Supreme Court Matter
Time Bound

F No.Z.28015/103/2017-BC (NHM-I)
Government of India
Ministry of Health & Family Welfare
(NHM Division-Blood Cell)
*****

NirmanBhavan, New Delhi,
Dated the 7th August, 2018

OFFICE MEMORANDUM

Subject: Draft Policy on Haemoglobinopathies - regarding

Please find enclosed a draft Policy on Haemoglobinopathies. It is requested to kindly provide comments/inputs so as to enable Ministry to finalize the same.

It is further requested to provide the comments/inputscomments/inputsby the 20th August, 2018 positively as in a linked matter (Writ Petition (C) No. 790 of 2017 in the matter of ReepakKansal Vs Union of India)the Hon'ble Supreme Court has directed to report compliance along with inputs/comments by 30 August,2018. The same may be also be mailed to I.yaden@nic.in/vini121@gmail.com.

7/08/2018

(Dr. Manohar Agnani)
Joint Secretary (Policy)
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DRAFT

Policy For Prevention and Control of Hemoglobinopathies – Thalassemia, Sickle Cell Disease and variant Hemoglobins In India

Ministry of Health and Family Welfare

Government of India

New Delhi

2018

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I. Executive Summary

Thalassemia and Sickle cell diseases are two common genetic disorders that are chronic, life-restricting and require long and specialized treatment. They cause severe distress and financial loss to the family and are a great drain on the health resources of the country. With the fall in infant mortality rate due to control of communicable and nutritional disorders in the last decade in India, these disorders have become important causes of morbidity and mortality. It is estimated that there are almost 3.6 to 3.9 crore carriers of β-thalassemia in India, and about 10000 to 15,000 babies with β-thalassemia major are born each year and around 150000 are of patients with Thalassemia major. For sickle cell disease there are about 25, 00, 000 carriers of the gene (Hemoglobin AS), and about 1, 25,000 patients of sickle cell disease.

Recognizing the great socio-economic burden these disorders place on the family, society and the health services, and the knowledge that India has the technology, know-how and the means to adequately prevent, treat and control both thalassemia and sickle cell disease, the Government of India has formulated a policy aimed at informing and providing broad guidance on prevention and management of these disorders.

A technical committee was constituted comprising of experts and representatives of parent organizations to formulate a policy on hemoglobinopathies. The Committee members examined whether to have a separate policy for thalassemia or a common policy for hemoglobinopathies that encompasses Thalassemia and sickle cell. The committee was of the view that a common policy would be advisable as these disorders have common clinical features, arising from defects in the same gene (βglobin), may occur together and have similar management strategies. Differences in management, where they exist, will be stated. This document is based on the recommendations made by this committee.

This policy encompasses the public health goals of providing the best possible evidence - based treatment for those affected and reducing the birth of affected children through carrier screening and prenatal diagnosis. This empowers prospective parents to have normal children and reduce the burden of these disorders in future generations. There are many challenges in developing a plan for treatment and prevention of Hemoglobinopathies in India. The epidemiological data is incomplete, and the precise burden of these disorders is unknown. Treatment consists mainly of giving repeated blood transfusions, bringing with it the challenges of motivating donors to give blood, and avoiding the transmission of infections such as HIV, hepatitis B and C. The excess iron that gets into the body through the blood transfusions needs to be removed by use of the expensive chelators. Bone marrow transplantation as a curative treatment requires an HLA-matched donor, specific infrastructure and trained doctors and nurses. The physicians need

specialized training to treat the affected patients, as well as monitor and manage the complications of therapy. Treating sickle cell disease is equally challenging, especially as patients are often living in remote areas, and have poor socio-economic status. The management of pain and vaso-occlusive crises is difficult.

The policy envisages provision of services for patients with hemoglobinopathies through a hierarchical infrastructure by strengthening existing public health facilities.

The policy envisages creation of centres of excellence in states that will have advanced facilities required for comprehensive care for patients with thalassemia/sickle cell disease, including a bone marrow transplant unit and a prenatal diagnostic center. The centers of excellence will provide technical support for thalassemia in the medical colleges, tertiary care hospitals, district level health facilities and primary health centers, as well as impart training to the health professionals. The policy recommends creation of a hemoglobinopathy unit (clubbed with hemophilia for logistic purposes), in government medical colleges **/** tertiary care facilities as well as district level hospitals to carry out therapy as well as preventive activities**.** Therapy will be provided through day care. The policy also envisages capacity building through training of doctors in chelation therapy, and for monitoring and managing complications. Special care will be taken to look for complications in the liver, heart and endocrine glands and providing evidence-based treatment.

The policy recognizes that for prevention, the focus should be on creating awareness of these disorders in the community for better acceptance of carrier screening. This is recommended for all pregnant mothers, based on automated red cell counts with confirmation by HPLC analysis for Hb A2 and other hemoglobin variants. For women identified to be carriers, their husbands will be screened and in couples where both the partners are carriers, prenatal diagnosis will be offered to ensure that they have a baby unaffected with a clinically significant hemoglobinopathy. Carrier screening could also be undertaken for high school and college students., Premarital and preconception carrier screening should be instituted with appropriate genetic counseling. All subjects screened would be given a card indicating their status, whether normal, carrier or diseased through systems of colour coding. For sickle cell disease, policy recommends newborn screening to be initiated in areas of high prevalence. Those detected to have Hb SS or compound heterozygously of Hb S and β-thalassemia will be provided prophylaxis (oral penicillin or erythromycin) with immunizations, especially pneumococcal and Hib vaccine, and followed up carefully for development of any infection. The policy envisages that facilities will be provided for avoidance or early recognition and treatment of complications such as vaso-occlusive crisis (splenic or bone infarction, cerebrovascular accidents), and blood or exchange transfusions where indicated. Plans to manage pain, which is a constant and troublesome feature of sickle cell disease, will be instituted and psychological support will be provided.

An appropriate mechanism is recommended to be institutionalized at national level for policy guidance and for prevention and control of hemoglobinopathies. This will facilitate and enable periodic review and course corrections as required. A similar mechanism is also recommended to be instituted at state level based on need and disease burden for devising and oversight of implementation strategies for hemoglobinopathies in the government health facilities

In the rural areas, Asha**s** are envisaged to be trained to identify subjects with severe anemia which could be likely to be due to thalassemia major or sickle cell disease and counsel such patient to enable contact multipurpose worker (Female) for referral to the primary health centre for further testing and confirmation. The primary health centers should be equipped with equipment prescribed as per the IPHS norms to measure the hemoglobin, and red cell indices using, and carry out carrier screening of β-thalassemia based on osmotic fragility test, of sickle cell by solubility test / sickle cell test, and Hb E by DCIP (dichlorophenolindolphenol) test. The doctors will examine the patient for features of thalassemia major or sickle cell disease. In case of doubt, either the patient will be referred to the district hospital or blood will be drawn in an EDTA tube and sent to the district hospital for further testing**.** The policy envisages a system of referral from sub-centers or primary health centers, to district hospital to medical college or tertiary care hospital to the COE (center of excellence**)** including through use of digital technology such as tele consultations

The policy recommends creation of a web-based Application to be housed in the National Health Portal for providing information in simple language with translation in the common Indian languages, about the disease, its complications, their management, and the places where different facilities are available.The policy advocates a multi-stakeholder approach with partnership & participation of patients, parent support organizations academic institutions, not for profit agencies, and health care industry.

The Policy advocates for provision of medicines, including iron chelating agents, hydroxyurea, leukocyte filters and infusion pumps free of cost to the poor patients. In line with Make in India", the policy advocates for promotion of manufacture of the equipment and chemicals in India, and including through waiver of GST and custom duties to reduce cost of treatment for the affected families The policy recommends setting up of a patient registry for thalassemia and sickle cell disease to obtain information on the number of persons affected and the number of carriers to estimate patients who require various services.. The data on carrier screening performed in different regions will be collated to determine the burden of hemoglobinopathies.

The policy advocates promoting research to develop innovative treatments for thalassemia major and sickle cell disease, and devise new diagnostic methods, keeping in mind the continuously evolving technology in this field.

Public health and hospitals is a state subject these policy guidelines are meant to provide guidance to the states and they should adopt these policy guidelines or adopt with such modifications as appropriate.

II. Introduction

Hemoglobinopathies are inherited disorders of red blood cells and constitute an important cause of morbidity and mortality. They impose a heavy burden on the affected families and the health sector. Thalassemia major, sickle cell disease and Hb E are the three most important clinical syndromes among hemoglobinopathies in India.

(a) Prevalence

India has the largest number of children with Thalassemia major in the world – about 150,000. There are almost 42 million carriers of β- thalassemia trait. While an average prevalence rate of 3-4% has been established across the country, a higher frequency has been observed in certain communities, such as Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, Saraswats, Lohanas and Gaurs. An estimated 10,000 -15,000 babies with thalassemia major are born every year. Hb E is varianthemoglobin that significantly contributes to the disease burden of hemoglobinopathies, especially in West Bengal, and the North Eastern States. In certain communities in this region, the carrier frequency of Hb E is as high as 50%. However, HbE alone, whether heterozygous or homozygous form, does not cause clinically significant disease.

The prevalence of sickle cell disease is variable, with very high frequency in many tribal communities. The carrier frequency goes up to 35% in certain regions of Central, Southern and Western States. However, it is not restricted only to the tribal communities, as due to migration and inter marriages affected persons are found in most states.

(b) Disease Burden:

The severity of these disorders manifests in children of 'healthy' carrier couples, and this makes their prevention and support for management an issue of public health importance. They require lifelong blood transfusions and iron chelation treatment, with monitoring and management of disease complications. Presently, the only cure available for thalassemia major is bone marrow transplantation(BMT), which is possible in only a few patients, mainly because of non-availability of a suitable HLA matched donor. Risks of transplant include mortality and serious morbidity in some patients. These complications are higher in older patients or those who have severe disease. Sickle cell disease also requires lifelong supportive care that includes pain management, infection prophylaxis or treatment, hospitalization and blood transfusions. The cost of supportive care and management of a child with thalassemia major is estimated at Rs 100000-. 250,000 / year depending on the age and presence of complications. Cost of a BMT is estimated at Rs. 14-

15 lakhs. With more and more patients being brought under the net of care by transfusion and chelation, the requirement for blood transfusions has increased exponentially.

In India, the technology, know-how and the means to treat and control thalassemia major, sickle cell disease and hemoglobinopathies are available. Guidelines for adequate therapy for those affected, and prevention through carrier screening, genetic counseling and prenatal diagnosis, have already been prepared. A newborn screening program has been initiated for sickle cell disease in some states, with plans to extend it to other areas. This will be accompanied by provision for antibiotic prophylaxis for those having sickle cell disease (HB SS). These subjects will be given immunizations and followed up for prevention and early diagnosis and treatment of complications to forestall severe morbidity and mortality. A better future is envisioned for those affected with thalassemia major and sickle cell disease, by providing optimal treatment and ensuring birth of normal children. This document lays down the national policy on hemoglobinopathies, with special focus on thalassemia major and sickle cell disease.

III. Guiding Elements of Policy on Hemoglobinopathies:

Hemoglobinopathies are genetic disorders with Mendelian pattern of inheritance. Genes are, therefore, the primary determinants of the disease with environmental, nutritional and infectious factors playing only a limited modifying role at best. The policy framed is based on the characteristics listed below, some of which are applicable to all Mendelian disorders, while others are specific to hemoglobinopathies:

- Hemoglobinopathies are disorders with autosomal recessive inheritance and thus have equal prevalence in males and females.

- Every person carries two copies of a gene, one inherited from each parent. In autosomal recessive disorders, parents are carriers. They are individuals with only one abnormal gene, the other being normal; while in the patients both copies of the gene are abnormal.

- In a couple where both partners are carriers, there is 25% chance of having a child affected with disease in each pregnancy. A couple, where only one partner is a carrier, is not at risk of having a child with disease.

- Thalassemia major, Thalassemia intermedia, Sickle cell disease and Hb E, occurring singly or in combination, are the major clinical syndromes causing socio economic burden of - hemoglobinopathies in India.

- Management of thalassemia is difficult with lifelong blood transfusions, about 12 to 30 annually, and an adequately monitored iron chelation therapy. Bone Marrow Transplant is the only curative option available at present.

- Careful follow up is required to prevent complications in which the liver, the heart, or endocrine glands are involved.

- SCD requires lifelong management of anemia, pain and vaso-occlusive crisis. Newborn screening is recommended for sickle cell disease in the high prevalence areas, providing an opportunity for antibiotic prophylaxis to save lives and interventions that can improve survival and quality of life.

- Cost effective prevention programmes are possible, as carrier state can be detected by blood tests and prenatal diagnosis of fetus is possible in the first trimester of pregnancy.

- Community education and awareness along with carrier screening and prenatal diagnosis, with attention to cultural, ethical, legal issues are essential components of a successful prevention program. Significant reductions in birth of affected children are achieved through sustained implementation over two to four decades.

This policy on hemoglobinopathies encompasses the public health goals of prevention, to reduce their prevalence, empower prospective parents to exercise their right not to have a child with a serious genetic disorder but have a normal child, and protects the rights of an affected child to have access to optimal care.

Public health and hospitals being a state subject these policy guidelines are meant to provide guidance to the states and they should adopt these guidelines or adopt with such modifications as appropriate.

IV. Vision and Objectives

VISION:

The vision is to enable access to affordable and quality care to all patients with Thalassemia, Hb E and Sickle Cell Disease, and to lower the prevalence of hemoglobinopathies through awareness and screening programs.

OBJECTIVES

A. Provide affordable and quality care for all patients with Thalassemia major and Sickle Cell Disease including through:

1. Strengthening treatment centres in in central government institutions and States in all districts to provide access to affordable and quality services for the management of patients with Thalassemia major by regular and safe blood transfusions and iron chelation therapy; treatment for Sickle Cell Disease with penicillin prophylaxis, immunizations and hydroxyurea, monitor for early detection of any complications, and for their optimal management to prevent morbidity and mortality.

2. Setting up National/Regional Centres of Excellence as a referral and training centres for hemoglobinopathies.

3. Strengthening facilities for separation of blood components and blood storage.

4. Initiation of newborn screening for Sickle Cell Disease where required, and institute prophylactic antibiotic therapy to improve survival rates and reduce morbidity.

5. Establishing facilities for bone marrow transplants in tertiary care institutions.
6. Institution of central Hematopoietic Stem Cell donor registry, to facilitate bonemarrow transplants in those patients lacking sibling donors, in appropriately identified patients.

B. Reduce the prevalence of hemoglobinopathies through the following activities -

1. Extensive awareness and education programmes in the community, schools and colleges.

2. Inclusion of basic knowledge about genetics, inheritance and prevention of thalassemia major and sickle cell diseases in the school curriculum.

3. strengthening laboratories at the District level for facilitating and supporting screening and diagnosis of carriers, including extended family members of patients with thalassemia and sickle cell.

4. Screening for carrier status of β-thalassemia, HbS and HbE in adolescent students in schools and colleges, to empower them to make informed decisions regarding marital and reproductive choices in future.

5. Screening of pregnant women, preferably in the first trimester, for carrier status, and for those who test positive, screen their husbands and enable the at-risk couples to avail services for prenatal diagnosis to prevent the birth of an affected child.

6. Strengthening facilities for prenatal diagnosis in Medical Colleges and selected tertiary care hospitals in the State.

7. Screening of new born children for early detection of sickle cell disease and provide appropriate intervention followed up by counselling of families.

8. Cascade screening of blood relatives of those affected with thalassemia major or sickle cell disease, as well as screen subjects in high risk communities.

V. <u>Guidance for achieving stated policy objectives:</u>

1. **Key components** to achieve policy objectives:

   i. Advocacy measures
   ii. Instituting appropriate mechanism at central and state level to oversee the program, and implementation strategies
   iii. Strengthening centers for treatment of thalassemia major, sickle cell disease and hemoglobinopathy syndromes
   iv. Developing appropriate treatment protocols for for providing the services and referrals, starting from sub centre and primary health centers. to district hospital, to tertiary care facilities, to medical colleges, and centers of excellence,
   v. Registering all patients with Thalassemia and sickle cell disease at the nearest Government hospital for availing free medicines and/or blood transfusion
   vi. Ensuring equitable access to treatment to be equitable, i.e. should be equally available to all sections of the society.

vii. Generating awareness about the disease, carrier screening of pregnant women, relatives of the affected and other community members, and prenatal diagnosis of the pregnancy in high risk couples to reduce the birth of affected children,

viii. Ensuring trained manpower and equipment to carry out the planned activities.

ix. Training of staff at different levels to perform their duties, starting from laboratory tests and their interpretation, genetic counseling, prenatal diagnosis, bone marrow transplantation and medical care of those with thalassemia major and sickle cell disease and the complications of these disorders.

x.

2. Advocacy:

i. Sustained Advocacy measures to inform population of the burden of disease and to build support for making available resources for its prevention and management of haemoglobinopathies.

i. Convergence with linked ministries and departments (e.g. Ministry of Human Resource Development, Women and Child Development and Ministry of Social Justice and Empowerment, Ministry of Tribal Affairs) at the national and state level to raise awareness and garner support for the program.

ii. Engage with patient / parent's organizations and NGOs in the implementation of the national policy.

3. Institutional Mechanism at the Center and State level.

At the central level the policy advocates for institution of an appropriate mechanism for policy guidance and oversight of the implementation of initiatives/interventions for prevention and control of hemoglobinopathies. A similar an appropriate mechanism will be institutionalized at the **state level,** to supervise and oversee implementation of initiatives/interventions for hemoglobinopathies in the public health facilities - medical colleges / tertiary health centers, the district hospital and villages.

4. Information, education and awareness activities:

i. Spread appropriate knowledge about thalassemia and sickle cell disease in the community and among the health care providers.

ii. Create awareness in the schools, by adding it to the general science curriculum of school children to provide a wider understanding of genetics and blood diseases.

iii. Prepare IEC material that is easily understood, informative and useful, and translate it into various regional languages.
iv. Engage prominent spokespersons to reinforce the messages
v. Use mass media and mid-media activities to spread the information about hemoglobinopathies, e.g. electronic (television, radio etc.), and print media including hoardings in public areas and hospitals
vi. Carry out social mobilization by involving NGO /Thalassemia Societies in each state, and wherever there are no such societies, encourage the community to establish them.

5. Specific preventive strategies:

i. Inform individuals about their carrier status to empower them for reproductive and marital choices.
ii. Disseminate information about school-based screening programs and the role of testing in preventing and controlling the disease.
iii. Train staff at all levels in genetic counseling of those detected to be carriers of β-thalassemia or sickle cell gene, or who are affected with disease.
iv. Importance of antenatal screening and information about pre-natal testing facilities.
v. Encourage inclusion of Parent Organizations and other NGOs in the planning of the activities for Hemoglobinopathies

6. **Strategy for treatment of Hemoglobinopathies**

i. Provide optimal treatment through a referral hierarchical system starting from the primary health care center to the community health center, district hospital, tertiary care center, medical college to the centre of excellence including through use of digital technology
ii. Adequate trained manpower to deliver therapeutic and preventive services.
iii. Necessary equipment to for providing the listed services.
iv. Train the staff in the required skills to discharge their duties in an optimal manner.

7. **Elements of Optimal Management of thalassemia will be**

i. Adherence to best practice guidelines
ii. Adequate and safe blood supply for transfusion
iii. Monitoring and controlling iron overload

iv. Availability of iron chelating agents and other drugs
v. Monitoring the complications (liver, heart, endocrine glands)
vi. Management of complications
vii. Multidisciplinary care by physicians with training in Hemoglobinopathies, and networking with secondary and tertiary centres.
viii. Establish hemoglobinopathy/hemophilia units at district level and above, operating in a hierarchical manner to carry out the treatment and to monitor for complications by necessary laboratory and imaging studies.
ix. Provision of necessary immunizations as per the best standard of practice
x. Psychosocial support and holistic care
xi. Recognize rights of patients.

8. Elements of Optimal management for the sickle cell syndromes:

i. Neonatal screening to identify patients early and initiate infection prophylaxis (oral penicillin or erythromycin), plus immunizations including pneumococcal and Hib vaccines in addition to routine immunizations.
ii. Careful follow up to detect or diagnose complications. Aim to prevent or intervene early.
iii. Expertise in the management of day today problems, such as pain the bones etc. and complications such as vaso-occlusive crises, severe anemia, jaundice etc.
iv. Stroke control, including monitoring children with trans cranialDoppler.
v. Blood transfusions and exchange transfusions according to criteria laid down.
vi. Monitoring and management of iron overload.
vii. Education of patients/families: for early recognition of symptoms and complications.
viii. Pain management at home and in hospital.
ix. Psychosocial support and Rehabilitation.

VI. IMPLEMENTATION OF SCREENING STRATEGIES

The policy advocates for linking screening with existing state maternal health, child health and anemia programmes/interventions. This will help to greatly reduce maternal and infant mortality.

i. Prior to screening all pregnant women attending antenatal clinics and school students in Class VIII and above, provide information and educate regarding its importance.
ii. Screen for carrier status of β-thalassemia, Hb S and Hb E, based on the criteria provided in the National guidelines for Hemoglobinopathies
iii. All IEC material, reports and documents to explain the limitations of the screening tests.
iv. Nursing staff will counsel pregnant women identified to be carriers during antenatal screening.
v. Distribute different color cards and counsel individuals with heterozygous carrier state and/or asymptomatic homozygous or compound heterozygous states, or those who are normal.
vi. Distribute specific information sheets prepared for carriers and patients along with screening and diagnostic reports.
vii. Screen adolescents in schools in class VIII or above once before passing out of school and educate about Thalassemia and Sickle Cell Disease.
viii. Initiate awareness and screening programs in colleges with the help ofParent-patient organizations. Counsel the students to use the information about carrier status for making appropriate reproductive choices.
ix. Encourage pre-marital and pre-conception screening for hemoglobinopathies. However, in keeping with recommendations of international organizations like WHO and Thalassemia International Federation do not make them mandatory.
x. Screen all pregnant mothers in the antenatal clinics followed up by testing of husbands of detected carriers, and prenatal diagnosis of willing at-risk couples.

xi. Offer New Born Screening (NBS) for sickle cell diseases in the high-risk areas**.** If there is a Newborn Blood Spot (NBS)screening programme for congenital hypothyroidism in the area, establish link with it.

xii. Encourage extended family screening through counseling of families of those affected with disease, or students detected to be carriers in schools and colleges.

xiii. Maintain confidentiality of the detected carriers wherever screening for carriers is carried out. When the data is forwarded for purposes of collation the name of the affected persons to be anonymized.

xiv. Train health care providers at all levels, such as Ashas, nursing staff, laboratory technicians, district level counselors, doctors and staff of NGOs for the implementation of the control program, especially counseling of carriers and the affected, and the preventive strategies.

xv. Involve national organizations of obstetricians, pediatricians, Hematologists and related specialties in the implementation of interventions

xvi. **VII. LABORATORY TESTING FACILITIES:**

The tests to diagnose Thalassemias and Sickle Cell Disease and carrier state vary according to the age of the patient e.g. some tests are useful in adults and older children only, while some tests can be used both for newborns and adults. Standard operating protocols for proper techniques of obtaining samples for different tests, their storage and transport, testing methods and interpretation of results will be followed to ensure quality of screening and diagnostic tests.
Training to impart the necessary skills for performance, diagnosis and interpretation of various tests will be given to all the professional staff.

Regular Quality Control Exercises have to be undertaken for all investigations at every level- PHC, District hospitals, and Medical Colleges.

- Adhere to approved guidelines training and resource material for performance of various tests.
- Establish referral laboratories at state and regional levels for confirming diagnosis in ambiguous cases and conducting DNA based confirmatory genetic tests.
- These laboratories will be supported by centres of excellence.

Recommended tests and protocols for screening at Primary healthcare (Block) level, community settings (outreach locations) and at District level are listed below.

(1) Primary healthcare level (Block level- PHC and CHC)

(a)Antenatal tests:

i. Complete blood counts as per the IPHS norms a - (for Hb and RBC indices) for β-thalassemia carriers, solubility test / POC-Strip test for sickle cell carriers/ DCIP for Hb E carriers
ii. Any abnormality in the above or doubtful cases to be referred for HPLC (D10) Thalassemia screen - β-thalassemia and Sickle cell check panel V2.0 (for Hemoglobin fraction separation and quantitation) at district level
iii. HPLC (cation-exchange) for hemoglobinopathies will be provided at the district hospital.
iv. In case where the mother and the father are both identified to be carriers or doubtful cases will be referred to the tertiary care center or the medical college or the center of excellence for genetic testing of the couple and for prenatal diagnosis.

(b) Referral to the district hospitals/medical college and to the center of excellence *Screening of adolescents in schools (outreach) by the District hospital team:*

i. A Complete blood counts with cell counter with finger prick having direct capillary insertion mode (for Hb and RBC indices), solubility test / POC- strip test / DCIP as per IPHS norms
ii. Any abnormality in the above or doubtful cases will be referred for HPLC (cation-exchange) / Thal screen- β-Thalassemia and Sickle cell check panel V2.0 tests for Hemoglobinopathies at the District hospital followed by appropriate counseling
iii. Collection of samples will be preceded by an educational talk by the trained counselor available at Block level, or by the District based counselor provided under the Hemoglobinopathies program.
iv. Delivery of reports would be accompanied with a session of genetic counseling by the designated counselor.
v. Thus, pre-screening talk and post-test counseling will be mandatory.

c). *Children with severe anemia (Hb<8.0 gm/dl):*

i. Identified at the periphery will be referred to Community health center, or district hospital for CBC, serum ferritin and HPLC analysis.
ii. If mutation analysis is necessary the sample/case should be referred to the appropriate facility where molecular testing can be done.

(d). Newborn screening for Sickle Cell Disease

i. POC Rapid strip test for Sickle Cell Disease followed by confirmation by HPLC /Electrophoresis on Dried Blood Spot samples collected by heel prick. Positive samples to be transported to District lab for confirmation.

ii. If facilities for HPLC/Thal screen- β-Thalassemia and Sickle cell check panel V2.0 isavailable at District lab, then these tests should be added on to the district lab test directory.

iii. Sampling may be integrated with Newborn dried Bloodspot Screening for other disorders. Samples to be transported to District laboratory for analysis.

iv. In areas of high sickle cell prevalence isoelectric focusing, electrophoresis/POC Strip test for sickle cell to be standardized and offered as point of care tests or at the district level. These tests will reduce costs.

v. All positive screening tests in newborns to be confirmed by HPLC at the district hospital laboratory.

vi. Pre- screening and post-test counseling to be undertaken by designated counselor / staff**.**

(2) **The District hospital laboratory**:

i. This should be strengthened with required instruments and a designated computer system for storage of records and hosting online hemoglobinopathies database. These laboratory tests should be added to the Directory of Laboratory tests at the district facility.

ii. Hemoglobinopathies testing facility (HPLC and Hemoglobin electrophoresis) should be made available for monitoring and verification.

iii. All laboratory data to be stored in hard copies, as well as in provided screening laboratory computer system software format. Required anonymized data with assigned Identifiers (ID) to be uploaded on online software database periodically after verification by authorized personnel.

iv. Software to be set up to discuss difficult cases with the higher centers or refer for additional tests if not available.

v. The Lab technician, nurses, counselor and Doctors of the Daycare center will be trained to do data entry of reports.

vi. Additionally, a Pathologist will be trained for performing hematologic techniques, and pediatrician/physician for their interpretation and genetic counseling
vii. Training of 3-4 nurses to be carried out to ensure adequate staff coverage for the at least 6 bedded daycare facilities.
viii. The bed strength may be increased from six beds, depending on the needs of the District.
ix. A designated technician and a nurse and counselor to be attached to the daycare center.
x. A pathologist at District Hospital should be designated as Nodal Officer for blood bank services and hematologic tests.

(3) Referral Centre laboratories:

The laboratories at the hospitals of some districts can be selected for up-gradation to serve as Regional /Medical Colleges State level referral laboratories. Alternately the laboratories at the regional/medical college /tertiary care centers would function as referral laboratories.These laboratories should have HPLC machines, as well as the necessary equipment and staff for molecular tests, and for prenatal diagnosis.

i. The pre-natal tests will require training of Obstetricians, Geneticists and Pathologists. The lab technicians, Counselors and Nurses of these departments will also require rigorous training.
ii. Adherence to Quality Control procedures will be mandatory
iii. Linkage of Districts hospitals with Apex centres will be established
iv. Tele – medicine to be used to discuss difficult cases with the center of excellence or referred for sequencing or additional tests if not available.
v. Additionally, a pediatrician/physician/hematologist should be trained, along with training of 4-5 nurses to ensure adequate staff coverage for the 10 bedded daycare facilities.
vi. Bed strength may be further increased depending on local needs.

(4) Centers of Excellence:

These are to be identified by the State and will provide the overall supervision and co-ordination for the IEC activities and testing and treatment strategies. The Centre of Excellence may be an individual centre or collaboration between 2 centers depending on the facilities and expertise available. There should be national collaboration and even International Collaboration if

required. Funds and necessary staff should be provided to further strengthen these centers to handle the additional load of patients.

(5) Data collection and Registry of patients with Thalassemia/Sickle cell disease

The policy envisages a robust system of data collection to be entered systematically in a registry. Data will be collected both of patients - to assess treatment needs for blood and medicines etc. and carriers. Data entry should be initiated at level of Primary health center, Community health center, district level hospital or above.

VIII. Human Resources (HR):

Qualified /trained Human Resource asrequired as per the needs to carry out required functions to strengthen the Block, District, tertiary level or Centre of excellence level facilities.Existing Staff medical officers , lab technicians , staff nurses and counselors, data entry operators at Block and District Hospital available can also be utilized after training.

IX. Training of the staff at different levels :

The staff employed in the project at various levels should be trained and sensitised in the activities to be performed by them through special training programmes organized. The Center of excellence in each state or experts coopted for the purpose would train other staff in the project e.g. in medical colleges, district hospitals and primary health centers. If.Modular training with hands on training should cover the following skills:

i. Genetic counseling (for all staff)
ii. Performance of laboratory tests for carrier screening and diagnosis of hemoglobinopathies. (for laboratory technicians)
iii. Interpretation of laboratory tests and preparation of various reports(for pathologists and hematologists)
iv. Obstetrical procedures for obtaining fetal tissue like amniocentesis and chorionic villus sampling (for obstetricians, minimum 2 weeks)
v. Molecular biology techniques for identification of molecular mutations and for prenatal diagnosis (for scientists, 2 weeks).
vi. Training for treatment of patients with thalassemia major, and sickle cell disease and taking care of the various complications. (for physicians and pediatricians)
vii. Training in blood bank practices (for blood bank technician and medical officer)

viii. Training in data entry in computers (all staff)

ix. Pre and post training evaluation and periodic evaluation to maintain excellence in service.

X. TREATMENT AND MANAGEMENT:

Treatment of patients with thalassemia major and sickle cell disease will be carried out through a hierarchical system, going down form centre of excellence to tertiary care /medical college to district and the primary health center.Standard Treatment Protocols should be developed both for thalassemia major as well as sickle cell disease which can be adapted by States to suit the local conditions.

1. Centers of Excellence (COE):

Each state should have at least one COE. One state could also have multiple COEs depending upon the size of the state /load of patients, as approved by the State committee. Each COE should have or aspire to have the following resources which could be enhanced by the state Government to help them to optimally contribute towards this project.

A. Scope of activities

a. Day care thalassemia /sickle cell / hemophilia facility to provide transfusion/infusion support. Should have resources and personnel to counsel, provide and monitor chelation and adequacy of supportive care
b. Day care should actively be involved in research and maintain database of patients and carriers in the region covered by it.
c. Day care should be active and provide round the year in-house and out-reach training programs.
d. It should be directly or indirectly involved in conducting and supervising screening programs in the region that it oversees.
e. The designated COE should have active staff and facilities to maintain comprehensive data of all cases and carriers within the region they oversee.

B. Additional required infrastructure and equipment for COE:

a. A comprehensive diagnostic facility including automated hematology blood cell counters, HPLC/Electrophoresis, iron studies, molecular testing and ability to provide laboratory support for ante-natal diagnosis. The diagnostic facility should have an active QC program with both internal and external components.

b. A blood bank facility with tertiary care capacity. Should have ability to do extended blood grouping and detection and typing of allo-antibodies.
c. Facilities for providing HLA typing - at least low / intermediate resolution molecular HLA typing.
d. Center should have the capability to comprehensively evaluate and monitor cardiac and endocrine function in the patients including a MRIT2* facility. A provision for the installation of T2* MRI software will be made available at every COE across the country.
e. Trans-cranial Doppler facility should be made available at every COE to annually screen children with sickle cell anemia from 2 years to 16 years of age.
f. There should be availability of a bone marrow transplant facility with adequately trained physicians, nurses and allied health staff.
g. Required computer software and hardware along with network access should be made available.

C. Required personnel

a. A dedicated hematology department or medical / pediatric faculty with special interest in hematology.
b. Molecular Biologist and support staff.
c. Dedicated nurses and technicians.
d. Dedicated data entry operators / bio-statistician

While all COE should aspire to have all the above it is recognized that this may not be possible in every case and in this situation the alternate models of COE's can also be considered:

i. Two centers coming together to complement their facilities in such a way that between the two centers all the above stated resources are available to be considered a single COE. An arrangement must be made such that there is a single head of such a combined facility to facilitate smooth functioning.
ii. Centers arrange a MOU with other hospitals, laboratories including private entities if required for favorable, cost-effective and priority access to certain resources they may not have such as ante-natal diagnosis or a bone marrow transplant unit.

2. **Non-COE Medical Colleges (NCMC):**

All medical colleges should be actively involved in this program and their activity should be guided and monitored by the COE in their region. Each non-COE Medical college should have or aspire to have the following facilities. Resources should be enhanced / provided by the

government to help them attain these requirements. Each NCMC should actively work with the regional COE to coordinate their activities. Periodic meetings to facilitate this to be encouraged. Each NCMC should have a set of districts assigned to them in such a way that between all the NCMC in a state all the districts [are] covered.

A. Scope of activities:

b. Day care facility to provide transfusion support. Have resources and personnel to counsel and monitor chelation and adequacy of supportive care.
c. Active in-house and out-reach training programs.
d. Should be directly or indirectly involved in conducting and supervising screening programs in the region that they oversee.
e. The designated NCMC should have an active staff and facilities to maintain comprehensive data of all cases and carriers within the region they oversee. They should report this data to the regional COE

B. Required infrastructure and equipment:

a. A diagnostic facility including hematology automated counters, HPLC system and facilities for iron studies. They should also aspire to have basic molecular techniques established for diagnosis of mutations and to carry out prenatal diagnosis. The diagnostic facility should have an active QC program with both internal and external components.
b. A blood bank should have facility for extended blood grouping and antibody identification.
c. Required computer software and hardware along with network access can be shared with that available in the centers blood bank.

C. Required personnel:

a. A hematologist or a dedicated medical / pediatric faculty with special interest in Hematology if a Hematologist is not available
b. Each NCMC should have a dedicated nurse and technician
c. Each NCMC to have one date entry staff to collate the data and supply the same to the regional COE.

3. District Medical Centers /Hospitals (DMC):

Each DMC is envisaged to have the following resources:

A. *Suggested scope of activities*

a. Day care facility to provide transfusion/infusion support. Have resources and designated medical officer or nursing staff to counsel and monitor chelation and adequacy of supportive care.
b. At every DMC attention should be given to counseling extended family members of affected patients and ideally a dedicated social counselor should be available at each DMC.

B. Required infrastructure and equipment

a. A diagnostic facility including automated cell counters, HPLC and iron studies. The diagnostic facility should have an active QC program with both internal and external components.
b. A blood bank facility or a blood storage facility.

C. Required personnel

a. A designated medical officer who could be a member of the medical clinical units in a DMC (medical, pediatric or Obstetric officer). They should receive training from the regional COE before being designated.
b. Dedicated nursing staff and technician must be available for this program in every DMC.
c. Should work with data entry operator to comprehensively capture all cases and be actively involved in screening programs in the community.
d. Each DMC would be closely monitored by the NCMC, under which it comes

4. Community Health Center / Primary Health Centre (CHC / PHC):

It will be ensured that all CHC / PHC in different regions within a state and across the country provide a minimum quality of care. All patients receiving treatment at these centers should at regular intervals be monitored at the DMC / NCMC / COE. Where possible, depending on resources they should have the following:

A. Suggested scope of activities

a. Should facilitate regular blood transfusion and chelation for patients within their region.
b. Should coordinate with the DMC to organize regular community education and screening programs.

B. Required infrastructure and equipment

a. Blood storage facility or mechanism to get blood delivered from DMC
b. Diagnostic facility to generate a blood count with a basic three-part differential cell count.

C. Required personnel

a. A medical officer (SHO) who receives basic training from the DMC / NCMC / COE.
b. A nurse who receives basic training from the DMC / NCMC / COE.

5. Asha / Anganwadi workers

The policy envisages training of Anganwadis workers / Ashas to identify patients with thalassemia major or with sickle cell disease and enable their contact with multi purpose worker (F) for referral to primary health centre for further testing.

XI. Additional aspects of treatment related issues that need to be implemented:

1. **Blood products:** All blood bank to provide free blood without replacement to such patients:

    a. Standard TTI screening with Elisa based methods should be available for all units. All blood banks specially for catering to Thalassemia should aspire to have NAT testing established.
    b. Only packed cells should be used
    c. All blood banks should aspire to move towards leucodepletion at source and where this is not doneaccess should be made for leucodepletion with the use of filters at bedside.
    d. All the blood banks should screen for at least ABO and Rh (C,c,D,E,e) and Kell blood groups to help identify and characterize antibodies in case of later allo-immunization.

e. While directed donation can be considered, however, close family member directed donations should be avoided especially if an allogeneic stem cell transplant is being considered later.
f. Dedicated voluntary donors may be encouraged.

2. Chelators:

a. The conventional three chelators (Desferasirox, Desferral, Deferiprone) should be available at all treatment centers
b. For Deferasirox at least two generic brands should be made available. The choice of brand should be guided in discussion with the regional COE. In cases of intolerance alternate brands may be provided.
c. All COE's should arrange to have stock of infusion pumps available to be used at the discretion of the treating physician.
d. Attempt should be made to maintain serum ferritin level below 1000 ng/ml.

3. Hydroxyurea

a. Hydroxyurea should be available at all treatment centers.
b. At least two generic brands of capsule hydroxyurea should be available and if possible, syrup form should also be provided. The choice of the brands could be guided by the COE as per the guidelines.

4. Penicillin prophylaxis for patients with sickle cell disease

a. Oral Penicillin should be provided at all treatment centers. It should be given to all children up to 5 years of age who have sickle cell disease (Hb SS) .i.e. 125 mg twice daily for children less than 3 years of age and 250 mg in children 3 years and more in age.
b. Prophylactic penicillin can be discontinued at 5 years of age, unless the child has undergone a splenectomy or an invasive pneumococcal disease. Pneumococcal vaccination should be ensured before discontinuation of Penicillin

5. Vaccination:

a. Hepatitis B vaccination should be administered to all patients with thalassemia and sickle cell disease at diagnosis and periodically

b. Pneumococcal conjugate vaccine (PCV) andHibvaccineshould be available at all treatment centers.

6. Bone Marrow Transplantation:

a. All patients who are less than 10 years of age should be screened for HLA matched siblings (High Resolution HLA Typing).
b. This should be free of cost for the BPL patients, and considerably subsidizedfor others.
c. For patients who have a HLA matched sibling donor financial resources for BMT must be provided for BPL patients, and subsidized for the rest. Corporate organizations may be approached to provide the finances for BMT under their CSR.

d. Eeach State can draw up its own policy for the same.

XII. Management and resource requirements for patients with Thalassemia intermedia or Non-Transfusion Dependent Thalassemia (NTDT):

a. ***Blood Transfusion****:*

Unlike thalassemia major, where the level of anemia makes transfusion mandatory, thalassemia intermedia patients may not have hemoglobin levels low enough to warrant mandatory blood transfusion and regular care. However, progression of both the anemia and ineffective erythropoiesis may eventually result in serious complications. If patients are given transfusion support during growth spurt or to maintain hemoglobin, safe blood banking and transfusion guidelines as per transfusion dependent patient guidelines must be followed. A baseline red blood cell phenotype should be performed for patients, who should then be seen at a thalassemia center every three to six months.

b. ***Monitoring:***

Monitoring of growth, endocrine, bone problems including extra-medullary hematopoiesis and surveillance for gall stones, liver, cardiac disease should be carried out regularly. If required, patient should be referred to COE or NCMC for consultation.

c. ***Hydroxyurea:***

A trial of hydroxyurea with appropriate monitoring for side effects may be done to attempt to reduce the need for blood transfusions and increase the hemoglobin levels. Hydroxyurea should be used at a starting dose of 10mg/kg/day and escalate the dose according to response and toxicity to be titrated to the maximum tolerated dose.Response should be evaluated after 3-6 months and should be defined as total hemoglobin increase of >1gm/dl at 6 months. It should be initiated in consultation with experts present in NCMC or COE.

d. ***Iron Chelation:***

Iron overload can occur even if transfusions are not given in NTDT patients. Assessment of iron overload should be done in 1-2 years' interval, if the patient is not on regular blood transfusion. Iron chelation should be started when serum ferritin > 750-800 microgram/L and it should be monitored as per the guidelines

e. ***Splenectomy:***

Splenectomy is reserved for cases of massive splenomegaly with or without hypersplenism. It should generally be avoided in NTDT patients less than 5 years of age. Pre-splenectomy vaccination should be given. Patient should be referred to COE/NCMC if splenectomy is indicated.

XIII. Parent Organizations

Parent organizations play an important role in providing social and moral support to families that have children with thalassemia and sickle cell disease. In India they have a critical role in improving the lives of affected children, arranging camps for blood donations, carrier screening, evaluation and treatment of children, CMEs for improving knowledge and skills of physicians with participation of national and internationals experts, and obtaining various concessions for the affected children and families form the Government. It is hoped that under the national policy support will be provided for initiating parent associations in town and areas in states where none exist at present.

XIV. Research and International Collaboration

12.1 Research

It is expected that standard operating protocols will be prepared to be followed in the implementation of the national policy. However, in this rapidly expanding field of molecular medicine with social ramifications there will be ample scope for research for improving diagnostic tests, treatment and counseling to change health seeking behavior in a better way. Moreover, adaption of the standard procedures wouldbe required to suit the local conditions. There is more than one method of testing for various hemoglobinopathies. Research is required for finding out cheaper but robust methods of diagnosis. Therefore, the staff at each level, whether at the primary health center or in the medical college should carry out research and innovation in the tasks they perform.

12.2 International collaboration

Many countries in the West have been running successful control programs and treatment centers for hemoglobinopathies for several years.India has much to gain from their experience, so that mutual collaborations and discussions would be extremely useful for the success of the program in India. **Thalassaemia International Federation** (TIF) expertise may be used.

International cooperation and collaboration should be fostered in advancing clinical care and furthering basic and applied research in hemoglobinopathies. Issues that need coverage include health education, psychosocial needs, public health, medical care, research, program development, and development of community-based organizations

XV.Recommendations:

The following measures are recommended for implementation.

i. Constitution of appropriate mechanism at at National and state level for policy guidance and oversight,
ii. Create a web-based application for providing information about the disease and its complications, the places where specific facilities are available for the patients, and information regarding parent organizations.,
iii. The Government should make adequate resources for a s prevention and management of Hemoglobinopathies.

iv. Set up thalassemia/hemophilia units at the COE, medical colleges/tertiary care hospitals and district hospitals, with providing adequate staff and equipment. **Hemophilia and thalassemia are linked together for logisticpurposes**.

v. Initiate a patient registry for thalassemia and sickle cell disease, putting systems in place for reporting and data collection.

vi. Improve research and development for new treatments such as gene therapy / editing, new diagnostic modalities, and innovative care and support,

vii. Take measures, legislative or otherwise, for allowing duty free import of essential drugs and equipment for the care of hemoglobinopathies, exempt GST and other taxes on the medicines and equipment along with the consumables

The success of the implementation programme depends on monitoring at all stages and taking corrective measures.

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