

DELIVERABLE 5.5 ASSESSMENT OF RHD GUIDELINES AWARENESS AND IMPLEMENTATION 2

ERN-EuroBloodNet European Reference Network on Rare Hematological Diseases

EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

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Short Description

Report on results from the survey conducted to assess the state of the art of Transcranial Doppler screening and stroke prevention programs in European Expert Centers

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1. INTRODUCTION

RARE DISEASES GUIDELINES IMPLEMENTATION: GAPS AND NEEDS

“There is probably no other area in public health in which 27 national approaches could be considered to be so inefficient and ineffective as with rare diseases (RD). The reduced number of patients for these diseases and the need to mobilise resources could be only efficient if done in a coordinated European way.” – European Commission COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02).

It is well known that the field of RD suffers from a shortage of medical and scientific knowledge. For a long time, doctors, researchers and policy makers were unaware of RD and until very recently there was no real research or public health policy concerning issues related to the field. There is no cure for most of RD, but the appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy.

Clinical Practice Guidelines (CPGs) and other Clinical Decision Making Tools (CDMTs) have been developed during last decades to assist practitioners and patient decisions about appropriate healthcare for specific conditions, however, given the low prevalence of RD, few of them have been addressed to the management of these conditions. Despite the efforts performed in the last years to increase the number of CPGs and CDMTs covering RDs, up to date they are still few and most of them difficult to find.

On the other hand, it is well known the important differences on the level of practical implementation of the available guidelines among Member States (MS), and even among healthcare providers in the same countries. Nevertheless, there is no a systematic procedure to evaluate their real translation into clinical practice that would help to promote those CPGs and CDMTs poorly implemented while ensuring their impact in patients' quality of life.

SICKLE CELL DISEASE PEDIATRIC PATIENTS: RECOMMENDATIONS AND CHALLENGES

Children with sickle cell disease (SCD) are at increased risk of cerebrovascular events such as stroke, silent infarcts and neurocognitive impairment. The role of Transcranial Doppler ultrasound scanning (TCD) to identify sickle cell anemia (SCA) children at high risk of stroke is well established.

Adams et al. demonstrated in 1998 that a first stroke could be prevented by monthly transfusions in children with abnormal TCD findings and recommended those with abnormal cerebrovascular flow velocities are offered prophylactic blood transfusion therapy to prevent stroke between ages 2 to 16 years.

Therefore, TCD screening for stroke prevention in now is a mandatory in all guidelines for the management of children with SCA. An example of the inclusion of these recommendations are [ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children](#) that can be found at the [ERN-EuroBloodNet repository of Clinical Practice Guidelines \(CPGs\) and Other Decision Making Tools \(CDMTs\)](#).

However, there is still no uniform implementation of the program globally and in European countries (Rees 2016). Moreover, the information available on the quality of the TCD screening is limited to educational experiences in a few countries (Inusa 2019) but to evaluation of stroke prevention programs has been performed in Europe.

As more disease modifying therapies become available for children with SCD, it is mandatory to know TCD availability, screening practices, and real-world data on stroke prevention in Europe.

2. OBJECTIVES

A European mapping exercises on highly specialized procedures has been conducted in collaboration with ERN-EuroBloodNet experts for the identification of TCD availability for SCD pediatric patients aiming to:

- Assess the state of the art of TCD screening and stroke prevention programs in European Expert Centers
- Identify issues related to the lack of access, lack of training for staff, lack of adequate protocols for implementation of TCD and treatment afterwards, etc, which could be addressed through dedicated actions in the network.

3. METHDODOLOGY

DEFINITION

For the conduction of the mapping exercise an online survey was designed in collaboration with an international ERN-EuroBloodNet expert team dealing with SCD pediatric patients including: Raffaella Colombatti (MD, Pediatrician, AO Padua, Italy), Maddalena Casale (MD, Pediatrician, AOU - Second University - Naples, Italy), Daniela Cuzzubbo (MD, Pediatrician, Ospedale Pediatrico Meyer Firenze, Italy), Corrina McMahon (MD, Pediatrician, Children's Health Ireland, Ireland), Mariane de Montalembert (MD, Pediatrician, Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, France), Vincenzo Voi (MD, Pediatrician, AOU S.Luigi Gonzaga, Italy)

Survey is focused on addressing key parameters on the TCD screening and stroke prevention programs for the identification of gaps on their implementation.

Questions defined are focused on the inclusion of TCD as part of annual standard of care, availability of specialized team for the performance of this highly specialized procedure, methodology and protocols followed, as well as difficulties found for the implementation of the TCD.

Additional questions on number of patients and % with TCD performance on annual basis, as well as the decision making process for the initiation of transfusion or other therapies and target are also included.

Survey was implemented in Google drive and tested among the team. Final version of the questionnaire was released based on feedback from real testing by experts. Full questionnaire is available in **Annex I. ERN-EuroBloodNet European mapping of Transcranial Doppler availability for children with sickle cell disease.**

CONDUCTION

The mapping exercise was launched in February 2021 with an introductory letter of the exercise explaining the main objectives and including the link to the survey to ERN-EuroBloodNet members representatives, substitutes and experts from their multidisciplinary teams and scientific societies of hematology.

The exercise was opened during one month through [dedicated pieces of news](#) for ERN-EuroBloodNet website and distributed through ERN-EuroBloodNet dedicated Newsletter and communication channels (Twitter, LinkedIn). Survey was also disseminated through the [Belgian Hematology Society website](#) (Fig 1)

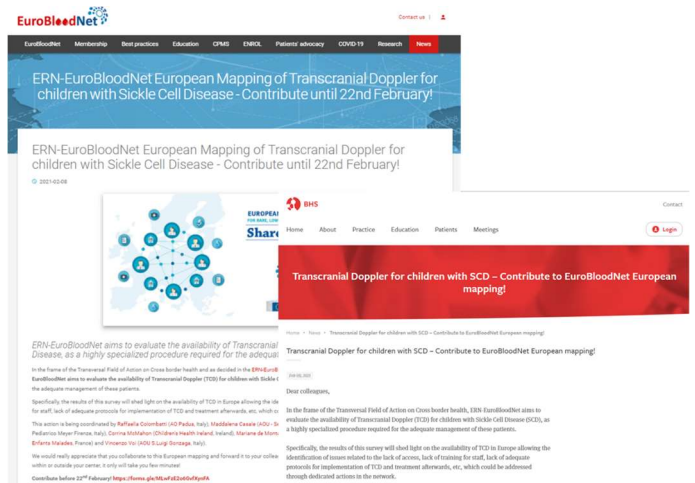


Fig 1. Dissemination of the mapping

4. RESULTS

81 hematologists or pediatricians from 77 centers in 16 European countries responded to the survey (14/16 in Western Europe). 51% of the participating centers were ERN-EuroBloodNet members and affiliated partners, while the 18% were under the process of being recognized as full members. Age coverage of the centers included only pediatric (24%), only adult (3%) or both (58%). Moreover, 12 centers concentrated more than 200 patients currently in follow up in the age range 1-16 years, and 16 centers between 101-200 patients, representing big centers in terms of number of SCD pediatric patients (Fig 2)

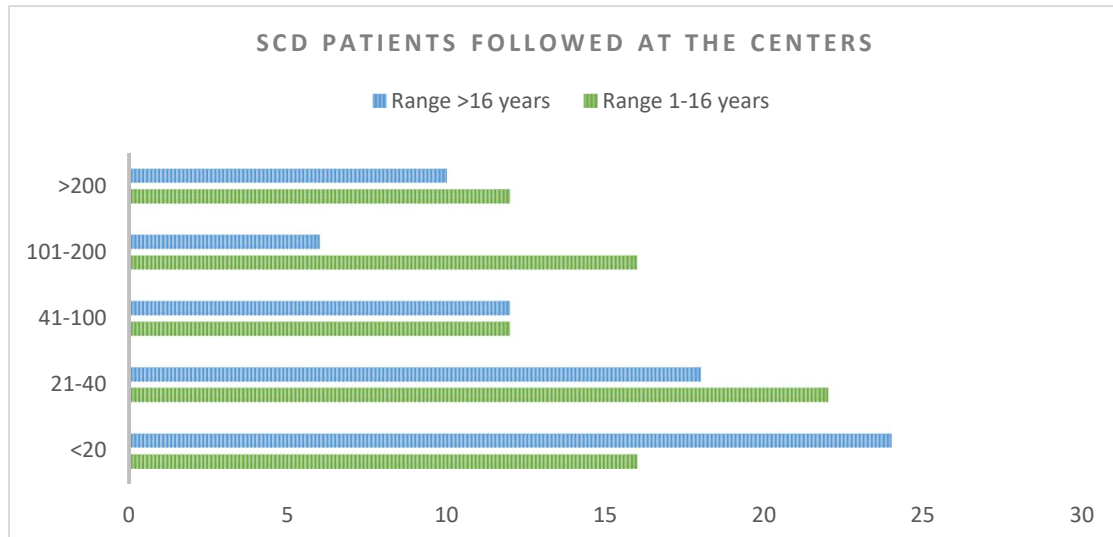


Fig 2. Number of centers concentrating >200, 101-200, 41-100, 21-40 or <20 patients in ranges 1-16 years or >16 years.

36% Physicians reported not having a dedicated TCD/TCDi service for children with SCD, thus exams had to be performed by cardiologists (10%), general radiologists (28%), TCD is not performed (31%), patients have to be sent in another center (31%) (Fig 3).

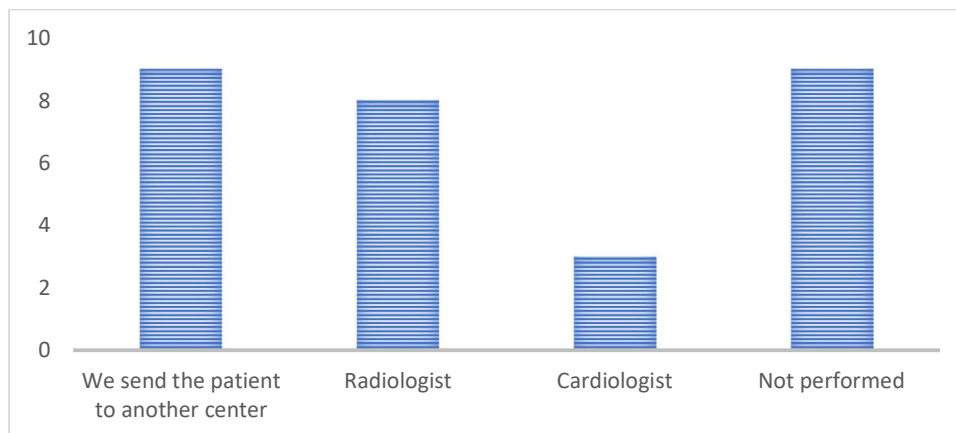


Fig 3. Number of answers gathered on the performer of exams in case of lack of dedicated TCD/TCDi service for children with SCD

74% reported requesting annual TCD for their patients, but to the question “What percentage of your patients receives annual TCD” only 28% confirmed that all their patients managed to actually receive annual TCD, due to lack of trained staff (43%), lack of TCD instruments (11%), refusal of patients due to logistical difficulties (22%) (i.e TCD in another city), lack of funds for dedicated staff or equipment (11%), or other reasons (Fig 4)

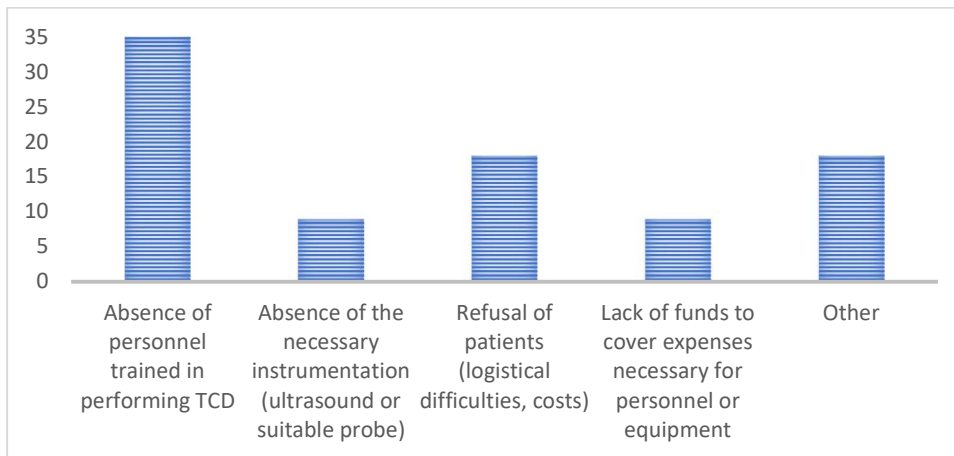


Fig 4. Number of answers gathered on the greatest difficulties in implementing TCD screening in the centers

Only 74% of hematologists were aware of the protocol in use at their center by the staff performing TCD; the STOP criteria were applied by 64% of the physicians, mainly due non evaluation of the Internal Carotid Artery. The extracranial part of the carotid artery was evaluated only in 30% of the respondents.

In case of abnormal/conditional TCD results, the approach varies and is not uniform across centers.

COMMUNICATION AT AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING AND DISSEMINATION OF RESULTS

The abstract "[Limited Access to Transcranial Doppler Screening and Stroke Prevention for Children with Sickle Cell Disease in Europe: Results of a Multinational Eurobloodnet Survey](#)" presenting the results from the mapping was selected to be presented during the American Society of Hematology (ASH) 2021 edition for an oral presentation provided by Raffaella Colombatti (AO Padua) (Fig 5).

Two dedicated piece of news were launched in ERN-EuroBloodNet website and disseminated on the newsletter and social media channels:

- [The results of two projects promoted by ERN-EuroBloodNet will be presented at the 63RD ASH Annual Meeting and Exposition !](#)
- [ERN-EuroBloodNet at the 63RD ASH Annual Meeting and Exposition!](#)

A peer review publication is under preparation.



Fig 5. R.Colombatti presenting the communication at ASH

5. CONCLUSIONS & NEXT STEPS

Despite there are well established recommendations for TCD screening for stroke prevention included in guidelines management of children with SCA, the lack of uniform implementation of the program in EU countries is still a reality, exacerbated by the limited educational experiences for the performance of this highly specialized procedure in the screening context in few countries.

The ERN-EuroBloodNet mapping exercise conducted to assess the state of the art of TCD screening and stroke prevention programs in EU demonstrates that less than 30% of children with SCD followed in European Centers receive annual TCD according to recognized guidelines.

Moreover, this first multinational European survey allowed the identification of issues related to the lack of access to TCD, lack of trained staff and lack of adequate protocols for implementation of TCD and treatment afterwards, providing the evidence needed for the identification of tangible gaps to be addressed through multiple specific actions during ERN-EuroBloodNet next period of implementation, including educational targeted activities (ie. dedicated webinars for health professionals or training actions targeting protocols implementation) and the promotion of the development of Clinical Practice Guidelines (CPGs) or Other Clinical Decision Making Tools (CDMTs) on the area.

ANNEX I

ERN-EUROBLOODNET EUROPEAN MAPPING OF TRANSCRANIAL DOPPLER AVAILABILITY FOR CHILDREN WITH SICKLE CELL DISEASE



DATA ON THE SURVEY COLLECTOR

NAME: _____ SURNAME _____

CENTER _____

COUNTRY _____

ADULT CENTER _____ PEDIATRIC CENTER _____ BOTH _____

Filled in on _____ (format DD/MMM/YYYY)

Is the Center an EUROBLOODNET MEMBER: YES NO

Is the Center recognized by a NATIONAL SCIENTIFIC SOCIETY: YES NO

If YES, which Society? _____

Has the Center a person or a team dedicated to SCD patients? YES NO

1) How many patients with SCD in the age range of 1 – 16 or >16 are CURRENTLY being followed at your center?

Range 1-16 years	Range >16 years
< 20 <input type="checkbox"/>	< 20 <input type="checkbox"/>
21 - 40 <input type="checkbox"/>	21 - 40 <input type="checkbox"/>
41 - 100 <input type="checkbox"/>	41 - 100 <input type="checkbox"/>
101 - 200 <input type="checkbox"/>	101 - 200 <input type="checkbox"/>
> 200 <input type="checkbox"/>	> 200 <input type="checkbox"/>
Other _____	Other _____

2) Does your center include TCD for SCD patients as part of annual standard of care?

YES NO

If YES, do you follow a standardized protocol (e.g. STOP Protocol)?

YES NO DON'T KNOW

If YES, do you ask for TCD (non imaging) or iTCD (Imaging)? _____

If NO, WHY? _____

3) Is there a dedicated TCD/iTCD Unit in your hospital? YES NO

If YES, which staff performs TCD for SCD (multiple options possible)?

- NEUROLOGIST (not SCD expert)
- TECHNICIAN (not SCD dedicated)
- NEUROLOGIST with expertise in SCD
- TECHNICIAN with expertise in SCD
- RADIOLOGIST
- OTHER _____

If NO, who performs the TCD (multiple options possible)?

- HEMATOLOGIST
- CARDIOLOGIST
- OTHER
- WE SEND THE PATIENT TO ANOTHER CENTER

4) Which methodology is available for SCD patients in your center?

- | | |
|---------------------------|--------------------------|
| NONE | <input type="checkbox"/> |
| TCD non-imaging | <input type="checkbox"/> |
| TCD imaging | <input type="checkbox"/> |
| TCD non-imaging & imaging | <input type="checkbox"/> |
| I don't know | <input type="checkbox"/> |

5) FOR WHAT AGE RANGE DO YOU ASK TCD

- 2-16
- 1-16
- 1-18
- All ages
- Other _____

6) Do your patients perform TCD/iTCD in another hospital? YES NO

If YES, how far from your Center? _____
 If YES, who books the appointments?
 The family has to book the appointment
 Staff in our Center Books the appointment
 Other

7) Do all your patient have annually a TCD/iTCD? YES NO
 If not, why? _____

- 8) What is the % of patients who have actually an annual TCD?
- 100%
 - 80-99%
 - 60-79%
 - 50-59%
 - <50%

9) How many TCD/iTCD for SCD does your center perform in a year?

TCD NON-IMAGING		TCD IMAGING	
None, we send them elsewhere	<input type="checkbox"/>	None, we send them elsewhere	<input type="checkbox"/>
1-10	<input type="checkbox"/>	1-10	<input type="checkbox"/>
11-40	<input type="checkbox"/>	11-40	<input type="checkbox"/>
>40	<input type="checkbox"/>	>40	<input type="checkbox"/>

10) Are you aware of the Protocol that is performed at your center? YES NO

If YES, which vessels of the intracranial circle are checked (multiple choices possible)?

<input type="checkbox"/> MCA	<input type="checkbox"/> PCA
<input type="checkbox"/> ICA	<input type="checkbox"/> ACA
<input type="checkbox"/> BA	<input type="checkbox"/> Extracranial

11) Are you aware of the thresholds used by your center to classify the results of TCD?

YES NO

If yes, can you specify (numbers or categories)? _____

10) If a patient is found to be CONDITIONAL, what is the approach in your center (multiple choices are possible)?

- Repeat TCD after 1 month
- Repeat TCD after 3 months
- Repeat next year
- Start Treatment: _____
- Perform MRI&MRA
- Other _____

If a patient is found ABNORMAL what is the approach in your center (multiple choices are possible)?

- Repeat TCD after 1 month
- Repeat TCD after 3 months
- Repeat next year
- Start Treatment: _____
- Perform MRI&MRA
- Other _____

If the patient is LOW what is the approach in your center (multiple choices are possible)?

- Repeat TCD after 1 month
- Repeat TCD after 3 months
- Repeat next year
- Start Treatment: _____
- Perform MRI&MRA
- Other _____

11) Who makes the decision to start possible therapy after the results of the TCD?

- Physician (Pediatrician OR Haematologist?)
- Technician
- Physician Neurologist
- Other _____

12) When do you start a transfusion program?

- never
- in case of abnormal TCD
- in case of abnormal and conditional
- depending on the parents' choice
- Other _____

13) What is the target of transfusion in case a transfusion program is started?

- HbS <30%
- HbS <50%
- normalization of TCD
- Other _____

14) What is the greatest difficulty in implementing TCD screening in your center?

- absence of personnel trained in performing TCD
- absence of the necessary instrumentation (ultrasound or suitable probe)
- refusal of patients (logistical difficulties, costs)
- lack of funds to cover expenses necessary for personnel or equipment
- Other _____
- Comments: _____



https://ec.europa.eu/health/ern_en



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