCHILD are available in both English and Spanish. Finally, an administrative dashboard for IRONCHILD captures program usage information as families log onto the program and navigate the sessions (e.g., number of log-ins; responses to question prompts; goals set; goal attainment).

Figure. Screenshots from the web-based intervention IRONCHILD



A. Logo; B. IRONCHILD log-on page; C. Virtual health education Maria; D. Home page with orientation to content sessions; E. Screenshot of Topic Introduction content in English and Spanish; F. Question/response example; F. Screenshot of Session 2 content.