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Systematic Review of Interventional Sickle Cell Trials Registered in Clinicaltrials.gov

Jeffrey D Lebensburger¹, Lee M Hilliard¹, Lauren E Pair¹, Robert Oster², Thomas H Howard¹, and Gary R Cutter³

¹Division of Pediatric Hematology and Oncology, Department of Pediatrics University of Alabama at Birmingham, AL, USA

²Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, AL, USA

³Department of Biostatistics, University of Alabama at Birmingham, AL, USA

Abstract

Background/Aims—The registry clinicaltrials.gov was created to provide investigators and patients an accessible database of relevant clinical trials.

Methods—To understand the state of sickle cell disease (SCD) clinical trials, a comprehensive review of all 174 “closed”, “interventional” sickle cell trials registered at clinicaltrials.gov was completed January 2015.

Results—The majority of registered SCD clinical trials listed an academic center as the primary sponsor and were an early phase trial. The primary outcome for SCD trials focused on pain (23%), bone marrow transplant (13%), hydroxyurea (8%), iron overload (8%), and pulmonary hypertension (8%). Fifty two trials were listed as terminated or withdrawn including 25 (14% of all trials) terminated for failure to enroll participants. At the time of this review, only 19 trials uploaded results and 29 trials uploaded a manuscript in the clinicaltrials.gov database. A systematic review of pubmed.gov revealed that only 35% of sickle cell studies completed prior to 2014 resulted in an identified manuscript. In comparison, of 80 thalassemia trials registered in clinicaltrials.gov four acknowledged failure to enroll participants as a reason for trial termination or withdrawal and 48 trials (60%) completed prior to 2014 resulted in a currently identified manuscript.

Conclusion—Clinicaltrials.gov can be an important database for investigators and patients with sickle cell disease to understand the current available research trials. To enhance the validity of the website, investigators must update their trial results and upload trial manuscripts into the database. This study, for the first time, quantifies outcomes of SCD trials and provides support to the belief that barriers exist to successful completion, publication, and dissemination of sickle cell trial results.

Correspondence to: Jeffrey Lebensburger DO, Division of Pediatric Hematology and Oncology, 1600 7th Ave. South, Lowder 512. Birmingham, AL 35233. (tel) 205-638-9285, jlebensburger@peds.uab.edu.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Keywords

Sickle cell disease; clinical trials; thalassemia; disparities research

Introduction

Sickle cell disease (SCD) is one of the most common inherited blood disorders, affecting almost 100,000 people in the United States.¹ Patients with SCD suffer clinical events including painful crises, acute chest syndrome, and stroke and are at risk for early mortality from infection, cardiovascular and renal disease.² Successful completion and dissemination of clinical trials results can provide SCD care teams with the necessary evidence to effectively treat patients. Several SCD clinical trials have dramatically improved the care for patients, and in the case of penicillin prophylaxis trials, served as evidence to drive the adoption of universal newborn screening for sickle cell disease.^{3–5} The risk of life-limiting strokes and recurrent strokes during childhood was dramatically reduced by successful completion, publication and dissemination of randomized clinical trials.^{6–9} Finally, randomized controlled trials of hydroxyurea, an oral therapy for sickle cell disease, proved effective in preventing complications of SCD for infants to adults, and new evidence suggests that it may improve the lifespan for SCD patients.^{10–15}

Despite the success of some SCD clinical trials, numerous trials have failed to enroll, complete, and/or publish their manuscripts. Prior research in clinical trial enrollment for African American patients in many diseases has identified potential barriers including: mistrust of research or physicians, access to trials, eligibility criteria, and lack of knowledge about trials.^{16–20} As a disease of predominantly Black patients, this disparity in enrollment could exaggerate and hinder the advancement in care of this disease. Several manuscripts have highlighted both patient/parent and provider barriers to SCD clinical trial enrollment.^{21–27} While manuscripts and researchers have speculated on the success and failure of various SCD clinical trials, no systematic review has evaluated SCD trials to quantify their final outcomes.

[Clinicaltrials.gov](http://www.clinicaltrials.gov) was created in 2000 to comply with the FDA Modernization Act of 1997 and since 2007, Federal law (Section 801 of the FDA Amendments Acts) mandates registration of all applicable, prospective clinical drug trials of health outcomes within 21 days of enrolling their first applicant. Applicable trials include “clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subjected to FDA regulation” (www.clinicaltrials.gov). The International Committee of Medical Journal Editors (ICMJE) also require registration of all intervention trials prior to enrollment and as a condition of manuscript publication. The [clinicaltrials.gov](http://www.clinicaltrials.gov) database can be searched to determine the current status of registered SCD clinical trials, objectives of trials, and history of reported changes to each trial. We undertook a systematic review of all “closed” and “interventional” SCD trials registered at [clinicaltrials.gov](http://www.clinicaltrials.gov) to determine the characteristics of completed SCD trials as well as the successful enrollment and completion of initiated trials.

Methods

The sickle cell clinicaltrials.gov database for this manuscript was created using trials completed by August 5, 2013. Three hundred and fifty three trials were identified using the search term “sickle” on clinicaltrials.gov. The database was restricted to “closed” (n=224; 63.3%) and then “interventional” trials (n=163; 72.8%). All trials were reviewed, and 16 were removed as not appropriate to include as a sickle cell trial by the authors (JL and LP). The most common reason for this exclusion involved trials that were included in the initial query, but only included the term sickle in the background of the trial rather than as the population studied (examples include NCT00485511: A Trial of Hydroxyurea for Spinal Muscular Atrophy or NCT00706810 Combination of Hydroxyurea and Verapamil for Refractory Meningiomas). An updated review of clinicaltrials.gov database was performed on January 6, 2015 which identified 27 additional completed SCD trials for inclusion in Tables 1 and 2. To compare the results of SCD trials to another disease, an additional data set was created for “thalassemia” “closed” and “interventional” using the same methods. Thalassemia was selected as these trials are often lead by non-malignant hematologists (often those interested in hemoglobinopathies) and trial results are often published in the same peer review journals. Ninety one “thalassemia” trials were identified in the initial query and 11 trials removed as they were not trials of thalassemia; the main reason for removal were trials of patients with sickle beta thalassemia. Finally, to compare the differences in percent and reasons for trial termination in SCD to other diseases, a systematic review of clinicaltrials.gov was performed for hemophilia, cystic fibrosis, diabetes, HIV, and asthma trials that were completed or terminated by January 6, 2015 (Table 2).

The tabular view of clinicaltrials.gov was utilized to examine the 12 criteria included in our database: 1) closed with or without results reported in www.clinicaltrials.gov, 2) sponsor (primary and collaborator), 3) start date, 4) stop date, 5) clinical focus of trial (primary outcome), 6) phase, 7) trial design, 8) publication of manuscript, 9) enrollment number, 10) age of subject enrollment, 11) primary investigator and 12) if terminated or withdrawn, the reason listed for trial termination or withdrawal. The primary sponsor for each trial was recorded as well as any additional collaborators. From this information, nominal data was created listing sponsors and collaborators as either “academic”, “industry”, or “NIH”; studies with a primary sponsor and an additional listed primary collaborator were also recorded (i.e. NIH/Academic or Academic/Industry). The clinical focus of each trial (i.e. pain, acute chest syndrome) was obtained by reviewing the primary aims/objectives and secondary aims/objectives listed on clinicaltrials.gov. The authors (JL and LP) agreed on final “focus of trial” category for the study. Within the “Study Design” section of clinicaltrials.gov, information on “Endpoint Classification”, “Intervention model”, “Masking” and the “Study Phase” was recorded directly. Clinicaltrials.gov allows manuscripts from the trial (or background manuscripts) to be uploaded into the site, but this is not a required field. To determine if the clinical trials were published but not uploaded into clinicaltrials.gov, www.pubmed.gov was searched for all manuscripts closed before January 2014 (n=147) by 1) primary investigator last name and sickle, or 2) sickle and intervention studied (Table 3 and Supplementary Table 1). To further enhance the accuracy

of the data, for manuscripts from a primary investigator that had multiple possible manuscripts from a specific trial the primary investigator or drug company was contacted by email or phone to determine the appropriate manuscript to assign to the trial. To determine differences between expected enrollment and final enrollment, a review of the “History of Changes” feature in clinicaltrials.gov allowed for every entry in clinicaltrials.gov to be reviewed so that the first enrollment number recorded in clinicaltrials.gov could be compared to the enrollment number listed in the current dataset. To enhance the validity of the analysis of enrollment number from published manuscripts, the manuscript was reviewed to determine the published enrollment number and this was compared to the current and prior enrollment numbers listed in the clinicaltrials.gov database.

Characteristics of trial attributes were summarized using descriptive statistics. To examine potential associations between trial attributes and publication success in sickle cell trials and separately in thalassemia trials, the chi-square test, or Fisher’s exact test if the assumptions for the chi-square test were not tenable, was used to compare proportions. The same method was also used to compare proportions of publication success between the two types of trials. Logistic regression analysis was performed to determine attributes that were individually predictive of publication success. These analyses adjusted for the type of trial (SCD/thalassemia). A final multivariate logistic regression model including only attributes that were statistically significant predictors of publication success, as well as the type of trial (SCD/thalassemia), was then examined. An interaction term for trial attribute by disease (sickle cell vs. thalassemia) was also included in this model. Given the differences in trial attributes by disease (sickle cell and thalassemia) that we report, we did not want to assume that these diseases share a common odds ratio when evaluating the association of publication success and trial attribute. Odds ratios and their corresponding 95% confidence intervals were calculated for all logistic regression models. The goodness of fit of the model was verified by the use of the Hosmer-Lemeshow test. All statistical tests were two-tailed, and a p-value < 0.05 was considered as being statistically significant. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Characteristics of SCD trials

Trials were equal in using a randomization design; 86 SCD trials were listed as randomized and 86 were listed as non-randomized (Table 1). Academic centers were the most common sponsor of sickle cell trials and the majority of trials were completed within the United States. The most identified trial objectives were 39 pain trials (23%), 22 bone marrow transplant trials (13%), 13 fetal hemoglobin induction/hydroxyurea trials (7.5%), 13 pulmonary hypertension trials (7.5%), 13 iron overload trials (7.5%), eight endothelial function trials (5%), eight red cell physiology trials (5%), six acute chest syndrome trials (3%), and six platelet trials (3%). The remaining trial objectives were <5 trials per trial objective. Fifty six trials (34%) enrolled only pediatric participants, 59 (35%) included pediatric and adult participants, 51 (31%) enrolled only adult participants. Most commonly, trials were registered as phase 2 trials, unblinded and classified as a “Safety/Efficacy” trial.

Early closure of clinical trials

As of January 2015, 52 of 174 trials (30%) updated their registry to reflect a status as “terminated” or “withdrawn”. Three (6%) of these 52 clinical trials (all phase III trials) were terminated early for clinical benefit and six (10%) of terminated trials (three phase III trial) were terminated for futility or inadequate data. Twenty five of the 44 terminated trials (57%) and two of the eight withdrawn trials (25%) specifically acknowledged difficulty enrolling/accruing participants as the reason for the termination or withdrawal of their trial. To compare SCD trials to another hemoglobinopathy, only 8/80(10%) thalassemia clinical trials listed on clinicaltrials.gov were terminated or withdrawn which is significantly lower than sickle cell trials ($p=0.002$). Two of the eight (25%) terminated thalassemia trials specifically acknowledged recruitment issues. Sickle cell clinical trials had a much higher rate of trial termination and trial termination due to enrollment difficult than several other chronic diseases (Table 2).

Enrollment in SCD clinical trials

To evaluate successful enrollment of participants in clinical trials, 49 of the 52 identified published SCD trials listed an expected enrollment on clinicaltrials.gov (review of “History of Changes” described in methods). The initial median expected enrollment recorded in clinicaltrials.gov was 142 participants, and the published median enrollment number of participants was 113 (80% of expected). However, the standard deviation of expected vs. actual enrollment rate among trials was great (35%). Twenty three (47%) trials enrolled 90% of their expected enrollment, 12 trials (24%) enrolled 60–90% of expected and 14 trials (29%) enrolled <60% of their expected enrollment. No statistical difference was identified when comparing trial enrollment by phase, randomization, masking, or funding source. When evaluating published phase III SCD trials alone ($n=15$), eight trials (60%) enrolled 90% of their expected participants. A second analysis of enrollment success was performed for the 95 trials that were not published using the “History of Changes” feature to compare the first recorded enrollment number to the current enrollment number. Fifty one of the 95 unpublished trials revised their enrollment number; 36 of these (71%) revised their enrollment to less than 80% of the initial expected enrollment.

Dissemination and publication of SCD clinical trials

Only 19 of the 147 (13%) registered SCD trials closed before January 2014 uploaded a summary of their trial results into clinicaltrials.gov; similarly, 10 of 80 (13%) thalassemia trials uploaded a summary of their results into clinicaltrials.gov. Overall, 35% of the registered SCD trials resulted in an identified published manuscript which was lower than the 60% of thalassemia trials that were published ($p<0.001$) (Table 3). Of the 52 published SCD manuscripts, 28 (56%) trials uploaded a link to their manuscript into clinicaltrials.gov and 24 additional manuscripts were identified only through a systematic search of www.pubmed.gov. Publication success by SCD trial objectives included: 10 pain trials, four BMT trials, seven of medications trials to increase fetal hemoglobin (including hydroxyurea), three pulmonary hypertension, seven iron overload, two endothelial function, three red cell physiology, two acute chest syndrome, and three platelets. To compare successful publication of clinical trials, SCD trials were compared to thalassemia trials (48

out of 80 registered thalassemia trials had publications) by type of study. Thalassemia trials were more likely to be published than SCD trials if they were international trials, “Safety and Efficacy” trials, phase II trials, and “Adult and Pediatric trials” (Table 3). Using multivariable logistic regression analysis for publication success, thalassemia trials were more likely to be published than SCD trials (Adjusted OR 3.1, $p<0.001$) and trials that enrolled over 50 participants were more likely to be published (Adjusted OR 2.7, $p=0.036$) (Supplementary Table 1). The interaction term for trial attribute by disease was not statistically significant ($p=0.13$).

Discussion

To improve clinical care for pediatric patients with SCD, it is vital that clinical trials continue to be developed, funded, completed, and results disseminated to the public and health professionals. The NIH Reporter and clinicaltrials.gov provide access to current clinical trials but the NIH reporter is limited to NIH funded trials while clinicaltrials.gov was created to enhance public knowledge about all therapeutic clinical trials. This systematic review, for the first time to our knowledge, provides the most comprehensive review of the scope of all completed SCD clinical trials. However, this review highlights some deficiencies in the clinicaltrials.gov database that, if addressed, could improve public access to health information. Few investigators upload their trial results and/or links to trial manuscripts into the website database at the completion of the study which is concerning as the Food and Drug Administration Amendments Act requires specific trials to update aspects of trial results within one year of trial completion and failure to comply can lead to a penalty of up to \$10,000.²⁸ This lack of adherence to regulations could be due to the evolution of requirements and changes in requirements for clinicaltrials.gov that have occurred over the past few years. The Department of Health and Human Services and the National Institutes of Health is attempting to enhance transparency in clinicaltrials.gov and streamline the approach for research teams to register and report their trials.²⁹ The lack of adherence to clinicaltrials.gov requirements could be based on lack of education among clinical trialists about clinicaltrials.gov requirements, inadequate resources and staff to update the trials, or the multiplicity of requirements on NIH grants and their publications, which causes confusion. Nevertheless, while this shortcoming in maintaining a reliable clinicaltrials.gov database is not unique to sickle cell disease, the lack of complete trial information and dissemination of trial results to the public is contradictory to the goals of clinicaltrials.gov and investigators should work to address this identified deficiency. Second, existence of the information on [Clinicaltrials.gov](https://clinicaltrials.gov) is not a measure of the utility of the data on the site and/or whether the data are accessed, but without it being there, it obviously cannot be accessed. For the first time to our knowledge, this systematic review provides quantified results to support the long-held assertion that barriers exist to successful enrollment, completion, and publication of SCD trials. Among the 41 terminated sickle cell trials, three trials were closed for clinical benefit (penicillin prophylaxis and transfusion to prevent strokes) and spurred a change in clinical practice that remains current today and has improved the lives of children with SCD.^{4, 8, 9} Of concern, 20 sickle cell trials were terminated for slow enrollment. If completed, these trials may have improved the ability of sickle cell practitioners to treat acute chest syndrome, vaso-occlusive pain crisis in patients

with HbSS/SB0 thalassemia as well as determine the role for hydroxyurea in patients with HbSC. However, it is also possible that these trials were not well conceived and the lack of enrollment represented the potential quality of the trial, something not addressed by [ClinicalTrials.gov](https://clinicaltrials.gov).

Among the published manuscripts of trials that were terminated for poor enrollment, barriers to enrollment was highlighted in one manuscript and briefly described in four others.^{22, 25, 30–32} This failure to successfully complete SCD clinical trials should continue to prompt investigators to conduct research into barriers to successful trial enrollment and retention, identify obstacles to enrollment in trial design, and evaluate strategies to improve enrollment by enhancing the informed consent process for participants. Research should focus on understanding the likely barriers to enrollment and strategies to successfully overcome them from the participant perspective as well as for investigators. From the patient perspective, previous research into barriers in SCD has identified: mistrust of the scientific community, time commitment required for clinical trials, prior personal exposure to research, and specific to pediatrics, the concept that parents must enroll their young child into a clinical trial for their child.^{21, 33, 34} These barriers may not be unique to sickle cell disease, but provide evidence that SCD investigators should work to develop strategies to overcome these barriers when designing an enrollment plan. In this day and age of social media, it is also pertinent to engage the community to encourage trials and trial participation if the community wants to see progress move more rapidly. From the investigator perspective, a few sickle cell studies that were terminated early performed an analysis of their obstacles in trial conduct, which included limitations in research infrastructure or funding for dedicated research staff, overstated expected enrollment by investigators during trial planning, and difficulty enrolling participants based on strict eligibility requirements, including both time constraints and potential bias in not approaching all eligible participants.^{22, 25, 35} As a rare disease, it is vital that investigators continue to focus both on improving participant engagement and limiting obstacles in trial design and compliance. This design and possibly pilot testing should be conducted during the planning phase rather than during the conduct of the trial, as ineffective enrollment once a trial has been funded may take too long to correct and can lead to early termination.

This systematic review has some limitations worth noting. First, using the “History of Changes” feature on clinicaltrials.gov, it was noted that some trials did not include their enrollment number in the recruitment information section until subsequent revisions had been made to their dataset. This made it difficult to determine if the first listed enrollment number in this review truly represented the expected enrollment used in trial design. Since our review found that there was poor enrollment for SCD trials, the difference in expected vs. actual enrollment would be conservative and likely enhance the belief that enrollment is a barrier for successful completion of SCD trials. A second limitation was that the created database may not have identified all published literature, specifically for those manuscripts that were not uploaded into clinicaltrials.gov or indexed in pubmed, as well as abstracts or manuscripts currently under review/revision/recently accepted. Third, this review did not differentiate between publications of primary vs. secondary endpoints. In addition, as noted elsewhere the requirements for use of [Clinicaltrials.gov](https://clinicaltrials.gov) have evolved over the past decade, and retrospective posting was not required. Finally, despite the FDA and ICMJE

requirements to register therapeutic clinical trials, some trials may not have been reported to clinicaltrials.gov.

Despite some limitations of clinicaltrials.gov, this review highlights potential benefits including that clinicaltrials.gov can provide easy access to information from all sickle cell clinical trials. To improve the validity for this website and enhance access to health information for all members of the SCD community, investigators must understand the regulations that require registration of SCD trials, update their trial results and download publications into the database. Similarly funding agencies need to understand this is an ongoing task and should provide continuing resources to accomplish these requirements. Additionally, this review provides quantified support that barriers do exist to successful completion of SCD trials. To enhance analysis of successful and terminated trials, investigators should provide more accurate records for planned vs. actual enrollment, upload all trial manuscripts (primary and secondary outcomes manuscripts), and document reasons for trial termination. This research provides support to the belief that 1) investigators must develop strategies that engage SCD patients to participate in clinical research, 2) enhance SCD physician training in recruitment and retention of SCD patients, 3) engage the target community to improve their understanding and participation in SCD trials; and 4) promote research that identifies barriers and facilitators to enrollment, retention, and completion of active SCD trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Attributes of Sickle Cells Trials Completed by January 2015

Sickle Cell Trial	Trial Number
<i>Trial Attributes¹</i>	<i>n (% of trials)</i>
Randomization	
Yes	86 (50)
No	86 (50)
Funding	
Academic only	71 (41.05)
NIH only	29 (16.8)
Industry only	47 (27.2)
Academic and NIH	20 (11.6)
Industry and NIH	3 (1.7)
Academic and Industry	3 (1.7)
Focus of Trial	
Pain	39 (22.5)
BMT	22 (12.7)
Hydroxyurea/HbF Induction	13 (7.5)
Pulmonary Hypertension	13 (7.5)
Iron Overload	13(7.5)
Endothelial Function	8 (4.6)
Red Cell Physiology	8 (4.6)
Acute Chest Syndrome	6 (3.4)
Platelet	6 (3.4)
Others	45 (26.0)
Study Type	
Safety and Efficacy	69 (40.0)
Efficacy	25 (14.5)
Safety	19 (11.0)
PK or PD	8 (4.6)
Interventional	4 (2.3)
Blinding	
Single	4 (2.4)
Double	55 (33.0)
Open Label	108 (64.7)
Phase	
I	31 (20.8)
I and II	15 (10.1)
II	63 (42.3)

Sickle Cell Trial	Trial Number
<i>Trial Attributes^I</i>	<i>n (% of trials)</i>
II and III	2 (1.3)
III	29 (19.5)
IV	9 (6.0)
Enrollment Age	
Pediatric	56 (33.7)
Pediatric and Young Adult	13 (7.8)
Young Adult and Adult	20 (12.0)
Adult and Pediatric	26 (15.6)
Adult	51 (30.7)
Trial Size	
20	41 (24.8)
21–50	48 (29.1)
> 50	76 (46.1)

^I Trials with unknown attributes were not presented

Table 2

Percent and Reasons for Trial Termination among Several Clinical Trials

Disease	Number of Closed Interventional Trials	All Terminated (% trials terminated)	Terminated Trials due to Low Enrollment	Reasons for Trial Termination
Sickle Cell Disease	174	44 (25%)	<u>25 trials terminated for low enrollment</u> 14% of all trials 57% of terminated trials for low enrollment	25- Low enrollment 9- No reason 6- Futility/inadequate data 1- Adverse Events 1- Funding 3- Clinical Benefit (8 withdrawn trials- 2 for enrollment)
Thalassemia	100	9 (9%)	<u>4 trials terminated for low enrollment</u> 4% of all trials 44% of terminated trials for low enrollment	4- Low enrollment 4- No reason 1- Futility/inadequate data (5 withdrawn; 0 for enrollment)
Cystic fibrosis	382	33 (8.6%)	<u>12 trials terminated for low enrollment</u> 3.1% of all trials 36% of terminated trials for low enrollment	12- Low enrollment 11- No reason 3- PI reason 3- Methodology/Technical aspect 2- SAE/DMC/unfavorable risk-benefit analysis 1- Administrative reasons 1- FDA issue
Asthma	1572	84 (5.3%)	<u>19 trials terminated for low enrollment</u> 1.2% of all trials 23% of terminated trials for low enrollment	19- Low enrollment 26- No reason 9- Futility/inadequate data 7- Methodology/ protocol 5- PI reason 5- Sufficient data to analyze outcome 4- IND withdrawn/drug not available 4- Funding 2- Replaced with updated study 2- safety concerns 1- Similar trial at another center
Hemophilia	179	17 (9.5%)	<u>2 trials terminated for low enrollment</u> 1.1% of all trials 11% of terminated trials for low enrollment	2-Low enrollment 8- No reason 3- DSMB/Safety 1- Funding 1- Efficacy 1- Trial design 1- Similar trial at another center 1- Logistics
HIV	3754	211	<u>45 trials terminated for low enrollment</u> 1.2% of all trials 21% of terminated trials for low enrollment	45- Low enrollment 100- No reason 19- Futility/inadequate data 15- Safety concerns/clinical hold 10- IND withdrawn/drug issue 7- Sufficient data to analyze outcome 5- Funding 4- Change in care guidelines/ equipoise 2- Methodology/protocol 2- Replaced with other/updated trial 2- DSMB/IDMC recommendation
Diabetes	6936	455 (6.6%)	<u>108 trials terminated for low enrollment</u> 1.6% of trials 23.7% of terminated trials for low enrollment	108 - failure to enroll 146 - no reason 59 - Futility/inadequate data 33 - Methodology/protocol 28 - PI 26 - Safety concerns 15 - Sufficient data to analyze outcome 14 - Funding 13 - IND withdrawn/drug issue 6- Regulatory 4 - Replaced with updated study

Disease	Number of Closed Interventional Trials	All Terminated (% trials terminated)	Terminated Trials due to Low Enrollment	Reasons for Trial Termination
				2 – Ethical issue

Table 3

Comparison of publication success between completed sickle cell trials and thalassemia trials prior to 2014

<i>Trial Attribute¹</i>	Publication Success # of Trials published per attribute (% trials published per attribute)		<i>p</i>
	<i>Sickle Cell Trial</i>	<i>Thalassemia Trial</i>	
Randomisation			0.15
Yes	28 (53.9)	18 (39.1)	
No	24 (46.1)	28 (60.9)	
Funding			0.18
Academic only	15 (28.9)	17 (35.4)	
NIH only	13 (25)	8 (16.7)	
Industry only	15 (28.9)	17 (35.4)	
Academic and NIH	7 (13.5)	3 (6.3)	
Industry and NIH	2 (3.9)	0 (0)	
Academic and Industry	0 (0)	3 (6.3)	
Location			<.0001 *
US	43 (82.7)	17 (35.4)	
International	3 (5.8)	22 (45.8)	
US and International	6 (11.5)	9 (18.8)	
Focus of Trial			<0.001 *
Pain	10 (19.2)	0 (0)	
BMT	4 (7.7)	5 (10.4)	
Hydroxyurea/HbF Induction	6 (11.5)	5 (10.4)	
Pulmonary Hypertension	3 (5.8)	1 (2.1)	
Iron Overload	7 (13.5)	27 (56.3)	
Endothelial Function	2 (3.9)	0 (0)	
Red Cell Physiology	3 (5.8)	0 (0)	
Acute Chest Syndrome	2 (3.9)	0 (0)	
Platelet	3 (5.8)	0 (0)	
Others	12 (23.1)	10 (20.8)	
Study Type			<0.001 *
Safety and Efficacy	21 (48.8)	30 (68.2)	
Safety	4 (9.3)	3 (6.8)	
Efficacy	0 (0)	7 (15.9)	
PK or PD	4 (9.3)	2 (4.6)	
Interventional	2 (4.7)	0 (0)	
Others	12 (27.9)	2 (4.6)	
Blinding			0.09
Single	2 (4)	1 (2.2)	

	Publication Success # of Trials published per attribute (% trials published per attribute)		
<i>Trial Attribute^I,</i>	<i>Sickle Cell Trial</i>	<i>Thalassemia Trial</i>	<i>p</i>
Double	18 (36)	8 (17.8)	
Open	30 (60)	36 (80)	
Phase			0.006*
I	9 (19.2)	3 (6.8)	
I and II	4 (8.5)	3 (6.8)	
II	16 (34)	20 (45.5)	
II and III	0 (0)	2 (4.6)	
III	16 (34)	6 (13.6)	
IV	2 (4.3)	10 (22.7)	
Enrollment Age			
Pediatric	18 (34.6)	4 (8.5)	<0.001*
Pediatric and Young Adult	4 (7.7)	0 (0)	
Young Adult and Adult	7 (13.5)	2 (4.3)	
Adult and Pediatric	9 (17.3)	25 (53.2)	
Adult	14 (26.9)	16 (34)	
Trial Size			0.47
20	5 (10.2)	7 (19.4)	
21–50	14 (28.6)	10 (27.8)	
> 50	30 (61.2)	19 (52.8)	
Enrollment Achieved (%)			0.19
< 30	7 (14.3)	4 (12.1)	
30–60	7 (14.3)	3 (9.1)	
60–90	12 (24.5)	3 (9.1)	
90	23 (46.9)	23 (69.7)	

^I Trials with unknown attributes were not presented

* Denotes statistical significance at $p < 0.05$