

Establishing Initial Data and Assessing the Feasibility of a Community Collaborative to Improve  
Adherence to Essential Management in Beta-Thalassemia Patients in Pune, India

Sahil S. Kejriwal

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Reading Committee:

Kelly Edwards, Chair

Kristin Beima-Sofie

Nanibaa' Garrison

Miruna Petrescu-Prahova

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Sahil S. Kejriwal

University of Washington

**Abstract**

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Sahil S. Kejriwal

Chair of the Supervisory Committee:

Kelly Edwards

Public Health Genetics

There are several large endogamous communities in the city of Pune, India that have a high prevalence of  $\beta$ -thalassemia major, which has led to local efforts to address the medical and psychosocial burden of the disease. Essential medical management of  $\beta$ -thalassemia major includes periodic blood transfusions, iron chelation therapy, and routine tests to monitor for secondary complications. Adherence to essential medical management, is an important aspect of tertiary prevention as it can significantly reduce morbidity and mortality, and improve quality of life of affected individuals. Multidimensional and multilevel conceptualizations of adherence posit that apart from patient-related factors, adherence behavior is influenced by opportunities and constraints at various ecological levels and additional dimensions. Also, the World Health Organization posits that links between organizations across sectors is an essential health system

building block for tertiary prevention of chronic conditions. With this in mind, the overall aim of this dissertation was to establish initial data that can contribute towards the improvement of adherence to essential management through strategic cross-sector collaboration, for the thalassemia community in Pune.

Specific aims include: 1) Identifying contextual multidimensional and multilevel factors that influence adherence to essential management, 2) Determining the degree of connectivity between cross-sector stakeholder organizations that influence adherence to essential management, identifying key players in the network, and characterizing perceptions regarding interorganizational collaboration, and 3) Assessing the feasibility of using the Collective Impact approach to foster structured cross-sector collaboration to improve adherence to essential management.

Specific aim 1 was achieved through in-depth interviews with 49 patients, caregivers, and key informants. Specific aim 2 was achieved through administration of a network survey to representatives of 43 stakeholder organizations and in-depth interviews with 3 influential informants. Specific aim 3 was achieved through a guided assessment using the Collective Impact Feasibility Framework, and findings from all prior interviews and the network survey.

Deductive content analysis of interviews conducted as part of specific aim 1 revealed 150 multidimensional and multilevel opportunities and constraints that influenced adherence to essential management. While most of the findings were supported by prior studies, some of them were unique to our study since no prior studies related to thalassemia had used a multidimensional and multilevel orientation to identify adherence-influencing opportunities and constraints to all aspects of essential management. Opportunities and constraints were conceptualized as having a cascading influence, where they worked synergistically or against

each other to influence adherence to essential management; this can serve as foundational data for multifactorial interventions in the future. The findings can also be disseminated to multilevel stakeholders to inform current practice patterns, organizational protocols, and policymaking.

Social network analysis of the network surveys administered as part of specific aim 2 revealed that only a small proportion of connections existed between organizations within sectors and across sectors, indicating scope for network strengthening. Influential informant interviews revealed six barriers that might explain these findings. Encouragingly, most existing connections consisted of multiple relational ties and were therefore strong. Based on their positions within the network, seven organizations were identified that could be considered as strategic partners for network strengthening interventions.

Findings from all interviews and surveys revealed that poor adherence to essential management was a social problem of significant scale and complexity since it affected a majority of thalassemia patients, and was influenced by multidimensional and multilevel opportunities and constraints. Many of the constraints could be addressed by cross-sector collaboration, but as per findings from specific aims 1 and 2, the system was found to be broken, disconnected and fragmented. All these aspects of the problem suggest that Collective Impact is an appropriate approach to address this problem. However, readiness of the community to adopt this approach must be increased. This can be done by garnering buy-in of all influential champions, exploring collaborative-based funding models, building trust between organizations, and creating a sense of urgency around the problem. Once the community is ready to adopt the approach, findings from our study can also contribute towards the initiation phase of a Collective Impact initiative, which involves using data to make a case for change, identifying key issues and gaps, and facilitating community outreach

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## **DEDICATION**

*To all thalassemia warriors,  
without whom this work would have no meaning*

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## INTRODUCTION

$\beta$ -thalassemia major is an inherited hemoglobinopathy characterized by microcytic anemia, erythroid marrow expansion, splenomegaly, and iron accumulation in various tissues. It is caused by homozygous mutations in the HBB gene that codes for the  $\beta$  subunits of the hemoglobin tetramer; this results in low hemoglobin levels and excess alpha subunits, which cause the aforementioned clinical sequelae. In the absence of treatment, affected individuals die by the age of 3 years (Modell & Darlison, 2008). The condition has a relatively high prevalence in India, with 3-4% of the population being carriers (Colah, Italia, & Gorakshakar, 2017). Essential management of  $\beta$ -thalassemia major involves periodic blood transfusions, frequent administration of iron chelation therapy, and routine medical tests to monitor for secondary complications; adherence to essential management can significantly improve longevity and the quality of life of affected individuals. Community immersion and field interactions with numerous patients, caregivers, and key informants revealed that non-adherence to essential management was a significant issue that was hindering positive health outcomes for a majority of affected individuals and was influenced by numerous stakeholder organizations across the community, healthcare, and government sectors. The objective of this dissertation was to establish initial data to inform evidence-based interventions to improve adherence to essential management for the thalassemia community in Pune, India. An additional objective was to determine the appropriateness of using Collective Impact approach - which offers a structured, organized way of initiating and maintaining cross-sector collaboration to solve complex social problems - to improve adherence to essential management for individuals affected by  $\beta$ -thalassemia major residing in the city of Pune, India.

Given the resource-intensiveness of a Collective Impact approach, it was essential first to determine the appropriateness of using it in the context of thalassemia adherence in India. We

achieved this by determining the complexity and scale of the problem while assessing the landscape of stakeholder organizations and their connectivity. We did this using qualitative interviews and a network study to establish initial data regarding the following: 1) multi-level and multidimensional factors that influence adherence to essential management; 2) current cross-sector connectivity between stakeholder organizations that influence adherence; and 3) perceived benefits of and barriers to cross-sector collaboration.

The first chapter of this dissertation provides an overview of existing literature regarding the pathophysiology, epidemiology, and prevention and control of thalassemia in India. It also provides an overview of the literature regarding management and adherence as it pertains to  $\beta$ -thalassemia major, interorganizational collaboration, Collective Impact, and frameworks used to guide the study. The second chapter focuses on the findings of a qualitative evaluation of multidimensional and multilevel factors that influence adherence to essential management. The third chapter determines connectivity between stakeholder organizations that influence adherence, including perceived benefits and barriers to collaboration. The fourth chapter combines findings from chapters 2 and 3 to assess the feasibility of using a Collective Impact approach to foster cross-sector collaboration to improve adherence to essential management in affected individuals. The fifth chapter summarizes and synthesizes findings from chapters 2, 3, and 4 to provide evidence-based direction to the stakeholder organizations, which might help improve adherence to essential management in Pune's thalassemia community.

## **CHAPTER 1**

### **Background**

#### **1. $\beta$ -thalassemia pathology and management**

##### **a. Genetics**

$\beta$ -thalassemia major is an inherited autosomal recessive hemoglobin disorder that occurs due to mutations in the HBB gene located on the short arm of chromosome 11; it codes for the  $\beta$ -globin peptide chain of the adult hemoglobin molecule, which is a tetramer made up of two  $\alpha$ -globin and two  $\beta$ -globin peptide chains. Individuals affected by  $\beta$ -thalassemia major inherit a defective HBB allele from each of their heterozygous parents and are therefore homozygotes or compound heterozygotes. Heterozygous individuals are carriers and have the  $\beta$ -thalassemia trait but they are almost always completely asymptomatic. However, homozygous and compound heterozygous individuals are symptomatic and can be classified as  $\beta$ -thalassemia intermedia or  $\beta$ -thalassemia major depending on age of onset and clinical severity (Cao & Galanello, 2010; Olivieri, 1999)

The HBB gene shows a high degree of allelic heterogeneity; currently more than 200 different pathogenic variants have been identified that have been curated by the Center for Comparative Genomics, Murdoch University, Australia in an online database<sup>1</sup>. Additionally, a database exists that exclusively lists HBB variants that cause  $\beta$ -thalassemia major in the Indian population<sup>2</sup> (Cao & Galanello, 2010; Olivieri, 1999)

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<sup>1</sup> The Globin Gene Server: <http://lovd.bx.psu.edu/>

<sup>2</sup> ThalInd: <http://ccg.murdoch.edu.au/thalind>

## **b. Pathogenesis**

Individuals affected by  $\beta$ -thalassemia major produce very small quantities of the  $\beta$ -globin peptide or none at all depending on the specific type of mutation, and can be further sub-classified as  $\beta^1$ -thalassemia and  $\beta^0$ -thalassemia respectively (Cao & Galanello, 2010; Olivieri, 1999). Inadequate quantities of  $\beta$ -globin peptide chains lead to an imbalance between the  $\alpha$ -globin and  $\beta$ -globin peptide chains of the adult hemoglobin tetramer. The excess  $\alpha$ -globin peptide chains are not capable of forming soluble tetramers with each other, and therefore are either denatured and degraded, or precipitate within the red blood cell. This leads to ineffective erythropoiesis, hemolysis, and iron-mediated toxicity in existing red blood cells. In concert, these issues lead to severe microcytic anemia, which in turn leads to excess production of erythropoietin and splenomegaly. Microcytic anemia, excess erythropoietin and splenomegaly stimulate erythroid marrow expansion, which results in iron overload due to increased iron absorption, skeletal deformities and osteopenia (Cao & Galanello, 2010). Hence the primary clinical sequela of  $\beta$ -thalassemia major is severe microcytic anemia, which leads to excess erythropoietin, splenomegaly, erythroid marrow expansion, skeletal deformities, osteopenia, and iron overload (Olivieri, 1999).

$\beta$ -thalassemia major is always characterized by severe manifestations, but the severity differs from patient to patient due to the high degree of allelic heterogeneity and the effects of genetic modifiers. Causative genetic variants alter the expression of  $\alpha$ -globin peptide chains, which leads to varying degrees of imbalance between the  $\alpha$ -globin and  $\beta$ -globin peptide chains of the adult hemoglobin tetramer from patient to patient, making it difficult to predict severity of the disease (Cao & Galanello, 2010).

**c. Course of illness, risk factors, management, and prognosis.**

Fetal hemoglobin (HbF), which is made up of two  $\alpha$ -globin peptide chains and two  $\gamma$ -globin peptide chains, is the predominant form of hemoglobin in fetal red blood cells. A few months before birth the quantity of HbF starts reducing and the quantity of adult hemoglobin (HbA) starts increasing. Around 6 months after birth, HbF is at very low levels, and is largely replaced by HbA. At around 6 months of age, neonates affected by  $\beta$ -thalassemia major start manifesting symptoms of the disease because they do not produce enough  $\beta$ -globin peptide chains to form HbA (Olivieri, 1999). Symptoms include severe microcytic and hypochromic anemia, which is characterized by increased number of red blood cells, low mean corpuscular volume (MCV), and low mean corpuscular hemoglobin (MCH) (Cao & Galanello, 2010). Other symptoms include hepatosplenomegaly, progressive pallor, irritability, diarrhea, feeding problems, failure to thrive, and recurrent fever.

In the absence of treatment, children affected by  $\beta$ -thalassemia major usually die by 3 years of age (Modell & Darlison, 2008). However, frequent blood transfusions coupled with consistent iron chelation therapy to reduce the iron overload can greatly improve prognosis of affected individuals.

Blood transfusions alone rectifies anemia, reduces erythropoiesis and absorption of iron, and extends lifespan by around one decade, after which accumulation of iron due to frequent transfusions and excess absorption by expanded erythroid bone marrow causes severe complications and subsequent death (Cao & Galanello, 2010). Complications include progressive dysfunction of the liver, heart, and endocrine glands (Olivieri, 1999). Typical changes in the heart include dilation, hypertrophy, and myocardial fiber degeneration. These changes are sometimes further aggravated by pulmonary hypertension and myocarditis (Olivieri, 1999). Cardiac

complications are the most common cause of death in affected individuals. Iron accumulation also results in liver disease, which is often worsened due to hepatitis C viral infection acquired during blood transfusions. Iron accumulation in endocrine glands, especially the anterior pituitary, leads to issues with sexual maturation and fertility. Additionally, endocrine gland damage can also lead to an increased frequency of diabetes mellitus, pulmonary hypertension, restrictive lung disease, hypoparathyroidism, hypothyroidism, hypogonadism, osteopenia, and right ventricular dilatation (Olivieri, 1999).

Transfusion programs seek to maintain a pre-transfusion Hb level of 9.0-10.5 g/dL through a blood transfusion every 2-5 weeks. The target hemoglobin level per transfusion is 12.0g/dL and should not go beyond 14.0-15.0 g/dL, as this increases the risk for stroke (Trompeter & Cohen, 2014). Patients that undergo splenectomies require significantly (30%) less blood on average, compared to unsplenectomised patients; in fact, splenectomy might be considered in individuals that have very high blood requirements, in order to lower the requirements and consequently mitigate the chances of iron overload (Taher & Tyan, 2014). Lapses in blood safety protocols can cause several adverse events, of which non-haemolytic febrile transfusion reactions and allergic reactions are relatively common. Affected individuals who are transfused but are not given iron chelation therapy to offset iron accumulation usually die in the second decade of life (Trompeter & Cohen, 2014).

Safe blood transfusions along with consistent iron chelation therapy have greatly increased the lifespan of affected individuals to over 40 years of age by greatly reducing the incidence of multisystemic complications (Galanello & Origa, 2010). Therefore, adequate iron chelation is a key component of the treatment regime. There are currently three different chelation agents available: desferrioxamine, deferiprone, and deferasirox. These chelators have different

pharmacological properties, dosages, routes of administration, and adverse effects (J. Porter & Viprakasit, 2014).

Desferrioxamine is administered after the first 10-20 blood transfusions, in doses of 40-50 mg/kg, intravenously or subcutaneously over 12 hours, 5 to 7 times a week. Possible adverse effects include but are not limited to auditory and ocular issues, bone growth retardation, and allergies. Due to the high cost and difficulty of administration via an infusion pump or intravenously, adherence to therapy is often an issue. An international survey conducted by Ward et al. (2002) on 1573 affected individuals from ten countries - including India - reported that approximately 47% of patients missed at least one dose of desferrioxamine in the preceding month. Approximately 45% of the affected individuals from India reported administering desferrioxamine on three days or less per week, which was lower than any other country; 51% reported inaccessibility of the drug as the reason for missing a dose.

Deferiprone is usually administered after 6 years of age, orally in 75-100 mg/kg doses per day divided into 3 doses. Possible adverse effects include but are not limited to gastrointestinal issues, arthralgia, and agranulocytosis. Due to its relatively low cost and ease of administration, it is used widely in many developing countries including India. However, in high-income countries it is only used when desferrioxamine therapy is inadequate or contraindicated.

Deferasirox is administered orally as a suspension in water once daily in 20-40 mg/kg doses. Possible adverse effects include but are not limited to gastrointestinal issues, elevated creatinine, and elevated hepatic enzymes. Due to its ease of administration, once daily dosage, and low risk of adverse effects on growth and sexual development, this therapy is preferred for use in younger children, and therapy can be started as early as 2 years of age.

More recently, combination therapies that involve administration of 2 chelation agents are becoming more commonly used in individuals that do not respond adequately to monotherapies. The most widely studied and commonly used combination therapy involves desferrioxamine and deferiprone. Other combination therapies require further investigation to be considered as treatment alternatives (J. Porter & Viprakasit, 2014).

While the main goal of chelation therapy is to minimize the accumulation and maintain safe levels of iron at all times, this is quite often not the case. Thus, close monitoring of iron levels followed by necessary dose-adjustment is necessary. Serum ferritin is measured to keep track of increases and decreases in iron burden, and the effectiveness of chelation therapy. Other methods of determining status of iron overload are: biopsy and magnetic biosusceptometry for liver iron concentration monitoring, and MRI for liver and cardiac iron concentration monitoring. Adherence to the iron chelation regime is often compromised due to practical, psychosocial, or financial issues (J. Porter & Viprakasit, 2014). In cases where iron accumulation has reached toxic levels and causes heart damage, rescue and emergency therapy must be initiated, which is done by increasing the intensity of the chelation regime. However, once iron has accumulated in various tissues, it is usually irreversible despite these efforts (J. Porter & Viprakasit, 2014).

Inadequate iron chelation increases the risk for a range of different complications that results from iron accumulation including cardiac, hepatic, splenic, and endocrine issues. Additionally, frequent blood transfusions are a risk factor for various infectious diseases.

Cardiac complications in  $\beta$ -thalassemia major can be iron mediated or non-iron mediated, or a combination of both. They include: reversible myocyte failure, endothelial dysfunction, arrhythmia, pulmonary hypertension, vascular stiffness, thrombosis, and myocyte scarring (Walker & Wood, 2014). Surveillance protocols involve the use of echocardiography and cardiac

MRI. Management involves prevention through adherence to chelation therapy, and more specific interventions for each complication (Walker & Wood, 2014).

Hepatic complications usually arise due to iron accumulation or viral infection by hepatitis C and B, which increase risk for hepatocellular carcinoma. The management of liver iron overload involves surveillance using serum ferritin levels and MRI, strict adherence to chelation therapy, and more intensive therapy involving deferasirox (Brissot, 2014). Treatment for hepatitis infection varies according to genotype (Y. Aydinok, 2014).

Splenic complications can include hypersplenism or symptomatic splenomegaly. Splenectomy is usually performed to rectify these issues, and to reduce blood transfusion requirements and iron accumulation (Taher & Tyan, 2014). However, there are side effects associated with splenectomies, which include sepsis, iron overload in other organs, thromboembolic events, and pulmonary hypertension (Taher & Tyan, 2014). Recently, the frequency of splenectomies has dropped drastically due to early intervention and better management (J. Porter & Viprakasit, 2014).

$\beta$ -thalassemia major patients are at greater risk for infections due to factors related to therapeutic management or the disease itself. Infections and immune modulation can arise due to aspects of medical management such as frequent blood transfusions, poor adherence to iron chelation therapy, splenectomies, and the use of central venous catheters. In contrast, infections caused directly by  $\beta$ -thalassemia major include ineffective erythropoiesis, anemia, and hemolysis (Y. Aydinok, 2014). Implementation of strict blood safety measures, strict adherence to blood transfusion and iron chelation regimens, and timely administration of antibiotics are the key methods of preventing and managing infections (Y. Aydinok, 2014). In some cases of infection,

deferiprone therapy must be stopped and replaced with alternative chelators in order to improve recovery time (Y. Aydinok, 2014)

Endocrine-related complications due to iron accumulation include growth retardation, delayed puberty and hypogonadism, hypothyroidism, hypoparathyroidism, impaired glucose tolerance, diabetes mellitus, and adrenal insufficiency (V. Sanctis, Skordis, & Soliman, 2014). Prevention and management of these complications involves early intervention and strict adherence to blood transfusion therapy, timely administration of newer chelators such as deferasirox, correction of nutritional deficiencies, and timely administration of hormonal therapy (V. Sanctis et al., 2014)

If therapeutic interventions are administered according to clinical guidelines, with adequate psychosocial support to promote adherence, affected individuals can experience lower mortality and morbidity, and greatly improved quality of life (M. Angastiniotis, 2014).

## **2. Types of prevention and how they pertain to the control of genetic disorders in India.**

From a public health standpoint, the tripartite definition of prevention proposed by Caplan (1964) classifies prevention interventions into three categories: primary prevention, secondary prevention, and tertiary prevention. These three categories form a continuum along the prevention spectrum as they target the public health issue at varying stages of vertical development (Silverman, 2003)

Primary prevention: The goal of primary prevention is to reduce the incidence of a disease in a defined population (Silverman, 2003). With regards to the management of genetic disorders, this can be achieved through pre-conception or prenatal carrier screening followed by pre-

implantation screening, or prenatal diagnosis and subsequent selective termination of affected pregnancies.

Secondary prevention: The goal of secondary prevention is to reduce the prevalence of a disease in a given population through early intervention (Silverman, 2003). Many life-threatening genetic disorders can be identified cost-effectively at a population-level using newborn screening. Early detection of the disorder allows for early interventions, which in many cases can minimize morbidity, mortality, and improve quality of life.

Tertiary prevention: The goal of tertiary prevention is to reduce disability due to a disease (Silverman, 2003). Many genetic disorders are treatable, i.e. the symptoms can be controlled through various medical interventions, which can minimize disability, and in many instances increase lifespan.

The key public health targets for  $\beta$ -thalassemia control and burden reduction at the population level are the preconception/prenatal stage, neonatal stage, and post-onset stage. These three stages correspond to primary, secondary, and tertiary prevention respectively. The prevention interventions that correspond to these stages are detailed below with justifications regarding their suitability for  $\beta$ -thalassemia control, and socio-cultural aspects that might impede their implementation, in the Indian scenario.

#### **a. Primary Prevention: Population Wide Carrier Screening**

In the long-run, carrier screening programs have a dual benefit of reducing the incidence of  $\beta$ -thalassemia major and sparing scarce resources that would have otherwise been used for medical management. In fact, some estimates suggest that a comprehensive carrier screening

program for  $\beta$ -thalassemia would cost 1-12% of the projected ultimate annual cost of management of the condition (Alwan & Modell, 2003).

The autosomal recessive inheritance pattern of  $\beta$ -thalassemia is a key characteristic of the condition that enables carrier screening. As previously mentioned, carriers of one defective HBB allele are usually asymptomatic. However, carrier couples have a 1 in 4 chance of having a child affected by  $\beta$ -thalassemia major. Due to the high prevalence of  $\beta$ -thalassemia carriers in certain ethnicities, extensive lack of awareness about carrier status, and a social predilection for endogamous relationships, there is a higher incidence of affected births in certain communities/populations (Das, 2012). Screening programs in such places have the potential to identify a large number of carriers and enable subsequent interventions to reduce the incidence of  $\beta$ -thalassemia major births, and consequently reduce incidence of the disease.

Carrier screening can be offered either before conception or during the early stages of pregnancy. There are several options available to individuals that are found to be carriers, these include: conception with a non-carrier, prenatal diagnosis followed by selective termination, preimplantation genetic screening, and donor gametes from a non-carrier. Apart from the availability of perinatal services and assisted reproductive technologies, another crucial aspect of carrier screening programs are genetic counseling services. The role of genetic counseling in carrier screening programs involves education, risk communication, informed consent, guided decision making, and psychosocial management.

Carrier screening programs are two tiered, where the first stage involves a full blood examination; if an individual has a low MCH and MCV they are candidates for confirmatory testing which involves measure HbA<sub>2</sub><sup>3</sup> levels using Hb gel electrophoresis or high-performance

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<sup>3</sup> HbA<sub>2</sub> is another adult hemoglobin tetramer that is found in low concentrations in blood

liquid chromatography. MCH and MCV together have a high sensitivity and specificity >90%, whilst measurement of HbA<sub>2</sub> is the gold standard for diagnosis (Maheshwari, Arora, & Menon, 1999). These methods have been available for many years and have been shown to be cost-effective.

Carrier screening programs often vary from region to region and are contingent upon the availability of required medical services and prevailing sociocultural and religious norms (Cousens, Gaff, Metcalfe, & Delatycki, 2010)

India is socio-culturally and genetically diverse. It has numerous endogamous communities and some cultures endorse consanguineous marriages due to their social benefits. As a result, certain genetic disorders often show a disproportionately high frequency in particular communities. For example, the Punjabi, Sindhi, Gujarati, Marwari, Gaur, and Saraswat communities have a relatively high frequency of  $\beta$ -thalassemia carriers [Agnihotri-Gupta, 2007] and have their own specific mutations in the HBB gene. There is a large body of literature that has identified the most common mutations amongst these endogamous communities; approximately 63 mutations have been identified in India so far, of which the 5 most common ones have a combined frequency amongst carriers of 80%-90% (Edison et al., 2008). Hence the molecular basis of the disease in the Indian population has been well defined (Das, 2012; Old, 2012). Regions that have large populations of individuals belonging to these communities are amenable to selective carrier screening interventions that target individuals who are at a greater risk of being carriers than the general population (Silverman, 2003)

In India, at present carrier testing and prenatal screening are offered in private healthcare settings on the recommendation of medical professionals. It is only offered to couples that are considered high-risk and is not a routine part of prenatal care in most hospitals. However, large

public and private hospitals in major cities such as New Delhi, do offer the test routinely (Agnihotri-Gupta, 2007)

Even though local primary prevention programs have been set up in major cities such as Mumbai and New Delhi, India still does not have a national primary prevention program. However, numerous statements regarding the importance of such programs have appeared in relevant journals (Petrou, 2010). Additionally, a multi-center study on controlling the incidence of  $\beta$ -thalassemia major through awareness, carrier screening, and genetic counseling has laid out a framework for developing primary prevention programs in India (Verma, Saxena, & Kohli, 2011).

- (i) Cultural and social aspects of carrier testing, prenatal diagnosis, and selective termination

Interviews conducted by Gupta (2007) suggest that being a  $\beta$ -thalassemia carrier is potentially stigmatizing and greatly reduces marriage prospects. Since the institution of marriage is an essential component of Indian society, this stigma has the potential to cause a significant amount of social harm to carriers. Further evidence of stigma was provided by Chattopadhyay's (2006) study, which showed that some of the barriers to the  $\beta$ -thalassemia prevention campaigns in West Bengal, and its underutilization, were rooted in access and awareness issues, low-risk perception, poverty, and most importantly, in Bengali cultural notions related to blood, marriage, identity, personhood, and kinship. Chattopadhyay (2006) inferred that genetic mutations are perceived as a corruption of blood, and therefore being a  $\beta$ -thalassemia carrier is perceived as impure and affects marriageability, especially for women. Hence there is a conflict between social and medical interests.

Medical decisions related to pregnancy management are usually made individually and autonomously in Western countries, however this is not the case in India (Agnihotri-Gupta, 2007). For example, in India the pregnant woman's in-laws often directly influence decision making in this regard. This often complicates matters and interferes with the couple's decisions regarding carrier testing and termination of an affected pregnancy. Additionally, the patriarchal nature of Indian society often results in blaming only the woman for carrying an affected fetus or giving birth to an affected child. Due to the low health literacy rate in India, couples often do not understand or appreciate the benefits of carrier screening, which is an additional hurdle to obtaining informed consent and executing carrier screening programs for  $\beta$ -thalassemia (Agnihotri-Gupta, 2007).

While efforts to introduce population-wide carrier screening have been marred by sociocultural issues, studies have shown that premarital screening of extended family members of an affected individual is usually acceptable because of their familiarity with the severity of the condition (Agnihotri-Gupta, 2010; Tahmankar et al., 2009).

Apart from sociocultural hurdles it is important to appreciate that India has a staggering population of approximately 1.3 billion people, of whom 70% live in rural areas with very limited access to even basic healthcare. This makes it very challenging to implement a carrier screening program amidst so many other major public health concerns such as water, sanitation, and infectious diseases.

#### **b. Secondary Prevention: Population wide newborn screening**

Newborn genetic screening is a public health intervention that is intended to identify newborns affected by treatable genetic conditions that manifest shortly after birth but are not

clinically evident during the newborn period. From a medical standpoint the main benefit of newborn screening is early detection so that early treatment interventions can be made to improve prognosis and reduce morbidity and mortality, and improve quality of life of affected individuals. Additional impacts that might be psychosocially beneficial include resolution of the diagnostic odyssey, early anticipatory guidance, and family planning options to prevent the birth of a second affected child through prenatal genetic testing. However, the main benefit of newborn screening is contingent on access to confirmatory testing, medical facilities and personnel for follow-up care (Grosse, Boyle, Kenneson, Khoury, & Wilfond, 2006).

Newborn screening panels in several high-income countries include  $\beta$ -thalassemia major. The heel prick method is used to collect small quantities of blood on Guthrie cards 5-8 days after birth. The dried blood spot card is punched for further analysis. Measurement of HbA<sub>2</sub> using high-performance liquid chromatography (HPLC) or capillary electrophoresis (CE) along with measurements of MCV and MCH are used to detect  $\beta$ -thalassemia major (Worthington, 2012)

There are many reasons that  $\beta$ -thalassemia major is a suitable condition to include on newborn screening panels in several high-income countries including the UK and USA. The prevalence of  $\beta$ -thalassemia carriers is high enough due to a large immigrant populations from Asian and African countries, and the health outcomes if left untreated are severe enough to warrant public health intervention. The onset of initial symptoms occurs at around 6 months of age, which is early and severe enough to justify newborn screening. The natural history of  $\beta$ -thalassemia major and its progression from asymptomatic to symptomatic are well understood; starting treatment before the initial onset of symptoms can greatly improve outcomes for affected individuals. As mentioned earlier there are well-established treatment guidelines for the

management of  $\beta$ -thalassemia major, which involves consistent blood transfusions, iron chelation therapy and multisystemic surveillance. Treatment facilities are widespread in high-income countries and are accessible by a majority of people. Newborn screening is cost-effective in these countries because medical management of individuals that develop complications as a result of late intervention, is more expensive than setting up a program to detect cases early at a population level so that early interventions can be made. Newborn screening programs are well integrated into the existing healthcare systems in these countries to ensure that case finding is a continuous process. The aforementioned justifications correspond to Wilson and Jungner's classical criteria for establishing the suitability of establishing newborn screening for a disease (Wilson, J.M.G., Jungner, 1968)

(i) Newborn screening in India.

Being a low-income country, India is significantly different from high-income countries with regards to its medical infrastructure, health professional capacity, health disparities and developments in the field of medical genetics. Due to inadequacies in these important factors it is possible that  $\beta$ -thalassemia major and many other genetic conditions do not fulfill the Wilson-Jungner criteria in the Indian context. Implementing a nationwide newborn screening program in India would necessitate uniform access to the screening program and to follow-up care for those that are found to be affected (Miller, 2009) not doing so has the potential to cause harm. This harm might be due to increased psychosocial distress, false hopes regarding treatment, detachment from the "screen-positive" child at a crucial stage of its development, self-medication, or the uptake of unsubstantiated alternatives to medical care, which can result in a wastage of often scarce family financial resources. Also, non-uniform access would only worsen

existing health disparities. These are legitimate concerns in India because a large majority of families are rural, socioeconomically disadvantaged<sup>4</sup> and lack health insurance (Chatterjee, 2010).

(ii) Cultural and social aspects of newborn screening

Implementing a newborn screening program for early detection of  $\beta$ -thalassemia major can have negative consequences due to Indian sociocultural factors. If a child is diagnosed with  $\beta$ -thalassemia major or any other autosomal recessive condition via newborn screening, the parents are considered obligate carriers. As mentioned previously, being identified as carrier can be stigmatizing and can have negative social consequences, especially for women, who are held responsible for producing an “acceptable” child (Agnihotri-Gupta, 2010). Another concern raised by Agnihotri-Gupta (2007) is that the uptake of newborn screening by the Indian population might be hindered due to underdeveloped policies regarding privacy and confidentiality in India, i.e. parents might avoid newborn screening out of fear that the results might be used against them in some way. Additionally, India does have legislation in place that is similar to the Genetic Information Non-Discrimination Act (GINA), which protects individuals from discrimination by employers and health insurance companies; this is called The Rights of Persons with Disabilities Act, 2016 (Gazette of India, 2016). This legislation aims to empower people with disabilities, including thalassemia through 1) respect for inherent dignity, individual autonomy, inherent differences, evolving capacities, and identity preservation; 2) non-discrimination, social inclusion, and accessibility; 3) equality of opportunity and equality between men and women. However,

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<sup>4</sup> South Asia: India. In (2012). The World Factbook. Central Intelligence Agency. Retrieved from <https://www.cia.gov/library/publications/the---world---factbook/geos/in.html>

implementation issues and general lack of awareness in India regarding rights might further contribute to rejection of newborn screening by couples in India.

**c. Tertiary Prevention – Medical and psychosocial management of  $\beta$ -thalassemia major**

$\beta$ -thalassemia major is amenable to tertiary prevention because there are established management protocols and clinical guidelines, adherence to which can greatly mitigate disability due to the condition and extend lifespan, thereby reducing morbidity and mortality, and improving quality of life of affected individuals. Holistic care for chronic genetic conditions must include interventions that span biological, psychological, and social domains. Therefore, it is important that tertiary prevention programs go beyond medical interventions and include interventions that lessen the psychosocial burden of the disease as well. These might include: 1) psychoeducational interventions to improve coping and adaptation; 2) media interventions to increase awareness and reduce discrimination/stigma, 3) social support services to assist with high medical expenses, 4) job training to increase employability, and 5) political and legislative interventions to subsidize care, improve accessibility to public services, and safeguard the rights of affected individuals and their families (Silverman, 2003).

There are 10,000-15,000 new cases of  $\beta$ -thalassemia in India every year (Das, 2012), most of whom are being sub-optimally managed (Mohanty et al., 2013). Due to poor access to medical facilities and expensive chelation drugs, most children with  $\beta$ -thalassemia in India do not receive adequate treatment. They often receive only blood transfusions without chelation, which does extend lifespan and reduces morbidity, but leads to complications caused by iron overload (Bandyopadhyay et al., 2013). Additionally, many treatment facilities experience issues related to blood safety and inadequacy (Das, 2012).

Due to the high incidence of the condition there are numerous thalassemia experts in India, most of whom have been trained via workshops and other educational programs organized by important advocacy groups. These groups have been instrumental in inviting experts in thalassemia care from abroad, and having them train local doctors in best practices (Verma et al., 2011). All these efforts have greatly increased the quality of care for affected individuals in India.

Iron chelation has become much more affordable and regimens are more closely adhered to ever since the introduction of deferiprone in 1994. The introduction of deferasirox further improved iron chelation, especially in pediatric patients (Verma et al., 2011). In fact, a number of Indian states provide free blood transfusions and iron chelation agents to affected individuals either free of cost or at a subsidized rate (Verma et al., 2011).

Due to the multi-systemic clinical sequelae of  $\beta$ -thalassemia major, healthcare professionals across all relevant disciplines are required to provide comprehensive care. While comprehensive multidisciplinary care is available in large private hospitals and centers of excellence situated in major cities (Verma et al., 2011), smaller cities and rural regions lack such facilities and have access to only conservative management methods or none at all (Bandyopadhyay et al., 2013).

(i) Socio-cultural aspects of  $\beta$ -thalassemia care

The main social issue that poses a hurdle to  $\beta$ -thalassemia care is the low average socioeconomic status and the relatively high cost of blood transfusions and chelation therapy. The GDP per capita in India as per World Bank 2013 estimates is approximately \$1500, whereas the annual cost of transfusions and chelation therapy per child ranges between \$2500 and \$4000 (Bandyopadhyay et al., 2013). Hence, this is not affordable by most affected individuals and their

families. Additionally, the high cost of treatment makes management of this condition very challenging even for the government due to India's low health budget.

While, primary prevention programs are rightly touted as being the most cost-effective long-term solutions for controlling the burden of  $\beta$ -thalassemia major at the community level, high-risk countries such as India could benefit from developing programs for secondary and tertiary prevention as well. Even though these might be initially expensive, they will become economically viable as primary prevention program will reduce the incidence of the condition. Also, they will remain essential for managing those cases that were not successfully prevented by the primary prevention program (Cowen, 2008; Silverman, 2003). Additionally, the existence of secondary and tertiary prevention programs honors individual rights to autonomy by providing alternatives that might be more suited to their personal beliefs and circumstances. The successful use of combined programs that focus on primary, secondary, and tertiary prevention can greatly reduce the burden of  $\beta$ -thalassemia major in a country. This is exemplified by the way it was dealt with in Cyprus, where 1 in 7 individuals is a carrier. Through a combination of prevention strategies that involved stakeholders across multiple sectors, the incidence of  $\beta$ -thalassemia major has dropped to virtually zero over the last 40 years (Cowen, 2008)

### **3. Adherence to essential management in individuals affected by $\beta$ -thalassemia major**

An essential aspect of tertiary prevention of chronic conditions including thalassemia is adherence to long-term treatment. As per the World Health Organization, adherence refers to “the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (Sabate, 2003). Adherence to long-term treatments has been a significant barrier to improving health outcomes of

people with chronic disease globally. A review article by Osterberg & Blaschke (2005) found that prior studies on pediatric and adult patients with chronic conditions reported similar adherence rates of approximately 50% in developed countries, which declined with age. The situation is perhaps far worse in developing countries such as India (Sabate, 2003). This is frightfully low given that science and medicine has chalked out paths to significantly improve outcomes for many of these conditions. Apart from worsening outcomes of affected individuals, adherence issues also substantially increase healthcare costs for patients and the health system (Osterberg & Blaschke, 2005; Vekeman et al., 2016). The consequences of poor adherence push families further into poverty due to the burden associated with caring for the affected individual.

For individuals affected by  $\beta$ -thalassemia major, adherence would refer to the extent to which the individual undergoes blood transfusions, administers iron chelation therapy, and undergoes routine tests as per agreed recommendations from their treating physician.

Blood transfusion therapy: Being a key aspect of essential management, any negative experiences related to adherence to blood transfusion regimes must be prioritized for intervention. Studies have shown that in India, blood safety or even the simple acquisition of blood has been an issue for many families (R. K. Agarwal et al., 2017; Bandyopadhyay et al., 2013; F. T. Shah, Sayani, Trompeter, Drasar, & Piga, 2019; Singh et al., 2003); this has the potential for dire consequences. Additionally, blood transfusion regimes have been shown to interrupt educational and social activities (Roy & Chatterjee, 2007; F. Shah, 2014). Determining additional factors in the Indian context might be very helpful in planning remedial interventions.

Iron chelation therapy: Chronic blood transfusions puts affected individuals at risk for iron overload, which can be mitigated by administering iron chelation therapy. It has been mentioned in many studies that chelation therapy is inadequate for a majority of affected patients in India

(Moirangthem & Phadke, 2018; F. T. Shah et al., 2019; N. Shah, Mishra, Chauhan, Vora, & Shah, 2010). Additionally, poor adherence to iron chelation therapy has been shown to be a predictor of psychological problems in Indian children affected by  $\beta$ -thalassemia major (Deepika Shaligram, Girimaji, & Chaturvedi, 2007) and vice versa. Identifying factors that influence adherence to iron chelation therapy can be very helpful in planning context-specific interventions to improve these and thereby reduce morbidity, mortality and the cost of complications (Delea et al., 2007).

Routine testing: Complications related to iron overload are almost inevitable and have been shown to have negative medical and psychosocial consequences for affected individuals and their caregivers (Telfer et al., 2005). Routine medical testing is an essential aspect of care for prevention, timely diagnosis and management of these complications. Unfortunately, experiences related to this aspect of essential management have not been studied in India. Ascertaining factors that influence adherence to this can form the basis for future remedial interventions.

Most past research on adherence to essential management in thalassemia patients have studied the correlation between patient-related, socioeconomic-related, and treatment-related factors and adherence to iron chelation therapy (Mostafa & Elaziz, 2014; F. Trachtenberg et al., 2011; Vosper, Evangelis, Porter, & Shah, 2018; Ward et al., 2002). These studies were conducted in countries including Turkey, Jordan, Egypt, Malaysia, UK, USA, and Taiwan; there were also two international studies (Scalone et al., 2008; Ward et al., 2002). While such studies are helpful in identifying factors that have a large influence on adherence, the quantitative methodology used would not allow for the identification of factors that have a small influence but work in concert or potentiate each other to influence adherence.

Past research that used qualitative methods were few and far between; four studies were identified that used qualitative interviews to determine factors that influence adherence. Ganzella

& Zago (2011) and Abdul Wahab et al. (2011) administered qualitative interviews and focus group discussions respectively on Brazilian and Malaysian patients to learn about their experiences with treatment, which in turn revealed factors that influenced their adherence to blood transfusion and iron chelation therapy. Atkin & Ahmad (2000) administered qualitative interviews on patients in the UK to determine factors that influenced adherence to iron chelation therapy. The only qualitative study that sought to determine factors that influence adherence across all aspects of essential management, was a study conducted by Harandi, Taghinasab, & Nayeri (2017) that administered qualitative interviews to Iranian patients.

There have been many commentaries, expert opinions, and review articles that have reported factors that influence adherence to essential management as primary findings (Berdoukas, Farmaki, Wood, & Coates, 2011; J. B. Porter, Evangelini, & El-Beshlawy, 2011; F. Shah & Kaltsounis, 2018), or incidental findings (R. K. Agarwal et al., 2017; Bansal, 2018; F. T. Shah et al., 2019). While there were similar publications from India (Moirangthem & Phadke, 2018; Palanisamy, Kosalram, & Gopichandran, 2017; Parmar et al., 2017), there was a dearth of quantitative and qualitative studies on Indian populations regarding adherence to any of the three aspects of essential management.

Taken together, there was a surprising scarcity of studies regarding factors that influenced adherence to all aspects of essential management in India or elsewhere. Also, we could not find any studies that sought to determine factors that influence adherence based on contemporary conceptualizations of adherence that go beyond patient-related factors.

Traditionally, adherence to treatment was understood very narrowly, where the onus was placed almost completely on the patient. But over the past two decades our understanding of adherence and the factors that influence it have broadened. A WHO document regarding adherence

to long-term treatments (Sabate, 2003) conceptualized adherence as a phenomenon that was determined by the interaction of 5 dimensions that include: patient-related, therapy-related, condition-related, social/economic-related, and health system/healthcare team related factors (illustrated in Figure 1). Factors in these five dimensions could exert a positive or negative influence on adherence. The framework also appreciated that many factors within these dimensions were not independent predictors of adherence but influenced it. Brief descriptions of the dimensions are as follows:

Patient-related factors: These factors have been more traditionally associated with adherence. They include resources, knowledge, attitudes, beliefs, perceptions and expectations of the patient regarding the treatment.

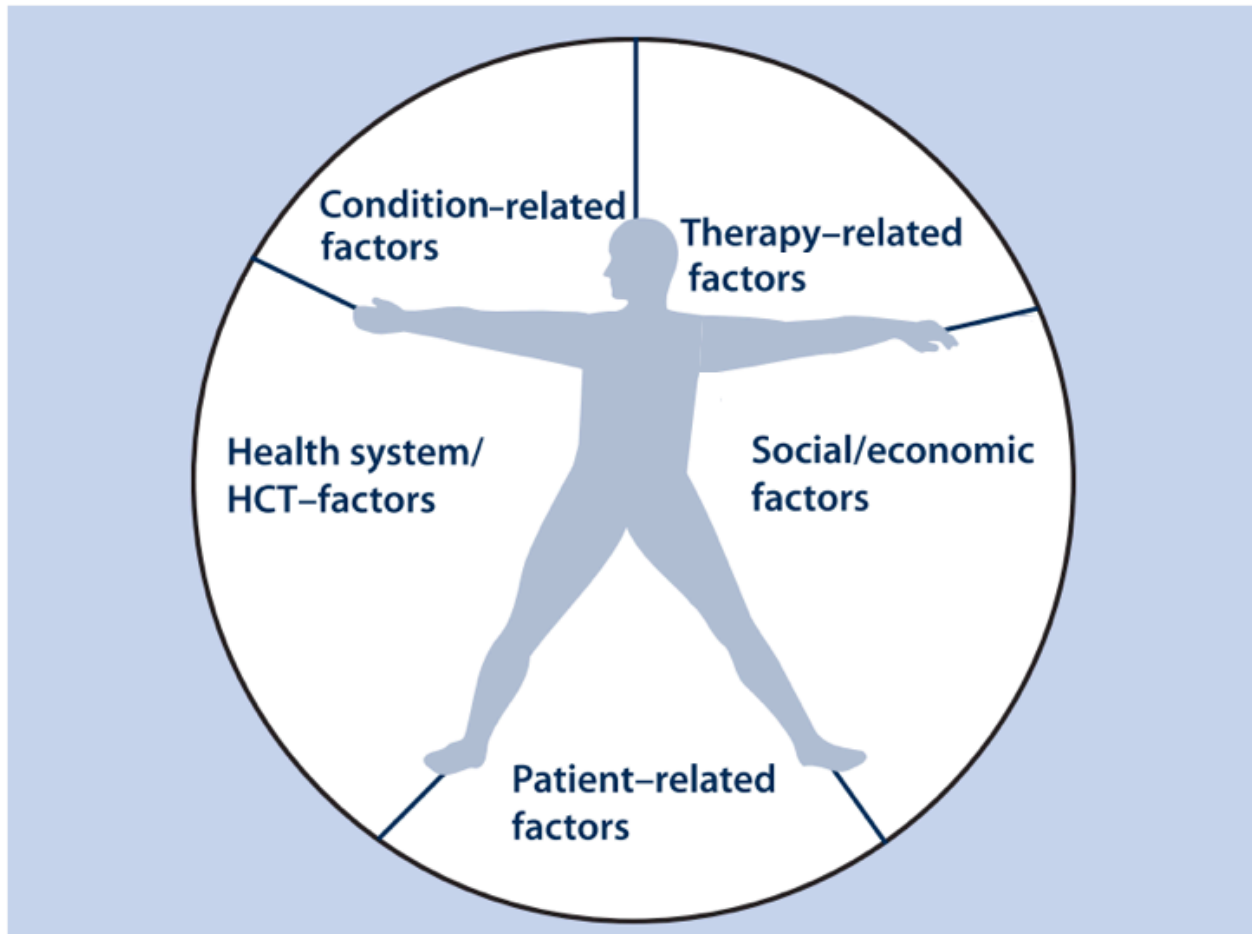
Therapy-related factors: These factors are features of the therapy that make it easy or difficult to adhere to treatment. Examples might include duration, complexity, and adverse effects of the treatment.

Condition-related factors: These factors are features of the health conditions that influence the patient's adherence. These might include disease severity, presence of disability, and psychological co-morbidities.

Social/economic-related factors: These include factors such as socioeconomic status, age, literacy, employment status, social support networks, living conditions, access to treatment facilities, and other economic and sociocultural factors that might influence a patient's ability to adhere to treatment.

Health system/healthcare team-related factors: These include but are not limited to factors such as the patient-provider relationship, provider knowledge and competence, provider

availability, availability of self-management support, quality of health services, and access to medications.

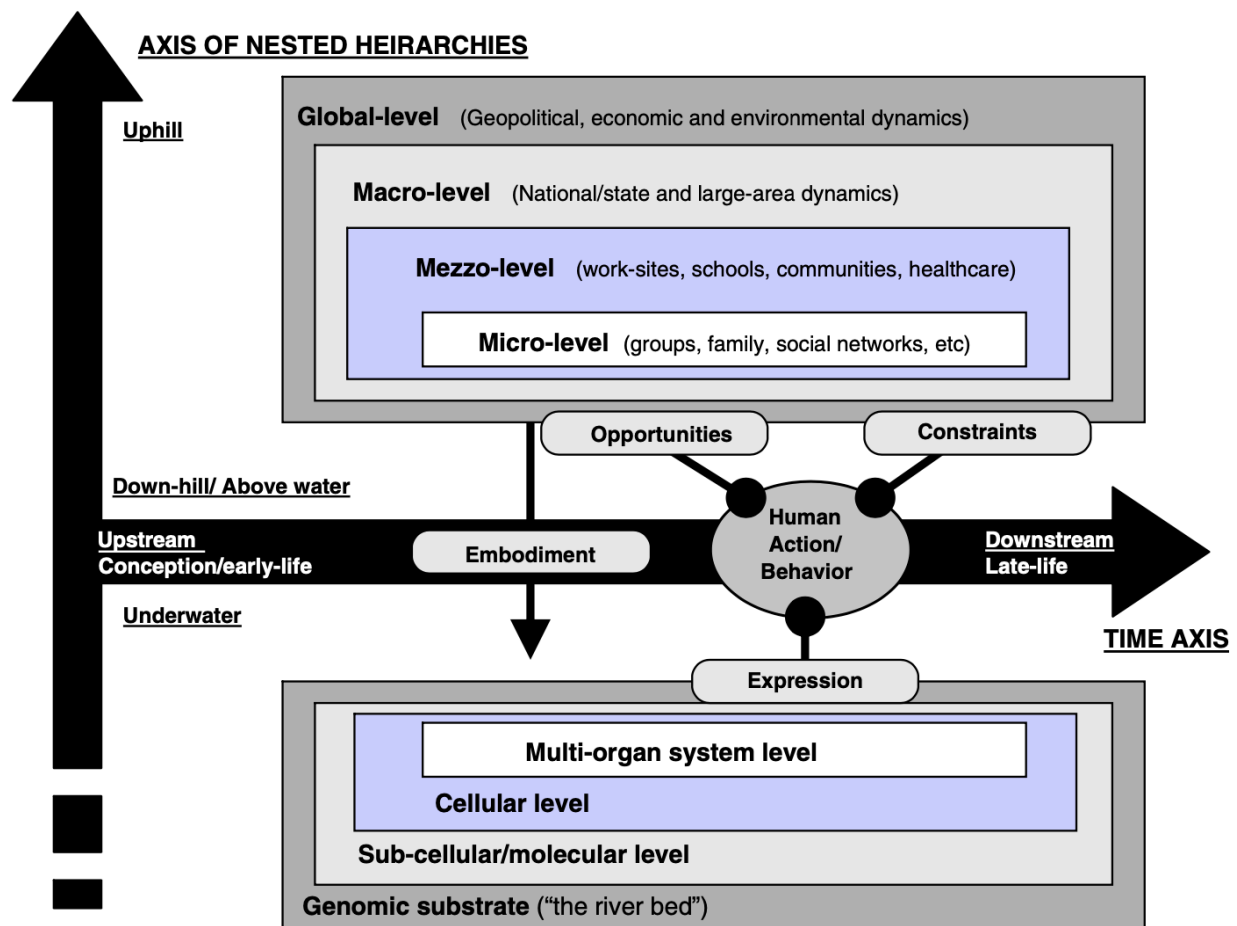


**Figure 1: WHO dimensions of adherence:** A contemporary conceptualization of adherence that includes but also goes beyond patient-related factors (Sabate, 2003)

Berben, Dobbels, Engberg, Hill, & de Geest (2012) added an ecological lens to the aforementioned framework, where they conceptualized adherence as being influenced by factors at the individual, micro, mezzo, and macro-levels. 1) Individual-level factors refer to patient characteristics, 2) micro-level factors refer to interactions between patients, healthcare teams and social support, 3) mezzo-level factors refer to characteristics of the organizations that are involved in patient care, and 4) macro-level factors refer to laws and policies that influence patients or the

health systems that services them. Hence adherence behavior can be viewed as being influenced by multidimensional factors, as illustrated in Figure 1, within a hierarchy of influence ranging from individual-level behaviors to macro-level policies.

This ecological conceptualization of adherence is also supported by the Society-Behavior-Biology nexus proposed by Glass & McAtee (2006), that has visualized environmental factors influencing health behaviors as a running stream flowing downwards from distal macro-level factors to proximate micro-level factors (illustrated in Figure 2). Macro-level factors are related to phenomena that take place at a large scale and influence many people, such as the state or national level and might include national or state policies, and cultural belief systems. Micro-level factors are related to phenomena that take place at a smaller scale and influence individuals, such as intra-personal family dynamics and social networks. There are factors that fall in between the macro and micro-levels; these mezzo-level factors are related to phenomena that take place at a medium scale and influence a large group of people, such as community and healthcare organizations. Lastly, there are also biological factors that influence health behaviors, ranging from genomes to organ-systems, that influence experiences/outcomes. The macro, mezzo, micro, and individual-levels are hierarchical levels of influence that interact with each other to impose opportunities and constraints on human behavior. Factors from different hierarchical levels influence people differently at different stages of life and determine their trajectory of development.



**Figure 2: The Society-Behavior-Biology nexus** conceptualizes human behaviors, including health promoting behaviors such as adherence, as being influenced by social and biological factors from different hierarchical levels of influence.

Based on the aforementioned conceptualizations, the etiology of factors that influence adherence might be best understood through a model that examines multidimensional constraints and opportunities across different hierarchical levels of influence, across the life-course. The WHO suggests that investigations regarding factors that influence adherence should seek to systematically explore multiple constraints across dimensions in order to inform the development of effective interventions to improve adherence (Sabate, 2003). Therefore, developing tertiary prevention interventions to improve adherence to essential management in thalassemia patients

would necessitate identification of multidimensional opportunities and constraints across ecological levels that influence adherence to blood transfusions, iron chelation, and routine testing.

The aforementioned conceptualizations also propose that healthcare system/healthcare team-related factors (Sabate, 2003) and mezzo-level factors (Glass & McAtee, 2006) i.e. those that pertain to communities, healthcare organizations, schools and workplaces, can influence adherence behavior. This suggests that organizations in the healthcare sector, community sector, and other sectors potentially play a role in promoting adherence to essential management for individuals affected by  $\beta$ -thalassemia major.

#### **4. Interorganizational collaboration**

Interorganizational partnerships have emerged as a superior and holistic approach to addressing complex public health challenges especially those that have resulted from the epidemiological transition from communicable to non-communicable diseases. The reason is that interorganizational networks can lead to more efficient use of resources, reduce redundancy in services, fill service gaps, improve communication and access to information, and allows for holistic and innovative addressing of multiple determinants of health (Huerta, Casebeer, & Vanderplaat, 2006; Karam, Brault, Van Durme, & Macq, 2018; K. Provan & Milward, 2001). While the importance of interorganizational collaboration has been appreciated for a while, traditionally research and consequent evidence-based interventions have mostly focused on issues at the level of the individual or organization rather than the network.

Interorganizational networks can be studied from different perspectives including the organizational level and the whole network level (Bergenholtz & Waldstrøm, 2011; Wasserman & Faust, 1994). As alluded to by Bergenholtz & Waldstrøm (2011) the former tends to focus on

depth of relational data whereas the latter focuses on network structure - each at the expense of the other. Bergeholtz & Waldstrøm (2011) suggested that in recent times, studies regarding interorganizational collaboration from the whole network perspective have become more common. Unlike studies done from an organizational perspective, these studies elucidate the structures and the processes of the whole network rather than those of the organizations that are part of it. With regards to chronic disease prevention, the purpose of such studies is to determine network outcomes, governance, development, or structure (K. G. Provan, Fish, & Sydow, 2007), which can help in building community capacity by strengthening community partnerships, or monitoring/evaluating network-level interventions over time (K. G. Provan, Veazie, Teufel-Shone, & Huddleston, 2004; K. Provan, Veazie, Staten, & Teufel-Shone, 2005).

Barnes, MacLean, & Cousens (2010) used network analysis to determine which organizations and sectors were dominant in a health promotion network to address childhood obesity in Canada, and the types of links between them. The reason they chose to use this approach was that while there was anecdotal evidence regarding the benefits of the network to the organizations involved and the broader community, little was known about the key organizations and the nature of links between them. They found that information sharing - rather than resource sharing or joint activities - was the predominant type of relationship between organizations; hence there was potential for further collaboration. Additionally, they found that educational organizations were central players in the network due to their links with health and social service organizations; hence they were uniquely positioned to promote healthy lifestyles amongst children in order to prevent or reduce obesity. The study findings were potentially useful to policymakers, who were interested in using network approaches to govern the provision of health and human services to address childhood obesity.

K. Provan, Harvey, & De Zapien (2005) used network analysis to track the evolution of a then recently formed collaborative in a small community along the US-Mexico border, that aimed to prevent and treat diabetes. Based on a comparison between past and current connectivity, and the predominance of relationships based on shared information rather than shared resources, joint activities, or shared referrals, they concluded that the collaborative had been slow to develop since its inception. They also found that organizations that were central players also tended to have a higher reputation; however, such an association was not found for trust or perceived benefit of being part of the network. The authors saw value in a network approach because it sought to help the community in building an effective and sustainable collaborative based on systematically generated evidence rather than one based on the general perceptions of participating organizations. Also, sharing the findings with network leaders had the potential to contribute towards evidence-based strategies to strengthen the network.

Tsai & Petrescu-Prahova (2016) used network analysis to characterize existing interorganizational and cross-sector connections, and identify central players, in order to lay the groundwork to initiate and develop a community collaborative to prevent chronic diseases amongst Chinese immigrant health workers in Seattle, USA. They found that most interorganizational links were based on information sharing, suggesting potential for further collaboration. Service oriented sectors were the only ones found to have strong interconnectedness, suggesting potential for improved connectivity amongst and between organizations in other sectors. Co-ethnic service agencies were found to be central players, suggesting that they could strongly influence the successful initiation and implementation of prevention efforts. Hence the network analysis yielded data that not only helped understand the network structure but could also potentially contribute towards strengthening it.

Yessis, Riley, Stockton, Brodovsky, & Von Sychowski (2013) used network analysis to evaluate collaborative actions to facilitate interorganizational collaboration, by a multi-year initiative that aimed to prevent obesity at a population level in Ontario, Canada. The study found that the initiative itself was possibly the most well positioned to mediate relationships between other organizations in the network. Furthermore, they found that organizations from the education sector largely had a higher probability of having a stronger relationship with other organizations. The authors also administered surveys to understand network organizations' perceived benefits of collaboration; the most being an increased ability to create change. The insights generated by this study could help in the advancement of the initiative's advocacy efforts to improve interorganizational collaboration and provide foundational data for future studies.

Kwait, Valente, & Celentano (2001) conducted a network analysis on interorganizational relationships amongst HIV/AIDS service organizations in Baltimore, USA, through which they sought to determine the extent to which organizations provided services via network links, and the roles that organizations had developed within the network. The study also helped compare the network positions of organizations that were created in response to the AIDS epidemic with those that existed prior to it. Their findings indicate that most interorganizational collaborations were based on shared information or referrals. This suggests that the organizations were using network links primarily to meet the short-term needs of their clients, rather than their long-term needs through joint programs that would require more structured coordination between them. The study also identified five organizations that held central positions in the network, most of which were created in response to the AIDS epidemic. The results of the study could provide insights regarding HIV/AIDS service delivery functioning in Baltimore that could potentially help in policymaking,

capacity building activities, and developing context-specific interventions to increase collaboration.

Recognizing that integration between family planning and HIV care services could increase their quality, access and uptake, Thomas, Reynolds, Bevc, & Tsegaye (2014) used a network approach to characterize referral links between these services in two Ethiopian cities that had a relatively high frequency of HIV/AIDS. They found that the density of the referral network was low, as a result of which women were at risk of not receiving risk-reducing holistic care. In a move towards understanding the reason for the findings and potentially strengthening the referral network, the study findings were shared with the participating organizations. Representatives from these organizations mentioned that limited interaction opportunities, high staff turnover, lack of a feedback mechanism for referrals, and interorganizational competition were barriers to referrals. Interventions to resolve these issues had the potential to strengthen the network, which could subsequently be evaluated by repeating the network study and comparing the findings longitudinally.

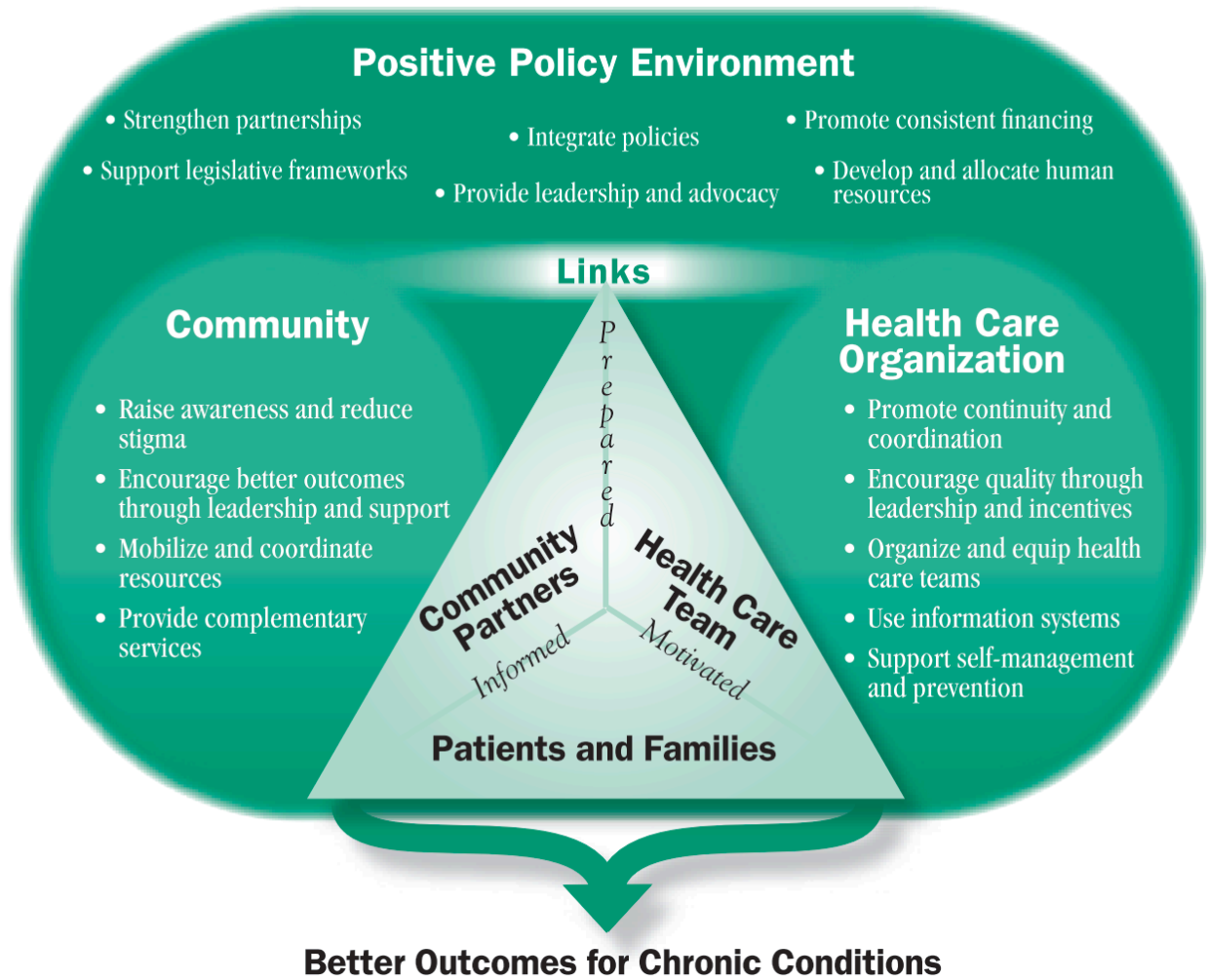
Recognizing of the importance of interorganizational partnerships in care provision for chronic health conditions, especially in developing countries, the WHO Innovative Care for Chronic Conditions (ICCC) framework (World Health Organisation, 2002), emphasizes the need for links between community and health care organizations, and a policy environment that promotes and supports them.

In light of the epidemiological transition from communicable to non-communicable diseases, the ICCC framework was adapted for international settings from the widely recognized Chronic Care Model (CCM) by the WHO in order to improve outcomes for patients with chronic conditions (J. E. Epping-Jordan, Pruitt, Bengoa, & Wagner, 2004). The components of this

framework span across micro, mezzo, and macro-levels since effective functioning within and between these levels is a requisite for better health (World Health Organisation, 2002). At the micro-level, the model emphasizes partnerships between health-care teams, community partners, and affected individuals and their families to promote medical and psychosocial support. At the mezzo-level the framework emphasizes collaboration between healthcare organizations and community organizations so that their services complement each other to generate resources, improve efficiency, and address service gaps that result from resource constraints in the healthcare sector. This is also in appreciation of the fact that care for chronic conditions extends beyond the healthcare setting to include support from community organizations in their personal lives. These links must also be enabled by policymakers at the macro-level through the emphasis of policy activities involving intersectoral partnerships between healthcare and community organizations, development and allocation of human resources, financing, legislation, leadership, and advocacy. Figure 3 illustrates the various components of this model.

The ICCC framework (World Health Organisation, 2002), provides a conceptualization of interorganizational collaborations to improve treatment adherence in the thalassemia community via partnerships between government, healthcare, and community sectors. The Collective Impact model, which provides a structured approach to solve complex social problems through cross-sector collaboration to, might be a feasible means to operationalize this.

## Innovative Care for Chronic Conditions Framework



**Figure 3:** The WHO Innovative care for chronic conditions framework emphasizes links between community and healthcare organizations that are supported and strengthened by the policy environment.

### 5. Collective Impact

Like many other chronic health conditions  $\beta$ -thalassemia major is a rare genetic disorder that impacts the lives of affected individuals medically, psychologically, and socially. Thus, there are numerous stakeholders that influence the welfare of affected individuals and their families. In addition to affected individuals and their families, stakeholders might include individuals such as

influential leaders across various sectors, or collective entities such as schools, hospitals, and non-profits.

The severe and multisystemic nature of  $\beta$ -thalassemia major requires not only coordinated care from a multidisciplinary team, but also collaboration with community organizations due to the psychosocial impacts of the condition (J. E. Epping-Jordan et al., 2004). Isolated efforts by the different stakeholders involved across healthcare and community organizations might result in wastage of resources and a fragmented approach towards improving the lives of affected individuals and their families, which eventually limits the potential for positive health outcomes in terms of impact, quality, sustainability and scalability. However, a collaborative approach where stakeholders align their efforts and work collectively towards mutually agreed upon goals, can result in holistic, long-term and sustained impact on the lives of affected individuals and their families (Kania & Kramer, 2011).

Given limited resources in India, a community health program that augments the efficiency of the existing system through cross-sector collaborations has the potential to improve health outcomes for  $\beta$ -thalassemia major patients and their families. This might be achievable through a Collective Impact initiative. Thus, the long-term goal of building a community collaborative around the Collective Impact model is to improve adherence and consequently mortality, morbidity, and quality of life of individuals affected by  $\beta$ -thalassemia major in Pune, India.

#### **a. Phases and components of a Collective Impact initiative**

The Collective Impact approach is based on evidence that large-scale social change comes from better cross-sector coordination rather than from the isolated interventions of individual stakeholders (Hanleybrown, Kania, & Kramer, 2012). The approach offers a structured way to

foster collaborations between stakeholders involved in a social problem, in order to improve outcomes (Kania & Kramer, 2011). An analysis of several successful community initiatives led to the distillation of three preconditions and five conditions for a successful collaborative. The three preconditions include 1) availability of influential champions to provide local leadership, 2) financial resources to support interorganizational collaboration, and 3) a sense of urgency around the problem. The five conditions are that stakeholder organizations must have a 1) common agenda, 2) common measurement system to track progress, 3) mutually reinforcing activities, and 4) ongoing communication; also 5) a backbone organization is required to mediate collaboration and ensure that the aforementioned conditions of Collective Impact are sustained (Hanleybrown et al., 2012)

There are four components of a Collective Impact initiative that are developed over the span of the initiation, organization, and sustained impact phases. Components include: 1) governance and infrastructure, 2) strategic planning, 3) community involvement, and 4) evaluation and improvement. The steps involved in the development of these four components are described below alongside the phase in which they occur (Hanleybrown et al., 2012). Steps are labeled as (a), (b), (c), or (d) corresponding to the component that they refer to. A visual representation can be found in Figure 1.

1. Initiation phase: (a) Identification of influential champions across sectors and formation of a group consisting of champions from each sector; (b) Mapping the landscape of health services, community resources, and policies, and their contribution to patient experiences to make a case for change; (c) Engaging the community to facilitate outreach; (d) Collection and analysis of baseline data to identify issues.

2. Organization phase: (a) Formation of a backbone organization and processes that

facilitate collaboration between different stakeholders and mediate collaborative activities; (b) Creation of a common agenda including goals and strategies; (c) Engaging the community and building public will; (d) Establishment of shared metrics including indicators and measurement approaches.

3. Sustained impact phase: (a) Facilitation and refinement of the backbone and processes to ensure sustainable progress, development and maintenance of the program; (b) Collaborative Implementation of strategies; (c) Continued community engagement and advocacy; (d) Systematic evaluations, tracking, and reporting of progress towards goals.

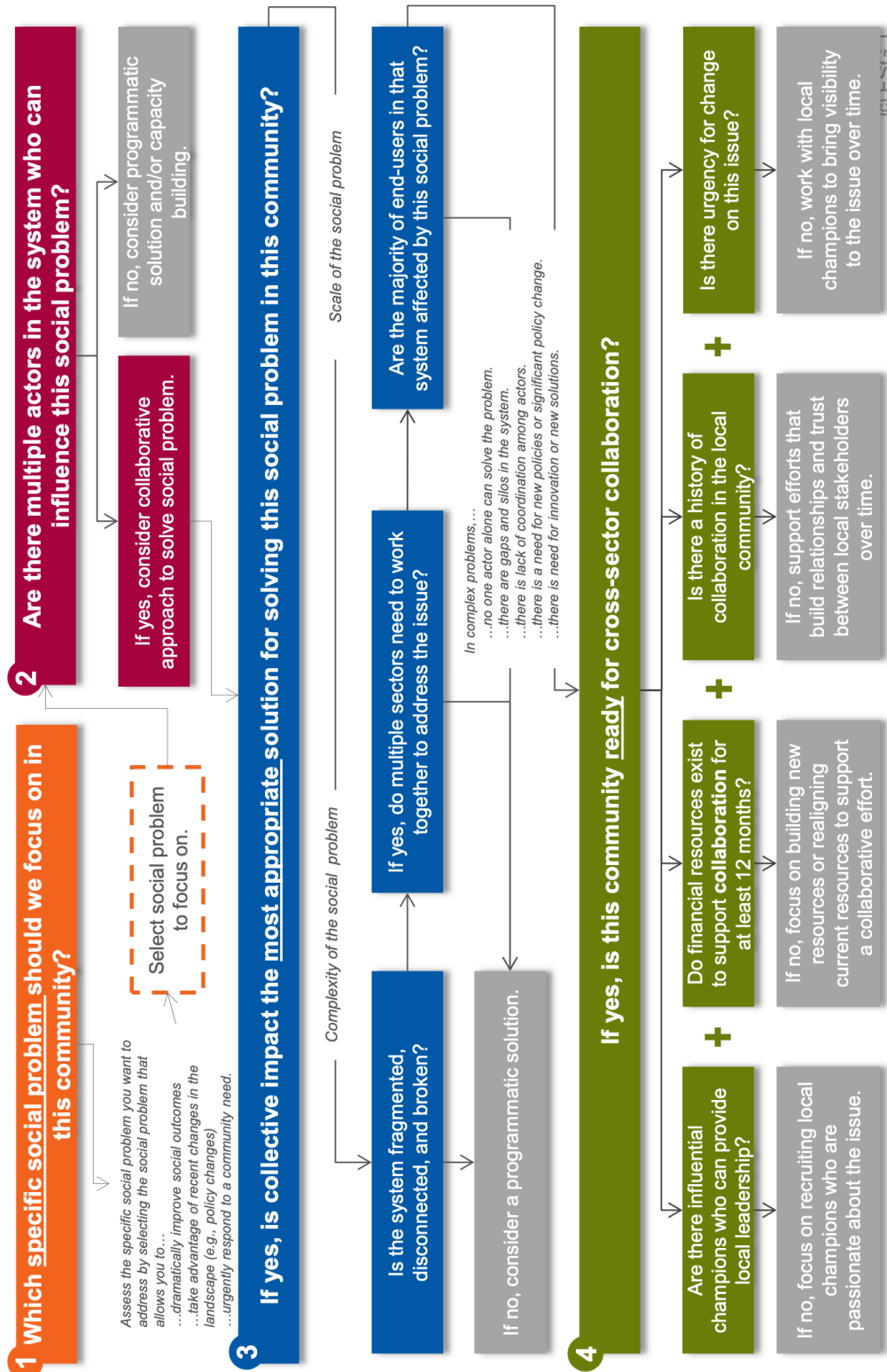
A community collaborative based on the Collective Impact framework, requires the deployment of scarce resources in order to establish, augment, and sustain community partnerships and interventions; hence it is essential to do a feasibility assessment before embarking on a Collective Impact initiative.

#### **b. Collective Impact Feasibility Framework**

After specifying a social problem and determining whether there are multiple stakeholders who can influence it, a Collective Impact Feasibility assessment involves two main steps: 1) assessing appropriateness of the approach to solve the given problem and 2) assessing readiness of the community to adopt the approach (FSG, 2015).

In the context of thalassemia adherence in Pune, assessing appropriateness of the Collective Impact approach would require determination of the complexity and scale of the adherence problem. As per the Collective Impact Feasibility Framework (FSG, 2015), this can be accomplished by determining whether 1) the system is fragmented, disconnected, and broken, 2) cross-sector stakeholder collaboration is required to address it, and 3) a majority of patients are

affected by adherence problems. As per the Collective Impact Feasibility Framework, determining readiness would require an assessment of whether 1) there are influential champions to provide local leadership, 2) there are financial resources to support the collaborative for at least 12 months, 3) there is trust and a history of collaboration between stakeholder organizations, and 4) there is a sense of urgency around the adherence problem.



**Figure 4: The Collective Impact Feasibility Framework (FSG, 2015) provides guidance for the assessment of the appropriateness and readiness of a community to adopt a Collective Impact initiative.**

## **CHAPTER 2**

### **Multidimensional and multilevel factors that influence adherence to essential management in individuals affected by $\beta$ -thalassemia major in Pune, India.**

#### **1. Introduction**

India has approximately 10,000-15,000 thalassemia affected births per year, 45 million carriers, and over 100,000 people living with  $\beta$ -thalassemia major (Colah et al., 2017). While improvements in management have increased the longevity of affected individuals in India, especially in urban regions, very few live as long as their counterparts in the developed world due to poor access to quality medical care, inadequate safe blood, and unaffordable iron chelators (M. B. Agarwal, 2009). The longevity and quality of life of affected individuals can be significantly enhanced by minimizing chronic anemia, iron accumulation, and secondary complications. This is contingent upon adherence to guideline-based essential management that includes safe blood transfusions to maintain an adequate hemoglobin level, iron chelation therapy to prevent the accumulation of iron in various tissues and organs, and routine medical tests to monitor blood indices, iron accumulation, adverse effects, and infections (Maria Domenica Cappellini, Alan Cohen, John Porter, Ali Taher, 2014).

Previously published studies that highlight the issue of adherence and its impact on health outcomes of thalassemia patients, have largely focused on iron chelation (Evangeli, Mughal, & Porter, 2010; Y. L. Lee, Lin, & Tsai, 2009; Shaker, 2015; F. L. Trachtenberg et al., 2012; Vekeman et al., 2016; Vosper et al., 2018) with little to no focus on blood transfusions (F. T. Shah et al., 2019; N. Shah et al., 2010) and routine testing – both of which are essential components of guideline-based management. Furthermore, existing studies are largely concerned with patient-

related and socioeconomic-related dimensions (Evangeli et al., 2010; Y. L. Lee et al., 2009; F. L. Trachtenberg et al., 2012; Vosper et al., 2018), and less so with condition-related, therapy-related, and health care team and health system-related dimensions of adherence to long-term therapies outlined by the WHO (Sabate, 2003), all of which might present additional opportunities for intervention. Formal determination of factors across these dimensions and specific to a given context is a necessary initial step towards improving adherence through context-specific interventions.

In working towards evidence-based, context-specific interventions to improve adherence to essential management, this study sought to determine context-specific opportunities and constraints across the 5 dimensions of adherence proposed by the WHO (Sabate, 2003) and across ecological levels, in individuals affected by  $\beta$ -thalassemia major residing in and around the city of Pune, India. This was achieved through in-depth qualitative interviews with adult patients, caregivers, and key informants since they are the primary stakeholders that have firsthand or secondhand experience in coping with the condition, and therefore have unparalleled knowledge about such factors.

A large majority of past studies pertaining to adherence to essential management in thalassemia have employed quantitative methods where correlations have been drawn between reported or measured adherence rates and psychosocial variables (Evangeli et al., 2010). However, given the difficulties associated with collecting reliable data regarding adherence rates (Farmer, 1999), and our intention to generate context-specific initial data through community engagement, we decided use a qualitative approach that would allow for the identification of previously reported and unreported factors in the local context.

## **2. Methods**

### **a. Ethical considerations and investigator's experience**

This study was approved by the University of Washington Institutional Review Board, Seattle, USA (IRB ID: STUDY-00006828). Additionally, this study was also approved by the Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital Institutional Ethics Committee, Pune, India (Ph.D 0619072-072).

All interviews were conducted by the lead investigator (SK) as part of his PhD dissertation research. The lead investigator had prior experience in using in-depth interviews as a qualitative research method for an unpublished research project that he conducted as part of his Masters' degree requirement. Additionally, he had received graduate level training in various qualitative research methods, community engagement, and clinical genetics.

The lead investigator obtained either in-person verbal or written consent – based on individual institutional requirements - if the prospective participant was willing to participate after the purpose and risks of the study were discussed in their preferred language.

### **b. Study design and justification**

In-depth interviews with individuals affected by  $\beta$ -thalassemia major, caregivers, and key informants were used to collect qualitative data on first-hand accounts of experiences related to adherence to blood transfusions schedules, iron chelation therapy regimens, and routine testing schedules.

In order to develop and implement interventions to effectively address poor adherence to thalassemia management, it is first important to determine context-specific factors that contribute towards it. Quantitative approaches are not ideal for this purpose because they tend to be pre-

structured and fail to account for the contextual realities of those affected. While there was no official data available regarding its incidence and prevalence in Pune city, the presence of large resident Sindhi, Punjabi, and Maratha communities suggest that there are a large number of individuals affected by  $\beta$ -thalassemia major in the city, since these communities have been reported to have a relatively high prevalence of  $\beta$ -thalassemia trait (Patel et al., 2014; Sheth et al., 2008). Furthermore, the presence of several ongoing community efforts that sought to address unmet medical and psychosocial needs of the thalassemia community were also suggestive of a significant number of affected families in the city. Given, that there is very limited literature in this regard for the thalassemia community in Pune, exploratory research that uses qualitative methods can help determine factors specific to affected individuals in Pune, and thereby set the stage for future studies and interventions to improve adherence.

### **c. Participant selection and recruitment**

Prior to study commencement, the lead investigator spent 6 months immersing himself in the thalassemia community by participating in events organized by the local advocacy group and through informal interactions with key stakeholders, including affected adults who were actively involved with local community organizations.

Recruited participants included 3 distinct populations: 1) men and women >18 years of age affected by  $\beta$ -thalassemia major living in or around Pune city, 2) caregivers of children (<18 years of age) affected by  $\beta$ -thalassemia major living in or around Pune city, and 3) key informants with significant experience providing psychological or social support to affected individuals. Individuals who were pregnant, severely mentally or physically disabled, or resided >25km outside Pune city, were excluded from the study. Key informants included physicians, medical social

workers, social workers, and psychologists employed in private, public, and social sector healthcare institutions. Key informants were included in order to capture: a) additional influential factors that are specific to their sector or at levels of influence that go beyond individual and micro-levels, and b) factors that patients/caregivers were not comfortable sharing.

Maximum variation sampling (Patton, 2002) was used to ensure diverse representation of participant experiences. For patients and caregivers, sampling included consideration of their socioeconomic status, age, gender, treatment facility, and number of affected individuals in family. Key informant sampling was structured to capture participants with diverse sectoral viewpoints and healthcare provider cadres. Interviews were conducted in English and Hindi, or a combination of the two (“Hinglish”), based on the interviewee’s language preference.

Participant recruitment took place between October 2018 and July 2019. Potential patients and caregivers were identified through NGO and hospital records and introduced to the lead investigator by relevant representatives of those institutions via phone or in-person. Prospective key informants were identified through informal field interactions and referrals. Data collection was discontinued after the 49<sup>th</sup> interview, after achieving data saturation (Morse, 1995; Sandelowski, 1995). A total of 49 out of 55 prospective participants agreed to participate. Those who declined cited lack of interest or time. No participants withdrew from the study. Participants were interviewed at their residence, an external location, or on the hospital premises depending on personal preference and institutional policies.

#### **d. Data Collection**

A semi-structured interview guide was developed based on existing literature regarding factors that influence adherence to essential management of  $\beta$ -thalassemia major and other chronic

conditions. The interview guide was pilot tested and revised after interviews with 4 participants who were recruited based on variations in age and socio-economic status. The guide was used to ask participants open-ended questions followed by probing questions when necessary, to elicit responses regarding current factors that positively or negatively influenced their ability to adhere to blood transfusions, iron chelation therapy, routine testing, and alternative therapies.

Interviews ranged from 20 to 90 minutes, were audio-recorded, translated and subject to non-verbatim transcription by the lead investigator. It was not always possible to conduct interviews with a single participant due to cultural norms, accompanying family members, shared caregiving responsibilities, unavailability of completely private space, or if the caregiver was not able to leave the affected child unaccompanied. Forty-one interviews were conducted with single participants and 8 were conducted with more than one participant.

#### **e. Analysis**

The WHO multidimensional model for patient adherence (Sabate, 2003), alongside existing literature on treatment adherence, was used to guide qualitative analysis. Specifically, domains from the model as well currently identified patient behaviors affecting adherence, were used to inform codebook development. This model along with existing adherence literature was used to guide qualitative deductive content analysis (Assarroudi, Heshmati Nabavi, Armat, Ebadi, & Vaismoradi, 2018; Elo & Kyngäs, 2008; Hsieh & Shannon, 2005) of the transcribed interviews, where existing theory is used to guide the analytical process. Each interview was considered as a single unit of analysis. The Dedoose QDA software package (Dedoose Version 8.0.35, web application for managing, analyzing, and presenting qualitative and mixed method research data, 2018) was used to deductively code manifest content areas that corresponded to the different

dimensions of adherence using a coding tree that was developed based on existing literature and repeated reading of the interview transcripts. Simultaneously, inductive coding was also used on 10 transcripts to identify new codes, which were then added to the coding tree and applied to all the remaining transcripts after quality-assessment via double coding of 5 transcripts. Coding rules and anchor samples were assigned to each code. Codes were classified into sub-categories, which were more broadly categorized into generic categories based on similarity. These generic categories were then linked to the 5 dimensions of adherence as per the WHO adherence to long-term therapy framework. The findings were validated by two participants, who confirmed that they mirrored the experiences of the thalassemia community in Pune.

### 3. Results

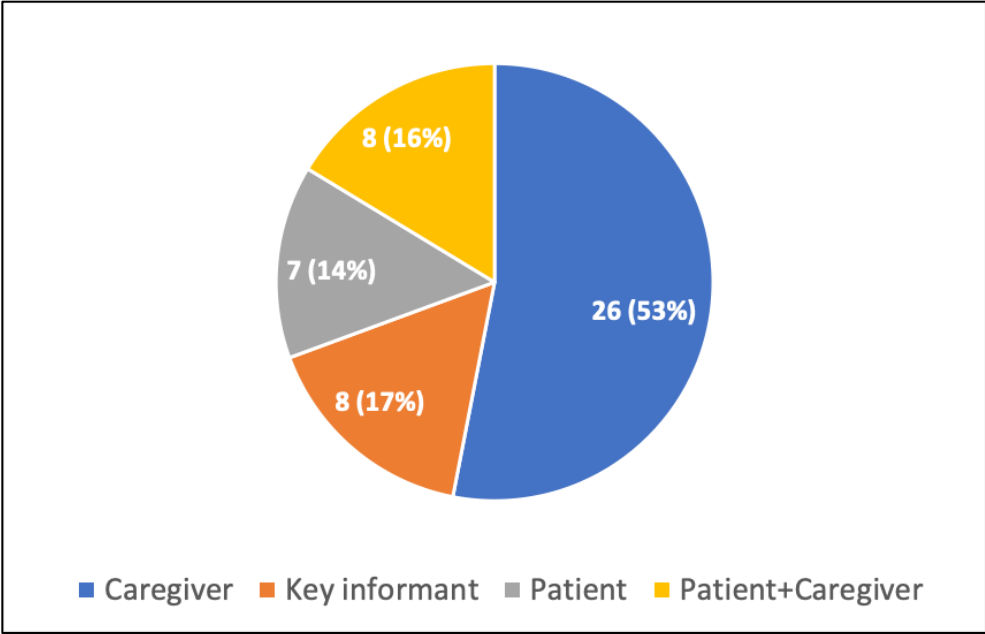
Serial #	Interviewee(s)	Affected individuals in family	Gender(s)	Age group (years)	Treatment facility
1	Caregiver	1	M	6-12	Private
2	Caregiver	2	M,M	6-12	Public
3	Caregiver	1	M	6-12	Social
4	Caregiver	1	M	13-17	Public
5	Caregiver	1	M	6-12	Public
6	Caregiver	1	M	6-12	Public
7	Caregiver	1	M	6-12	Private
8	Caregiver	1	M	0-5	Public
9	Caregiver	1	F	0-5	Private
10	Caregiver	1	F	6-12	Private
11	Caregiver	1	M	0-5	Public
12	Caregiver	2	M,F	6-12	Public
13	Caregiver	1	F	6-12	Public
14	Caregiver	1	M	6-12	Public
15	Caregiver	1	F	13-17	Private
16	Caregiver	1	F	6-12	Social
17	Caregiver	1	F	13-17	Private
18	Caregiver	1	F	13-17	Private
19	Caregiver	1	F	6-12	Private

20	Caregiver	1	F	6-12	Social
21	Caregiver	1	M	6-12	Private
22	Caregiver	1	M	6-12	Private
23	Caregiver	1	M	6-12	Public
24	Caregiver	1	M	6-12	Private
25	Caregiver	1	F	6-12	Alternative therapy
26	Caregiver	1	F	6-12	Public
27	Patient	1	M	18-26	Alternative therapy
28	Patient	1	M	18-26	Private/Social
29	Patient	1	M	18-26	Private/Social
30	Patient	1	F	27-32	Social
31	Patient	1	F	27-32	Private/Social
32	Patient	1	F	18-26	Private
33	Patient	1	F	18-26	Private
34	Patient+Caregiver	1	M	27-32	Private
35	Patient+Caregiver	1	F	27-32	Social
36	Patient+Caregiver	2	M,F	18-26	Alternative therapy
37	Patient+Caregiver	1	M	18-26	Social
38	Patient+Caregiver	1	M	18-26	Private
39	Patient+Caregiver	1	M	18-26	Private
40	Patient+Caregiver	1	M	18-26	Social
41	Patient+Caregiver	2	M,F	18-26	Alternative therapy

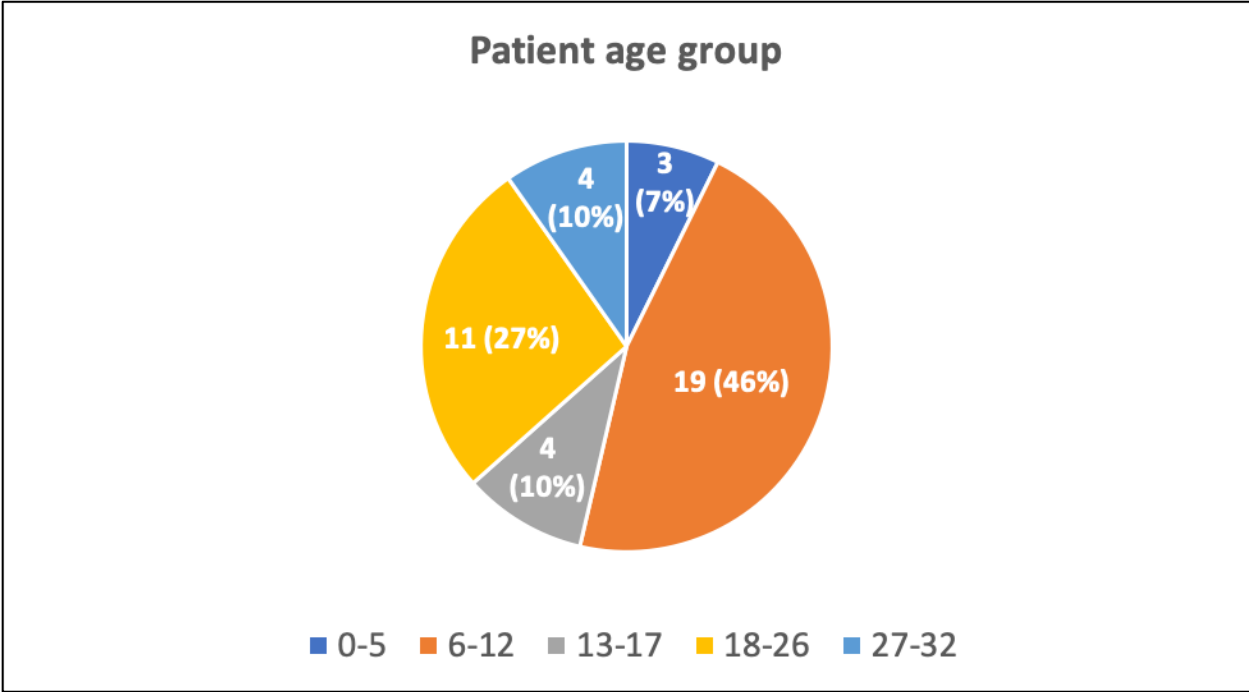
**Table 1: Patient/caregiver descriptors**

Serial #	Interviewee(s)	Profession	Interview setting
1	Key informant	Social worker	Workplace
2	Key informant	Physician	Workplace
3	Key informant	Social worker	Hospital
4	Key informant	Physician	Hospital
5	Key informant	Counselor	Workplace
6	Key informant	Social worker	Workplace
7	Key informant	Social worker	Workplace
8	Key informant	Counselor	Workplace

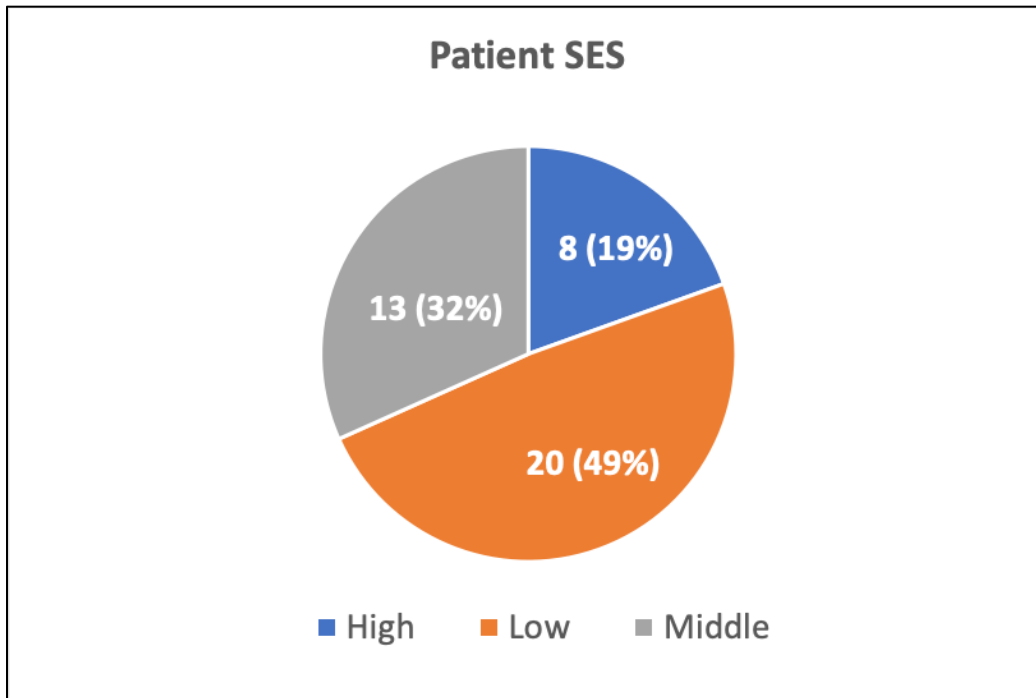
**Table 2: Key informant descriptors**



**Figure 5: Distribution of interviewees**



**Figure 6: Distribution of patient age groups**



**Figure 7: Distribution of patient socioeconomic status**

**a. Sample characteristics**

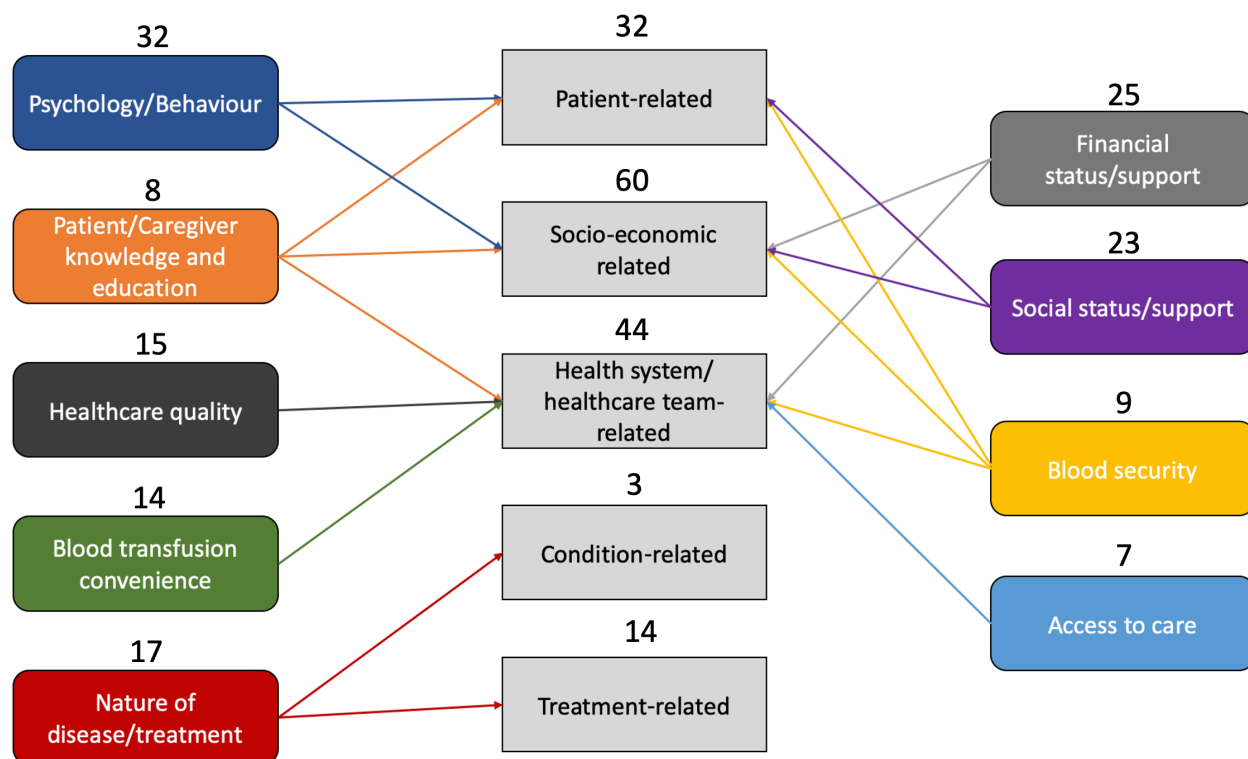
We interviewed 49 participants. As illustrated in Figure 5, 53% of interviewees were caregivers, and the remainder were key informants, patients, and patient-caregiver duos/trios. As illustrated in Figure 6, most of the participants had affected children aged 6-12 years, followed by affected adults aged 18-26 years, with a relatively small number of affected individuals in the remaining age groups. As illustrated in Figure 7, 49% interviewees were of low socioeconomic status, followed by 32% of middle socioeconomic status, and 19% of high socioeconomic status. In terms of patient gender, 21 interviewees had affected male children or were affected males themselves; 16 had affected female children or were affected females themselves. There were 4 interviewees that belonged to families with 2 affected individuals; of these 3 had one affected male and female child, and 1 had two affected male children. Of the interviewees who were adult

patients and/or caregivers 16 visited private sector transfusion facilities, 11 visited public sector transfusions facilities, and 7 visited social sector transfusion facilities, and 3 visited private and social sector transfusion facilities. Interestingly 4 interviewees had affected children or were patients themselves who were using alternative therapy as a primary management strategy. Of the 8 key informants, half were social workers, a quarter were physicians, and a quarter were counselors.

## **b. Findings**

Deductive content analysis yielded 150 codes that corresponded to 79 constraints and 71 opportunities that influenced adherence to essential management. These factors were classified into 43 subcategories, which were further collapsed into 9 broad interrelated “generic categories”; these included: 1) Blood security; 2) Blood transfusion convenience; 3) Access to care; 4) Healthcare quality; 5) Financial status/support; 6) Social status/support; 7) Psychology/behavior; 8) Self-management knowledge; 9) Nature of disease/treatment.

Some generic categories fit neatly into a single dimension and others spanned multiple dimensions of the WHO multidimensional adherence framework. The links between the generic categories and 5 dimensions are illustrated in Figure 8.



**Figure 8: Links between generic categories and WHO dimensions of adherence.** The numbers placed on top of each generic and main category denote the number of factors within each of them.

A list of the sub-categories within each generic category, and codes (opportunities and constraints) within each sub-category can be found in Appendix G. Opportunities and constraints have also been linked to the main categories, the aspects of essential management that they influence, and their ecological level of influence. Figure 8 illustrates the links between the generic categories and the main categories and the number of opportunities and constraints within each of them.

Due to the interrelatedness of opportunities and constraints within and across categories it is difficult to describe them contextually based on the WHO 5 dimensions of adherence, hence they have been described as per their generic categorization.

- (i) Blood Security

Opportunities and constraints in this category that influenced adherence were either socio-economic-related, health system/HCT-related, or patient-related as per the WHO multidimensional adherence framework, across the individual, micro, mezzo, and macro-levels of hierarchy as per the ecological model. The factors in this category were associated with the patient or caregiver's ability to access adequate safe blood in time for their scheduled blood transfusion. Subcategories included supportive hospital/blood bank, ease of blood procurement, and blood safety.

Adherence to blood transfusion schedules is dependent on the patient's ability to access safe blood in time for their next transfusion. All interviewees reported having access to packed red blood cell units at no charge from any blood bank through a supportive government policy that was implemented a few years ago in the state. Interviewees reported that this policy had undoubtedly made it easier for them to procure blood and adhere to their transfusion schedules. Despite this, a majority of interviewees reported difficulties related to blood procurement at certain times of the year that negatively influenced adherence to their blood transfusion schedules. They reported that blood procurement was particularly challenging during the summer months and festive season due to a shortage of donors in city, many of whom were students or working professionals.

*C: Yes, it's hot and college students are on vacation, so there are fewer blood donation camps that are organized. And even patients go for holidays to their village, and they want to get transfused before they leave, so that is the reason there is a lot of demand, and a shortage... so we need to get blood from outside*

*(Caregiver, Low SES, Public sector hospital, 6-12y)*

Blood procurement was found to be even more difficult during this time for patients with rare blood groups, and those with a lack of donors in their social circles. However, many interviewees also reported that they were assisted by hospitals, blood banks, and donors from within their social circles during times of blood shortage, which positively influenced adherence to their blood transfusion schedules. Hospital and blood banks were reported to provide support by coordinating blood from other blood banks, contacting pre-identified donors, and prioritizing thalassemia patients for fresh blood. However, there were also reports of hospital or blood banks who were unsupportive in that they made the blood procurement process difficult or did not make fresh blood easily available to patients.

Several interviewees also reported facing issues with procuring safe blood, i.e. blood that was fresh, leukofiltered and had undergone nucleic acid testing (NAT). The availability of fresh blood was particularly problematic during blood shortages, which resulted in patients having to come in for their next transfusion at a shorter interval.

*K: ....in Maharashtra blood is free of cost. But only free blood is not important, we also require high quality blood. If high quality blood is not available then the patient will suffer from infections, and they will go on to face many issues in their lives such as HIV.*

*I: Are there ever situations where patients are hesitant to take blood transfusions because of the chance of infection?*

*K: Yes, this does happen ...people are scared.*

*(Key informant: Counselor)*

Very few blood banks were reported to provide NAT tested and leukofiltered blood, a lack of which greatly increases the chances of transfusion reactions and transfusion-transmitted infections. Blood safety was further compromised due to the high price of bedside leukofiltration

devices despite subsidization through patient organizations. However, several interviewees also reported that their blood bank provided them with safe blood that was NAT tested and/or leukofiltered, or reported being able to procure bedside leukofiltration devices for free at substantial discounts from their treating hospital or patient organizations. Proactiveness, resourcefulness, and knowledge were also seen to play important roles in accessing safe blood in a timely manner.

(ii) Blood transfusion convenience

Opportunities and constraints in this category that influenced adherence were health system/HCT-related as per the WHO multidimensional adherence framework, at the mezzo-level of hierarchy as per the ecological model. The factors in this category were associated with the convenience of getting blood transfusions as per the prescribed schedule. Subcategories included: duration of transfusion, transfusion timings, special accommodations for thalassemia, ward infrastructure and policies.

The duration of the transfusion process was brought up by many interviewees, which includes the time taken for all processes from the time they enter the transfusion facility until the time that they leave. A short duration was reported as being more convenient since interviewees were able to attend to other obligations and/or responsibilities, whereas longer durations were reported as inconvenient as they conflicted with the same. There were also reports of patients having to be admitted for multiple consecutive days in order to increase their hemoglobin to guideline-recommended levels, because they were not able to adhere to the transfusion schedule and maintain a pre-transfusion hemoglobin level as per guideline recommendations. Apart from the time spent at the transfusion facility, several interviewees reported having to spend significant

time coordinating blood transfusion related resources such as leukofilters, intracatheters and blood; the reasons for this were either unavailability or inability to afford the resources provided at the hospital. Interviewees reported that typically the time taken for the blood transfusion process was between 4 hours to 24 hours. Given the long duration of the process, interviewees reported that days and timings for transfusions set by the hospital influenced their ability to adhere to the transfusion schedule. Some hospitals had dedicated days and times for thalassemia patients in order to accommodate patient or caregiver's professional or educational schedules; interviewees reported that this positively influenced their ability to adhere to their transfusion schedules. In fact, there were reports of some hospitals offering weekend transfusions specifically for thalassemia patients.

*C: The best amenity over here is that it opens in the morning at 7am, so I can tell the company that I will come by afternoon. So, I can still do a half day of work. Since it opens at 7am, the entire procedure is done by 11am-12pm.*

*(Caregiver, Low SES, Public sector hospital, 6-12y)*

Conversely, some interviewees also reported that few of the ten blood transfusion facilities represented in the sample had unsuitable days or timings for transfusions, which conflicted with their schedules and therefore negatively influenced adherence to their transfusion schedules. Some interviewees reported that the hospitals made an effort to schedule transfusion appointments around their schedules if there was a conflict, and even scheduled the next transfusion appointment for them based on the estimated hemoglobin drop rate. Some hospitals even made the effort to proactively call patients to remind them about their scheduled transfusion appointment.

Apart from dedicated timings, interviewees also reported that some hospitals had dedicated thalassemia wards or beds, which enabled thalassemia patients to get their transfusions along with other thalassemia patients; this positively influenced their ability to adhere to the transfusion schedule. Conversely, there were also reports of transfusion facilities that did not have dedicated thalassemia wards or beds, which led to patients having to share space with trauma patients, or patients with other severe medical conditions; this caused significant psychological discomfort and was reported to negatively influence their ability to adhere to the transfusion schedule.

*K: The other problem is that seriously ill patients also are admitted to that ward... there is no separate ward like there is for pediatric patients, where they have good facilities. Over there it's not like that, they have to get admitted with all the other patients. If there are serious sick patients like for example if someone has consumed poison then they need to wait longer, and their blood transfusion gets further delayed.*

*(Key informant: Social worker)*

Interviewees also reported additional special accommodations for thalassemia patients including prioritization of thalassemia patients for blood transfusions, and provision of food and refreshments during transfusions, both of which made the transfusion process more convenient. Additionally, interviewees also alluded to the importance of good ward infrastructure, recreational activities, cleanliness, and ward policies that allowed patients to be accompanied by caregivers, in making the transfusion experience pleasant for patients.

### (iii) Healthcare quality

Opportunities and constraints in this category that influenced adherence were health system/HCT-related as per the WHO multidimensional adherence framework, across the micro and mezzo-levels of hierarchy as per the ecological model. The factors in this category were

associated with the patient and caregiver's experience with the healthcare system in receiving compassionate healthcare of sufficient quality. Subcategories included: quality of physicians and interactions, quality of nursing/hospital staff and interactions, broader healthcare issues, integrated care.

Many factors that were identified in this category were physician-related. Interviewees reported that treating physicians provide adequate consultation time, support, guidance, tailored management, supervision, and/or quality communication with regards to essential management.

*C: He never tells us not to do something. He gives us the choice to do whatever we want. At the beginning I had heard about the benefits of wheat grass, so I discussed it with him.....so he just said that wheat grass does not have any side-effects so I can give it if I want.*

*(Caregiver, High SES, Private sector hospital, 6-12y)*

However, some interviewees reported the opposite. One key informant, who provided counseling services for thalassemia-affected families in Pune and had significant professional experience in the healthcare and community sector organizations, mentioned that most physicians do not make appropriate referrals to specialists or ancillary healthcare professionals such as medical social workers and counselors. While many interviewees mentioned that they were able to follow-up regularly with their treating physician, some mentioned that following up with the treating physician was challenging.

*P: Okay, and then other thing...and in Pune you have to run after the doctor. The hematologist should take care of the patient, and the patient should follow up with them, but over here at least in my case, it is not happening parallely. I don't know about other people, but that's for me.*

*(Patient, Middle SES, Private sector hospital, 18-26y)*

Those who mentioned that they were able to follow-up regularly were usually able to do so because of low consultation fees, perceived benefit of regular consultations, or if their treating facility had integrated physician consultations into the blood transfusion process. Those who mentioned that they were not able to follow-up regularly were usually not able to do so due to high consultation fees, negligence, or fear of the physician. Notably, in many interviews good follow-up with physicians was linked to good adherence to routine testing; this was because treating physicians mandated that the prescribed routine tests be done before their next appointment, or the hospital took responsibility for getting the tests done either before or on the appointment day and kept a record of their test results. One particular hospital also sent out text message reminders to patients for the tests that they needed to have done, however several interviewees reported limited perceived benefits of routine testing, because their treating physicians didn't seem to use the test results to tailor medical management

Many interviewees talked about their satisfaction or dissatisfaction with the hospital and nursing staff. Most interviewees praised the nursing and hospital staff for their efficiency, attentiveness, supervision, experience, helpfulness and kindness; some of them even lauded competent nurses who were able to find a vein quickly without discomforting the patient. However, some interviewees expressed their dismay at the rude, careless, or incompetent nurses who would have to prick the patient multiple times to find a vein, and uncooperative hospital staff who made it difficult for them to procure fresh blood.

*C: She gets scared of the needle. What happens is that the nurse is not always able to insert the needle in the first attempt. Sometimes she needs to get pierced 3-4 times on either of her arms.*

*(Caregiver, Low SES, Private sector hospital, 6-12y)*

*P: Yes sure no problem. The nurses are not so good, I think. For them it's a routine thing. They don't give a damn what we are going through, so I think they should be a little more caring and a little more sensitive towards the patients you know. A little more understanding would help."*

*(Patient, High SES, Private sector hospital, 18-26y)*

Some interviewees reported that in certain hospitals continuity of care was significantly disrupted during the transition from childhood to adulthood as the patients had to be managed in a different ward by different physicians and hospital staff. Since these wards were not specialty wards for thalassemia patients, they did not have adequate infrastructure, resources or processes in place to cater to the medical needs of thalassemia patients. This was reported to lead to a much longer transfusion process that often took multiple days, which in turn led to nonadherence to other aspects of essential management as well. A few interviews also indicated that caregivers and patients did not follow up with their physician regarding difficulties that they were facing in adhering to the prescribed iron chelation therapy, due to fear of their physician's short temper. Several key informants mentioned that variations in management strategies amongst physicians also lead to confusion amongst patients and caregivers, which negatively influenced adherence to essential management. Lastly, a few interviewees who were adult patients indicated that their blood transfusion schedule was not being monitored by their treating physician, and that they were switching between different iron chelators without prior consultation with them.

(iv) Nature of treatment/condition

Opportunities and constraints in this category that influenced adherence were either condition-related or treatment-related as per the WHO multidimensional adherence framework, at the individual-level of hierarchy as per the ecological model. The factors in this category were

associated with the clinical features of thalassemia, and features of treatment and management. Subcategories included: transfusion/drug administration experience, adverse effects or contraindications, effects on symptoms, treatment frequency, and palatability.

While oral chelation therapy such as deferiprone and deferasirox were widely reported to be easy to administer and therefore had significantly improved adherence to iron chelation therapy, many patients still relied on desferrioxamine therapy, which must be administered either subcutaneously or intravenously. Interviewees reported that most patients who have been prescribed desferrioxamine experienced difficulties with sleep, mobility, daily activities, social activities, and professional activities due to the long duration of administration (~12 hours), and inconvenient mode of administration, which necessitates using either an infusion pump at home or using an intravenous drip at home or a hospital. Additionally, a few interviewees reported experiencing pain at the injection site, bone issues, and fatigue as adverse effects. All these factors negatively influenced adherence to iron chelation therapy.

*“P: Yes, it is challenging because I must wear a pump for 12 hours for each infusion. So, when I used to work... after work I used to get home and not wear the pump immediately because I would be doing other things at home... if I didn't wear the pump on time the previous night I would get late for work. Also, it was not comfortable for me to wear it every day because the injection site used to swell up and cause pain and discomfort. So, it's not only the needle prick that hurts but I also experience pain while the infusion is actually happening.”*

*(Patient, Middle SES, Social sector hospital, 27-32y)*

There were a few reports of adverse effects due to oral chelators as well, but a large majority of interviewees did not experience these. One interviewee did mention that she used to skip her deferasirox dose on busy mornings because it had a diuretic effect on her that interfered with her schedule. Additionally, there were interviewees who reported skipping doses or taking a

drug holiday when they had allergies or infections since they thought that the use of the drug was contraindicated in such situations. One key informant, who was a medical social worker with significant experience assisting families affected by thalassemia, mentioned that when some individuals experience adverse effects due to the iron chelation medication, they discontinue it and seek therapy from alternative medicine practitioners without consulting with their treating physician. While most reports of adverse effects were related to iron chelation therapy, there were a few interviewees who reported blood transfusion reactions as well, which may promote stubbornness in the patients and therefore negatively influence adherence to blood transfusion schedules. A few interviewees also mentioned that the patient would skip iron chelation doses on days that they had to go for blood transfusions. Some interviewees reported that the patient was not able to adhere to the iron chelation therapy because it tasted unpleasant whereas some mentioned that they had no issue adhering to the iron chelation therapy because it had a neutral taste or was pleasantly flavored.

Interviewees reported that high-dose frequency and life-long commitment to iron chelation therapy resulted in tedium, where the patients became tired of taking the medication every day and started skipping doses or stopped taking it altogether. Some interviewees reported having to take around 14 tablets a day, some of which they occasionally forgot to take. Some interviewees also reported that they were not able to go for transfusions as frequently as prescribed because the interval between transfusions was too short, and that interfered with their educational or professional schedules. A few interviewees reported having had splenectomies which lengthened the interval between transfusions and made it easier for them to adhere to the transfusion schedule. Uniquely, one interviewee even described an anecdote regarding the possibility of reduced adherence to iron chelation therapy as a consequence of having a splenectomy i.e. that

splenectomies reduce immunity and therefore increase the chances of infections, as a result of which they have to miss their iron chelation doses more frequently since they are contraindicated during infections.

With regards to blood transfusions, many caregivers and affected individuals mentioned that the symptoms of reduced hemoglobin - such as weakness, fatigue, and poor appetite - were obvious, and served as indicators for them to schedule a blood transfusion.

*C: She feels weak and starts eating less. So, when we see a difference in her eating pattern, we understand that her blood is less. So, we get a blood test done and schedule an appointment here for the transfusion.*

*(Caregiver, Low SES, Social sector hospital, 6-12y)*

Similarly, some interviewees indicated that they noticed the symptoms of high ferritin levels, such as breathing difficulties and fatigue, which motivated them to adhere more strictly to their iron chelation medication. Similarly, short-term and long-term symptomatic improvements due to adherence to blood transfusion schedules and iron chelation therapy were also reported to positively influence adherence. One key informant reported that a lack of noticeable short-term symptomatic improvements due to iron chelation therapy negatively influenced adherence.

*K: The other thing that negatively affects compliance is that they are slow acting. Oral chelators are slow acting. They are effective but you have to take it for years, until your ferritin levels reduce. So, you have to wait for multiple years to see the action... and again it's a repetitive process to take medications every day on an empty stomach before going to school. Those who can adjust to it do, and those who cannot miss their doses."*

*(Key informant: Physician)*

- (v) Patient/caregiver knowledge and education

Opportunities and constraints in this category that influenced adherence were Health system/HCT-related, patient-related, or socioeconomic-related as per the WHO multidimensional adherence framework, across the micro and mezzo-levels of hierarchy as per the ecological model. The factors in this category were associated with the patient or caregiver's understanding of thalassemia and its treatment. Subcategories included: understanding/knowledge about disease and treatment, patient/caregiver education.

Many interviews indicated that patients and their caregivers either did or did not possess knowledge regarding thalassemia and essential management, which influenced adherence to essential management. Some interviewees indicated being knowledgeable regarding guideline-recommended pre-transfusion hemoglobin and the importance of its maintenance.

*P: Well every 15 days I check my hemoglobin levels. If it's below 10 then I give the transfusion center a call and schedule a transfusion for the very next day, but if it is 10 or above, I leave a gap of around 5 to 10 days and then get my transfusion.*

*(Patient, Middle SES, Social sector hospital, 27-32y)*

Some interviewees also demonstrated having knowledge regarding transfusion administration, such as the flow rate, and the importance of doing routine tests such as the hemogram and serum ferritin. However, some interviewees indicated a lack of knowledge or misinformation regarding blood transfusions, where they would delay transfusions because they were under the impression that getting transfusions earlier would worsen iron accumulation. Additionally, some interviews also indicated that they did not understand the medical benefit of taking iron chelation therapy or the routine tests. Some even indicated that they did not know which tests needed to be done routinely. There were also reports of caregivers understanding the need for strict adherence to iron chelation therapy because of visible differences between adherent

and non-adherent patients, and the possibility of death due to iron overload. However, there were some interviewees who did not understand the importance of adhering to routine testing schedules, specifically for serum ferritin. There were also a few interviewees who seemed to be misinformed regarding the longevity of thalassemia patients and regarding their candidacy for bone marrow transplantation, which also influenced their adherence to essential management. There were also reports of the important role that knowledge amongst other family members played in the management of the patient. For example, family members that possessed knowledge regarding the importance of adhering to iron chelation medication would remind the patient to take it in case the primary caregiver or patient forgot.

Interviewees also highlighted the important role of patient and caregiver education in promoting adherence. Patient organizations regularly organized awareness programs during which patients and caregivers are educated about the importance of adherence. Key informants who were medical social workers also mentioned that they periodically organized support group meetings at the hospital to educate patients regarding the same. Awareness events, support group meetings, and transfusions in dedicated wards provided an opportunity for patients and caregivers to provide peer support to each other.

*K: If you go and speak to any parent right now, they will know that there is a treatment and that their child can get better, and that they will try their best. But when we first started the support group, we had to spend a lot of time understanding why patients had these incorrect perceptions. Just because a child has thalassemia doesn't mean that they have to die prematurely... they can grow into adults and earn money... these are things that we had to gradually put into the minds of the parents.*

*(Key informant: Medical social worker)*

Lastly, there were reports of caregivers and patients learning from tragic experiences within their own families or others', where patients had passed away prematurely due to poor adherence to essential management.

(vi) Access to treatment and medication

Opportunities and constraints in this category that influenced adherence were Health system/HCT-related as per the WHO multidimensional adherence framework, at the mezzo-levels of hierarchy as per the ecological model. The factors in this category were associated with the patient or caregiver's ability to access essential management or alternative treatment. Subcategories included: procurement/availability of medicines/disposables/tests, availability of rural facilities, and proximity to home.

Many interviewees reported that it was more often than not easy to procure iron chelation medications from medical stores, patient organizations, or - in some cases - treating hospitals. However, many interviewees also reported that it was occasionally difficult for them to procure them due to unavailability at medical stores or dispensing delays at hospitals that were providing them for free.

*P: These medications are not available at any chemist. It is not available at chemists next to where we live... they don't know anything about these medications, because there are no thalassemia patients who go to them. So, they need to specially order it.*

*(Patient, Middle SES, Social sector hospital, 18-26y)*

This was reported to happen only rarely for the oral chelators, but very frequently for desferrioxamine. In fact, there were several reports regarding a "black market" for

desferrioxamine, where eligible patients would receive it for free from various patient organizations across the country and sell them to other patients during shortages.

*P: But this thing creates hindrance for other patients. How? I will tell you: He has registered here, here, and here, but if you're just taking medications from them when you're not really using them, which can be of some need for some poor people.*

*(Patient, Middle SES, Private sector hospital, 18-26y)*

A few interviewees also reported being able to procure medications through family or friends who owned medical stores when the medication was not available at the medical store that they frequented. Furthermore, several interviewees mentioned that while there are government provisions for free oral chelators, patients must be registered and receive transfusions from the government hospital in order to access them. However, perceptions amongst middle- and high-income patients regarding differences in the quality of care between private and public hospitals deterred them from accessing these government benefits.

With regards to blood transfusions and routine testing, many interviewees mentioned that the proximity of the transfusion center or test center made it very convenient for them to go for transfusions or have the routine tests done as per the prescribed schedule. One interviewee mentioned that it was sometimes difficult for her to procure disposables such as leukofilters and intracatheters that are used for blood transfusions. A few interviewees, who would make an annual trip back to their village, mentioned that they were not able to go for blood transfusions there due to unavailability of quality blood transfusion services. Only one interviewee mentioned that they had access to quality blood transfusions services at their village.

Some patients mentioned that it had become easier for them to adhere to T2\*MRI screening as per the guidelines because it had recently become available in Pune; previously they had to

make a day trip to an imaging center in Mumbai, which is approximately 180 km away, to get the test done.

(vii) Financial status/support

Opportunities and constraints in this category that influenced adherence were socioeconomic-related and health system/HCT-related as per the WHO multidimensional adherence framework. across the individual, mezzo, and macro-levels of hierarchy as per the ecological model. Subcategories included: financial support, free/subsidized tests/transfusions/treatment, financial ability, expensive treatment, financial issues, and unsustainable thalassemia services/amenities.

Almost all interviewees reported that the cumulative expenses associated with iron chelation therapy, routine testing, physician consultation fees, hospital charges, or disposables were very high, and that financial constraints due to insufficient income, delayed salaries, and competing financial responsibilities had a significant negative influence on adherence to all aspects of essential management.

*C: So, I had to take care of the family expenses, and the expenses for his medication, which is very expensive... Asunra (desferrioxamine brand) ... So, I give him Desirox (desferrioxamine brand), but the problem that I face is that I have to pay the school fees for 3 children, so I'm not able to cope with that. And I'm not able to fulfil my children's wishes. And I can't take him in anywhere (for a trip), so then the other kids at home say that the other kid's fathers' take them out, but their father doesn't take them anywhere. So, this is a problem that I face. And apart from the pills he needs to take a continuous injection with the machine.*

*(Caregiver, Low SES, Public sector hospital, 6-12y)*

One key informant mentioned that patients would delay their transfusions because they couldn't afford to pay for the hematogram to determine their pre-transfusion hemoglobin.

Additionally, some interviewees who were aware about the benefits of using a leukofilter during their transfusions reported not being able to afford them, which led to compromised blood safety. Interviewees indicated that they often had to delay medication purchases due to delayed salaries or insufficient income. Several caregivers who were daily wage earners also mentioned that they had to forgo a day's pay whenever they needed to visit the hospital for transfusions or go to the medical store in the city center to purchase chelation medications. One interviewee mentioned that she switched to an unprescribed chelator because she could not afford the one that was prescribed. A few patients mentioned that they were not able to follow-up with their treating physician because of a high consultation fee. Several interviewees who were aware about the benefits of routine testing had to delay them because they couldn't afford them. The high cumulative expenses also negatively influenced other aspects of the caregiver's and patient's quality of life and ability to fulfill other social and financial responsibilities. However, there were some interviewees who indicated that they were financially stable and could therefore afford the high treatment-related expenses.

Some interviewees reported not receiving financial support of any kind to help them cope with high treatment related expenses, and also reported that government policies that had made provisions for free chelators were not inclusive in that patients could only access them if they were being treated at government hospitals. However, most interviewees reported that patients receive free or subsidized blood transfusions, routine testing, iron chelation medication and disposables through financial support received from hospitals, patient organizations, medical stores, testing centers, or pharmaceutical companies.

*K: No, the patients don't need to pay a single rupee here. We provide the intracatheter, and we give the blood for free, the leukofilter for free, we are serving them for free, we are not charging any bed charges, and we are even providing them with snacks for free.*

*(Key informant: Physician)*

Many of these financial support channels were made possible through interorganizational collaborations, corporate social responsibility (CSR) mandates, and supportive government policies. For example, inter organizational collaborations between certain patient organizations and hospitals had enabled access to highly subsidized routine testing, while CSR mandates and supportive government policies had enabled access to free chelation medication through certain hospitals. However, based on the past experiences of a few key informants the long-term sustainability of such services was questionable. Collaborations between certain patient organizations and hospitals had also enabled access to expensive desferrioxamine infusion pumps at no charge or on a rental basis. Despite all the subsidized services available in Pune, the financial status of some families was so low that they still could not afford them. For example, a particular hospital had made arrangements to halve the price of the serum ferritin test for thalassemia patients to approximately \$3.5, which had to be spent every 3 months; this price was lower than those offered by any other testing lab. Unfortunately, some caregivers were still not able to get the test done on time because they could not afford it.

(viii) Social status/support

Opportunities and constraints in this category that influenced adherence were socioeconomic-related and patient-related as per the WHO multidimensional adherence framework, across the individual, micro, mezzo, and macro-levels of hierarchy as per the ecological model. The factors in this category were associated with the social advantages and

disadvantages experienced by the patient or caregiver that influenced adherence, and the social support that they were receiving for it. Subcategories included: support/issues with management schedule, social/counseling support, family support/issues, commuting difficulties, literacy level, unawareness regarding/inaccessible amenities, and broader social issues.

Many interviewees reported that conflicting social, educational, or professional activities, responsibilities or obligations negatively influenced their ability to adhere to blood transfusion schedules and iron chelation therapy. While most interviewees reported being supported to some extent by their employers or educational institutions in order to accommodate their prescribed management schedules, some reported that they received no support in this regard; support included exam re-scheduling and days off for transfusions. One caregiver even mentioned that schoolteachers would supervise affected individuals to ensure that they took their iron chelation medication during school hours. Hospitals also provide support by handing out medical letters addressed to school authorities, and trying to schedule patients on days that wouldn't conflict with their schedules. One key informant mentioned that thalassemia patients put a lot of pressure on themselves and work extremely hard to perform well in professional settings since they are undermined by their employers and are at higher risk of being laid off; unfortunately this causes conflicts with their treatment schedule and therefore negatively influences adherence to it. Some caregivers reported having selected jobs that allowed them to take days off for treatment-related purposes, or jobs that had the option of a late-shift that allows them to fulfill treatment-related responsibilities without having to take days off. One caregiver with two affected children reported finding it difficult to adhere to the prescribed schedule as it was different for both children due to an age gap, as a result of which transfusions for the older child were always delayed by a few days.

Interviewees also reported the availability of social support from medical social workers, counselors, support groups and peers; however, some reported receiving none. Several key informants indicated that counseling and support groups could help psychologically distressed caregivers and individuals by educating them about the condition, available treatments, and the possibility of good health outcomes if essential management is strictly adhered to. Examples were also provided by key informants, where such interventions managed to involve an otherwise uninvolved parent in the affected child's management, thereby promoting shared responsibility amongst couples, which in turn improved adherence to blood transfusions. Support group meetings were also reported to provide an opportunity for affected individuals and their caregivers to meet and provide peer support to each other. One key informant mentioned that support groups promoted adherence because it gave patients and caregivers an opportunity to meet adherent patients, and visually perceive the positive impact of adherence on their well-being. Some interviewees also reported that they were able to receive peer support through social media and digital mediums such as WhatsApp, where patient organizations had created groups aimed at disseminating important treatment and socioeconomic support related information.

Interviewees highlighted the important role that medical social workers played in promoting adherence through counseling and support groups in order to address difficulties that they were facing in adhering to the prescription and reminding them to do routine tests as per the schedule. Medical social workers were also reported to provide them with access to free or subsidized resources such as iron chelation therapy, blood, and routine tests. However, several key informants mentioned that there were not enough counselors, support groups, and peer support to address psychosocial issues being experienced by patients. At the end of the interview, one caregiver mentioned that this was the first time that they had spoken at such length with anyone

regarding their experiences, which indicates that they were not receiving counseling to help them cope with their issues. Key informants also highlighted the importance of supportive family and friends in treatment adherence; this was confirmed by many caregivers and patients. Examples of such support included: accompanying the affected individuals for transfusions, reminders to take iron chelation medications, financial assistance, and planning social activities around the patient's transfusion schedule. There were also a few reports of a lack of support from family or friends. Interviewees also reported that shared responsibility of the medical management of the child between both parents had a positive influence on adherence to blood transfusions, whereas the opposite was true for situations where only one parent was responsible for the child's medical management. The reason for this was that if the parent was unavailable or unwell they would have no one to accompany the patient for blood transfusions or supervise iron chelation administration and other aspects of care.

Many key informants mentioned that illiterate caregivers and patients found it difficult to navigate within hospitals to access essential management-related health services, which in turn negatively influenced adherence. Distance of the testing center or transfusion facility from the patient's home was reported to cause commuting difficulties, which also negatively influenced adherence to essential management. Interviewees also reported that broad social issues such as preferential treatment of male children and social rejection and stigma towards people with disabilities, negatively influenced adherence to essential management. One interviewee mentioned that he never used to carry iron chelation medications to his village during his annual trip because he feared being stigmatized or rejected by the other villagers if they found out that his children had thalassemia.

As described in the previous section, financial support was available through hospitals, patient organizations and the government. Unfortunately, several interviews indicated that affected families lacked awareness regarding the existence of these amenities. Some interviewees also mentioned that patients were unable apply for government support due to missing government issued documents regarding their financial status and proof of residence.

*K: The ones who work in Pune but have their native place somewhere else like Solapur. So, if he needs to add the child's name to the ration card, he can only do that at a government at his native place. Even if he needs to get an Aadhar card made for his child then he needs to go back to his native place to get it made... There are many children who have been buying the medications for more than 2 years but still have not been able to enroll in the scheme.*

*(Key informant: Social worker)*

(ix) Psychological/Behavioral

Opportunities and constraints in this category that influenced adherence were patient-related as per the WHO multidimensional adherence framework, at the individual-level of hierarchy as per the ecological model. The factors in this category were associated with the patient or caregiver's psychological state and behaviors that influenced their ability to adhere to treatment. Subcategories included: Use of adherence strategies, resourcefulness/proactiveness, patient traits, caregiver/patient issues, burnout, supervision, caregiver competence, familiarity with transfusion facility, and discomfort with medication brand changes.

Interviewees mentioned various strategies that they used to improve adherence to blood transfusions. Several interviewees who were caregivers mentioned that they tried to normalize the blood transfusion experience by keeping patients busy with recreational activities during the transfusion. Quite uniquely, one caregiver used to permit one day of the week during which her two affected adult children didn't have to take medications. This was done with the intention of

making them more socially functional by not making thalassemia the focus of their lives. Other well-managed patients also mentioned that thalassemia was not the focus of their lives; if it was then they would be more likely to feel burdened by it and become tired of treatment. This approach was also supported by several other caregivers, who explicitly mentioned that they treated their children like “normal children”.

*C: But they don't take it on Sunday. And on Sunday I don't even force them to take it, because they need to take so many medicines every day. Ever since she was 6 months old, and he was 4 months old, and he was premature, the medications have been on so I don't force them on Sunday.*

*(Caregiver, Middle SES, Alternative therapy, 18-26y)*

*C: I tell everyone that I never treated my children as though they had thalassemia. I treated them like normal children. I never used to pressure them too much... even though I knew that they had to go through blood transfusions and take many medications... there's always something...but I never made it the focus of their lives... I have raised them as normal kids.*

*(Caregiver, Middle SES, Alternative therapy, 18-26y)*

Numerous interviewees mentioned that they prioritized time or money for quality blood transfusions, iron chelation therapy or routine testing over other conflicting social/professional activities, professional opportunities or expenses. Prioritization of treatment was also indicated by interviewees who ensured that they carried medication along with them while on vacation or planned their vacations around their blood transfusion schedules.

*C: Our thought process is that if it's Diwali today and we have a blood transfusion scheduled, it's not like the hospital is closed, and instead of 4 nurses there will definitely be 2. So, everything is working, so we should not make an excuse just because it's Diwali. If you have to go, then you have to go.*

*(Caregiver, High SES, Private sector hospital, 18-26y)*

*C: I make sure that his blood transfusion is not delayed. I don't care if I'm inconvenienced but I won't let anything get in the way of my child's treatment.*

*(Caregiver, Low SES, Public sector hospital, 6-12y)*

Another adherence strategy reported by interviewees was overstocking of iron chelators to ensure that the patient does not miss doses as a result of running out or unavailability of the medication. Several interviewees mentioned that adherence to iron chelation was straightforward for them because they had managed to incorporate it into their daily routine. Phone reminders and reminders from other family members helped them to not skip doses. Some interviewees also reported unique strategies that facilitated adherence such as token re-enforcement, where the caregiver would “reward” the patient with a treat for being compliant before and during the blood transfusions. However, both these strategies could backfire as illustrated in the following excerpts:

*C: When he was younger and we had to bring him here, we used first take him to the park, and then to the hospital. So now whenever we're actually going to the park, he questions whether we're taking him to the hospital. He used to get excited when we used to take him to the park, but then used to become very sad and start crying when we brought him to the hospital.*

*(Caregiver, Low SES, Public sector hospital, 6-12y)*

*K: I still remember when we were kids our dad used to force us to go for transfusions, and my sister used to cry and say that she did not want to go. So, then my dad used to tell her that he would take her out to eat dosa if she came...So then gradually we started considered blood transfusion days as picnic days... we fell into a pattern and started looking at blood transfusions positively.*

*(Key informant: Counselor)*

Two key informants mentioned that affected individuals often became tired of taking treatment, especially when they see no improvement in their social lives and are unable to fully accept that they have thalassemia. This eventually leads to “burn-out” where they lose the will to

live. Burn out might lead them to adopt negative coping behaviors, where they become stubborn or demotivated regarding adherence to treatment, because they blame thalassemia for the bad things that happen in their lives and feel hopeless about leading a normal life.

*K: Yes, there are psychological factors as well. We call those sorts of patients “burn-out cases”, when they basically lose the will to live. They basically don’t want to take their medications any more.*

*(Key informant: Counselor)*

*P: It had become a routine for me to keep taking those medications, I got sick of it, so then I just stopped taking them.*

*(Patient, Middle SES, Social sector hospital, 18-26y)*

There were several interviews in which caregivers demonstrated meticulousness, excellent organization skills, mindfulness and optimism, all of which positively influenced adherence. For example, one caregiver took it upon himself to keep a record of each and every pre-transfusion hemoglobin result ever since his son was diagnosed. Another caregiver quite astonishingly remembered very specific dates, such as the exact date that the patient had a transfusion reaction. Another caregiver had charted out a six-month plan for her son’s transfusions.

*C: Well we know that we need to get the transfusion on Saturday, so we plan accordingly. I call them on Monday or Tuesday to ask them whether there is a camp scheduled, since those are scheduled by then. So, if it’s a big camp then I know that the chances of getting blood are high. And in case there is no big camp then I have 2-3 donors on call, so even if the camp is not a big one I can always call the donors, so I’m relaxed. And if there are no donors then ill plan accordingly. I actually have a six month plan ready because my older daughter is in the 12th grade and she will be going to Ahmedabad after that. And I teach classes as well, so I have a schedule.*

*(Caregiver, High SES, Private sector hospital, 6-12y)*

A mindful caregiver mentioned that she got the tests done at the hospital even though they are more expensive because she knows that it would be uncomfortable for her child to get pricked multiple times. Another caregiver would make sure that he never said bad things about the hospital staff to his son, which demonstrated that he was mindful of the negative consequences that that might have on his son's adherence.

*C: Even today sometimes he pulls on the catheter, and it comes out, and then has to be reinserted. So, these things happen, but he has no problem coming here. He is compliant with the doctors. Even if he gets hurt then he will come to me crying and complain, but I won't say anything bad about the doctors... I will ask him: did you do something wrong P? Then he'll admit to pulling the catheter out. I know that they are doing their duty, and I know he will resist.*

*(Caregiver, High SES, Private sector hospital, 6-12y)*

There were also many interviews that indicated that patients' maturity, self-discipline, and cooperative behavior positively influenced adherence to blood transfusions and iron chelation. However, it was also observed that mature patients didn't want to burden their family members with their medical expenses, which negatively influenced adherence to iron chelation therapy and routine testing. There were also many interviewees that reported that patients' stubbornness, fear of needles, forgetfulness, and inability to wake up in time to take medications, negatively influenced adherence to iron chelation therapy and the prescribed blood transfusion schedule. Some interviews also indicated that negligence and carelessness on the part of patients and caregivers negatively influenced adherence to essential management; this usually resulted from hopelessness regarding improvements in the quality of their lives and longevity. Some interviewees also indicated issues with parental supervision, which negatively influenced adherence to iron chelation therapy. For example, a few caregivers mentioned that the affected child would forget to take their medication or administer it incorrectly but failed to accept that that

was a failure on their part because it was their responsibility to supervise the administration of the medication.

Lastly, one key informant mentioned that brand changes of iron chelation medication dispensed for free at government institutions also could negatively impact adherence to iron chelation therapy, because caregivers might not be comfortable administering a new brand of medication, especially when the discontinued brand was working very well for the patient.

*K: There are a lot of problems with adherence in the older kids. You can give the younger kids a couple of slaps and make them do it, but the older kids become very stubborn. As they get older, they feel that it's pointless to take their iron chelation medications because it's really not going to change anything for them.*

*(Key informant: Social worker)*

Many interviewees who were relatively well managed demonstrated resourcefulness and proactiveness that positively influenced their ability to adhere to essential management. Examples included: procurement of disposables such as leukofilters and intracatheters from wholesalers at a discounted price, procurement of chelation medications for free from friends who reside in states where they are available for free, proactively seeking options for free/subsidized routine testing, procurement of medications before they run out, checking hemoglobin levels before the patient presents with symptoms, and finding cheaper testing options. Many of the interviewees who demonstrated resourcefulness and proactiveness also emphasized the importance of maintaining good relations with stakeholders in the thalassemia care ecosystem - such as patient organizations, hospitals, physicians, medical stores, and testing centers - and its positive influence on their ability to adhere to essential management. However, there were interviews that indicated that some caregivers were not resourceful and had a reactive approach to the patient's medical management.

One key informant mentioned that possible reasons for this were illiteracy and poverty. For example at times when there is a blood shortage, some caregivers chose to delay the transfusion by a few days rather than seek blood from other blood banks; while this indicates a lack of resourcefulness, one key informant mentioned that patients do this because they become very familiar or comfortable with getting their transfusions at a particular hospital, and would prefer having it done there - despite the delay - rather than having it done at another hospital.

#### **4. Discussion**

The aspects of essential management for  $\beta$ -thalassemia major include blood transfusions, iron chelation therapy, and routine testing for complications; alternative treatment includes traditional medicine or the use of fetal hemoglobin induction therapy in conjunction with nutraceutical supplements. We identified 150 multidimensional and multilevel opportunities and constraints that influenced adherence to essential management and alternative treatment. Most of the factors influenced more than one aspect of essential management, whereas some influenced only a single aspect of it. Of the 150 opportunities and constraints - 116 were found to influence adherence to blood transfusions, 104 were found to influence adherence to iron chelation therapy, and 72 were found to influence adherence to routine testing. Also, 39 factors were found to influence adherence to alternative treatment. Approximately half of the factors positively influenced adherence, and the other half negatively influenced it

The 150 opportunities and constraints were categorized into 43 subcategories, which in turn were more broadly categorized into 9 generic categories that included the following: 1) Blood security; 2) Blood transfusion convenience; 3) Access to care; 4) Healthcare quality; 5) Financial status/support; 6) Social status/support; 7) Psychology/behavior; 8) Patient/caregiver knowledge

and education ; 9) Nature of disease/treatment. Some of these categories corresponded with a single dimension of the WHO multidimensional adherence framework, others spanned across multiple dimensions.

#### **a. Context and past studies**

Past studies on adherence to essential management of  $\beta$ -thalassemia major patients have mainly focused on patient-related and socioeconomic-related factors that influence adherence to iron chelation therapy. However, there were a few that brought up challenges related to blood transfusions, but none that brought up routine testing. Furthermore, previously investigated factors exerted their influence at the individual and micro ecological levels. Also, past studies did not systematically explore other influential factors in other WHO dimensions of adherence at various ecological levels. Most past studies also adopted a quantitative approach, where adherence was measured using questionnaires and psychometric scales (F. Trachtenberg et al., 2011; Vosper et al., 2018). There were a handful of studies that used qualitative approaches including interviews and focus groups (Abdul Wahab et al., 2011; Atkin & Ahmad, 2000; Ganzella & Zago, 2011; Harandi et al., 2017), and there were a few commentaries or expert opinions (Berdoukas et al., 2011; Dehshal, 2014; J. B. Porter et al., 2011; F. Shah, 2014; F. Shah & Kaltsounis, 2018). Also, there were some studies that were not specifically regarding adherence, but incidentally reported factors that were found to influence adherence in our study (Mathew & Sobti, 2017; Parmar et al., 2017; F. Shah & Kaltsounis, 2018; F. T. Shah et al., 2019). Our study adopted an expanded definition of adherence as per the WHO multidimensional adherence framework, whereas past literature adopted different definitions of adherence, used different approaches, and were done in different contexts. While these difference made it difficult to compare our results to other studies,

some comparisons were possible since previously reported factors also fit into the broader generic categories that were developed.

(i) Financial support/issues

Moirangthem & Phadke (2018) and Palanisamy et al. (2017) reported that patients from a tertiary care center in the state of Uttar Pradesh, and indigenous communities in the state of Tamil Nadu received financial support for treatment via government, voluntary, or charitable organizations. (Al-Kloub, A Bed, Al Khawaldeh, Al Tawarah, & Froelicher, 2014) reported that in a Jordanian patient population financial constraints negatively influenced physician follow-up, which in turn resulted in poor adherence to the routine testing schedule. Abdul Wahab et al. (2011) reported high hospital expenses contributed to financial constraints in a Malaysian patient population. With regards to their study in the state of Uttar Pradesh, Moirangthem & Phadke (2018) also mentioned that several patients were not adhering to the prescribed iron chelation regimen because of how expensive the medications were. Cappellini (2005) and J. B. Porter et al. (2011) also alluded to the need for patients to have infusion pumps to administer desferrioxamine at home, as a factor that negatively influences adherence; several patients in our study also mentioned that the infusion pump was too expensive for them to afford as a result of which they had to resort intravenous administration.

(ii) Blood security

In their review article F. T. Shah et al. (2019) mentioned that blood shortages and blood of varying quality results in under-transfused or unsafely transfused thalassemia patients in resource-poor countries. R. K. Agarwal et al. (2017) confirmed in their study that blood shortages do occur

in India, especially in the summer months, which results in under-transfused patients despite free access to blood through a supportive government policy. Das (2012) also reported that many treatment facilities in India experience issues related to blood safety. However, R. K. Agarwal et al. (2017) also reported that a good working relationship between transfusion facilities and blood banks ensured easy procurement of adequate quality and quantity of safe blood for thalassemia patients. The study conducted by Palanisamy et al. (2017) on patients from indigenous patients in the state of Tamil Nadu reported the importance of the availability of blood donors within their social networks in facilitating adherence to the prescribed blood transfusion schedule.

(iii) Blood transfusion convenience

R. K. Agarwal et al. (2017) mentioned that technology-assisted appointment scheduling was a factor that helped in maintaining adequate pre-transfusion hemoglobin levels in an Indian patient population. Yamashita, Foote, & Weissman (1998) alluded to the benefits of thalassemia patients being transfused in a dedicated ward, as it would provide an opportunity for patients to provide peer support to each other.

(iv) Access to care

Dehshal (2014) reported that difficult procurement of medications contributed towards poor adherence to iron chelation therapy in Iranian patients; Vosper et al. (2018) reported similar findings in their study on a population of patients from the UK. An international survey by Ward et al. (2002) also confirmed that patients, especially those from India and Iran, were overall less adherent to iron chelation therapy due to inaccessibility of the medication.

(v) Social issues/support

There have been many past studies that have reported social issues, social support, and their influence on adherence to essential management in thalassemia patients. Vosper et al. (2018) reported that “doing a different activity from usual or being away from home” was negatively correlated with adherence to iron chelation therapy in a patient population in the UK. In their study, F. L. Trachtenberg et al. (2014) observed that in patients from the USA, UK and Canada, iron chelation adherence was associated with decreased social functioning, which might be an explanation for non-adherence due to conflicting social activities in our study. Similarly, interview data from a study conducted by Abdul Wahab et al. (2011) also indicated that affected individuals from Malaysia thought that oral iron chelation therapy negatively affected their social activities. The same study also found that some employers were not supportive regarding a patient’s or parent’s need to accommodate their blood transfusion schedule. F. Shah (2014), mentioned that adult patients found it difficult to adhere to blood transfusion schedules due to professional and social life conflicts. The positive impact of social support through social workers, peers, and support groups on adherence to essential management, especially iron chelation therapy, was reported in several studies (Palanisamy et al., 2017, Yamashita et al., 1998, Evangeli et al., 2010, Harandi et al., 2017). There were many reports regarding family stability and support from family and friends, or a lack thereof, and it’s influence on adherence to all aspects of essential management (Abdul Wahab et al., 2011; Yesim Aydinok, Erermis, Bukusoglu, Yilmazi, & Solak, 2005; Davis & Lawrence, 2006; Evangeli et al., 2010; Harandi et al., 2017; W. S. Lee, Toh, Chai, & Soo, 2011; Palanisamy et al., 2017; J. B. Porter et al., 2011; F. Shah, 2014; Ward et al., 2002) They also mentioned that commuting difficulties due to long distance of the transfusion center was also an issue for patients who lived outside the city. Several studies reported caregiver or patient

literacy as being an important factor that influenced adherence (Al-Kloub et al., 2014; Evangelini et al., 2010; J. B. Porter et al., 2011). Interestingly, Parmar et al. (2017) conducted a study in Southern Indian states, where they found that female patients had a better pre-transfusion hemoglobin and serum ferritin level as compared to males, which indicates better adherence; this is converse to what was reported by interviewees in our study.

(vi) Patient/caregiver knowledge and education

Many studies highlighted the correlation between patient or caregiver knowledge regarding the disease or management, and its impact on adherence. W. S. Lee et al. (2011) and Y. L. Lee et al. (2009) reported that knowledge regarding desferrioxamine was statistically significantly correlated to adherence to it for patient populations in Taiwan and Malaysia. A commentary by Dehshal (2014) and a qualitative study by Harandi et al (2017) reported that knowledge regarding the disease and treatment, and the need for strict adherence led to better adherence to blood transfusions and iron chelation therapy. Supporting the aforementioned, Cappellini, (2005), J. B. Porter et al. (2011), Treadwell & Weissman, (2001) reported that lack of knowledge regarding the disease and treatment and the need for strict adherence led to poorer adherence to iron chelation therapy. Based on their study of a patient population from the USA, Treadwell & Weissman (2001) alluded to knowledge regarding the disease and treatment amongst other family members in addition to the caregiver positively influenced adherence to iron chelation therapy. A review article by Davis & Lawrence (2006) reported that a study by Vullo, De Sanctis, Borgatti, & Atti, (1989) reported that attending group conferences (awareness events) was positively correlated with adherence to iron chelation therapy.

(vii) Nature of the disease/treatment

Owing to the need to administer desferrioxamine via an infusion pump or intravenously over a long duration of 8-12 hours, it was frequently reported as being painful and inconvenient to administer by multiple sources (Abdul Wahab et al., 2011; Ganzella & Zago, 2011; J. B. Porter et al., 2011; Thuret et al., 2009; F. L. Trachtenberg et al., 2012). However, there were few recent reports of this in the literature, perhaps due to wider availability of oral chelators in recent times. The oral chelators i.e. deferiprone and deferasirox were reported as being convenient to administer (Haghpanah, Zarei, Zahedi, & Karimi, 2014; Harandi et al., 2017); however, there was one study that reported that the need to dissolve deferasirox and drink it as a suspension, was regarded as inconvenient by some patients (Berdoukas et al., 2011). Many studies also reported that adverse effects - either localized at the injection site or systematic - were a common cause of non-adherence to iron chelation therapy, especially desferrioxamine (Abdul Wahab et al., 2011; Berdoukas et al., 2011; Dehshal, 2014; Ganzella & Zago, 2011; W. S. Lee et al., 2011; J. B. Porter et al., 2011; Thuret et al., 2009; F. L. Trachtenberg et al., 2014). Berdoukas et al. (2011) reported that some patients experienced gastrointestinal discomfort as an adverse effect of deferiprone, which was also cited as a reason for skipping doses on transfusion days by a few interviewees from our study. Short-term and long-term symptomatic consequences of delayed or timely blood transfusions and iron chelation were frequently mentioned as factors that influenced adherence (Berdoukas et al., 2011; Davis & Lawrence, 2006; Harandi et al., 2017; Yamashita et al., 1998). A high dosage frequency was also reported to negatively influence adherence to iron chelation therapy (Berdoukas et al., 2011; Dehshal, 2014; J. B. Porter et al., 2011; F. L. Trachtenberg et al., 2014). Similar to what was reported by a few interviewees in our study, in their expert review Berdoukas et al. (2011) reported that the chalky taste of deferasirox made it less palatable, and therefore was a constraint to adherence to iron chelation therapy.

(viii) Healthcare quality

The importance of the quality of physicians and nurses, their communication with patients, and follow-up (Harandi et al., 2017) were reported frequently in the literature. Evangelini et al. (2010) reported that lower perceived quality of care was a constraint to adherence to iron chelation therapy for a patient population from the UK. Dehshal (2014) reported that shared decision making and the quality of physician-patient relationships were important influencers of adherence; the importance of the latter was also alluded to by Harandi et al. (2017) and Ward et al. (2002). Dehshal (2014), F. Shah (2014), and F. T. Shah et al. (2019) mentioned the importance of well-trained physicians with adequate knowledge regarding essential management as being an important factor that enabled adherence. Harandi et al. (2017) and J. B. Porter et al. (2011) also mentioned the importance of the quality of the relationship between hospital staff and patients, in promoting adherence. Our finding regarding the positive influence of hospitals taking responsibility for getting routine tests done, was supported by R. K. Agarwal et al. (2017), who also reported the same in their study in on patient populations from several southern Indian states; this was also supported by J. B. Porter et al. (2011) who mentioned the importance of integrated care in promoting adherence.

(ix) Psychology/Behavior

A majority of the adherence literature that pertains to thalassemia emphasizes the importance of psychological and behavioral characteristics of patients and caregivers in influencing adherence to iron chelation therapy. Harandi et al (2017) and J. B. Porter et al. (2011) reported that token reinforcement and normalization of the patient's experience through social

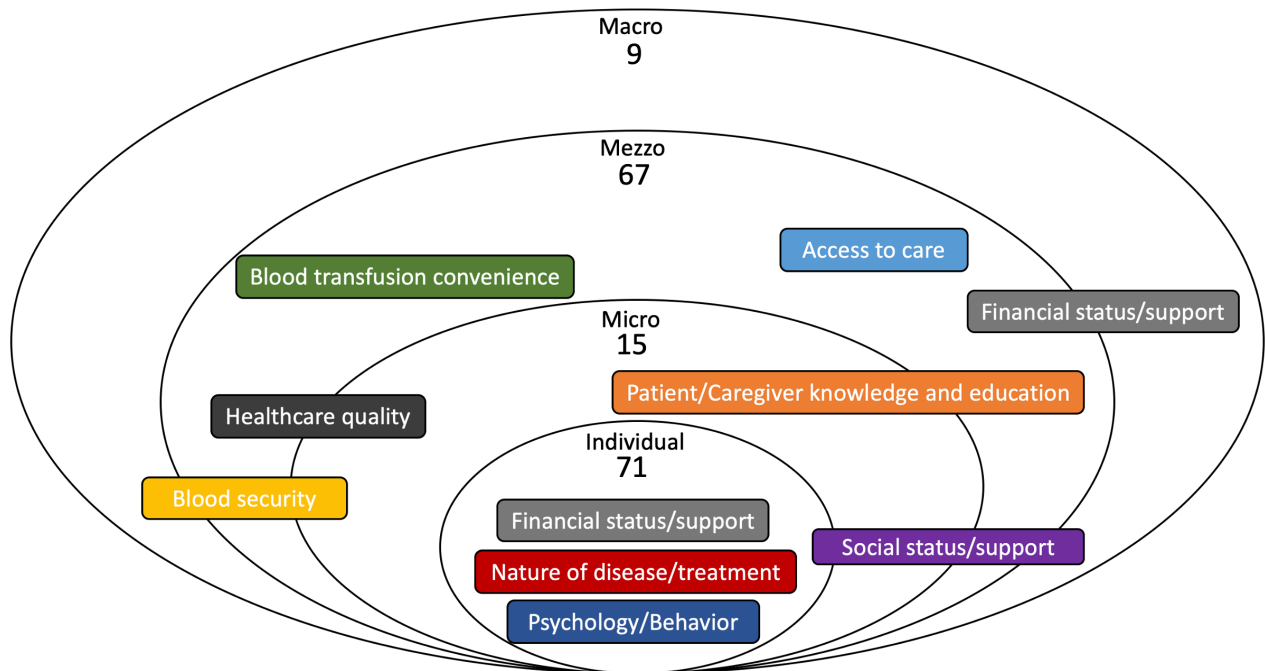
activities were strategies that might be effective at improving treatment adherence. Several past studies report that stubbornness or oppositional behavior as being factors that have a significant negative influence on adherence, especially amongst adolescent patients (Abdul Wahab et al., 2011; Davis & Lawrence, 2006). On the other hand Al-Kloub et al. (2014), Evangeli et al. (2010), and F. L. Trachtenberg et al. (2014), reported a positive association between age or maturity and treatment adherence in affected individuals. Abdul Wahab et al. (2011) also reported that caregivers and patients from a Malaysian population feared blood transfusions due to questionable blood safety, which served as a constraint to adherence to blood transfusions. J. B. Porter et al. (2011) reported that forgetfulness negatively influence adherence to iron chelation therapy. Many studies alluded to various psychological factors that were reported by interviewees in our study, as being negatively associated with adherence to iron chelation therapy or blood transfusions; these included: hopelessness (F. Shah, 2014), tired of treatment, demotivation and denial (J. B. Porter et al., 2011), and psychological distress including depression and anxiety (Al-Kloub et al., 2014; Dehshal, 2014; Evangeli et al., 2010; Ganzella & Zago, 2011; Harandi et al., 2017; J. B. Porter et al., 2011; F. Shah, 2014). Al-Kloub et al. (2014) and Harandi et al. (2017) also reported the influence of parental supervision on adherence to iron chelation therapy in patient populations from Jordan and Iran.

Many of the factors that were reported in our study were not reported in past studies regarding adherence to essential management in thalassemia patients, but it is very likely that they have been reported in the broader adherence literature, which is beyond the scope of this discussion. Findings that have not previously been reported in past studies pertaining to thalassemia might be attributable to our qualitative and exploratory approach which led to the

identification of context-specific factors, or it could also be attributed to our use of a multidimensional definition of adherence.

**b. Processes by which opportunities and constraints influence adherence - an ecological conceptualization**

As depicted in Figure 9, factors that influence adherence were also further classified according to their ecological level of influence. Of the 150 factors that were found to influence adherence to essential management, 71, 15, 67, and 9 were found to exert their influence at the individual, micro, mezzo, and macro ecological levels respectively; 2 factors exerted their influence at the individual and mezzo ecological levels, 5 factors exerted their influence at the micro and mezzo ecological levels, and 5 factors exerted their influence at the mezzo and macro ecological levels.

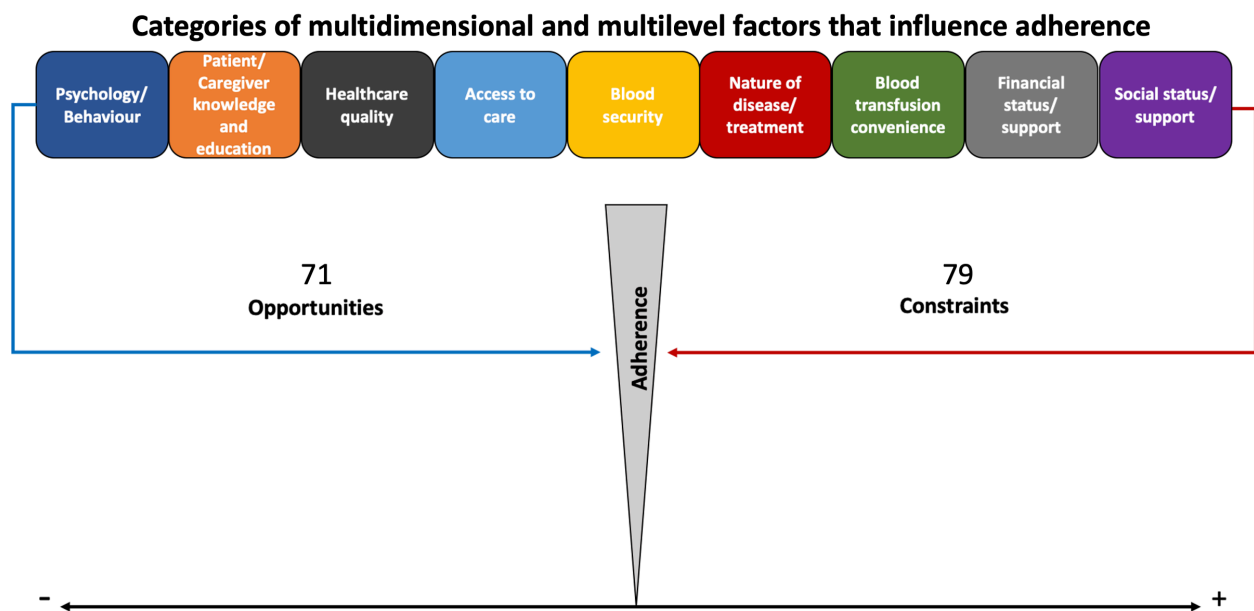


**Figure 9: Links between categories of adherence-influencing factors and ecological levels.** While some categories fit neatly into a single ecological level, others extend across more than one ecological level.

According to the Society-Behavior-Biology nexus proposed by Glass & McAtee (2006) factors that influence human behaviors - such as treatment adherence - can be broadly divided into environmental and individual factors. They visualized environmental factors as a running stream flowing downwards from distal macro-level factors to proximate micro-level factors. Macro-level factors are related to phenomena that take place at a large scale and influence many people, such as the state or national level and might include national or state policies, and cultural belief systems. Micro-level factors are related to phenomena that take place at a smaller scale and influence individuals, such as intra-personal family dynamics and social networks. There are factors that fall in between the macro and micro-levels; these mezzo-level factors are related to phenomena that take place at a medium scale and influence a large group of people, such as community and healthcare organizations. The aforementioned ecological conceptualization is also mirrored in the WHO Innovative Care for Chronic Conditions (ICCC) framework, which posits that prevention and disease management is influenced by factors that go beyond patients and their families (individual-level) to include: their relationships with healthcare teams and community partners (micro-level), factors related to healthcare and community organizations (mezzo-level), and the broader policy environment (macro-level). Hence the macro, mezzo, micro, and individual-levels are hierarchical levels of influence. Factors from different hierarchical levels interact and influence each other differently at different stages of life to impose opportunities or constraints that shape human behaviors such as adherence. Berben et al. (2012) suggest that the etiology of adherence behavior might be best understood using an ecological conceptualization. Based on the aforementioned, we think that the findings of this study would be best understood

and utilized based on an ecological conceptualization of adherence where multidimensional and multilevel opportunities and constraints interact with each other to influence adherence behavior.

In line with an ecological conceptualization of adherence, our study revealed that the identified multidimensional and multilevel factors served as either opportunities or constraints that had a cascading influence on adherence to essential management in the thalassemia community. This has been illustrated in Figure 10, which was adapted from Glass & McAtee (2006).



**Figure 10: Cascading influence of multidimensional and multilevel factors on adherence to essential management.**

Examples of the cascading influence of multidimensional and multilevel opportunities and constraints on adherence to essential management are given below. Factors that serve as opportunities or constraints are in bold text, and corresponding features including the WHO dimension of adherence and ecological level of influence are mentioned in brackets alongside each factor, or groups of factors that have the same features.

In many interviews, participants indicated that they had sufficient **knowledge of the disease and treatment** and **understood the importance of adhering to it** (patient-related opportunity, individual-level), and demonstrated **maturity** and **self-discipline** (patient-related opportunity, individual-level). However, the same individuals also reported not being able to adhere to essential management due to **financial constraints** (socioeconomic-related constraint, individual-level), due to which they were not able to afford **expensive chelators** (socioeconomic-related constraint, mezzo-level), or because they found it **difficult to procure iron chelation medication** (health system/HCT-related constraint, mezzo-level).

Some interviewees reported being able to adhere to the routine testing schedule despite **financial constraints** (socioeconomic-related constraint, individual-level) because they possessed **knowledge of the disease and treatment** and **understood the importance of adhering** to the routine testing schedule (patient-related opportunity, individual-level), which led them to **prioritize it** (patient-related opportunity, individual-level).

One interview illustrated how a combination of factors had contributed towards her being able to adhere to desferrioxamine therapy. Her **resourcefulness** (patient-related opportunity, individual-level) enabled her to get an **infusion pump on a rental basis** through **support from a patient organization** (socioeconomic-related opportunity, mezzo-level), which she knew how to administer due to **knowledge** (patient-related opportunity, individual-level) that she acquired through **awareness events** (health system/HCT related opportunity, mezzo-level). She was able to administer it despite the **long duration of administration** (treatment-related constraint, individual-level) because of **support from her educational institution** (socioeconomic-related opportunity, mezzo-level), **family and friends** (socioeconomic-related opportunity, individual-level)

Another interviewee reported non-adherence to oral iron chelation therapy despite **understanding the importance of adhering** to it (patient-related opportunity, individual-level), and receiving **free chelators** through a **supportive government policy** (socio-economic-related opportunity, macro-level). The reason for this was that the child would either **sleep through the dose** and miss it or was too **stubborn** to take it (patient-related constraint, individual-level). Another reason was **poor supervision from the caregiver** (socioeconomic-related constraint, individual-level). Another interviewee, who was also receiving **free chelators**, indicated that a **lack of counseling** (socioeconomic-related constraint, micro-level) led to **hopelessness** (patient-related constraint, individual-level), which in turn led to non-adherence to iron chelation therapy.

Uniquely, a patient who could afford the **expensive chelators** (socioeconomic-related constraint, mezzo-level) due to **financial stability** (socioeconomic-related opportunity, individual-level), and had also **understood the importance of adhering** to chelation therapy (patient-related opportunity, individual-level), reported being occasionally non-adherent because she had grown **tired of the treatment** (patient-related constraint, individual-level), and was disappointed with the **unsatisfactory care from her physician** (health system/HCT-related constraint, micro/mezzo-level) as he **wouldn't prescribe** changes to her chelation therapy regime (health system/HCT-related constraint, mezzo-level) to help reduce her high serum ferritin levels.

A key informant talked about the link between **unsuitable transfusion timings** (health system/HCT-related-constraint, mezzo-level) and non-adherence i.e. that the former resulted in patients having to take a few days off from work every month, which resulted in backlog and unhappy employers; this in turn led to high work pressure and subsequent prioritization of **conflicting professional responsibilities** (socioeconomic-related constraint, individual-level) over adherence to the essential management.

Another key informant described the impact of non-adherence early on in life due to **negligent caregivers**, which led to the development of thalassemia facies, short stature and other phenotypic features; this in turn led to **social rejection** (socioeconomic-related constraint, mezzo-level) and subsequent burnout, which included **psychological distress, hopelessness** and **negative coping** (patient-related constraint, individual-level). This in turn worsened adherence to essential management.

A few interviewees highlighted the link between **unsatisfactory nursing staff** (health system/HCT-related constraint, micro/mezzo-level) and non-adherence to the blood transfusion schedule. Inexperienced nurses would **prick patients multiple times to find a vein** (health system/HCT-related constraint, mezzo-level), which was **painful** (treatment-related constraint, individual-level) and instilled **fear** of being pricked in the patient and subsequent **stubbornness** to go for blood transfusions (patient-related constraint, individual-level).

Interestingly a particular interview illustrated how the interaction and influence of multilevel factors across dimensions threw affected families into a cycle of poverty. **Expensive disposables** used for transfusions along with **high cumulative expenses** related to care (socioeconomic-related constraint, mezzo-level) led to **financial constraints** (socioeconomic-related constraint, individual-level), which in turn led the primary caregiver having to prioritize **conflicting professional responsibilities** and being **unavailable to accompany the patient** for transfusions on time (socioeconomic-related constraint, individual-level). This led to a very low pre-transfusion hemoglobin, which resulted in the caregiver and patient having to go through **multi-day transfusions** (health system/HCT-related constraint, mezzo-level) to increase his hemoglobin to an acceptable level. Not only did this further increase the already **high cumulative**

**expenses**, but it also led to the caregiver having to take multiple days off from work, which led to even more **financial constraints** (socioeconomic-related constraint, individual-level).

### **c. Dissemination strategy and potential interventions**

A dissemination strategy can be developed based on the ecological level at which factors exert their influence. For factors that were found to influence adherence at the individual or the micro-level, the results could be disseminated to individuals who have direct interactions with patients; these might include physicians, nurses, social workers, counselors, and patient organization representatives. For factors that were found to influence adherence at the mezzo-level – the results could be disseminated to executives of health care organizations and community organizations, who are capable of influencing change at the organizational level; specifically, these might include: key hospital administrative staff, blood bank directors, and patient organization leaders. For factors that were found to influence adherence at the macro-level – the results could be disseminated to senior leadership of organizations who have ties with policymakers at the macro-level; specifically, these might include: government hospital champions, state and national level government authorities, and patient organization leaders.

Potential interventions can also be planned by using the same approach. Factors that are constraints to adherence present opportunities for interventions by stakeholders within the ecological level that the constraint exerts its influence, whereas factors that positively influence adherence can be augmented through interventions to further enhance facilitation of adherence. In line with the literature and a multidimensional, ecological conceptualization of adherence, interventions should employ multiple strategies that target factors across dimensions and ecological levels (Andrzejczyk, 2012; Sabate, 2003) as these are likely to be more effective than

interventions that target factors individually. Local stakeholders can use the factors identified to design multi-faceted interventions accordingly.

A widely reported facilitator of adherence to essential management was interorganizational collaboration, which had led to financial support and better availability of resources related to essential management. This suggests that interorganizational collaboration might be an effective means to address constraints to adherence. Many constraints that were identified could foreseeably be addressed via interventions that involve multiple organizations. For example:

- Psychological and behavioral barriers to adherence could be addressed through collaborations between healthcare and community organizations, where the former refers affected individuals and caregivers to the latter to receive training and counseling regarding adherence strategies, positive coping mechanisms, and self-management.
- Communication regarding available amenities and subsidies for affected individuals and their families between hospital and community organization personnel, can also aid in timely direction to available resources, thereby promoting adherence.
- Patients and caregivers can't always voice their concerns directly to hospital authorities out of fear; perhaps community organizations can serve as intermediaries who communicate adherence-related pain-points experienced by patients to the hospital authorities; this might help improve the quality of healthcare services as they pertain to the promotion of adherence.
- While hospitals - especially those in the private sector - may compete with each other, information sharing between them can help in the adoption of practices or services that have been known to facilitate adherence.

- Patients can be referred between hospitals and laboratories for medical tests that are not widely available.
- Collaborative educational events between hospitals and community organizations can be organized in order to improve patients' and caregivers' knowledge regarding thalassemia and the importance of adherence.
- Blood banks can collaborate with each other to facilitate easier blood procurement.
- Collaboration between community organizations and pharmacists or pharmaceutical companies, where medications are purchased at bulk rates and then distributed to the thalassemia community at a price that is lower than the market price, can help promote adherence in affected individuals facing financial constraints.

The aforementioned collaboration possibilities are exemplary of links between community and health care organization in the delivery of health services for chronic conditions, which has been emphasized by the ICCC framework (World Health Organisation, 2002).

#### **d. Strengths and limitations**

A significant strength of our study was that our decision to use qualitative interviews to explore the adherence phenomena enabled us to identify context-specific factors that influenced adherence and also enabled us to explore some of the processes by which factors across adherence dimensions and ecological levels interacted with each other to influence adherence to essential management.

One of the limitations of our study was that several interviews took place in semi-private hospital settings, as there was no completely private space available to conduct the interviews.

This might have caused interviewees to withhold information regarding health system or healthcare team-related factors that negatively influenced their ability to adhere to essential management. Another limitation of our study is that we may have missed out on recruiting patients who had very poor adherence, as they are less likely to be in contact with patient organizations and hospitals, which is where our study participants were recruited from.

#### **e. Future directions**

No single methodology can capture all the opportunities and constraints that influence adherence. While our study identified a wide range of opportunities and constraints to essential management, there could be less common ones that can be uncovered by further studies. Many past studies reported that patient-related behavioral factors, such as self-efficacy and psychological disorders, were important determinants of adherence, which were not reported in our study. The aforementioned studies used validated psychometric tools, which would likely be a suitable approach for the identification of such factors.

The significant challenges associated with adherence in adolescents affected by thalassemia has been frequently reported in the literature. Additional studies that correlate opportunities and constraints that influence adherence to the life-stage of the patient would be beneficial as they would allow for targeted interventions based on a patient's age.

Some interviews in our study suggested deviations from treatment guidelines. In light of this, studies that determine factors that influence treating physicians' adherence to treatment guidelines, might be beneficial towards improving health outcomes for the thalassemia community in Pune, India.

Lastly, further exploration of opportunities and constraints that influence adherence can help improve current interventions and can also help design more effective multifaceted interventions that target multiple factors (Kripalani, Yao, & Haynes, 2007) .

#### **f. Implications**

Improving adherence of thalassemia patients to essential management has the potential to greatly improve their health outcomes and quality of life. No study has previously sought to identify opportunities and constraints that influence adherence to all three aspects of essential management in thalassemia patients residing in Pune, India. In fact, to the best of our knowledge this is the first study of its kind in India. Taken together, our study identified multidimensional and multilevel opportunities and constraints that influence adherence to essential management in individuals affected by  $\beta$ -thalassemia major residing in and around Pune, India. An ecological conceptualization of adherence, that appreciates the interaction between opportunities and constraints and their cascading influence on adherence, provides a suitable lens to interpret our study findings. Local stakeholders including community, healthcare, and government organizations can use these findings to design multifaceted, evidence-based interventions that target multiple factors across the 5 dimensions of adherence and across ecological levels. Additionally, researchers can use this initial data to select variables for quantitative studies that seek to establish correlations between various variables and adherence.

## **CHAPTER 3**

### **Network characteristics and connectivity of cross-sector organizations that influence adherence to essential management in $\beta$ -thalassemia major patients residing in Pune, India.**

#### **1. Introduction**

The management of  $\beta$ -thalassemia major essentially involves blood transfusions to prevent anemia, iron chelation therapy to prevent iron overload, and routine testing to monitor for complications. Adherence to these three interventions can greatly increase the quality of life and longevity of affected individuals (Maria Domenica Cappellini, Alan Cohen, John Porter, Ali Taher, 2014). An ecological conceptualization of adherence to long-term therapies for chronic conditions, including thalassemia, posits that adherence is influenced by opportunities and constraints that go beyond affected individuals, their families and their relationships with health care teams and community partners to include those related to healthcare and community organizations, and the broader policy environment (Michael Angastiniotis & Eleftheriou, 2009; Berben et al., 2012; J. E. Epping-Jordan et al., 2004). Supporting this conceptualization, the Innovative Care for Chronic Conditions (ICCC) framework emphasizes the importance of links between healthcare organizations and community organizations as part of its strategy to reduce the burden of chronic conditions in developing countries (World Health Organisation, 2002).

The reason for emphasizing the aforementioned links in the context of developing countries is that resources are often scarce, and the multitude of needs of the patient community cannot be met by any individual organization (K. G. Provan et al., 2004). Furthermore, the broader public health literature suggests that collaboration between organizations is essential for health needs of a community to be sustainably met, as the coordination and integration of health services can

improve their availability, efficiency, effectiveness, and reach (K. Provan & Milward, 2001; K. Provan, Veazie, et al., 2005).

While the importance of interorganizational links has been highlighted in the literature, to our knowledge a context-specific study that maps stakeholder organizations that influence adherence to thalassemia management and explores links between them has not been conducted in India or other countries. With this in mind, this exploratory study aims to identify and determine the cross-sector connectivity between stakeholder organizations that influence adherence to essential management in the community, healthcare, and government sectors; it also aims to determine connectivity between stakeholder organizations within the community and healthcare sectors.

Past studies related to thalassemia sought to understand the status quo through individual or organizational characteristics, with the intention to make interventions targeting those levels (Moirangthem & Phadke, 2018; Palanisamy et al., 2017; D. Shaligram, Girimaji, & Chaturvedi, 2007). However, given that adherence (or a lack thereof) is not simply a consequence of individual or organizational behavior, such interventions might not be sufficient. Unlike past studies, the current study was conducted with the intention to lay the ground-work for evidence-based strategic interventions to improve the integration and coordination of health services at the network level rather than the individual or organizational levels (K. Provan & Milward, 2001).

## **2. Study setting**

This study took place in Pune, the second largest city in the state of Maharashtra in western India. Pune has an area of approximately 330 km<sup>2</sup> and projections based on the most recent population census in 2011, indicate that it has a population of 3.1 million. Given the absence of

epidemiological studies regarding  $\beta$ -thalassemia major in Pune, there is no official data available regarding its incidence and prevalence; however, field inputs suggest that there are over 500 affected individuals in Pune city. The presence of large resident Sindhi, Punjabi, and Maratha communities also suggests that there are many individuals affected by  $\beta$ -thalassemia major in Pune city, since these communities have been reported to have a relatively high prevalence of  $\beta$ -thalassemia trait (Patel et al., 2014; Sheth et al., 2008).

Community immersion prior to study commencement suggested that in Pune, India, healthcare organizations that provide services for thalassemia patients are ample; they are run by trusts, private entities, the government and the armed forces. Apart from blood banks and laboratories associated with these healthcare facilities, there are also standalone blood banks and laboratories that catered to the blood and testing requirements of the thalassemia community. There are local and non-local community organizations dedicated to improving the quality of life of thalassemia patients through psychological, social, and economic support. Additionally, there are other community organizations with broader mandates that are making significant contributions towards improving quality of life of the thalassemia community. Personal communications during community immersion suggested that charitable organizations, private donors and commercial entities (through their CSR mandates) also play an indispensable role in supporting the aforementioned stakeholder organizations either financially by providing funds, or non-financially by regularly organizing large blood donation camps.

### **3. Methods**

#### **a. Ethical consideration and investigator's experience**

This study was approved by the University of Washington Institutional Review Board, Seattle, USA (IRB ID: STUDY-00006828). Additionally, this study was also approved by the Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital Institutional Ethics Committee, Pune, India (Ph.D 0619072-072).

All network surveys and influential key informant interviews were administered by the lead investigator (SK) as part of his PhD dissertation research. Prior to study commencement, the lead investigator spent a total of 6 months immersing himself in the thalassemia community through participation in events organized by the local advocacy groups, and through informal interactions with key stakeholders and adults affected by thalassemia who were actively involved with the community organizations. The lead investigator also had prior experience in conducting qualitative interviews for an unpublished research project as part of a previous graduate degree requirement.

#### **b. Study design and justification**

This cross-sectional, exploratory, whole network study employed a mixed methods approach that included network surveys and in-depth interviews. The reason for choosing to use a quantitative network approach coupled with qualitative in-depth interviews was to gain insights not only regarding network structure, but also regarding the context-specific processes that might be responsible for it.

Network surveys were administered to expert informants of stakeholder organizations across private, public and social sectors that influence patient adherence to blood transfusions, iron chelation, and routine testing in Pune city. The purpose of the network surveys was to collect data regarding relational ties between stakeholder organizations, based on which network structure and

characteristics could be inferred. In-depth interviews were administered to influential informants in order to understand their perceptions regarding interorganizational collaboration, specifically: its utility, necessity, practicality and potential for improvement. Given that each of them had a minimum of 20 years of experience with the thalassemia community in Pune city, we thought that in-depth interviews would be the most suitable approach to obtain detailed real-world insights regarding the network.

### **c. Participant selection and recruitment**

Participating stakeholder organizations were based within the city limits of Pune and belonged to either the private, public, or social sectors. The organizations could be categorized as follows: healthcare organization, blood bank, diagnostic lab, community organization, government office, and medical store. All participating organizations influenced patient adherence to blood transfusions, iron chelation, or routine testing either by making them accessible, or through behavioral interventions and awareness initiatives. Though important, organizations that provided financial support to the aforementioned organizations were excluded from the study because such information was regarded as confidential by many stakeholder organizations, which would have led to incomplete data. Additionally, organizations that collaborated with the aforementioned organizations to improve the supply of blood through blood donation camps were also excluded from the study. Lastly, nominated state-level or national-level community organizations and government offices that did not have a physical presence (office or representative) in Pune city, were included in the study but not surveyed as it was not feasible to do so due to their geographical location.

For the network surveys, an initial sampling roster of 30 organizations was compiled through a combination of field interactions, internet search, and consultation with a key informant who had been part of the thalassemia community for more than three decades and had vast professional and personal experience with the aforementioned stakeholder organizations. The roster was expanded to 43 after participant nominations during survey administration and finally included 13 hospitals, 2 medical stores, 8 standalone blood banks, 5 standalone diagnostic labs, 3 local community organizations, 5 state-level community organizations, 4 national-level community organizations, 2 state government offices, and 1 national government office. Most participants held directorial or other senior positions in these organizations and had been employees for more than 5 years, which maximized the likelihood that they had knowledge regarding all links with other organizations. If it was established that there was no single expert informant in the stakeholder organization that was aware of all relational ties, the survey was administered to more than one expert informant, either individually or together; this was done for 4 organizations, 3 of which had two expert informants, and 1 of which had three expert informants. Prior to survey administration, all participants were given explanations regarding the purpose of the study and its potential benefits to the thalassemia community, assurances of confidentiality, and the potential risks of participating. The network surveys were administered in-person at the participants' workplaces.

For the qualitative in-depth interviews, 3 influential informants were identified after numerous interactions during field immersion. In order to capture diverse opinions, they were selected based on their extensive involvement with the thalassemia community and their combined professional experience across sectors. Each of them had more than 20 years of personal and professional involvement with the thalassemia community, and amongst them had extensive

professional experiences in the private, public, and social sectors. In-person verbal or written consent - based on individual institutional requirements – was obtained from all of them after explaining the purpose of the study and potential risks involved.

#### **d. Data Collection**

Network data collection involved in-person administration of a survey (Appendix D), that was a combination of a roster and name generator, to expert informants from each stakeholder organization. The most common method used to collect relational ties that organizations share is via a network survey that can be administered digitally or in-person. While most surveys are administered online for ease of data collection, the lead investigator of this study administered them in-person as it has been suggested that this improves the quality of the data (K. Provan, Harvey, et al., 2005). The network survey was piloted with one non-participant to check for ease of administration, participant fatigue, and clarity of the survey questions; modifications were made based on feedback received. The lead investigator administered the survey in-person in the participants' preferred language. To start with, details regarding characteristics of the organization and expert informant relevant to the study were ascertained. These included the sector that the organization belonged to, the position of the participant within the organization, and the thalassemia-related services that they offered. Following this survey questions were used to collect network data regarding 3 types of relational ties: joint activities, shared referrals, and shared interactions, related to improving access or adherence to blood transfusions, iron chelation, or routine testing. First, each relational tie was described to the participant, for example "Joint activities include but are not limited to: free or subsidized testing camps, awareness events for patients or physicians, etc.", following which participants were asked to recall organizations in

each of these categories that they shared relational ties with. Organizations that were mentioned by respondents but were not on our roster were considered as nominations and were added to the list. Following this the participant's attention was drawn to the list of organizations and they were asked if they recognized any additional organizations from the list with whom they shared the aforementioned relational ties. A relational tie was considered a confirmed link as long as it was reported by a single organization.

A semi-structured interview guide (Appendix E) consisting of four open-ended questions was developed to elicit influential informants' perceptions regarding the utility, necessity, practicality, and improvement potential of interorganizational collaboration to improve treatment adherence. The interviews ranged from 30 minutes to 45 minutes, were audio-recorded, translated and subject to non-verbatim transcription by the lead investigator. The interviews were conducted at participants' private workplaces by the lead investigator in English, Hindi, or a combination of the two languages ("Hinglish").

#### **e. Analysis**

Social network analysis was used to characterize the structure of relational ties within and across sectors (community, healthcare, government), and identify key players within the network. For this purpose, the Kumu web application ("Kumu [Relationship mapping software]," 2020) was used to calculate density scores, degree centrality, betweenness centrality, and multiplexity; these are described below in more detail. Additionally, the Kumu web application was also used to create network sociograms for each of the three relational ties that were investigated.

Density: The amount of social activity or connectedness in the network is captured in the literature using this measure. The density score of organizations within sectors was calculated by aggregating the number of relational ties between all dyads within a sector and dividing that by all possible ties within it. The density score of organizations across sectors was calculated by aggregating the relational ties between two sectors and dividing that by all possible ties between them. Density scores range between 0 and 1, where 0 indicates that there no observed ties, whereas 1 indicates that all possible ties are observed. Hence the higher the density score, the more the social activity in the network (K. Provan, Harvey, et al., 2005; Robins, 2015).

Multiplexity: When multiple relational ties are assessed for organizations in the network, a multiplexity score can be calculated by aggregating the number of relational ties between organizations. The multiplexity score would be indicative of the strength of the relationship between two organizations, where higher scores would indicate that the organizations have a stronger relationship since they are bound by multiple types of relational ties, and lower scores would indicate that the organizations have a weaker relationship since they are bound by fewer relational ties (K. Provan, Harvey, et al., 2005; Robins, 2015).

Centrality: While there are several ways to identify key organizations in a network through different types of centrality measures, the most commonly used measures are degree centrality and betweenness centrality. Degree centrality is calculated by determining the total number of relational ties that an organization has. High degree centrality of an organization indicates that it is connected to many other organizations, which suggests active involvement in the network (Robins, 2015). Betweenness centrality is calculated based on how frequently an organization sits

on the shortest path between pairs of organizations. High betweenness centrality of an organization indicates that it is frequently connected directly or indirectly to two or more unconnected organizations, which suggests that it has the potential to improve connectivity between those organizations (Robins, 2015). Network-level centralization values that range from 0 to 1 can be calculated from organization-level centrality scores, where higher centralization values are indicative of dominance by one or a few agencies (Tsai & Petrescu-Prahova, 2016).

Interviews were transcribed and translated verbatim by the lead investigator, and then subjected to inductive content analysis (Hsieh & Shannon, 2005), where each interview was considered as a single unit of analysis. The Dedoose QDA software package (Dedoose Version 8.0.35, web application for managing, analyzing, and presenting qualitative and mixed method research data, 2018) was used to inductively code manifest content. Each transcript was read carefully by the lead investigator, and codes were developed based on excerpts that captured participants' perception or opinion regarding the utility, necessity, practicality, or improvement potential of interorganizational collaborations. These codes were applied to all excerpts that captured similar perceptions or opinions in all three transcripts. Following this, the codes were either combined or sub-coded based on similarity between codes or diversity within a code. The final code list was more broadly categorized into a hierarchical structure, which was then used to describe the perceptions and opinions of participants.

#### **4. Results**

The 43 organizations were categorized as community sector, healthcare sector, and government sector organizations; this choice of sectoral categorization was informed by the ICCC framework (World Health Organisation, 2002). The community sector organizations included:

local community organizations (3), a non-local community organization (1), a local patient organization (1), state-level patient organizations (2), national-level patient organizations (4), and a state-level physician-community organization (1). The healthcare sector organizations included: local hospitals with attached blood banks (13), local stand-alone blood banks (8), local diagnostic labs (4), a national-level diagnostic lab (1), and pharmacies (2). The government sector included: state-level government offices (2), and a national-level government office (1).

From the aforementioned organizations, 7 did not have a physical presence (office or representative) in Pune city. These included: a state-level community organization (1), a state-level patient organization (1), a state-level physician-community organization (1), national level patient organizations (2), a state-level government office (1), and a national level government office (1). Even though these organizations did not have a physical presence in Pune, community engagement by the lead investigator prior to data collection suggested that they may exert an influence on adherence to essential management through relational ties with local organizations. However, these organizations could not be surveyed due to feasibility issues, but we included in the analysis the relational ties that these organizations had with organizations that we surveyed.

We were not able to survey two of the 36 organizations that had a physical location in Pune. The representative of a local hospital with attached blood bank declined participation, and the representative of a national-level diagnostic lab was unreachable despite repeated contact attempts. Hence the response rate amongst these 36 organizations was approximately 94%.

#### **a. Overall network structure and key players**

Table 3 describes density scores for the communications, joint activities and shared referrals networks. The density scores indicate that organizations in the network engage in

communication - which is the most basic form of collaboration - 36% and 48% more than they engage in joint activities and shared referrals respectively, which are more advanced forms of collaboration. The density score for the whole network indicates that during the period of data collection, the organizations were engaged in 10% of all possible relational ties.

Betweenness centrality measures (Table 3) indicated that a few organizations held gatekeeper positions in the network, where they bridged pairs of organizations: P1 (local patient organization), B1 (local blood bank), G1 (state government office), H8 (hospital), H9 (hospital), and P11 (local community organization). These 6 organizations had high betweenness centrality scores across the communications, joint activities, and shared referrals networks - except G1, which didn't feature in the shared referrals network.

Degree centrality measures (Table 3) indicated that a few organizations held central positions across all three networks, where they had the highest number of ties with other organizations. Two organizations - P1 (patient organization) and B1 (blood bank) had high degree centrality scores across the communications, joint activities, and shared referrals network, whereas G1 (state government office), H8 (hospital), H9 (hospital), and P11 (local community organization) featured in the top 5 in two of the three networks. H3 (hospital) had a high degree centrality score only in the referrals network.

<b>Link type</b>	<b>Density</b>	<b>Degree centrality (top 5)</b>	<b>Betweenness centrality (top 5)</b>
Communication	0.14	P1 (23), B1 (18), G1 (18), H9 (16), H8 (13)	P1(0.328), G1(0.149), H9(0.139), B1(0.097), P11/H8(0.096)

Joint activities	0.09	G1 (18), P1 (13), B1 (10), P11 (10), H8 (9)	G1(0.344), P1(0.268), P11(0.184), H9(0.088), H8/B1 (0.087)
Referrals	0.07	P1 (12), H3 (10), H9 (10), B1/P11 (9)	P1 (0.173), H9(0.116), P11(0.111), H8(0.086), B1(0.082)

**Table 3: Whole network structural measures**

**b. Within-sector network structure**

The communications network had the highest density amongst all three network types for both sectors. Thirty-two percent of all possible communication was happening within the community sector; this was still higher than any joint activities and referrals happening in the sector by 64% and 125% respectively (Table 4). Only 13% of all possible communication was happening within the healthcare sector, but this was still higher than any joint activities and referrals happening in the sector by 109% and 60% respectively (Table 4).

**Community**

Link type	Density
Communication	0.32
Joint activities	0.20
Shared Referrals	0.14

**Healthcare**

Link type	Density
Communication	0.13
Joint activities	0.06
Shared Referrals	0.08

**Table 4: Within-sector network density**

Amongst the actual connections in the community sector approximately 40% consisted of all three types of ties, 30% consisted of two types of ties, and 30% consisted of one type of tie (Table 6). Amongst the actual connections in the healthcare sector, approximately 22% consisted of all three types of ties, 63% consisted of two types of ties, and 14% consisted of one type of tie (Table 6).

**c. Cross-sector network structure**

The cross-sector communication network between the community and healthcare sectors had the highest density amongst all three network types. Only 14% of all possible communication was happening between these sectors, which exceeded joint activities and referrals happening between the sectors by 62% and 77% respectively (Table 5). Amongst the actual connections between these sectors approximately 48% consisted of all three types of ties, 21 % consisted of two types of ties, and 21 % consisted of one type of tie (Table 6).

The density of the cross-sector communication network between the community and government sectors was only 4% since there was just 1 tie. There were no joint activities or shared referrals between these sectors (Table 5).

The densities of the cross-sector communication and joint activities network between the healthcare and government sectors were 26% and 25% respectively. There were also shared referrals between these sectors (Table 5).

**Community-  
Healthcare**

<b>Link type</b>	<b>Density</b>
Communication	0.14
Joint activities	0.09
Shared Referrals	0.08

**Community-Government**

Link type	Density
Communication	0.04
Joint activities	0.00
Shared Referrals	0.00

**Healthcare-Government**

Link type	Density
Communication	0.26
Joint activities	0.25
Shared Referrals	0.00

**Table 5: Cross-sector network density**

	3 ties	2 ties	1 tie
<b>Within-sector</b>			
Community	7	5	5
Healthcare	11	31	7
<b>Cross-sector</b>			
Community-Healthcare	18	10	10
Community-Government			1
Healthcare-Government		21	

**Table 6: Within-sector and cross-sector multiplex ties**

**d. Influential informant interviews**

Three influential informants were recruited for this component of our network study. Their combined experiences associated with thalassemia in Pune - of more than 60 years - spanned across the community, healthcare, and government sectors. Additional descriptive information regarding

the informants has been withheld to preserve confidentiality. Inductive content analysis yielded 20 codes, that were organized into 9 sub-categories, which in turn were broadly classified into 2 categories: 1) Benefits of collaboration, and 2) Barriers to collaboration.

(i) Benefits of collaboration

This category captured perceived benefits of interorganizational collaboration to improve adherence to essential management including, 1) improved access to care and support, 2) resource generation, equity, and efficiency, and 3) strength in unity.

(a) Improved access to care and support

Our analysis indicated that one of the perceived benefits of interorganizational collaboration was improved access to the health services required for essential management of thalassemia including blood transfusions, iron chelation therapy, and routine testing. Additionally, collaboration resulted in better access to and more effective patient education, counseling, and peer support. Exemplary quotations from 2 influential informant interviews are as follows:

*X: The treatment cost can reduce, because if all the doctors come together then they will help each other out... influence each other... and support each other. They can contact each other seeking expertise regarding difficult cases that they have come across.*

*Y: In order to improve patient adherence support groups are very important... so, at the support group you will have doctors, counsellors... one-to-one counselling will happen.*

(b) Resource generation, equity, efficiency

Another perceived benefit was the ability to generate more resources for efforts to improve adherence, make more efficient use and ensure that resources are distributed fairly amongst those who need them so as to prevent resource abuse.

*Z: If the NGOs work together they can create a registry that consolidates all patients, and they can send the list to the government...that we have so many patients and this is how many leukofilters we need, and how much iron chelation medication we need, and this is how much the tests will cost. So that would make things easier and more streamlined.*

*X: Like if a patient is registered under NGO 'A', they cannot go to 'B' and ask for funds because that is not right...then they are taking undue advantage and they might not be utilizing the same funds*

(c) Strength in unity

Interviewees also mentioned that collaboration between various organizations can influence public perception regarding the burden of the disease, and attract the attention of the media, government authorities, and funding bodies. It can also help in the implementation of national-level policies to make care more accessible. Additionally, unity would also enable organizations to focus on their areas of strength, rather than duplicating efforts of other organizations; one interviewee mentioned that this was working very effectively in a neighboring city.

*X: The government has made blood transfusion free, if they make chelation free how they will have to work it out... and filters. If two things - chelation and filters- they make free, the burden on NGOs will go down, (and then) we can focus on annual health check-ups, on the quality of life of children.*

*Y: It will happen. If they come under one roof, then benefits that have been made through a national-level policy where each state gets free iron chelation, free treatment, free transfusions. This is already happening in many states.*

*Z: Over there what has happened is that each NGO has taken on one aspect. There is a center that has started at Borivali, where they give transfusions, chelation, and the rest of the management; that is what they are focusing on.*

(ii) Barriers to collaboration

This category captured perceived barriers to interorganizational collaboration to improve adherence to essential management. These included 1) funding concerns, 2) institutional differences, 3) lack of interest in collaboration, 4) unaligned goals, 5) uncollaborative behavior, and 6) lack of political will.

(a) Funding concerns

Interviewers indicated that stakeholder organizations had concerns related to funding sources, i.e., they were not sure about collaborating with other organizations because it might lead to the latter approaching the formers' donors and hijacking their funding channels. Another interviewee mentioned that currently donors might not feel confident funding collaboratives and would therefore prefer to fund individual organizations.

*X: NGOs have a fear that if they join hands with another NGO, the latter might approach their donors and hijack their funding, so they don't want to disclose.*

*Y: ...they will ask "who is getting the funds? How are you going to use it?" Now if I tell them that it's a common platform... Government, NGOs, this – that, it will be lost. They might not have the confidence that it will work.*

(b) Institutional differences

Two interviewees mentioned that institutional differences had been barriers to past efforts towards collaboration. They mentioned that organizations had differences in internal processes, working patterns, decision-making, and also in the socioeconomic status of the patients that they

served. These differences led to failed attempts at collaboration or dissatisfaction amongst patients who were referred to other organizations.

*X: Yes, many organizations have tried to collaborate, but that doesn't work...there are many differences between them. The patient groups are also different. The government hospital will have lower class patients, whereas the NGOs will have middle class patients, middle-upper class patients and rich patients, and a few patients from the lower class.*

*Y: The people who used to speak at events organized were from a more socioeconomically affording class. So, when our patients were not able to afford chelation, they used to talk about chelation pumps, so they used to always come back and ask why they were not getting those things. So, they used to feel out of place with that group.*

(c) Lack of interest in collaboration

Interviewees indicated that some stakeholder organizations did not perceive a collaborative approach as having much long-term utility in improving the status quo, and that a “center of excellence” approach - where all services were provided under one roof - was the way forward. Interviewees also indicated that some stakeholder organizations lacked the time, motivation or willingness to initiate and maintain collaborative ties.

*Z: Again, people have their own interests and feel that “No why should I share? Why should I do this why should I do that? Why should I share with you? If you are doing that, you do what you are doing, I am going to do this”.*

*Y: When you collaborate, it is disintegrating. If there is a place where the patients can come and get their treatment, investigation, and everything all under one roof...so they have agreed that they will do something like this for Sickle Cell and hemoglobinopathies...they are all coming up now...in the interest of the patient I feel that there should be one Center of Excellence rather than multiple collaborations.*

(d) Unaligned goals

All interviewees mentioned that divergent, selfish, or vested interests of stakeholder organizations were significant barriers to collaboration. They suggested that some organizations did not have the patients' best interest in mind, and were instead more interested in recognition, fame, and in some cases even exploiting patients for financial returns.

*X: If people come on a common platform...like everybody (who) works for the cause, does it for the sake of the cause, and not because they want published papers, not because they have an axe to grind, not because they have medicines that they are giving, for which they get money.*

*Y: Yes, collaboration is possible if all the organizations come together and work for the cause. They should see only the cause and nothing else...they should forget about everything else and focus on the cause. Thalassemia prevention, cure, treatment...the focus should be on only these three things...no name, no fame, no nothing...remove all these three things. Just focus on awareness, treatment, and management.*

(e) Uncollaborative behavior: Lack of trust, competition, egotism

Interviewees indicated that some organizations were competitive rather than collaborative, where there was a duplication of the same event by an organization on the same day, which would end up confusing patients.

*X: What happens over here is that if an event is organized by one NGOs then other NGOs replicate it. Take HLA camps for example. Every organization is doing HLA camps on one or another day.*

As exemplified by the following quote, interviewees mentioned that ego issues also got in the way of collaboration:

*Y: Some people think that they are superior, and other people have less knowledge. So that doesn't work. A patient, or a parent can also have big ideas that can help few patients or many patients. So, you can't underestimate any person out there.*

Lastly, interviewees also suggested that there was a lack of trust between some stakeholder organizations because of past events, where an organizations actions came across as exploitative and unethical.

*Z: There were some trials going on and those trials were done on them without their knowledge, and they had to come to that particular center and get the drugs. Now these people (parents) were selling their gold...selling everything.*

(f) Lack of political will

One interviewee also mentioned that the state government must have the will to make policy interventions to improve the quality of life of people affected by thalassemia.

*X: State government has to take it up as a major issue, but they should feel the need, so unless somebody in the government gets thalassemia major, they will not wake up.*

## **5. Discussion**

This study identified stakeholder organizations in Pune, India that influenced thalassemia patients' adherence to essential management. These organizations could broadly be divided into healthcare, community, and government sectors. The community sector comprised 12 organizations including local, state-level, and national patient and community organizations. The healthcare sector was more heterogenous and comprised 28 organizations including local hospitals, blood banks, diagnostic labs, and pharmacists. The government sector comprised 3 organizations including 3 state-level and national government offices.

Social network analysis of survey data on three different relational ties allowed us to measure the connectivity between organizations overall, within the community and healthcare

sectors, and also between the community, healthcare, and government sectors. Connectivity was measured using the density of ties within and between sectors for each of the three relational ties: communication, joint activities, and shared referrals. Density was calculated as the number of observed ties divided by the number of possible ties within and between sectors. Our results indicate that the density of the communication network (0.14) was higher than the joint activities (0.09) and shared referrals (0.07) networks overall, within, and across sectors (Table 3). Density of all three ties was higher amongst organizations within the community sector (0.32) as compared to those in the healthcare sector (0.20). Amongst cross-sector connections, the density of the communications and joint activities networks between organizations in the healthcare and government sectors was the highest (0.26, 0.25), followed by those between the healthcare and community sectors (0.14, 0.09). The density of the communications networks was lowest between organizations in the community sector and the government sectors (0.04); there were no joint activities between organizations belonging to these two sectors. The density of the shared referrals network was highest amongst organizations in the community sector and the healthcare sector (0.08) since there were no referrals between organizations of the healthcare and government sectors, or between the community and government sectors. Interestingly, a majority of observed connections in the network had a multiplex score of 2 or 3, which indicates that organizations collaborated in more than one way and so most existing connections were strong.

Degree and betweenness centrality measurements were used to identify seven organizations that consistently featured as the central players and gatekeepers across all three network types. These included: 2 patient organizations (community sector), 1 blood bank (healthcare sector), 2 hospitals (healthcare sector), and 1 government office (government sector).

Additionally, there was 1 hospital (healthcare sector) that featured as a central player in the referrals network.

Influential informant interviews led to the identification of 3 perceived benefits of collaboration including 1) improved access to care and support, 2) resource generation, equity and efficiency, and 3) strength in unity. All three have been reported extensively in the network literature as they are amongst the key benefits of interorganizational collaboration (Casey, 2008; K. Provan, Harvey, et al., 2005; Yessis et al., 2013). Influential informant interviews also led to the identification of 6 perceived barriers to collaboration, including 1) funding concerns, 2) institutional differences, 3) lack of interest in collaboration, 4) unaligned goals, 5) lack of trust and competition, and 6) lack of political will. All of these factors have been reported extensively in the network literature (Brinkerhoff, 2002; Casey, 2008; K. G. Provan et al., 2004; K. Provan, Harvey, et al., 2005; K. Provan, Veazie, et al., 2005; Retrum, Chapman, & Varda, 2013).

The importance of collaborative ties amongst cross-sector organizations in delivering fragmented services to meet the unmet needs of underserved chronic disease patient populations, especially in low-resource settings, has been highlighted time and time again in the literature (Alter & J, 1993; K. Provan, Harvey, et al., 2005; K. Provan & Milward, 1995). The main reason is that such collaboration can allow for the provision of integrated and coordinated services that reduce duplication of effort and improve the efficiency and effectiveness of resource allocation in resource-scarce contexts (Alter & J, 1993; Huxham & Vangen, 2005; K. Provan, Harvey, et al., 2005).

The community sector had better within-sector connectivity in terms of communication, joint activities and shared referrals, as compared to the health-care sector. The organizations within the community sector were more homogenous as compared to the health care sector, as the former

only consisted of patient and community organizations whereas the latter consisted of hospitals, blood banks, diagnostic labs, and medical stores. This might be the reason for better connectivity of the community sector since there is a tendency for organizations to collaborate with others that are similar to them (Bevc, Retrum, & Varda, 2015). Another possible reason for better connectivity amongst organizations within the community sector as opposed to the healthcare sector was that all the organizations in the former were non-profits and were therefore more likely to collaborate for the benefit of patients, whereas many of the organizations in the latter were for-profits and were therefore more likely to compete with each other (K. Provan & Milward, 2001). Most connections between organizations in the healthcare sector were between blood banks, both standalone and those that were attached to hospitals. An important reason for this may have been goodwill amongst blood banks to help thalassemia patients access blood more conveniently, and implementation of a government policy to enable access to free blood for thalassemia patients (Government of India, 2017). Within the healthcare sector there were a few joint activities or referrals among hospitals and between hospitals and diagnostic labs for improved access to diagnostic testing that were not available in-house. While the within-sector connectivity for each of the three types of relational ties was better amongst organizations in the community sector as compared to those in the healthcare sector, they were low for both sectors in absolute terms. Possible reasons for this that were offered by influential informants included: 1) insecurity regarding funding channels, 2) differences in institutional process and client socioeconomic status, and 3) lack of interest in collaboration due to limited perceived utility, divergent goals, vested interests, competition or lack of trust.

The ICCC framework was developed by the WHO to improve systemic care for individuals affected by chronic conditions. A key aspect of the framework is links between the community

and healthcare sectors at the mezzo-level. Furthermore, the framework also emphasizes the importance of a supportive policy environment at the macro-level that promotes such collaborations between sectors (World Health Organisation, 2002). Our findings suggest that the links between the healthcare sector and the community sector could be improved since only 14% of all possible communication, 9% of all possible joint activities, and 8% of all possible shared referrals were actually occurring between them. Based on qualitative interview findings, possible reasons for existing ties may have included improving access to blood, chelators, or routine tests, and improving patient education, counseling, or peer support. However potential barriers that may account for non-existent or weak ties might include lack of trust due to vested interests, lack of interest in collaboration due to limited perceived utility, and institutional differences in administrative processes and socioeconomic status of patient served. As previously mentioned, there is a tendency for organizations to collaborate with other organizations that are similar to themselves; this might provide an explanation as to why organizations in different sectors might find it difficult to collaborate with each other. Additionally, while there is a brief mention in the National Guideline for the Control and Prevention of Hemoglobinopathies in India (NHM, 2016) regarding the importance of community organizations and advocacy, there seem to be no mechanisms proposed for initiating and maintaining cross-sector partnerships between organizations in the community and healthcare sectors. Resource constraints might be another potential reason for poor connectivity between these sectors; this is supported by the fact that the density of communications (0.14) - the least resource intensive tie - between organizations in these sectors was stronger than the joint activities (0.09) and shared referrals networks (0.08), which require more resources to develop and maintain.

The cross-sector density of the communications and joint activities networks between the government and healthcare sectors were relatively high (0.26, 0.25). However, it is important to note that a large contributor towards this was the ties between hospital-attached blood banks or stand-alone blood banks, and the state government office that regulates all of them. If these ties were dis-counted, the density of the communications and joint activities networks would reduce significantly (0.07, 0.05). Regardless, these densities are still higher than what was observed between the government and community sectors where the density of the communications network was 0.04, and there were no ties reported for the other two connection types. These results indicate that the connectivity between the government and healthcare sectors is superior to the connectivity between the government and community sectors. The probable reason for an absence of shared referral ties from the community and healthcare sectors to the government sector is that there is no reason for them to refer patient to a government office, whereas they may refer patients to organizations within or across their sectors in order for them to access essential management or socio-economic support services. However, the government offices can communicate or engage in joint activities with organizations from the other two sectors in order to improve access to blood, iron chelators, or other aspects of medical management or socioeconomic benefits.

Interestingly, even though density scores were low within and across sectors, multiplexity analysis revealed that 70%-100% of connections between organizations within sectors and across sectors had scores of 2 or 3; this indicates that while within-sector and cross-sector connectivity was low, the existing connections were strong as they went beyond basic communication to include joint activities and/or shared referrals. Network connections with multiplex scores of 1 might also be indicative of budding relationships between organizations, which might strengthen, dissolve, or be maintained based on mutual assessments and benefits gained (K. Provan & Milward, 2001). As

suggested in a prior study by Yessis et al. (2013), it is also possible that the network might evolve to serve patients better through multiplex relational ties between a few organizations within and across sectors rather than through a denser network of weaker ties involving many organizations. In fact, K. G. Provan, Harvey, et al. (2005) suggest that a blend of a few strong and weak ties, as being an effective approach.

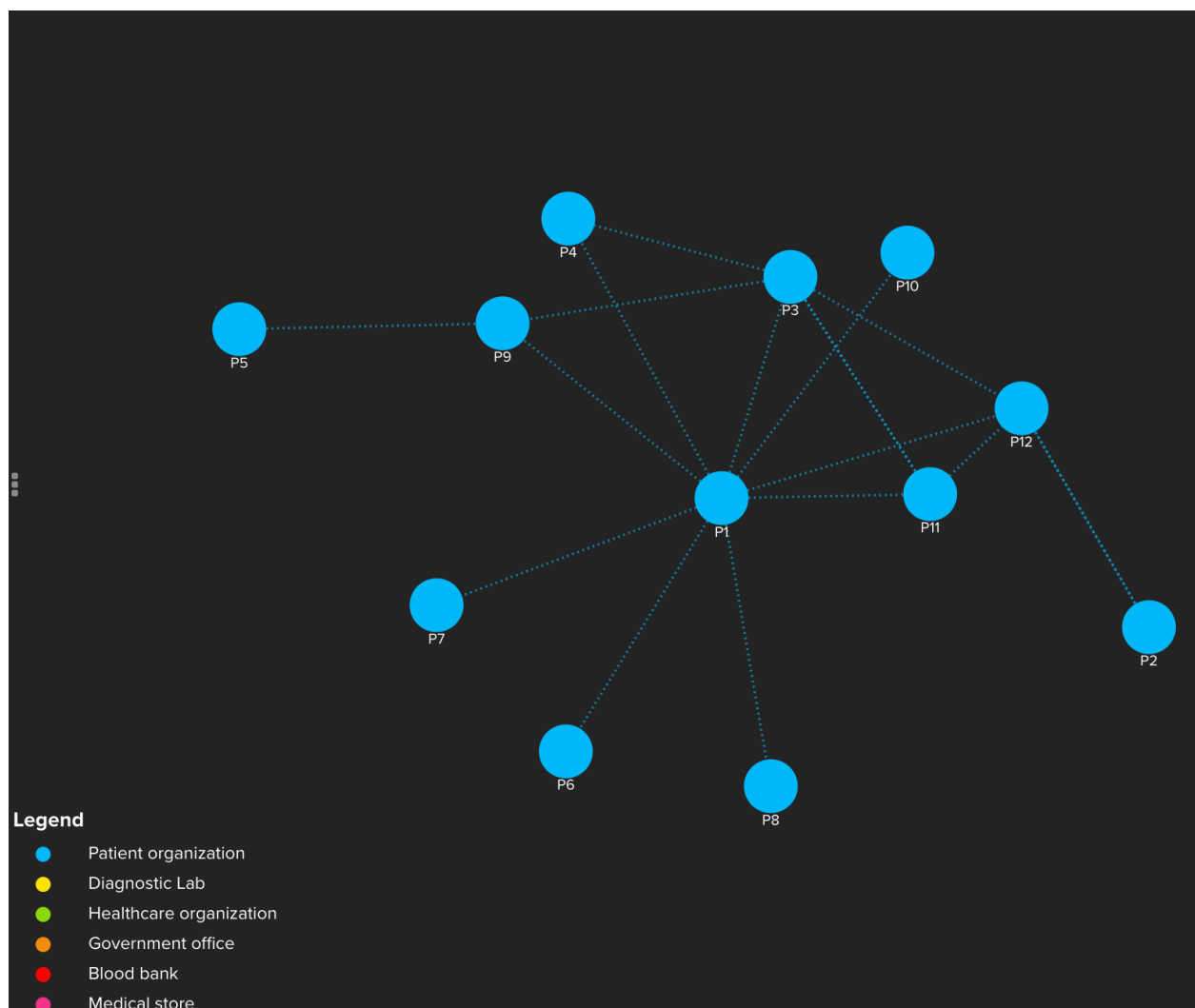
This study sought to identify and determine the connectivity stakeholder organizations in Pune city that influenced adherence to essential management in thalassemia patients. The intention of this was to establish initial network data that could help in planning interventions to strengthen the network. The seven central players (most well-connected) and gatekeepers (most bridges between organizations) might be the most well-positioned to facilitate planning and implementation of future interventions to strengthen collaboration in order to improve patient adherence to essential management. The centrality of these organizations can be cross-checked with opinions regarding the same from key stakeholders in the network; this can help confirm our findings or identify stakeholder organizations that are perceived as being important but did not feature in the results of our analysis (K. G. Provan et al., 2004). Interventions can also be made to strengthen the position of such organizations by initiating ties with other organizations in the network. Additionally, stakeholder organizations that had been identified as central players or gatekeepers can be made aware of their position in the network, which might inspire them to take action towards strengthening the network in order to improve adherence to essential management in thalassemia patients.

### **Strengths and Limitations**

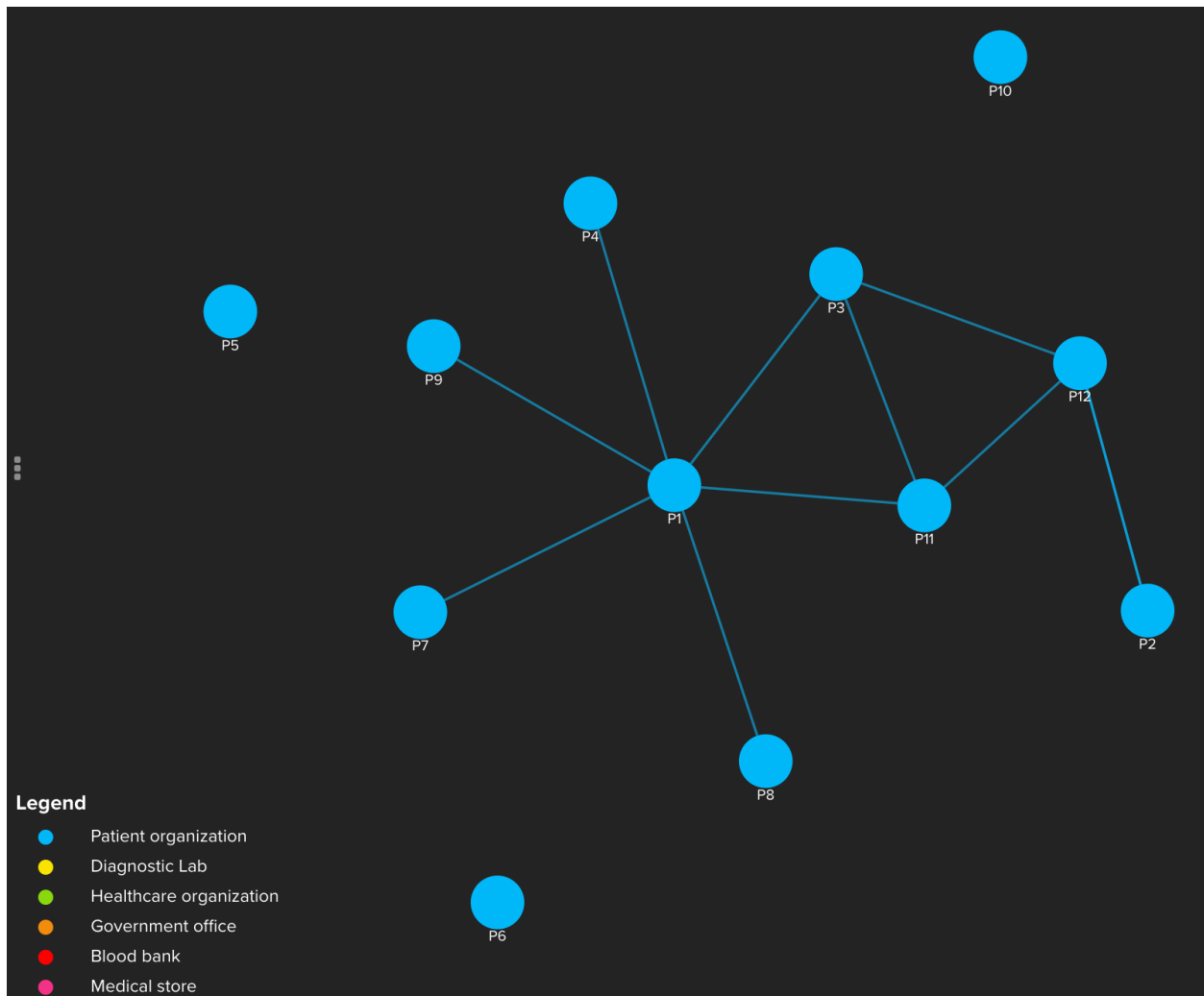
A key strength of our study was that we used a mixed methods approach, where we sought to understand the structure of the network of organizations using a network theory, and the processes that might be influencing the network structure using qualitative interviews (Robins, 2015). However, if resource constraints were not present, qualitative interviews with additional participating stakeholder organizations would have yielded more insights regarding the processes responsible for the existing network structure. Another limitation of our study was that we calculated network density using only unconfirmed links; had we calculated it using confirmed links as well, the density scores would have likely been lower as has been the case in past studies that calculated both; this would have allowed us to differentiate between strong and weak ties. However, we used multiplexity scores to determine the same.

This is the first study that has sought to identify and determine the connectivity between stakeholders that influence adherence to essential management in thalassemia patients residing in and around Pune city. Our study suggests that while a majority of existing connections between organizations are strong, the connectivity between organizations within and between sectors across all relational tie networks is low. The first step towards increasing connectivity and strengthening relationships between organizations would be to disseminate the findings to all stakeholder organizations, while preserving confidentiality. This can be done by highlighting the importance of cross-sector links for improving outcomes for thalassemia patients, sharing network metrics, and informing them about their position within the network in terms of degree and betweenness centrality. This information will hopefully prime them to consider forging new relationships or strengthening existing ones. Furthermore, organizations that were identified as central players and gatekeepers can be engaged in a similar manner but can also be made to explore the potential that they have to strengthen the network. The same organizations can be engaged to develop and

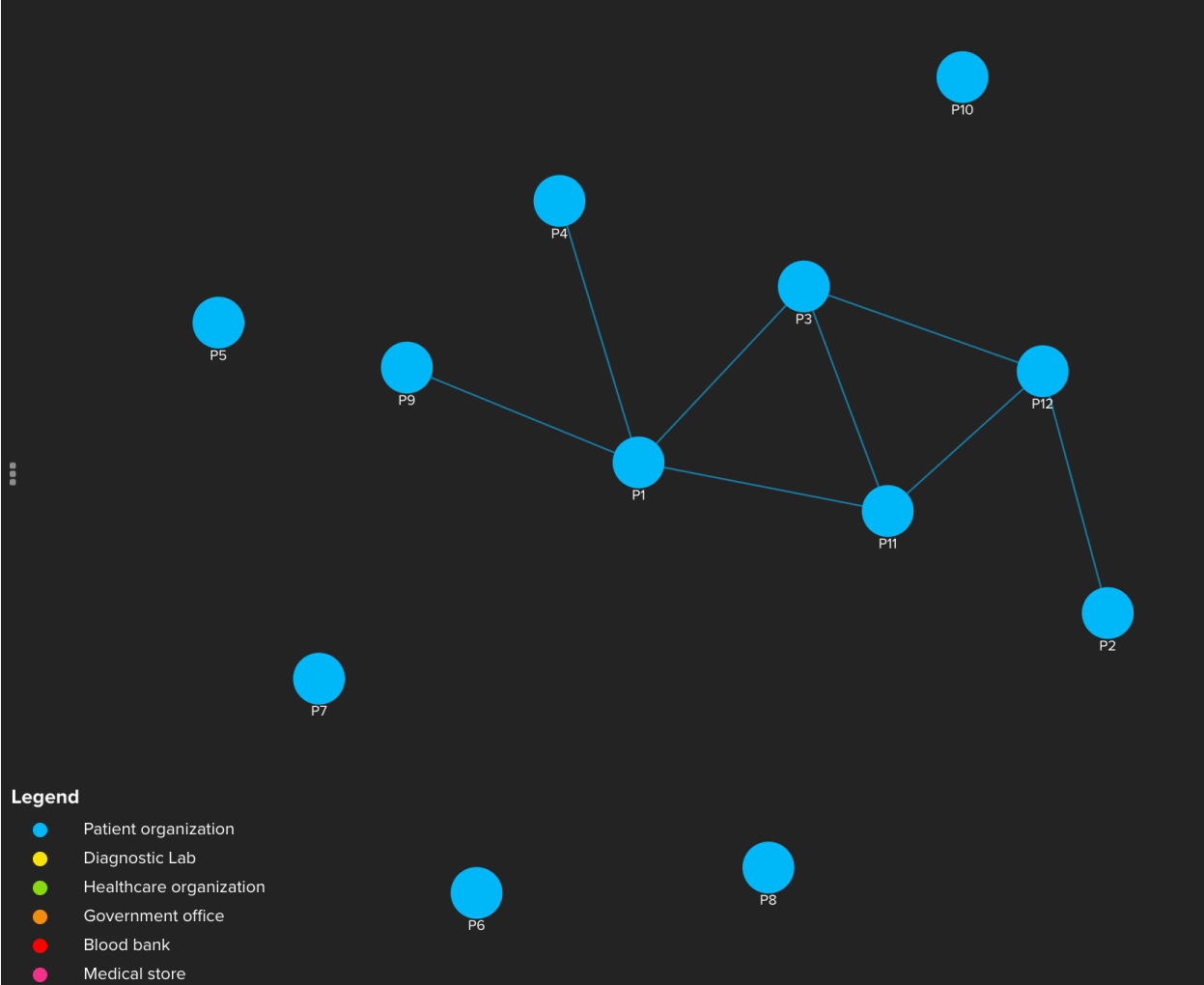
implement context-specific interventions to achieve this. The network study can be performed repeatedly to longitudinally track the evolution of the network and evaluate the effectiveness of implemented interventions. However, there were significant barriers reported by the influential informants that will undoubtedly be difficult to overcome; the most significant of these being lack of trust. In order to maximize their effectiveness, interventions will have to be planned while keeping these barriers in mind.



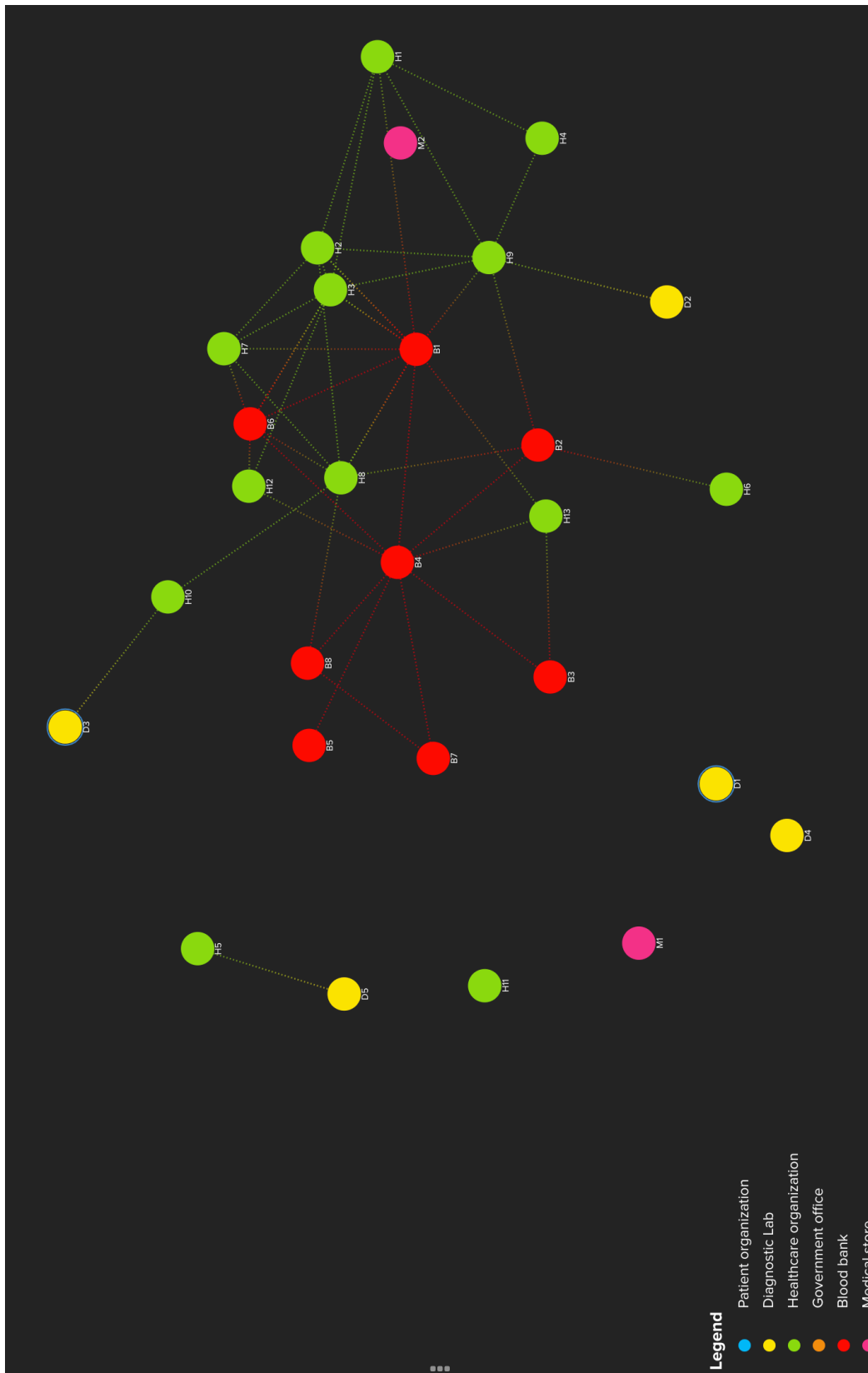
**Figure 11: Sociogram of communication network - Community sector (n=12, density=0.32)**



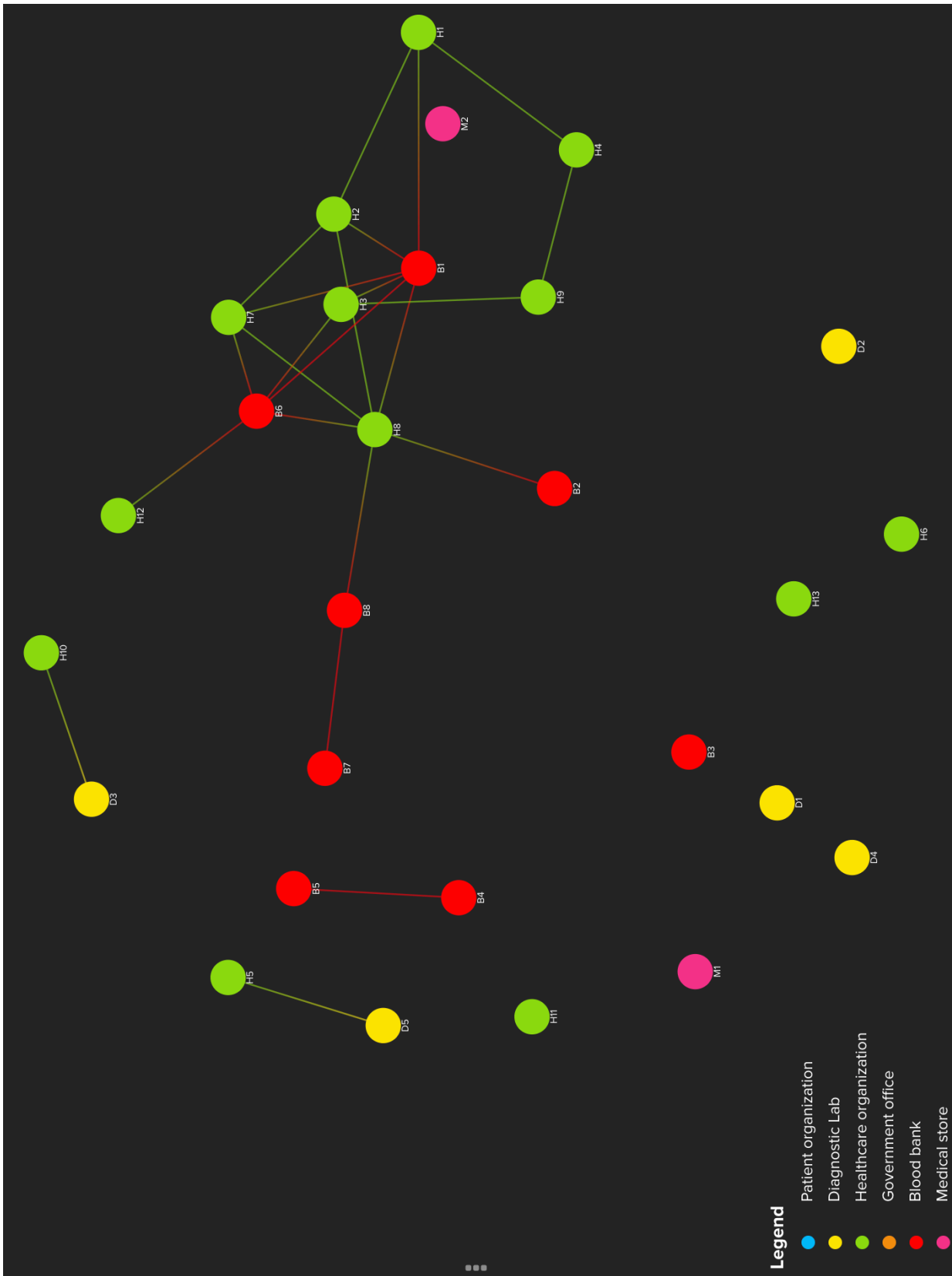
**Figure 12: Sociogram of Joint activities network - Community sector (n=12, density=0.20)**



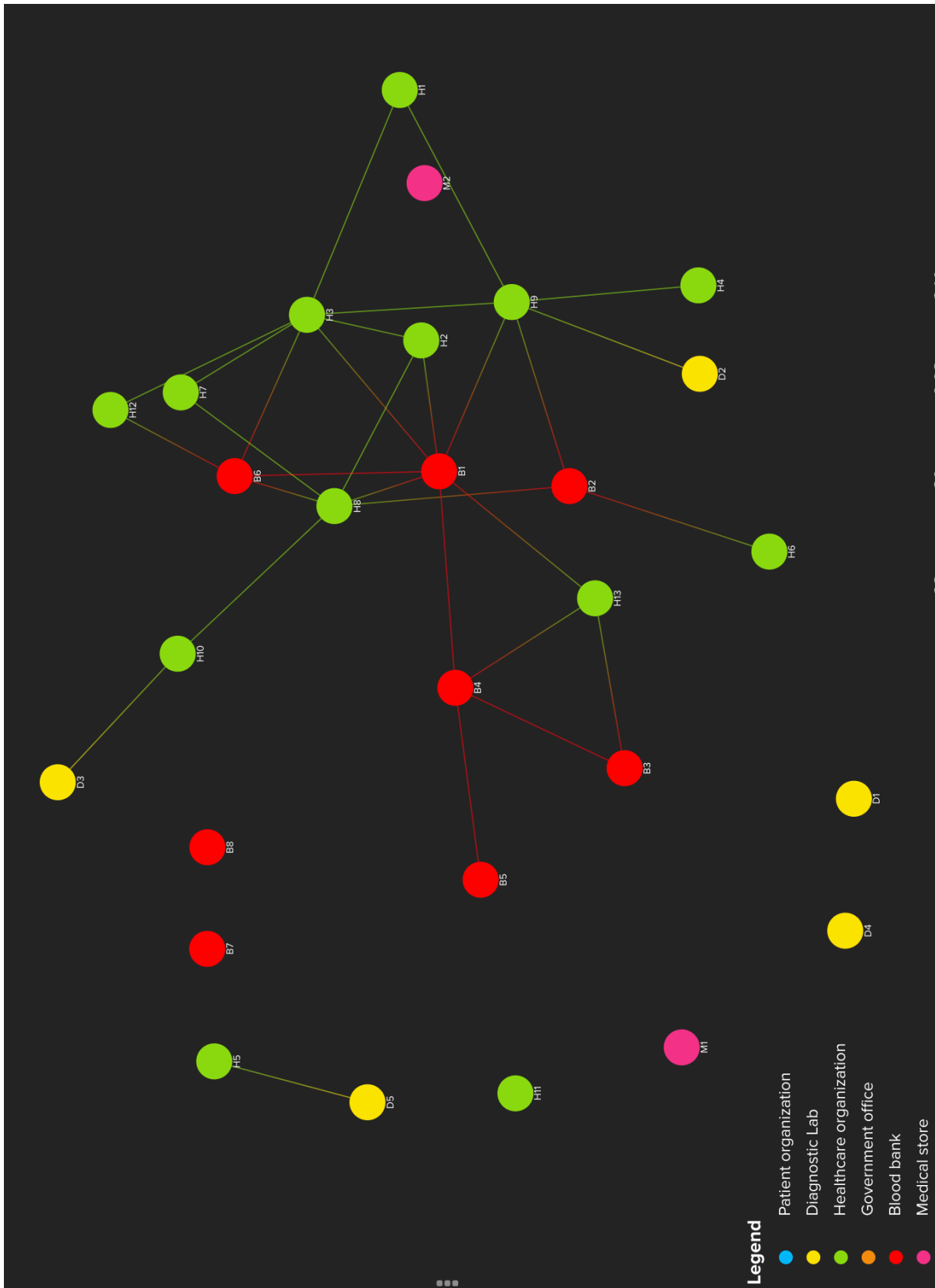
**Figure 13: Sociogram of Referrals network - Community sector (n=12, density=0.14)**



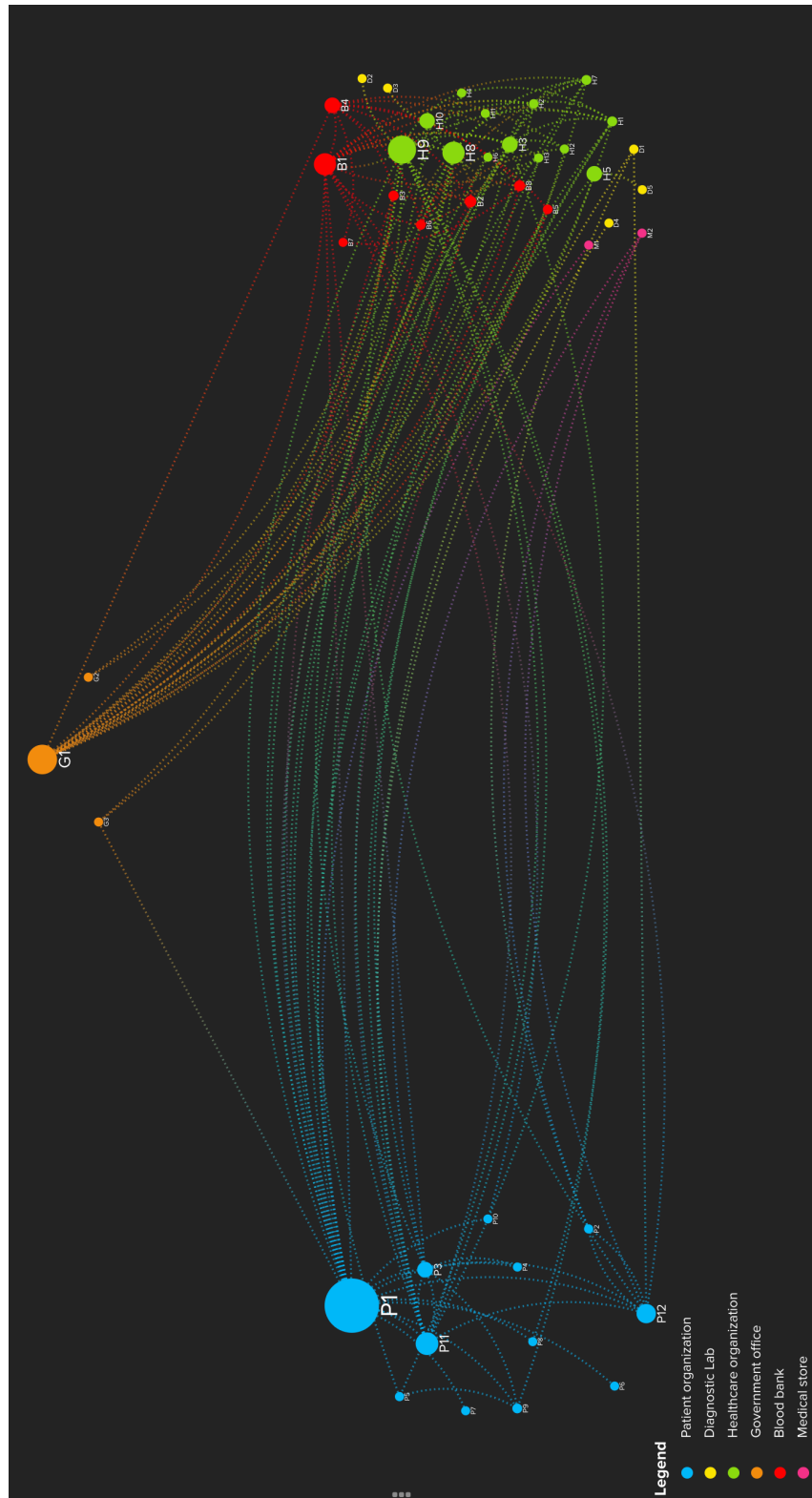
**Figure 14: Sociogram of Communication network - Healthcare sector (n=28, density=0.13)**



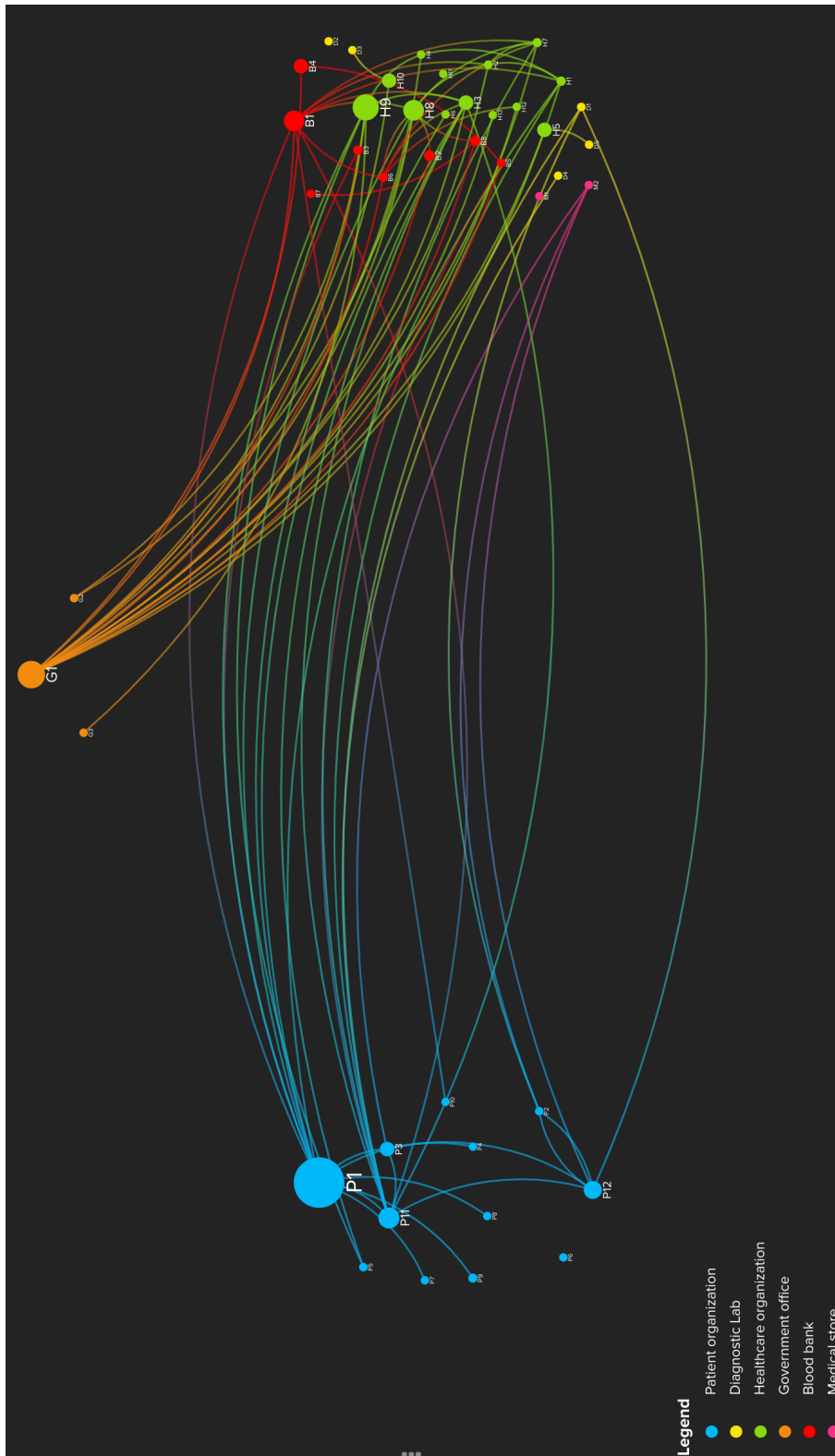
**Figure 15: Sociogram of Joint Activities network - Healthcare sector (n=28, density=0.06)**



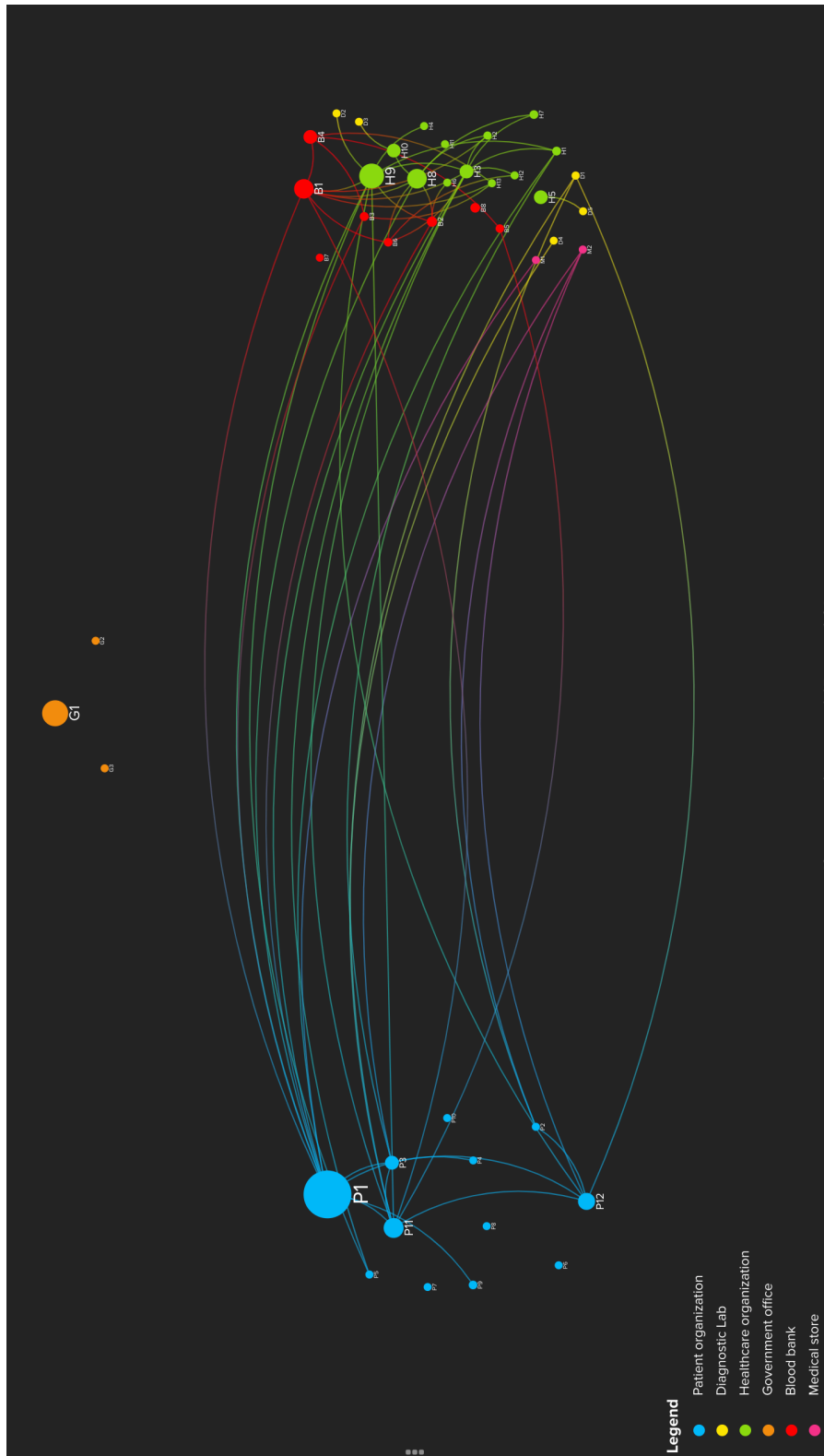
**Figure 16: Sociogram of Referrals network - Healthcare sector (n=28, density=0.08)**



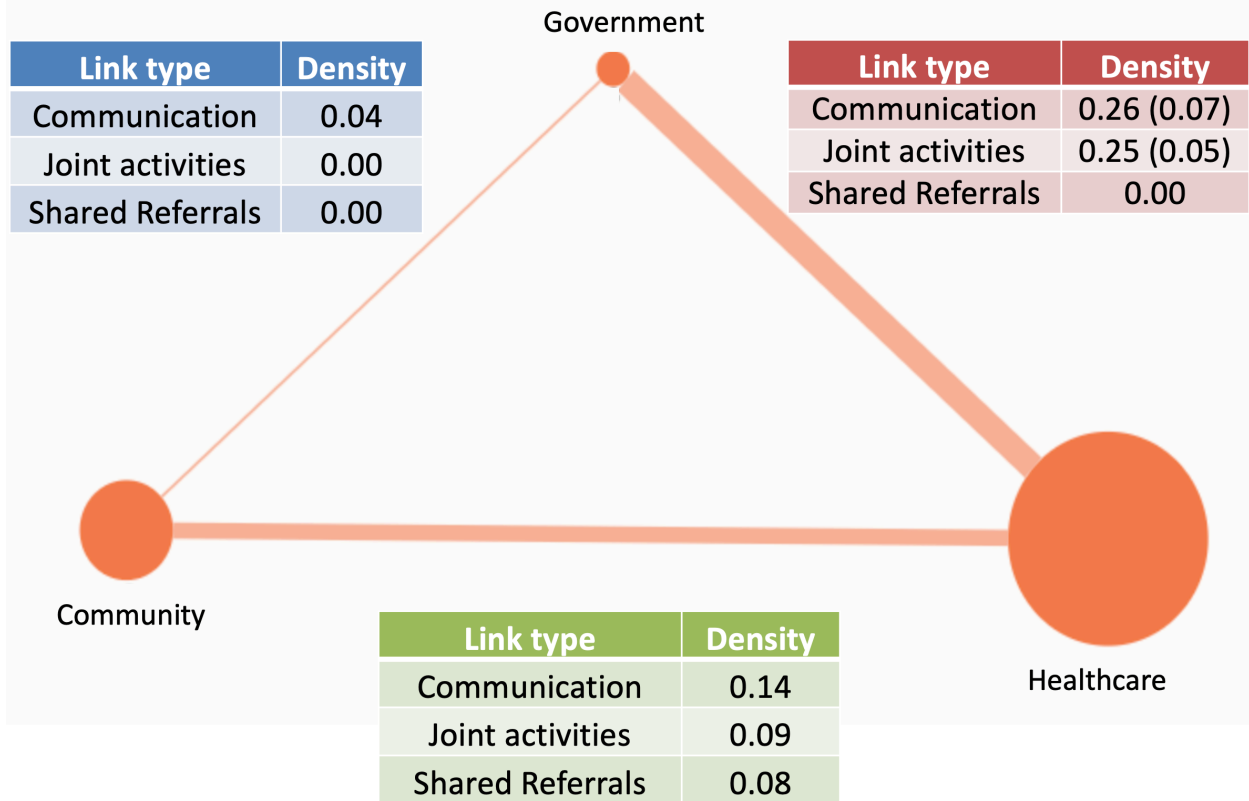
**Figure 17: Sociogram of Communications network – All sectors (n=43, density=0.14).** Size of the nodes correlate with the number of connections they have.



**Figure 18: Sociogram of Joint activities network – All sectors (n=43, density=0.09).** Size of the nodes correlate with the number of connections they have.



**Figure 19: Sociogram of Referrals network – All sectors (n=43, density=0.07).** Size of the nodes correlate with the number of connections they have.



**Figure 20: Cross-sector density block model.** Size of the sector nodes correlate with the number of organizations within it. The width of the line connecting sector nodes correlates with cross-sector density scores.

## **CHAPTER 4**

### **The feasibility of using a Collective Impact initiative to improve adherence to essential management for $\beta$ -thalassemia major.**

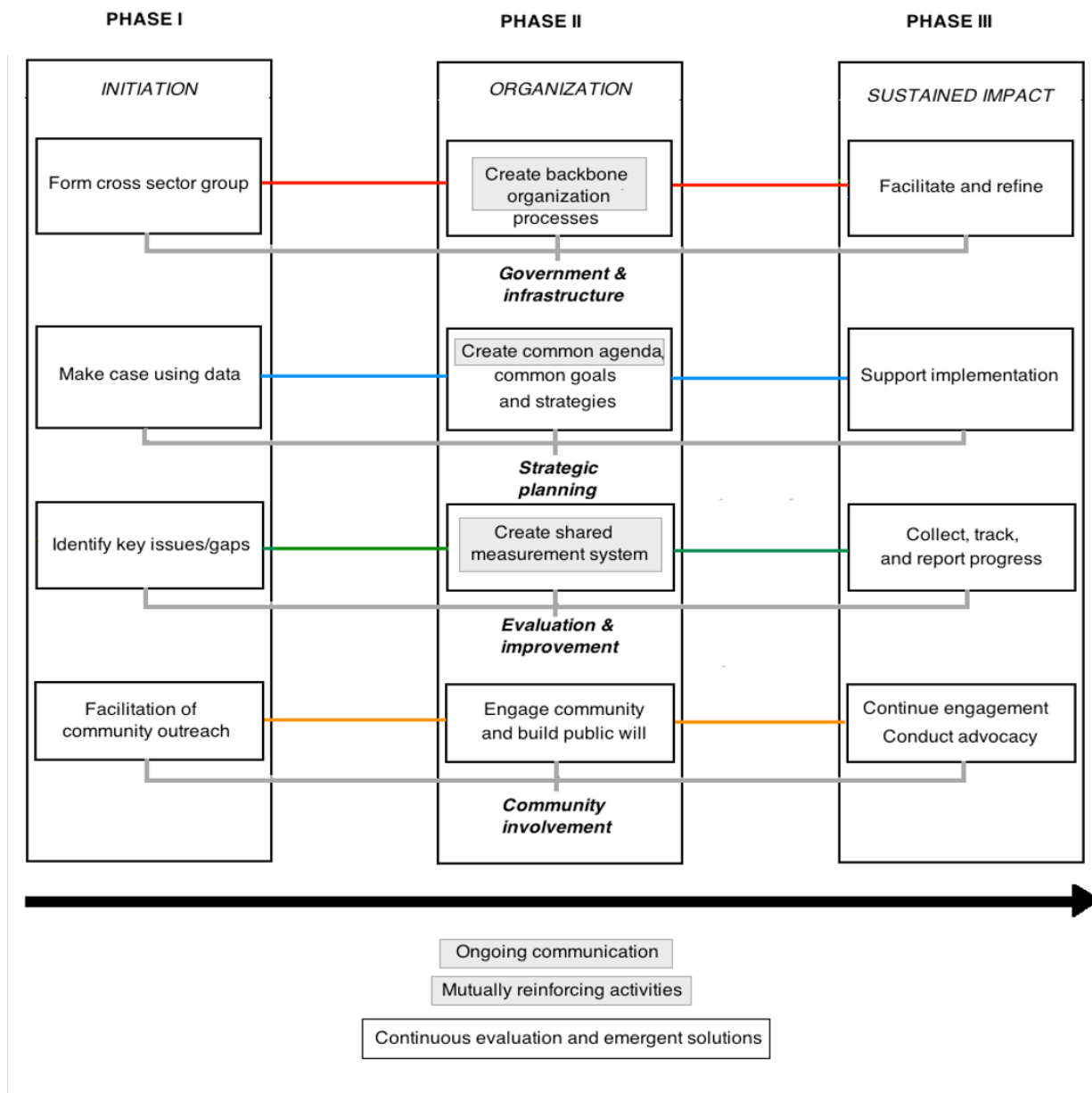
#### **1. Introduction**

$\beta$ -thalassemia major is a hereditary, chronic hemoglobin disorder characterized by severe microcytic anemia, microcytic anemia, erythroid marrow expansion, splenomegaly, and iron accumulation in various tissues. Essential management involves periodic blood transfusions, frequent iron chelation therapy, and periodic medical tests to monitor for secondary complications. Adherence to essential management is a notable issue in thalassemia care that contributes to poor health outcomes (J. B. Porter et al., 2011; F. Shah & Kaltsounis, 2018; F. T. Shah et al., 2019). Currently, adherence is conceptualized by the WHO as being influenced by factors that are related to the treatment, condition, patient, socioeconomics, and health system/healthcare teams (Sabate, 2003). It is not difficult to perceive that many factors that fall into these categories, particularly the last two, are influenced by services offered by various organizations, their internal practices, and relationships between them. These organizations might be from the healthcare sector as well as other sectors such as the community and government sectors, since care and support for chronic conditions extends beyond the walls of healthcare organizations. Within community settings in India where resources are often scarce, interorganizational collaboration can be instrumental in bridging the service gap between organized clinical care and the real world of patients and their families, and may also result in more efficient use of existing resources (JoAnne E. Epping-Jordan, 2005; World Health Organisation, 2002). The Collective Impact approach (Kania & Kramer, 2011)

might serve as model to facilitate and sustain such collaboration in order to improve adherence in the thalassemia community.

The Collective Impact approach is based on evidence that large-scale social change comes from better cross-sector coordination rather than from the isolated interventions of individual stakeholders (Hanleybrown et al., 2012). The approach offers a structured way to foster collaborations between stakeholders involved in a social problem, in order to improve outcomes for those affected (Kania & Kramer, 2011). An analysis of several successful community initiatives led to the distillation of five essential ingredients for a successful collaborative: Stakeholders must have a a) common agenda, b) common measurement system to track progress, c) mutually reinforcing activities, d) ongoing communication, and e) a backbone organization (Hanleybrown et al., 2012).

Furthermore, there are four components of a Collective Impact initiative that are developed over the span of the three phases: 1) initiation, 2) organization, and 3) sustained impact. Components of these phases include: (a) governance and infrastructure, (b) strategic planning, (c) evaluation and improvement, and (d) community involvement (Hanleybrown et al., 2012). The aforementioned conditions and features of a Collective Impact initiative have been illustrated in Figure 21.



**Figure 21: Features of a Collective Impact initiative** [adapted from Hanleybrown et al. (2012)]. This schematic outlines the three phases of a Collective Impact initiative and components within each of them. The conditions of Collective Impact are mentioned in grey rectangular fields.

While a relatively new model, Collective Impact has been successfully used to improve health outcomes of patients affected by other relatively common chronic conditions including asthma and diabetes. A Collective Impact initiative in Dallas, USA led to the reduction of

childhood asthma-related emergency rooms visits by 49% in 3 years (Brands, Robert, & Shaum, n.d.). Another Collective Impact initiative in Somerville, USA that focused on preventing childhood obesity managed to reduce TV watching by 23% reduced excessive consumption of sugary beverages by 22%, and increased physical activity by 56% over the span of 8 years (Chomitz, Arsenault, Garnett, & Hudson, 2013).

Before embarking on a community collaborative based on the Collective Impact framework, where scarce resources have to be deployed to establish, augment, and sustain community partnerships and interventions, it is essential to do a feasibility assessment. The Collective Impact feasibility assessment involves two main steps: 1) assessing appropriateness of the approach to solve the given problem and 2) assessing readiness of the community to adopt the approach (FSG, 2015).

In this chapter, we aim to assess the appropriateness of using a Collective Impact approach to improve adherence to essential management in members of the thalassemia community in the city of Pune, India. The assessment will be guided by the Collective Impact Feasibility Framework (Figure 4) and will draw heavily from findings of two concurrent studies regarding opportunities and constraints that influence adherence, and stakeholder network connectivity, that were done in partnership with the thalassemia community in the city of Pune. Specifically, the following questions based on the Collective Impact Feasibility Framework will be addressed: a) Is the system of stakeholder organizations and factors that influence adherence fragmented, disconnected, and broken?; b) Do multiple sectors need to work together to address this issue?; c) Are the majority of patients in the community affected by adherence problems?

## **2. Methods**

### **a. Ethical considerations**

This study was approved by the University of Washington Institutional Review Board, Seattle, USA (IRB ID: STUDY-00006828). Additionally, this study was also approved by the Byramjee Jeejeebhoy Government Medical college and Sassoon General Hospital Institutional Ethics Committee, Pune, India (Ph.D 0619072-072). All interviews and network surveys were administered by the lead investigator (SK) as part of his PhD dissertation research.

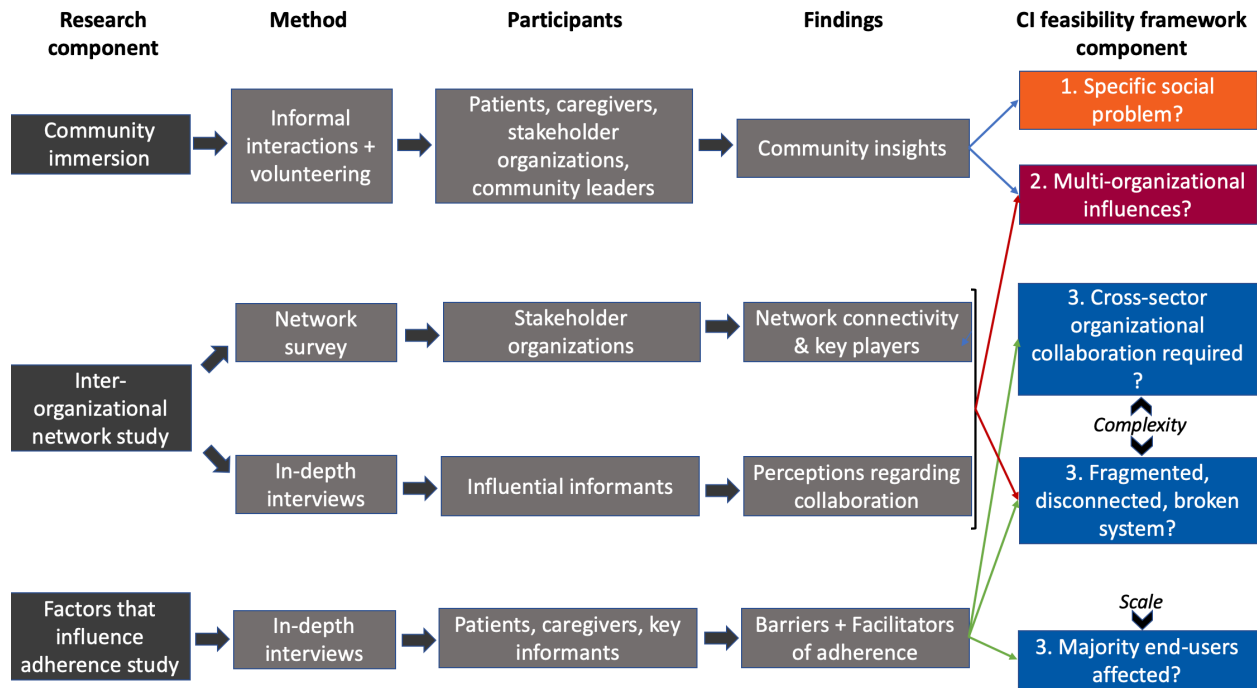
### **b. Study design and justification**

The feasibility assessment guided by the Collective Impact Feasibility Framework (Figure 4) drew on data from two concurrent studies that primarily sought to determine contextual opportunities and constraints that influence essential management, interorganizational connectivity, key players, and perceptions regarding collaboration. Both studies were preceded by a period of community immersion. As illustrated in Figure 19 the findings generated through these methods enabled identification of a significant social problem being faced by the thalassemia community in Pune, ascertainment of whether multiple stakeholder organizations influenced it, and determination of the appropriateness of Collective Impact via characterization of the complexity and scale of the problem.

The Collective Impact Feasibility Framework requires the identification of a specific social problem that on solving has the potential to dramatically improve health outcomes, is an unmet community need that requires an urgent response, or allows one to take advantage of the local policy landscape. Furthermore, the social problem must be influenced by multiple stakeholder organizations. Community immersion was an essential step in the identification of a specific social

problem within the thalassemia community in Pune that met one or more of the aforementioned criteria.

As per the Collective Impact Feasibility Framework complexity of a problem can be characterized by determining whether the current system is fragmented, disconnected and broken, and if multiple sectors need to work together to solve the social problem. Given that there have been no context-specific past studies that have sought to characterize the adherence problem, exploratory research that used in-depth interviews to identify opportunities and constraints that influence adherence and the underlying processes by which they influence it, provided a suitable means to identify symptoms of a broken system and determine whether multiple sectors needed to work together to fix it. Additionally, a network study provided a suitable means to assess fragmentation/disconnectedness of the system through the measurement of interorganizational connectivity and identification of perceived barriers to and utility of collaboration. While a quantitative approach would have been most suitable to estimate whether or not a majority of patients experienced problems related to adherence, in-depth interviews with patients, caregivers, and key informants from diverse circumstances provided a qualitative determination of this.



**Figure 22: Relationship between research components and Collective Impact Feasibility Framework.**

### c. Participant selection, recruitment, data collection, analysis

Prior to study commencement, the lead investigator SK spent a total of 6 months immersing himself in the thalassemia community in Pune, India through participation in events organized by the local advocacy group, and through informal interactions with key stakeholders and adults affected by  $\beta$ -thalassemia major who were actively involved with the local community organizations.

For the qualitative study to determine opportunities and constraints of adherence, maximum variation sampling was used to identify prospective participants including adult patients, caregivers and key informants. Detailed descriptions of sampling and recruitment protocols can be found in Chapter 2. A total of 55 prospective participants were approached, of whom 49 consented to participate, and 6 disagreed to participate due to lack of interest or time. None of the participants withdrew from the study. As no new information was being revealed data

collection was discontinued after the 49<sup>th</sup> interview, which is in line with the literature regarding data saturation (Morse, 1995; Sandelowski, 1995).

For the network study, participating stakeholder organizations that influenced adherence were from the city of Pune and included: hospitals, blood banks, diagnostic labs, community organizations, government offices, and medical stores. The final sampling roster consisted of 43 stakeholder organizations. A network survey was administered to one or more representatives from these organizations. Additionally, qualitative in-depth interviews were conducted with 3 influential informants with cross-sector representation. Detailed descriptions of sampling and recruitment protocols can be found in Chapter 3.

Semi-structured interview guides were used for the in-depth interviews in both studies. The interview guide for the adherence study was developed to elicit information regarding opportunities and constraints that influence adherence to essential management, whereas that of the network study was developed to elicit perceptions regarding the benefits and barriers of collaboration. All interviews were audio-recorded, transcribed and translated by the lead investigator.

A network survey was developed for the network study through which data on 3 types of relational ties i.e. communication, joint activities, and shared referrals were elicited from 43 stakeholder organizations. Detailed descriptions regarding the development of the data collection tools can be found in Chapter 3.

Deductive and inductive content analysis were used to analyze interview data from the adherence study and the network study respectively. Deductive content analysis was guided by the WHO multidimensional adherence framework (Sabate, 2003). Social network analysis was used

to analyze network data from the network study. Detailed descriptions regarding the analyses can be found in Chapters 2 and 3.

### **3. Results**

Community immersion via informal interactions and volunteering activities led to identification of poor adherence to essential management as a significant issue being experienced by the thalassemia community in Pune. Furthermore, multiple stakeholder organizations were identified that potentially influenced adherence to essential management.

The 49 in-depth qualitative interviews with patients, caregivers, and key informants led to the identification of 150 factors that influence adherence to essential management and alternative treatment, most of which influenced more than one aspect of it, whereas some influenced only a single aspect of it. Seventy-nine factors were constraints, whereas 71 factors were opportunities. Furthermore the 150 factors were categorized into 43 subcategories, which in turn were more broadly classified into 9 generic categories: 1) Blood security; 2) Blood transfusion convenience; 3) Access to care; 4) Healthcare quality; 5) Financial status/support; 6) Social status/support; 7) Psychology/behavior; 8) Patient/caregiver knowledge and education; 9) Nature of disease/treatment. Some of these categories corresponded to a single dimension of the WHO multidimensional adherence framework whereas others spanned across multiple dimensions. Factors were also further classified according to their ecological level of influence. A majority of them exerted their influence at the individual (patient/caregiver) and mezzo (community/health care organizations) ecological levels, whereas some exerted their influence at micro (community/healthcare-related interactions and relationships) and macro (policy/society) ecological levels. Some factors exerted their influence at more than one ecological level. In line

with an ecological conceptualization of adherence, our study revealed that the identified factors serve as opportunities and constraints that have a cascading influence on adherence to essential management (Figure 10). A more detailed description of findings can be found in Chapter 2.

Our network study led to the identification of 43 stakeholder organizations that could be broadly categorized as community, healthcare, and government sector organizations. The community sector organizations included: local community organizations (3), a non-local community organization (1), a local patient organization (1), state-level patient organization (2), national-level patient organizations (4), and a state-level physician-community organization (1). The healthcare sector organizations included: local hospitals with attached blood banks (13), local stand-alone blood banks (8), local diagnostic labs (4), a national-level diagnostic lab (1), and pharmacies (2). The government sector included: State level government offices (2), and a national level government office (1).

Social network analysis of the survey data revealed that no more than 14%, 32%, and 26% of possible activity was happening for any of the three relational ties among stakeholder organizations overall, within sectors, and across sectors respectively. More than 70% of existing connections in the network had a multiplex score of 2 or 3, indicating that they had relational ties that went beyond communication to include one or both of the other two types of relational ties in addition to it. A more detailed description of findings can be found in Chapter 3.

Three in-depth interviews with influential informants led to the identification of 3 perceived benefits and 6 perceived barriers to collaboration. Perceived benefits included 1) improved access to care and support, 2) resource generation, equity, efficiency, and 3) strength in unity. Perceived barriers included 1) funding concerns, 2) institutional differences, 3) lack of

interest in collaboration, 4) unaligned goals, 5) uncollaborative behavior (lack of trust, competition, egotism), and 6) lack of political will.

#### **4. Discussion**

Insights gained through community immersion indicated that adherence to essential management was a significant problem for thalassemia patients in Pune, which if solved could dramatically improve health outcomes for them. These insights along with the identification of 43 stakeholder organizations that influenced adherence to essential management as part of the network study, served as indications that multiple organizations influenced the problem. Every patient or caregiver who was interviewed reported constraints that influenced their ability to adhere to essential management, regardless of their socioeconomic status; this suggests that adherence issues are a large-scale problem that affect a majority of patients in the thalassemia community. The identification of 150 multidimensional and multilevel opportunities and constraints that influence adherence speaks to the complexity of the problem and the need to involve stakeholder organizations that exert their influence at various ecological levels. Furthermore, given that these factors work in concert or against each other to influence adherence, interventions would need to be planned to account for this and would necessitate that multiple stakeholder organizations across sectors work together to formulate interventions. While we identified 71 factors that served as opportunities, we also identified 79 that served as constraints to adherence to essential management, which suggests that the current system is broken in that it fails to adequately address constraints to adherence. Furthermore, the network study findings indicate that connectivity between stakeholder organizations overall, within, and across sectors was low, which suggests that stakeholder organizations were working in silos rather than in a coordinated manner; this is also

indicative of a disconnected and fragmented system. This was supported by stakeholder perceptions that indicated several barriers to collaboration. All the aforementioned findings suggest that adherence to essential management was a complex social problem that affected a majority of the thalassemia community in Pune and required multiple stakeholder organizations to work together in order to solve; hence the Collective Impact approach lends itself well to the problem. A detailed analysis based on the Collective Impact Feasibility Framework, is as follows:

**a. Which specific social problem should we focus on in this community?**

Through community-immersion, it was determined that poor adherence to essential management was common and contributed towards poor health outcomes in Pune's thalassemia community. Given its potential to greatly improve the quality of life and longevity of affected individuals, existing literature and clinical guidelines (Maria Domenica Cappellini, Alan Cohen, John Porter, Ali Taher, 2014) highlight the importance of adherence to essential management in thalassemia care. Therefore, improving adherence to essential management had the potential to dramatically improve health outcomes for the thalassemia community in Pune. The first step towards making interventions to improve adherence to essential management, was to determine the context-specific opportunities and constraints that influenced it, which was achieved through the study described in Chapter 2.

**b. Are there multiple stakeholders in the system who can influence adherence?**

Given the chronicity of thalassemia, adherence to essential management must be life-long, and as per contemporary conceptualizations it is dependent on factors that go beyond patient-related factors to include health system/healthcare team-related factors, social/economic-related

factors, disease-related factors, and treatment-related factors (Sabate, 2003). Given its complex and multifactorial nature, there were potentially multiple organizations belonging to several sectors that exerted their influence on a patient's ability to adhere to essential management. Community immersion and a network study in Pune identified 43 such organizations, which could be broadly categorized into government, community, and healthcare sectors. Furthermore, in-depth interviews with patients, caregivers, and key informants revealed 71 opportunities and 79 constraints that influenced adherence that could be classified into 9 categories. Collaboration between multiple organizations across sectors could foreseeably address some constraints across all these categories. For example: blood banks, government offices, hospitals, and community organizations could potentially influence a patient's ability to procure safe blood in a timely manner. Blood banks could augment their blood collection efforts to increase the availability of blood, and could offer leucodepletion and nucleic acid testing (NAT) to improve the safety of blood; government offices could formulate policies that ensure availability of adequate quantity and quality of blood at all blood banks; transfusion facilities at hospitals could provide assistance to patients in procuring blood from blood banks; community organizations could also develop strong relationships with blood banks by assisting them in organizing blood collection drives, and helping patients procure blood during times of shortage. Table 7 depicts potentially influential stakeholder organizations alongside each generic category.

Generic category	Community organizations	Hospitals	Blood banks	Medical stores	Testing centers	Government offices
Financial status/support	X	X		X	X	X
Blood security	X	X	X			X
Psychology/behavior	X	X				
Patient/caregiver knowledge and education	X	X				
Social status/support	X					X
Healthcare quality		X				X
Nature of disease/treatment	X	X				
Blood transfusion convenience		X				X
Access to care	X	X		X	X	X

**Table 7: Potentially influential stakeholder organizations for systemic constraints**

**c. Is the system fragmented, disconnected, broken?**

The two concurrent studies regarding network connectivity and factors that influence adherence yielded findings that suggest that the system is fragmented, disconnected and broken.

Of the 79 constraints identified in the adherence study, 40 were systemic in that they were influenced by a lack of suitable government policies (macro-level), organizational policies/services/activities (mezzo-level), and interpersonal relationships with community or healthcare partners (micro-level). Such constraints can be considered as contributors towards a broken system that prevent affected individuals from adhering to essential management. A more detailed description of systemic constraints in each generic category is as follows:

(i) Blood security

Despite policies being in place for access to free blood, a majority of interviewees reported difficulties related to blood procurement at certain times of the year that negatively influenced adherence to their blood transfusion schedules. They reported that blood procurement was

particularly challenging during the summer months and festive season due to a shortage of donors in city, many of whom were students or working professionals. Blood procurement was found to be even more difficult during this time for patients with a lack of donors in their social circles. There were also reports of hospital or blood banks who were unsupportive in that they made the blood procurement process difficult or did not make fresh blood easily available to patients. Several interviewees also reported facing issues with procuring safe blood, i.e. blood that was fresh, leukofiltered and had undergone nucleic acid testing (NAT). The availability of fresh blood was particularly problematic during blood shortages, which resulted in patients having to come in for their next transfusion at a shorter interval. Very few blood banks were reported to provide NAT tested and leukofiltered blood, a lack of which greatly increases the chances of transfusion reactions and transfusion-transmitted infections. Blood safety was further compromised due to the high price of bedside leukofiltration devices despite subsidization through patient organizations.

(ii) Blood transfusion convenience

Some interviewees reported that their hospital had unsuitable days or timings for transfusions, which conflicted with their schedules and therefore negatively influenced adherence to their transfusion schedules. There were also reports of transfusion facilities that did not have dedicated thalassemia wards or beds, which led to patients having to share space with trauma patients, or patients with other severe medical conditions; this caused significant psychological discomfort and was reported to negatively influence their ability to adhere to the transfusion schedule. The duration of the transfusion process was also brought up by many interviewees, which includes the time taken for all processes from the time they enter the transfusion facility until the time that they leave; longer durations were reported as inconvenient. Apart from the time

spent at the transfusion facility, several interviewees reported having to spend significant time coordinating blood transfusion related resources such as leukofilters, intracatheters and blood; the reasons for this were either unavailability or inability to afford the resources provided at the hospitals.

(iii) Healthcare quality

Some Interviewees reported that treating physicians did not provide adequate consultation time, support, guidance, tailored management, supervision, and/or quality communication with regards to essential management. One key informant also mentioned that most physicians did not make appropriate referrals to specialists or ancillary healthcare professionals such as medical social workers and counselors. Some interviewees also mentioned that following up with the treating physician was challenging due to high consultation fees, negligence, or fear of the physician. Several interviewees reported limited perceived benefits of routine testing, because their treating physicians didn't seem to use the test results to tailor medical management. Some interviewees expressed their dismay at the rude, careless, or incompetent nurses who would have to prick the patient multiple times to find a vein. Some interviewees reported that in certain hospitals continuity of care was significantly disrupted during the transition from childhood to adulthood as the patients had to be managed in a different ward by different physicians and hospital staff. Since these wards were not specialty wards for thalassemia patients, they did not have adequate infrastructure, resources or processes in place to cater to the medical needs of thalassemia patients. This was reported to lead to a much longer transfusion process that often took multiple days. Several key informants mentioned that variations in management strategies amongst physicians also lead to confusion amongst patients and caregivers, which negatively influenced

adherence to essential management. Lastly, a few interviewees who were adult patients indicated that their blood transfusions schedule was not being monitored by their treating physician, and that they were switching between different iron chelators without prior consultation.

(iv) Patient/caregiver knowledge and education

Some interviewees indicated a lack of knowledge or misinformation regarding blood transfusions, where they would delay transfusions because they were under the impression that getting transfusions earlier would worsen iron accumulation. There were also a few interviewees who seemed to be misinformed regarding the longevity of thalassemia patients and regarding their candidacy for bone marrow transplantation, which also influenced their adherence to essential management. Such misinformation was spread at the transfusion ward, between patients and caregivers who were simultaneously receiving blood transfusions.

(v) Access to treatment and medication

Many interviewees reported that it was occasionally difficult for them to procure chelation medication due to unavailability at medical stores or dispensing delays at hospitals that were providing them for free. This was reported to happen only rarely for the oral chelators, but very frequently for desferrioxamine. In fact, there were several reports regarding a “black market” for desferrioxamine, where eligible patients would receive it for free from various patient organizations across the country and sell them to other patients during shortages. Furthermore, several interviewees mentioned that while there was a government policy in place that provided for free oral chelators, patients were required to be registered and receive transfusions from the government hospital in order to access them; most patients could not access these government

benefits as they were receiving their blood transfusions from hospitals in the private sector. Additionally, one interviewee mentioned that it was sometimes difficult for her to procure disposables such as leukofilters and intracatheters that are used for blood transfusions. A few interviewees, who would make an annual trip back to their village, mentioned that they were not able to go for blood transfusions there due to unavailability of quality blood transfusion services.

(vi) Financial status/support

Almost all interviewees reported that the cumulative expenses associated with iron chelation therapy, routine testing, physician consultation fees, hospital charges, or disposables were very high. One key informant mentioned that patients would delay their transfusions because they couldn't afford to pay for the hematogram to determine their pre-transfusion hemoglobin. Additionally, some interviewees who were aware about the benefits of using a leukofilter during their transfusions reported not being able to afford them, which led to compromised blood safety. One interviewee mentioned that she switched to an unprescribed chelator because she could not afford the prescribed chelator. A few patients mentioned that they were not able to follow-up with their treating physician because of a high consultation fee. Several interviewees who were aware about the benefits of routine testing had to delay them because they couldn't afford them. Some interviewees reported not receiving financial support of any kind to help them cope with high treatment related expenses, and also reported that government policies that had made provisions for free chelators were not inclusive in that patients could only access them if they were being treated at government hospitals.

(vii) Social status/support

Some interviewees reported not being supported by their employers or educational institutions in order to accommodate their prescribed management schedules. One key informant mentioned that thalassemia patients put a lot of pressure on themselves and work extremely hard to perform well in professional settings since they are undermined by their employers and are at higher risk of being laid off; unfortunately caused conflicts with their treatment schedule and therefore negatively influenced adherence to it. Some interviewees reported that they did not receive social support from medical social workers, counselors, support groups or peers; this was supported by several key informants who mentioned that there were not enough counselors, support groups, and peer support to address psychosocial issues being experienced by patients. Interviewees also reported that broad social issues such as preferential treatment of male children and social rejection and stigma towards people with disabilities, negatively influenced adherence to essential management. One interviewee mentioned that he never used to carry iron chelation medications to his village during his annual trip because he feared being stigmatized or rejected by the other villagers if they found out that his children had thalassemia. Unfortunately, several interviews indicated that affected families lacked awareness regarding the existence of free or subsidized amenities. Some interviewees mentioned that patients were unable apply for government support due to missing government issued documents regarding their financial status and proof of residence.

It is important to note that many of the aforementioned constraints had counterpart opportunities that were reported by other patients or caregivers. For example, while some interviewees reported receiving no financial support, many reported receiving free or subsidized management. This is indicative of inequities in the system that are possibly due to lack of access

or information. Hence the broken system is also a contributor towards inequities, which are indicative thereof.

(viii) Network connectivity and perceived barriers to collaboration

Social network analysis of network data collected from cross-sector stakeholder organizations within and between sectors revealed that the observed connectivity between stakeholders within and across sectors was only a small fraction of theoretically possible connectivity across all relational ties; this suggested that there were gaps and a lack of coordination in the stakeholder organization network. Connectivity between stakeholders from the community and healthcare sectors had room for improvement, as only 14% of possible communication, and no more than 9% of possible joint activities and shared referrals were happening among them. Poor connectivity between stakeholders from the community and government sectors was concerning, as only 4% of possible communication, and no joint activities or shared referrals were happening among them. While within-sector connectivity for any relational tie was 32% or less among organizations in the community sector, it was 13% or less among those in the healthcare sector. Possible reasons for this were provided by influential informants via in-depth interviews:

- (a) Organizations in the community sector were non-profits, and therefore depended on generating funds from donors, corporates, and other community organizations to sustain their efforts. It is was no surprise that non-profits were particularly wary about the redirection of funds from their sources to other non-profits. Interorganizational collaborations were viewed as prospective causes of such a scenario in the future, and were hence viewed as barriers to collaboration.

- (b) Some healthcare organizations and community organizations had taken a different approach to assisting the thalassemia community and sustaining their efforts by simultaneously creating value for themselves and the community. One way of doing this was through the development and application of new treatment modalities for patients to reduce their transfusion requirements. Such unconventional approaches were very different from those used by organizations that were accustomed to a traditional donor-driven model for generating funds and focused on supporting conventional guideline-based treatment modalities. These differences in approaches were not viewed as being compatible and were therefore reported as being a significant barrier to collaboration.
- (c) Stakeholder organizations had differences in internal processes, working patterns, decision-making processes, and also in the socioeconomic status of the patients that they served. These differences led to failed attempts at collaboration or dissatisfaction amongst patients who were referred to other organizations. Hence, these institutional differences were seen as barriers to collaboration.
- (d) Some influential informants perceived a collaborative approach as having only short-term rather than long-term utility in improving the status-quo. In fact, some were of the opinion that it was indicative of a more fragmented system because they held the belief that a “center of excellence” approach, where all services were provided under one roof, was the way forward. This mindset resulted in a lack of motivation to prioritize the initiation and maintenance of collaborative ties, and hence served as a barrier to collaboration.

(e) Competition between organizations can be productive when it leads to improvements in their services to patients. However, competition can also result in duplication of similar efforts, which is counterproductive since it amounts to an inefficient use of resources. Furthermore, some duplicate efforts have also reportedly led to confusion in the thalassemia community. Though similar efforts by different organizations might be well-intentioned, they had created mutual distrust amongst some organizations, and had thereby created a barrier to collaboration.

(f) Being a developing country that is dealing with the dual burden of infectious diseases and chronic diseases, national and state government public health departments in India have numerous responsibilities. At any given time, the number of individuals in the population that are affected by vector-borne infectious diseases such as malaria, chikungunya, and dengue, and chronic diseases such as diabetes and cancer, far exceeds those that are affected by thalassemia; hence these diseases are prioritized over thalassemia for public health interventions that often involve partnerships with non-governmental organizations. In such a situation, a high-ranking government official's keen interest in improving outcomes for thalassemia patients can influence the sustainable allocation of human and financial resources towards collaborative efforts with non-governmental organizations. However, our data indicated a lack of such political will, thereby making it a barrier to collaboration.

**d. Is cross-sector organizational collaboration required?**

As illustrated in Table 5, each generic category of opportunities and constraints can be influenced by more than one stakeholder organization; therefore, interventions that target constraints within these categories might require collaboration between these organizations. As illustrated in Figure 10 opportunities and constraints across generic categories can be conceptualized as working in concert or against each other to have a cascading influence on adherence. Therefore, interventions that target individual factors might not be sufficient to improve adherence. Interventions that target multiple factors are likely to be more effective but would necessitate collaborative development of interventions by the organizations that influence them. These organizations might not always be from the same sector. For example, a caregiver might be dissatisfied with the nursing staff because they need to prick the patient multiple times to find the vein, which causes pain and instils a fear of being pricked in the patient; this in turn leads the patient to be stubborn during subsequent transfusions. This issue involves factors that span across the following generic categories: Healthcare quality, Nature of treatment, Psychological/behavioral. Hence an appropriate multi-factorial intervention would involve stakeholder organizations that influence the aforementioned categories; in this case they would include hospitals, community organizations, and government offices. At the macro-level relevant government offices might introduce policies to ensure that nurses who attend to thalassemia patients are adequately experienced and trained so that they insert the intracatheter using as few pricks as possible; at the mezzo-level hospitals can implement such policies by ensuring that nurses in the thalassemia ward are adequately trained and adept at handling thalassemia patients; hospitals can then refer patients to social workers or counselors associated with hospitals or community organizations, who can then make micro-level interventions by counseling the caregivers and patients to address feelings of fear and stubborn behavior.

There were also several opportunities that were inadvertently working in concert to improve adherence in thalassemia patients in Pune. For example, patients who were facing financial constraints found it difficult to afford iron chelation medication and the infusion pump used to administer it; they also faced difficulties adhering to the prescribed iron chelation regime due to the long duration of administration. A particular community organization managed to collaboratively make the infusion pumps available to various other community organizations and hospitals, through which patients could rent them for a nominal fee. Furthermore, another community organization was partially reimbursing patients for the cost of iron chelation therapy and organizing awareness events to educate patients about the importance of adhering to the prescribed therapy despite the long duration of administration. Educational institutions were also reportedly accommodating patients' medical needs by permitting them to reach school a little later than scheduled. All these opportunities were working in concert to improve adherence in some patients. If such multi-factorial interventions were made consciously rather than inadvertently through interorganizational collaboration between the community, hospital, and education sectors, their impact might be felt by more members of the community. Opportunities that were identified also provide a valuable foundation to build innovative multifactorial interventions upon. A list of all opportunities and constraints to adherence that were identified through the previous study can be found in Appendix G.

Additionally, influential informants who participated in the network study also mentioned several benefits of interorganizational collaboration:

- (i) One of the perceived benefits of interorganizational collaboration was improved access to care required for essential management of thalassemia. Additionally, it would also result in better access to and more effective interventions at psychological/behavioral

level through patient education, counseling, and peer support. The improved health outcomes would reflect well on all agencies involved in the collaborative.

- (ii) Another perceived benefit was the ability to generate more resources for efforts to improve adherence, make the use of existing resources more efficient, and assure that resources are distributed fairly amongst those who need them so as to prevent resource abuse. This in turn would make organizations more financially sustainable. More efficient use of resources might also make funding a collaborative more attractive to donors, as it would enable their financial support to have a larger impact on the thalassemia community.
- (iii) Interorganizational collaboration was also believed to be able to influence public perceptions regarding the burden of the disease, and attract the attention of the media, government authorities, and funding sources. It can also help in the implementation of national-level policies to make care more accessible. It would also enable organizations to focus on their areas of strength, rather than duplicating efforts of other organizations.

Encouragingly, a large majority of the existing connections between stakeholder organizations within and across sectors were multiplex i.e. they shared more than one type of relational tie, which likely makes them more resilient to dissolution. Possible reasons for this as informed by community immersion and influential informant perspectives include: commonalities in organizational goals, strong personal ties between key representatives of these organizations, prior successful collaborations, and complementary rather than competing services. Further

exploration of factors that made these strong alliances possible can be valuable to organizations in the network who are inclined towards fostering strong ties with each other.

**e. Are a majority of end-users affected?**

While the study that sought to determine opportunities and constraints that influence adherence to essential management did not allow for a quantitative assessment of the scale of the problem, it did allow for a qualitative one. The purposive sampling methodology used led to the recruitment of participants across different socioeconomic backgrounds, ages, genders and treating hospitals; this was done in an effort to exhaustively capture the diverse experiences of the thalassemia community in Pune. The distribution of participant characteristics can be found in Figures 5, 6 and 7. Every single participant who was a patient or caregiver reported facing constraints to adherence, albeit of different types and to varying degrees. Given that the cost of treatment in India for a 30 kg individual affected by thalassemia amounts to approximately \$2800 per year (Ministry of Health & Family Welfare, 2016), which is beyond the affordability of a majority of middle and low-income Indian families, most families were unable to afford all aspects of essential management. Even families who could afford the treatment costs or were receiving it for free, could not escape non-financial constraints such as those related to blood procurement and safety, inadequate quality of physician interactions, inadequate quality of nursing staff, unsuitable transfusion timings, stubbornness, burnout, difficult administration of treatments, and adverse effects.

**f. Implications and future directions**

Based on the aforementioned discussion the problem of poor adherence to essential management in the thalassemia community of Pune was complex in that the system was clearly fragmented, disconnected, and broken, and required multiple organizations across various sectors to work together to fix it; the problem was also of sufficient scale in that a large majority of affected individuals were affected by it. Hence a Collective Impact approach would lend itself well as a means to improve adherence in the thalassemia community of Pune. However, the readiness of the community to adopt such an approach was questionable.

As per the Collective Impact Feasibility Framework, readiness for such an initiative is determined via the assessment of preconditions including: 1) availability of influential champions, 2) availability of financial resources, and 3) a history of collaboration in the community, 4) an urgency for change. Due to resource constraints and difficulties related to convening multiple stakeholders, this research was not able to rigorously assess the community's readiness for a Collective Impact initiative. However, findings from concurrent studies regarding factors that influence adherence and interorganizational connectivity, and community immersion that preceded them, provide some preliminary insights regarding the preconditions.

- (i) Are there influential champions who can provide local leadership?

Field interactions led to the identification of four influential informants who had decades of combined experience across government, community, and healthcare sectors, and were passionate about improving outcomes for the thalassemia community through improved adherence. Of these four, one was unresponsive to research participation requests, which in itself might indicate a disinterest in interorganizational collaboration. While two of the informants believed that interorganizational collaboration might be a suitable approach moving forward, one

informant was in favor of a center-of-excellence approach, where all adherence-promoting services are provided by a single center. So even though there were influential champions, not all of them might be interested in providing local leadership for a Collective Impact initiative. However, dissemination of information regarding Collective Impact, and of our findings regarding the appropriateness of a collective approach to solve the adherence problem - might alter influential informants' perceptions regarding the utility of interorganizational collaboration.

- (ii) Do financial resources exist to support collaboration for at least 12 months?

Influential informants from the study regarding interorganizational connectivity suggested that current funding models are individually-based. Different fundraising approaches or methods of aligning individual funding sources would be needed in order to generate resources that can support the initial phase of a collaborative involving multiple organizations.

- (iii) Is there a history of collaboration in the local community?

Findings from the study on interorganizational connectivity in Pune indicate that there were ongoing collaborations between a few organizations that facilitated adherence to essential management. However, influential informant interviews from the study indicated that there had been several past collaborative efforts that were unsuccessful due to unaligned goals or institutional differences. This had caused some stakeholder organizations to lose interest in collaboration altogether. Efforts that build trust and collaboration over time amongst stakeholder organizations would be needed in light of this.

- (iv) Is there an urgency for change in the local community?

Field interactions and observations suggest that while there was widespread awareness regarding poor adherence amongst stakeholder organizations, there was no proportional sense of urgency to improve it. Overall, there seemed to be a larger focus on primary prevention via carrier screening, transitioning patients to alternative therapies, or seeking opportunities for bone marrow transplantation. Disseminating the findings of this research to influential champions and the community at large can help create a sense of urgency around the problem of poor adherence in the thalassemia community in Pune and its detrimental impact on health outcomes. This can be done via presentations at scientific and community organization meetings, and publication in digital and print media, and scientific journals.

#### **g. Conclusion**

Given the community-wide scale of the adherence problem, need for multiple stakeholder organizations to work together to improve it, siloed functioning of stakeholder organizations, and multilevel constraints to adherence, our research findings suggest that Collective Impact is an appropriate approach to improve adherence to essential management in the thalassemia community. While our research lacks sufficient data to draw formal conclusions regarding the readiness of the community to adopt Collective Impact, it does suggest that efforts are required to develop and align the interests of influential champions towards a collaborative approach, build a sense of urgency around the issue, and develop a funding mechanism for such an initiative. Most challengingly, interventions will be required to build relationships and trust amongst local stakeholders in order to encourage deeper forms of collaboration that go beyond communication to include joint activities and shared referrals. Once significant progress has been made in this regard, it might be easier to comprehensively determine the financial resources available to launch

and sustain collaboration for at least 12 months. The results of this study can be disseminated to all influential champions and local stakeholders to make them aware of the scale of poor adherence amongst the community, and the factors that influence it; this might help bring visibility to the issue and develop a sense of urgency amongst them. Furthermore, publication of our research findings in journals and more socially accessible media platforms, has the potential to draw the attention of the public, scientific community, and government to the issue, thereby further increasing the sense of urgency.

## **CHAPTER 5**

### **Conclusion**

#### **1. Summary**

$\beta$ -thalassemia major is a hereditary, autosomal recessive hemoglobin disorder that is caused by mutations in the HBB gene, which codes for the  $\beta$  subunit of the hemoglobin tetramer. Inadequate  $\beta$  subunits result in significantly lower production of hemoglobin tetramers and an excess of alpha subunits. When left untreated this results in severe microcytic anemia, erythroid marrow expansion, splenomegaly and iron accumulation in various tissue and affected individuals die by 3 years of age. Essential management of  $\beta$ -thalassemia major involves periodic blood transfusions to address anemia, frequent administration of iron chelation therapy to address iron accumulation, and routine medical tests to monitor for secondary complications. Encouragingly, affected individuals who are well-managed can experience quality of life and longevity close to that of an unaffected individual. Unfortunately, a majority of affected individuals in India are sub-optimally managed (Mohanty et al., 2013).

Close to half of all  $\beta$ -thalassemia major births occur in India (Vincenzo De Sanctis et al., 2017). Estimates suggest that India has approximately 40-54 million carriers and 10,000-12,000 thalassemia affected births each year. Carrier frequencies are as high as 17% in some communities (Colah et al., 2010). In the absence of population-level interventions to prevent the disease, it is set to become a significant public health issue. Ideally, such interventions should seek to prevent births of affected individuals (primary prevention), diagnose affected individuals early to prevent clinical sequelae via early intervention (secondary prevention), and appropriately manage affected individuals in order to minimize medical and psychosocial consequences of the disease (tertiary

prevention). There seem to be disproportionately fewer efforts focused on tertiary prevention. This is problematic as sociocultural issues have been reported to be barriers to primary prevention interventions (Chattopadhyay, 2006), and curative options such as bone marrow transplantation are not within the reach of many due to financial reasons or unavailability of compatible donors.

With an intention to conduct research aimed at improving tertiary prevention, we engaged with the thalassemia community in the city of Pune, India which has large numbers of people from high-risk communities and consequently several thalassemia-related community and health-related efforts underway. Community engagement revealed that adherence to essential management was a significant issue being experienced by affected individuals in the thalassemia community in Pune. Hence, interventions to improve adherence could significantly contribute towards an improvement in tertiary prevention of thalassemia. However, interventions to improve adherence would require knowledge regarding contextual factors that influence it. Since no prior studies had been conducted in Pune that sought to determine these factors, we conducted in-depth interviews with patients, caregivers, and key informants to determine context-specific factors that influence adherence to essential management for  $\beta$ -thalassemia major in Pune.

Contemporary conceptualizations of adherence go beyond factors that are patient-related to include those that are related to the condition, treatment, socioeconomics, and the health system/healthcare team (Sabate, 2003). Furthermore, health-related individual behaviors such as adherence, have been more recently conceptualized as being influenced by opportunities and constraints imposed by an individual's environment (Glass & McAtee, 2006). These opportunities and constraints exert their influence in a hierarchical fashion ranging from proximal micro-level interpersonal interactions to macro-level social and political opportunities and constraints that influence larger populations; mezzo-level organizational opportunities and constraints fall in

between these two hierarchical levels. Hence, for our study we conceptualized adherence as being influenced by multidimensional and multilevel opportunities and constraints. The absence of prior studies led us to believe that an exploratory qualitative study that seeks to identify such opportunities and constraints from the viewpoints of affected individuals, caregivers, and key informants, can provide foundational data for multi-factorial interventions and future studies. Deductive content analysis of 49 interviews with patients, caregivers, and key informants, yielded 71 opportunities and 79 constraints that influenced adherence to essential management in Pune, which were classified into 9 categories that were linked to the WHO multidimensional adherence framework (Sabate, 2003). These opportunities and constraints were further classified based on their ecological level of influence. In line with an ecological conceptualization of adherence (Berben et al., 2012; Glass & McAtee, 2006), the multidimensional and multilevel constraints and opportunities were interpreted as working in concert or against each other to have a cascading influence on adherence. This led us to infer that interventions that target constellations of factors are likely to improve adherence more than those that target individual factors.

Interorganizational collaboration was a facilitator of adherence to essential management that was widely reported by interviewees, which suggested that it might be an effective means to address certain constraints to adherence. Many reported constraints could foreseeably be addressed via interventions that involve interorganizational collaboration. For example, patients and caregivers couldn't always voice their concerns directly to hospital authorities out of fear. Perhaps community organizations can serve as intermediaries who communicate adherence-related pain-points experienced by patients to the hospital authorities; this might help improve the quality of healthcare services as they pertain to the promotion of adherence. Lack of knowledge regarding available amenities and subsidies for thalassemia affected individuals and families was

another identified constraint to adherence. Communication regarding these between hospital and community organization personnel can also aid in timely direction to available resources, thereby promoting adherence.

The aforementioned collaboration possibilities are exemplary of links between community and healthcare organizations in the delivery of health services for chronic conditions. These cross-sector links have been emphasized by the Innovative Care for Chronic Conditions (ICCC) framework (World Health Organisation, 2002) as a building block towards improved care for chronic conditions in health systems. Coordinated provision of complementary services by community organizations and healthcare organizations can generate resources, improve efficiency, and address service gaps that result from resource constraints. Using a combination of network surveys and in-depth interviews, our network study was able to delve deeper to determine the current state of cross-sector and within-sector interorganizational connectivity and perceptions regarding interorganizational collaboration. It also helped identify stakeholder organizations in the system who were uniquely positioned to steer the system towards facilitating adherence to essential management.

Our network analysis of 43 organizations revealed that only a small proportion of possible links were present among organizations within and across community, healthcare and government sectors, which was indicative of a disconnected system. Encouragingly, a majority of existing links were strong in that they went beyond just communication to include joint activities and shared referrals, which are more resource intensive. This indicated that the network might evolve in a direction where organizations have a few strong links and many weak links with other organizations. This might be an effective configuration since having many strong links would be too resource intensive (Grannovetter, 1973). Inductive content analysis of 3 influential informant

interviews offered possible reasons for few links among organizations within and between sectors. These included funding concerns, institutional differences, lack of interest in collaboration, unaligned goals, lack of trust and competition, and lack of political will. All of these barriers have been reported extensively in the network literature (Brinkerhoff, 2002; Casey, 2008; K. G. Provan et al., 2004; K. Provan, Harvey, et al., 2005; K. Provan, Veazie, et al., 2005; Retrum et al., 2013). Stakeholder organizations from community, healthcare, and government sectors were found to be amongst the top 7 uniquely positioned stakeholder organizations in the network; these organizations would be most well-positioned to facilitate planning and implementation of future interventions to strengthen collaboration and should be made aware of their network positions.

The complexity and scale of poor adherence, and the presence of multiple stakeholder organizations that influence it, led us to speculate that the Collective Impact approach (Kania & Kramer, 2011) might serve as model to facilitate interorganizational cross-sector collaboration in order to improve adherence in the thalassemia community in Pune. The Collective Impact approach offers a structured way to foster collaborations between stakeholders involved in a social problem, in order to improve and sustain outcomes. The approach requires that stakeholders have an a) common agenda, b) common measurement system, c) mutually reinforcing activities, d) ongoing communication, and e) a backbone organization (Hanleybrown et al., 2012). It has been successfully used to improve outcomes for complex social problems such as chronic disease, poverty, and homelessness. A Collective Impact approach is a long-term strategy requires the mobilization of significant financial and human resources and can take several years to noticeably influence outcomes; hence, an assessment regarding the appropriateness of this approach and the community's readiness to adopt it was required before committing to the approach. We assessed the appropriateness of the approach in the context of improving adherence for the thalassemia

community in Pune using the Collective Impact Feasibility Framework (FSG, 2015), which drew on findings and insights gained from our study regarding opportunities and constraints that influence adherence, cross-sector interorganizational connectivity, and community immersion that preceded them.

Community immersion enabled the identification of poor adherence to essential management as a significant social issue for the thalassemia community in Pune. If adherence were improved, this could greatly improve health outcomes for affected individuals as it would prevent chronically low hemoglobin levels, iron overload, and severe secondary complications related to them; this would reduce morbidity and mortality, and improve the quality of life of affected individuals. Community immersion also revealed that multiple organizations influenced an affected individual's ability to adhere to essential management. We identified 79 constraints to adherence, at least one of which affected each participating patient or caregiver regardless of socioeconomic status, gender, age and treating hospital. Interorganizational collaboration between stakeholders from the community, healthcare and government sectors would be required to address many of the identified constraints. This could be achieved through enhanced communication, appropriate referrals, and aligned or joint activities to streamline medical and psychosocial service delivery to improve its quality, access, and comprehensiveness. However, network study findings indicated that there was poor connectivity between stakeholder organizations within and across sectors. The aforementioned inferences indicate that poor adherence to essential management was a large-scale social problem that affects a majority of the thalassemia community in Pune, and was influenced by a broken, disconnected and fragmented system that could potentially be fixed by cross-sector interorganizational collaboration. Based on the Feasibility Framework, these features indicate that Collective Impact would be an appropriate approach to improve adherence to essential

management for the thalassemia community in Pune. However, study findings also allowed for preliminary inferences regarding readiness, which suggested that the community might need to be prepared to adopt such an approach by garnering buy-in from influential cross-sector leaders, building trust between stakeholder organizations, determining ways to fund such an initiative, and creating a sense of urgency around the issue in the community (Hanleybrown et al., 2012).

## 2. **Moving towards readiness by establishing preconditions of Collective Impact**

Garnering buy-in from cross-sector influential champions, such as senior executives of community organizations, leading hematologists and pediatricians, hospital administrators, blood bank directors, and public health officials, is important for a Collective Impact initiative as they would likely lead and oversee all activities of such a program, were it to be initiated. This might be accomplished by sharing information about the Collective Impact approach and how it is different from other forms of collaboration in terms of its structure, process, and use of data. Furthermore, sharing qualitative findings regarding contextual factors that influence adherence, the current status of cross-sector connectivity, and the appropriateness of using a Collective Impact approach to address them, might be a powerful means to get them interested in the approach as it would provide actionable evidence regarding the complexity and scale of the problem and offer a potential solution to address it.

Backbone support is a feature of a Collective Impact initiative that is distinct from other forms of collaboration. Its purpose is to facilitate collaboration between different stakeholders and mediate collaborative activities by ensuring that the five conditions of Collective Impact are being upheld. A backbone organization requires dedicated staff with strong adaptive leadership skills and financial resources in order to perform their important role in sustaining collaboration between

stakeholders. Generating the financial resources for such an organization and for a Collective Impact initiative on the whole would require new models of funding, where donors gain the confidence to fund a collaborative rather than individual organizations; in fact, a backbone organization can also facilitate the generation of additional financial resources once it is constituted (Hanleybrown et al., 2012).

While there were a few ongoing collaborations in the community, trust between some key stakeholder organizations had eroded as a result of failed past attempts at collaboration. Rekindling communication between these organizations would be required in order to find ways in which their services can complement each other to facilitate adherence in the thalassemia community. Dissemination of our study findings, particularly the constraints to adherence and patient stories that are illustrative of them, might persuade organizations with a past history of failed collaborations between each other to reconsider them. The same applies to organizations that did not share any ties with each other whatsoever. Furthermore, visualization of the network via the sociograms and learning about their position in the network - in terms of the number of connections they have with other organizations - might encourage them to improve their position within the network by initiating communication with other organizations.

Despite it being a complex social problem that affected a majority of the thalassemia community, a sense of urgency about improving adherence to essential management seemed to be missing in the community. Dissemination of recommendations, based on the adherence study findings, to the community and stakeholder organizations might help create a sense of urgency around the issue. This can be done through tailored research briefs, journal publications, presentations, or social media platforms that are quite popular amongst affected individuals, caregivers, and healthcare workers alike.

Substantial progress in establishing the preconditions of Collective Impact i.e. buy-in of influential champions, financial resources, interorganizational trust, and an urgency for change, would indicate that the community is ready for Collective Impact. If and when this does happen, our study findings can influence the first phase of a Collective Impact initiative. This phase involves: 1) the identification of influential champions and formation of a cross-sector group 2) mapping the landscape and using data to make a case, 3) facilitating community outreach, and 4) analyzing baseline data to identify key issues and gaps (Hanleybrown et al., 2012). Community immersion and the organizational network study have already identified a few influential champions who might be candidates for a cross-sector group. The organizational network study has mapped the landscape of organizations that influence adherence and the connectivity between them. Community outreach has been facilitated via in-depth interviews with patients, caregivers, and key informants to identify factors that influence adherence. Lastly, analysis of findings regarding factors that influence adherence and interorganizational connectivity has identified key issues and gaps. However, establishing the preconditions of Collective Impact and subsequently transitioning into the first phase of Collective Impact might take a substantial amount of time. In the interim, the community could still benefit from a dissemination of recommendations based on the study findings, which might help in addressing some of the issues through interventions by individual organizations, or through strategic alliances between multiple organizations.

### **3. Dissemination and recommendations**

A dissemination strategy can be developed based on the ecological level at which factors exert their influence. For factors that were found to influence adherence at the individual or the micro-level, the results could be disseminated to individuals who have direct interactions with

patients. These might include physicians, nurses, social workers, counselors, and patient organization representatives. For factors that were found to influence adherence at the mezzo-level – the results could be disseminated to executives of health care organizations and community organizations who are capable of influencing change at the organizational level; specifically, these might include: key hospital administrative staff, blood bank directors, and patient organization leaders. For factors that were found to influence adherence at the macro-level – the results could be disseminated to senior leadership of organizations that have ties with policymakers; specifically, these might include: government hospital leaders, state and national level government authorities, and patient organization leaders. Research briefs based on the ecological level of dissemination have been prepared based on our findings and can be found in Appendix H.

#### 4. **Future directions**

As previously described the findings of the qualitative and network studies can be used to build readiness for a Collective Impact approach. However, regardless of whether or not the thalassemia community and stakeholder organizations in Pune reach this stage, our research findings can be used by to plan interventions that target multiple factors at various ecological levels. This might be through interventions by individual healthcare and community organizations or through collaborations between them. As previously described initial steps in this direction could involve dissemination of recommendations based on our findings to stakeholders across ecological levels. Furthermore, contemporary health promotion approaches such as intervention mapping can be used, where data regarding opportunities and constraints that influence essential management can be used to create a logic-model of the problem and a logic model for change across ecological levels. Following this a theory and evidence-based program can be designed to

change the status quo, which must then undergo production, implementation, and evaluation (Bartholomew-Edlredge et al., 2016).

While our qualitative study identified environmental opportunities and constraints that influence adherence behavior, the Society-Behavior-Biology nexus (Glass & McAtee, 2006) that guided our study also emphasized biological factors, ranging from multi-organ systems to genetic factors, that are embodied and manifest as human behavior. A variety of mutations in the HBB gene can cause  $\beta$ -thalassemia major and result in varying degrees of severity; this might exert an influence on treatment requirements and consequently adherence behavior, and therefore warrants further exploration. Quantitative studies can help determine correlations between the genotype of an affected individual and adherence behavior. A positive correlation might warrant consideration of genetic factors in assessments of a patient's propensity to be non-adherent to essential management. Identified opportunities and constraints can also provide foundational data for studies involving multivariate analyses that seek to quantitatively determine correlation between factors and their influence on adherence.

Stakeholder organizations might find the results of the social network study useful in understanding their position within the network, and also might help them strategize within-sector and cross-sector relationship building activities. Furthermore, the network study can be repeated in the future in order to track changes in network structure that might serve as an indicator of progress towards interorganizational cross-sector collaboration.

## Appendix A

### **English interview guide to determine factors that influence adherence to essential management for thalassemia - Patients and Caregivers**

#### **Introduction**

Hello, I am currently a PhD student at the University of Washington, Seattle. Thank you so much for taking time out to speak with me. Part of my research focuses on understanding factors that positively or negatively influence thalassemia patients' adherence to blood transfusion schedules, iron chelation regimens, and routine testing schedules. It is important to understand this from the perspective of patients, their parents, and key informants as their experiences have the potential to inform practical interventions to improve adherence in the future, thereby improving outcomes for the thalassemia community. This research has been approved by the ethics review board of the University of Washington, USA, and B.J. Medical College, Pune to protect your privacy and the confidentiality of the data that you provide. If you agree to participate, you may still withdraw from the study at a later stage if you choose to; you may contact me if such a situation arises (provide business card). Our conversation today will be recorded because it will be difficult for me to remember all your responses. I will also be taking some notes during our conversation to help me remember specific details. I assure you that all recordings will be deleted 1 year after the findings of the study are disseminated. I can also assure you that all the information that you provide during our conversation today will remain confidential, and your identity will not be revealed directly or indirectly. I encourage you to be honest and transparent about your experiences as this will give relevant stakeholders a truthful account of patients' current experiences, which will lay set the stage for the formulation of practical interventions.

#### A. Demographics:

I would like to start by asking you for some details about yourself so that we have a better idea about how your experiences might be related to your personal circumstances

- How old are you (your child) ?
- How many siblings (children) have you had with thalassemia
- For how many years have you (and your child) been living in Pune / Pimpri-Chinchwad?
- Which locality do you live in within Pune / Pimpri-Chinchwad?
- Which locality do you live in within Pune / Pimpri-Chinchwad?
- Are you currently employed (Does your child currently attend an educational institution?)

#### B. Experiences with blood transfusion

- **How frequently do you need to go for blood transfusion as per your physician's prescription?**

- **What factors make it easy to follow this?**
- **What factors make it difficult to follow this?**

Probes:

- Access to blood
  - Which blood bank do you use? Why?
  - What factors that make it easy / difficult to get blood from this bank?
  - Do you experience blood shortages? When and Why? What do you do in such situations?
  - Do shortages ever influence your ability to follow the transfusion schedule?
  - Do you pay for blood? Does this influence your ability to follow the transfusion schedule?
- Access to blood transfusion facility
  - Where do you go for blood transfusions? Why?
  - What factors make it easy / difficult to get your transfusions from here? (distance, cost, quality of care, time taken comfort, entertainment, weekend testing, paperwork, etc)
  - Do you pay for transfusions (leukofilters, blood testing, catheter, cost of bed, hospital charges). Does this influence your ability to follow the transfusion schedule?
- Social/educational/professional interruptions
  - Do blood transfusions interrupt your social life/school/work?
  - What accommodations, if any, does your school/workplace for your transfusion schedule?
  - What accommodations, if any, does the transfusion facility make for your work/school schedule?
  - What accommodations, if any, do your friends/family make for your transfusion schedule?
- Other factors
  - Cooperative child / Stubborn child
  - Perceived benefit of transfusions
  - Perceived severity of thalassemia
  - Literacy
  - Motivation
  - Medical communication/instructions/guidance/counseling
- What support, if any, do you receive from:
  - Physician/Hospital
  - Blood bank
  - Pharmacy
  - Government organizations
  - NGOs

- Employer/School
  - Family/Friends
  - Other
- What support do you wish you had that would make adherence to the transfusion schedule easier?

C. Experiences with iron chelation

- **Has your physician prescribed an iron chelation regimen? Which ones and how often do you have to take them?**
- **What factors make it easy to follow this?**
- **What factors make it difficult to follow this?**

Probes:

- Access to iron chelators:
  - Where do you acquire iron chelators from? Why?
  - What factors make it easy/difficult for you to acquire drugs from here?
  - Do you pay for iron chelators? Does this influence your ability to adhere to the prescription?
  - Do you experience shortages? When and Why? What do you do in such situations?
  - Do shortages ever influence your ability to follow the iron chelation prescription?
- What other factors negatively or positively influence your ability to follow the iron chelation prescription?
  - Convenience – ease of administration, time taken, conflicting schedule, complicated regimen
  - Reminder system/forgetfulness; clarity/conflicts about when to take the medication.
  - Supervision
  - Pleasantness – pain, taste
  - Side-effects
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Social acceptance
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation
  - Any other?
- What support, if any, do you receive from:

- Physician/hospital
  - Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do you wish you had that would make adherence to iron chelation medication easier?

D. Experiences with routine medical surveillance

- **Has your physician prescribed routine medical tests? Which ones and how often do you have to do them?**
- **What factors make it easy to follow this?**
- **What factors make it difficult to follow this?**

Probes:

- Access to tests
  - Where do you get these done? Why?
  - What factors make it easy/difficult to get them from here?
  - Do you pay for them? Does this influence your ability to adhere to the prescription?
- What other factors influence your ability to adhere to the testing schedule?
  - Convenience – ease of getting the tests done, time-taken, conflicting schedule, complicated testing schedule
  - Reminder system/forgetfulness; clarity/conflicts about when to do the test
  - Supervision
  - Pleasantness – pain, discomfort
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation
  - Any other?
- What support, if any, do you receive from:
  - Physician/Hospital/Testing center

- Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do you wish you had that would make adherence to the testing schedule easier?

E. Experiences with supplementary/complementary/alternate therapy

- **Has your physician or anyone else prescribed any other medication/supplements? If yes, which ones and how often do you have to take them?**
- **What factors make it easy to follow this?**
- **What factors make it difficult to follow this?**

Probes:

- Access to supplementary/complementary/alternate therapy
  - Where do you acquire these from? Why?
  - What factors make it easy/difficult to get them from here?
  - Do you pay for them? Does this influence your ability to adhere to the prescription?
  - Do you experience shortages? When and Why? What do you do in such situations?
  - Do shortages ever influence your ability to follow the prescription?
- What other factors negatively or positively influence your ability to follow the prescription?
  - Convenience – ease of administration, conflicting schedule, complicated regimen
  - Reminder system/forgetfulness; clarity/conflicts about when to take the medication.
  - Supervision
  - Pleasantness – pain, taste
  - Side-effects
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Social acceptance
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation

## **Appendix B**

### **Hindi interview guide to determine factors that influence adherence to essential management for thalassemia - Patients and Caregivers**

#### **Introduction**

हैलो, मैं वर्तमान में वाशिंगटन विश्वविद्यालय, सिएटल में एक पीएचडी छात्र हूँ। मेरे साथ बोलने के लिए समय निकालने के लिए बहुत-बहुत धन्यवाद। मेरे शोध का एक हिस्सा उन कारकों पर ध्यान केंद्रित करता है जो रक्त में संक्रमण की घटनाओं, लोहे की चेचक के उपचार, और नियमित परीक्षण के कार्यक्रम के प्रति थैलेसीमिया के रोगियों के पालन को सकारात्मक या नकारात्मक रूप से प्रभावित करते हैं। रोगियों, उनके माता-पिता और प्रमुख सूचनादाताओं के दृष्टिकोण से इसे समझना महत्वपूर्ण है क्योंकि उनके अनुभवों में भविष्य में पालन में सुधार के लिए व्यावहारिक हस्तक्षेप को सूचित करने की क्षमता है, जिससे थैलेसीमिया समुदाय के लिए परिणामों में सुधार होता है। इस शोध को आपकी गोपनीयता और आपके द्वारा प्रदान किए जाने वाले डेटा की गोपनीयता की रक्षा के लिए वाशिंगटन विश्वविद्यालय, यूएसए और बी.जे. मेडिकल कॉलेज, पुणे की नैतिकता समीक्षा बोर्ड द्वारा अनुमोदित किया गया है। यदि आप भाग लेने के लिए सहमत हैं, तो आप अभी भी बाद के चरण में अध्ययन से हट सकते हैं यदि आप चुनते हैं; यदि ऐसी स्थिति उत्पन्न होती है तो आप मुझसे संपर्क कर सकते हैं (व्यवसाय कार्ड प्रदान करें)। आज की हमारी बातचीत को रिकॉर्ड किया जाएगा क्योंकि आपके सभी जवाबों को याद रखना मेरे लिए मुश्किल होगा। मुझे विशिष्ट विवरणों को याद रखने में मदद करने के लिए हमारी बातचीत के दौरान कुछ नोट्स भी लेने होंगे। मैं आपको विश्वास दिलाता हूँ कि अध्ययन के निष्कर्ष के प्रसार के 1 वर्ष बाद सभी रिकॉर्डिंग हटा दी जाएगी। मैं आपको यह आश्वासन भी दे सकता हूँ कि आज हमारी बातचीत के दौरान आपके द्वारा प्रदान की जाने वाली सभी जानकारी गोपनीय रहेगी, और आपकी पहचान प्रत्यक्ष या अप्रत्यक्ष रूप से सामने नहीं आएगी। मैं आपको अपने अनुभवों के बारे में ईमानदार और पारदर्शी होने के लिए प्रोत्साहित करता हूँ क्योंकि यह प्रासंगिक हितधारकों को रोगियों के वर्तमान अनुभवों का एक सच्चा खाता देगा, जो व्यावहारिक हस्तक्षेपों के निर्माण के लिए मंच निर्धारित करेगा।

#### **A. Experiences with blood transfusion**

1. महने में आपको कितनी बार ब्लड ट्रांसफ्यूजन लेना पड़ता है?
2. आप इसका पालन कर पा रहे हैं? क्यों या क्यों नहीं? बताइये क्या सुविधाएँ या कठिनाइयाँ हैं जिसकी वजह से इसको लेना आसान या मुश्किल है.

#### **Probes**

- क्या ये आपके लिए आसान है या मुश्किल है? क्यों ?
- क्या ब्लड आपको आसानी से मिलता है? क्यों?

- आप किस ब्लड बैंक से खून खरीदते हैं? आपने यह बैंक क्यों चुना?
- इस ब्लड बैंक में ऐसी क्या सुविधाएँ हैं जिसकी वजह से वहाँ से लेना आसान है?
- इस ब्लड बैंक में ऐसी क्या कठिनाइयाँ हैं जिनकी वजह से वहाँ से ब्लड लेना मुश्किल है
- ब्लड ट्रांसफ्यूजन के लिए आप कहाँ जाते हैं? आपने यह जगह क्यों चुना?
- ट्रांसफ्यूजन फ़ैसिलिटी में ऐसी क्या सुविधाएँ हैं जिसकी वजह से वहाँ से आप ट्रांसफ्यूजन करवाते हैं?
- इस ट्रांसफ्यूजन फ़ैसिलिटी में ऐसी क्या कठिनाइयाँ हैं जिनकी वजह से वहाँ से ट्रांसफ्यूजन करना मुश्किल है
- ब्लड ट्रांसफ्यूजन आप के सोशियल लाइफ़ या स्कूल या काम में कठिनाइयाँ पहुँचाती है? डिटेल में बताइए?
- आपकी मेडिकल ज़रूरतों को अकमडेट करने के लिए कोई व्यवस्था किया गया है?
- क्या ब्लेड ट्रांसफ्यूजन शनिवार या रविवार के दिन पर कर सकते हैं?
- ब्लड ट्रांसफ्यूजन करना आपको महँगा लगता है? (Leukofilters, blood testing, cost of bed, missed day of work)
- आप अपने मेडिकल खर्च खुद ही कवर कर पाते हैं कि आप को सरकार, NGO, परिवार, अपनी नौकरी से सहायता मिलती है?
- हमने अभी तक जो discuss किया है, उसके अलावा ककोई और चीज है जो आपको blood ट्रांसफ्यूजन के लिए जाने में मुश्किल होता है / डिमोटिवेट करता है?

## **B. Experiences with iron chelation**

1. क्या आपके डॉक्टर ने आपको iron chelator लेने के लिए कहा है? कौन सा? आपको उन्हें कितनी बार लेने की आवश्यकता है?
2. आप इसका पालन कर पा रहे हैं? क्यों या क्यों नहीं? बताइये क्या सुविधाएँ या कठिनाइयाँ हैं जिसकी वजह से इसको लेना आसान या मुश्किल है.

### **Probes**

- क्या आपको लगता है कि ये दवाई लेना ज़रूरी है?

- आप iron chelators कहां से प्राप्त करते हैं? क्यूं? ऐसी कोई सुविधाएँ हैं जिनकी वजह से iron chelator प्राप्त करना आसान बन गया है? ऐसी कोई कठिनाई है जिनकी वजह से इसको प्राप्त करना मुश्किल हो गया है?
- क्या ये दवाईयाँ आपके लिए महंगे पड़ते हैं? आपको सरकार व NGO व नौकरी व स्कूल व परिवार से सहायता मिलती है?
- क्या ये दवाई लेना आसान है या कठिन है? क्या इसके वजह से आपको दवाई लेने का मन नहीं होता है?
- क्या आपको दवा लेने से दर्द या साइड इफेक्ट होता है? क्या इसके वजह से आपको दवाई लेने का मन नहीं होता है?
- क्या ये दवाई का स्वाद ठीक है या बुरा है? क्या इसके वजह से आपको दवाई लेने का मन नहीं होता है?
- आप दवाई लेना कभी भूल जाते हैं या आपको कुछ कन्फ्यूजन है कि ये दवाई कब लेना है?
- क्या आपके परिवार या दोस्त कभी आपको कहते हैं कि ये दवाईयाँ को नहीं लेना चाहिए? क्या कभी आप दवाई उनके सामने लेते वक़्त शर्माते हैं?
- जब आप बाहर घूम फिरते हैं तब दवाई लेना मुश्किल हो जाता है?
- और कोई सुविधाएँ यहाँ कठिनाइयाँ हैं जिनकी वजह से आप दवाई नहीं ले पाते हैं?

### **Experience with routine testing**

1. क्या आपके डॉक्टर ने आपको नियमित रूप से कोई टेस्ट करने के लिए कहा है? यदि हाँ तो कौन सा?
2. आप इसका पालन कर पा रहे हैं? क्यों या क्यों नहीं? बताइये क्या सुविधाएँ या कठिनाइयाँ हैं जिसकी वजह से इनको करना आसान या मुश्किल है.

### **Probes**

- आपको जानकारी है कि आपको ये टेस्ट कब करना है?
- क्या आप इसका पालन कर पा रहे हैं? यदि हाँ तो क्यों? ना तो क्यों? डिटेल में बताइए किन चीज़ों की वजह से आप ये टेस्ट का पालन कर रहे हैं, या नहीं कर पा रहे हैं?

- आप ये टेस्ट कहाँ से करवाते हैं? आप वहाँ से क्यों करवाते हैं? ऐसी क्या सुविधाएँ हैं जिनके वजह से वहाँ पे टेस्ट करवाना आसान है। ऐसे क्या कठिनाइयाँ हैं जिनकी वजह से वहाँ पर टेस्ट करवाना मुश्किल है?
  - क्या ये टेस्ट आपके लिए महंगे पड़ते हैं? आपको सरकार व अस्पताल व NGO व आपकी नौकरी व स्कूल आपके परिवार से पैसों की सहायता मिलती है?
  - क्या ये टेस्ट आप के सोशियल लाइफ़ या स्कूल या काम को बाधित करती हैं? आपके अनुसार इसके कारण क्या हैं?
  - आपकी मेडिकल जरूरतों को अकमडेट करने के लिए कोई व्यवस्था किया गया है?
  - क्या ये टेस्ट शनिवार या रविवार के दिन पर कर सकते हैं?
  - आप अपने मेडिकल खर्च खुद ही कवर कर पाते हैं की आप को सरकार, NGO, परिवार, अपनी नौकरी से सहायता मिलती है?
  - हमने अभी तक जो discuss की है, उसके अलावा क्या कोई और चीज है जो आपको ये टेस्ट करने में मुश्किल देता है/ डिमोटिवेट करता है?
-

## Appendix C

### **Interview guide to determine factors that influence adherence to essential management for thalassemia - Key informants**

Hello, I am currently a PhD student at the University of Washington, Seattle. Thank you so much for taking time out to speak with me. Part of my research focuses on understanding factors that positively or negatively influence thalassemia patients' adherence to blood transfusion schedules, iron chelation regimens, and routine testing schedules. It is important to understand this from the perspective of patients, their parents, and key informants as their experiences have the potential to inform practical interventions to improve adherence in the future, thereby improving outcomes for the thalassemia community. This research has been approved by the ethics review board of the University of Washington, USA, and B.J. Medical College, Pune to protect your privacy and the confidentiality of the data that you provide. If you agree to participate, you may still withdraw from the study at a later stage if you choose to; you may contact me if such a situation arises (provide business card). Our conversation today will be recorded because it will be difficult for me to remember all your responses. I will also be taking some notes during our conversation to help me remember specific details. I assure you that all recordings will be deleted 1 year after the findings of the study are disseminated. I can also assure you that all the information that you provide during our conversation today will remain confidential, and your identity will not be revealed directly or indirectly. I encourage you to be honest and transparent about your experiences as this will give relevant stakeholders a truthful account of patients' current experiences, which will lay set the stage for the formulation of practical interventions.

#### F. Demographics:

I would like to start by asking you for some details about yourself so that I have a better idea about how your experiences might be related to your background

- What is your relationship with the  $\beta$ -thalassemia community in Pune?
- What is your educational and professional background?

#### G. Experiences with blood transfusion

- **What factors negatively or positively influence a patient's ability to follow their prescribed transfusion schedule?**

Probes:

- Access to blood
  - Which blood banks do thalassemia patients usually choose? Why?
  - What factors make it easy / difficult for them to get blood from these banks?
  - Do they experience blood shortages? When and Why? What do they do in such situations?

- Do shortages ever influence their ability to follow the transfusion schedule?
- Do any patients pay for blood? Does this influence their ability to follow the transfusion schedule?
- Access to blood transfusion facility
  - Where do patients usually go for blood transfusions? Why?
  - What factors make it easy / difficult for them to get blood transfusions? (distance, cost, quality of care, time taken comfort, entertainment, weekend testing, paperwork, etc)
  - Do patients have to pay anything for transfusions (leukofilters, blood testing, catheter, cost of bed, hospital charges). Does this influence their ability to follow the transfusion schedule?
- Social/educational/professional interruptions
  - Do blood transfusions interrupt their social life/school/work?
  - What accommodations, if any, do their schools/workplaces make for their transfusion schedule?
  - What accommodations, if any, does the transfusion facility make for their work/school schedule?
  - What accommodations, if any, do their friends/family make for their transfusion schedule?
- Other factors
  - Cooperative child / Stubborn child
  - Perceived benefit of transfusions
  - Perceived severity of thalassemia
  - Motivation
  - Medical communication/instructions/guidance/counseling
- What support, if any, do they receive from:
  - Physician/Hospital
  - Blood bank
  - Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do patients wish they had that would make adherence to the transfusion schedule easier?

#### H. Experiences with iron chelation

- **What factors negatively or positively influence a patient's ability to follow their prescribed transfusion schedule?**

Probes:

- Access to iron chelators:
  - Where do you patients usually acquire iron chelators from? Why?
  - What factors make it easy/difficult for patients to acquire drugs from here?
  - Do they have to pay for iron chelators? Does this influence their ability to adhere to the prescription?
  - Do they experience shortages? When and Why? What do they do in such situations?
  - Do shortages ever influence their ability to follow the iron chelation prescription?
- What other factors negatively or positively influence their ability to follow the iron chelation prescription?
  - Convenience – ease of administration, time taken, conflicting schedule, complicated regimen
  - Reminder system/forgetfulness; clarity/conflicts about when to take the medication.
  - Supervision
  - Pleasantness – pain, taste
  - Side-effects
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Social acceptance
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation
  - Any other?
- What support, if any, do you they receive from:
  - Physician/hospital
  - Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do patients wish they had that would make adherence to iron chelation medication easier?

I. Experiences with routine medical surveillance

- **Do physicians prescribe routine medical tests for patients?**
- **What factors positively or negatively influence patients' ability to follow the routine test schedule?**

Probes:

- Access to tests
  - Where do patients usually get these done? Why?
  - What factors make it easy/difficult to get them from the places you mentioned ?
  - Do patients pay for all these tests? Does this influence their ability to adhere to the prescription?
- What other factors influence their ability to adhere to the testing schedule?
  - Convenience – ease of getting the tests done, time-taken, conflicting schedule, complicated testing schedule
  - Reminder system/forgetfulness; clarity/conflicts about when to do the test
  - Supervision
  - Pleasantness – pain, discomfort
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation
  - Any other?
- What support, if any, do patient's receive from:
  - Physician/Hospital/Testing center
  - Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do patients wish they had that would make adherence to the testing schedule easier?

J. Experiences with supplementary/complementary/alternate therapy

- **Do physicians or anyone else prescribe any other medication/supplements? If yes, which ones?**
- **Does this affect adherence to blood transfusion, iron chelation, or routine medical tests?**
- **What factors positively or negatively influence patients' ability to adhere to the prescription?**

Probes:

- Access:
  - Where do patients acquire these from? Why?
  - What factors make it easy/difficult for them to acquire them?
  - Do patients pay for them? Does this influence their ability to adhere to the prescription?
  - Do they experience shortages? When and Why? What do they do in such situations?
  - Do shortages ever influence their ability to follow the prescription?
- What other factors negatively or positively influence their ability to follow the prescription?
  - Convenience – ease of administration, conflicting schedule, complicated regimen
  - Reminder system/forgetfulness; clarity/conflicts about when to take the medication.
  - Supervision
  - Pleasantness – pain, taste
  - Side-effects
  - Perception of benefit
  - Medical communication/instructions/counseling/guidance
  - Trust in physician
  - Social acceptance
  - Support (school, employer, friends, family, older thalassemia patients)
  - Personal/religious beliefs
  - Literacy
  - Motivation
  - Any other?
- What support, if any, do they receive from:
  - Physician/Hospital/Treatment center
  - Pharmacy
  - Government organizations
  - NGOs
  - Employer/School
  - Family/Friends
  - Other
- What support do they wish they had that would make adherence to the prescription easier?

## Appendix D

### Network data collection tool: Roster + Name generator

**Network data collection instrument:**

**Date:**

**Organization:**

**Name:**

**Position:**

**Tenure:**

**Key services/facilities:**

Prevention
Treatment
Cure
Other

1. Which institutions from \_\_\_\_ sector do you work closely with to improve access and adherence to treatments and routine testing for thalassaemia patients in Pune. Do you do any activities together, refer patients to each other?

2. (Refer to list) With which of these institutions do you do joint activities related to thalassaemia treatment and routine testing?  
 Eg: Free/subsidised testing camps, awareness events for patients/physicians, blood donation camps, disability certificate applications, free/subsidized drugs, free/subsidized transfusions, free/subsidized blood filters, free/subsidized desferal pumps, free/subsidized psychological support, free/subsidized social support.)

3. (Refer to list) Which of these institutions do you often refer patients/families to or receive referrals from?

4. (Refer to list) Which of these organization do you share any kind of communication with regarding thalassaemia patients?

	1	2	3	4
	<b>Organization</b>			
<b>#</b>	<b>Medical institutes</b>	<b>Commun.</b>	<b>Activities</b>	<b>Referrals</b>
1	Ruby Hall			
2	Deenanath Mangeshkar			



4	Lalpath labs				
6	Hemotec				
7	Gowilkar labs				
<b>#</b>	<b>Government</b>	<b>Commun.</b>	<b>Activities</b>	<b>Referrals</b>	
1	State blood transfusion council				
2	Mahatma Jyotirbhai Phule Scheme office				
3	National Health Mission				
<b>#</b>	<b>NGOs</b>	<b>Commun.</b>	<b>Activities</b>	<b>Referrals</b>	
1	Thalassemia Society Pune Chapter				
2	Maharashtra Thalassemia Society				
3	MVR Foundation				
4	Wishing Factory				
5	Young Thalassemics Association				
6	Thalassemics India				
7	NTWS				
8	Think Foundation				
9	Indian Red Cross				
10	Bombay Hematology Group				
11	PATUT				
12	SOFOSH				
<b>#</b>	<b>Medical stores</b>	<b>Commun.</b>	<b>Activities</b>	<b>Referrals</b>	
1	Prakash Medicals				
2	Sai Prabha Medical Store				

## **Appendix E**

### **Interview guide for influential informant interviews in network study**

Hello,

Thank you for making the time to meet me today. As per our phone conversation, I am at the final stage of my research where I am interviewing stakeholders from the government, social, and healthcare sectors who play a key role in thalassemia care in Pune city. Being a key stakeholder in thalassemia care, it will be essential to understand your point of view regarding benefits, barriers, practicality and improvability of collaboration between organizations across sectors that influence adherence to blood transfusion schedules, iron therapy regimens, and routine testing schedules. This research has been approved by the ethics review board of the University of Washington, USA, and B.J. Medical College, Pune to protect your privacy and the confidentiality of the data that you provide. If you agree to participate, you may still withdraw from the study at a later stage if you choose to; you may contact me if such a situation arises (provide business card). Qualitative research requires analysis of interviews, for which an audio-recording of the interview will be ideal. All data collected will be de-identified, i.e. the names and personal details of interviewees will be kept confidential. I assure you that your identity will not be revealed directly or indirectly. In case you are not comfortable with the interview being audio-recorded but would still like to participate. I will capture the information that you provide by taking notes during the interview.

The interview will take approximately 30-45 minutes and will consist of the following questions:

- 1) Do you think that efforts to increase treatment adherence can dramatically improve health outcomes of thalassemia major patients residing in Pune city? Why or why not?
- 2) Do you think that collaboration across organizations from the same sector and different sectors such as the private, government, and social sectors is required to improve treatment adherence in patients residing in Pune city? Why or why not?
- 3) Do you think that collaboration across organizations from the same sector and different sectors to improve treatment adherence is possible in Pune City? Why or why not?
- 4) What, if anything, can be done to improve collaboration across organizations from the same sector and different sectors to improve treatment adherence in patients residing in Pune city?

## Appendix F

### Consent forms for participants recruited from Sassoon hospital - English and Marathi

#### INFORMED CONSENT FORM

1. I, Mr/Mrs. \_\_\_\_\_, age \_\_\_\_\_ years residing at \_\_\_\_\_ hereby give my informed consent to participate in the project titled: Establishing initial data and assessing the feasibility of a community collaborative based on the collective impact approach, to improve adherence to treatment for beta-thalassemia major patients in the cities of Pune and Pimpri-Chinchwad.
2. There is no compulsion on me to participate in this project and I am giving my free consent for it.
3. I am ready and willing to undergo all tests and treatments in the present project.
4. I have read and I have been explained the general information and purpose of the present project.
5. I have been informed / I have read the probable complications while participating in the present project.
6. I know that I can withdraw from the present project at any time.
7. Any data or analysis of this project will be purely used for scientific purpose and my name will be kept confidential except when required for any legal purpose.
8. I can read English / I can understand data read out to me in English.

Signature of Volunteer

Signature of parent/Guardian in case  
Of minor person.

Witnesses:

- 1.
- 2.

Signature of  
Principal Investigator

## संमती पत्र

१. मी \_\_\_\_\_ (नांव), वय \_\_\_\_\_ वर्ष, राहणार \_\_\_\_\_ माझ्या स्वेच्छेने पुणे आणि पिंपरी-चिंचवड शहरातील बीटा थॅलेसेमिया रुग्णांच्या उपचारांच्या संदर्भात सुधारणा करण्यासाठी प्रारंभिक डेटा तयार करणे आणि समुदायातील सहयोगी व्यवहार्यतेचे मूल्यांकन करणे. प्रकल्पामध्ये सहभागी होण्यास संमती देत आहे.
२. माझ्यावर प्रस्तुतच्या प्रकल्पामध्ये सहभागी होण्यासाठी कोणाचाही दबाव नाही.
३. प्रस्तुतच्या प्रकल्पात येणाऱ्या तपासण्या व औषधोपचार घेण्यास मी तयार आहे.
४. प्रस्तुतच्या प्रकल्पाची सर्वसाधारण माहिती मला समजेल अशा भाषेत मी वाचली आहे / मला समजावून सांगण्यात आले आहे
५. मला प्रस्तुतच्या प्रकल्पात संभाव्य धोक्यांची माहिती सांगण्यात आलेली आहे / मी वाचलेली आहे.
६. या प्रकल्पामधून मी कधीही बाहेर पडू शकतो / शकते याची मला माहिती आहे .
७. या प्रकल्पात निघणारे निष्कर्ष केवळ शास्त्रीय कारणांसाठी वापरले जातील / प्रकाशित केले जातील याची मला कल्पना आहे , तसेच माझी ओळख कायदेशीर बाबीव्यतिरिक्त इतर वेळेस गुप्त ठेवली जाईल.
८. मला मराठी वाचता येते / मराठी वाचून दाखविलेले समजते.

सहभागी व्यक्तीची सही

सहभागी व्यक्ती अज्ञान असल्यास त्याचे पालक किंवा घोषित पालकाची सही.

साक्षीदार :

१.

२.

प्रमुख संशोधकाची सही

पीसी/-

## Appendix G

### List of identified factors that influence adherence to management

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
BLOOD SECURITY						
	HST	Supportive hospital/blood bank	Supportive hospital/blood bank	BT IC RT	Opportunity	Mezzo
		Ease of blood procurement		BT		
	HST		Blood shortage/unavailability/difficult procurement		Constraint	Mezzo
	HST		Easy/assisted blood procurement		Opportunity	Mezzo
	HST		Access to free blood		Opportunity	Macro
	SE		Availability of friends/relatives who donate blood		Opportunity	Micro
	P		Rare blood group		Constraint	Individual
	SE		Unavailability of friends/relatives who donate blood		Constraint	Micro
		Blood safety		BT		
	HST		Adequate quantity or quality of blood		Opportunity	Mezzo
	HST		Inadequate quantity or quality of blood		Constraint	Mezzo

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level	
FINANCIAL STATUS/SUPPORT							
		Financial support		BT IC RT			
	SE						
	SE		Supportive government policies		Opportunity	Macro	
	SE		Support from patient organization		Opportunity	Mezzo	
	SE		Interorganizational collaboration/coordination/communication		Opportunity	Mezzo	
	SE		Pharmacist/wholesaler/medical store support		Opportunity	Mezzo	
	SE		Testing center support		Opportunity	Mezzo	
	SE		CSR activities		Opportunity	Mezzo	
	SE		Support from pharma		Opportunity	Mezzo	
			Free/subsidized tests/transfusions / treatment		BT IC RT		
	SE		Free/subsidized blood transfusions		Opportunity	Mezzo/Macro	
	SE		Free/subsidized testing		Opportunity	Mezzo/Macro	
	SE		Free/subsidized chelators		Opportunity	Mezzo/Macro	
	SE		Free/subsidized disposables		Opportunity	Mezzo/Macro	
	SE		Free/rented desferal pumps		Opportunity	Mezzo	
			Financial ability		BT IC RT		
	SE		Financial constraints			Constraint	Individual
	SE		Financial stability			Opportunity	Individual
			Expensive treatment		BT IC RT		
	SE		Expensive chelators			Constraint	Mezzo
	SE		Expensive novel therapy			Constraint	Mezzo
	SE		Expensive testing			Constraint	Mezzo
	SE		Expensive consultation fees			Constraint	Mezzo
	SE		Expensive disposables			Constraint	Mezzo
	SE		Expensive hospital charges			Constraint	Mezzo
	SE		Difficulties experienced due to unaffordable desferal pump			Constraint	Mezzo
		Financial issues		BT IC RT			
SE		Lack of financial support			Constraint	Mezzo/Macro	
SE		High cumulative expenses			Constraint	Mezzo	
SE		Unsupportive government policies			Constraint	Macro	
HST		Unsustainable thalassemia services/amenities	Unsustainable thalassemia services/amenities		Constraint	Mezzo	

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
PSYCHOLOGY/BEHAVIOUR						
		Use of adherence strategies		BT IC RT		
	P		Treatment prioritization		Opportunity	Individual
	P		Incorporated into routine		Opportunity	Individual
	SE		Strategic caregiver/family support in executing medication		Opportunity	Individual
	SE		Caregiver's efforts towards normalization		Opportunity	Individual
	P/SE		Reminder system		Opportunity	Individual
	P		Overstocking/Buying before running out		Opportunity	Individual
		Resourcefulness/proactiveness		BT IC RT		
	P		Resourceful/proactive patient/caregiver		Opportunity	Individual
	P		Maintains good relations		Opportunity	Individual
	P		Unresourceful/reactive patient		Constraint	Individual
		Patient traits		BT IC RT		
	P		Stubborn patient		Constraint	Individual
	P		Mature patient		Opportunity	Individual
	P		Cooperative patient		Opportunity	Individual
	P		Self-discipline		Opportunity	Individual
	P		Pampered patient		Constraint	Individual
		Caregiver/patient issues		BT IC RT		
	P/SE		Carelessness/Negligence		Constraint	Individual
	P		Fear		Constraint	Individual
	P		Forgetfulness		Constraint	Individual
	P		Sleeping through dose		Constraint	Individual
	P		members with medication expenses		Constraint	Individual

		Burnout		BT IC RT		
	P/SE		Hopelessness		Constraint	Individual
	P		Tired of treatment		Constraint	Individual
	P		Demotivated		Constraint	Individual
	P		Psychological distress		Constraint	Individual
	P		Negative coping		Constraint	Individual
	P		Denial		Constraint	Individual
		Supervision		IC		
	SE		Poor supervision from caregiver		Constraint	Individual
	SE		Regular supervision		Opportunity	Individual
		Caregiver competence		BT		
	SE		Meticulous caregiver		Opportunity	Individual
	SE		Mindful caregiver		Opportunity	Individual
	SE		Organized caregiver		Opportunity	Individual
		Familiarity with transfusion facility				
	P		Familiarity with transfusion facility	BT	Opportunity	Individual
		Discomfort with medication brand changes				
	P		Discomfort with medication brand changes		Constraint	Individual

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
PATIENT/CAREGIVER KNOWLEDGE AND EDUCATION						
		Patient/caregiver knowledge and education		BT IC RT		
	P		Knowledge of disease/treatment regimen		Opportunity	Individual
	P		Understanding need for strict adherence		Opportunity	Individual
	P		Lack of knowledge of disease/treatment regimen		Constraint	Individual
	P		Lack of understanding need for strict adherence		Constraint	Individual
	SE		Knowledge of other family members regarding disease		Opportunity	Individual
	SE		Misguiding/unsuitable information from peers		Constraint	Micro
		Patient/caregiver education		BT IC RT		
	HST		Patient education provision		Opportunity	Micro/Mezzo
	HST		Awareness events		Opportunity	Mezzo

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
SOCIAL STATUS/SUPPORT						
		Support/issues with management schedule		BT IC		
	SE		Conflicting activities/responsibilities/obligations		Constraint	Individual
	SE		Supportive educational institution/employers		Opportunity	Mezzo
	SE		Unsupportive educational institution/employers		Constraint	Mezzo
	SE		More than one affected child		Constraint	Individual
		Social/counseling support		BT IC RT		
	SE		Social worker support		Opportunity	Micro
	SE		Peer support		Opportunity	Micro
	SE		Counseling		Opportunity	Micro
	SE		Lack of counseling		Constraint	Micro
	SE		Support group		Opportunity	Mezzo
	SE		Lack of patient support group		Constraint	Mezzo
	SE		Lack of peer support		Constraint	Micro
		Family support/issues		BT IC RT		
	SE		Supportive friends/family		Opportunity	Individual
	SE		One parent's responsibility		Constraint	Individual
	SE		Unwell/unavailable primary caregiver		Constraint	Individual
	SE		Both parents/family share responsibility		Opportunity	Individual
	SE		Unsupportive friends/family		Constraint	Individual

	P	Commuting difficulties	Commuting difficulties	BT RT	Constraint	Individual
		Literacy level		BT IC RT		
	SE		Illiteracy		Constraint	Individual
	SE		Literacy		Opportunity	Individual
		Unawareness regarding/inaccessibility of amenities		BT IC RT		
	P		Unawareness regarding free/subsidized services / patient organizations		Constraint	Individual
	SE		Inability to apply for government benefits		Constraint	Macro
		Broader social issues		BT IC		
	SE		Female gender		Constraint	Individual
	SE		Social rejection/stigma		Constraint	Mezzo

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
NATURE OF DISEASE/TREATMENT						
		Transfusion/drug administration experience		IC RT		
		T	Inconvenient mode of administration		Constraint	Individual
		T	administration		Opportunity	Individual
		T	Long duration of administration		Constraint	Individual
		T	Painful		Constraint	Individual
			Adverse effects/contraindications		IC	
		T	Adverse effects		Constraint	Individual
		T	No adverse effects		Opportunity	Individual
		T	Contraindication during other illness		Constraint	Individual
		T	No chelator on transfusion days		Constraint	Individual
			Effects on symptoms		BT IC	
		C	Noticeable symptoms of low hb / high fe		Opportunity	Individual
		T	Notice symptomatic improvement		Opportunity	Individual
		T	No short-term symptomatic changes		Constraint	Individual
			Treatment frequency		BT IC	
		C	Splenectomised		Opportunity	Individual
		T	transfusions		Constraint	Individual
		C	Life-long treatment		Constraint	Individual
		T	High dose frequency		Constraint	Individual
			Palatability		IC	
		T	Bad tasting medicine		Constraint	Individual
		T	Pleasant tasting medicine		Opportunity	Individual

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
HEALTHCARE QUALITY						
		Quality of physician and interactions		BT IC RT		
	HST		Satisfactory care from physician		Opportunity	Micro/Mezzo
	HST		Good provider-patient communication		Opportunity	Micro
	HST		Good follow-up with physician		Opportunity	indi/Mezzo
	HST		Unsatisfactory care from physician		Constraint	Micro/Mezzo
	HST		Poor follow-up with physician		Constraint	Indiv/Mezzo
	HST		Poor provider-patient communication		Constraint	Micro
		Quality of nursing and hospital staff and interactions		BT		
	HST		Satisfactory hospital and nursing staff		Opportunity	Micro/Mezzo
	HST		Unsatisfactory hospital/nursing staff		Constraint	Micro/Mezzo
	HST		Quick vein finding		Opportunity	Mezzo
	HST		Multiple pricks to find vein		Constraint	Mezzo
		Broader healthcare issues		BT IC RT		
	HST		differential		Constraint	Mezzo
	HST		No prescription/self-medication		Constraint	Mezzo
	HST		Patient confusion due to variation in management strategies amongst doctors		Constraint	Mezzo
			Lack of continuity of care		Constraint	Mezzo
	HST	Integrated care	Hospital responsible for getting tests done	RT	Opportunity	Mezzo

BLOOD TRANSFUSION CONVENIENCE						
		Transfusion timings		BT		
	HST		Suitable transfusion days/timings		Opportunity	Mezzo
	HST		Easy appointments		Opportunity	Mezzo
	HST		days/timings		Constraint	Mezzo
		Duration of transfusion		BT		
	HST		Short process for transfusion		Opportunity	Mezzo
	HST		Long process for transfusion		Constraint	Mezzo
	HST		Multi-day transfusions		Constraint	Mezzo
		Special accomodations for thalassemia		BT		
	HST		Dedicated thalassemia facilities		Opportunity	Mezzo
	HST		Prioritisation of thalassemia patients		Opportunity	Mezzo
	HST		Lack of dedicated thalassemia facilities		Constraint	Mezzo
	HST		Food and refreshments		Opportunity	Mezzo
		Ward infrastructure and policies		BT		
	HST		Good ward infrastructure		Opportunity	Mezzo
	HST		Infrastructural inadequacies of blood transfusion wards		Constraint	Mezzo
	HST		Caregiver not allowed to accompany patient		Constraint	Mezzo
	HST		Caregiver allowed to accompany		Opportunity	Mezzo

Generic category	WHO dimension	Subcategory	Factor	Aspect of essential management	Opportunity/Constraint	Ecological level
ACCESS TO CARE						
		Procurement/availability of medicines/disposables/tests		BT IC RT		
	HST		Easy procurement of medicines.		Opportunity	Mezzo
	HST		Difficult medicine procurement		Constraint	Mezzo
	HST		Availability of previously unavailable tests		Opportunity	Mezzo
	HST		Unavailable disposables		Constraint	Mezzo
		Availability of Rural facilities		BT		
	HST		Transfusion facility in rural area		Opportunity	Mezzo
	HST		Poor availability of transfusion facilities in rural areas		Constraint	Mezzo
	HST	Proximity to home	Proximity to home	BT/RT	Opportunity	Mezzo

## **Appendix H**

### **Research briefs for multilevel dissemination**

#### **A. Individual/micro-level research brief**

##### **(i) What factors can help patients adhere better to essential management?**

1. Adherence strategies and caregiver behaviors such as: prioritizing treatment even when inconvenient, incorporation of iron chelation administration into daily routine, treatment normalization, setting reminders, and caregiver supervision can greatly improve adherence to essential management. Meticulous and mindful caregivers are also likely to be more careful about adhering to aspects of essential management, for example they might maintain a notebook that consolidates information about each transfusion and a timeline of treatment modifications.
2. Resourcefulness, proactiveness and organizational skills: These can play an important role in a patient/caregiver's ability to purchase medications in a timely manner, safeguard themselves against blood shortages, or seek out free/subsidized services.
3. Patient behaviors can also play in an important role in determining adherence. Mature patients are more likely to be self-disciplined regarding their iron chelation regime and are also more like to be cooperative rather than stubborn during blood transfusions.
4. Provision of education can play an important role in enhancing patients', caregivers', and other family members' knowledge regarding thalassemia, its management, and the importance of strict adherence to the prescribed transfusions schedule, iron chelation regimen, and routine testing schedule.
5. Support from social workers, peers, and support groups can play an important role in helping patients and caregivers cope with the financial and psychosocial consequences of thalassemia and directing them to appropriate community resources. They can also help in teaching them important self-management skills.
6. Affected individuals that belong to families where other family members are supportive and where both parents are involved in the child's care, are more likely to be adherent to essential management.
7. Good quality of interactions and follow-up with healthcare professionals including physicians, nursing staff and other hospital staff, can support the patient/caregiver's level of comfort during blood transfusions, timely modification of iron chelation treatment regimens, and prompt detection of secondary complications.

**(ii) What factors get in the way of patients' adherence to essential management?**

1. Financial constraints: Affected individuals are not always able to buy iron chelation medications, do routine tests, or come in for blood transfusion on time because of financial constraints due to insufficient/delayed salary, or competing financial priorities.
2. Rare blood group: Affected individuals that have a rare blood group such as O negative, may find it difficult to procure blood in a timely manner, especially during summer shortages.
3. Unavailability of friends/relatives who donate blood: Some families have moved to Pune from other towns or live on the outskirts and therefore may not have friends or relatives who can donate blood or replace blood units that have been transfused.
4. Stubbornness: Blood transfusions are not pleasant experiences, especially for younger patients. They may develop a fear of transfusions, as a result of which they might behave stubborn and refuse to come in as per schedule. Pampering children with treats every time they need to come in for a transfusion can backfire and lead to more stubbornness.
5. Desire not to burden family members with medication expenses: This might be a cause for non-adherence to iron chelation therapy in some adolescent patients who have begun to understand the financial impact of their condition on their families.
6. Burnout: Due to life-long treatment and psychosocial consequences of thalassemia, adolescent patients might grow tired of adhering to treatment, and feel hopeless about the future. In the absence of an intervention these individuals can become psychologically distressed and develop negative coping mechanisms such as neglecting treatment, tobacco smoking and excessive alcohol consumption.
7. Medication changes: Patients who are accustomed to taking the same iron chelation medication don't always find it easier to adapt to a newly prescribed chelator or a different brand of the same chelator.
8. Lack of disease/treatment related knowledge: A lack of knowledge regarding thalassemia and its treatment, and a lack of understanding regarding the importance of adherence can have a profound negative influence on adherence. Sometimes patients and caregivers may even receive incorrect information from other affected individuals and their caregivers.
9. Schedule conflicts: Some patients aren't able to adhere adequately to blood transfusion schedules and iron chelation schedules due to conflicting activities, responsibilities, or social obligations.
10. More than one affected child: Parents who have more than one affected child may find it difficult to bring them in for blood transfusions as per the prescribed schedule because of

differences in the transfusion interval for each child. As a result of this one of the children risks being under-transfused.

11. **Commuting difficulties:** Some caregivers may not have the ability to read and therefore may find it difficult to navigate to the hospital and within the hospital premises.
12. **Unawareness regarding amenities:** Affected individuals and their caregivers may not be aware of free or subsidized thalassemia-related services available through healthcare organizations, patient organizations, and government schemes.
13. **Female gender:** Due to broader social issues some affected female patients may not receive the same degree of care from their caregivers as their male counterparts would.
14. **Inconvenient mode of administration:** Affected individuals who have been prescribed the injectable chelator, desferrioxamine, may find it difficult to adhere to the prescribed regime because of the long duration of infusion or pain at the injection site. Oral chelators are preferred due to their ease of administration.
15. **Adverse effects:** Some patients might not be adhering to their iron chelation medication due to side effects. They may not have brought this to the attention of the treating healthcare worker.
16. **No short-term symptomatic changes:** Since the benefits of iron chelation therapy are not immediately noticeable, there is a tendency for patients to be less adherent to it.
17. **Treatment frequency:** As affected individuals age the interval between transfusions decreases and the dosage of their chelators increases. Some patients need to take over 10 pills a day. As a result, patients tend to become less adherent to their transfusion schedules and iron chelation regimes.
18. **Unpalatable medication:** Some affected individuals find the prescribed medication unpalatable, which can lead to skipped doses. Consider prescribing a more palatable brand of the medication.

## **B. Mezzo/macro-level research brief**

### **(i) What factors can help patients adhere better to essential management?**

1. Financial support via government schemes, patient organizations, medical stores, testing centers, CSR activities, and pharma companies, can facilitate subsidization of blood transfusions, iron chelation therapy, routine testing, and the equipment required for them such as leukofilters, intracatheters, and infusion pumps.
2. Ease of procurement of safe and fresh blood, especially during summer shortages, can promote adherence to the blood transfusion schedule. This can be facilitated via assistance

in finding donors, maintaining fixed donor lists, coordination between blood banks, and making bedside leukofilters and nucleic acid testing (NAT) widely available.

3. Support extended by educational institutions and employers to accommodate an affected individual or caregivers' medical needs can help promote adherence. For example, educational institutions may formulate more liberal medical leave policies for affected students and make arrangements for them to catch-up on missed classes. Employers may permit more flexibility in working hours, especially on days that an affected employee needs to go in for blood transfusions or administer desferrioxamine.
4. Awareness events and support group sessions organized by healthcare and community organizations can help increase patients' and caregivers' knowledge regarding the thalassemia and the importance of adhering to management. They can also help them cope with the psychosocial consequences of thalassemia.
5. Healthcare organizations can implement policies that promote high quality interactions with physicians and make follow-up easier. This could be done through subsidized consultation charges or reserving consultation hours especially for thalassemia patients.
6. Healthcare organizations should invest in training their nurses in phlebotomy techniques that allow for quicker vein finding in thalassemia patients. This can make the experience of getting a transfusion more pleasant for them, which in turn can promote adherence to the blood transfusion schedule.
7. Integration of routine tests into clinical workflow for thalassemia patients can help promote adherence to routine tests.
8. Convenient transfusion timings, easy appointment scheduling, streamlined administrative processes, and short waiting times can improve adherence to blood transfusion schedules.
9. Special accommodations for thalassemia patients such as dedicated timings or beds, food and refreshments, good transfusion ward infrastructure, and reasonable policies that allow caregivers to accompany the patient, can make the transfusion experience more comfortable for the patient and thereby promote adherence.
10. Ensuring availability of iron chelation medications at government dispensaries, medical stores, through community organizations, or directly from pharmaceutical company warehouses can make medicine procurement easier for affected individuals, thereby promoting adherence.

**(ii) What factors get in the way of patients adhering to essential management?**

1. High cumulative costs of medication, tests, consultation fees, disposables, hospital charges, and infusion pumps can make treatment unaffordable for many patients; this can be

worsened by a lack of financial support. This can have a huge negative impact on adherence to essential management.

2. Some affected individuals might experience social rejection due to stigma related to thalassemia, especially in rural communities. Apart from having negative psychosocial consequences, this might even result in patients not carrying their iron chelation medication back to their villages during vacations.
3. Some patients might be confused about the prescribed treatment due to variation in management strategies being used by treating physicians in Pune. It is important to educate patients about the benefits, risks, and financial implications of each so that patients and caregivers can make an informed decision.
4. Some blood transfusion facilities might not have special accommodations in place for adolescent and adult thalassemia cases. This results in a stark difference in care once they transition into adolescence. This can disrupt the continuity of care and lead to poor adherence. Efforts should be made to transition patients to transfusion facilities that have special accommodations for adolescent and adult patients.

## **Bibliography**

- Abdul Wahab, J., Naznin, M., Nora, M. Z., Suzanah, A. R., Zulaiha, M., Aidil Faszrul, A. R., & Kamaruzaman, W. S. (2011). Thalassaemia: A study on the perception of patients and family members. *Medical Journal of Malaysia*, 66(4), 326–334.
- Agarwal, M. B. (2009). Advances in management of Thalassemia. *Indian Journal of Pediatrics*, 76(2), 177–184. <https://doi.org/10.1007/s12098-009-0048-7>
- Agarwal, R. K., Sedai, A., Ankita, K., Parmar, L., Dhanya, R., Dhimal, S., Faulkner, L. (2017). Multi-institutional, retrospective review of blood transfusion practices and outcomes in a large cohort of thalassemia patients in South India. *Pediatric Hematology Oncology Journal*, 2(4), 74–78. <https://doi.org/10.1016/j.phoj.2017.12.001>
- Agnihotri-Gupta, J. (2007). Private and public eugenics: Genetic testing and screening in India. *Journal of Bioethical Inquiry*, 4(3), 217–228. <https://doi.org/10.1007/s11673-007-9059-0>
- Agnihotri-Gupta, J. (2010). Exploring Indian women’s reproductive decision-making regarding prenatal testing. *Culture, Health and Sexuality*, 12(2), 191–204. <https://doi.org/10.1080/13691050903429316>
- Al-Kloub, M. I., A Bed, M. A., Al Khawaldeh, O. A., Al Tawarah, Y. M., & Froelicher, E. S. (2014). Predictors of non-adherence to follow-up visits and deferasirox chelation therapy among jordanian adolescents with thalassemia major. *Pediatric Hematology and Oncology*, 31(7), 624–637. <https://doi.org/10.3109/08880018.2014.939792>
- Alter, C., & J, H. (1993). *Organizations working together*. SAGE Publications.
- Alwan, A., & Modell, B. (2003). Recommendations for introducing genetics services in developing countries. *Nature Reviews Genetics*, 4(1), 61–68. <https://doi.org/10.1038/nrg978>
- Andrzejczyk, A. (2012). Ascertaining Barriers for Compliance: Policies for safe, effective and cost-effective use of medicines in Europe. *ABC Project Final Report*, 146–178.
- Angastiniotis, M. (2014). Lifestyle and quality of life. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 224–235). Nicosia: Thalassemia International Federation.
- Angastiniotis, Michael, & Eleftheriou, A. (2009). Requirements for a reference or expert thalassemia center: The structure/model for centers dealing with chronic/hereditary blood disorders. *Hemoglobin*, 33(SUPPL. 1), 1–2. <https://doi.org/10.3109/03630260903351890>

- Assarroudi, A., Heshmati Nabavi, F., Armat, M. R., Ebadi, A., & Vaismoradi, M. (2018). Directed qualitative content analysis: the description and elaboration of its underpinning methods and data analysis process. *Journal of Research in Nursing*, 23(1), 42–55. <https://doi.org/10.1177/1744987117741667>
- Atkin, K., & Ahmad, W. (2000). Pumping iron: Compliance with chelation therapy among young people who have thalassaemia major. *Sociology of Health and Illness*, 22(4), 500–524. <https://doi.org/10.1111/1467-9566.00216>
- Aydinok, Y. (2014). Infections. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 134–145). Nicosia: Thalassaemia International Federation.
- Aydinok, Yesim, Erermis, S., Bukusoglu, N., Yilmazi, D., & Solak, U. (2005). Psychosocial implications of Thalassaemia Major. *Pediatrics International*, 47(1), 84–89. <https://doi.org/10.1111/j.1442-200x.2004.02009.x>
- Bandyopadhyay, U., Kundu, D., Sinha, A., Banerjee, K., Bandyopadhyay, R., Mandal, T., & Ray, D. (2013). Conservative management of Beta-thalassaemia major cases in the sub-division level hospital of rural West Bengal, India. *Journal of Natural Science, Biology and Medicine*, 4(1), 108–112. <https://doi.org/10.4103/0976-9668.107269>
- Bansal, D. (2018). Financial Burden of Treatment of Transfusion Dependent Thalassaemia. *Indian Journal of Pediatrics*, 85(2), 85–86. <https://doi.org/10.1007/s12098-017-2547-2>
- Barnes, M., MacLean, J., & Cousens, L. (2010). Understanding the structure of community collaboration: The case of one Canadian health promotion network. *Health Promotion International*, 25(2), 238–247. <https://doi.org/10.1093/heapro/daq002>
- Bartholomew-Edlredge, K., Markham, C., Ruiter, R., Fernandez, M., Kok, G., & Parcel, G. (2016). *Planning Health Promotion Programs: An Intervention Mapping Approach* (4th ed.). Jossey-Bass.
- Berben, L., Dobbels, F., Engberg, S., Hill, M. N., & de Geest, S. (2012). An Ecological Perspective on Medication Adherence. *Western Journal of Nursing Research*, 34(5), 635–653. <https://doi.org/10.1177/0193945911434518>
- Berdoukas, V., Farmaki, K., Wood, J. C., & Coates, T. (2011). Iron chelation in thalassaemia: Time to reconsider our comfort zones. *Expert Review of Hematology*, 4(1), 17–26. <https://doi.org/10.1586/ehm.10.74>
- Bergenholtz, C., & Waldstrøm, C. (2011). Inter-Organizational Network Studies — A Literature Review. *Industry and Innovation*. (February 2013), 37–41. <https://doi.org/10.1080/13662716.2011.591966>
- Bevc, C. A., Retrum, J. H., & Varda, D. M. (2015). New perspectives on the “silo effect”:

Initial comparisons of network structures across public health collaboratives. *American Journal of Public Health*, 105, S230–S235. <https://doi.org/10.2105/AJPH.2014.302256>

- Brands, C., Robert, P., & Shaum, R. (n.d.). *Attacking Childhood Asthma : A Dallas Success Story*.
- Brinkerhoff, J. (2002). *Partnership for International Development: Rhetoric or Results?* Lynne Rienner Publishers.
- Brissot, P. (2014). Liver disease. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 114–125). Nicosia: Thalassemia International Federation.
- Cao, A., & Galanello, R. (2010). Beta-thalassemia. *Genetics in Medicine*, 12(2), 61–76. <https://doi.org/10.1097/GIM.0b013e3181cd68ed>
- Caplan, G. (1964). *Principles of preventive psychiatry*. Basic Books.
- Cappellini, M. D. (2005). Overcoming the challenge of patient compliance with iron chelation therapy. *Seminars in Hematology*, 42(2 SUPPL. 1), 10–12. <https://doi.org/10.1053/j.seminhematol.2005.01.001>
- Casey, M. (2008). Partnership - Success factors of interorganizational relationships. *Journal of Nursing Management*, 16(1), 72–83. <https://doi.org/10.1111/j.1365-2934.2007.00771.x>
- Chatterjee, P. (2010). India tries to break cycle of healthcare debt. *Bulletin of the World Health Organization*, 88(7), 481–560.
- Chattopadhyay, S. (2006). 'Rakter dosh'-corrupting blood: The challenges of preventing thalassemia in Bengal, India. *Social Science and Medicine*, 63(10), 2661–2673. <https://doi.org/10.1016/j.socscimed.2006.06.031>
- Chomitz, V., Arsenault, L., Garnett, B., & Hudson, D. (2013). *Shape Up Somerville: Building and sustaining a healthy community*.
- Colah, R., Gorakshakar, A., Phanasgaonkar, S., D'Souza, E., Nadkarni, A., Surve, R., Mohanty, D. (2010). Epidemiology of  $\beta$ -thalassaemia in Western India: Mapping the frequencies and mutations in sub-regions of Maharashtra and Gujarat. *British Journal of Haematology*, 149(5), 739–747. <https://doi.org/10.1111/j.1365-2141.2010.08131.x>
- Colah, R., Italia, K., & Gorakshakar, A. (2017). Burden of thalassemia in India: The road map for control. *Pediatric Hematology Oncology Journal*, 2(4), 79–84. <https://doi.org/10.1016/j.phoj.2017.10.002>
- Cousens, N. E., Gaff, C. L., Metcalfe, S. A., & Delatycki, M. B. (2010). Carrier screening for Beta-thalassaemia: A review of international practice. *European Journal of Human*

*Genetics*, 18(10), 1077–1083. <https://doi.org/10.1038/ejhg.2010.90>

- Cowen, R. (2008). Parents, politicians, physicians, and priests. In *In Heredity and Hope: The case for genetic screening* (pp. 181–222).
- Das, R. (2012). The management of inherited blood diseases in the Indian subcontinent. In D. Kumar (Ed.), *Genomics and Health in the Developing World* (1st ed., pp. 1082–1095). New York: Oxford University Press.
- Davis, M., & Lawrence, K. (2006). *Compliance with Chelation Therapy in the Beta-Thalassemic Adolescent: A Nursing Perspective*. 3(1), 42–47.
- *Dedoose Version 8.0.35, web application for managing, analyzing, and presenting qualitative and mixed method research data*. (2018). Los Angeles, CA: SocioCultural Research Consultants, LLC.
- Dehshal, M. H. (2014). Addressing adherence to treatment: a longstanding concern. The patients' perspective. *Thalassemia Reports*, 4(3). <https://doi.org/10.4081/thal.2014.4865>
- Delea, T. E., Edelsberg, J., Sofrygin, O., Thomas, S. K., Baladi, J. F., Phatak, P. D., & Coates, T. D. (2007). Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: A literature review. *Transfusion*, 47(10), 1919–1929. <https://doi.org/10.1111/j.1537-2995.2007.01416.x>
- Edison, E. S., Shaji, R. V., Devi, S. G., Moses, A., Viswabandhya, A., Mathews, V., Chandy, M. (2008). Analysis of  $\beta$  globin mutations in the Indian population: Presence of rare and novel mutations and region-wise heterogeneity. *Clinical Genetics*, 73(4), 331–337. <https://doi.org/10.1111/j.1399-0004.2008.00973.x>
- Elo, S., & Kyngäs, H. (2008). The qualitative content analysis process. *Journal of Advanced Nursing*, 62(1), 107–115. <https://doi.org/10.1111/j.1365-2648.2007.04569.x>
- Epping-Jordan, J. E., Pruitt, S. D., Bengoa, R., & Wagner, E. H. (2004). Improving the quality of health care for chronic conditions. *Quality and Safety in Health Care*, 13(4), 299–305. <https://doi.org/10.1136/qshc.2004.010744>
- Epping-Jordan, JoAnne E. (2005). Integrated approaches to prevention and control of chronic conditions. *Kidney International, Supplement*, 68(98), 86–88. <https://doi.org/10.1111/j.1523-1755.2005.09816.x>
- Evangelini, M., Mughal, K., & Porter, J. B. (2010). Which psychosocial factors are related to chelation adherence in thalassemia a systematic review. *Hemoglobin*, 34(3), 305–321. <https://doi.org/10.3109/03630269.2010.485080>
- Farmer, K. C. (1999). Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics*, 21(6), 1074–1090.

[https://doi.org/10.1016/S0149-2918\(99\)80026-5](https://doi.org/10.1016/S0149-2918(99)80026-5)

- FSG. (2015). *Collective impact feasibility framework*.
- Galanello, R., & Origa, R. (2010). Beta-thalassemia. *Orphanet Journal of Rare Diseases*, 5(11), 1–15.
- Ganzella, M., & Zago, M. M. F. (2011). The experience of thalassaemic adults with their treatment. *Revista Latino-Americana de Enfermagem*, 19(4), 968–976. <https://doi.org/10.1590/S0104-11692011000400016>
- Gazette of India. *The Rights of Persons with Disabilities Act.* , (2016).
- Glass, T. A., & McAtee, M. J. (2006). Behavioral science at the crossroads in public health: Extending horizons, envisioning the future. *Social Science and Medicine*, 62(7), 1650–1671. <https://doi.org/10.1016/j.socscimed.2005.08.044>
- Government of India. (2017). *Guidelines for Recovery of processing charges for blood and blood components, Ministry of Health & Family Welfare* (p. 7). p. 7. Retrieved from [http://www.naco.gov.in/sites/default/files/Guidelines on recovery of Processing Charges for Blood %26 Blood Components.pdf](http://www.naco.gov.in/sites/default/files/Guidelines%20on%20recovery%20of%20Processing%20Charges%20for%20Blood%20Components.pdf)
- Grannovetter, M. (1973). Strength of Weak Ties. *The American Journal Of Sociology*, 78(6), 1360–1380.
- Grosse, S. D., Boyle, C. A., Kenneson, A., Khoury, M. J., & Wilfond, B. S. (2006). From public health emergency to public health service: The implications of evolving criteria for newborn screening panels. *Pediatrics*, 117(3), 923–929. <https://doi.org/10.1542/peds.2005-0553>
- Haghpanah, S., Zarei, T., Zahedi, Z., & Karimi, M. (2014). Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. *Hematology*, 19(4), 187–191. <https://doi.org/10.1179/1607845413Y.00000000121>
- Hanleybrown, F., Kania, J., & Kramer, M. (2012). Channeling Change : Making Collective Impact Work. *Stanford Social Innovation Review*, 9, Blog. Retrieved from [http://www.ssireview.org/pdf/Channeling\\_Change\\_PDF.pdf](http://www.ssireview.org/pdf/Channeling_Change_PDF.pdf)
- Harandi, T. F., Taghinasab, M. M., & Nayeri, T. D. (2017). Exploring Iranian  $\beta$ -Thalassemia major patients' perception of barriers and facilitators of adherence to treatment: A qualitative study. *Electronic Physician*, 9(9), 1–17. <https://doi.org/10.19082/5212>
- Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research*, 15(9), 1277–1288.

<https://doi.org/10.1177/1049732305276687>

- Huerta, T. R., Casebeer, A., & Vanderplaat, M. (2006). Using networks to enhance health services delivery: perspectives, paradoxes and propositions. *Healthcare Papers*, 7(2), 10–26. <https://doi.org/10.12927/hcpap..18551>
- Huxham, C., & Vangen, S. (2005). *Managing to collaborate: the theory and practice of collaborative advantage*. Abingdon, UK: Routledge.
- Kania, J., & Kramer, M. (2011). Collective impact. *Stanford Social Innovation Review*, 9(1), 36–41.
- Karam, M., Brault, I., Van Durme, T., & Macq, J. (2018). Comparing interprofessional and interorganizational collaboration in healthcare: A systematic review of the qualitative research. *International Journal of Nursing Studies*, 79(December 2016), 70–83. <https://doi.org/10.1016/j.ijnurstu.2017.11.002>
- Kripalani, S., Yao, X., & Haynes, R. B. (2007). Interventions to enhance medication adherence in chronic medical conditions: A systematic review. *Archives of Internal Medicine*, 167(6), 540–550. <https://doi.org/10.1001/archinte.167.6.540>
- Kumu [Relationship mapping software]. (2020).
- Kwait, J., Valente, T. W., & Celentano, D. D. (2001). Interorganizational relationships among HIV/AIDS service organizations in Baltimore: A network analysis. *Journal of Urban Health*, 78(3), 468–487. <https://doi.org/10.1093/jurban/78.3.468>
- Lee, W. S., Toh, T. H., Chai, P. F., & Soo, T. L. (2011). Self-reported level of and factors influencing the compliance to desferrioxamine therapy in multitransfused thalassaemias. *Journal of Paediatrics and Child Health*, 47(8), 535–540. <https://doi.org/10.1111/j.1440-1754.2011.02017.x>
- Lee, Y. L., Lin, D. T., & Tsai, S. F. (2009). Disease knowledge and treatment adherence among patients with thalassemia major and their mothers in Taiwan. *Journal of Clinical Nursing*, 18(4), 529–538. <https://doi.org/10.1111/j.1365-2702.2007.02150.x>
- Maheshwari, M., Arora, S., & Menon, P. (1999). Carrier Screening and Prenatal Diagnosis of Beta-Thalassemia. *Indian Pediatrics*, 36, 119–1125.
- Maria Domenica Cappellini, Alan Cohen, John Porter, Ali Taher, V. V. (2014). *In Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd Edition*. Thalassaemia International Federation.
- Mathew, A., & Sobti, P. C. (2017). The burden of thalassemia in Punjab: A roadmap forward. *Pediatric Hematology Oncology Journal*, 2(4), 85–87. <https://doi.org/10.1016/j.phoj.2018.01.001>

- Miller, F. A. (2009). The complex promise of newborn screening. *Indian Journal of Medical Ethics*, 6(3), 142–148. <https://doi.org/10.20529/ijme.2009.046>
- Modell, B., & Darlison, M. (2008). Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization*, 86(6), 480–487. <https://doi.org/10.2471/BLT.06.036673>
- Mohanty, D., Colah, R. B., Gorakshakar, A. C., Patel, R. Z., Master, D. C., Mahanta, J., Muthuswamy, V. (2013). Prevalence of  $\beta$ -thalassemia and other haemoglobinopathies in six cities in India: A multicentre study. *Journal of Community Genetics*, 4(1), 33–42. <https://doi.org/10.1007/s12687-012-0114-0>
- Moirangthem, A., & Phadke, S. R. (2018). Socio-demographic Profile and Economic Burden of Treatment of Transfusion Dependent Thalassemia. *Indian Journal of Pediatrics*, 85(2), 102–107. <https://doi.org/10.1007/s12098-017-2478-y>
- Morse, J. (1995). The significance of saturation. *Qual Health Res.* 10(1): 3-5
- Mostafa, S., & Elaziz, M. A. (2014). Factors Affecting Compliance Plan of Thalassemic Children and their Mothers in Outpatient Clinic at Zagazig University Hospitals. *Journal of Biology, Agriculture, and Healthcare.* 4(3), 42–52.
- Old, J. (2012). Thalassemias and abnormal hemoglobins of the Indian subcontinent. In D. Kumar (Ed.), *Genomics and Health in the Developing World* (1st ed., pp. 1067–1081). New York: Oxford University Press.
- Olivieri, N. F. (1999). Medical Progress: The B-thalassemias. *New England Journal of Medicine*, 341(2), 99–109. <https://doi.org/10.1017/cbo9780511596582.022>
- Osterberg, L., & Blaschke, T. (2005). Adherence to Medication. *Controlled Clinical Trials*, 10(3), 333–334. [https://doi.org/10.1016/0197-2456\(89\)90126-8](https://doi.org/10.1016/0197-2456(89)90126-8)
- Palanisamy, B., Kosalram, K., & Gopichandran, V. (2017). Dimensions of social capital of families with thalassemia in an indigenous population in Tamil Nadu, India - A qualitative study. *International Journal for Equity in Health*, 16(1), 1–12. <https://doi.org/10.1186/s12939-017-0609-8>
- Parmar, L., Sedai, A., Ankita, K., Dhanya, R., Agarwal, R. K., Dhimal, S., Faulkner, L. (2017). Can inequity in healthcare be bridged in LMICs – Multicentre experience from thalassemia day care centres in India. *Pediatric Hematology Oncology Journal*, 2(4), 88–93. <https://doi.org/10.1016/j.phoj.2017.12.006>
- Patel, A. P., Patel, R. B., Patel, S. A., Vaniawala, S. N., Patel, D. S., Shrivastava, N. S., Naik, M. R. (2014).  $\beta$ -thalassemia mutations in Western India: Outcome of prenatal diagnosis in a hemoglobinopathies project. *Hemoglobin*, 38(5), 329–334.

<https://doi.org/10.3109/03630269.2014.951889>

- Patton, M. (2002). Ch 7: Qualitative interviewing. In *Qualitative research & evaluation methods* (pp. 339–425).
- Petrou, M. (2010). Screening for beta thalassaemia. *Indian Journal of Human Genetics*, *16*(1), 1–5. <https://doi.org/10.4103/0971-6866.64934>
- Porter, J. B., Evangeli, M., & El-Beshlawy, A. (2011). The challenges of adherence and persistence with iron chelation therapy. *International Journal of Hematology*, *94*(5), 453–460. <https://doi.org/10.1007/s12185-011-0927-3>
- Porter, J., & Viprasit, V. (2014). Iron overload and chelation. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 42–97). Nicosia: Thalassaemia International Federation.
- Provan, K. G., Fish, A., & Sydow, J. (2007). Interorganizational networks at the network level: A review of the empirical literature on whole networks. *Journal of Management*, *33*(3), 479–516. <https://doi.org/10.1177/0149206307302554>
- Provan, K. G., Veazie, M. A., Teufel-Shone, N. I., & Huddleston, C. (2004). Network analysis as a tool for assessing and building community capacity for provision of chronic disease services. *Health Promotion Practice*, *5*(2), 174–181. <https://doi.org/10.1177/1524839903259303>
- Provan, K., Harvey, J., & De Zapien, J. (2005). Network structure and attitudes toward collaboration in a community partnership for diabetes control on the US-Mexican border. *Journal of Health, Organisation and Management*, *19*(6), 504–518. <https://doi.org/10.1108/14777260510629706>
- Provan, K., & Milward, H. (1995). A preliminary theory of interorganizational network effectiveness: A comparative study of four community mental health systems. *Administrative Science Quarterly*, *40*, 1–33.
- Provan, K., & Milward, H. (2001). Do networks really work? A framework for evaluating public-sector organizational networks. *Public Administration Review*, *61*(4), 414–423. <https://doi.org/10.1111/0033-3352.00045>
- Provan, K., Veazie, M., Staten, L., & Teufel-Shone, N. (2005). The use of network analysis to strengthen community partnerships. *Public Administration Review*, *65*(5), 603–612. <https://doi.org/10.1111/j.1540-6210.2005.00487.x>
- Retrum, J. H., Chapman, C. L., & Varda, D. M. (2013). Implications of Network Structure on Public Health Collaboratives. *Health Education and Behavior*, *40*(1 SUPPL.). <https://doi.org/10.1177/1090198113492759>

- Robins, G. (2015). *Doing Social Network Research: Network-based Research Design for Social Scientists*.
- Roy, T., & Chatterjee, S. C. (2007). The experiences of adolescents with thalassemia in West Bengal, India. *Qualitative Health Research*, 17(1), 85–93. <https://doi.org/10.1177/1049732306296400>
- Sabate, E. (2003). *Adherence to long-term therapies World Health Organization 2003*.
- Sanctis, Vincenzo De, Kattamis, C., Canatan, D., Soliman, A. T., Elsedfy, H., Karimi, M., Angastiniotis, M. (2017).  $\beta$ -thalassemia distribution in the old world: An ancient disease seen from a historical standpoint. *Mediterranean Journal of Hematology and Infectious Diseases*, 9(1), 1–14. <https://doi.org/10.4084/mjhid.2017.018>
- Sanctis, V., Skordis, N., & Soliman, A. (2014). Endocrine diseases. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 146–157). Nicosia: Thalassemia International Federation.
- Sandelowski, M. (1995). Sample size in qualitative research. *Research in Nursing & Health*, 18(2), 179–183. <https://doi.org/10.1002/nur.4770180211>
- Scalone, L., Mantovani, L. G., Krol, M., Rofail, D., Ravera, S., Bisconte, M. G., Cappellini, M. D. (2008). Costs, quality of life, treatment satisfaction and compliance in patients with  $\beta$ -thalassemia major undergoing iron chelation therapy: The ITHACA study. *Current Medical Research and Opinion*, 24(7), 1905–1917. <https://doi.org/10.1185/03007990802160834>
- Shah, F. (2014). Addressing adherence to treatment: a longstanding concern. The health care professional. *Thalassemia Reports*, 4(3). <https://doi.org/10.4081/thal.2014.4864>
- Shah, F., & Kaltsounis, G. (2018). *Adherence to treatment : Doctor vs patient perspective on m e r u s e o n o n e r a l . 8*. <https://doi.org/10.1002/ajh.21993.3>.
- Shah, F. T., Sayani, F., Trompeter, S., Drasar, E., & Piga, A. (2019). Challenges of blood transfusions in  $\beta$ -thalassemia. *Blood Reviews*, (xxxx), 100588. <https://doi.org/10.1016/j.blre.2019.100588>
- Shah, N., Mishra, A., Chauhan, D., Vora, C., & Shah, N. R. (2010). Study on effectiveness of transfusion program in thalassemia major patients receiving multiple blood transfusions at a transfusion centre in Western India. *Asian Journal of Transfusion Science*, 4(2), 94–98. <https://doi.org/10.4103/0973-6247.67029>
- Shaker, W. H. (2015). Factors affecting Adolescents ' Adherence to Therapeutic Recommendations after Thalassemia. *International Journal of Scientific and Research Publications*. 5, 23–26

- Shaligram, D., Girimaji, S. C., & Chaturvedi, S. K. (2007). Psychological problems and quality of life in children with thalassemia. *Indian Journal of Pediatrics*, 74(8), 727–730. <https://doi.org/10.1007/s12098-007-0127-6>
- Shaligram, Deepika, Girimaji, S. C., & Chaturvedi, S. K. (2007). Quality of life issues in caregivers of youngsters with thalassemia. *Indian Journal of Pediatrics*, 74(3), 275–278. <https://doi.org/10.1007/s12098-007-0043-9>
- Sheth, J. J., Sheth, F. J., Pandya, P., Priya, R., Davla, S., Thakur, C., & Flavin, V. (2008).  $\beta$ -Thalassemia mutations in western India. *Indian Journal of Pediatrics*, 75(6), 567–570. <https://doi.org/10.1007/s12098-008-0109-3>
- Silverman, M. (2003). Theories of primary prevention and health promotion. In T. P. Gullotta & Bloom (Eds.), *Encyclopedia of primary prevention and health promotion* (pp. 27–42). New York: Kluwer Academic/Plenum Pub.
- Singh, H., Pradhan, M., Singh, R. L., Phadke, S., Naik, S. R., Aggarwal, R., & Naik, S. (2003). High frequency of hepatitis B virus infection in patients with  $\beta$ -thalassemia receiving multiple transfusions. *Vox Sanguinis*, 84(4), 292–299. <https://doi.org/10.1046/j.1423-0410.2003.00300.x>
- Taher, A., & Tyan, P. (2014). The Spleen. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 126–133). Nicosia: Thalassemia International Federation.
- Tahmankar, P., Agarwal, S., Arya, V., Kumar, R., Gupta, U., & Agarwal, S. (2009). Prevention of homozygous beta thalassemia by premarital screening and prenatal diagnosis in India. *Prenatal Diagnosis*, 29, 83–88. <https://doi.org/10.1002/pd.2176>
- Telfer, P., Constantinidou, G., Andreou, P., Christou, S., Modell, B., & Angastiniotis, M. (2005). Quality of life in thalassemia. *Annals of the New York Academy of Sciences*, 1054, 273–282. <https://doi.org/10.1196/annals.1345.035>
- Thomas, J. C., Reynolds, H., Bevc, C., & Tsegaye, A. (2014). Integration opportunities for HIV and family planning services in Addis Ababa, Ethiopia: An organizational network analysis. *BMC Health Services Research*, 14. <https://doi.org/10.1186/1472-6963-14-22>
- Thuret, I., Hacini, M., Pégourié-Bandelier, B., Gardembas-Pain, M., Bisot-Locard, S., Merlat-Guitard, A., & Bachir, D. (2009). Socio-psychological impact of infused iron chelation therapy with deferoxamine in metropolitan France: ISOSFER study results. *Hematology*, 14(6), 315–322. <https://doi.org/10.1179/102453309X12473408860424>
- Trachtenberg, F. L., Gerstenberger, E., Xu, Y., Mednick, L., Sobota, A., Ware, H., Yamashita, R. (2014). Relationship among chelator adherence, change in chelators, and quality of life in Thalassemia. *Quality of Life Research*, 23(8), 2277–2288. <https://doi.org/10.1007/s11136-014-0671-2>

- Trachtenberg, F. L., Mednick, L., Kwiatkowski, J. L., Neufeld, E. J., Haines, D., Pakbaz, Z., Yamashita, R. (2012). Beliefs about chelation among thalassemia patients. *Health and Quality of Life Outcomes*, 10(1), 148. <https://doi.org/10.1186/1477-7525-10-148>
- Trachtenberg, F., Vichinsky, E., Haines, D., Pakbaz, Z., Mednick, L., Sobota, A., Neufeld, E. J. (2011). Iron chelation adherence to deferoxamine and deferasirox in thalassemia. *American Journal of Hematology*, 86(5), 433–436. <https://doi.org/10.1002/ajh.21993>
- Treadwell, M. J., & Weissman, L. (2001). Improving adherence with deferoxamine regimens for patients receiving chronic transfusion therapy. *Seminars in Hematology*, 38(1 SUPPL. 1), 77–84.
- Trompeter, S., & Cohen, A. (2014). Blood transfusion. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 28–41). Nicosia: Thalassemia International Federation.
- Tsai, J. H. C., & Petrescu-Prahova, M. (2016). Community interagency connections for immigrant worker health interventions, King County, Washington State, 2012-2013. *Preventing Chronic Disease*, 13(6), 1–10. <https://doi.org/10.5888/pcd13.160013>
- Vekeman, F., Sasane, M., Cheng, W. Y., Ramanakumar, A. V., Fortier, J., Qiu, Y., Adams-Graves, P. (2016). Adherence to iron chelation therapy and associated healthcare resource utilization and costs in Medicaid patients with sickle cell disease and thalassemia. *Journal of Medical Economics*, 19(3), 292–303. <https://doi.org/10.3111/13696998.2015.1117979>
- Verma, I. C., Saxena, R., & Kohli, S. (2011). Past, present & future scenario of thalassaemic care & control in India. *Indian Journal of Medical Research*, 134(10), 507–521.
- Vosper, J., Evangelini, M., Porter, J. B., & Shah, F. (2018). Psychological Factors Associated with Episodic Chelation Adherence in Thalassemia. *Hemoglobin*, 42(1), 30–36. <https://doi.org/10.1080/03630269.2018.1433686>
- Vullo, C., De Sanctis, V., Borgatti, L., & Atti, G. (1989). Trattamento ferrochelante [Iron-chelating treatment]. *Haematologica*, 74(5), 241–251.
- Walker, M., & Wood, J. (2014). Cardiac complications. In *Guidelines for the clinical management of thalassemia* (3rd ed., pp. 98–113). Nicosia: Thalassemia International Federation.
- Ward, A., Caro, J. J., Green, T. C., Huybrechts, K., Arana, A., Wait, S., & Eleftheriou, A. (2002). An international survey of patients with thalassemia major and their views about sustaining life-long desferrioxamine use. *BMC Clinical Pharmacology*, 2, 1–9.

<https://doi.org/10.1186/1472-6904-2-3>

- Wasserman, S., & Faust, K. (1994). Structural analysis in the social sciences. *Social Network Analysis: Methods and Applications*.
- Welfare, M. of H. & F. (2016). *National Health Mission - Guidelines on Hemoglobinopathies in India: Prevention and control of hemoglobinopathies in india*.
- Wilson, J.M.G., Jungner, G. (1968). *Principes and practice of screening for disease*. (34), 163.
- World Health Organisation. (2002). *Building Blocks for Action Innovative Care for Chronic Conditions WHO Library Cataloging-in-Publication Data Innovative care for chronic conditions: building blocks for action: global report*. Retrieved from <http://www.who.int/chp/knowledge/publications/icccglobalreport.pdf>
- Worthington, D. (2012). *Sickle cell and thalassaemia: handbook for laboratories* (3rd ed.). NHS Sickle Cell and Thalassaemia Screening Programme.
- Yamashita, R., Foote, D., & Weissman, L. (1998). Patient Cultures - Thalassaemia Service Delivery and Patient Compliance. *Ann N Y Acad Sci*, 850(9), 521–522.
- Yessis, J., Riley, B., Stockton, L., Brodovsky, S., & Von Sychowski, S. (2013). Interorganizational Relationships in the Heart and Stroke Foundation's Spark Together for Healthy Kids™: Insights From Using Network Analysis. *Health Education and Behavior*, 40(1 SUPPL.). <https://doi.org/10.1177/1090198113490724>