GLOBAL THALASSAEMIA REVIEW
TIF'S PERSPECTIVE

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FORWARD

This **GLOBAL THALASSAEMIA REVIEW** is dedicated to the joint work and collaboration of the Thalassaemia International Federation (TIF) with the World Health Organisation (WHO) in its status as an NGO in official relations since 1996 (2018-2025).

TIF, in fulfilling its mission, has been guided and supported by the principles and vast experience of the WHO in the context of both disease specific decisions, resolutions and programmes, including public health programmes and policies, that are related to the control and management of a genetic, hereditary, multiorgan disease like thalassaemia. For such a disease there is today ample knowledge and experience on how to effectively prevent and appropriately manage it at the clinical level. Moreover, in recent years, research advances have been impressive both in the area of management but also in the area of cure giving great hope to the patients for their future.

TIF, in its early efforts was guided by the Hereditary Disease Programme of the WHO headed by close and invaluable collaborators including Professors Anver Kuliev and Victor Boulyjenkov, who have supported and guided our work in a number of ways. In addition, and as TIF achieved the status of an "NGO in official relations with the WHO", a number of other eminent health care professionals and relevant programmes' leaders have supported our work including amongst others, Dr Neelam Dhingra, Mr Junping Yu, and Dr Yuyun Maryuningsih as well as the different Directors and officials of WHO Regional and country offices and Collaborating Centres around the world.

TIF continues its efforts with an undivided commitment to continue through its work and partnerships with the global patient/parent associations and the large network of heath care professionals across the world, to fight for the rights of patients for equal access to quality health, social and other care.

On behalf of the Board of Directors of TIF and the TIF office staff, we would also like to express our wholehearted gratitude and respect, to every single health care professional who has been with us from the beginning and without the support of whom the work of TIF would not have progressed positively towards achieving its mission. Special and particular gratitude goes to all patients, wherever they may live, who fight on an everyday basis for access to quality medical, social and other care including the safety, quality and adequacy of blood, for continuous availability of key essential drugs, social inclusion and, in more recent years, for access to innovative therapies and drugs that promise better quality of life and where possibly holistic cure – a long-awaited scientific development.

Gratitude also goes to the researchers, academics, healthcare professionals, the industry and the relevant competent stakeholders for acknowledging and respecting the many and multiple unmet needs of patients with these disorders, and for investing in improving their lives, giving them hope and optimism.

I hope that this Global Review which is a dynamic activity of TIF to be updated on a continual basis as reliable and new information becomes available, will give some, even gross, insights into the naked truth with regards to the provision and quality of services for this disease across the globe aiming to sensitize governments and competent authorities to revisit and implement the incredible work and the recommendations offered by WHO's Resolution WHO EB118.R1 Thalassaemia and Other Heamoglobinopathies (2006), as well as the many other WHO related resolutions, recommendations and programmes.

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President

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1. INTRODUCTION

THE THALASSAEMIA INTERNATIONAL FEDERATION (TIF) was born because of the realization that there are gross inequalities in the provision of disease specific services around the world and the belief that 'we can do better' for all patients if collective advocacy on behalf of the global patient community is presented to service providers and decision makers at national and international level.

Beta thalassaemia, which is the condition which was, historically, the first concern of the founding members of the Federation, is an inherited inability of the organism to form beta globin chains, necessary to complete the haemoglobin molecule. The chain imbalance in the molecule is the basis of the pathophysiology [1, 2] resulting in ineffective erythropoiesis, severe anaemia, the need for regular, lifelong blood transfusions and iron accumulation in vital organs of the body requiring chelation on a daily and lifelong basis. As patients grow, various co-morbidities, based on the quality and level of disease specific services provided, make their appearance, requiring a well-coordinated and expert multidisciplinary care approach. Although there is a spectrum of severity, ranging from transfusion dependency from infancy to relative non-dependency (NTDT), the severe form (TDT) is more common in most populations. TDT, depending on the quality of services, or lack of services, has the following possibilities:

- No treatment including no blood transfusion– death in early childhood, generally before the age of 5 years
- Treatment based only on blood transfusion therapy - early death before reaching the second decade of life
- Inadequate management – i.e. suboptimal transfusion therapy and ineffective iron load monitoring and treatment can only result in the postponement of death and poor quality of life. Survival is usually into the late teens or young adulthood. This is the experience of the majority of the global patient population, as this publication aims to demonstrate [3, 4]. Progress towards optimal patient care is slowly benefitting more patients but there is much ground to be covered
- Optimal care (Table 1) is available to a minority of patients across the world who are being cared for in reference centres. These are mostly found in countries in which high disease prevalence is coupled with strong health infrastructures and relative prosperity. Long patient survival has been achieved in these countries but even so, this is still not equivalent to that of the general population. Quality of life is also greatly improved with optimal care, with patients achieving educational, career and social goals, at least in their majority
- Curative treatments at present include haemopoietic red cell transplantation (HRCT) and in more recent years gene-based approaches have been authorized (FDA, EMA). At the time of writing this review, these approaches have reached only a tiny minority of patients. These curative treatments hold great hope that in the years to come [5, 6, 7], they will be generally available for all patients across the world.
- A paragraph on innovative drugs and clinical trials.
- In addition, drugs are in development for modifying disease programming, one of which has already gained authorization and others are in different stages of research and different phases of clinical trials.

Table 1. Necessary services for optimal management of TDT – the latest clinical trial updates (December 2024)

1	Adequate and safe blood donation for regular lifelong transfusions
2	Maintaining a pre-transfusion Hb of not less than 9g/dl to correct anaemia and minimise endogenous, ineffective erythropoiesis, and so marrow expansion.
3	Regular and specialised monitoring of iron load in vital organs
4	Daily iron chelation therapy with expert individual (personalised) management of iron overload
5	Coordinated, well-structured expert multidisciplinary approach to both monitor and, prevent the development of complications and managing organ involvement
6	Psychological support for the timely response to stress factors including special focus on self-management and adherence to treatment
7	Social and financial support minimising or even eliminating out of pocket expenses

Based on these disease specific requirements, TIF advocates for an ideal service for thalassaemia and other red cell disorders, including:

1. Application of the Six Domains of Healthcare Quality as described by the IOM (Institute of Medicine, USA): Safety (avoiding harm to patients), Effectiveness (providing services based on scientific knowledge, evidence based), patient-centered element (provision of care that is respectful of and responsive to individual patient preferences, needs, and values), providing timely care (reducing waits and sometimes harmful delays), efficient and equitable service in which quality is independent of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status. https://www.ahrq.gov/talkingquality/measures/six-domains.html.
2. Service that is staffed by well trained and experienced doctors and nurses, without frequent turnovers. This includes a hierarchy based on merit.
3. Adoption of internationally accepted guidelines and standards for clinical management.
4. Presence of a multidisciplinary team which collaborates with the teating physician in monitoring and managing the condition and its complications.
5. The presence of an electronic registry and medical record for each patient, and appropriate technology to monitor patient progress over time.
6. Appropriate blood for transfusion and iron chelation medication provision at all times.
7. Universal health coverage based healthcare and social national system to prevent out of pocket expenses burden the family.
8. Availability and accessibility of diagnostic and laboratory services that are specialized are available in reference centres.
9. The development, implementation and regular upgrading of a nationally coordinated prevention programme for at risk couples who wish to avoid the birth of affected children.

The provision of such services is not available equally and to the same quality standards to affected patients within and across countries [3,4]. In fact, only a minority of patient benefits from the medical and scientific advances which have led to improved outcomes and survival in the management of haemoglobin disorders in the last 2-3 decades. This is evident in the outcomes which are observed across all regions of the world. Thalassaemia is not unique in experiencing such inequalities. All chronic and rare disorders are the poor relatives in the stratification of what are considered priorities on the national healthcare and budgetary agendas [8,9]. Inequity is a global phenomenon which affects all aspects of life and is not confined to healthcare.

Certainly, addressing global inequity in health is not a matter of simply exerting political pressure. Many public health, economic, social, racial and political factors influence policy making and health related decisions [, 10, 11]. Nor is it a simple matter of affordability of services, even though economic prosperity does play a major role. Even within high resource countries health inequities and social gradients are found which are known to affect health outcomes [12].

THE ECONOMIC DETERMINANTS OF HEALTH

The question that has to be discussed is whether these inequalities in health outcomes are avoidable. One position is that since health service provision depends on socioeconomic circumstances which have such a wide variation globally, it is the socio-economic conditions that must be addressed first to allow for progress in quality of services. Faced with limited resources, spending should be prioritized to health threats which affect the majority, thus safeguarding an adequate level of community wellbeing. This logical approach has been the basis of the investment in primary care, of aiming for 'maximum health gain for the money spent' [8], which has led to the Alma Ata declaration of 1978 by the WHO. This approach has had a positive impact on health services globally. 'The importance of genetic disorders tends to be recognized when infant mortality falls below 40/1000 live births', and this is related to the fact that before health authorities can consider and acknowledge addressing congenital and lifelong conditions as priorities, reduction of other causes of infant mortality must be first effectively achieved [13]. It is the philosophy based on which cost-benefit has become the motto of health planners and certainly, the application of evidence-based costing.

THE RIGHT OF EACH INDIVIDUAL TO HEALTH

The individual facing disability and premature death cannot be viewed simply as a health or financial burden. Any civilized society must protect its most vulnerable members based on the universal acceptance that health is a fundamental human right. Recognizing health as a right means recognizing the individual's need to achieve the best possible in life. This need can only be visible if the affected individual speaks out and presents experiences and suffering to the community as well as to providers – the patient's voice. This is very rarely heard where and when it is needed most and which is mainly at the level of services planning. Patient experience is not just the experience of ill health. It includes discrimination, poor access to medications, to proactive monitoring, to social integration, education, relations, friendships, networking, marriage and so many aspects and values of life. Reducing patients to a number (YYL, DALYs, QALYs) may be helpful in addressing and managing public health issues. but no indicator can adequately reflect on the experience of individual lives. So, the question is: should the focus then be on the individual or on the wider social good? This dilemma is not just a philosophical query but must be seen in the context of practical health planning and balanced decisions taken. It moves the economists' view of health to an ethical and philosophical realm that few have attempted to visit let alone try to tackle.

THE ROLE OF TIF

The creation of Thalassaemia International Federation (TIF) in 1987, was considered as a continuation of the successful effort made in the 1960s and 1970s in the control of haemoglobin disorders in, mainly and primarily, the Southern Mediterranean countries, including Greece, Italy and Cyprus. Devoted parents mainly, but also young (at the time) patients, joined efforts with the few (at the time) interested, involved physicians and scientists, and WHO, sharing their vision that through a global umbrella organization research for further improvements could be achieved and this would encourage, strengthen and aid health authorities across the world to focus on haemoglobin disorders and the development of disease specific plans encompassing procedures and monitoring which were absent at the time from the majority of the "affected" countries of the world. This was, and still is the vision of TIF that mandates its mission, work and activities. The influence of united social groups was a real experience in some high prevalence countries and transferring their experience to other countries was based mainly on advocacy derived from successful outcomes in the national programmes established in their countries and which indeed changed the fortunes of patients wherever these were applied. The idea of sharing experiences in advocacy across borders, of transferring knowledge and

presenting a united voice to local health authorities in individual countries and to official health regional and international bodies through an international consortium of patients/parents with medical back up, became a practical reality in 1987 in an international meeting in Milano, Italy where TIF was born. Since then, TIF has grown both geographically and in membership – at the time of writing this report representing over 270 patient associations in over 68 countries across Europe, Middle East, West Pacific, Southeast Asia, the Americas and North Africa.

The contribution of TIF has been invaluable through the decades and its impact on the education of involved healthcare professionals as well as on the lives of patients themselves has been worldwide recognised healthcare professionals, decision makers, the community at large and in strengthening and empowering networks and collaborations in research and academia.

The difficulty and multiple challenges in providing adequate care is faced particularly in low- and middle-income countries (LIMC) as well as in countries in which the haemoglobin disorders are very rare in the indigenous populations, irrespective of economic or social development. Despite some very significant improvements in the control and care achieved over the decades, gross inequalities which seem to be related to these two main factors, i.e. specific challenges country income and the rarity of these disorders continue, results in the majority of thalassaemia patients still poorly managed with high rates of morbidity and early death.

LOW- & MIDDLE-INCOME COUNTRIES (LMIC)

There can be no doubt that resource restrictions play a major role in the inability of LIMC countries to reduce amenable mortality in chronic non-communicable diseases like thalassaemia, which are indeed resource demanding. If the objective is to reach the individual patient with evidence based clinical interventions aiming to reduce not only the possibility of early death but also to reduce complications through monitoring and secondary prevention, then examining resource availability must be supplemented by an enquiry into reasons why resources are not reaching our patient. This implies a need to examine factors that affect implementation. Where resources are limited certainly competition with other health needs is a factor that most of TIF's national associations have to face. This means persuading health planners to provide thalassaemia patients with a larger slice of a pie that is already limited in size compared to the mouths that it is meant to feed. **Advocacy in such a competitive situation is forced on support groups as a sad reality which results inevitably in winners and losers, a very unfair state for families and patients to have to work in. Yet survival of the most vocal, and the most politically connected is a reality within which TIF and its associations have been working for decades.** Raising awareness, educating the public (an active participant in hereditary disease services), educating healthcare professionals and above all sensitizing health planners are all part of the same strategy to gain attention and support. Through such actions, patient driven associations endeavor to increase resources but support is often given in half measures in the effort of providers to satisfy as many of the pressure groups as possible. **Even when support is gained implementation of services requires planning which in turn requires in depth knowledge of the total needs of a multi-organ disease, affecting different age groups differently and requiring a comprehensive approach for best outcomes.** The clinical expertise required is often lacking even among specialised medical professionals and is poorly understood by health planners resulting in "wasting" money and most importantly poor patient outcomes.

In addition to these challenges the social determinants of health and their role in service implementation must be understood and addressed. Housing, employment, family income, education, culture and religion (both so influential in disease prevention). In chronic disease, the availability or lack of health coverage and thus the threat of financial hardship, even bankruptcy, is an additional very important factor threatening both social and mental health. There is no doubt that economic hardship is correlated to poor health, poverty is the biggest enemy of health.

As an umbrella organization TIF provides its members with the tools to promote their needs including:

HIGH RESOURCE COUNTRIES WHERE THE THALASSAEMIAS ARE RARE IN THE INDIGENOUS POPULATION

- Advocacy through capacity building workshops but also supports national groups by participating in visits to health authorities and bodies at national, regional and international level when requested.
- Education programmes addressed to both professionals and patients through publications, fellowships, organization of events and in more current years through tele-medicine, webinars and electronic platforms (TIF e-Academy).
- The establishment of "expert" patient groups and/or better patient advocacy groups to provide in a documented and evidence-based way the "patient's perspective" and unmet needs to decision makers at all levels.
- The creation of national and international advisory panels
- Developing and maintaining epidemiological tools such as registries, electronic medical records and keeping its own epidemiological database with information both from the published literature and its contact with countries and member groups
- Promoting self-management for patients, including the development of Mobile Apps
- Working with WHO at both central, regional and country levels to influence and educate governments to promote and/or strengthen disease-specific policies
- Encouraging research into more affordable and sustainable monitoring and other interventions. An example is the early detection of organ iron toxicity with alternative measures where MRI is not available.

It is easy to assume that robust and well-financed health systems necessarily provide optimal care. When a chronic condition is rare and even more when a hereditary condition is not part of the local population's pattern of disease, then weaknesses are experienced. In the countries of the Americas and of Europe north of the Mediterranean coast, migrations both historical and recent have introduced haemoglobin disorders to a varying extent, even though they are still rare [14]. Although population movements have been a phenomenon known throughout history, the recent increase of population shifts from South to North and East to West, have brought with them an increase in these chronic diseases which are over and above the general acute health issues that are expected. **Migrations from Iraq, Thailand, Syria, Afghanistan and Turkey, for example are entering Europe from the Eastern borders of Greece and the Balkans; many are carriers of thalassaemia genes and HbE. One example is that of Germany where in 2014 only about 1,000-1,500 sickle cell patients were recorded [15], while in 2016 a neonatal screening study revealed a frequency of SCD of one in 2385 newborns, probably of Sub-Saharan ancestry [16].**

The clinical experience in these settings is often lacking and even diagnosis may be delayed or inaccurate. Specialised clinical care may be provided in selected centres, but most migrants are scattered and often do not know where to seek expert help, while on the other hand local physicians provide basic blood transfusions but with no expertise in management as recommended in International Guidelines (Guidelines for the Management of Transfusion-Dependent Thalassaemia, TIF, 2021). Language and cultural difficulties, the concerns about

housing and employment all lead to the patient taking second place even within the family. There is absence of national registries so that the issue may not be 'visible' to health authorities and since patient numbers and location are not known, planning of services is absent or insufficient to meet the needs.

REFUGEES TO OTHER HIGH PREVALENCE AREAS

The flow of refugees from war zones to neighbouring countries, which have also a high burden of these disorders remains of utmost concern for TIF. Protracted emergencies have created a great humanitarian crisis. **Many patients from Syria have gone to Lebanon, which hosts around 1.5 million Syrian refugees (**UNHCR, 2024**) while Jordan has received around 730,000 (**UNHCR, 2024**) and Egypt about 159,000 (**UNHCR, 2024**).** These are countries, which have an indigenous haemoglobinopathy problem, a burden with which they are hardly coping for their own population. Yet little knowledge exists about the fate of the refugee patients in these countries. Who is responsible for their care is not really known while at the same time war conflicts may change from one day to another and humanitarian organisations need to be alert to redirect or revisit their activities and programmes.

THE GLOBAL THALASSAEMIA REVIEW

The Global Thalassaemia Review was put together by TIF as a collection of independent reports, to document the existing situation across the world in the context of the various components of public health, clinical and social services which are deemed essential for patient wellbeing. The main concern in the Review is the transfusion dependent patient who demands the most services in terms of quantity and quality and for whom TIF has gathered through the years of its work the most in number and redistributing data or information. All patients with other haemoglobin disorders and congenital anaemias are also expected to benefit and their well-being and quality of life are considered in the daily agenda of TIF, since they usually share the same haematology services but for whom however and data are also confined. The focus is on the historical conventional treatments for thalassaemia in the dawn of an era when innovative therapies are emerging. If conventional therapy is not reaching the majority, innovative therapies, however successful, will only increase inequalities.

- The preparation of the individual chapters in this Review, by different authors, means that it is anticipated that there will be overlap in subject matter and information. However, this is accepted since the message of inequality and the need for more efforts to overcome deficiencies is the same and at the core of this Global Review. It was also necessary for each author to provide some form of introduction and basis for his/her comments in the content, part of which may appear in a similar way and style in other chapters.
- The way the chapters were written is quite descriptive and each one of them can form a separate, complete topic on its own. Due to severe lack of published information, statistical analysis of data is very limited in this Review. The objective however was to bring to light deficiencies which are documented and easily discernible in terms of poor patient outcomes.

The main components that contribute to the effective control of thalassaemia have been almost exhaustively covered in this review including: prevention, blood transfusion services, iron load monitoring and iron chelation treatment services, the value of multidisciplinary care and expert centres in the management of haemoglobin disorders, social and disability needs, very importantly the cost of disease and disease burden and last but not least, the value and role of national registries and patient engagement.

This Global Review was completed by a compilation and analysis of the available information at TIF and/or from published information in the literature and focused on the description of disease related services and other related significant components mainly drawn from demographic data. There was an attempt by the authors to describe the services not only at regional level, but also at country level.

Heterogeneity and inequality in patients accessing appropriate services for their needs are what this Review is addressing and for which TIF has meticulously worked through the years.

For most chapters, attempts were made by the authors to provide even a gross assessment of the availability of disease specific services and to grade their effectiveness Acknowledging the fact that TIF's intentions are to publish each chapter separately in a later point in time, it is anticipated as previously mentioned that the reader will encounter some degree of content overlap particularly in the introduction, discussions and conclusions sections of some of the chapters.

TIF deeply and sincerely apologizes in advance for any omission or misinterpretation may have occurred with regards to assessing individual country's services. Lack of nationwide registries, patient health records and published information in literature will have contributed to such issues. Apart from the very valuable insights regarding services, this Review brings also to the forefront the substantial value of publishing information and sharing experiences and best practices amongst involved stakeholders – governments, competent authorities, heath care professionals, patients, academia, industry and indeed this is an element significantly lacking in the field of heamoglobin disorders.

THIS REVIEW IS CONSIDERED BY TIF AS A DYNAMIC ACTIVITY AIMING TO BE UPDATED ANNUALLY, AS NEW AND RELIABLE INFORMATION BECOMES AVAILABLE TO TIF OR TO THE PUBLISHED LITERATURE.

CONCLUSION

The problem of inequality in healthcare provision is almost universal and well known, but TIF has decided to focus and record its experience with thalassaemia patients across the world. The data gathered, even from peer reviewed publications concern local or regional data and not national ones is often of questionable accuracy. Yet, the attempt to give as clear a picture as possible, not only of the global situation but also of each country, may offer some insights into the priorities that need to be tackled and policies to pursue. Passively accepting morbidity and mortality in young people cannot be acceptable particularly when regarding a condition/disorder for which there is ample knowledge and documented expertise for decades now on how to effectively prevent and appropriately treat. Authorities and decision makers must be sensitized and made aware that survival of the fittest or the richest cannot remain silent realities which no one wishes to acknowledge.

Above all, this collection of facts and approximations is meant to guide TIF in its own pursuit of answers and guidance as to what can be practically done to allow a section of the community who can benefit from what medical science has to offer and live a life that is guaranteed by international proclamations. The whole philosophy is that 'we can do better'. TIF is a firm believer in this philosophy and passionately fights for the patient voice to be heard and the despair of many to become an element of the past; in this effort, one organisation cannot change the world. International bodies like WHO, governments, health planners,

economists, the academia, the industry, the patient support organizations at local, national and regional level, must all join hands and minds to bring about change.

TIF is very grateful to the WHO for its long-term invaluable guidance and productive collaboration in the context of its work as 'an NGO in official relations' with the WHO. This Global Review is a deliverable of its 3-year plans of collaboration 2018-2020, 2021 – 2023, and 2024 - 2026.

The findings of this Review will support TIF in sensitizing governments and competent authorities on their responsibility towards adopting and implementing the recommendations provided in the context of the WHO decisions on thalassaemia and other heamoglobin disorders with regards to the control of these disorders.

TIF in addition, acknowledges and is greatly indebted to the scientists/health care professionals at country and international level who have been working and collaborating for decades with TIF through its educational programme across the six WHO Regions of the world. TIF also expresses through this Review, its deep appreciation to the medical societies for their close and productive collaboration in relevant projects including, mainly but not confined to, the European Hematology Association (EHA) and to other than thalassaemia disease-oriented NGOs. Last and most importantly, TIF is grateful to every individual patient and parent who mainly but also on an individual basis through their national patient organizations' work, and share with TIF their challenges, concerns, successes, weaknesses and strengths making it possible through their trust and confidence to TIF and through their active and meaningful involvement and engagement at the decision-making level in their countries, for TIF to continually advocate and fight for the improvements in disease specific policies at the national level but also of its own services towards the patients it represents all over the world.

"We do not live to be treated. We are treated to live"

G. Constantinou
Expert Patient

"Violating human and patients' rights for equal access of patients to quality health and other care is not acceptable"

Thalassaemia International Federation

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