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Title: Addressing Recruitment Challenges in the ENGAGE-HU Trial in Young Children with Sickle Cell Disease

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Background: Sickle cell disease (SCD) is a genetic disorder that causes significant medical and neurologic morbidity in children. Hydroxyurea (HU) is the primary medication used to prevent these complications. National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend offering HU to children as young as 9 months of age with SCD (HbSS or HbSB0 thalassemia) using a shared decision-making approach. Although HU has proven efficacious it remains underutilized and caregivers report that they are not always actively involved in the decision to initiate this therapy. Reasons for limited HU uptake likely include lack of clinician knowledge and training and negative caregiver perceptions. Thus, we developed the Engage-HU trial as a novel approach to address HU utilization barriers. A critical consideration for this trial was that SCD primarily affects individuals of African and Hispanic/Latino descent. In these minority populations, intervention trials are sometimes terminated early because of recruitment difficulties related to mistrust of research, caregiver burden, and transportation issues. As such, the Engage-HU trial design included best-practice strategies for recruiting people of color in research. This study describes these strategies, the initial recruitment plan, preliminary recruitment outcomes and strategies, and our procedural adaptations.

Study Design and Methods: Engage-HU is a randomized control trial (NCT03442114) to assess how clinicians can engage caregivers in a shared discussion that considers their values and preferences and includes evidence that supports HU. Engage-HU compares two dissemination methods for clinicians to facilitate shared decision-making with caregivers of young children with SCD: 1) the American Society of Hematology Pocket Guide, and 2) the HU Shared-Decision Making (H-SDM) Toolkit. The study aims to recruit 174 caregivers and evaluate the effectiveness of the dissemination methods on patient-centered outcomes (caregiver confidence in decision-making and perceptions of experiencing shared decision-making) as well as HU uptake and child health outcomes. Eligible children are aged 0 to 5 years, candidates for HU, and their caregiver has not made a decision about HU in the past 3 months. The trial is being conducted at 9 sites in the United States and uses a stepped-wedge design. Data will be analyzed based on the intent-to-treat principle. All participants will remain in the arm of the study to which they were randomized, regardless of whether or not they receive the assigned dissemination method. The primary endpoints are caregiver decisional uncertainty and caregiver perception of shared decision-making measured using validated tools. Data will be analyzed using a linear mixed effects regression model with a robust variance estimator and maximum likelihood estimation with observations clustered within site.

The Engage-HU trial includes adaptations to increase recruitment such as tailored messaging, a relational recruitment approach, streamlined data collection, and a Stakeholder Advisory Committee. However, even with these adaptations, the first 6-months of the trial yielded lower than anticipated recruitment. Rather than terminate the trial or accept low enrollment, the research team implemented a series of recruitment strategies to address barriers including helping to improve research coordinator knowledge of the study purpose and adjusting no-show and follow-up procedures (e.g., calls to families after missed appointments and reminder calls before appointments). Site clinicians and clinic staff were provided with additional training so they could give more context about Engage-HU to caregivers and the study principal investigator led monthly “all coordinator” calls to provide support by sharing updates and experiences about successful recruitment. Implementation of these strategies resulted in triple the number of enrollments over the next 7-months compared to the previous 6-months (Table 1). Our goal in

sharing this information is to provide lessons learned that can be implemented in future trials with the systematically underserved SCD population. It is also anticipated that methods described here may also inform clinical approaches to better engage caregivers of young children around critical clinical conversations, such as initiating medications like HU.

Table 1. Preliminary recruitment outcomes for ENGAGE-HU before and after implementation of strategies to improve enrollment

Patient Recruitment	Before Strategies Months 1 – 6	After Strategies Months 7 – 13
Patients identified for pre-screening	**52**	**164**
Patients that could *not* be pre-screened	**2**	**32**
HU not currently suitable	1	15
Hemoglobin too high to start HU	0	8
Provider requested approach at a later date	1	9
Patients that could *not* be screened	**10**	**36**
No-show or cancelled	9	33
Research staff unavailable	1	3
Patients screened	**42**	**96**
Reasons refused study		
Did not give a reason	11	9
Wanted to think about it	1	11
Thought it would take “too much time”	7	8
Said “no” to Hydroxyurea	1	1
Thought it would be “too much of a burden”	1	3
Reasons ineligible for the study		
Patient already on HU	2	8
Patient had previously been offered HU	0	4
No legal guardian available for consent	1	4
SCD care being transferred	4	0
Siblings eligible, other sibling enrolled	0	2
Patients enrolled	**14**	**46**