THALASSAEMIA INTERNATIONAL FEDERATION
In official relations with the World Health Organization

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Thalassaemia International Federation's submission on the UK NICE's consultation document on Zynteglo®

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The Thalassaemia International Federation (TIF)1 expresses its opinion on the NICE's consultation document on Zynteglo® - Gene therapy product. TIF makes this submission in coordination with, and support of, its two UK members, the UK Thalassaemia Society (UKTS) based in London and the North of England Bone Marrow and Thalassaemia Association (NEBATA), based in Manchester. Moreover, TIF makes this submission in view of the UK's leading role in healthcare, combatting health inequalities and in promoting innovative treatments; any decisions made by NICE and the NHS may influence decisions by health authorities across the world particularly those that may lack national Health Technology Assessment (HTA) bodies.

In the context of its mission to promote access to optimal quality care to all patients with thalassaemia (and also many with Sickle Cell Disease (SCD), in countries where the two conditions coexist and who share the same services, worldwide), TIF acts as their voice and advocates and promotes their rights in accordance with international standards. Today 160 National Thalassaemia Associations in 62 countries across the 6 Regions[2] of the world are members of TIF. The pursuit of curative treatment/therapies, in particular gene therapy for thalassaemia has been the core of TIF's mandate that led to the establishment of TIF by a handful of patients/parents and doctors back in 1986.

[1] *The Thalassaemia International Federation (TIF) is a patient-oriented non-profit, non-governmental umbrella federation, established in 1986 with Headquarters in Nicosia, Cyprus. Our mission is to promote access to optimal quality care for all patients with thalassaemia worldwide. To-date membership boasts 232 members from 64 countries across the globe. TIF works in official relations with the World Health Organisation (WHO) since 1996 and enjoys active consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017 and the Council of Europe since 2019. Most remarkably, TIF has been awarded, in the context of the 68th World Health Assembly in May 2015, the 'Dr Lee Jong-wook Memorial Prize' for the Federation's outstanding contribution to public health. More information about the Federation is available at www.thalassaemia.org.cy*

[2] *Regions as defined by the World Health Organisation (WHO):*

1. *Eastern Mediterranean Region (EMRO)*
2. *South-East Asia Region (SEARO)*
3. *Western Pacific Region (WPRO)*
4. *Region of the Americas (PAHO)*
5. *African Region (AFRO)*
6. *European Region (EURO)*

Today, TIF through its work, collaborations and networking - in official relations with the World Health Organisation (WHO), the United Nations Economic and Social Council (ECOSOC), the Council of Europe, the European Commission and other important health stakeholders globally - has achieved in bringing patients and parents from all over the world together. The hope of patients with these disorders and in particular transfusion dependent thalassaemia being cured was indeed the link in the chain holding patients together and united and fighting with patience and persistence over so many decades.

We offer these responses to the questions raised in the consultation document, with great concern.

1. **Has all of the relevant evidence been taken into account?**

One comment from the report which causes some concern and indeed surprise, is that despite the description of expert patients and physicians participating the NICE meeting, was the statement on page 6 of NICE referring to TDT as a disorder that had an effect on life expectancy in the past! Conventional therapy provided at its best, by knowledgeable/expert clinicians, able to tailor treatment to individual needs, (see UK and TIF guidelines) and given full adherence of patients to daily treatment, has not blessed us to date with a patient much more than 60 years and is unlikely to do so in the future since patients born all those years ago accumulated tissue damage due to inadequate therapy available in their youth. Likewise, the younger generation of patients, born in the era of improved monitoring, multidisciplinary care and more convenient iron chelation, have never been shown to be complication free.

Even though it is expected that their prognosis may be better, years of life lost and years lived with disability are still a major concern. Tissue damage due to free iron (not protein bound) occurs as soon as any given iron chelating agent is not present to 'mop up' these free iron radicals. This is not simply because patients are not adherent but that chelation itself needs very careful management which is difficult to sustain on an everyday basis over the many years during which patients are expected to integrate into society, get educated, work, pay taxes and get married taking responsibility for their own and others' lives. Damage to organs still occurs even though reduced, in more recent years, cardiac deaths are still a cause of death even in the UK.

From the consultation document, it is not clear that evidence was received or appropriately considered from heart and liver specialists.

Liver damage and hepatocellular carcinoma for example are on the increase along with other malignancies in thalassaemia patients (both TDT and NTDT). The most recent analysis of UK data includes 612 TDT patients (this cohort is around 60% of the thalasaemia population in the UK). The 10 year crude mortality rate is 6.2%. If compared to the age/sex adjusted death rate in the general population, which is 1.2%, this

suggests that even in a country offering optimum conventional care there are unmet needs for these patients and a ‘normal ‘ life span is not supported (Jobanputra M et al. BJH 2020). In this analysis the complication of TDT in the UK were shown to occur in more than one third of patients, including endocrine disorders (excluding diabetes) 40%, osteoporosis 40%, and diabetes 34%. Cardiac disease was observed in 18% of patients overall, with atrial fibrillation and heart failure being the most common with a prevalence of 11% and 9%, respectively.

From the consultation document it is not clear that the reduced quality of life caused by the pain of bone disease, disability caused by heart disease, additional daily treatments of insulin and other hormones, have been adequately considered as a need for a curative therapy in the NICE analysis. Any illusions that today’s treatment will allow for a life expectancy of 75-80 years must be dispelled. Any thought that improvements in treatment that are not curative can allow ‘normality’ as experienced by people free of this condition, is not acceptable.

A UK patient, member/lead of TIFs Patients’ Advocacy Group mentioned that:
“Every year, at least 17 days are lost for transfusion, 17 days for blood tests, 5 days for other tests and many other days for additional visits and tests related to medical comorbidities such as diabetes, heart, liver, bone, fertility problems while many and multiple challenges to productively integrate in society are most of the time left in the “invisible” part of the story”

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

The progress in the clinical management of these disorders achieved through the years and particularly since the 1970s, has been truly impressive and unquestionable. This has contributed significantly in those countries which have developed national control programmes such as UK, to converting a childhood, fatal, genetic disease into a chronic one, with many expectations, on behalf of the patients, and with anticipations of living longer, growing well, ageing, integrating productively and fully into society and generally living a “near” normal life while, however in expectance of the total cure.

The UK has contributed in particular to the global understanding and treatment of thalassaemia with its clinical, academic and research work immensely including the development of the first ever standards of care and Guidelines in collaboration with TIF, which have been adopted through the years, by most ‘affected’ countries around the world.

We note that NICE criteria of cost effectiveness is currently under review and, in the spirit of UK Government and NICE commitments to make greater use of data analytics and real-world evidence and in keeping with the NHS' goal of providing more rapid access to new technologies to more patients, **we urge the committee to set a review date once these standards have been agreed. In the interim, we support the view that patients' perception and experience is an essential element of cost effectiveness considerations, which cannot be considered appropriate if they are inflexible.**

TIF, following the conditional approval of the European Medicines Agency (EMA) of the first gene therapy product under the name Zynteglo®, asked the patients' and their families' thoughts and perspective on this cure that has finally become a reality, through a survey sent across continents. Of the 849 respondents, 53% of parents on behalf of their children, and 56% of patients across all ages, would accept to undergo gene therapy now (if they met the criteria). Only 19% of patients and 10% of parents respectively with thalassaemic children would not accept this treatment, while the rest, adopted a wait and see attitude (https://thalassaemia.org.cy/). In view of the fact that this is a new advanced therapy the overall response is a positive one with a degree of uncertainty and not unjustly on the part of a small percentage of patients and parents. Limiting factors are of course the cost and the availability, which all patients are aware of but are hoping for those governmental actions and commitments that would allow access to those who wish or need to go through it.

Gene therapy is the potential cure from which many patients can benefit, as compared to HSCT which can only benefit a minority. Gene therapy has been a key theme discussed in every TIF conference since 1986, where scientists explained how research was progressing and how this innovative therapy would work rendering patients transfusion independent, free of iron induced complications, free of the need for daily treatment and regular monitoring. In fact, the understanding of all patients was that gene therapy has the potential of converting a chronic patient to a non- patient i.e. an individual that is no longer a patient and one who can assume full integration in the community. Freedom from disease and a quality of life equal to the general population, may sound as an overambitious dream but it certainly has been a long awaited final conclusion to a life of uncertainty and usually unwanted outcomes.

It is exactly this reliance on governmental support and understanding that is challenged by the NICE consultation and has led to a great disappointment in the global patient community and first of all to the UK patients. The UK government is, through this report, being advised by its experts not to provide this choice and not to support those patients who may wish to undergo this curative treatment.

Whatever, shortcomings gene therapy may have in these early days, is a potentially curative treatment that patients must be given the possibility to choose. Many of the patients who wish to be cured, in the absence

until now of any other curative treatment, their only choice is HSCT which is far more dangerous and carries many and multiple risks. They all have a good reason to make this choice.
It is our submission that the limits of the data available in respect of the therapy under review is part and parcel of its innovative nature as a therapy targeting the cure of a rare disease. The consultation document questions whether transfusion independence is sustainable and whether there will be any long term adverse events since only few patients have reached even a 5 year post treatment follow up. However, in this context, questions arise on some of the points raised in his report, mainly by patients but also physicians:

- HSCT is a long time approved medical procedure. One may ask on what evidence was this procedure approved when Drs Thomas and Lucarelli initiated this treatment for thalassaemia. It was indeed at a time when thalassaemia was almost universally a lethal disease in childhood. On the other hand in the best of circumstances still at this time, it carries with it 5-10% mortality and if we include older age groups, those where matched unrelated donors are used and even haploidentical donors are used then mortality may reach 20% in the best of hands and morbidity even higher. Yet these are approved by regulatory authorities. These curative interventions are indeed cheaper than gene therapy but are they safer and cheaper in the long term considering successful results?
- When faced with the cure of a lifelong disorder how valid is the question of cost-effectiveness? The term cure, may be challenged, because of inadequate long term follow up of many patients; but since a few seem to have been followed over some years, then the assumption that others may also be finally cured is not unreasonable or unanticipated, even if such an outcome is not universal (HSCT is also not applicable to all patients).
- What or how long is long term follow up for expert committees to be satisfied on outcomes? Another 5 years of the small group that has been treated in the trials? 10 years? Unless we allow more 'volunteer' patients to be treated this question will still rely on an inadequate number. **It is not clear from the consultation document what criteria data will be required to meet for further consideration.**
- When cost of conventional treatment is being considered, blood transfusion and iron chelation are the main elements. The cost of annual MRI, cardiac assessment, daily insulin, specialist consultations, endocrinology test and hormone replacement, dietary supplements are usually forgotten.

<u>Last but not least</u>

3. **Are the recommendations sound and a suitable basis for guidance to the NHS?**

   ✓ The statements about current life expectancy by NICE are not based on clear data. Malignancy and chronic organ disease (eg liver) is being seen increasingly in older thalassaemia patients

and there is virtually no quality evidence about morbidity and mortality above 60 tears of age. It would be helpful if NICE could formulate a clearer opinion about the evidence for current expectations with conventional therapy or made it clearer what further information could be available to better inform future appraisals.

- ✓ Very few patients are able to maintain the required frequency of chelation, transfusion and monitoring throughout a lifetime. This impacts on negatively on morbidity and mortality. It is far from clear that life expectancy with thalassaemia using non-curative therapies will approach normal values.

- ✓ The very long term risks of this form for gene therapy will not be known by definition until the very long term- but patients should not reasonably be denied curative therapy in the meantime if it is shown over a reasonable period to be safe and effective. Data are available up to 5 year with Zynteglo or closely related approach. It would be helpful of NICE could give a clearer vision of what the 'long term' realistically means. If all new treatments were to be withheld until very long term follow up were available (beyond 5 years) , it is doubtful whether new treatments could be developed. Therefore can NICE be clearer about what period of follow up would be reasonable before approval could be given by NICE.

It is our respectful submission that, on the basis of our submissions under headings 1 and 2 above, the recommendations are not sound and suitable bases for guidance. Specifically, we request that the committee:

- Ensure input from specialists is included in evidence reviews, in respect of additional complications for patients;
- Location-specific data is consulted on application of standards of quality care and equality of access across the UK; and this is supplemented by
- Life-expectancy calculations noting location-specific trends, and proximity to specialist centres such as in London and in Manchester.

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid discrimination, disparity or inequalities?**

It is our submission that in the current climate and growing sensitivity to health inequalities, the guidance should be carefully reviewed. The report conclusions appear to be based on an overall picture for the United Kingdom, and neglects significant disparities in standards of treatment and inequalities of access to

optimal care within the UK's regions, which subsequently affects life expectancy. Our members work with bodies within the UK to promote standardised treatments, and are acutely aware from their own member patients and families of the tragic loss of life resulting from these disparities. It is not, in our submission, accurate to state that current treatment for is sufficiently accessible to all TDTs in the UK such that the curative therapies are not necessary to consider. In a climate of growing sensibility to health inequalities, we are surprised to read that the committee considers that standards of care are equal and adequate across the UK.

- In the UK and most of Europe these disorders are found in ethnic minorities and rarely in indigenous people. Does this affect judgment and prioritization on national health agendas?
- In the UK and in other countries of Europe, haemoglobin disorders are still in the extremely rare category, receiving theoretically optimal treatment to sustain life long uncomplicated health states, even though many patients live far from expert centres and may not be benefitting.
- While persons of south Asian origin are a large proportion of those affected by thalassaemia in the UK, there are many patients from a range of other backgrounds. **We note with serious concern that the focus on stigma in south Asian communities forms the bulk of the committee's observations in this regard, without further reference to comorbidities and implications on standards and access to quality care within this and other minority ethnic groups.**

These are some questions, not meant to challenge the consultation but they do arise in patients minds and need to be addressed. The real disappointment is that the consultation makes no reference to allowing patients to decide, or to support those who wish to undergo treatment but leaves all with an unqualified denial of support. The question that arises is whether this committee can take away the hope of the possibility of a cure of a lifelong disorder, even in the presence of today's uncertainties and concerns about results over time, when no time limit is provided to draw reliable conclusions. Unless patients go through this treatment and are closely and long term followed up, how will we ever know? How will we ever take advantage of such a remarkable scientific achievement for the benefit of the patients who have been hoping and wishing for years to be cured? If there is no recognition by the Government of this basic right to be given the choice, then we are certainly dealing with violation of rights. If there is no support how can a patient make the choice. **In this regard we respectfully submit that - although the consultation was theoretically open to a range of stakeholders including the public – the consultation document is complex, technical and not easily accessible to the average patient in the UK. In order to genuinely canvas such opinion, we would request that consultation documents are summarized in an accessible manner and sufficient time is granted (the current consultation has been open for less than one month)**, **for informed and meaningful responses. We therefore request that the initial consultation window is extended.**

Conclusion

While we recognize that there are complex considerations at play, we sincerely hope that these do not impact the prospects of thalassaemia patients in the UK of benefiting from cutting edge treatments.

TIF can assure the eminent members of NICE that **the dream and hope for EVERY patient wherever he/she many live, was, is and will be the total cure and this comes with the Gene Therapy**

We at your disposal for any further information, clarification or interaction.

On behalf of the Board of Directors of Thalassaemia International Federation (TIF) and
TIFs Medical-Scientific Advisory Board

Panos Englezos
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