Dear Principal Secretary,

You may be aware, that despite Haemoglobinopathies being a preventable genetic disease, a large number of patients continue to be born with blood disorders mainly due to lack of awareness and lack of programme and systematic strategies to prevent them.

Haemoglobinopathies are a major health problem, placing an immeasurable emotional, psychological and economic burden on lakhs of families in the country. Data on the prevalence of β-thalassemia ranges from 2.9-4.6%, and for sickle cell anemia especially among the tribal population ranges from 5-40%, while hemoglobin variants like HBE in eastern India can be as common as 3-50%. At times, there could be various permutation and combination among the various hemoglobinopathies e.g., one parent could be a carrier of Sickle cell disease and the other of β Thalassemia or one parent carrier of Sickle cell disease and the other haemoglobin variant. Hence the strategy is required for a unified approach.

Considering the burden and the cost of management, suitable control measures need to be undertaken urgently. This could be both primary and secondary prevention. Primary being identifying the carriers and avoidance of marriage of carrier couples and secondary by preventing the birth of affected child through prenatal diagnosis.

Keeping these in view, comprehensive guidelines have been prepared on prevention and control with regard to hemoglobinopathies. I am hopeful that these comprehensive guidelines will help the states to address the issues concerning Hemoglobinopathies

I will urge you to plan for prevention and control of hemoglobinopathies in the PIP for 2016-2017, while doing the preparatory work in this financial year itself.

Yours sincerely

(C. K. Mishra)

Secretary/Principal Secretary (Health) of all States/UTs.

Copy to: Mission Directors (NHM) of all States/UTs.
PREVENTION AND CONTROL OF HEMOGLOBINOPATHIES IN INDIA - THALASSEMIAS, SICKLE CELL DISEASE AND OTHER VARIANT HEMOGLOBINS

National Health Mission Guidelines on Hemoglobinopathies in India

Ministry of Health & Family Welfare Government of India
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PREVENTION AND CONTROL OF HEMOGLOBINOPATHIES
SECTION A

POLICY DOCUMENT

National Health Mission:
Policy for Prevention and Control of Hemoglobinopathies in India

Executive Summary:

Hemoglobinopathies are inherited disorders of red blood cells. They impose a heavy burden on families and the health sector in India being an important cause of morbidity and mortality. India has the largest number of children with thalassemia major in the world – about 1 to 1.5 lakhs, and almost 42 million carriers of β thalassemia. About 10,000 -15,000 babies with thalassemia major are born every year. Sickle cell disease affects tribal groups, as well as some other communities in certain states, such as central part of India, Gujarat, Maharashtra and Kerala. Carrier frequency varies from 1 to 35 % and there are a huge number of people with sickle cell disease.

In India, the technology, know-how and the means to adequately treat and control both thalassemia and sickle cell disease are available, but this has not been initiated as a policy for various reasons. The new initiatives and vision under the National Health Mission provide a golden opportunity to administer adequate therapy to those affected making them lead a better life and preventing the birth of children affected with hemoglobinopathies, through carrier screening, genetic counseling and prenatal diagnosis. For sickle cell disease, newborn screening program will be initiated and appropriate treatment and vaccines given to those with sickle cell disease to prolong their life and prevent untimely death.

The World Health Organization has clearly outlined the goals for control of hemoglobinopathies - provide affordable and adequate therapy for those affected, while at the same time reduce the number of births of children with the disease, through strong political, administrative and financial support. Keeping these guiding principles with regard to hemoglobinopathies, the vision of the National Health Mission is to provide optimal treatment to those affected, and prevent the birth of further children with disease through carrier screening, genetic counseling and prenatal diagnosis. This will be achieved through development of treatment centres with the help of state health departments; carrying out awareness, education and screening programmes in the community and schools; establishing laboratories for carrier screening for hemoglobinopathies and screening for newborn screening for sickle cell disease at the district level; screening pregnant women and their husbands, to prevent the birth of children affected with thalassemia major or sickle cell disease; establishing prenatal diagnostic centers in medical colleges in the states that do not have one; setting up bone marrow transplant units and public cord blood stem cell collection and storage facilities in major cities to provide a source of HLA matched stem cells, and involving parent organizations for implementation of the programs outlined above.

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Background:

Hemoglobinopathies (thalassemias and abnormal variant hemoglobin) are the commonest genetic disorders worldwide. An estimated 7% of the world population carry an abnormal hemoglobin gene, while about 300,000 -500,000 are born annually with significant hemoglobin disorders. They consist of two major groups - Sickle cell syndromes and thalassemias. Sickle cell syndromes include Sickle Cell Disease (SCD, HbSS), also called Sickle Cell Anemia (SCA), as well as disorders due to sickle cell gene combined with another hemoglobinopathy such as Hb C, D, or thalassemia. Sickle cell syndromes are more frequent and constitute 70% of affected births world-wide, while the remaining ones are due to thalassemias.

Hemoglobinopathies constitute a major burden of disease, mainly in malaria endemic countries, but have now become global due to population migration. In 2006, World Health Assembly passed a resolution urging member states “to develop, implement and reinforce comprehensive national, integrated programmes for the prevention and management of hemoglobinopathies.” The member states were also urged to develop and strengthen medical genetics services and community education and training.

In India, Thalassemia Major (TM) and the severe form of Thalassemia Intermedia (TI) constitute the major burden of disease. Both are commonly managed by regular lifelong blood transfusions and regular iron chelation. These thalassemia syndromes are caused by inheritance of abnormal (beta) β thalassemia genes from both parents or abnormal beta-Thalassemia gene from one parent and abnormal variant hemoglobin gene (HbE, HbD) from the other parent. Sickle cell disease (SCD), is another hemoglobin disorder that requires lifelong management and contributes to infant and childhood morbidity and mortality. SCD is cause by inheritance of the abnormal HbS gene from both parents or Hb S gene from one parent and HbE or HbD or Thalassemia gene on the other. Person carrying only one of these abnormal genes are called ‘carriers’ as they do not suffer from any disease but carry the abnormal gene and transmit it to the next generation. Carriers cannot be recognized clinically but only by performing blood tests.

Where both mother and father are ‘carriers’, there is a chance that their children may inherit the abnormal gene from both parents and thus suffer from a severe thalassemia syndrome or a Sickle Cell syndrome (see figure below). If only one of the parents is a ‘carrier’, the child may also be a carrier like his parents but cannot have a disease state.
Genetic disorders where both genes are required to be abnormal for the disease to manifest are called ‘autosomal recessive’ disorders. Genetic epidemiology of the disorders with recessive inheritance is such that the recessive gene, ‘naturally selected’ at some point of evolution due to survival advantage, continues to spread through asymptomatic healthy carriers, till it reaches an equilibrium with the disadvantage due to the severe disease manifesting in children having abnormality in both their genes. It is the severity of these autosomal recessive disorders, manifested in children born to “healthy” carrier couples, that makes prevention and carrier detection an important public health issue.

**Burden of Hemoglobinopathies in India**

In India, β-Thalassemia is prevalent across the country, with an average frequency of carriers being 3-4% 4,5,6. A higher frequency has been observed in certain communities, such as Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, Saraswats, Lohanas and Gaur6. HbS is highly prevalent in the tribal populations of Southern, Central and Western states reaching as high as 48% in some communities 8. HbE is common in the North Eastern states, and has a carrier frequency as high as 50%, in some areas. It is found in lower frequencies in the Eastern states of West Bengal, Bihar and Uttar Pradesh, while HbD is present in about 2% of people in Punjab.

It is estimated that about 10-15000 babies with Thalassemia Major (TM) are born every year10. The only cure available for the children with thalassemia major, is bone marrow transplantation (BMT). However, this can help only a few patients, because of cost, paucity of BMT centers, or non-availability of a suitable HLA matched donor. Therefore, the mainstay of treatment is repeated blood transfusions, followed by regular iron chelation therapy to remove the excessive iron overload, consequent to the multiple blood transfusions. Thus it is a transfusion dependent disorder, and it places a great burden on healthcare services.
With decline in childhood mortality due to infectious diseases, more children with TM are surviving and presenting for diagnosis and treatment.

In a cost / benefit analysis done in Israel, cost of treatment of one patient for average life expectancy in Northern Israel was calculated to be $2,000,000 and cost of running a thalassemia control programme for one year was $400,000. Prevention is thus extremely cost effective rather than treatment of those who are affected.

In India, the cost of transfusing and chelating a 30 kg body weight child for one year was estimated at Rs. 200,000 for one year in 2008. With an estimated birth of 10,000 children with Thalassemia Major every year, and average survival for 50 years, the cost of managing 500,000 children (10,000 x 50) works out to Rs.10000 crores, and Rs.100 crores if only 1% were to survive to 50 years. Based on the experience of a pilot project funded and implemented under National Health Mission in Uttarakhand, the cost of screening 1 lakh adolescents was estimated at Rs.1 crore. Screening was based on Hb by digital Hemoglobinometer and NESTROFT as primary screening test followed by CBC and HPLC. Serum Ferritin was done in required cases to confirm concomitant iron deficiency anemia in suspected thalassemia carriers. Cost of DNA test for detection of causative mutation in HPLC confirmed cases was about 1000-1500 per case. The cost will be reduced further by about 30%, if screening for mild and moderate anemia is excluded.

**Impact of prevention programmes worldwide**

In Cyprus, it was estimated that if no steps for prevention were taken then there would be an increase in prevalence of affected births from 1:1000 to 1:138 and 600 % increase in blood requirement was estimated over a twenty year period. Successful implementation of a prevention and control programme has brought down the birth rate to almost zero and an augmented care programme has enabled the affected to have fulfilling lives. In Sardinia, Italy the introduction of the voluntary carrier screening programme initiated in 1975, and it reduced the incidence of β-thalassemia from 1:250 to 1:4000. In Latium (Italy) voluntary screening programme for secondary school children and young adults in place for more than three decades has brought down the incidence of affected births to zero. In Montreal, Canada successful voluntary screening programme in high schools for Thalassemia was started in 1980 and has led to a 95% decrease in the incidence of β-thalassemia9.

It is evident from the above illustrated examples that an effectively implemented prevention and control programmer can successfully bring down the birth of children affected with thalassemia major to almost zero, though it takes time. This reduces the burden of disease and enables better lifelong care of those already affected and surviving with the disease, born before implementation of the programme and those born before implementation or the initial period of the programmer.
WHO Criteria for setting up screening programme for thalassemia (1)

Generally when the Infant Mortality Rate (IMR) falls below 50, the burden of genetic disorders like thalassemia becomes apparent, due to the survival of children affected with thalassemia, who would otherwise have succumbed to the disease. Thus the time for formulation of a national policy for implementation of prevention and control of hemoglobinopathies in India is overdue. The WHO has listed the components of a control programme as follows:
- A strong political will and support
- Adequate finances for staff, equipment and chemicals
- Optimal treatment of those affected
- Carrier screening
- Genetic counseling, premarital or antenatal
- Prenatal diagnosis in couples where both the partners are carriers
- Awareness programme in the community, starting from the schools
- Monitoring of the programme

Development of control programme for hemoglobinopathies in India

The need for adopting and implementing a strategically planned prevention and control programme through the public health system across the country in India has been stressed upon by medical experts and patient-parent organizations for the past two decades. A brief record of these efforts and initiatives, that have shaped the development of the current policy guidelines is provided below:

1997 - Recommendations of the ICMR-DBT Brain Storming Session on Hemoglobinopathies held in April at National Institute of Immunohaematology, Mumbai comprising experts from major groups working on hemoglobinopathies in India. A comprehensive programme was envisaged including care and control components at each district extending to block level with screening of target population within the existing health system under the aegis of the national government. A pilot project in one state at district level was specifically recommended before extending the program to the block level and to the rest of the states.

1999 - Patient-parent organizations, especially Delhi based Thalassemics India and National Thalassemia Welfare Society supported by Thalassemia International Federation, became highly active, motivating parent groups to set up thalassemia Societies across the country wherever required, running public awareness campaigns, drawing attention of the government agencies towards the need to support children with thalassemia and initiate prevention programmes by screening during pregnancy, prenatal diagnosis and family screening.

2000 - Indian Council of Medical Research undertook an extensive multicenter study under ‘Jai Vigyan’ project to create awareness in the population and to determine the prevalence of beta-thalassemia and other hemoglobinopathies in six States from different regions of the country.
The result of the study conducted between 2000 and 2005 were published in 2012. Jai Vigyan project experience showed that NESTROFT missed an average of 13% of β thalassemia carriers. However, this was mainly due to the quality of water used at different centers, the preparation and dilution of the buffer and the frequent change of technicians who put up the test. When the NESTROFT buffer was prepared centrally and sent to the different centers, the results improved considerably. Red cell indices (CBC) also missed around 3 to 4% of beta thalassemia carriers at different centers. However, if NESTROFT and RBC indices were taken together in the first step, less than 2% of beta thalassemia carriers were missed. Around 25 to 40% of HbS and HbE carriers were missed by both the methods. In a national programme beta-thalassemias as well as HbE-beta thalassemias and sickle cell disorders will have to be screened. In regions where HbS is prevalent additionally Solubility test for HbS carriers and DCIP test in regions where HbE is prevalent, would have to be included as well. In all cases a strict quality control for the hematology analyzers, reagents and training programmes will be needed. At NIIH recent experience with capillary electrophoresis showed that the homozygotes for different Hb variants were picked up but not identified and the samples had to be re-run after mixing with normal samples for identification (communicated by Dr. Roshan Colah). Thus HPLC is at present still the preferred method.

2004 - Indian Red Cross – Gujarat branch, implemented a programme from the year 2004 where they have screened more than 20 lakhs students. In addition to this from 2009 till date through Antenatal Screening and Prenatal Diagnosis birth of 144 children with Thalassemia major has been prevented. The Society has been very active doing commendable service in this area.

2006 - An Indo-US Symposium on Genetic Disorders with Focus on Hemoglobinopathies was held at Banaras Hindu University, Varanasi, sponsored by Indo-US Science and Technology Forum. The Varanasi Region Thalassemia Welfare Society brought together scientists and medical experts from major Indian groups working on thalassemias and experts from a US Center of Excellence in hemoglobinopathies, Canada and UK to assess the prerequisites for a national programme including collation of data and mapping of resources. A follow up conference was organized by Department of Hematology, PGIMER, Chandigarh in 2008.

2009 - Publication of collated published data on β-globin gene mutations in India and creation and publication of a web based informatics resource (registry) ThalInd- for β Thalassemia and hemoglobinopathies, in collaboration with Centre for Comparative Genomics, Western Australia14.

2011 - Publication of a comprehensive review assessing progress on all aspects of thalassemia care and control in India by Department of Medical Genetics, Sir Ganga Ram Hospital, New Delhi, one of the leading centres for hemoglobinopathies in India14

2012 - Initiation of a pilot project on thalassemia and other Birth Defects in the State of Uttarakhand (Action on Birth Defects Project) under NRHM and continued under Rashtriya Bal Swasthya Karyakram (RBSK).
Hemoglobinopathies are the first among genetic disorders for which a national policy for prevention and control has been framed and being put forth through this document. The elements of the policy are guided by WHO directives and guidelines on hemoglobinopathies including thalassemia and sickle cell disorders1,2 and on services for prevention and management of genetic disorders in developing countries13.

The policy provides a framework based on strategies for prevention and management of hemoglobinopathies documented in publications of Thalassemia International Federation (TIF), various peer reviewed publications, reports of acknowledged groups and on experiences derived from implementing these strategies in public health set up under NHM.

The guiding elements of NHM Guideline on Hemoglobinopathies are-

1. Hemoglobinopathies are genetic disorders with an autosomal recessive inheritance implying that
   - they are equally prevalent in males and females
   - have a ‘carrier’ and ‘disease’ state
   - the abnormal gene is passed on from one generation to another
2. The carrier state refers to a person carrying only one abnormal gene. Such individuals do not have any disease and clinically have no symptoms,
3. The disease state occurs when an individual’s both genes are abnormal, one abnormal gene being inherited from each of the parents.
4. A couple where both the partners are carriers of an abnormal gene (mutated gene)
   - have a 25% risk in each pregnancy of giving birth to a child with disease state.
   - have 25% chance in every pregnancy of having a ‘normal’ child
   - have a 50% chance in each pregnancy to give birth to a ‘carrier’ child
   Thus, a carrier couple can have ‘normal’, ‘carrier’ or ‘disease’ affected children.
5. Thalassemia Major, Thalassemia Intermedia and Sickle Cell Disease are the major disorders that require lifelong management and are to be considered for prevention. Hematopoietic Stem Cell Transplant (HSCT), commonly known as Bone Marrow Transplant (BMT), is the only curative treatment but is possible in very few patients due to high costs and non-availability of matched donors.
6. Untreated Thalassemia Major is invariably fatal by 2-5 years of age. Commonly Thalassemia Major (TM) is managed by regular blood transfusions (Packed Red Blood Cells) and iron chelation therapy. Availability of leukodepleted packed red blood cells (pRBC) and iron chelators are to be ensured for adequate management along with facilities for regular monitoring. Adequately treated patients can live a fulfilling life.
7. It is possible to know whether the child to be born will be affected by disease, or be a carrier or normal by detecting the mutations of both parents in the fetal tissue. The process is called Prenatal Diagnosis (PND). As Thalassemia Major is a severe and burdensome disease termination of pregnancy is permitted under Indian laws.
8. Newborn screening can detect abnormal hemoglobin variants – carriers as well as those with disease states. On the other hand, thalassemia major can be detected hematologically mostly after 3-6 months of age and confirmed at one year of age.
9. Carrier state is asymptomatic, but can be detected by relatively simple blood tests, opening up the possibility of controlling hemoglobinopathies by preventing birth of affected children by,
Avoiding marriage between two carriers
Prenatal diagnosis in pregnancies of couples where both partners are carriers, with the option of termination of pregnancy in case of an affected features.

10. Cost effective population screening programmes are possible for detection of carriers, as low cost screening tests with high negative predictive value are available for detection of carriers of β-thalassemia (also referred to as β Thalassemia Trait (BTT)), HbS Carriers (HbS Trait) and HbE carriers (HbE Trait).

11. Genetic counseling, community education and awareness play a very important role in successful implementation of prevention programmes. Services and screening programmes should be sensitive to cultural and social practices and religious beliefs. Awareness of ethical and legal issues is required to avoid misuse of legal provisions, and be culturally sensitive.

12. The time between initiation of implementation and visibility of impact is affected by the group that is chosen for carrier screening-adolescent, premarital, pre-conceptional or antenatal. Sustenance of preventive programmes for long periods of time extending to decades is required to achieve expected outcomes.

NHM VISION AND POLICY FOR PREVENTION & MANAGEMENT OF HEMOGLOBINOPATHIES

Mission: To provide a better future for all Thalassemia and Sickle Cell Disease patients and their families and to lower the prevalence of hemoglobinopathies by reducing the number of births of children affected by Thalassemia Major and Sickle Cell Disease.

GUIDELINES FOR PREVENTION

Based on the rights of prospective parents at risk of having a child with a serious genetic disorder

- Establish carrier screening services for screening of pregnant women and their husbands, to prevent the birth of children with Thalassemia major or intermedia and SCD.
- Create laboratory facilities for testing and confirmation of hemoglobinopathy carriers at district level (DEIC labs).
- Establish regional centers in States with facilities for prenatal diagnosis and laboratory facilities for DNA analysis. Increase feasibility of antenatal screening by training of personnel in sampling techniques with help of tertiary centers.
- Train healthcare personnel for delivery of genetic counseling services for families at risk
FACETS OF THE PREVENTION GUIDELINES

Public health goal of reduction in the prevalence of hemoglobinopathies

- Community education and awareness programmes to remove any myths regarding transmission of disease, gender bias, stigma related to disease and carrier states and informing the community about appropriate prevention options and their availability through public health facilities.
- Installation of sustainable and cost effective carrier screening programmes at school level for adolescents backed by adequate and effective prescreening educative programmes on genetic disorders in general and hemoglobinopathies in particular and post screening non directive genetic counseling ensuring confidentiality and generating trust to enable expected outcomes.
- Establishing services at the community level for pre-marital, pre-conceptional screening backed by genetic counseling services.
- Extended family screening of all known and detected carriers and patients
- Implementation of strategies to achieve public health goal of reduction in prevalence of these genetic disorders will be done in accordance with the guidelines laid down by WHO in its January 5-7 1999 Report on Genetic Disorders and Birth Defects emphasizing on preserving and respecting the social and cultural diversity and dignity and rights of the affected and by voluntary genetic testing after informed consent.

Excerpts from the WHO document are given below, to inform those who run the programme.:  

-These (public health) goals should never be set in ways to impose genetic tests or reproductive decisions on individuals.

-Accepted ethical guidelines of public health programs in genetics stipulate that genetic testing should always be voluntary, respecting the autonomous decisions of the patients, and should be preceded by proper information in the form of non-directive genetic counseling (WHO, 1998).

-Public health goals cannot override the cultural and personal values and beliefs of individuals and their reproductive rights, and oppose stigmatization and discrimination of affected persons (WHO, 1998).

-Governments should recognize that within any country there exists diversity of cultures and opinions about a number of issues relevant to genetics, such as human reproduction issues as well as about the significance of disabilities.
GUIDELINES FOR MANAGEMENT

of affected children based on patients’ rights of access to care

- Provide optimal care to all patients of thalassemia and sickle cell disease patients by establishing day care facilities for transfusion and monitoring with the help of state health departments.

- Ensure availability of safe blood to children with thalassemia, strengthen existing blood banks with facilities for component separation and leucodepletion, and help the states to set up new blood banks or blood storage facilities where there are none. Promote voluntary blood donation to fulfill the blood requirements.

- Provide financial support for obtaining medicines for iron chelation, an essential component of management without which the entire blood transfusion given over years will go waste.

- Developing and implementing protocols for early diagnosis and intervention in cases of sickle cell disease (SCD) and Thalassemia major. Newborn screening SCD – in order to provide timely intervention with prophylactic penicillin and vaccinations (see management section) and targeted screening of children with anemia, to identify those having thalassemia trait or disease. Establish more Hematopoietic stem cell transplant (HSCT) centers for performing HSCT, previously termed bone marrow transplant (BMT); with the help of state health departments augment facilities for public cord blood stem cell collection and storage facilities in order to provide a source of HLA matched stem cells.

- Inform the community about appropriate treatment and management options and making these available through public health facilities.

Target of Public Health Strategies

Implementation strategies would be adopted to achieve the following public health goals:

1. Achieving maximum convergence with other health programmes for cost effectiveness:-

   - Management facilities for day care to be created at DEICs.
   - Newborn screening to be done by Dried Blood Spot samples, these samples can used to screen for other metabolic disorders
   - Adolescent screening will be combined with screening and treatment of anemia.
   - Antenatal screening for hemoglobinopathy will be carried out along with testing for HIV, hepatitis B, VDRL diabetes mellitus, hypothyroidism etc.

2. Preventive strategies adopted will aim at creation of an informed society that is willing to voluntarily participate in screening programmes, to achieve the public health goal of reduction in prevalence of hemoglobinopathies. All preventive options available at each step should be clearly communicated and non-directive counseling will be provided to enable the individual to make an informed decision.
3. A system of surveillance and registry will be established to track and evaluate outcomes such as number of patients registered under care programme and their record, number of carrier couples opting for prenatal diagnosis and number of carriers detected in school or at premarital stage avoiding marriage with another carrier. Other statistics to be included are the number of couples opting for adoption or limiting family size, and those treated by BMT.

4. Training of Doctors, Nurses, Laboratory Technicians, Social Workers and other healthcare personnel: to develop required skills for management of affected patients, clinical and laboratory diagnostic procedures including fetal DNA sampling by Chorionic Villus Sampling, community education and counseling and data recording and reporting procedures. This would be an important component for optimum prevention and management of thalassemia.

5. Research and Analysis: Research, documentation, data analysis and evidence generation for future strategies.

Political Will and Advocacy

A strong political initiative and continued support is required for the success of a prevention programme for hemoglobinopathies. This has been repeatedly observed in the case of the successful preventive programs for hemoglobinopathies from countries like Cyprus, Greece and Italy, which been successful in preventing the birth of children with thalassemia major through committed government initiatives and support. There are also examples of successful control programs for thalassemia even in developing countries, e.g., in Iran, Maldives, Sri Lanka and Pakistan. In India, the Government has taken the decision to support the prevention and management of thalassemia and framing of this document is the definite step initiated to this end.

Information, Education and Awareness

It is important to make the community understand about hemoglobinopathies, the treatment and prevention modalities. The strategies that will be adopted to achieve this are:

1. Mass communication and media – to incorporate with NHM- IEC at national and district state level.
2. Mid media activities – incorporation of the messages regarding thalassemia within the NHM Programme.
3. Including information and messages about hemoglobinopathies in school text books and school health programs and adolescent programme.
4. Provide information on prevention of thalassemia prevention in RBSK. Organize Quiz programmes based on prescreening power point assisted educative talks and educational booklets distributed to students during school visits. These strategies were found to be very effective in class IX-XII students in Uttarakhand in assessing and reinforcing retention of information.
5. Inter Personal Communication and one to group communication- to be incorporated with Antenatal Care care, ICDS program, at Sub Centre, AWC and PHC level, institutionalizing counselling for thalassemia during ANC, PNC and at blood bank.
6. Incorporation of a chapter at undergraduate level by putting in MCI curriculum. Special awareness and education campaigns will be initiated for the following target groups.

1. Eligible couples- Increase awareness of the disease, and motivate for screening for carrier status.
2. Youth - Increase the awareness on the prevention and care of the disease.
3. Affected families- Encourage voluntary screening for thalassemia in the relatives (cascade screening).
4. Children who have thalassemia major- Inform about care and prevention of complications.
5. General community- Reduce myths and misconceptions.

**Budget:**
- Budgetary support from the State and Central government to facilitate prevention and treatment of patients with thalassemia and sickle cell disease.

**Involvement of Stakeholders:**
- Non-government organizations (NGO), community based organizations (CBOs), support groups, Corporate and Private sectors will be involved in the prevention programme.

**SURVEILLANCE**

**Patient registries:**
A national registry will be created which would be worthwhile and would be an important tool for planning future patient services. Apart from numbers, the registry will collect other useful data, such as the location of patients to identify areas of high concentration; the ethnicity or other characteristic of patients; the age distribution which helps to evaluate the success if the control program, records of deaths and their cause which is a basic source of information directing the treatment choices.

The national registry will be computerized web-based and centrally controlled by health authorities. The quality of data will be assured and errors minimized. Data analysis will provide information both for planning services, for research and also for medical auditing and program evaluation. The registry will also be adequately funded to ensure sustainability and standards.

**Screening and surveys to identify the number of carriers**
Identification of healthy carriers will be achieved through simple hematological tests, which are low cost and sensitive. The same tests will be used for epidemiological surveys designed to estimate the proportion of carries in a given population. The carrier rate will be measured from both surveys and screening programme that will give an overall indication on the magnitude of the problem in a given population and identify at-risk groups within a population. In a prevention programme the number of individuals to be screened will depend on whether it is necessary for the whole population of reproductive age to be identified, as is the case in high prevalence areas, or whether targeted screening of at-risk groups is required, as is the case where the genes are present in ethnic minorities. The service indicator for screening varies therefore according to the policy which suits the population structure.
References:

2. WHO resolution on Sickle Cell Disease (WHA59.20) and Thalassemia (EB118.R1), 29 May 2006.

-13-
SECTION B

GUIDELINES FOR PREVENTION OF HEMOGLOBINOPATHIES (THALASSEMIA AND VARIANT HEMOGLOBIN DISORDERS)
SECTION B

INTRODUCTION

Hemoglobinopathies may be either qualitative or quantitative defects of hemoglobin. The major hemoglobinopathies consist of thalassemias (mainly α and β thalassemias) and variant hemoglobins (HbS, and HbE and HbD Punjab). In India, the major symptomatic hemoglobinopathy disorders are Beta (β) thalassemia and sickle cell anemia. They result in clinical syndromes known as Thalassemia Major (TM), Thalassemia Intermedia (TI) and Sickle Cell Disease (SCD). These guidelines pertain to prevention of major hemoglobinopathy syndromes- thalassemia and sickle cell disease.

Hemoglobin Structure:

Each hemoglobin molecule has a 3D structure composed of helical polypeptide chains. Hemoglobin consists of four polypeptide subunits; 2 alpha chains and 2 beta chains. Hemoglobin transports oxygen in the blood from the lungs to the rest of the body. These bind with iron ions to carry oxygen. Each heme molecule can carry four molecules of oxygen.

Figure 1:

Structure of Hemoglobin molecule

Genetics

At the genetic level the normal adult hemoglobin molecule is produced by two beta (β) and four alpha (α) globin genes. The normal adult hemoglobin molecule or HbA is composed of two alpha and two beta subunits (α2β2), only then it can work or function normally (Figure 1, Table 1). If one of the two β-globin genes is not working or functioning perfectly well, then the individual is called a carrier of β-thalassemia. In case the mutant gene gives rise to a variant hemoglobin, the individual is a carrier of that variant Hemoglobin like HbS, HbE or HbD.
Table 1: Normal Hemoglobin and its Genetics

| When the two β- and the four α-globin genes that produce normal adult hemoglobin (HbA, α2β2) work or function normally then the individual is normal. That is they are neither asymptomatic carriers nor suffer from any of the hemoglobinopathies. Any alteration in gene that leads to a change in genetic composition but may or may not alter its function is called ‘mutation’ | Normal Adult Hemoglobin :  HbA (α2β2)  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha chain</td>
<td>alpha chain</td>
<td>beta chain</td>
<td>beta chain</td>
</tr>
<tr>
<td>There are 4 alpha genes: αα/αα 2 on each chromosome</td>
<td>And 2 beta genes : β/β 1 on each chromosome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If one or two genes are absent/non-functional (αα/αα0) or (αα/α0α0) then, he/she is a carrier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If one gene is absent/nonfunctional (ββ0), he/she is a carrier</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Each parent contributes 1 beta gene and 2 alpha genes

<table>
<thead>
<tr>
<th>Mother</th>
<th>Father</th>
</tr>
</thead>
<tbody>
<tr>
<td>α α α α β β</td>
<td>α α α α β β</td>
</tr>
</tbody>
</table>

Child inherits from Mother  
Child inherits from Father

| α α | β | α α | α α | β |

Two α and any one β  
Two α and any one β

When one of the parents carries a non-functional β-globin gene, i.e. when he/she is a β-thalassemia carrier (heterozygote) and the other parent carries two normal functional β-globin genes, then each child born to these parents (i.e. at every pregnancy) has a one-in-two (50%) chance of inheriting the non-functional β-globin gene from the carrier parent (fig 2A). When both genes are affected the child is homozygous for mutant genes and presents with severe disease. If both the parents have mutations in the beta-globin gene, the offspring have 25 % risk of inheriting the mutant genes from their parents, and they may suffer from thalassemia major or intermedia depending on the severity of mutation and some other modifying factors. (Fig 2B)  
If the mutation in the beta-globin gene is that causes production of the variant hemoglobin HbS, the child will suffer from Sickle Cell Disease. (Fig. 2C)
Inheritance of thalassemia trait, if only one parent is a carrier

**Pattern A**

Parents: one is a carrier of Beta thalassemia, the other is normal. Red depicts the affected gene, blue is normal.

- **42 million asymptomatic carriers of beta thalassemia gene**, N1, C
- **Normal Mother**, N2, N3

Children: 50% chance of carrier children, 50% chance of normal children

(N1, N2, N3 - normal gene, C - affected gene)
Inheritance and risk if thalassemia major when both parents carry the thalassemia gene (both parents are thalassemia trait)

**Pattern B:** In India: 12,000 infants are born each year with Beta thalassemia major. Both parents are carrier of Beta thalassemia (red is affected gene, blue is normal).

- Carrier Father: N1, C1
- Carrier Mother: N2, C2
- Carrier Children: N1, C2; N2, C1
- Thalassemia child: C1, C2
- Normal child: N1, N2

(N1, N2 - normal gene  C1, C2 - affected gene)
Children: 50% chance of carrier children, 25% chance of normal child and 25% chance of thalassemia major child
Inheritance of Sickle cell disease, when both parents are carriers of HbS

**Pattern C:** In India, 9 lakhs silent carriers of Sickle cell Anaemia, 45000 children suffer from Sickle Cell Disease. Both parents are carriers of sickle cell gene. Green - sickle cell gene, blue normal gene

<table>
<thead>
<tr>
<th>Carrier Father</th>
<th>Carrier Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1, S1</td>
<td>N2, S2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carrier Children</th>
<th>Normal Child</th>
<th>Affected Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1, S2</td>
<td>N1, S2</td>
<td>S1, S2</td>
</tr>
</tbody>
</table>

(N1, N2- normal allele, S1, S2- sickle cell affected allele)

Children: 50% chance of carrier children, 25% chance of normal children and 25% chance of sickle cell disease affected child
Inheritance of two different hemoglobinopathies, e.g. HbS and Beta thalassemia

**Pattern D:** If both parents are carriers of Hemoglobinopathy gene.
Both parents carriers/heterozygotes
One parent carrier for sickle cell gene-green
The other parent carries for beta thalassemia gene-red

- **Carrier Father**
  - T1, N1
  - Carrier for HbS or Beta thalassemia

- **Carrier Mother**
  - N2, S1
  - Normal Child

- **T1, N2**
  - N1, S1
  - Compound heterozygote

- **N1, N2**
  - T1, S1
  - Children are at 50% risk for developing carrier state of HbS or Beta thalassemia, 25% chance of having a normal child and 25% chance of a compound heterozygote. This is a serious disease.

N1, N2-Normal gene, T1- beta thalaseemia affected gene, S1- sickle cell affected gene
Fig 2E

Inheritance of Hb E, when both parents are carriers of the affected gene.

Pattern E: If both parents are carriers of HbE
(Red is affected gene, Blue is normal)

- N1, N2 - Normal gene, H1, H2 - HbE affected gene
- Children: 50% chance of HbE carrier children, 25% chance of normal child and 25% chance of Hb E disease. These children usually present with symptoms of thalassemia intermedia syndrome
Inheritance of HbD, when both parents carriers of affected gene.

**Pattern F:** If both parents are carriers of HbD Punjab disease (Red is affected gene, blue is normal.)

**N1, H1**: Carrier Father

**N2, H2**: Carrier Mother

**N1, H2**

**N2, H1**

**H1, H2**

**N1, N2**

*HbD homozygote child*

*Normal Child*

N1, N2- Normal gene, H1, H2- HbD affected gene

Children: 50% chance of Hb D carrier children, who have normal haemoglobin
25% chance of normal child and 25% chance of Hb D disease. These children usually present with mild anemia only.

Compound heterozygote states can also occur with other hemoglobin variants such as HbD Punjab/E disease, HbS/D Punjab disease and HbS/E disease etc. These can be found due to migration and inter marriages from previously identified hemoglobinopathy pockets across the country.
Table 2:
Common terms used in context of Hemoglobinopathies.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genetic constitution of an individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>It is the detectable physical or clinical expression of genotype as a result of its interaction with environment</td>
</tr>
<tr>
<td>Mutation</td>
<td>It is a permanent inheritable change in a gene that definitely alters the genotype but may or may not alter phenotype</td>
</tr>
<tr>
<td>Allele(s)</td>
<td>The altered genes produced are called ‘alleles’ Even normal genes are referred to as alleles. As genes exist in pairs, alleles are also in pairs</td>
</tr>
<tr>
<td>Heterozygous (Heterozygote)</td>
<td>Condition (Individual) with one mutant and one normal allele</td>
</tr>
<tr>
<td>Homozygous (Homozygote)</td>
<td>Condition (individual) with similar alleles on both chromosomes</td>
</tr>
<tr>
<td>Compound Heterozygous</td>
<td>Condition with different types of mutant alleles on both chromosomes.</td>
</tr>
<tr>
<td>Recessive allele</td>
<td>An allele that causes disease only in homozygous or compound heterozygous state</td>
</tr>
<tr>
<td>Dominant allele</td>
<td>An allele that causes disease in heterozygous state</td>
</tr>
<tr>
<td>Carrier / Trait</td>
<td>A heterozygote for a recessive allele is also referred to as ‘carrier’ or ‘trait’ e.g. ‘β- Thalassemia Trait’ (BTT) or ‘Hb S Trait’. BTT is also referred to as Thalassemia Minor</td>
</tr>
<tr>
<td>β0 – thalassemia</td>
<td>Thalassemia syndrome in which there is complete absence of normal hemoglobin, HbA.</td>
</tr>
<tr>
<td>β+ thalassemia</td>
<td>Thalassemia syndrome in which some amount of normal hemoglobin, HbA is present</td>
</tr>
</tbody>
</table>

Common genotypes associated with clinically significant β-thalassemia syndromes (Thalassemia Major and Thalassemia Intermedia) and Sickle Cell syndromes prevalent in India. Thalassemia Major and Thalassemia Intermedia may be caused by homozygous β0 thalassemia or homozygous β+ thalassemia alleles but may also be caused by several other compound heterozygous genotypes. Hb Lepore, δβ are some other mutant alleles associated with β thalassemias. Similarly Sickle Cell Disease may be caused by several other compound heterozygous genotypes. Inheritance pattern and clinical significance of other homozygous and compound heterozygous states common in Indian populations are depicted in figures 2D, E and F.

A. β-Thalassemia syndromes (TM and TI) [βT – indicating a β-thalassemia mutant allele]
1. βT/ βT ( includes β0/ β0, β0/ β+ and β+/ β+ genotypes)
2. βT/ Hb Lepore
3. βT/ δβ
4. βT/ HPFH
5. βT/ HbE
6. βT/ HbD
All of the syndromes can be suspected on the basis of presence of increased proportion/percentage of Fetal Hemoglobin (HbF) associated with moderate to severe anemia usually between 3-12 months of age and confirmed at 1 year of age. Homozygous β0 genotype can be detected on newborn screening due to complete absence of HbA with confirmation of diagnosis at one year of age. Genotypes 5 and 6 can also be detected on newborn screening due to presence of variant Hbs and confirmed at 1 year of age. Genotype 6 is usually asymptomatic or mild TI syndrome.

B. Sickle Cell Disease syndromes

1. βS/βS  [βS- indicating the mutant allele for HbS; ]
2. βS/βT
3. βS/ HbD
These can be detected on newborn screening due to presence of variant Hemoglobins

Screening for detection of asymptomatic heterozygotes or carriers is the basis of strategies for prevention of these β- thalassemia and sickle cell syndromes.

C. Major asymptomatic carrier states of β-globin gene found in India (includes compound heterozygote states or homozygous states that are asymptomatic):-

1. β- Thalassemia Trait (BTT);
2. HbS Trait (Sickle Cell Trait) (mainly in Central, Southern and Western states)
3. Hb E trait (mainly in North Eastern and Eastern India);
4. Hb D trait (mainly in North India esp. Punjab),
5. δβ thalassemia trait,
6. Hb Lepore trait
7. HPFH Trait
8. Compound heterozygote for Hb D and Hb E (βD/βE)
9. Compound heterozygote for Hb D and β-Thalassemia (βD/βT)
10. Compound heterozygote for Hb S and Hb E(βS/βE)
11. Compound heterozygote for Hb S and HPFH(βS/HPFH)

Homozygous HbD (βD/βD) and HbE (βE/βE) genotypes are very mild syndromes presenting with mild or no anemia and may be detected only on screening for carriers.

Screening for Hemoglobinopathies.

For detection of carriers in community cost effective testing protocols are used. Selection of tests for initial screening is based usually on a low cost with high negative predictive value. Low cost screening tests with high negative predictive value are now available and recommended for screening for thalassemia trait (BTT), HbS and HbE. Complete Blood Counts provide highly valuable Red Blood Cell indices supporting the diagnosis of BTT related traits and for long have been and are being used for screening of BTT.

Hemoglobin Cation Exchange -HPLC is the commonest test used worldwide for secondary screen or laboratory diagnosis of hemoglobinopathies. It provides percentage quantification of different Hemoglobin fractions. DNA based tests identify the defect at gene level and provide final confirmation of the defect.
Table 3: General scheme for screening for Hemoglobinopathies

<table>
<thead>
<tr>
<th>Initial screening (1 and 2)</th>
<th>Test tube based Turbidity test in Community settings</th>
<th>NESTROFT (For BTT) SOLUBILITY TEST (For HbS) DCIP TEST (For HbE) *Optional : Hemoglobin estimation by Digital method/ WHO Hb scale etc ( field)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2). * Based on RBC indices- MCV &amp; MCH * Based on serum Iron studies</td>
<td>Complete blood counts (CBC) Serum ferritin (which reflects iron stores) however in case of acute illness caution to be exercised as ferritin is an acute phase reactant</td>
<td></td>
</tr>
<tr>
<td>Diagnostic test</td>
<td>*Based on Hemoglobin fraction pattern</td>
<td>Hemoglobin HPLC for both thalassemia disease, variant Hemoglobinopathies or thalassemia trait or sickle cell trait/disease</td>
</tr>
<tr>
<td>Confirmatory test</td>
<td>DNA Based tests</td>
<td>Reverse Dot Blot hybridization, ARMS, Gap PCR, DNA Sequencing - for unknown mutations</td>
</tr>
</tbody>
</table>

**Diagnosis of detection of Hemoglobinopathies**

Detection and diagnosis of patients and carriers of hemoglobinopathies is made on the basis of Hb pattern on HPLC or Electrophoresis aided by RBC indices and peripheral smear findings and Serum Ferritin values are taken into consideration where required.

Three types of Hemoglobin are present in a normal individual—HbA, HbF (Fetal Hemoglobin), and HbA2. At birth HbF is the predominant hemoglobin comprising approximately 80% of total hemoglobin and slowly reduces with rise in HbA. HbA constitutes the major component comprising 96-98% of total Hemoglobin in an adult. Adult levels are reached by one year of age.

Clinical syndromes of β-thalassemias caused by reduction in synthesis of HbA, show an increased proportion of HbF which is the basis of their diagnosis as they manifest with reduction in total Hb levels causing anemia after 3 months of age with decline in total HbF levels. In Sickle Cell Disease (SCD) presence of the variant Hemoglobin (HbS) along with varying amounts of HbF is the basis of diagnosis.
Table 4:

Typical findings in β0 and β+ Thalassemia (TM, Severe TI) after 1 year of age1,2

<table>
<thead>
<tr>
<th>Tests</th>
<th>Findings</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Counts (CBC)</td>
<td>Severe anemia with microcytic hypochromic red cell indices (Hb&lt;7g/dl; MCV:50-70fl; MCH: 12-20pg; )</td>
<td>Hb: 12-17 MCV:82-95 MCH:27-32</td>
</tr>
<tr>
<td>Peripheral blood smears</td>
<td>RBCs showing anisopoikilocytosis (tear drop cells, target cells), microcytosis hypochromia, nucleated red cells markedly increased in relation to degree of anemia</td>
<td>Normocytic Normochromic</td>
</tr>
<tr>
<td>Hemoglobin HPLC</td>
<td>HbA : 0-30%; HbF : 70-100%; HbA2 : 2-5%</td>
<td>HbA: 96-98%; HbF: &lt;2%</td>
</tr>
</tbody>
</table>
| HPLC pattern in Sickle cell syndromes | HbA: 0-30%  
HbS: >50%  
HbF: <50%  
HbA2: <3.6% (Only given here as typical finding of homozygous Hb SS. Details and differentiation in lab manual) | HbA2: 2.3-3.3%                   |

Note: Hb is not reduced in all SCD. MCH and MCV are reduced in SCD due to Hb S/β-thalassemia genotype. Peripheral smears may show irreversibly sickled cells.

In carriers, the decrease in HbA is not enough to cause anemia but HbA2 has been consistently found to be increased in Beta Thalassemia Trait and is the basis of detection of carriers of beta thalassemia. Those carriers who do not show an increase in HbA2 are referred to as ‘silent carriers’ and can be detected by DNA analysis only. These are missed by routine screening methods. Other carrier states can also be detected on the basis of HPLC pattern. Major criteria and cut-off values are provided in the table below.
Table 5:

Diagnostic criteria for \( \beta \)-thalassemia trait (BTT) and other common carrier states

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HbA2</th>
<th>HbF</th>
<th>Variant Hb</th>
<th>MCV and MCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.3-3.5</td>
<td>&lt;2.0</td>
<td>-</td>
<td>80-100fl ; 27-32pg</td>
</tr>
<tr>
<td>( \beta )TT *</td>
<td>4.0-8.0</td>
<td>0.5-4.0%</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td>HbLepore Trait</td>
<td>&lt;2%</td>
<td>5-15%</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td>( \delta )β thalassemia trait</td>
<td>&lt;3.0%</td>
<td>5-20%</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td>HPFH trait</td>
<td>Normal</td>
<td>15-30%</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td>Hb S Trait</td>
<td>3-4%</td>
<td>35-40%</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>HbD Trait</td>
<td>Normal</td>
<td>40-45%</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Hb E Trait</td>
<td>Normal</td>
<td>25-30%</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

*Values of HbA2 between 3.5 and 3.9% are considered equivocal and require detailed evaluation before a diagnosis of BTT can be made. Variant may Hb S may be as low as 20% and HbE as low as 15% when associated with \( \alpha \)-gene deletions.

Following points are relevant in planning and implementation of screening strategies:

- Some of the homozygous and compound heterozygous states are also asymptomatic and may be detected only during screening. If detected they are to be reported as these mutant alleles may be transmitted to the offspring leading to a disease causing genotype. They may also lead to diagnostic errors.

- While \( \beta \)-thalassemia is prevalent almost across the country, variant hemoglobins-HbS, HbE and HbD are prevalent in certain populations and areas of some states.

- All population screening protocols have limitations and detection of all of the asymptomatic states is not possible.

- \( \beta \)-thalassemia carrier genotypes referred to as ‘silent’ carriers will not be detected on screening or by HPLC. Only carrier states with clear diagnostic cut off values are detectable. Some of the values will fall in equivocal range and may lead to missed detection. Similarly no primary or initial screening test is available for HbD.

- Presence of anemia and alpha thalassemia modifies the RBC indices and Hb fractions. A diagnostic algorithm based on HbA2 is provided at the end of this section

Timing of screening for Hemoglobinopathies.

No one strategy can meet the needs of every population. Timing of screening is an important determinant of outcomes of prevention and control strategies as it determines the options available for prevention and control, guides community education and counselling needs and indicates issues related to consent of the target population.
TABLE 6:
TIMING OF SCREENING FOR HEMOGLOBINOPATHIES

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Suitable for screening for Sickle Cell Disease and few cases of Thalassemia major</td>
</tr>
<tr>
<td>Adolescence</td>
<td>Most suitable for carrier screening, as a long term sustainable strategy.</td>
</tr>
<tr>
<td>Premarital</td>
<td>Carrier screening at this stage is effective in a well-informed community.</td>
</tr>
<tr>
<td>Preconception</td>
<td>Carrier screening is effective in communities where termination of pregnancy in case of affected fetus is permitted. Married couples can also seek pre-implantation genetic diagnosis if available</td>
</tr>
<tr>
<td>Antenatal Prenatal diagnosis (PND)</td>
<td>Serves as a net to screen those who have not been screened at earlier stages. If both parents are carriers i.e. “at-risk” couple: then the status of the fetus for Thalassemia disease or sickle cell disease can be ascertained through prenatal diagnosis</td>
</tr>
</tbody>
</table>

Benefits and limitations of each strategy should be taken into consideration. Newborn screening provides opportunity for early detection of Sickle Cell Disease and some severe forms of Thalassemia.

Adolescent screening provides opportunity for screening of carriers before they have selected partner for marriage. Premarital screening provides opportunity to a carrier to make an informed decision before going into marriage. Pre-conceptional and Antenatal screening provide opportunity to a carrier who may have been unaware of her or her partner’s carrier status, not to give birth to an affected baby.
Fig 3 Showing the usual reported prevalence of hemoglobinopathies from India
SUMMARY GUIDELINES FOR IMPLEMENTATION OF PREVENTION AND CONTROL STRATEGIES

From the previous discussions it is obvious that all the screening approaches have their benefits and limitations. Broadly screening can be divided into two groups on the basis of expected outcomes:

- Screening for early detection of Thalassemia (TM and severe TI) and Sickle Cell Disease to achieve reduction in mortality and morbidity with improvement in quality of life of the affected.
- Screening for detection of carriers of β- Thalassemia Trait and Sickle Cell Trait to reduce birth of children affected with Thalassemia or Sickle Cell Disease.

In India all of the approaches need to be adopted and applied as below:

Table 7: Screening guidelines for implementation

<table>
<thead>
<tr>
<th>Group</th>
<th>Screening for Disease- Thalassemia major/intermedia and Sickle cell disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Universal screening for genotypes with clinically significant SCD: βS/ βS, βS/ β0, βS/ β+, βS/ βD by Dried Blood Spot (DBS) sampling in states or districts where prevalence of SCD is high. Reporting of suspected cases of Thalassemia Major due to β0/ β0 genotype manifesting as complete absence of HbA in the Hb pattern, for confirmation on follow up at 12 months of age Other conditions detected as a by product of newborn screening that require to be reported are carriers of variant hemoglobins: HbS Trait (β/ βS), HbD Trait β/ βD, HbE Trait β/ βE and clinically insignificant compound heterozygotes - βS/ HPFH βS/ βE</td>
</tr>
<tr>
<td>Childhood 6 months to 6 years</td>
<td>Universal screening of all children with severe anemia (Hb&lt;7 gm/dl) for Thalassemia Major. This strategy will also identify many cases, though not all, of Thalassemia Intermedia. As all children with clinically significant thalassemia develop severe anemia, restricting screening to this subgroup can be cost effective without the risk of missing severe thalassemia syndromes. Children with Sickle cell disease having severe anemia will also be detected. These children comprise preschool age group and can be reached through Anganwadis.</td>
</tr>
<tr>
<td>Group II</td>
<td>Screening for Carriers of β-thalassemia trait (BTT or βTT)</td>
</tr>
<tr>
<td>Adolescence</td>
<td>Universal screening of adolescents through schools in class VIII It is easy to reach out to adolescents through schools and there is a high acceptance rate with retention of information among students when backed by intense education programme including lectures in school before screening. The approach helps in removing whatever stigma is there due to applicability to all students. Growing into adulthood with knowledge of carrier status provides time to ‘adapt’ the information for choice of partner for marriage. Carriers unable to make a choice of avoiding marriage with another carrier still have the option of prenatal diagnosis and other options for carrier couples to be exercised later. The experience of adolescent screening in government schools implemented as part of a pilot project on Birth Defects in Uttrakhand has also been positive with high acceptance rate and retention of information by the students.</td>
</tr>
<tr>
<td>Type</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Premarital</td>
<td>Screening to be offered to those individuals or couples who seek it as social norms vary from community to community, family to family, it might be welcomed by some but not by others. Though the approach presents both options to a carrier - that is of not going ahead with marriage or option for prenatal diagnosis later in each of the pregnancies. Choosing the first option becomes a delicate issue at this stage and will depend on the families and the couple’s level of emotional bonding already established. Religious beliefs and customs also influence.</td>
</tr>
<tr>
<td>Preconceptional</td>
<td>Screening to be offered to those individuals or couples who seek it with appropriate genetic counseling. Though most will opt for prenatal diagnosis with termination of pregnancy, some with religious restrictions might find the option of adopting a child better rather than having their own child withstanding the 25% risk factor. Couple can also seek Pre Implantation Genetic Diagnosis (PGD) if available.</td>
</tr>
<tr>
<td>Antenatal</td>
<td>Universal screening should be offered to all pregnant women during first trimester at all levels. As most pregnant women are likely to come in contact with health services, uptake is expected to be high. States providing it should back it up with prenatal diagnostic services either through referral network or by developing centres within their health system.</td>
</tr>
<tr>
<td>Cascade screening</td>
<td>Screening of siblings and extended family members of patients and carriers of β-thalassemia and variant Hbs S, others may be attempted like-D, E, Lepore, HPFH. Cascade screening of families of detected carriers as an integral component of screening strategy protocol in the Uttarakhand project was found to be more effective in adolescent screening where it was perceived as extension of benefit of school programme to siblings and extended family as no affected child is there in the family unlike in case of applying cascade screening to extended family of affected child where either the family is unwilling to communicate it to their extended family or misinformed members of extended family try to distance themselves from the nuclear family with affected child.</td>
</tr>
</tbody>
</table>

Montreal Screening programme implemented in Canada in High school students (equivalent to Indian class 11,12 students) has been considered as the Gold standard for a school population screening programmes.
IMPLEMENTATION OF PREVENTIVE STRATEGIES IN INDIA:

Identification of carriers before marriage (most effective strategy), or testing for carrier status of both parents during early pregnancy, through target population screening.

If both parents are carriers then preventing the birth of an affected child through determination of the thalassemia and sickle cell disease status of the fetus (through prenatal diagnosis)

New-born screening: suitable for screening for sickle cell disease & sickle cell carrier and few cases of thalassemia major

IDENTIFICATION OF CARRIERS:

- Mean Prevalence of β thalassemia carriers in India is nearly 4 % (2.9-4.6%) and they are asymptomatic.

Implementation of carrier screening

- Pre-marital screening
- Pre-conception screening
- Screening early in pregnancy: Ante-natal, in the first trimester
- Cascade screening: screening of siblings and extended family members
- Screening at school level

Screening for detection of carriers: Thalassemia, Sickle cell disease and other variant hemoglobinopathies at all 4 levels: School, Pre-marital, Pre-conception, Ante-natal +

Cascade screening:

Primary Level centres for carrier screening: Test to be done in the field: at the school (RBSK Team), AWCs (for out of school children), sub-centres for ante-natal and pre-conception mothers including clinical detection for Pallor.

Clinically it is very difficult to pick up mild and moderate anemia but it is easy to pick up severe anemia. Excepting digital hemoglobinometer / WHO Hb scale, none of the other 3 tests require any special equipment and the total cost of all the three tests is nominal.
NESTROF Test (Naked Eye Single Tube Red cell Osmotic Fragility Test)  
For Beta thalassemia trait  
This test has a high specificity and sensitivity and is easy to perform. The positive test has to be followed by a confirmatory test.  
Sensitivity of 91-100%, specificity of 85.47%. Positive predictive value of 66% and negative predictive value of 97-100%  
References:3,4,6,14, 15.

DCIP test (Di-Chlorophenol-Indo- Phenol)  
For hemoglobin E carriers for hemoglobin E should not be missed in eastern states like Assam and Bengal. When married to a person with β Thalassemia trait, they can have a child who may require transfusion throughout his life.  
Screening test for hemoglobin E: 100% sensitivity, 98.7% specificity, positive predictive value of 98.6% and negative predictive value of 100%  
*Ref: Bull WHO, 2004; 82(5): 364-72

Solubility Test  
For Hemoglobin S  
Solubility test is better for mass screening, because it is rapid (takes just about 5 min), reliable with minimal observer variation, does not need any microscope and requires very small blood sample. It is also a cost-effective test. The sensitivity is 100% while specificity is on an average 91.66%. Positive Predictive value of 80% & Negative Predictive value of 100%.  
Ref: Journal of Research in Medical Education & Ethics 11/2012; 2(3):214-216

Hb test by Digital Hemoglobin meter  
For Mild, moderate and severe anemia  
Treat Mild and moderate anemia as per guidelines. *Severe anemia needs to be referred whether picked clinically or through Hemoglobin meter. **The best predictor was a combination of definite pallor of the conjunctiva and pallor of the palms, with a sensitivity of 80% and a specificity of 85%

NESTROF: Negative  
NESTROF: Positive

For Hemoglobin E

For Sickle cell anemia

*Pallor has poor sensitivity for predicting mild anemia, but correlates well with severe anemia10.
Secondary Level at the District Hospitals: Lab at DEIC/ District Hospital

Test to be done:

- HPLC
- RBC indices through 3part cell counter
- Serum ferritin, if required
- Peripheral smear, if required (Serum iron, TIBC if available)

Instruments required: HPLC, Three part cell counter, Microscope and Elisa Reader
Detection of carriers is based mainly on Hb pattern on HPLC.

Carrier States to be specifically screened for on the basis of given criteria are:

Beta Thalassemia Trait
Hb S Trait
HbE Trait

Note: Other traits and asymptomatic conditions mentioned in the list that may be picked up in the course of screening are to be reported. In cases of diagnostic difficulties where cut off values are ambiguous they may be referred to State level, Tertiary or Referral centres.

State Level Centers:

Molecular lab for PCR at state medical colleges
Screening for common mutations prevalent in the particular population or region through Reverse Dot Blot: RDB (Reverse Dot Blot Hybridization). Screening for 8 common mutations may cover >80% of mutations in a population.

For screening of common and other rarer mutations in Indian population can be done by ARMS (Amplification Refractory Mutation System)

Tertiary level Regional / National Centers :

National centers to have lab with facilities for DNA sequencing or through RFLP analysis (indirect method) to detect unknown mutations.

New born screening:
Through Dried Blood Spot sampling for CH, CAH, G6PD and Hemoglobinopathies.

To be conducted in districts of States with high prevalence of Sickle Cell anemia.
Fig 4. Algorithm for population screening.

Targeted Population screening for Carrier status:

Step 1
- Screening at school level
  - NESTROFT: β thalassemia Trait
    - Positive predictive value of 66-97% 
    - Negative predictive value 97-100%
  - SOLUBILITY TEST: SCD Trait
    - Positive Predictive value: 80%
    - Negative Predictive value: 100%
  - DCIP: HbE variant
    - Positive Predictive value: 98.6%
    - Negative Predictive value of 100%
  - DIGITAL HEMOGLOBINOMETER: for Anemia. Especially for identification of mild & moderate anemia

Pre-marital screening
Pre-conception screening
Screening early in pregnancy: Ante-natal, in the first trimester
Cascade screening: screening of siblings and extended family members

If NESTROFT, SOLUBILITY TEST, DCIP test positive (10-15%): Hemoglobinopathies (β thal trait, abnormal HbS, Hemoglobin E trait or may be Iron deficiency or rarely α thalassemia. Further investigations required.

If NESTROFT, SOLUBILITY TEST, DCIP test negative (80-85%): No Hemoglobinopathies: except Iron deficiency or? α thalassemia rarely. No further investigations would be required

Step 2
- At District Hospital: DEIC lab
  a) RBC indices through 3 part cell counter
  b) HPLC for abnormal hemoglobin including β- Thalassemia Trait; HbE trait (Eastern India); HbD trait (North India esp. Punjab), Sickle Cell Trait (HbS)(Central, Southern and Western States)
  c) Serum ferritin, if required to differentiate between Iron deficiency & Hemoglobinopathies:
    - Microscope and Elisa Reader
  d) Peripheral smear: Microscope

Step 3
- Hemoglobinopathy detected by HPLC: Confirmatory testing by DNA based tests. Non directive counselling is the most important step providing information regarding implication of carrier status, and all available options and Family screening: Cascade Screening

Step 4
- Hemoglobinopathy detected in a pregnant woman: Further confirmation required especially for Prenatal diagnosis to know the status of the fetus if both parents are carriers:
  At Regional centre: Reverse Dot Blot / ARMS + PCR electrophoresis: screening for common mutations

Hemoglobinopathy detected: Non directive counselling is the most important step providing information regarding implication of carrier status and all available options and Family screening: Cascade Screening

-35-
If both parents are carriers then preventing the birth of an affected child of “at Risk Couple” is possible and a priority.

Centre with Facilities for Prenatal Diagnosis (PND): Centres with facility for Obstetrical care, NICU and a genetic lab: Testing can be done before a baby is born to find out if he or she has thalassemia. The biochemical and molecular methods to identify the particular phenotype/genotype is the key to PND. The first diagnosis of Hemoglobinopathies in utero was performed by using fetal blood samples by globin chain synthesis analysis. Since there are 17 mutations as well as rare ones causing \( \beta \)-thalassemia in Asian Indians, the point mutation detection by reverse dot blot (RDB), allele-specific oligonucleotide hybridization for common mutations along with the amplification refractory mutation system (ARMS) technique was developed for PND.

Genetic recombination technique was used for the first time for diagnosing \( \beta \)—thalassemia from amniotic fluid cell’s DNA. Development of early and safe CVS has enabled PND to be undertaken in the first trimester of pregnancy.

There are three fetal sampling methods available for prenatal diagnosis:

1. CVS
2. Amniocentesis
3. Fetal blood sampling.

All of them are conducted under ultrasound guidance.

1. Chorionic villus sampling (CVS): Using ultrasound as a guide, the specialist obstetrician removes a small sample of cells from the chorionic villi, i.e. cells that contain the same genetic information as the fetus and which will eventually form the placenta. The cells are removed either with a thin needle (21 gauge needle) inserted through the mother's abdomen (trans-abdominal) or a thin catheter inserted through the vagina (trans-cervical). The cells are then analyzed and a diagnosis is made through processing of fetal DNA. As with other prenatal diagnosis methods, information on potential risks and benefits of using this procedure is provided to the couple by the specialist obstetrician. CVS is done in the first trimester of pregnancy namely between 10-12 weeks of gestation.

2. Amniocentesis: Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother's abdomen. A small amount of amniotic fluid, containing cells from the fetus, is withdrawn. This is then analysed in the laboratory to determine whether the fetus has \( \beta \)-thalassemia (major or intermedia) or sickle cell disease.

Amniocentesis is conducted after 16 weeks of gestation in patients who come late for sampling or in those where the fetal position is such that it prevents the collection of chorionic villi.

The cells (amniocytes) are separated by centrifugation
DNA analysis is conducted

The prerequisites of parental sampling include:
Thalassemia carrier status of the couple under investigation.
Blood group of the mother to prevent Rh incompatibility, if present.
Written consent of the couple undergoing the test.
3 Fetal blood sampling (Cordocentesis)

The fetal blood sample is collected in mid-trimester pregnancy at 18-20 weeks of gestation. The sampling is done by cordocentesis, cardiac puncture or from the hepatic vein. The sample is processed either by HPLC or by DNA analysis.

Limitations: Termination of pregnancy in case of an affected child, which is difficult for the mother, and may be ethically unacceptable for many people. Causes emotional stress, due to increased attachment towards her child.

**Fig 5**

Diagram to show different sampling techniques for obtaining sample for sending to the laboratory for prenatal testing.

The choice available to an 'at risk' couple: Today, parents who are aware that they are both carriers of β-thalassemia or Sickle Cell disease have a number of choices with regard to having a family. These should be discussed as early as possible with an expert health professional and/or a genetic counselor and include:

Prenatal testing is a choice to many families. The mutation studies are performed and then the doctor proceeds to find out whether the fetus is affected or not and then the family is given the option of pregnancy intervention (termination) for an affected child.

Where and if this is culturally, ethically and religiously accepted by the couple and the country;

- Not to have children;
- To adopt children;
- To proceed to in-vitro fertilization (e.g. PGD).
New-born Screening for sickle cell anemia:

The objective of the new-born screening programme is to detect infants at risk of sickle cell disease within the neonatal period, in order to allow early diagnosis and to improve outcomes through early treatment and care. It is essential that infants with these conditions are reliably diagnosed and that they are clearly reported as having a sickle cell disease and that the necessary clinical follow up is arranged.

The analytical methods used will also detect most cases of β thalassemia major and related conditions. α and β thalassemia carriers will not be detected. There is substantial evidence that early administration of prophylactic penicillin markedly reduces the incidence of pneumococcal sepsis in children with sickle cell anemia. There is also evidence that pneumococcal vaccines can increase immunity to pneumococcal infections in people with sickle cell disease.
Table 9:

**Newborn screening- HPLC patterns at birth by Variant NBS**

<table>
<thead>
<tr>
<th>Genotype (Phenotype)</th>
<th>Hb pattern on HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb SS (SCD)</td>
<td>F S</td>
</tr>
<tr>
<td>Hb S/β0* thalassemia (SCD)</td>
<td>FS</td>
</tr>
<tr>
<td>Hb S/β+ thalassemia (SCD)</td>
<td>FSA</td>
</tr>
<tr>
<td>Hb S/HbD Punjab (SCD)</td>
<td>FSD</td>
</tr>
<tr>
<td>Hb S/E# (SCT)</td>
<td>FSE</td>
</tr>
<tr>
<td>Hb S/HPFH*# (SCT)</td>
<td>FS</td>
</tr>
<tr>
<td>β0/β0 Thalassemia (TM)</td>
<td>F</td>
</tr>
</tbody>
</table>

Note: [F=HbF; S=HbS; A=HbA; D=HbD; E=HbE.; SCD=Sickle Cell Disease; SCT=Sickle Cell Trait; TM=Thalassemia Major. Hb fractions written from right to left starting from Hb fraction in highest amount]

HPLC repeated at 1 year of age for confirmation of diagnosis

* It is not possible at birth to differentiate Hb S/β0 and Hb S/HPFH from Hb SS, as all of these conditions show similar pattern

# In general Hb S/HPFH and HbS/HbE are regarded as milder conditions and behave as Sickle Cell Trait

**Conclusion:**

Hemoglobinopathies are one of the major public health problems in India. To achieve success in their prevention and control, an on-going holistic approach is required. It is expected that with optimal collaboration and support, effective prevention and control of thalassemia can be achieved. This will lead to a healthier new generation which enjoys a better overall quality of life.
REFERENCES FOR GUIDELINES FOR PREVENTION OF HEMOGLOBINOPATHIES


### Annexure B-1 Names of tests and associated acronyms used in diagnosis of disease and carrier states of hemoglobinopathies along with their brief description. (Source)

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>Estimation of Hemoglobin in gm % by digital Hemoglobinometer using a finger prick sample in field / screening point (school).</td>
</tr>
<tr>
<td>NESTROFT</td>
<td>Naked Eye Single Tube Red cell Osmotic Fragility Test in a single tube with a saline concentration of 0.36%. Can be done on finger-prick sample as screening test for selecting samples for Hb HPLC for detection of β Thalassemia Trait.</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Counts are obtained by an automated Blood Cell Counter. Used for determination of Hb level and for RBC parameters (RBC, MCV, MCH, MCHC and RDW) for evaluation of type of anemia. MCV and MCH are the most important indices in diagnosis of thalassemia.</td>
</tr>
<tr>
<td>PBS or GBP</td>
<td>Microscopic examination of a stained peripheral blood smear on a glass slide provides a General Blood Picture. Required to evaluate cases mainly of severe anemia and moderate anemia. GBP in thalassemia major and severe TI is quite characteristic and highly supportive of diagnosis.</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Reticulocytes (or Retics) are young RBCs identified by staining by supravital stains like New Methylene Blue. They are usually found to be increased in hemolytic anemias when there is destruction of normal population of RBCs. G6PD enzyme levels are normal in young RBCs even in G6PD deficiency thus a falsely normal or high level of G6PD enzyme may be obtained if test done after clinical symptoms have appeared.</td>
</tr>
<tr>
<td>Solubility test</td>
<td>Used as a simple low cost screening test for sickle cell Hemoglobin (HbS) based on the property of insolubility of HbS in a high molarity phosphate buffer solution forming tactoids (water crystals) producing turbid solution. It does not distinguish between heterozygous or homozygous states. HbD and HbG showing similar mobility as HbS on electrophoresis are soluble. False positives are common due to polycythemia and other abnormal hemoglobins and high HbF may result in a ‘false negative’ test thus should be used only as a screening test. The test is unreliable up to 6 months of age due to high HbF and thus cannot be used for newborn screening.</td>
</tr>
<tr>
<td>Sickling Test</td>
<td>It is a simple functional test for distinguishing Hb S disorders- HbSS; HbS/E; HbS/βthal, HbS/βthal; HbS/HbD; from other variants having same mobility as HbS. The test is based on ‘sickling’ of RBCs in reduced oxygenation. There are some other rare variants other than HbS that also produce sickling.</td>
</tr>
<tr>
<td>DCIP Test</td>
<td>Di-Chloro –Indo-Phenol Test is a simple screening test for detection of HbE based on oxidation of the exposed –SH group by DCIP at neutral pH leading to precipitation of the variant hemoglobin leading to a particulate cloudy solution or precipitated HbE at the bottom of the tube observed by naked eye. The test is positive in other unstable hemoglobins also including HbH.</td>
</tr>
<tr>
<td>Test Type</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Serum Ferritin by ELISA</td>
<td>At some stage of diagnostic protocol it becomes important to determine iron status to arrive at diagnosis. It may be necessary to exclude iron deficiency and in carriers of thalassemia and variant hemoglobins or to establish coexistent iron deficiency that may alter hematologic parameters. Normal or increased iron are found in thalassemia. Quantitative assay of serum Ferritin is a cost effective method for establishing iron deficiency.</td>
</tr>
<tr>
<td>Hb HPLC</td>
<td>The test based on automated High Performance Liquid Chromatography of Hemoglobin to separate different hemoglobin fractions is used for detection of Thalassemia and common hemoglobinopathies.</td>
</tr>
<tr>
<td>Newborn Hb-HPLC</td>
<td>Sickle Cell Disease and other hemoglobin variants. Hemoglobin fraction pattern at birth is very different from that at 1 year of age. Also for universal newborn screening Dried Blood Spot samples are used. Thus the HPLC equipment used for newborn screening for hemoglobinopathies is programmed for separation and analysis of Hb fractions from a dried blood spot sample of a newborn. Other than β0 Thalassemia, none of the β- thalassemia syndromes can be detected in a newborn sample on the basis of Hemoglobin analysis.</td>
</tr>
<tr>
<td>PCR based DNA Analysis</td>
<td>Detection of causative mutation is the confirmatory test for diagnosis of hemoglobinopathies. Even in abnormal hemoglobins like HbS, sometimes, a DNA analysis is required to identify the causative mutation as there are other variants that can cause sickling. Several PCR based methods most commonly Reverse Dot Blot Hybridization, and ARMS are used for detection of a limited number of known mutations, and DNA sequencing is used for unknown mutations.</td>
</tr>
</tbody>
</table>
## Annexure B 2

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name / description</th>
<th>specifications/ purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Binocular Microscope</td>
<td>For peripheral blood examination</td>
</tr>
<tr>
<td>2</td>
<td>Automated Blood Cell Counter (3 part differential)</td>
<td>3 part differential automated blood cell counter for complete blood counts of samples for anemia and thalassemia or hemoglobinopathies,</td>
</tr>
<tr>
<td>3</td>
<td>Hemoglobin HPLC Equipment</td>
<td>Equipment capable of loading a minimum of 10 test at one for Hb fraction estimation - HbA0, HbA1c, HbF, HbA2 and common Hb for analysis of samples for thalassemia and hemoglobinopathies</td>
</tr>
<tr>
<td>4</td>
<td>ELISA Reader with washer</td>
<td>for Neonatal TSH ELISA of Dried Blood Samples of newborns, Serum Ferritin in case of anemia to establish or rule out iron deficiency</td>
</tr>
<tr>
<td>5</td>
<td>Hemoglobin HPLC equipment for Newborn Screening*</td>
<td>HPLC equipment that can process Dried Blood Samples for separation of Hb fractions to enable diagnosis of Sickle Cell Syndromes and Hb D, HbE and HPFH syndromes and traits(for Regional Centres where sickle cell anemia is common)</td>
</tr>
<tr>
<td>6</td>
<td>Refrigerator 180-310 L Domestic</td>
<td>1 for storage of samples , reagents in use kits, 1 for stock kits and reagents</td>
</tr>
<tr>
<td>7</td>
<td>Incubator</td>
<td>For conduction of DCIP test (portable incubator might be required if test to be done in community/field settings)</td>
</tr>
<tr>
<td>8</td>
<td>Laboratory centrifuge</td>
<td>For separation of serum , plasma</td>
</tr>
<tr>
<td>9</td>
<td>Rotor sample mixer</td>
<td>For mixing samples</td>
</tr>
<tr>
<td>10</td>
<td>Syringe Needle destroyer</td>
<td>For safe disposal of needles and syringes</td>
</tr>
<tr>
<td>11</td>
<td>Air Conditioner</td>
<td>Must for maintenance and working of equipments</td>
</tr>
<tr>
<td>12</td>
<td>Micropipettes-Variable volume</td>
<td>100 to 1000 l- 2 and 5 to 20 μl 2</td>
</tr>
<tr>
<td>13</td>
<td>Micropipettes-Fixed volume</td>
<td>2 for use in lab and 4/block for use by Block teams for conducting NESTROFT</td>
</tr>
<tr>
<td>14</td>
<td>Deep Freezer</td>
<td>For long term storage of samples</td>
</tr>
<tr>
<td>15</td>
<td>10 KVA UPS</td>
<td>To ensure continuous power supply for equipments</td>
</tr>
<tr>
<td>16</td>
<td>Desktop Computer with Internet</td>
<td>For DEIC based field</td>
</tr>
<tr>
<td>17</td>
<td>Laptop with Datacard</td>
<td>For DEIC based field staff (optional)</td>
</tr>
</tbody>
</table>
Annexure B3-Methods of sampling for New born screening: Through Dried Blood spot for Congenital hypothyroidism (CH), Hemoglobinopathies and CAH, G6PD
SECTION C

MANAGEMENT OF THALASSEMIA AND SICKLE CELL ANEMIA
SECTION C

1. MANAGEMENT OF THALASSEMIA MAJOR

It is important to reassure carriers of thalassemia trait, that they are not ill and will not develop problems due to their carrier status. They need to be aware, so that they can avoid marriage with another carrier, or know of their risk of having a thalassemia major child if the partner is also a carrier, and optimally utilizing available prenatal testing modalities.

The optimal current management of thalassemia major children is lifelong and needs to be meticulous in order to reduce complications.

The management outline:

a) Repeated blood transfusion of packed red blood cells (pRBCs) should be done at 2 to 4 weeks interval, b) Iron chelation for iron overload, c) Monitoring of complications due to the disease and their treatment d) Management of complications (endocrine, cardiac, skeletal etc.), e) Bone marrow transplantation (BMT), f) Psychological support.

a) Blood Transfusion Therapy:
It is important to strengthen the blood banks and ensure component therapy, this is mandatory.

Following investigations should be undertaken prior to therapy:

1. Red cell typing of ABO & Rh-D (forward and reverse).

2. In newly diagnosed patients, prior to transfusion therapy, patients should have extended red cell antigen typing that includes at least C, c, E, e, and Kell, in order to provide phenotype matched blood where possible and to help identify and characterize antibodies in case of later allo-immunization.

3. Direct Coombs test (DCT) and antibody screening followed by compatibility testing should be performed for all patients. Those positive for antibodies should be given phenotype matched blood. Patients requiring antigen negative RBCs may be referred to a center where this is available.

4. Screening for patients for hepatitis B, hepatitis C and HIV.

5. Initiation of Hepatitis B vaccination for the patient and family members (If not vaccinated earlier). Routine vaccinations should continue as per the recommended schedule. In addition, all thalassemics should receive hepatitis A, chickenpox and typhoid vaccinations.

Transfusion Regimen: Pre-transfusion Hemoglobin (Hb) should be kept at between 9- 10.5 g/dl.
Type of blood to be transfused: Packed red blood cells (pRBC) are the component of choice and whole blood should not be given. All the pRBCs should be leucodepleted and preferably pre-storage leuco-depletion is recommended. Where it is not possible, bed side filtration may be done. Packed red blood cells (preferably not more than 2 weeks old) should be transfused. Mandatory screening of blood for HIV, hepatitis B, hepatitis C, malaria and syphilis is to be ensured. Nucleic acid testing (NAT) is optional to reduce the chance of transfusion transmitted infections.

Amount of blood to be transfused: Packed red blood cells 15ml/kg body weight should be administered at the rate of 5ml/kg/hr. The patient may require 1-2 units of pRBCs, or even more depending upon their body weight and pre-transfusion hemoglobin. To raise Hb by 1gm/dl we need to transfuse 3.5ml/kg of pRBCs (at least Hct 60%). In the presence of congestive cardiac failure or Hb less than 5 g/dl, child should be given total volume of 5ml/kg or less of packed red cells at the rate of 2ml/kg per hour, with close monitoring.

Storage and transport of blood: Blood units should preferably be transported in monitored insulated boxes which maintain a temperature of between 2-8oC. Blood units need to reach the transfusion centres as soon as possible.

Evaluation of transfusion treatment and clinical record
The following data should be regularly recorded at each transfusion:
- Date of transfusion
- Time of initiation and time of completion of transfusion.
- Bag number of the blood unit transfused
- Weight/ volume of packed cells transfused
- Patient demographics (height, weight, pre-transfusion Hb, blood group and other details)
- Size of liver and spleen.
- Transfusion details to be entered into a transfusion card to ensure proper data base maintenance and traceability.

The transfusions are usually needed at 2-4 week intervals. When more frequent blood transfusions are needed, or the required level of hemoglobin is not maintained as with previous transfusion regimen of the patient, then further tests are needed to be done. Red blood cell allo-immunization tests should be done by the blood bank, and if these are negative, then the child should be evaluated for hypersplenism.

A child being admitted with very low Hb should receive a repeat transfusion, as the hemoglobin (Hb) will again drop in the 2-4 week period. This will enable the pre-transfusion Hb rise to a minimum level of 9 g/dl.
**Blood Bank Facilities**

Thalassemia patients are dependent on blood transfusion therapy to maintain optimum hemoglobin levels. In order to provide optimum transfusion support to this special category of patients, advanced blood banking facilities are required.

These include-

- Component preparation facilities.
- Leucoreduced packed RBCs (Ideally pre-storage leuco-reduction in the blood bank is recommended, if not available then use of leucocyte filters at the time of pRBC transfusion is needed.)
- Advanced immune-hematology facilities which include regular antibody screening and antibody identification in cases of positive screening tests, referral needs to be facilitated to ensure timely assessment and management.
- Semi-automated/automated serological /molecular typing would be preferable

**Hemovigilance:**

a. If a transfusion reaction is suspected it should be reported to the blood bank immediately and work up done. (details in Annexure 1)

b. Transfusion reaction reporting form will be filled up by blood bank (Annexure 2)

c. Monitoring and reporting of any adverse reaction and near miss cases to the blood bank is essential. For reporting to Hemovigilance Programme of India see website -http://nib.gov.in/haemovigilance.html

b) Iron Overload

Each milliliter of pRBCs contains 1.16 mg of iron. On an average each unit of packed cells contains 200 to 250 mg of iron. A patient, who receives 15-30 units of pRBC units per year, receives an excess of 3-6 grams of elemental iron. Hence, iron overload occurs and is a serious problem amongst thalassemics.

In thalassemia major, iron absorption from the intestine increases to as much as 3 to 5 mg per day, depending upon severity of anemia, resulting in an additional 1-2 gm of iron loading per year. Absorption of iron also depends upon the iron content in food. The iron absorption may increase up to even 10 mg per day if iron supplements are given, and hence they are contraindicated.
Evaluation of Iron Overload

1. Serum Ferritin: Serum ferritin reflects the overall iron stores in the body tissues and thus is a useful indicator of iron storage status. Serum ferritin is an acute phase reactant, so its value varies with the presence of any infection or inflammation in the body. Thus a single value of this test is of no practical utility for monitoring iron overload. The trend of serum ferritin values should be monitored for assessing iron overload. This test needs to be performed once in six months.

2. MRI of liver and heart: The serum ferritin test may not be able to give information regarding organ specific iron overload. The T2* MRI though available in a few centers in the country, is a good non-invasive method of estimating quantitative iron overload in both the heart and liver. Iron overload in both these organs is independent of each other, and hence both should be tested separately. Having a T2* MRI facility in each region of India will allow referral and evaluation of the patients in a streamlined manner.

3. Liver Biopsy: Liver biopsy though highly reliable, is an invasive method which entails increased risk to the patient. It should be reserved only for special indications.

Iron Chelation

When to start chelation? The serum ferritin levels should be assessed after 10 to 15 transfusions and chelation therapy should be initiated when the serum ferritin value is more than 1000µg/L.

Chelation Drugs:

1. DESFERRIOXAMINE:
The recommended dose is 25-50mg/kg/day, subcutaneously with the help of an infusion pump, over 8-12 hours. A ten percent (10%) desferrioxamine solution is prepared in water for injection i.e. one vial of desferrioxamine (500 mg) is dissolved in 5ml water for injection. If more than one vial is to be administered, then 2.5 to 5 ml of water for injection can be added per vial of desferrioxamine. The re-constituted desferrioxamine solution should not be stored for more than 24 hours. Intravenous desferrioxamine is required at times in the presence of severe iron overload. The desferrioxamine should never be added directly into the blood bag. Oral Vitamin C (50-200 mg) should be given after starting the infusion.

Side- effects: Frequent pain, swelling, induration, erythema, burning, pruritus, and rashes at site of injection/ infusion may occur occasionally accompanied by fever, chills and malaise. High doses of desferrioxamine, especially in patients with a low serum ferritin may lead to visual and auditory side effects. Desferrioxamine increases the susceptibility to Yersinia enterocolitica and Yersinia pseudo tuberculosis infections.
Monitoring: Hb, Serum ferritin and sitting height.

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2. **DEFERIPRONE:**

This was the first oral iron chelator, introduced in 1995. The standard dose is 50-100 mg/kg/day in two or three divided oral doses. It is available as 250 & 500 mg capsules. Due to its low molecular weight, it is more efficient in removing iron from the heart, compared to desferrioxamine.

Monitoring: Hb, TLC, DLC, and platelet count every 2-4 weeks and during every febrile episode and Serum ferritin monitoring is necessary.

3. **DEFERASIROX:**

This is a new oral iron chelator introduced in India in 2008. This has been proven to be effective and safe. It is administered at a dose of 20-40 mg / kg / day. It is to be given on an empty stomach, dispersed in water or juice. Food may be given 30 minutes after intake of the medicine.

Side effects: Diarrhea, skin rash (usually disappears within 2 weeks even on continuation of medication). Non- progressive increase of serum creatinine, as well as rise in the level of AST and ALT.

Monitoring: BUN, Serum creatinine, AST/ALT, urine routine, should be monitored before starting the medicine and every month after the initiation of the medicine. Serum ferritin monitoring is mandatory as with all chelation therapy.

4. **COMBINATION THERAPY:**

Combination of desferrioxamine and deferiprone is advisable in patients not responding to maximum dosages of monotherapy. Addition combinations can be done under the supervision of hematologists.

c) **Monitoring of thalassemics in a day care centre:**

The iron chelation therapy is an important component and needs regular monitoring to see for efficacy of chelation and necessary modifications in the drug dosage. The patients need to be evaluated for toxicities and other complications which may develop.

**Table 1: Monitoring at each transfusion**

<table>
<thead>
<tr>
<th>Pre transfusion hemoglobin</th>
<th>Liver size (by clinical examination)</th>
<th>Spleen size (by clinical examination)</th>
<th>Transfusion reaction</th>
</tr>
</thead>
</table>

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### Table 2: Monthly monitoring for patients

<table>
<thead>
<tr>
<th>Date</th>
<th>Amount of blood transfused</th>
<th>Pre- transfusion Hb</th>
<th>If on deferasirox-SGPT, SGOT, BUN, s.creatinine, Urine R/E</th>
<th>If on deferiprone- Complete blood counts</th>
<th>Next date of transfusion</th>
<th>Note: Routine post-transfusion Hb checking is not recommended.</th>
</tr>
</thead>
</table>

### Table 3: Monitoring every 6 months for all patients

<table>
<thead>
<tr>
<th>Date</th>
<th>S. ferritin (ng/ml)</th>
<th>SGPT</th>
<th>SGOT</th>
<th>BUN</th>
<th>s.creatinine</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
</table>

### Table 4: Monitoring every year

<table>
<thead>
<tr>
<th>Date</th>
<th>Anti HBs antibody</th>
<th>HCV IgG antibody</th>
</tr>
</thead>
</table>

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HIV 1 & 2
The following tests to be performed annually after the age of 10 years
Blood sugar (fasting) or GTT
TSH
ECG
Echocardiography
MRI T2*
Heart
Liver
DEXA Scan

<table>
<thead>
<tr>
<th><strong>Table 5 : Tests to be performed when indicated by physician</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
</tr>
</tbody>
</table>

Requirements for opening a thalassemia care centre in government hospital/medical colleges:
The following facility is an important component of thalassemia care, and has several advantages:

- It is convenient, economical and provides a supportive environment friendly area for children with a chronic illness.
- It helps in developing a good rapport with staff and better compliance and efficient monitoring of patients.
Aim of a Thalassemia care center—essential services and amenities—

1. Transfusion services on daily basis in multiple shifts to accommodate more patients.
2. Should have night shift for working or school going patients.
3. Staff turnover should be as low as possible to provide continuity of care.
4. Should have management protocols for transfusion therapy, transfusion reactions and chelation therapy to serve as guidelines for staff.
5. Must have a well-trained doctor to handle complications related to transfusion reactions in a hospital setting.
6. Transfusions in the domiciliary setting, is highly discouraged.
7. It is desirable to have recreational facilities to keep children entertained during transfusion.

Function of Thalassemia daycare centre

For the care of thalassemia patients the following requirements are mandatory in terms of blood.
- Component therapy in the form of PRBC.
- Establishment of leucodepletion facilities and extended red cell phenotyping
- Provision of leucodepleted blood bags, bedside filters, if not available. Provision of oral iron chelators (medicines).
- Care of transfusion transmitted infections (TTI) of positive patients.

Necessary equipment needed for the daycare center are—
- Supporting Blood bank which provides component therapy.
- Electronic weighing scale.
- Transfusion charts for monitoring.
- Emergency kit for managing blood transfusion reactions.
- Blood transfusion sets and availability of leucodepleting filters, if blood bank does not provide pre-storage leucodepletion.
- Availability of iron chelating drugs.

D) Management of complications of iron overload and indications of Splenectomy

Even with adequate iron chelation patients may go on to develop complications. Iron overload results in toxicity to the heart, liver, and harms the endocrine system—affecting growth and development. It can even result in skeletal and bone mineralization problems. The patients may be affected by transfusion transmitted diseases like hepatitis B, C or HIV. Toxicity from iron chelation medicines, if occurs may also need to be managed. Therefore a multi-specialist team including a pediatrician, cardiologist, gastroenterologist, and endocrinologist are necessary. Psychological counseling and support are needed to deal with the consequences of a chronic disease.

Splenectomy is needed only in few cases where hypersplenism is symptomatic. Splenectomy causes many late complications and may increase the risk of infections and allo-immunization hence should not be performed routinely.
E) Bone Marrow Transplantation (BMT) Stem Cell Transplantation:

Bone marrow transplantation is the only curative therapy for β Thalassemia major and is a well-established and accepted therapy. The outcomes of this procedure depend on patient characteristics. The Lucarelli classification divides patients into groups based on pre transplant morbidity and this predicts the risk of serious complications and morbidity with transplant. Younger children, with adequate iron chelation, no hepatomegaly or hepatic fibrosis do best with this procedure. The older children with organomegaly, iron overload, cardiac or hepatic compromise require additional medications and extra therapy. There is a risk of bone marrow graft rejection and graft versus host disease. These complications are more in older children and are often due to allo-immunization, non -leucodepleted blood products or transfusion from first degree relatives leading to sensitization. Other complications like veno-occlusive disease of the liver occurs in children with heavy iron overload, irregular chelation, hepatitis or fibrosis of liver. This is a serious complication of transplant and can lead to multi-organ failure and death.

HLA typing of siblings and matching leads to the commonest source of transplants - the HLA matched brother or sister. The sibling can be normal or a carrier for thalassemia, both are acceptable. Unrelated HLA matched transplants are both more expensive and more difficult, but may be needed if no sibling donor is available. Cord blood transplant can be done from a sibling or another person but is not usually preferred for thalassemia patients, due to risk of rejection, but may be tried if no bone marrow matched donor is available. Even cord blood transplant needs HLA matching. At present a national stem cell donor registry is lacking and is the need of the hour.

F) Psychological support and counseling

Thalassemia is a chronic disease and the need for continuity of care and psychological support for chronic diseases is widely accepted. The patient has the right to long survival and good quality of life, with the opportunity to fulfill normal life expectations including, work and marriage. This means full integration into the community as a productive member without stigmatization.

Also counseling is essential when introducing antenatal screening in an at-risk population. The patients need counseling to ensure lifelong adherence to chelation therapy and to help them deal with inevitable complications and deal with issues like employment, marriage and other problems.
REFERENCES FOR MANAGEMENT OF THALASSEMA


2. MANAGEMENT OF NON TRANSFUSION DEPENDENT THALASSEMIA (NTDT)

Current attention is now being given to a group of thalassemia states together called not transfusion dependent thalassemia (NTDT). They are responsible for serious complications and often the diagnosis is missed or unsuspected due to their unusual or late presentation. A common error is to diagnose them to have iron deficiency and empirically treat them with iron supplementation which in these cases can have significant adverse effects.

The pathology and clinical features of NTDT are linked

1. The chronic anemia and ineffective erythropoiesis, results in growth retardation, skeletal abnormalities, extra-medullary hematopoiesis (EMH). Anemia is compounded by hemolysis, which results in gall stones.
2. Signs and symptoms related to iron overload. These patients have increased intestinal absorption of iron and are predisposed to iron overload and all its complications even though they are not transfused or have been transfused only occasionally.
3. These patients have a tendency to hypercoagulable states and can present with features of thromboembolism. The pathophysiology of this is complex and involves abnormalities in both red cells and platelets, this hypercoagulable state is significantly worsened post splenectomy.
4. These patients can present with pulmonary hypertension, chronic leg ulcers, hypogonadism and other endocrine abnormalities. These patients also frequently have osteopenia and fractures.

Confirmation of diagnosis of NTDT:

Following exclusion of the possibility of iron deficiency the next step would be to confirm the subtype of NTDT (after excluding transfusion dependent thalassemia’s). The diagnosis is made as for other hemoglobinopathies by HPLC or capillary hemoglobin electrophoresis to evaluate the abnormal hemoglobin.

Molecular tests for thalassemias

Often the HPLC of the patient and their parents are needed to identify the disease. Many times further evidence may be required by molecular testing. This is needed to diagnose alpha thalassemias, when one parent is a silent carrier or a compound heterozygote state.

References


Management of Non Transfusion Dependent Thalassemia (NTDT) –

1. Monitoring of iron overload- which can occur even if transfusions are not given.

2. Monitoring of growth and endocrine and bone problems, including extra- medullary hematopoiesis.

3. Surveillance for gall stones, liver, cardiac disease.

4. Trial of hydroxyurea, with appropriate monitoring for side effects to reduce the need for blood transfusions and increase the hemoglobin. In studies including NTDT patients, the primary hematological outcome was improvement in total hemoglobin level. Mean increase ranged between 0.5 and 2.5 g/dl with an average of around 1.5 g/l [1]; Most physicians start with hydroxyurea dose 10 mg/kg/day and escalate the dose according to response and toxicity (maximal tolerated dose) up to a maximum of 20 mg/kg/day. Response should be evaluated after 3 and 6 months of therapy and should be defined as a total hemoglobin level increase of >1 g/dl at 6 months.

The following safety measures should be evaluated and treatment discontinued or tailored accordingly.

These include: Complete blood counts, every two weeks for the first three months then monthly.

Hepatic and renal function studies, every two weeks for the first three months then monthly.

5. If patients are given transfusion support during growth spurt or to maintain hemoglobin, safe blood banking and transfusion guidelines as per thalassemia dependent patient guidelines must be followed.

References


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3. SICKLE CELL DISEASE (SCD)

General principles of Management.

India has also a very huge populations of tribal communities about 18 crore and expected to have 1.80 crore sickle cell trait and 14 lakhs of sickle cell disease1. The basic principles of preventive care for children with sickle cell disease include prevention of infections by encapsulated organisms due to the functional asplenia present in these children. Though these children may be asymptomatic in the newborn period, early diagnosis may be the only measure to save children from life threatening infections. These patients benefit from pneumococcal immunization and penicillin prophylaxis2. Prevention of other complications can be achieved by prescribing Hydroxyurea and judicious use of blood transfusions. Hydroxyurea benefits children who suffer from painful crisis, helps to prevent organ damage, reduce transfusion requirement and improves overall survival. The other need is appropriate management of complications and crises. These children can have pain crisis, acute chest syndrome, splenic sequestration crisis and rarely even aplastic crises which is due to Parvo B19.

By regular health maintenance and parental counseling, the early high mortality seen in these children has gone down. Physicians need to be aware of fever, jaundice, pallor and should monitor the spleen size on each health visit. Basic tests like complete blood count, reticulocyte count, routine biochemistry tests like LFT, RFT are useful to monitor the patients. An HbF estimation is necessary. Other tests such as Transcranial Doppler ultrasonography (TCD), magnetic resonance imaging (MRI) with or without angiography, and neuro-psychometric (NPM) studies may be done if provision is available, or child can be referred to a centre where they can be performed. Educational material should be given to the caregiver and older children, so they understand about the disease, and especially about fever. Sickle cell carriers- usually have mild disease, but may need follow up for regular health maintenance, some will need intervention for fever, pain etc. Genetic counseling should be made available to all carriers.

Fever

Mandatory routine Pneumococcal vaccination and penicillin prophylaxis have reduced the risk of mortality for SCD children. All children with SCD who have fever (>38.5°C or 101°F) or /and other signs of infection (chills, lethargy, irritability, poor feeding, vomiting) should be assessed promptly. A minimum evaluation should include a blood culture, complete blood count, reticulocyte count, and chest x ray ( if younger than 3 years of age). Immediately after the blood culture is taken, the child should always be given broad-spectrum antibiotics, preferably intravenously. Prophylaxis: Newborn to 3 years: Penicillin VK, 100-125 mg orally twice daily (PO BID), 3 to 5 years: Penicillin VK, 200-250 mg PO BID.
Pain

This is common in all children with SCD, dactylitis (“hand-foot syndrome”), vaso-occlusive pain may involve the limbs, abdominal viscera, ribs, sternum, vertebrae etc. Pain relief needs to be appropriately done, and includes good hydration along with NSAIDS and even opioids can be used. Medicines usually prescribed are acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and mild opioids, such as codeine, for young children. Oral morphine can safely be used if needed, under adequate supervision.

Hydroxyurea

This has been proven to decrease complications in children, such as- pain crisis, acute chest syndrome and strokes, it does so by several mechanisms including increasing levels of HbF. The dose at initiation is Hydroxyurea, 10-15 mg/kg/day in a single daily dose for 6-8 weeks, it is available as a 500mg capsule; follow the CBC every 2 weeks; if possible monitor Hb F every 6-8 weeks; serum chemistries every 2-4 weeks. If no major toxicity, escalate dose every 6-8 weeks until the desired endpoint is reached.

Treatment Endpoints: Decrease in pain, increase in HbF to 15-20%, increase hemoglobin level if severely anemic, improved well-being, acceptable myelotoxicity. Failure of HbF (or MCV), then check for compliance. We can increase the dose slowly up to a maximum of 35 mg/kg/day.

Acute chest syndrome (ACS)

This is an acute illness characterized by fever and respiratory symptoms, accompanied with a new pulmonary infiltrate on a chest x ray. Even though the ACS usually is self-limited, it can present with or result in respiratory failure. The cause is thought to be pulmonary fat embolization (PFE), as defined by the finding of lipid laden macrophages are seen in 59% of broncho-alveolar lavage specimens, or infection, which is seen in one third of patients.

Oxygen is to be given to moderately hypoxemic patients (PaO2 = 70-80 mmHg, O2 saturation = 92-95 %) nasally at a rate of 2 liters/minute. Assessment of blood oxygenation is needed and a baseline arterial blood gases (ABG), and estimation of the alveolar-arterial (A-a) oxygen gradient and the PaO2/FiO2 ratio, is useful for appropriate management. Simple transfusions (or rarely exchange transfusions) decrease the proportion of sickle red cells. Intravenous broad-spectrum antibiotics should be given if febrile or severely ill ACS as it is difficult to exclude bacterial pneumonia or super added infection of lung infarct. The guidelines suggest using erythromycin and cephalosporin. The rationale for a macrolide or quinolone antibiotic is because atypical pneumonia may be the causative organism. Pain control and incentive spirometry can prevent chest atelectasis. The subsequent frequency of ACS can be reduced with Hydroxyurea by 50%, if the patient is compliant.
Transfusion

This is needed in only special indications, not all patients will require blood transfusion, most patients with Arab-Indian haplotype, only rarely needed. If transfusions needed, then a pre transfusion extended red cell typing is required [Rh Sub group (Cc, Ee), Kell, Kidd, S/s], as these patients frequently develop Delayed Hemolytic Transfusion Reaction (30% cases) and allo immunization. Children receiving regular transfusions will need to have s. ferritin monitoring and chelation therapy.

Strokes and transient ischemic attacks (TIAs)

The children who develop these complications will benefit from hydroxyurea, may regular need blood transfusions to decrease HbS levels, and post stroke may need anticoagulation, along with monitoring. Though rare, this is a serious condition, for appropriate evaluation and monitoring referral to a higher centre for these children is essential. Patients may need TCD, computerized axial tomography, MRI, and MRI with angiography. Comprehensive management of SCD requires a multi-specialty team, especially for such children with these complications.

Table 6: Daycare center sheet for patients of sickle cell disease, (additional information needed for their care in a daycare unit)

<table>
<thead>
<tr>
<th>Date</th>
<th>Age of child</th>
<th>Weight/height</th>
<th>Episodes of fever</th>
<th>Pain crises</th>
<th>Name of pain medicine, dose</th>
<th>Hemoglobin level</th>
<th>Need for transfusion</th>
<th>Patient taking penicillin prophylaxis</th>
<th>Date and dose of pneumococcal vaccine</th>
<th>Patient on hydroxyurea, dose</th>
<th>Other complications</th>
</tr>
</thead>
</table>

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Other complications.

Rare complications include leg ulcers, pulmonary hypertension, avascular necrosis head of femur, psycho social issues etc.
At least an annual review by a hematologist will be necessary for these children, they will need to transit to adult care for further management as they grow older. Some patients may benefit from allogeneic hematopoietic stem cell transplant.

Sickle cell disease transplant indications are very selective, due to the risks of morbidity associated with the transplant procedure.

**Indication for allogeneic Hematopoietic stem cell transplant (HSCT) for sickle cell disease as suggested by Walters et al (3).**

1. Stroke or central nervous system event lasting longer than 24 hours, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions.
2. Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism.
3. Impaired neuropsychological function with abnormal cerebral MRI scan
4. Stage I or II sickle lung disease
5. Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
6. Bilateral proliferative retinopathy with major visual impairment in at least one eye
7. Osteonecrosis of multiple joint
8. Red-cell alloimmunization during long-term transfusion therapy

**Evidence supported management strategies in Sickle cell disease.**
- Penicillin prophylaxis prevents pneumococcal sepsis in children [evidence from Prophylactic Penicillin Studies I and II (PROPS I & II)].
- Pneumococcal vaccine prevents pneumococcal infection in children.
- Transfusions to reduce Hb S levels to below 30% prevent strokes in children with high central nervous system blood flow [evidence from the Stroke Prevention Trial in Sickle Cell Anemia (STOP I)].
- Hydroxyurea decreases crises in patients with severe sickle cell disease [evidence from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) trial]

**References**

Annexure C-1 Transfusion Reactions Work-up

Acute transfusion reactions occur within 24 hours of transfusion.

<table>
<thead>
<tr>
<th>SNo</th>
<th>Type of Reaction</th>
<th>Clinical Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hemolytic Transfusion Reaction</td>
<td>Fever/chills, hypotension/tachycardia, cola coloured urine, nausea, vomiting, pain in flanks/back/abdomen/chest</td>
</tr>
<tr>
<td>2</td>
<td>Bacterial Contamination</td>
<td>Fever/chills, hypotension, nausea, vomiting, dyspnoea, diarrhoea.</td>
</tr>
<tr>
<td>3</td>
<td>Transfusion related Acute Lung Injury</td>
<td>Dyspnoea or cyanosis, fever, tachycardia, hypotension</td>
</tr>
<tr>
<td>4</td>
<td>Febrile non hemolytic transfusion reaction</td>
<td>Fever, chills, rigors, cold, headache, nausea, vomiting</td>
</tr>
<tr>
<td>5</td>
<td>Allergic/Anaphylactic reaction</td>
<td>Pruritis, urticaria, flushing, angioedema, hoarseness, stridor, wheezing, chest tightness, dyspnoea, cyanosis, anxiety, nausea, abdominal cramps and diarrhoea</td>
</tr>
</tbody>
</table>

The signs and symptoms of acute transfusion reactions often overlap and diagnosis may not be possible without a complete workup. During blood/blood component transfusion closely monitor the patient for the signs and symptoms of a transfusion reaction.

Action to be taken n case a reaction is suspected-

a) Stop the transfusion immediately and keep the IV line open with normal saline.
b) Institute immediate resuscitative care as per the nature of the transfusion reaction
c) Send the following to the Blood Bank.
   - Blood bag and transfusion set
   - Post-transfusion blood sample-2ml EDTA and 3ml plain
d) Fill the Reaction form with details of the nature of reaction.
e) The blood bank staff will re-check all records and do a Direct Coombs test and repeat all pre-transfusion tests to confirm compatibility of the implicated unit.

Investigations to be sent if hemolytic/septic reaction is suspected:

a) Blood Culture-from patient and from component bag
b) Complete hemogram
c) Plasma haemoglobin
d) Urine hemoglobin  
e) Coagulation profile  
f) Bilirubin (conjugated/unconjugated)  
g) Urea  
h) Creatinine and Serum electrolyte.

ANNEXURE C-2

TRANSFUSION REACTION REPORTING FORM

Patient Details

Name
Age/sex
Ward no. Bed no.
CR no (or HID OF HOSPITAL PATIENT)
Diagnosis
Indication for transfusion
blood group of patient
Date and time of transfusion

Details of Transfused Unit

Transfused product (PRBC/leucodepleted PRBC/RDP/FFP/cryoppt/SDP/ other specify below)

Unit no.
Date of collection
Date of expiry
Blood group of unit
Date and time of issuing unit from blood bank
Date and time of starting transfusion
Duration of transfusion

Patient monitoring

<table>
<thead>
<tr>
<th>Time after starting transfusion</th>
<th>Hypotension</th>
<th>Chills</th>
<th>Rigors</th>
<th>Fever</th>
<th>Urti-caria</th>
<th>Difficulty breathing</th>
<th>Pain abdomen</th>
<th>Head-ache</th>
<th>Myalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post transfusion blood sample collected Yes No
(note should be wit in one hour of reaction.
Post transfusion urine sample collected Yes No
(maybe collected within 6 hours of occurrence of reaction, visual observation too, report to blood bank)
Annexure C- 3:

Plan for day care centre:

This plan is for a 10 bedded day care centre, where daily 10-15 patients can be accommodated. 300 patients per month could be managed for thalassemia and sickle cell disorders, in such a center.

<table>
<thead>
<tr>
<th>Sno.</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1.   | Recurring salaries  
Staff nurses (2)  
Counsellor (1)  
Attendant (1)  
Doctor (1)  
Technician-1 |
| 2.   | Recurring Medicines  
Blood bags and other blood bank disposables  
* NAT tested bag will cost extra Rs 600/bag  
** Extended red cell phenotyping per bag will cost extra Rs1200/bag  
*** Leucodepleted filter will cost extra Rs 650/bag  
Iron Chelation medicines  
Multivitamins and minerals |
| 3.   | Recurring essentials  
Bed sheets  
Cleaning  
Dustbins  
Bio waste  
Stationary (case files, prescription pads, pens, follow up sheets, measuring tape, height charts, A4 papers, record books) |
| 4.   | Non recurring equipment  
Beds  
IV stands  
Plastic kidney trays  
Needle destroyer  
BP instruments  
Stethoscopes  
Examination table with step stool with mattress  
Almirah  
Refrigerator 220 L  
Weighing scales  
Telephone |

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SECTION D:

OPERATIONAL GUIDELINES: IMPLEMENTATION FRAMEWORK, HUMAN RESOURCE REQUIREMENTS AND BUDGET ESTIMATES
SECTION D

1. Implementation framework

Screening of different target groups- newborns, young children and adolescents -for prevention of hemoglobinopathies and detection for early intervention and management will be undertaken under RBSK through coordination between DEICs and the Mobile Health Teams at AWCs and schools from district to block level. Screening for hemoglobinopathies can easily be conformed to the screening and referral process undertaken for other conditions under RBSK with changes in schedule and strengthening wherever required. Screening of pregnant women will be undertaken at DH, SDH, CHC and PHC under JSSK in coordination with RBSK.

Figure 1. Showing schematic framework of programme implementation
Figure 2. Hemoglobinopathies Screening module under RBSK

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Population to be screened</th>
<th>Conditions to be screened</th>
<th>Tests to be done</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 weeks</td>
<td>Newborns (Day 2-7 DBS) born at: Govt. Hospitals At home</td>
<td>Sickle Cell Disease (SS, SD, Sβ⁰, SE) β⁰-Thalassemia (β⁰/β⁰) Hb Variant traits Hb S Trait (β/β⁰) Hb E Trait (β/β⁰) Hb D Trait (β/β⁰)</td>
<td>Complete Blood Count PBS; S. Ferritin or sTfR Hb HPLC by NBS Variant Follow up with Hb- HPLC at 6 months and 12 months</td>
</tr>
<tr>
<td>6 weeks -6 years</td>
<td>Children with severe anemia (6 months to 6 years) referred to DEIC</td>
<td>Thal Major and severe Thal Intermedia β-Thalassemia (β⁰/β⁰, β⁰/β⁺, β⁺/β⁺, β⁰/β⁺, β⁺/β⁺, β⁺/β⁺, HPFH)</td>
<td>Hb HPLC</td>
</tr>
<tr>
<td>6- 18 years</td>
<td>Adolescents At school: Screening of all class VIII students of govt. and aided schools and non school going at AWCs backed with continued IEC for Class IX to XII students</td>
<td>β-Thalassemia Trait and variant Hb Traits and mild Thal Intermedia Hb S Trait (β/β⁰) Hb E Trait (β/β⁰) Hb D Trait (β/β⁰)</td>
<td>NESTROFT + DCIP + SOLUBILITY TEST Hemoglobin HPLC Complete Blood Counts Serum Ferritin, if required</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>Pregnant Women (10-12 weeks) at Antenatal Clinic at PHC/ CHC/ DH</td>
<td>β-Thalassemia Trait and variant Hb Lepore (δβ) Trait (β/β⁺, β⁺/δβ⁺)</td>
<td>DNA based tests for detection of mutation are essential for prenatal diagnosis and thus all carrier couples should be further tested for detection of causative mutation at the earliest</td>
</tr>
</tbody>
</table>

All patients should also be tested for causative mutations. In adolescents, detection of the causative mutation can be undertaken at a later stage but should be clearly mentioned in the report and during counseling.
2. Establishment of Laboratory services

Carrier States to be specifically screened for on the basis of given criteria are:

- Beta Thalassemia Trait
- Hb S Trait
- HbE Trait

Note: Any other traits and asymptomatic conditions that may be picked up in the course of screening are to be reported. In cases of diagnostic difficulties where cut off values are ambiguous they may be referred to State level, Tertiary or Referral centres.

Fig 6. Availability of Tests at Various Centres

Referral system for diagnosis.
1. Screening test-degree of anemia, NESTROFT/solubility test/DCIP
2. CBC, S FERRITIN, HPLC
3. HPLC, Mutation studies, other tests, prenatal diagnosis

2.1 Establishment of Laboratory services at DEIC/ District Hospital:

Tests required to be done:

- HPLC
- RBC indices through blood cell counter
- Serum ferritin, if required
- Peripheral smear, if required (Serum iron, TIBC if available)

Instruments required: HPLC, three part cell counter, Microscope and Elisa Reader

Detection of carriers is based mainly on Hb pattern on HPLC.
The DEIC lab established under RBSK or District Hospital labs can be upgraded to serve as secondary level diagnostic centres for the hemoglobinopathies programme. The Lab technicians working at the DEIC labs should be trained to conduct the tests required. The table below is a checklist of all the equipment required for conduction of the tests. Of these many of the equipments are likely to be present in the lab or granted under DEIC lab requirements as shown in the budget section of this document. The equipment specific for Hemoglobinopathies will be provided through this programme to strengthen the DEIC / District Hospital lab.

Table 3: Equipment required at DEIC / District level and State level / regional lab
[Those required at Regional/ State level labs or tertiary / referral labs indicated]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name / description</th>
<th>specifications/ purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Binocular Microscope</td>
<td>For peripheral blood examination</td>
</tr>
<tr>
<td>2</td>
<td>Automated Blood Cell Counter (3 part differential)</td>
<td>3 part differential automated blood cell counter for complete blood counts of samples for anemia and thalassemia or hemoglobinopathies,</td>
</tr>
<tr>
<td>3</td>
<td>Hemoglobin HPLC Equipment</td>
<td>Equipment capable of loading a minimum of 10 test at one for Hb fraction estimation - HbA0, HbA1c, HbF, HbA2 and common Hb for analysis of samples for thalassemia and hemoglobinopathies</td>
</tr>
<tr>
<td>4</td>
<td>ELISA Reader with washer</td>
<td>ELISA of Dried Blood Samples of newborns, Serum Ferritin in case of anemia to establish or rule out iron deficiency</td>
</tr>
<tr>
<td>5</td>
<td>Hemoglobin HPLC equipment for Newborn Screening*</td>
<td>HPLC equipment that can process Dried Blood Samples for separation of Hb fractions to enable diagnosis of Sickle Cell Syndromes and Hb D, HbE and HPFH syndromes and traits(*for Regional / State level labs where sickle cell anemia is common)</td>
</tr>
<tr>
<td>6</td>
<td>Capillary zone Electrophoresis System**</td>
<td>The equipment is based on electro osmotic flow provides high resolution electrophoretic separation with identification of most of the hemoglobin variants (**For national level tertiary referral centres to enable identification of unknown variants during the course of screening)</td>
</tr>
<tr>
<td>7</td>
<td>Refrigerator</td>
<td>180-310 L Domestic 1 for storage of samples , reagents in use kits, 1 for stock kits and reagents</td>
</tr>
<tr>
<td>8</td>
<td>Laboratory centrifuge</td>
<td>For separation of serum , plasma</td>
</tr>
<tr>
<td>9</td>
<td>Incubator</td>
<td>For conduction of DCIP test ( a portable incubator may be required if test to be conducted in outreach community settings like schools and AWCs)</td>
</tr>
<tr>
<td>10</td>
<td>Rotor sample mixer</td>
<td>For mixing samples</td>
</tr>
</tbody>
</table>
2.2. Tertiary level referral / national centres:

Selection of institutions as national referral centres for hemoglobinopathies with facility for Capillary Electrophoresis and DNA sequencing to detect unknown mutations. The states to evaluate and identify institutions that can be strengthened to function as national referral centres.

2.3 Establishment of facilities for Prenatal Diagnosis (PND):

If both parents are carriers of BTT or a variant Hb trait then prenatal diagnosis is required for preventing the birth of an affected child of “at risk couples”.

Centres with facility for obstetrical care, NICU and a genetic lab: Testing can be done before a baby is born to find out if he or she has thalassemia and determine how severe it may be. Molecular identification is necessary for PND. The molecular methods used for detection of common point mutations are reverse dot blot (RDB), allele-specific oligonucleotide hybridization or amplification refractory mutation system (ARMS).

**There are three fetal sampling methods available for prenatal diagnosis:**

1. Chorionic Villus Sampling (Chorionic villi are early placental tissue)
2. Amniocentesis
3. Fetal blood sampling.

**All of them are conducted under ultrasound guidance.**

The choice available to an 'at risk' couple: Today, parents who are aware that they are both carriers of β-thalassemia or Sickle Cell disease have a number of choices with regard to having a family. These should be discussed as early as possible with an expert health professional and/or a genetic counselor.

Prenatal testing is a choice to many families. The mutation studies are performed and then the doctor proceeds to find out whether the fetus is affected or not and then the family is given the option of pregnancy intervention (termination) for an affected child.
The provision of PND facilities to be established in two phases.

Phase-1- Establishing a referral system for referring couples in need of PND to existing centres with facilities for prenatal diagnosis. Pregnant women whose husbands are also detected to be carriers during antenatal screening should be referred for prenatal diagnosis to the nearest a tertiary level centre with facilities for prenatal diagnosis from the list of centres with facilities for prenatal diagnosis. The required financial support for test cost and permissible fare for two persons (mother and father or accompanying person) can be budgeted.

Phase- II-Establish facility for prenatal diagnosis at one or more district level government hospitals

Requirements for establishing prenatal diagnosis facility at state level government hospitals / state medical colleges

- Training of obstetricians and / or radiologists to build capacity for CVS, amniocentesis or Fetal blood sampling and training of pathologists, scientists and DEIC Lab Technicians in genetic testing
- To frame guidelines for setting up DNA analysis lab facility at select State level labs

Setting up a strict operational framework for prenatal diagnosis as per the PCPNDT Act to avoid misuse of the facility.

Table 4: List of Government Centres with facility for Prenatal Diagnosis

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of centre / institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>All India Institute of Medical Sciences, New Delhi</td>
</tr>
<tr>
<td>2.</td>
<td>Sanjay Gandhi Post Graduate Institute of Medical sciences, Lucknow</td>
</tr>
<tr>
<td>3.</td>
<td>Post Graduate Institute of Medical Education and Research, Chandigarh</td>
</tr>
<tr>
<td>4.</td>
<td>Government Medical College, Chandigarh</td>
</tr>
<tr>
<td>5.</td>
<td>Maulana Azad Medical College, Delhi</td>
</tr>
<tr>
<td>6.</td>
<td>CDFD Hyderabad</td>
</tr>
<tr>
<td>7.</td>
<td>National Institute of Immunohematology, Mumbai</td>
</tr>
<tr>
<td>8.</td>
<td>SAT Trivandrum Thalassaemia Control Unit</td>
</tr>
<tr>
<td>9.</td>
<td>NRS Medical College, Kolkata / Medical College, Kolkata</td>
</tr>
</tbody>
</table>
3. Screening and Management Protocols:

3.1. Primary level population screening protocol for hemoglobinopathy carriers for implementation in schools, AWCs, SCs, PHCs:

Implementation points for carrier screening are as given below

- **Carrier states to be screened for are-**
  - B-thalassemia trait (BTT)
  - HbE trait
  - HbS trait

HbE and HbS to be screened in districts of States having known high prevalence. Other carrier states and asymptomatic conditions detected during the course of screening, are to be reported.

Note: A carrier rate of 1% or more may be taken as cut off for implementation of universal Screening programmes in a defined population such as pregnant women, adolescents or geographically or administratively defined area such as a district or a state.

- **Objective of screening** is identification of carriers before marriage so as to avoid marriage between two carriers to eliminate possibility of birth of an affected child and/or identification of carrier status of both parents during early pregnancy. This will enable prenatal diagnosis of an affected fetus so as to provide an opportunity for termination of pregnancy avoiding birth of an affected child.

- **The screening protocol is based on initial screening** of all individuals by NESTROFT, DCIP test and Solubility test, all single test tube based simple tests respectively for BTT, HbE trait and HbS trait, done on a finger prick blood sample. Turbidity of the solution with drop of blood is indicative of a positive test. Samples of those with a positive test are collected and further tests - a Complete Blood Count (CBC) and an Hb- HPLC is done. Diagnosis is based on results of Hb HPLC.

  - As severe anemia itself can cause a positive test, those with severe anemia defined as an Hb of <8 gm/ dl as per National Iron Plus Initiative guidelines, are excluded from further testing and referred for treatment. Screening in these individuals is repeated after correction of anemia.

- **Treatment of mild and moderate anemia specially IDA with the aim of –**
  a) Replenishing iron stores in IDA to well within normal limits (corresponding to serum levels of around 100ng/ml) so as to decrease prevalence of anemia specially maternal anemia;
  b) Avoid unnecessary iron therapy in the absence of iron deficiency as reflected by serum ferritin levels;
  c) Enable cause appropriate treatment / management of anemia.
Limitations and precaution in implementing the screening protocol

- Only those β thalassemia carriers will be detected who have a HbA2 level of 4.0% or more on Hemoglobin analysis by HPLC. Those with HbA2 levels between 3.5 and 4.0% may be detected, and those with HbA2 levels <3.5, referred to as ‘silent’ carriers will be missed with the applied screening protocol. Some of these silent carriers may be detected by chance on DNA analysis.
- NESTROFT being used as the primary screening test, and its negative predictive value has been found to be ranging from 97-100%, some β thalassemia carriers that may not show a positive NESTROFT may also be missed.
- Some other carrier states and compound or homozygous states may be detected during the course of screening will be reported.
- For an effective screening minimizing false negative tests is necessary and it is recommended that calibrated digital hemoglobin-meters be used for determination of Hemoglobin on a finger prick sample as pallor has a poor sensitivity for mild and moderate anemia making it difficult to accurately distinguish severe anemia from moderate and mild anemia.
- When a new unit starts screening, create a control data by doing CBC and Hb-HPLC in all samples with Hb>8gm/dl in first 300-500 cases. Ideally there should be no BTT in the NESTROFT ‘negative’ group with a Microcytic Hypochromic CBC.
- It is essential to maintain quality of NESTROFT solution possibly by preparing this solution centrally and calibration of Hemoglobinometer.
- Samples collected should be transported to DEIC properly and timely.
- All adolescents with mild or moderate anemia should be referred to PHC or CHC or should be provided therapeutic iron and folic acid (IFA) by the visiting team in school.
- Follow up visit should be scheduled at PHC / CHC after 30 days of screening visit where counseling is provided to students along with detected to be carriers of thalassemia or variant trait and those with anemia should have Hb measurement and monitored for compliance with IFA therapy.
- Students to be followed up to be called along with families for further testing, collection of samples for confirmatory testing and counseling and family screening should also be conducted. Written consents on sample collection forms should be taken before collection of the sample for confirmatory testing.
- It is important that the pathologist / doctor accompanies the team on follow up visits.
Micro planning of screening of adolescents in schools

In districts undertaking Anemia- Thalassemia Carrier screening, screening of class VIII students and IEC activities for classes VIII to XII is to be done by DEIC based Field team of 1 Field IEC Officer and 1 Field Assistant who will join the Mobile Health Team of the respective Blocks in schools.

DEIC based Field Officer to prepare quarterly visit schedule for all govt. and govt. aided schools for one time screening of class VIII students in the district and communicate and coordinate with respective Block MHTs so that Staff Nurse of Mobile Health Team can join the Field team for screening of the blood disorders, anemia and hemoglobinopathies.

Microplanning for school visit by DEIC based field team for adolescent screening

<table>
<thead>
<tr>
<th>Date</th>
<th>School Name</th>
<th>School code</th>
<th>Block</th>
<th>No. of students</th>
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<tr>
<td></td>
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- Target for 1 team – 150 students / screening visit
  - 160 screening visits = 24000 students
  - Approximately 80 follow up visits

- IFA to be provided SNs from the team’s drug kit or refer to PHC / CHC for treatment as per State’s policy.

- A two member team of 1 Field Officer (FO) and 1 Field Assistant (FA) will join the Mobile Health Team and along with Nursing Staff (MHT) can on an average screen 150 students/day. About 160 working days are available for screening due to exam schedules. Strategy for screening schedule is as follows: one team of FO and FA will join the respective mobile health team of the block and along with SN of MHT making a 3 member team with capacity to screen 150 students/day.

- The Field Officers are to conduct the awareness and education talks for class VIII-XII students during the visit and also screens those who have been missed in class VIII.

- 2 such teams are required to accompany each of the two Block MHTs cover the target population of Class VIII students around 50000 / district (40000-60000) by conducting screening of 300 students/day for an average of 20 days / month on 4-6 days/week spread over 32 weeks in 8 months in a year. About 80 follow up visits will be conducted by the DEIC based Field Officer and Field Assistant in a year, at the nearest CHC / PHC or at school to follow up students with positive screening be carriers and those having mild or moderate anemia. During the follow up visit

-75-
Visit to schools in blocks distant from DEIC will require overnight stay of the team. DA will be permissible to team members.

Pathologists will be required to accompany the team in follow up visits and 10% of screening visits in school.

For a district with 50000-60000 students in class VIII, 2 DEIC based teams required and one vehicle hired on a daily basis.

**Note:** As students of class VIII and IX are relatively young to understand and retain the information regarding it is of vital importance that the specifically directed IEC campaign including a mandatory educational talk on anemia, hemoglobinopathies and other inherited disorders prior to conduction of the screening in the school for students from Classes VIII to XII be conducted each year. Also those who are missed in class VIII should be screened. As delineated earlier in the screening protocol, parents must be informed and involved during later part of the screening protocol – the follow up visit- for students with positive initial screening test.

**Points to remember:**

RBSK ID will be provided only once to the student when screened for the first time and is also entered on the students ID card that student has been screened for hemoglobinopathies carrier status. When the team visits next year, the same id is used to check if the students have been screened for hemoglobinopathies by tube tests.

**3.2. Secondary level screening for carriers at District Hospital / DEIC**

- The DEIC lab or a District Hospital lab is equipped with three part differential Blood Cell Counter and hence initial screening for β-thalassemia carrier state is done by collection of blood by venepuncture and conduct both NESTROFT and CBC on the sample.
- At secondary level DCIP and Solubility Tests are also to be added if there is any significant prevalence as they are simple and very low cost tests. Hb S and HbE carriers usually have a normal MCV and MCH and thus will be missed by CBC.
- Issuing of report of HPLC analysis must be accompanied by counseling and collection of sample for confirmatory test (DNA test).
- DEIC or District Hospital is expected to be the most common point for individuals or couples seeking premarital or pre-conceptual screening for carrier status as a result of awareness created by IEC campaigns.
- Pregnant women screened before 16 weeks if found to be carriers should be followed by screening of husband and referral to a tertiary centre for prenatal diagnosis. Ideal time for Chorionic Villus Sampling is 10-12 weeks. However, women coming after 12 weeks can be provided prenatal diagnosis by amniocentesis providing opportunity for termination of pregnancy before 20 weeks if required.
• All tests results with ambiguous or equivocal cut off values and unknown variants should be referred to a State level or national level tertiary centre. An incorrect diagnosis should be avoided at all costs.

Microplanning for screening of pregnant women (Antenatal Screening).

Step 1. Screening of all pregnant women on first visit (1st trimester) to CHC/ PHC by tube tests (NESTROFT, DCIP test, Solubility test) along with Hb, Urine test for protein, Blood Group, HIV, and Blood sugar.

Step 2. If Screening test positive, refer the patient along with husband by 104/ 108 service to District Hospital/ DEIC for further testing –

Step 3. The woman to be admitted at District Women Hospital for conduction of following tests provisioned under JSSK.

- CBC and Hemoglobin HPLC of both – wife and husband

If wife and husband both are detected to be hemoglobinopathy carriers on Hb HPLC testing an Ultrasound test (USG) of the wife (the pregnant woman) to be done to determine the gestational age of the fetus.

-If gestational age 12 weeks or less couple to be referred to nearest tertiary centre for prenatal diagnosis by CVS through coordination with the DEIC

-If gestational age >12 weeks but < 20 weeks consultation for possible PND by amnio centesis at the tertiary centre

-If gestational age >20 weeks, counseling for possible outcomes of pregnancy and follow up of pregnancy. If the baby born is an affected child determined by DNA based tests early intervention by registration in DEIC for management and care. Counseling of couple for prevention in future pregnancies.
3.3. Newborn Screening for Sickle Cell Disease in regions/districts with high prevalence

Newborn screening for sickle cell disease (SCD) is to be implemented in districts with high prevalence of HbS. The screening to be done by Dried Blood Spot samples collected by heel prick of newborns between 24 and 48 hours of age. The sickle homozygotes and heterozygotes should be recorded separately under the confirmatory testing column. The DBS samples can be used for screening of other metabolic disorders like Congenital Hypothyroidism, G6PD Deficiency, CAH and other IEMs.

- For screening of sickle cell disease the samples will be mailed to the State level lab equipped with Newborn Hb HPLC system.

- The SCD syndromes are to be screened on the basis of Hb pattern found at birth

- In addition complete absence of Hb A with presence almost 100% HbF at birth indicates homozygous β0thalassemia which is to be reported for follow up and confirmation at a later stage.

- A diagnostic test by Hb HPLC of venous blood to be done at 6 months of age for timely institution of therapy and repeated at 1 year of age for final diagnosis. Sickle Cell Disease and Thalassemia Major both usually do not require intervention till about 6 months of age.
Figure 3. Newborn screening for hemoglobinopathies

Testing by heel prick Dried blood spot sample of newborns, collected between 24-48 hours

Screening reports e-mailed to respective districts/ DEICs

Reports disseminated by DEICs to the source centre from where DBS was obtained to track the newborn by NBS ID/RBSK ID and MCTS No.

Hb HPLC on venous sample repeated at DEIC at 6 months and 1 year of age.

Newborn DBS samples are to be collected by Nurses at District level hospitals and DEIC staff nurses where applicable. At CHC and PHC, Staff Nurses /GNMs or ANMs and in cases of home deliveries ASHAs are to collect samples. This has to planned in a phase wise manner.

Availability of newborn heel prick lancets, DBS sample collection cards and training of health care personnel – Nurses, GNMs, ANMs, ASHAs – in collection of samples is crucial for successful implementation of newborn screening

Children affected with clinically severe thalassemia disease manifest with severe anemia usually after 6 months of age when Fetal Hb production starts reducing and in normal cases is replaced by adult hemoglobin HbA by the age of 1 year. In children affected with thalassemia, there is deficient synthesis of HbA due to lack of β- globin chains hence development of severe anemia is the earliest manifestation of the disease. This anemia is accompanied by normal or increased levels of iron. Later on other complications develop. Most of the severe cases of thalassemia that require management by regular blood transfusions manifest by 5-6 years of age.
Thus, selective screening of children between 6 months and 6 years of age presenting with severe anemia for thalassemia disease is a cost-effective approach for early detection of thalassemia.

Figure 4. Screening of children with severe anemia for early detection of thalassemia

Under the RBSK all children between 6 weeks to 6 years of age are screened for anemia by clinical examination at AWCs. Severe anemia, defined as Hb<7gm/dl in children, is usually detectable by clinical examination. These children are referred to DEIC for further investigation and treatment.

Similarly children with severe anemia without an obvious disorder attending pediatric clinics at District level hospitals or at CHC and PHC should be referred to DEIC for further screening and intervention.
3.5. Establishment of day care centre facilities for management of Thalassemia and SCD affected children at DEIC

Regular transfusion and iron chelation is the mainstay of management of patients with thalassemia disease. A thalassemia patient requires-a) Repeated blood transfusion of packed red blood cells (pRBCs) should be done at 2 to 4 weeks interval, b) Iron chelation for iron overload, c) Monitoring of complications due to the disease and their treatment d) Management of complications (endocrine, cardiac, skeletal etc.), Psycho-social support f) Bone marrow transplantation (BMT)/now known as Hematopoietic stem cell transplant (HSCT).

Management of thalassemia and SCD patients through a day care facility is convenient, economical and provides a supportive environment friendly area for children with a chronic illness.

It helps in developing a good rapport with staff and better compliance and efficient monitoring of patients.

Requirements of setting up a day care programme are:-

- A transfusion facility / ward with 5-10 beds as per requirement, IV stands
- Supporting blood bank which provides packed RBCs. NAT tested bags with extended immunophenotyping are preferable
- Supporting laboratory with facilities for routine hematology and biochemical testing
- Electronic weighing scale.
- Emergency kit for managing blood transfusion reactions.
- Blood transfusion sets and availability of leucodepleting filters, if blood bank does not provide pre-storage leucodepletion.
- Availability of iron chelating drugs, multivitamins and minerals
- Examination room with BP instrument, weighing scales, stadiometer, stethoscope
- Trained staff nurses to provide transfusion services on daily basis in multiple shifts to accommodate more patients with staff turnover as low as possible to provide continuity of care.
- Availability of management protocols for transfusion therapy, transfusion reactions and chelation therapy to serve as guidelines for staff.
- Well-trained doctor to handle complications related to transfusion reactions in a hospital setting.
- Desirable to have recreational facilities to keep children entertained during transfusion.

Thus DEICs with dedicated staff trained in dealing with children with defects and disabilities that includes a Pediatrician and / or Medical Officer, Staff Nurses, Laboratory technician, Counselor and a Psychologist with, laboratory and recreational facility provide an ideal setting for providing day care management facility for thalassemia and SCD patients.

Fig 8. Showing the entry points to the DEIC daycare or blood transfusion centers.
In a 10 bedded day care centre, daily 10-15 patients can be accommodated. 300 patients per month could be managed for thalassemia and sickle cell disorders.

3.6. Hematopoietic stem cell transplant and transplant specialized hematology

The only curative therapy for thalassemia major and sickle cell disease

Hematopoietic stem cell transplant (HSCT), previously commonly called Bone marrow transplantation is the only curative therapy and is well established. The outcomes of this expensive and difficult procedure depend on patient characteristics. Lucarelli classification divides thalassemia major patients into risk groups based on pre transplant morbidity and this predicts their risk of serious complications and morbidity with transplant. Younger children, with adequate iron chelation, no hepatomegaly or hepatic fibrosis do best with this procedure. The older children with organomegaly, iron overload, cardiac or hepatic compromise require additional medications and extra therapy. There is a risk of BM graft rejection in and graft versus host disease. These complications are more in older children and are often due to allo-immunization, non leuco-depleted blood products or transfusion from first degree relatives leading to sensitization. Other complications like veno-occlusive disease of the liver occur in heavily iron overloaded children or those who had irregular chelation, hepatitis and fibrosis of liver. This is a serious transplant complication and can lead to multi organ failure and death.

HLA typing of sibling and matching leads to the commonest source of transplants the HLA matched brother or sister. The sibling can be normal or a carrier for thalassemia, both are acceptable. The costing below is for such HLA matched sibling transplants. Alternatively
unrelated HLA matched donors have been used for transplant from the unrelated donor registries. The cost of such (unrelated) transplants are more due to the registry fees and the increased complications of an unrelated transplant.

Cord blood transplant can be done from a sibling or another person but is not usually preferred for thalassemia patients, due to risk of rejection, but can tried if no bone marrow matched donor is available. Even cord blood transplants needs HLA matching.

Sickle cell disease transplant indications are very selective, due to the risks of morbidity associated with the transplant procedure.

**Indication for allogeneic HSCT for sickle cell disease as suggested by Walters et al.**

1. Stroke or central nervous system event, lasting longer than 24 hours, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions.
2. Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism.
3. Impaired neuropsychological function with abnormal cerebral MRI scan
4. Stage I or II sickle lung disease
5. Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
6. Bilateral proliferative retinopathy with major visual impairment in at least one eye
7. Osteonecrosis of multiple joint
8. Red-cell alloimmunization during long-term transfusion therapy

For further details on management readers are advised to refer to Section C: Guidelines for Management of Hemoglobinopathies in Prevention and Control of Hemoglobinopathies: NHM policy on Hemoglobinopathies

For HSCT- few government centers have provision for this, but many private centers offer the procedure below is a list of some of the larger transplant centers in India
### Table 5.
#### List of centres with facilities for Hematopoietic Stem Cell Transplant

1. CMC Hospital Vellore
2. Tata Memorial Hospital, Mumbai
3. Hematology department, AIIMS, New Delhi
4. Apollo Specialty Hospital, Chennai
5. R and R hospital, New Delhi
6. Tata Medical Centre, Kolkata, W Bengal
7. PGI Chandigarh, Punjab
8. Sahayadri Hospital, Pune, Maharashtra
9. Rajiv Gandhi Cancer Centre, New Delhi
10. Narayana Hirudalaya, Bengaluru, Karnataka
11. Manipal Hospital, Bengaluru, Karnataka
12. Apollo Hospital, Ahmedabad Gujarat
13. Sterling Hospital, Ahmedabad, Gujarat
14. Deenanath Mangeshkar Hospital, Pune, Maharashtra
15. CMC Ludhiana, Punjab
16. Sterling Hospital, Vadodara, Gujarat
17. Malabar Cancer Centre, Thalassery
18. Meenakshi Mission Hospital, Madurai, TN
19. Kovai Medical Centre, Coimbatore, TN
20. GKNM Hospital, Coimbatore, TN
21. SRMC, Chennai, TN
22. SGPGI, Lucknow, UP
23. BL Kapur Memorial Hospital, New Delhi
24. Artemis Hospital, New Delhi
25. Fortis Hospital Gurgaon, Haryana
26. Apollo Hospital, New Delhi
27. Max Superspecialty hospital Saket, New Delhi
4. IEC: strategies and modules

It is the most important component of a hemoglobinopathies prevention and control programme. Hemoglobinopathies are the first group of single gene disorders with a Mendelian recessive inheritance pattern to be addressed through public health strategies. The strategies for educating the community about hemoglobinopathies, their treatment and prevention modalities will require to educate about inheritance pattern of the disease, carrier states and their role in prevention, the basis of transmission of the disease, variation in severity of the disease in the same family, factors in making choices for prevention, dissemination of information within the family and community. In the case of recessive genetic disorders, detection of carriers plays a key role in preventive strategies. The aim of IEC strategy is creation of an informed society willing to participate voluntarily in screening programmes and take steps for preventing births of children affected with the disease and access care for those affected with the disease.

The strategies to be adopted to achieve this are:-

Mass communication and media – to incorporate with NHM- IEC at national, state and district level. The messages should aim to remove any stigma and gender biases by promoting knowledge of genetics and inheritance by general and targeted campaigns and awareness about prevalence of disease and that it is preventable. People should be encouraged to acquire complete information about these disorders and should be made aware of specific initiatives of the government.

Mid media activities – IEC material and campaigns developed by the States should also focus on promotion of voluntary blood donation to fulfill requirement of blood and to improve access to care services to all affected by promoting knowledge of the treatment modalities available through the public health facilities. The display of posters at all health facilities and identified community places should be ensured. Non-government organizations (NGO) and community based organizations should be involved in.

Educational curriculum: States should work with education department for inclusion of information about hemoglobinopathies in the school text books and school health programs

IPC and One to group communication- These are very effective IEC tools with well trained counselors and informed healthcare personnel. Some specific points of application are listed below below:

1. Adolescent screening in schools: An organized IEC module to ensure communication and retention of information is vital for success of carrier screening programme for adolescents. It should comprise.

   - A pre-screening power point assisted 30 minute educational talk by Field IEC officer.
   - distribution of booklets on hemoglobinopathies and anemia urging the students to read and keep the booklet and organizing a quiz session based on booklet and talk. Encouraging better performing students by their participation in interschool quiz programmes events that may include other adolescent health issues.
-one to one communication at the time of collection of venous blood sample of those with positive screening test
- one to one counseling at the time of follow up visit at school or PHC/CHC for collection of sample for confirmatory testing of those with single positive diagnostic test.
- Genetic counseling at the time of providing final report
ReJat e, ed a d i an c ommunications make the screening process very effective
2. At AWCs and AFHCs during screening of out of school adolescents: One to one counseling in at least two to three sessions and reinforcement of information by healthcare workers – ASHAs

3. At SC, PHC, CHC and DH during antenatal screening of pregnant women

4. During Blood donation camps and at Blood banks offering screening and counseling to voluntary donors

5. At DEICS Inform Children who have thalassemia major about care and prevention of complications and affected families about the importance of family (cascade) screening

The IEC material – posters, booklets and powerpoint presentations with the centre will be provided to the States and States can develop their own material based on guidelines
5. Monitoring and Surveillance

5.1 Monitoring of patients registered at DEICs

Thalassemia Daycare Patient Monitoring Sheets have been formatted and need to be filled on every visit (appendix 1). This ensures adequate management and serves as a baseline of minimum monitoring that is needed for care. Each patient’s record file is maintained along with a computerized record file by the staff nurse in the DEIC computer. The monthly reporting of number of patients registered under care is to be done as indicated in the Monthly Progress Report format provided later in this section.

5.2. Recording of screening data with laboratory results

A. Hemoglobinopathies Screening Datasheet:

Software formats in Microsoft excel for recording screening data of adolescents and pregnant women of different tests of each screened individual have been provided in the laboratory services manual. The hard copies of the same can be maintained in registers at DEICs. The initial part of the adolescent screening data will be entered by the Field Officers in the same format maintained in their laptops and transmitted to DEIC where further laboratory data is filled in with diagnosis and outcomes. RBSK ID is assigned to each of the students screened for the first time and it serves to follow up the student through the subsequent years and their reports will be retrievable at the DEICs using this ID at any time. The number of NESTROFT / Solubility / DCIP test positive samples should be recorded in 3 separate columns or else it will be difficult to know the false negatives found under each. Similar formats will be provided to PHCs, CHCs and DH for entering screening data of pregnant women using the MCTS ID.

B. Newborn Screening Datasheet:

Newborn screening for hemoglobinopathies is to be converged with screening for other disorders such as Congenital Hypothyroidism, G6PD Deficiency and other inherited errors of metabolism using the DBS sample. Hence the Microsoft excel newborn screening datasheet format comprises a section on the newborn’s identity and is linked to the MCTS number and the DBS sample number with record of timing of sampling. Screening tests and confirmatory tests are recorded and outcomes recorded on their basis from a drop down menu. The number of NESTROFT / Solubility / DCIP test positive samples should be recorded in 3 separate columns or else it will be difficult to know the false negatives found under each. Formats of different reporting and recording forms that require to be printed have been provided in the laboratory services guidelines.
5.3 Monthly Progress Report

Three Microsoft excel based formats for MPR have been prepared

1. Hemoglobinopathies screening in adolescents, families and children with severe anemia
2. Pregnant women
3. Newborn screening for SCD

Data from all DEICs will be submitted in this format to the State HQ where it will be received in a similar format and data from all districts gets compiled to provide a combined state level data as well as a district level data. The MPR provides month wise relevant data on screening and its outcomes. Any gaps at different steps of screening are also reflected in the MPR so that corrective steps can be taken. Data on anemia is also provided as per WHO classification of mild moderate and severe anemia

Each month data can be updated and at any time the data can be viewed month wise as well as cumulative data.

A screenshot of the MPR for hemoglobinopathies screening in adolescents is shown in figure 10. A comprehensive training for using recording and reporting formats will be provided.

5.4. National web based registry of hemoglobinopathies:

A national web based registry or database is an important tool for planning future patient services. Apart from number of carriers and cases identified it collects other useful data, such as the geographical and ethnic origin, to identify areas and populations with high prevalence, types of mutations, genotypic and phenotypic data and outcomes of patients and other data which helps to evaluate the success and status of the control program, records of deaths and their cause which is a basic source of information directing the treatment choice.

ThalInd, is a web based database of beta thalassemia and abnormal hemoglobins created to serve as an informatics resource for hemoglobinopathies in India. The resource uploaded with collated data available in 2009 was created using the LOVD system, an open source platform independent system, promoted by the Human Genome Variation Society, the international consortium for genetic variants causing diseases. The resource aligned with the administrative health system and census based demographic resources accommodates data on mutations and their characteristics (molecular genetics), frequency of different mutations and their geographic and ethnic origin (population genetics), correlation of mutation with clinical data on gender and age distribution, disease type and severity (genotype-phenotype correlation), mortality and morbidity (disease burden) and registration of patients with thalassemia centres and support groups (infrastructural services). The database designed with multiple access level transferred to a sever under the ministry, upgraded and updated and modified to accommodate more types of data elements will serve as tool of surveillance of the programme.
<table>
<thead>
<tr>
<th>Year 2015-16</th>
<th>Target Population (No. of Enrolled students)</th>
<th>Anemia</th>
<th>Thalassemia Trait</th>
<th>Number of children (6wks- 6 yrs) screened</th>
<th>Thalassemia Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>Number Screened</td>
<td>School Screening</td>
<td>School Screening</td>
<td>Family Screening</td>
<td>Total</td>
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<tr>
<td></td>
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<td>Mid</td>
<td>Moderate</td>
<td>Severe</td>
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</tbody>
</table>
### 2. MPR format for Antenatal Screening

<table>
<thead>
<tr>
<th>Months</th>
<th>No. screened by CBC and NESTROFT</th>
<th>Screening positive by with NESTROFT/ Solubility test/ DCIP test positive</th>
<th>Total no with screening positive</th>
<th>Severe Anemia Hb &lt; 8 gm/dl</th>
<th>No. tested by HPLC</th>
<th>No. with positive HPLC</th>
<th>No. of women whose husband tested</th>
<th>No. referred for prenatal diagnosis</th>
<th>No. of women undergo PND</th>
<th>No. of women with positive PND</th>
<th>No. of women with positive PND undertak en MTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan</td>
<td>0</td>
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</tr>
</tbody>
</table>

### 3. MPR format for newborn screening for hemoglobinopathies

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of Newborns Screened</th>
<th>Screening Test (newborn DBS- HPLC) Positive</th>
<th>Number of confirmatory tests</th>
<th>Confirmatory Test Hb-HPLC at 1 year age) Positive</th>
</tr>
</thead>
<tbody>
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</table>
6. Human Resource

Table 1. The following table shows the existing and additional proposed staff under RBSK at State, District (DEIC) and Block (Mobile Health Team) level required for implementation of the hemoglobinopathies programme.

Success of the programme depends heavily on the quality of laboratory services provided, the conduction of population screening and the IEC activities to back up the screening programmes. The additional staff requirements have been proposed to strengthen the RBSK cell at State HQ and at DEICs these areas.

<table>
<thead>
<tr>
<th>Professional</th>
<th>State HQ</th>
<th>DEIC/</th>
<th>Existing staff at Block level-Mobile Health Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Expert 1 (Pathologist/Pediatrician)</td>
<td>Existing</td>
<td>Additional Proposed</td>
<td>Existing</td>
</tr>
<tr>
<td>Child Health Consultant</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IEC Co-ordinator</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Accountant/Ex. Asst.</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pathologist</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Medical Officer</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychologist</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Counselor</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nursing Staff</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lab Technician</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Data Entry Operator</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Manager</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Field Officer (IEC) Counselor</td>
<td>-</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Field Assistant (Lab attendant)</td>
<td>-</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Nursing Staff</td>
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</table>
6.1 Implementation of Screening: Roles and Responsibilities

- The Pathologist at the DEIC is responsible for verification of screening datasheet and MPR at the DEIC ensuring preparation of correct reports and communication of correct data to the State HQ, besides supervising the DEIC staff and laboratory work.
- Field Officer is the key person in implementation of the adolescent screening programme under the supervision of Pathologist at DEIC right from preparation of screening schedules to communication of screening results and counseling. He coordinates with the Mobile Health Team Nurse, conducts screening as per protocol and assures delivery of samples collected by the Nurse and Field Assistant to the LT at DEIC. Results when entered into the Hemoglobinopathies datasheet and verified by the Pathologist, the Field Officer prepares the list of detected carriers and communicates to respective schools or AWCs for follow up at PHC/CHC for counseling and collection of samples for confirmatory testing.
- Nursing Staff at DEIC is the key person in implementation of Newborn screening for sickle cell disease and screening of children with severe anemia for thalassemia disease. The DBS samples are collected by her and delivered to LT and babies with positive screening test are recalled for confirmatory testing. Children with severe anemia are presented to the Medical Officer by the Nursing Staff and after clinical examination, their blood samples are collected by her and submitted for investigation as per protocol. If on investigation child is diagnosed to be suffering from Thalassemia disease (TM, TI), she registers the child under care programme.
- Lab Technician has to receive all samples verifying the samples with the Field Officers and Nursing Staff and conduct all tests as per laboratory protocols. The one very important step is entry of all the test results correctly in the screening datasheet. It is encouraged that all values are entered in the datasheet by the LT himself or should be present at the time of entry with the Data Entry Operator to avoid errors. Any results that are doubtful or equivocal should be flagged and brought to the notice of the Pathologist.
- Data Entry Operator is responsible for filling up of the screening datasheet on a regular basis. He should be in regular communication with the Field Officer, LT and the nursing staff, the people who provide him the patient details and test results and outcomes. He is also responsible for making reports to be issued by the DEIC. The MPR is to be prepared by him and verified by the DEIC manager and the Pathologist and the Pediatrician.
- DEIC Manager is responsible for ensuring availability of all consumables and maintenance of equipment. He has to prepare the monthly Statement of expenditure and keep track of the budget estimates and allocations under the supervision of the doctors at the DEIC.

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6.2 Intervention and Management: Roles and Responsibilities

The staff nurse at the DEIC is the key person in running the management programme under the supervision and advice of the Pediatrician and / or the Medical Officer.

The DEICs routinely have two nurses. If the number of patients registered under care programme exceeds 60, deployment of additional 1-2 staff nurses will be required.

The main components of a day care management programme are:

- Registration of a patient under the care programme with creation of a record file for long term management with baseline clinical examination and investigations

1. Preparing transfusion schedule for each patient
2. Coordination with Blood Bank and Blood Bank Officer for ensuring timely availability of pRBC units by keeping a tabular record of number of patients, blood groups with extended immunophenotype (if facility available) and monthly transfusion schedule
3. Regular maintenance of growth charts and investigations
4. Regular maintenance and monitoring of chelation therapy
5. Arranging periodic detailed examination of each patient by the pediatrician
6. Looking for alert signs for development of any complications
7. Arranging sessions with counselor and psychologist
8. Maintaining an updated database of patients and family pedigrees
9. Identifying and arranging for tertiary referral of cases with diagnostic difficulties or complications like serious cardiac problems, allo-immunization etc.
7. Training

Training module:

1) Compulsory basic training (Orientation Programme- 2 day)

This will be for all levels of staff- physicians, nurses, technicians. It will be designed to cover the aims and objectives of the programme, explain the programme arms, roles of each staff and how to refer and connect patients for smooth movement and continuity of care. Explain the roles of the teams- screening and awareness, lab, management etc. This will focus on orientation and knowledge to ensure success of the programme.

2) Advanced level training (Induction Training- 3 day)

This will be focused training with specialized training in accordance with work requirement.

   A) Screening and awareness team
   B) Laboratory screening and diagnostic techniques
   C) Hemoglobinopathies patient management training for doctors and nurses

Training Plan:

A cascade training plan will be adopted.

1) Training of Trainers:
   National level training will be provided to doctors- Pathologists, Pediatricians and Medical Officers nominated by the State.
   Aim will be to provide orientation and induction training to all Pediatricians and Pathologists at national level State IEC Coordinators will be trained at national level
2) A 2 day Orientation and Induction training of all the other staff involved in implementation in batches at State level with trainers from national team
3) Medical Officers, Nursing Staff and Field Officers are the key persons and their 3 day Induction training will be organized at State level in batches with Technical Experts, Pathologists and Pediatricians as trainers.
4) State level induction training will be organized for Lab Technicians at a DEIC lab.
5) Field Assistants, Nursing Staff of MHTs and DEOs will be trained at DIEC
6) Hands-on training for gynecologists and sonologist for the interventive procedures may be included for prenatal testing, if needed.
Training curriculum:

1) Compulsory basic training:

Outline of programme, aims and objectives
Basic knowledge regarding thalassemia and sickle cell disease and other hemoglobinopathies
Basic genetics
Assessment of anemia, role of various tests
Basics of care
Options for cure
Correct blood transfusion techniques
Data base management, data entry
Documentation
Rules for referral

2) Advanced level training: training specific for role/team

I) Awareness and screening –
(Mobile teams and staff)
Genetics
Counseling skills
Prevention strategies
IEC presentation
Understanding of programme guidelines (refresher)

II) Laboratory techniques (refer to DEIC laboratory manual)- Screening tests
(technician, doctors at CHC, PHC)
How to conduct tests, fallacies and chances of error, when repeat testing needed.
Reporting and documentation.
Referral for diagnostic testing.

III) Laboratory techniques (refer to DEIC laboratory manual)- diagnostic tests
(technician, doctors at Medical colleges and DEIC centers). These will be conducted at medical
colleges, tertiary centers (and hopefully later at DEIC centers)

How to conduct tests, fallacies and chances of error, when repeat testing needed.
Quality control
Reporting and documentation.
Referral for management
Molecular testing and prenatal diagnosis

IV) Management course doctors and nurses
(Doctors of district hospitals, DEIC centers, transfusion daycare centers, others)
(Nurses of district hospitals, DEIC centers, transfusion daycare centers, others)
Genetics of hemoglobinopathies
Disease spectrum
Diagnosis
Management principles and guidelines (emphasis on blood transfusion and iron chelation)
Blood banking practises
Management monitoring
Monitoring for iron overload and its complications
Referral for complications e.g. allo immunization, cardiac, endocrine problems and HSCT
Guidelines for selection of patients for HSCT.
Basics of HSCT (to better guide families)

V) Blood banks

(Blood bank officers)
Upgradation of blood banks- component therapy and NAT screening.(optional)
Correct use of leuko depletion.
Follow blood bank guidelines for management of chronically transfused patients, monitor and investigate for blood transfusion reactions.
Assess and monitor chronically transfused patients
When to suspect for allo immunization?
Referral to other larger blood bank for testing and management.

Training modules:
The training programmes will be from 3-5 days for each group.
Requirements for conducting training program-
- For training a large and quiet room with adequate seating is needed. LCD projector arrangements needed, if conducted in a very large hall, may need a microphone.
- Adequate area for demonstration- tables for demonstration of tests, devices, etc.
- Power back up if high chances of power failure.
- Group photo and certificates of attendance

These programmes will be needed baseline and refresher courses annually in the initial phases to ensure understanding of the programme and compliance.

Training programme curriculum is prepared and will be circulated.
Each training module will have-
1) Lectures and discussion
2) Skill demonstration- hands on for the lab tests, visit to clinic or daycare center or blood bank as needed for group.Field visits for field team for real life training on organization and conducting of camps.
3) Counseling skills will be developed by role play

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8. Budget

The programme is to be implemented in convergence with existing programmes for child health mainly the RBSK in coordination with Blood Banks under Blood Cell. The facilities and services provided at DEIC and by the Mobile Health Team under RBSK are utilized. The budget.

**Budgetary estimates are provided under the following heads**

1. Establishment cost: for setting up screening and management facilities at DEIC Lab, clinic and office Equipment.
2. Consumables: Reagents, kits and drugs for screening (primary level (adolescents), secondary level (pregnant women), antenatal with PND, severe anemic children for Thalassemia disease, newborn screening for SCD) and for management of patients registered with DEIC
3. Hematopoietic Stem Cell Transplant
4. Human Resourcecost for additional HR Proposed to strengthen DEIC and RBSK cell State HQ
5. Mobility

For IEC activities and training states are expected to submit budgetary proposals as per established norms assessing the need on the basis of guidelines

8.1. Establishment cost: Laboratory equipments, office equipment, and up gradation of DEICs

<table>
<thead>
<tr>
<th>S. No</th>
<th>Budget Head</th>
<th>Description / purpose of equipment</th>
<th>Unit cost (in Rs.)</th>
<th>Quantity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Binocular Microscope</td>
<td>For examination of peripheral blood film</td>
<td>40,000.00</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>Digital Hemoglobinometer (optional)</td>
<td>For determining Hb in finger prick samples</td>
<td>30,000.00</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>Automated 3 part Blood Cell Counter</td>
<td></td>
<td>5,000,000.00</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>Fully automated five part hematology analyzer</td>
<td>3 part differential automated blood cell counter for complete blood counts of samples for anemia and thalassemia or hemoglobinopathies,</td>
<td>10,000,000.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td><strong>ELISA Reader with washer</strong></td>
<td><strong>For ferritin estimation</strong></td>
<td>3,00,000.00</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6.</td>
<td>Hemoglobin HPLC Equipment</td>
<td>Equipment capable of loading a minimum of 10 test at one for Hb fraction estimation - HbA0,HbA1c, Hbf, HbA2 and common Hb for analysis of samples for thalassemia and hemoglobinopathies</td>
<td>15,00,000.00</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7.</td>
<td>Hemoglobin HPLC equipment for Newborn Screening*</td>
<td>HPLC equipment that can process Dried Blood Samples for separation of Hb fractions to enable diagnosis of Sickle Cell Syndromes and Hb D, HbE and HPFH syndromes and traits</td>
<td>40,00,000.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8.</td>
<td>Capillary electrophoresis system</td>
<td>To detect different variant hemoglobins including the rare ones</td>
<td>3700000.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9.</td>
<td>Refrigerator</td>
<td>180-310 L Domestic 1 for storage of samples , reagents in use kits, 1 for stock kits and reagents</td>
<td>20000.00</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10.</td>
<td>Incubator</td>
<td>For conduction of DCIP tests ( Portable incubator may be required for outreach settings such as schools and AWCS</td>
<td>10000.00</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11.</td>
<td>Laboratory centrifuge</td>
<td>For separation of serum , plasma</td>
<td>20000.00</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12.</td>
<td>Rotor sample mixer</td>
<td>For mixing samples</td>
<td>20000</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13.</td>
<td>Syringe Needle destroyer</td>
<td>100 to 1000ul- 2 and 5 to 20ul-2</td>
<td>3000.00</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
8.2 Budget estimates for reagents and consumables for screening and management of patients registered with DEICs for care.

The cost of screening is calculated as cost per individual by calculating cost of initial screening test per person, that is done in the entire target population. Subsequent diagnostic test is done only in those with positive screening test and confirmatory test is done only in those with a positive diagnostic test. The total costs of screening, diagnostic and confirmatory tests are averaged against the total number comprising the target population to estimate screening cost per person.
(For budgeting, the target population is to be estimated).

<table>
<thead>
<tr>
<th>S. No</th>
<th>Budget Head</th>
<th>Details of costing</th>
<th>Unit of measure</th>
<th>Unit cost in Rs.</th>
<th>Quantity/target</th>
<th>Budget in lakhs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Primary level Hemoglobinopathies carrier screening</td>
<td>For estimation purposes the cost is calculated for a target population of 100000 where about 25% population is anemic and 15% show a positive NESTROFT and 1% carrier prevalence rate</td>
<td>Screening cost/person</td>
<td>((a+b+e+f+g+h)/100000)</td>
<td>97.25</td>
<td>100000</td>
</tr>
<tr>
<td>1.a</td>
<td>Hemoglobin cuvettes for digital hemoglobinometer (with disposable lancet and swab)</td>
<td>Estimated cost/test=Rs.25.00 No.of tests= Total target population +25% (Mild &amp; Mod anemia) in follow up =125000 tests</td>
<td>cost/test</td>
<td>31.25</td>
<td>125000</td>
<td>31.25</td>
</tr>
<tr>
<td>1.b</td>
<td>Reagents for NESTROFT (NaCl, Na2HPO4, NaH2PO4, deionized water and tubes)</td>
<td>Estimated cost/test = Rs.3.00 No.of tests=Total target population =100000 tests</td>
<td>cost/test</td>
<td>3.00</td>
<td>100000</td>
<td>3.0</td>
</tr>
<tr>
<td>1.c</td>
<td>Reagents for Solubility test for HbS(KH2PO4, K2HPO4, Sodium dithionite, saponin and tubes)</td>
<td>estimated cost/test = Rs.3.00* No. of tests=Total target population =100000 tests [*The cost has not been added in calculating screening cost/person. Can be added in regions where the test is used]</td>
<td>Cost/test</td>
<td>2.00</td>
<td>100000</td>
<td>3.0</td>
</tr>
<tr>
<td>1.d</td>
<td>Reagents for DCIP test for HbE(DCIP, EDTA, TrisHCl, saponin and tube)</td>
<td>Estimated cost/test = Rs.3.00* No. of tests=Total target population =100000 tests [*The cost has not been added in calculating screening cost/person. Can be added in regions where the test is used]</td>
<td>cost/test</td>
<td>2.50</td>
<td>100000</td>
<td>3.0</td>
</tr>
<tr>
<td>1.e</td>
<td>Blood Cell Counter Reagent for CBC</td>
<td>Estimated cost/test= Rs.30.00. No.of tests=15000 tests (15% of screened population)</td>
<td>cost/test</td>
<td>30.00</td>
<td>15000</td>
<td>4.50</td>
</tr>
<tr>
<td>1.f</td>
<td>Reagent for S. Ferritin by ELISA (Microwell ELISA kit)</td>
<td>Estimated cost/test= Rs.110.00. No.of tests=10000 tests (10% of screened population)</td>
<td>cost/test</td>
<td>110.00</td>
<td>10000</td>
<td>11.00</td>
</tr>
</tbody>
</table>

-100-
<table>
<thead>
<tr>
<th></th>
<th>Reagent for Hb HPLC</th>
<th>Estimated cost/test= Rs.250.00. No. of tests=15100 (15% of screened population)</th>
<th>cost/test</th>
<th>250.00</th>
<th>15000</th>
<th>37.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.g</td>
<td>Genetic test for mutation</td>
<td>Estimated cost /test= Rs.2000/test. For 1000 carriers</td>
<td>cost/test</td>
<td>2000.00</td>
<td>2000</td>
<td>20.00</td>
</tr>
<tr>
<td>2.</td>
<td>Secondary level screening for hemoglobinopathies(pre-natal, pre-conceptual and antenatal)</td>
<td>For estimation purpose cost of Screening at secondary level is Estimated for 2000 pregnant women/ lakh population/ year</td>
<td>Screeniing cost / person</td>
<td>(a+b+c+d)/100000=104.5</td>
<td>2000</td>
<td>2.09</td>
</tr>
<tr>
<td>2.a</td>
<td>Screening test (CBC+3 tube tests+(Syringe+EDTA vial+Tip+microcentrifuge tube)</td>
<td>Estimated cost/test= ( Rs. 30 +3.0+3.0+3.0+5)Rs.44.00. No. of tests=2000 tests (total target population)</td>
<td>Cost/person</td>
<td>44.00</td>
<td>2000</td>
<td>0.88</td>
</tr>
<tr>
<td>2.b</td>
<td>Reagent for Hb HPLC</td>
<td>Estimated cost/test= Rs.250.00. No. of tests=300 tests (15% of screened population)</td>
<td>Cost/test/person</td>
<td>250.00</td>
<td>300</td>
<td>0.75</td>
</tr>
<tr>
<td>2.c</td>
<td>Reagent for S. Ferritin by ELISA (Microwell ELISA kit)</td>
<td>Estimated cost/test= Rs.110.00. No. of tests=200 tests (10% of screened population)</td>
<td>cost/test</td>
<td>110.00</td>
<td>200</td>
<td>0.22</td>
</tr>
<tr>
<td>2.d</td>
<td>Genetic test for mutation</td>
<td>Estimated cost /test= Rs.2000/test No. of tests=20 tests(1% of target population)</td>
<td>cost/test</td>
<td>2000.00</td>
<td>10</td>
<td>0.20</td>
</tr>
<tr>
<td>3.</td>
<td>Antenatal screening with Prenatal Diagnosis</td>
<td>Screening cost is estimated for 20 couples - 1% of target population of 2000 pregnant women and their husbands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.a</td>
<td>Screening of pregnant women</td>
<td>Estimated cost / pregnant woman as per above (2)=104.5 No. of tests=2000 tests (total target population)</td>
<td>Cost/woman</td>
<td>104.5</td>
<td>20</td>
<td>0.0209</td>
</tr>
<tr>
<td>3.</td>
<td>Screening of husbands of pregnant women with (CBC+HPLC)</td>
<td>Estimated cost/test= ( Rs. 30 +Rs.250) Rs.280.00. No. of tests=20 tests (1% of screened population)</td>
<td>Cost/husband</td>
<td>280.00</td>
<td>20</td>
<td>0.056</td>
</tr>
</tbody>
</table>
### 3.b Referral for Prenatal diagnosis test to tertiary centres

<table>
<thead>
<tr>
<th>Estimated cost/couple= Rs. 4000 + cost of transport @Rs1000.00</th>
<th>=5000</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of PND tests=1test (1% )</td>
<td>Cost/ couple</td>
</tr>
</tbody>
</table>

### 4. Newborn screening for hemoglobinopathies

| Cost of screening of 2000 newborns ( expected births in a year/ lakh population) for a population with estimated carrier prevalence of 10% | Screeni ng cost/ newborn | (4a+4b+4c)/20000 | 2000 | 3.50 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 4.a Newborn DBS sample card

| Estimated cost /card=Rs. 10(cards made from Whatman Filter paper No.3) No. of cards= 2000 (total target population) | Cost / card | 10.00 | 2000 | 0.20 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 4.b Reagents for HPLC of newborn DBS sample

| Estimated cost/test= Rs. 150 No. of tests=2000 tests (Total screened population) | Cost / newborn | 150.00 | 2000 | 3.0 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 4.c Reagents for Hb HPLC of venous sample at 6 mths- 1 year age

| Estimated cost/test= Rs.250.00. No. of tests=200 tests (10% of screened population) | Cost / test | 250.00 | 200 | 0.50 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 5. Screening of children with severe anemia for Thalassemia disease

| Cost estimated for 1000 children with severe anemia referred to DEIC/ year | Screeni ng cost / child | (a+b+c)/1000= 175.00 | 1000 | 1.75 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 5.1 Blood Cell Counter Reagent for CBC

| Estimated cost/test= Rs.30.00. No. of tests=1000 tests ( total target population) | cost / test | 30.00 | 1000 | 0.30 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 5.2 Reagent for S. Ferritin by ELISA ( Microwell ELISA kit)

| Estimated cost/test= Rs.110.00. No. of tests=1000 tests (total target population) | cost / test | 220.00 | 1000 | 1.10 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 5.3 Reagent for Hb HPLC

| Estimated cost/test= Rs.250.00. No. of tests=100 tests ( expecting up to10% of screened population to show increased ferritin) | Cost / test | 250.00 | 100 | 0.25 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 5.4 Genetic test for mutation

| Estimated cost /test= Rs.2000/test. No. of tests=10 tests (1% of target population) | cost /test | 2000.00 | 10 | 0.20 |
|--------------|--------|
| No. of PND tests=1test (1% ) | Cost/ couple | 5000.00 | 10 | 0.05 |

### 6.0 Lab glassware and plasticware

<p>| Test tubes, slides, beakers, racks, flasks, funnels etc | Cost/DE IC/ year | 5000 |   |   |</p>
<table>
<thead>
<tr>
<th>S. No</th>
<th>Item/ procedure</th>
<th>Cost in Rs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bone marrow transplant procedure</td>
<td>1400000.00</td>
</tr>
<tr>
<td>1.1</td>
<td>HSCT isolation Room for 4 -6 weeks</td>
<td>120000</td>
</tr>
<tr>
<td>1.2</td>
<td>Drugs (Antimicrobial, anti fungals, growth factors etc.)</td>
<td>2,80000.00</td>
</tr>
<tr>
<td>1.3</td>
<td>Blood and Components (stem cell collection, Packed cells, platelet concentrates etc.)</td>
<td>175000.00</td>
</tr>
<tr>
<td>1.44</td>
<td>Investigations (HLA Typing, Pre transplant work up, virology surveillance, chimerism, Blood counts, microbiology Cultures, LFTs, Electrolytes, cyclosporine monitoring, radiology, Cross Match Drugs assays)</td>
<td>2,75,000.00</td>
</tr>
<tr>
<td>1.5</td>
<td>Disposables (syringes, three way, Leukocyte filters, TPN Bags, Hickman Catheter)</td>
<td>150000.00</td>
</tr>
<tr>
<td>1.6</td>
<td>Immunosuppressive drugs</td>
<td>1,50000.00</td>
</tr>
<tr>
<td>1.7</td>
<td>Total Parental Nutrition/ nutritional supplement</td>
<td>50000.00</td>
</tr>
<tr>
<td>1.8</td>
<td>Misc costs- (other drugs, special investigations, therapy for complications etc)</td>
<td>200000.00</td>
</tr>
</tbody>
</table>
Note: These figures are approximate and depend on:
1. The disease
2. The age and weight of the patient
3. The post transplant complications
4. An uncomplicated transplant in a 12 kg child may cost Rs. 9-10 Lakhs while serious complications (infections, VOD or graft versus host disease) after transplant can increase the cost to as much as Rs. 25 Lakhs or more, mainly because of costs related to prolonged hospitalization, additional immunosuppressive drugs (ATG/ALG), antibiotics, transfusions and parenteral nutrition.
5. Unutilized funds will be returned to the funding agency.

Under the CGHS no costing has yet been done with the reimbursement being made as per expenditure bills individual cases with verification from enlisted centres. The above mentioned costs are approximate and are provided as guideline for verification of bills by appropriate authority.
## 8.4 Budget estimates for additional proposed staff

<table>
<thead>
<tr>
<th>Professionals</th>
<th>Nos.</th>
<th>Brief job profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Expert (Lab services) (Optional) (at National level @Rs. 125000.00 / mth (negotiable)</td>
<td>1</td>
<td>A Pathologist with appropriate experience is required for capacity building of laboratory and screening services of the RBSK units of the states for implementation of the hemoglobinopathies programme and coordination, evaluation and analysis of all data at national level including maintenance of the registry. For details refer to TOR</td>
</tr>
<tr>
<td>Technical Consultant (RBSK lab services)* (State HQ) @ Rs. 90000-100000.00 / month (*The responsibility can be entrusted to other technical consultants such as India Newborn Action Plan Consultant or Child Health Consultant or Adolescent Health (RKSK) consultant at State level with appropriate qualifications, experience and training)</td>
<td>1</td>
<td>Required for a maximum period of 3 years to provide technical support to Regional and DEIC labs and co ordinate with the State HQ to develop capacity. Can be deputed from the State Medical College or any other Medical College or a term appointment for 3 years as per TOR. For details refer to TOR</td>
</tr>
<tr>
<td>IEC Co-ordinator (State HQ Blood cell-NHM) @ Rs. 42000.00/ month</td>
<td>1</td>
<td>The post is proposed for a period of 3 years (which may be extended further) in States undertaking Hemoglobinopathies programme with Adolescent Carrier Screening programme for running an intensive event based campaign. The success of Adolescent carrier screening is dependent on a highly effective IEC. For qualifications and detailed job responsibilities refer to annexure-TORs</td>
</tr>
<tr>
<td>Position</td>
<td>Salary</td>
<td>Details</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pathologist (Regional EIC / DEIC lab)</td>
<td>@Rs.200,000.00/month</td>
<td>Required for DEIC labs in districts with up scaled lab services for conduction and monitoring of diagnostic and screening tests and verification of test results all data generated at district level and for coordinating with State HQ for compilation of data and with tertiary referral labs. For qualifications and detailed job responsibilities refer to annexure-TORs</td>
</tr>
<tr>
<td>Field Officer cum Counselor (DEIC)</td>
<td>Rs.20000.00/month</td>
<td>Require in Districts undertaking Adolescent Hemoglobinopathies carrier screening to conduct population screening covering a population of 40000-60000 students enrolled in classes VIII of government and govt aided schools in convergence with Mobile Health Teams deployed under RBSK at bloc level. For qualifications and detailed job responsibilities refer to annexure-TORs</td>
</tr>
<tr>
<td>Field Assistant(DEIC)</td>
<td>Rs.10000.00/month</td>
<td></td>
</tr>
</tbody>
</table>

8.5 Budget estimates for mobility costs:

**Mobility budget will be required for**

1) DEIC based Field Teams to visit schools in all blocks and CHCs PHCs for screening visits not exceeding Rs. 35000/month with higher rates of 40 000 applicable in hilly districts. For distant blocks overnight stay is recommended.

2) Mobility budget should be provided for the Technical Expert for monitoring visits As per applicable norms.

3) The State IEC coordinator should be provided with mobility budget to make visits to all districts expecting field work on about 20 days / month and TA/ DA to be provided as per applicable norms.

Budget estimates for State and district level training need to be prepared as per RCH norms by the States. National level training programmes will be organized by the Centre.
ANNEXURE

TERMS OF REFERENCE OF ADDITIONAL HR PROPOSED

Job Title: Technical Expert (Laboratory services)
Place of posting: National level
Duration: 1 year contractual assignment extendable on yearly basis
As per requirements

Qualifications and Skills:
Essential:
MD (Pathology) with 10 yrs experience post MD in hematology and related genetic demonstrated by way of experience as independent consultant in
- public / private sector lab with regular hematology case load of >1000 cases/yr
OR
-teaching hospital with with a minimum of 5 publications (1st/2nd author) in pubmed indexed peer reviewed journals
OR
-self employed with demonstrated national or international level peer recognition of expertise by association with recognised - academic forums / awards/ expert recommendations / 3 or more
publications in pubmed indexed peer reviewed journals
Desirable: Experience in public health policy/ programmes associated with hemoglobinopathies or genetic disorders or birth defects including inborn errors of metabolism and inherited disorders; Experience with web based registries and databases
Proposed consolidated remuneration @ Rs.100000.00 /mth;
For candidates with added desirable experience in public health programmes of 2 yrs or more proposed remuneration @ Rs.125000.00 / month (negotiable)

Job description: Develop capacity for developing laboratory based screening services in States undertaking screening and intervention for Thalassemia, Sickle cell Anemia and other disorders such as Congenital Hypothyroidism, G6PD Deficiency and other disorders that may be added to the list under RBSK and for evaluation and analysis of countrywide collected data development and maintenance of national web based registry.

Job responsibilities:
The incumbent is expected to work in coordination with the national RBSK team and National Blood Cell and provide leadership in
-establishing DEIC labs Regional level and tertiary level labs and lab procedures
-preparing training procedures/ manuals and modules
-conducting training of personnel at State level (Technical consultants, Pathologist, Field Officers cum counselors, LTs ) for carrying out screening protocols.

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- conducting monitoring and evaluation visits and procedures and reviews
- developing and maintaining national level web based registry/database

Job Title: Technical Consultant (DEIC lab services)

Place of posting: State HQ

Duration: 1 year contractual assignment extendable to 3 years
for any further extension proposal to be made to GOI with justification by the state

Qualifications and Skills:

Essential:
MD (Pathology) with 3 yrs experience post MD preferably in hematology and clinical pathology/genetics by way of experience as independent consultant in
- public/private sector lab/teaching hospital

Desirable: experience in clinical/community genetics with relevant (1st/2nd author) publications in peer reviewed journals

Consolidated remuneration @ Rs.900000.00 /mth;

For candidates with added desirable experience proposed remuneration is @ Rs.100000.00 /month

Job description: Provision of this post has been made to provide technical expert support to States undertaking screening and intervention for Thalassemia, Sickle cell Anemia and other disorders that might be included for newborn screening such as Congenital Hypothyroidism, G6PD Deficiency and other disorders that may be added to the list under RBSK.

Job responsibilities:
In 3 years the incumbent is expected to
- help establish lab and lab procedures for regional and DEIC labs
- train personnel (Pathologist, Field Officers cum counselors, LTs and Staff Nurses and DEOs) for carrying out screening protocols.
- establish quality assurance procedures for lab services
- establish procedures for data collection, verification and compilation at all levels in the State as per provided formats

After 3 years, implementation to be done by Consultant (Child Health/INAP/Adolescent Health) at State level and Pathologists at Regional EIC and DEIC lab.

With support from a panel of designated national level experts from TRG lab services.
JOB TITLE: IEC CO-ORDINATOR

Duration: 3 years (one year extendable to 3 years as per yearly evaluation)

(State may consider further extension depending on impact evaluation of the campaign)

Place of Posting: Blood cell-NHM (State HQ),

Qualifications and Skills:

Essential:

Graduation [ BA (Sociology) /B.Sc (Biology group)/ BA (Mass Comm.)] from a recognized university;
Should have excellent communication skills both written and verbal both in Hindi and English;
Should have done a 6 months certificate course in Computer application;
Should have minimum 5 year documented or certified experience in governmental /public or registered non-profit organizations of standing of executing and running awareness campaigns aiming for voluntary community participation for example screening for thalassemia carrier status, testing for HIV infection, voluntary blood donation, family planning initiatives or any similar health related campaign where an individual from the community is motivated to voluntary participate or take actions leading to related health benefit
Desirable: Post graduate degree in Social Work / Sociology/Public Health/Mass Communication

Job Description: To improve impact of Anemia – Thalassemia programme implemented under the Project through mainly event based campaign in all districts of the State and through coordinating and monitoring activities of Field teams.

Job Responsibilities:

The incumbent will work as a member of the Blood cell based at the State Headquarter
He/She will be responsible for conducting Statewide effective event based IEC activities specifically directed to achieve three main objectives:-

- retention of thalassemia carrier status information by adolescents who are detected to be carriers of thalassemia trait during anemia- thalassemia carrier screening programme in govt and govt. aided schools so as to make use of the information in preventing births of thalssemic children in their families and community at large.
- to understand the importance of complete treatment of even mild and moderate anemia during adolescence leading to improved compliance to iron therapy in Iron Deficiency Anemia or any other therapy as per cause of anemia
- to stress upon the need of increased voluntary blood donation to fulfill the transfusion requirements of children affected with thalassemia.

The event based activities will be mainly conducted in govt and govt. aided schools where screening anemia- thalassemia carrier screening programme is being conducted.
- Reaching out to non school going adolescents and college students and young adults through innovative initiatives.

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-All of the districts in the State are to be covered with Field visits to all districts of state of about 20 days / month including outstation visits
-The IEC Field officer will responsible for monitoring and evaluation of DEIC based Field teams and for upgrading the communication skills required for the screening programme and counseling of Field Officers through on spot training and assistance
-Convergence with adolescent directed activities under RKSK and other such institutions and organizations involved in youth based activities directed towards control of thalassemia – anemia will need to be undertaken

**JOB TITLE: PATHOLOGIST, REGIONAL EIC LAB**

Place of posting: Regional EIC Lab

**Qualifications and Skills:**

Preferred- MD (Pathology) with experience in laboratory hematology in a general or specialized hematology lab of 3 years after acquiring MD degree.

**Desirable:** 2 yrs. experience post MD

As most of the disorders and tests that require skills and interpretation by a pathologist are related to hematology, training and skills in hematopathology are desired for the person heading the Regional EIC lab
A candidate with Diploma in Clinical Pathology may be recruited for the regional DEIC lab if the above mentioned requirements are not available and if required may be sent for training for in a hematology laboratory of an academic institution

**Job description:** The incumbent, to function as technical-in-charge of the Regional EIC lab that apart from carrying out all functions of a DEIC lab, functions as a referral lab for all DEIC labs in the region by:
-providing them logistic and technical support as and when required
-monitoring and ensuring proper functioning of the other District DEIC labs in the region by making at least bimonthly visits or more if and as and when required.

For other job responsibilities refer to TOR for Pathologist, DEIC lab

**JOB TITLE: PATHOLOGIST, DEIC LAB**

Place of posting: DEIC Lab

**Qualifications and Skills:**

Essential – Diploma in Clinical Pathology
Desirable: 3 yrs experience post DCP
Job Responsibilities

1. Will function as a team with Pediatrician and Medical Officer, DEIC forming medical professional support system of the DEIC and collaborate with other clinical and laboratory disciplines to determine accurate diagnosis and appropriate line of management and follow up, and timely intervention for complete prevention of disease and its sequelae in newborns and children screened for specific diseases covered under RBSK.

2. Will function as technical in-charge of all laboratory work of DEIC

   -directly conducting special tests specially peripheral smear examinations in all cases of severe anemia and other cases where diagnosis is not possible by way of given algorithms.
   -Will accompany the Field team to a minimum of 10% of screening visits to school for anemia thalassemia carrier screening and possibly all 2nd and 3rd follow up visits arranged at PHC/CHC
   -All lab reports of positive cases detected under screening for various disorders will be duly verified and signed by the Pathologist.
    - will be responsible for monitoring and training of Lab Technicians, Staff nurses for screening of newborns by Dried Blood sampling, Field Officers and Field Assistants for Anemia- Thalassemia carrier screening.

   -Verification of all datasheets and records and technical reports submitted by the DEIC and Regional EIC labs before submission to the State office.

   The State office will only compile the data received from different Districts and submit to GOI.

   -Pathologists of Regional EIC labs will regularly check and verify the data from DEIC labs in their region -Pathologists, DEIC lab will regularly coordinate with Regional EIC Lab.

3. Monitoring of budget and financial expenditure and statements prepared by DEIC manger as per guidelines obtained from the State office and keeping track with State RBSK cell and prepare PIP for the DEICs lab unit and its incorporation within the DEICs PIP.

4. Will report to CMS and coordinate with Nodal Officer (Pathologist and Pediatrician) nominated by the CMS to carry out all related administrative work
JOB TITLE: FIELD OFFICER CUM COUNSELOR (DEIC)

Place of posting: DEIC Lab

Qualifications and Skills:

Essential: MSW from a recognised institution with two year experience in health sector 6 months certificate course in Computers.

Desired experience and skills:

Should be able to carry out work independently in the field and should have good communication skills and affable disposition to carry out communication with officials, staff and community representatives and have good counseling skills and ability to deliver talks to groups/ gatherings with or without the aid of power point presentation and generate confidence among the target population. Ability to work on computer and internet with proficiency in MS Office package.

Job Responsibilities

Will be posted at a District level hospital at a District Early Intervention Centre and will be conducting screening for diseases by finger prick based blood tests in field- mostly schools and will work as a member of the entire DEIC team. Will be entirely responsible to plan, carry out and report Anemia - Thalassemia screening in schools in Class VIII students and if required out of school adolescents by mobilizing them through ASHAs and Anganwadi workers as per provided guidelines under the supervision of a Pathologist/ Pediatrician. Along with a Field Assistant (a trained lab attendant) and Staff Nurse/ ANM of Mobile Health Team will comprise a team to carry out the above work that entails:

- Preparation of detailed visit plan and screening schedule as per provided guideline
- Deliver talks to students mostly aided with power point presentation as part of counseling and informing process prior to screening and provide counseling to individual students when required. Ensure delivery of IFA tablets to anemic students by SN/ ANM and ensure compliance through motivation and monitoring during follow up visits at CHC/ PHC.
- Conduct screening tests on finger prick samples along with Field Assistant and SNs and ensure blood sample collection and their proper transport back to DEIC lab.
- Ensure that the required tests on samples delivered to the lab are conducted timely and report data is entered into datasheets to carry out follow up work in those found to be anemic and those found to be thalassemia trait carriers as per guidelines
- Maintain updated screening records in hard copy (screening formats) and soft copy and keep them coordinated with the records in the main computer in the DEIC. Provide records timely to the DEO and monitor and verify MPR before it is sent to the State.
- Maintain inventory of consumables involved in field testing, IFA tablets and IEC material (booklets, posters).

Coordinate with other Field Officers, DEIC teams, Pathologists, and State Office Blood cell NHM

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JOB TITLE: FIELD ASSISTANT (DEIC)

Place of posting: DEIC Lab

Qualifications and Skills:

**Essential:** Intermediate or equivalent examination passed from recognized institution
1 year work experience as lab attendant, ability to take blood samples

**Essential.**

Job responsibility:

As part of the DEIC based field team for anemia-thalassemia carrier screening will be required to accompany Field Officer for screening visits to field –schools, CHC/PHC.

- Will carry out lab attendant’s work at DEIC lab when not on field visit including minor tests as per guidelines.
- Will work as a team member of DEIC staff
- Will carry out specific Field Assistant duties directly under the supervision of Field Officer and Lab Technician as per directions of the Pathologist / Pediatrician
- Will be required to prepare required reagent solutions and other preparations for field visit and conduct screening tests on finger prick samples collect blood samples in those indicated and transport back to DEIC/hospital lab.

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VAICHIK ANEMIA

देश में एनीमिया व्यापक है, ये मैं मानता था,
पर खून की इतनी कमी है , मैं ये न जानता था!

एक बालिका से उसका बचपन चुरा के,
रजस्वला होते ही व्याह दिया गया,
जीवन सरिता में एक अनजाने देव को
अर्पण कर प्रवाह दिया गया।
उस कोमल कोपल से फिर कहा
तुम हमें एक वृक्ष बीज दो,
तुम सुता नहीं, सूर-सरिता हो,
हमारे कुटुंब को सींच दो,
स्वयं का नारी होना चरितार्थ करो,
हम कृत्वर्गों को कृतार्थ करो।
प्रचुर नारी नहीं, गृहलक्ष्मी नहीं,
उस अनन्मिज्ज बालक ने गम्भीर धारण किया,
हे प्रभु! ऐसा उत्पीड़न तूने किस कारण किया!

जिस रक्त की पहले ही बहुत कमी थी,
गर्भैस्थ शिशु की आँख भी उसी पर जमी थीं।
अचानक सबको ये आभास हुआ,
अन्याय ये कैसा अनायास हुआ।
जब मन पर पड़ा बोझ,
तो आरोम्भ हुई रक्त की खोज!

..............................
रक्त की खोज
सास ने कहा अपने लाल को,
रोना आता है मुझे देखकर तेरे हाल को,
माना तु इसका पति है, पर तु इस बालक का भी पिता है,
तु रक्तदान कदापि नहीं करेगा,
कमजोर पिता की कमजोर संतान होती है,
ऐसा सासत्रों में लिखा है
हमारी उम्र न हुई होती
तो मैं और तेरे बाबूजी
रक्तदान क्या जीवनदान करते
अपने रक्त से तेरे वंश में प्राण भरते
बहन बोली मैं तो खुद लाचार हूँ,
अपने घर प्रसवों के बाद, जीवन प्रयन्त बीमार हूँ।
पड़ोसी लेटा हुआ था अपने बिस्तर में आँधा,
रक्तदान के नाम से उसके दिमाग में एक सुझाव काँधा,
मुझसे तो अपने वज़न के कारण हिला भी नहीं जाता,
बहन बोली मैं तुम्हारे साथ रक्तकोश तक न जाता।
अरे बैठेड़ अपनी किस्मत आज्ञामाओ,
सुबह सवेरे पार्क चाले जाओ।
कहते हैं सभी स्वस्थ लोग वहीं होते हैं,
और दूसरों का भला करने को आत्मा होते हैं।
पार्क में दो महिलाएं गहनी पर गहन चर्चा करती हुई मिली
रक्तदान का नाम सुनते ही बंध से उछली
हम इन चक्करों में नहीं पदते,
न जाने लोग कैसी कैसी कहानियाँ हैं गढ़ते!}
हमने तो अपना नुकसान नहीं किया
जीवन में कभी रक्तदान नहीं किया!
सुना है रक्त से नई -नई बिमारियाँ होती हैं,
अरे हम गृहणणयाँ क्या रक्तदान के लिए होती हैं?
जोगिंग करते हुए भाईसाहब ने जान दिया,
आपने व्हल कैंसिनो में क्यों नहीं लिया,
अच्छी कवालिटी जैसे ऐ प्लस से लेना,
आजकल मार्केट में क्या नहीं मिलता,
बस थोड़े पैसे दे देना।
ताली योग करते हुए सजजन ने पहले ताली पीटी
फिर कहा मुझे तो है डायबिटीज़
और फिर से ताली बजाई
मानो रक्तदान की खिलाड़ी उड़ाई।
गंगेज महानुभव ने चिढ कर किया बहान
कभी तो सभी में है,
क्या कोई हमें करेगा केशदान।

कपाल भूती करते हुए अकाउंटेंट ने कहा
चार सी सी सी का कॉन्ट्रोल्यूशन!
हम तो पहले ही कर चुके हैं,
एटी सी सी में डोनेशन।

एक युवा एजीव्यूटिव ने हाथ पे लगी बैंडेड दिखाई
मैंने तो कल ही खुन दिया है,
अभी तो रिपोर्ट भी नहीं आई।

हताश हो मित्र से कहा, "मित्र खुन नहीं मिला",
"अरे उसका तो अभी आविष्कार ही नहीं हुआ
tुमने अखबार में नहीं पढ़ा"।

एक-एक कर अनेको अनेक लोग आये,
कुछ दौड़ते, कुछ चलते, और कुछ थे कुत्तों को साथ लाये,
स्वयं का स्वास्थ्य लाभ सभी का प्रयोजन था,
पर न कोई भी कर चुका कर चुका रक्त का संयोजन था!

…………………………………………

फकन्तु खोज से मिलता वो है जो हो चाहे वो गुप्त है,
आजकल नसों में तो स्वार्थ दौड़ता है, रक्त तो हो चुका तुप्त है।
शारीरिक एनिमिया का फिर भी उपचार है,
दृष्टिकोण की रक्ताल्पता से समाज लाबार है,
अफसोस! रक्त किसी कारखाने में नहीं बनता,
और शुक्र है की इसका शिल्पगृह हम सभी के पास है,
हम रक्त का स्रोत है या हमको वैचारिक एनिमिया है,
ये तो अपना अपना आभास है!

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