

**REDUCING THE MISERY BURDEN:
A ZAMBIA-BASED SICKLE CELL ANEMIA CLINICAL RESEARCH CENTER**

October 10, 2007

Executive Summary

Sickle cell disease (SCD), a genetic disorder, is a major cause of childhood mortality and general morbidity in Sub-Saharan Africa. A bi-national, Zambia-US multi-institutional consortium proposes to enhance clinical care and research on sickle cell disease in Zambia. The proposal is divided into two Phases.

In Phase I, the Specific Aims are:

- 1) To establish the feasibility of screening for SCD in order to identify cases that will benefit from early support services;
- 2) To develop a patient cohort for hematological and clinical monitoring, clinical research and healthcare interventions proven to decrease morbidity and mortality in SCD;
- 3) To determine the infectious agents responsible for infections to which SCD patients are prone in order to inform strategies for vaccination and/or antibiotic prophylaxis; and
- 4) To train healthcare workers and patients and families on optimal management of SCD.

In Phase II we propose:

- 1) To determine the safety and efficacy of a drug, hydroxyurea, widely used to reduce complications of SCD in developed countries but never tested in a malaria endemic population such as Zambia;
- 2) To encourage interest in SCD management and research by young physicians in both Zambia and the USA to enhance efforts in this underserved disorder, recently designated a major world unmet health need by the World Health Organization (WHO);
- 3) To report our results in the medical literature (journal articles) and at appropriate public health forums.

We anticipate that already high enthusiasm for this project both in Zambia and the USA will enable recruitment of human and financial capital to drive the project forward. Interest in clinical management and research concerning SCD have been relatively stagnant in the developed world, due to small SCD patient populations and their relative lack of economic influence. We believe that a new SCD program in a part of the world where SCD is far more prevalent and mounts different challenges will energize interest in service and research.

We request an initial 2-year budget request of \$2.5 million (attached), to be administered through Brigham & Women's Hospital, a 5013c affiliate of Harvard Medical School.

Sickle Cell Disease and its Misery Burden

Sickle cell disease is a severe inherited disorder affecting the protein hemoglobin that makes red blood cells red. Although inheritance of a single sickle cell gene from one parent confers resistance to death from malarial infection, receiving these genes from both parents (homozygosity) results in sickle cell disease and a host of debilitating complications. Episodically, the red blood cells of sickle cell disease patients convert from flexible discs that accommodate normal blood circulation into rigid elongated shapes resembling scythes (a process known as “sickling”). White blood cells of the immune system are fooled into thinking that these “sickled” red blood cells are foreign germs and eat them. Hence the patients have relatively few blood cells and are anemic, resulting in fatigue and growth retardation. The fooled immune system is diverted from its normal task of ridding the body of germs, and sickle cell patients therefore suffer from frequent and often fatal infections. Periodically sickled red blood cells, because of their rigidity and abnormal shape, form logjams in the circulation, depriving the tissues downstream of the jam from oxygen. This event results in severe pain, tissue destruction and, worst of all, strokes and brain damage. A complication common in children is a massive accumulation of sickled red blood cells in the spleen, which enlarges it and causes it to trap large amounts of blood. This problem, known as “splenic sequestration,” has a high mortality rate.

These complications include severe anemia (low red blood cell counts) causing fatigue and growth retardation and the ravages of sickling, which while variable among individuals, results in severe recurrent pain crises, loss of kidney, liver and lung function and, most devastatingly, loss of brain function - strokes. Patients with sickle cell disease endure frequent and prolonged bouts of pain, and many require multiple hospitalizations to address pain and other SCD complications – the burden of misery. The WHO estimates that in sub-Saharan Africa 50% of children born with sickle cell anemia have died by the age of five years from the combined effects of the severe anemia and infections.

Over a half century of research into SCD and advances in general medical care have extended the average life span of SCD patients in developed nations. The most significant scientific advance has been the use of a drug, hydroxyurea, which has been shown to decrease pain episodes by nearly half and reduce mortality significantly in the US and Canada. Nevertheless, in the USA where over 80,000 SCD patients live, the misery burden remains high. In Africa, where the prevalence of SCD is much higher, diagnosis and treatment are scant, and the misery burden is enormous. Blood transfusions are relatively uncommon, and hydroxyurea has not been tested in that setting. Overshadowed by the HIV-AIDS epidemic, SCD, which affects hundreds of thousands of babies born each year, has largely been ignored. It is a significant cause of infant morbidity and mortality and will remain a major problem long after HIV-AIDS no longer is. In light of this concern, the WHO at its fifty-ninth World Health Assembly in May 2006 specifically designated sickle cell disease a major public health concern. There is an urgent need to establish simple, cost-effective high-impact strategies to reduce the morbidity and mortality associated with sickle cell disease in countries most affected.

In December of 2006, physicians from 2000-bed University Teaching Hospital (UTH) in Lusaka, the capitol of Zambia, met with counterparts from Brigham & Women’s Hospital

(BWH), Boston, USA to plan a Zambian-based SCD clinical research center. The initial participants included Professor Chifumbe Chintu, Emeritus Dean of the University of Zambia Medical School, who founded the SCD clinic at UTH in 1973 and Thomas Stossel, American Cancer Society Professor of Medicine at Harvard Medical School and Senior Physician in the Hematology Division at BWH who has visited Zambia annually since 2004 to provide healthcare and has established a non-profit foundation for this activity. Over subsequent months, teams from the Department of Pediatrics and Pediatric Hematology at UTH and from BWH and Boston Children's Hospital (CHB) met separately and together to develop the work plan described in this proposal.

Why Zambia?

Although beset with the challenges encountered by other sub-Saharan developing nations, Zambia has distinct advantages for this project. Zambia has long been at peace with its neighbors and within itself and is actively fighting economic corruption. Tribal rivalries and political unrest that compromise many countries are not issues in Zambia. The Zambian SCD burden is large. It is estimated that 174 of every 10,000 births is to a child with sickle cell anemia. Also pertinent to this project, Zambia's healthcare system has, together with outside contributors such as the University of Alabama-sponsored Center for Infectious Disease Research in Zambia (CIDRZ) and US Centers for Disease Control (CDC), developed service and research capabilities in response to the HIV-AIDS epidemic that form a solid background for diversifying research efforts. Zambia is one of the most effective responders to the United States President's Emergency Plan for AIDS Relief (PEPFAR) initiative. Specifically, UTH Lusaka in collaboration with the US CDC is successfully conducting an early infant program for HIV diagnosis. The UTH SCD clinic has over 600 registered patients and is ably managed by Professor Chintu and Tendai M'Soka, MD PhD, a pediatric hematologist-oncologist, whom we are in close relationship with in regards to this project.

Proposal

A striking lack of research activities and basic health care infrastructure in the parts of the world most burdened with sickle cell disease subjects patients to preventable debilitation and childhood mortality.

This proposal seeks to establish a research center for SCD that will deliver uniform cost-effective clinical care, conduct research activities germane to continued improvement in care and educate and train local health care workers and patients and families burdened with sickle cell disease. A proposed budget for the first two years of the project is attached.

Specific Aims & Logic Model (Fig 1):

Aim 1: To establish the feasibility of SCD screening so that patients come earlier to medical attention and receive appropriate medical and support services. If successful, the screening program will progressively expand to encompass additional urban patient populations and eventually extend to the rural areas.

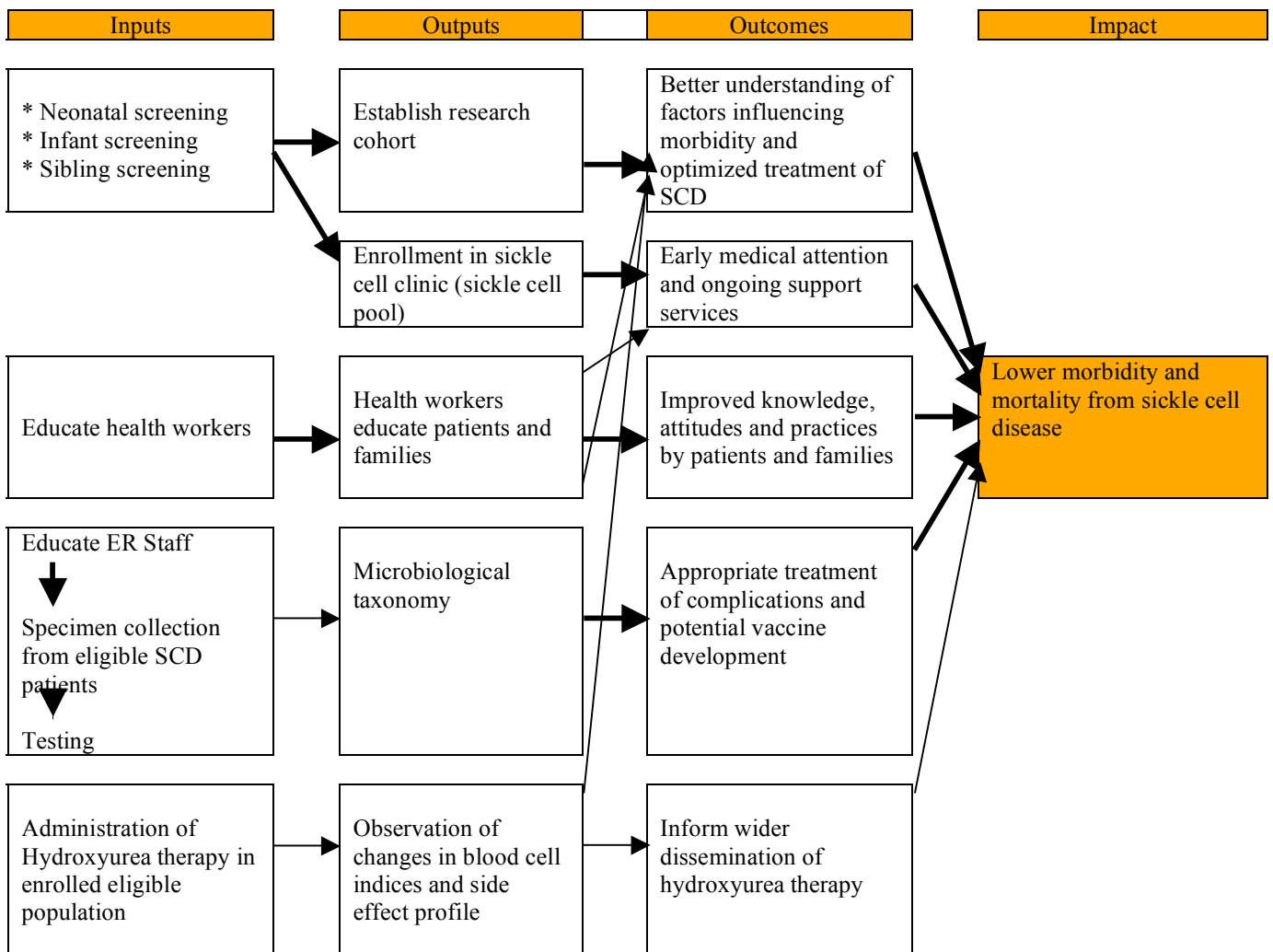
Aim 2: To establish a cohort of patients for hematologic and clinical monitoring, provision of simple, cost-effective medical interventions and for research activities in sickle cell disease in a malaria endemic population.

Aim 3: To establish the prevalence of microbial species responsible for infections in SCD patients, a major cause of morbidity and mortality. The results will inform strategies for disease prevention such as vaccination and antibiotic prophylaxis.

Aim 4: To train health care workers to educate patients and families affected by SCD concerning management principles such as folic acid supplementation, malaria prophylaxis, and early intervention for complications such as infection and splenic sequestration crisis.

Aim 5: To assess the safety and efficacy of hydroxyurea therapy in sickle cell disease in a malaria endemic African environment.

Fig. 1 Logic Model of the Proposed Zambia Sickle Cell Anemia Research Center



Program Plan (Fig 2)

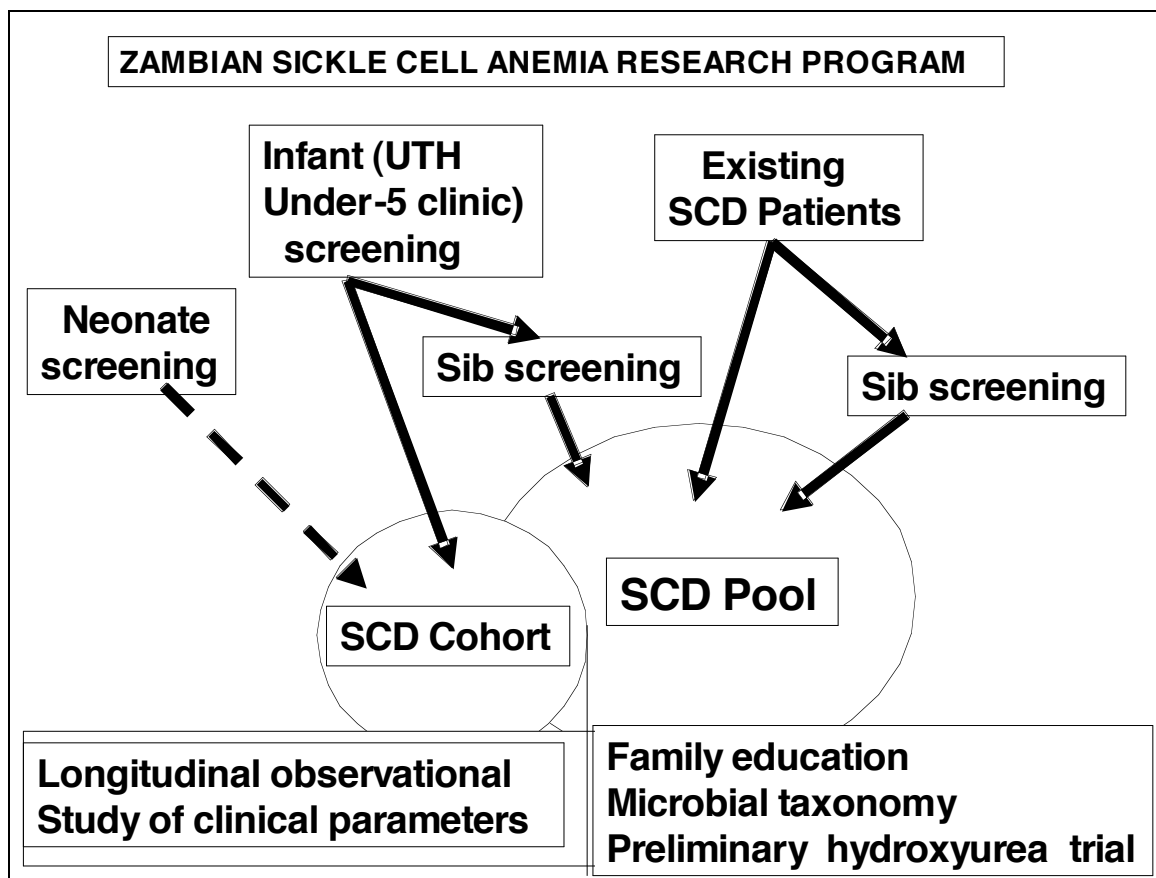


Fig. 2: Program Schema for the Zambia Sickle Anemia Cell Research Center

Phase I

Addressing Specific Aim 1:

Plan: Development of an Early Infant Screening Program for SCD

The initial goal is to screen for SCD so that identified patients come earlier to medical attention and receive support services. Our analyses indicate that screening newborn infants is presently not feasible due to difficulties in tracking newborns once discharged from hospital. Therefore, we plan a pilot program to screen early infants (at 6 weeks of age) who voluntarily present to the UTH well-baby Under-5 clinic and the Bauleni Clinic Under-5 clinic for cost-free vaccinations (See Fig. 2). This will accrue approximately 6000

infants per annum, 90% of whom return voluntarily to receive subsequent vaccinations and so present themselves for follow-up. All infants who present for 6-week vaccinations will be subjected to heel stick sampling of blood (dried filter specimen) for SCD screening in the same fashion as is successfully being carried out for the US Centers for Disease Control (CDC) HIV screening currently underway at UTH. Two nurses will be recruited to each of the two clinics to run the screening program. The logistics for collecting, batching, refrigeration, storage and documentation of samples is already well established based on the HIV screening program. We will be building on the existing HIV infrastructure in all aspects of this project that fundamentally similar.

We have established a contractual collaboration with the Massachusetts State Laboratory to perform the SCD technical screening on dried filter specimen sent from Lusaka to Boston by World courier during this pilot project. The longest estimated turnaround time for a specimen's result to be reported electronically to Dr M'Soka at UTH Lusaka is 5 weeks. A charting system will ensure that SCD status will become part of the record of the screened subjects. The turnaround time of 5 weeks assures that SCD patients will be notified before completion of their vaccinations. We are determined to establish screening on site as soon as is feasible which will decrease the 5-week turnaround substantially. Patients who test positive and do not automatically return for their vaccination appointments will be traced to their individual homes by designated community health workers. We hope to have eliminated a significant portion of the difficulty of tracking, experienced by other groups working in Africa, by sampling from this population that should return to the Under-5 clinic for vaccinations irrespective of our screening. Upon identification, and informed consent, baseline data will be collected and these infants will be enrolled as new patients in the UTH sickle cell clinic and in the Zambia Sickle Cell Cohort (described below). The new patients and all siblings will be encouraged to follow-up in the Sickle Cell Clinic for an initial new patient/family visit.

Sibling Identification and Sibling Studies

A second aspect of the screening program is to identify siblings of individuals with sickle cell disease. All siblings of each infant identified by the early infant screening program will be screened for sickle cell disease at the initial family visit to the UTH Sickle Cell Clinic. All siblings of active patients of the UTH Sickle cell clinic whose genotype is unknown will also be screened. All newly identified siblings will be registered as new patients of the Sickle Cell Clinic. All active patients of the Sickle Cell clinic will serve as the backbone of a UTH Sickle Cell pool to which newly identified siblings will be added (See Fig. 2).

The screening expansion strategy following on the anticipated success of the pilot program will include assessment and implementation of large scale screening approaches that can be accomplished most cost-effectively on site (at UTH). Candidate modalities include isoelectric focusing, HPLC or DNA genotyping.

Addressing Specific Aim 2:

Plan: Development of a Sickle Cell Patient Cohort

A plethora of valuable clinical information that has greatly impacted the understanding and clinical care of patients with sickle cell disease has been derived from the Jamaican Sickle Cell Cohort established in 1973 by Dr Graham Serjeant. We propose to establish a

similar cohort in Lusaka Zambia that would be unique in its population exposure to malarial infection. This would be the first Sickle Cell Cohort in a malaria endemic population followed from infancy in a systematic fashion. Operations of the Cohort will take place in the existing UTH Sickle Cell Clinic. Cohort patients will be seen in the UTH Sickle cell clinic at regular 3- to 6- monthly appointments and at any time they feel ill. Demographic information and clinical and hematological data will be collected upon study entry (baseline). Thereafter, clinical information will be collected at every clinic visit and hematologic parameters will be collected annually and at times of illness. Data will also be collected on acute and chronic complications of SCD. All patients will be given charge-free folic acid and pyrimethamine malaria prophylaxis. Patients and families will receive teaching on the importance of screening, folic acid supplementation, recognizing SCD complications, encouragement of malaria prophylaxis and letters to school officials for absenteeism. Benchmark feedback instruments to document effective education of the patients and families will be developed. Also education will quickly be reflected in earlier presentation to medical attention at times of illness.

Addressing Specific Aim 3:

Plan: Identification of Infectious Agents.

Results of this study will form the basis of subsequent strategies regarding vaccination and / or microbial prophylaxis in SCD patients. *S. pneumoniae* is a major offender in childhood sepsis in developed countries but is much less frequently the cause of febrile illness and mortality in children with sickle cell disease in Africa¹⁻⁵. Sepsis remains a major cause of morbidity and mortality in SCD patients in Zambia. Hitherto, a paucity of bacterial culture bottles, nasopharyngeal swabs and laboratory reagents at UTH Lusaka has precluded routinely obtaining microbial identification in SCD patients with fevers. Patients currently receive no prophylaxis and are treated with empirical antibiotic coverage.

The emergency room will be the main source of recruitment of patients. As a first step, emergency room staff at UTH will be educated on our intentions to conduct the study and the benefit that this is likely to have on SCD patients. Consecutive patients with sickle cell disease presenting to UTH Lusaka with a fever (temp >38C) will be included in this study. We anticipate recruiting 100 -120 patients per year. Specimen bottles will be stored in a location readily accessible from the pediatric emergency room. Immediately after the SCD patient with a fever is identified at triage and upon informed consent, specimens will be collected prior to antibiotic administration, for the following tests: complete blood count, thin peripheral blood film, 1 set of blood cultures, urine cultures and nasopharyngeal swabs. In addition, sputum cultures will be collected on patients with a productive cough. The microbiology laboratory at UTH Lusaka has the infrastructural capability for bacterial cultures, antibiotic sensitivity testing and performing ELISA and DFA. We will train already otherwise qualified laboratory technicians in exact procedures to be followed in testing specimen in this study. Dr M'Soka has recruited a second year resident at UTH Lusaka, Dr Mbinga Mbinga, who is interested in further study and management of sickle cell disease. He is dedicated to co-ordinating the logistics of this project under the supervision of Dr M'Soka. Dr Richard Moriarty, a pediatric infectious disease specialist at the University of Massachusetts Medical School has joined this project and established contact with the Boston University Medical Center laboratory capable of generating serotype data that can inform future vaccination strategies.

Addressing Specific Aim 4:

Plan: Train health care workers on methods of educating patients and families affected by SCD

Parent and patient education has been shown to be effective in reducing morbidity and mortality in SCD. ^(6,7) Volunteers from The Foundation for People Living with Sickle Cell Anemia and few interested healthcare workers who currently work at UTH will be recruited and trained for participation in this project. Each participant will be required to fill a questionnaire at the beginning of training to document basic knowledge, or lack thereof, of sickle cell disease. They will then undergo didactic instruction on sickle cell disease on the importance of screening, folic acid supplementation, recognizing SCD complications, importance of malaria prophylaxis and the importance of research activities in health care in general. They will also be trained to educate patient and families and afterwards be required to answer a second questionnaire to document effective learning. After training, the healthcare workers will be given specific materials, translated to the major local languages, indicating exactly what they are to tell the patients and families regarding sickle cell disease. This education of the patients and families will be carried out in the UTH Sickle Cell Clinic waiting area as patients and their families wait for doctor's appointments. Instruments will be developed to assess the improvement in knowledge, attitudes and practices of patients and their families with completion of this education. Education of health center personnel concerning SCD should translate into encouraging families to volunteer for screening. This approach has been effective in increasing HIV screening.

Phase II

Addressing Specific Aim 1:

Plan: Preliminary Hydroxyurea Therapy Trial

We plan to initially conduct an open-label trial to document the hematological responses and monitor side effect profile of hydroxyurea in SCD patients in a malaria-endemic area. The goal is to enroll HIV-negative male and non-pregnant female adults willing to utilize contraception and children over age 5 who consent/assent for the trial according to established criteria used in previous US-Zambian collaborative clinical research studies at UTH, who have had more than two pain crises in the year preceding enrollment, who are deemed likely to be compliant based on previous attendance at the UTH SCD Clinic and who have normal renal and hepatic function based on biochemical tests. Subjects will be given hydroxyurea capsules with dose escalations to a maximum dose of 20mg/kg, a level shown to be safe and effective in adults and children in previous controlled trials in US and Canada. Subjects will be monitored for changes in hemoglobin, red blood cell indices, white blood cell counts, and fetal hemoglobin level and for complications of SCD. Since the mean corpuscular volume is a highly sensitive indicator of hydroxyurea administration, compliance monitoring is facilitated. It is unlikely that an effect of hydroxyurea on chronic complications will emerge from this initial trial, but improvement in anemia and decreased frequency of admissions for SCD related illness should be an immediate benefit. Depending on the results of this preliminary trial, a randomized trial of hydroxyurea in SCD will be planned. Since efficacy of hydroxyurea

was proven with relatively small numbers of subjects in such trials in the past, we anticipate fairly rapid progression to a strategy designed to promote wider dissemination of hydroxyurea therapy in the Zambian SCD population with monitoring for compliance, tolerability and outcomes.

The Management Plan

The Co-principal investigators in Zambia and the US will be the central coordinators of all project activities. A full-time administrator in the US will be in charge of the operations of the project: scheduling meetings, running the budget, organizing travel and monitoring data movement between sites in Zambia and the US. Telephonic conference calls will be held every month for periodic situational reports. A secure website will be established and an email communication scheme will link all key personnel. Annual group meetings will be held in Zambia of all the key personnel and project advisors and semi-annual meetings of key project members will be held at a site convenient to the US and Zambia. Quarterly progress reports will dictate needed modifications of program processes, and an Annual Report will be provided to the Project Board of Scientific Advisors.

Program Scope and Advisory Support (Fig. 3).

We have recruited a critical mass of experienced advisors to assist us in development of the project and to evaluate it as it goes forward. These include Dr David Weatherall, Professor of Medicine Emeritus at Oxford University, UK, who has established and has worked in a Thalassemia center in Sri Lanka for the last decade, , Dr David Nathan, President Emeritus of Dana Farber Cancer Institute, Boston and Dr George Dover, Chief of Pediatrics, Johns Hopkins Medical School. Of particular value has been Dr Graham Serjeant, Professor Emeritus, University of West Indies who established the world's largest SCD clinical research center based in Jamaica. He has agreed to serve as an ongoing consultant to the Program.

We have consulted with Dr Marc Mitchell of the Harvard School of Public Health concerning program evaluation of the proposed project, who made our project a case example for students in his course on public health program evaluation. Four students enthusiastically embraced this case and have created logic models for SCD and for our program (Figure 1). We also worked with Dr Catherine Hayes, Tufts School of Dental Medicine concerning public health research design and with Dr Linda Wright, Deputy Director, National Institute of Child Health and Human Development, of NIH, who is currently running a neonatology resuscitation program in Zambia, regarding fiscal and personnel management.

We are also fortunate to have at our Institution a Division of Health Disparities run by Drs Paul Farmer and Dr Jim Yong Kim, former Head of HIV-AIDS Management for WHO, advised by Dr Howard Hiatt, Dean Emeritus of the Harvard School of Public Health. These individuals have established health support systems throughout the world and are currently actively building capacity in Rwanda and in South Africa. Dr Kim has evaluated and approved this proposal and has volunteered further interest in two capacities. In one, he will assist us in obtaining hydroxyurea at low cost for the trial proposed in the second phase. In another, he has indicated that should our pilot program succeed, he would be interested in incorporating a SCD effort into his wider activities in Africa. This would be an exciting development indeed.

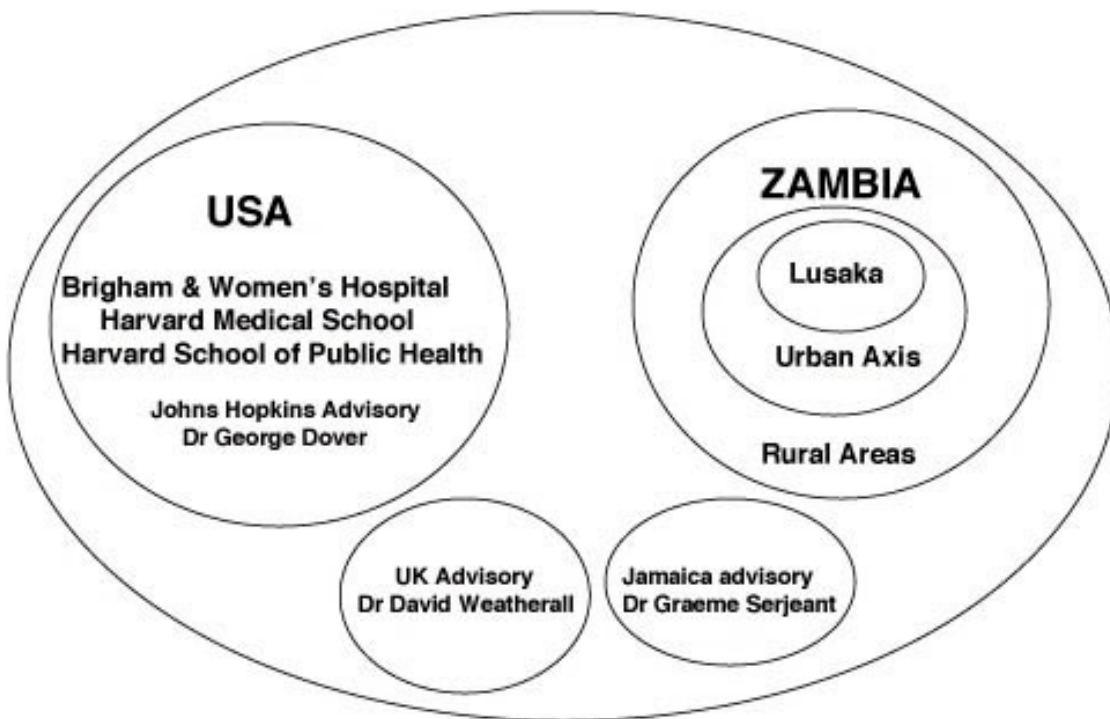


Fig 3. Program Scope and Advisory Support

Implementation

Dr M'Soka is responsible for ongoing logistics of the program in Lusaka where he will be advised by Drs Chintu and Wasomwe. In addition, he is recruiting young Zambian physicians who are excited about participating in an important national health issue besides HIV-AIDS. Developing the research plan with Drs M'Soka and Stossel have been Drs Maureen Okam, a hematologist trained in public health who is active in the SCD clinical program at BWH together with senior hematologists, Drs Hallowell Churchill, Ronald McCaffrey and H Franklin Bunn, a world-renowned expert on the structure and function of hemoglobin and of the pathophysiology of hemoglobinopathies and Dr Matthew Heeney, Director of the SCD Program at CH, who has participated in clinical studies of hydroxyurea therapy in the United States. Dr Stossel has and will continue to spend 2-4 weeks in Zambia every December, and the other US participants are eager to spend time there as well. Michael Huppert, Assistant Dean for Community Affairs at the University of Massachusetts has arranged for medical students and residents to Zambia, and they will work with Dr M'Soka. In addition, news of this project has energized Medical and Pediatric Residents at BWH, CH and Boston Medical Center to participate as well. International medicine infrastructures at these institutions will address the logistics of travel, immunization and liability that enable such participation. In addition, the programs or the individual participants will cover their costs.

Timetable.

We estimate that phase I to establish feasibility will be completed within one year, enabling the onset of phase II in year two. From then on, we propose to build in a stepwise fashion expansion of the program from the Lusaka area into the North-South urban axis covered by road and rail and then into the rural areas to the east and west.

Sustainability

We anticipate that success of the initial aims, manifest as a growing cohort of identified SCD patients, documentation of evidence for progress in health worker education concerning SCD and of delivery of services to SCD patients and families, compilation of a meaningful initial database regarding microbial ecology of infectious illnesses in SCD patients and progress in initiating the hydroxyurea clinical study will raise already high enthusiasm for this project both in Zambia and the USA that will enable recruitment of human and financial capital to drive the project forward. Interest in clinical management and research concerning SCD have been relatively stagnant in the developed world, due in part to the relatively small SCD patient populations, their relative lack of economic influence and a slow pace of progress compared to other areas of medicine. We believe that a new SCD program in a part of the world where SCD is far more prevalent and mounts different challenges will energize interest in service and research. The international presence should promote attention to 'The Foundation of People Living with Sickle Cell Anaemia in Zambia and encourage the evolution of new support groups in the USA and elsewhere. Most importantly, however, we look to the training component of the project as the most important element of sustainability, because it enhances Zambian resources.

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