

Title: IMPROVE QUALITY OF LIFE OF CHILDREN SUFFERING HEMOPHILIA A WITH IMPLEMENTATION THE HAEMOPHILIA EARLY ARTHROPATHY DETECTION WITH ULTRASOUND (HEAD-US) PROTOCOL FOR ROUTINE JOINT ASSESSMENT OF HAEMOPHILIA PATIENTS.

Grant ID 29564761

Main collaborators: Association of HCPs «Ukrainian Academy of Pediatrics», Leonid Dubey

Abstract:

Goal of the project: to implement the HEAD-US protocol in routine clinical joint assessment in patient with Hemophilia A for detection early arthropathy in order to improve quality of life as well as monitoring of management children with Hemophilia in Ukraine.

Target population: the project targeted the healthcare professionals who manage children with Hemophilia (pediatricians, pediatric hematologists, surgeons, and orthopedics).

Methods and assessment: the implementation of project will be organized by the Association of HCPs “Ukrainian Academy of Pediatrics” based on Pediatrics and Neonatology Department of postgraduate faculty of Danylo Galyttsky’s Lviv National Medical University located at the Thrombosis and Hemostasis Centre of the West Ukrainian Specialized Children’s Medical Centre. Approximately 100 (HCPs) will be involved into implementation program across Ukrainian cities.

The program will include lectures, practical classes, articles in medical press, and publications of information and educational materials (brochures, booklets, monuments, etc.) which will cover necessity of implementation, principals and user’s guidelines of HEAD-US protocol in a busy clinical practice.

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C. Reviewer Comments

A few panel members noted that the methods for delivery are well laid out, but the quality framework that you might use is not clear. Please elaborate on the quality framework in your Full Proposal.

The details of design and framework provided in the appropriate sections of the proposal (Project Design and Methods, Evaluation Design, Detailed Work plan and Deliverables Schedule).

The panel noted that no information was provided on how the initiative's impact will be assessed. Please provide details on assessment in the full proposal. In other words, please explain how you will measure the success and assess achievement of each of your goals.

The physicians (hematologists, orthopedists, traumatologists, pediatricians, sonographers) who will study the Hemophilia course at the Pediatrics and Neonatology Department of postgraduate faculty of Danylo Galyttsky's Lviv National Medical University will be involved in this training program (approximately 100). Also, the Hemophilia course will be done in the 4 cities across the year, during learning sessions. Baseline and follow up anonymous assessments (questionnaires) of knowledge among HCPs (attendees of Hemophilia courses) regarding Ultrasound examination and HEAD-US protocol will be provided before, after and in 3 month after training.

The frequency of usage of the HEAD-US at the end of the project implementation will be possible evaluate based on analysis the assessments (questionnaires, mentioned above).

Please provide more details around who will lead the training sessions, develop materials, etc.

Project will be led by Professor Leonid Dubey, PhD, DM's, Paediatric Haematologist, Head of Thrombosis and Haemostasis Centre (certificated by EUHANET as HCCC in 2014), national child haemophilia expert.

The assessments, training sessions, develop materials; post-hoc analysis, scientific articles will be prepared by:

1. Mykhailo Kuziuk, MD, pediatrician, co-founder and organizer of Hemophilia school.
2. Andriy Markin, MD, pediatrician, co-founder and organizer of Hemophilia school.
3. Maryna Sapyzhak, biologist of Thrombosis and Hemostasis Centre.
4. Solomia Lykavetska, MD, sonographer, of Thrombosis and Hemostasis Centre. She engaged CI/MRI/Sonographic monitoring and evaluation of the musculoskeletal system in children with hemophilia. Solomia together with orthopedist involved in reconstructive surgeries for children suffering Hemophilia; constantly training in Europe and Canada.
5. Kozlova Olena, MD, hematologist of Thrombosis and Hemostasis Centre, treats children with disorders of blood clotting; constantly training in Germany and Spain, publishes articles, takes part in the conferences; takes part in Hemophilia school.
6. Bogdan Romanyshyn, MD, orthopedics, surgeon, works with children suffering hemophilia arthropathy; makes artroplastic surgery operations. Focus area: orthopedics, reconstructive and plastic surgery.

All specialists have been trained and obtained huge experience in management children with Hemophilia.

The LOI noted that there will be development of clinical guidelines applied at the bedside. Can you please elaborate on what you mean by "clinical guidelines".

"Clinical guidelines" will be clinical recommendation for healthcare professionals on usage the HEAD-US protocol in daily clinical practice as a part of routine examination children with Hemophilia.

D. Main Section of the proposal (not to exceed 15 pages):

1. Overall Goal & Objectives:

Overall Goal to implement the HEAD-US protocol in routine clinical joint assessment in patient with Hemophilia A for detection early arthropathy in order to improve quality of life as well as monitoring of management children with hemophilia in Ukraine.

Objectives

1. To identify and overcome the barriers of implementation of HEAD-US protocol in routine clinical practice in Ukraine.
2. To develop clinical recommendation on usage the HEAD-US protocol in daily joints assessment in children with Hemophilia A in Ukraine.
3. To increase awareness regarding necessity of early joint assessment with joint sonography among HCPs as well as among parents of children with Hemophilia in Ukraine.

2. Current Assessment of need in target area.

Regular standardized assessment of affected joint has to be provided every 12 months, including ultrasound or MRI, according to Ukrainian Clinical Guidelines of Management children with Hemophilia. Also, US or MRI must be done in case of the acute bleeding. To evaluate the effectiveness of management and estimate the real condition of the affected joint arthropathy in most cases is quite difficult.

There are no attention to pay at the early detection of changes in soft tissue and bone and cartilage changes in guidelines, mentioned above. The reference to HEAD-US is absent at all in it. Ultrasound is considered as a subsidiary independent diagnostic procedure, which can be proceeded only trained specialist in ultrasound examination.

Nowadays, it is the well-known fact that bleeding is mostly self or parents-reported and prone to misclassification. Lundin et al. observed MRI changes in 38% of ankles in children without reported joint bleeds. Even during prophylaxis maintained minimum trough levels of Factor VIII (FVIII)/FIX of 1–2% does not guarantee prevention of bleedings¹. Detection of early blood-induced joint changes may improve monitoring of management as well as quality of life these patients. The possibility of subclinical joint bleeds makes it even more important to monitor treatment by examining joints for early changes in synovial tissue and cartilage.

Surgical treatment require up to 20% of children suffering from severe disease with lesions of the musculoskeletal system. Specialized orthopedic care to children with hemophilia in Ukraine is practically not available. As a specialized children's hospitals and other medical institutions for children has hematologists' conservative hemostatic treatment, without supervision of surgeons and orthopedists, specially trained to work with patients with hemophilia. In the absence of prophylaxis of bleeding complications and surgical rehabilitation in childhood hemophiliacs become severe disabilities, whose surgical and orthopedic treatment unpromising. In Ukraine has become disabled from 80-90% of sick children up to 14 years and 21 years of life - almost 100%.⁷

Take into account this numbers, it is crucial for Ukrainian children with hemophilia to identify hemophilic arthropathy at the earlier stage (implementation the HEAD-US protocol in routine clinical joint assessment) to adjust treatment and start earlier rehabilitation in order to decrease disability and improve quality of life this patient.

Introduce into daily practice ultrasound detection of joints status will provide more objective assessment of findings and increase sensitivity in detecting joint abnormalities. Unified recommendations may help us to detect cartilage changes earlier and decrease level of joints replacement and disability of patients with Hemophilia. These may lead to better quality of life, reduce

expenditures for healthcare, and increase school attendance of these patients, assistance to parents in nursing.

3. Target Audience:

The primary audience targeted the physicians (hematologists, orthopedists, traumatologists, pediatricians, sonografists) who will study the Hemophilia course at the Pediatrics and Neonatology Department of postgraduate faculty of Danylo Galyttzky's Lviv National Medical University will be involved in the this training program (approximately 100). The Hemophilia course will be done in the 4 cities across the year, during learning sessions.

We expected improve quality of medical care the children with hemophilia A and quality of life this children and their parents after implementation HEAD-US. More unified information and knowledge of professionals, parents and patients will increase early detection of hemophilic arthropathy, reduce disability and improve social adaptation of patients and consequently improve the quality of life of children with Hemophilia.

Approximately 50 children, aged 5-18 with Hemophilia A from the west part of Ukraine, will be examined in the Thrombosis and Hemostasis center according to Clinical Guidelines and HEAD-US protocol. We will evaluate how the protocol helps in routine clinical practice, how long it lasts, what prevents routine using and what different between clinical and visual joints changes.

Because children with hemophilia will be enrolled in this project, project lead will be responsible to have prospective approval of the project, informed consent/assent documents, and other relevant documents in the Ethics Committee of West Ukrainian Specialized Children's Medical Centre. Before provide HEAD –US protocol and examination related to the project, children's parents or legal representative, and children older 8 years old, will be asked to sign the ICF and Agreement form prepared for this project and approved by local Ethic Committee. Principal investigator, project lead and all study staff will keep patients' data confidential. All personal identifiable data will be kept with medical documentation at the project's center. Personal data will be linked with the medical documentation by unique identifier number assigned by project lead to each enrolled patient.

In order to provide more objective assessment of findings and increase sensitivity in detecting joint abnormalities and to explore barriers of usage HEAD-US in routine clinical practice we will develop clinical forms of patient's examination which help us to detect cartilage changes, collect number and dose of factor and other results to conduct it into the analysis, develop questionnaire for parents of haemophilia children in order to estimate subclinical joint bleed, adapt the questionnaires of quality of life for children with hemophilia in order to evaluate health-related quality of life, depending on joint status, measure of joint function by using Hemophilia Joint health score 2.1. Developing and collecting this data will give us understanding of changing's in the stain of the patient and it quality of life.

4. Project Design and Methods:

The project will be run by the Association of HCPs "Ukrainian Academy of Paediatrics" based on Pediatrics and Neonatology Department of postgraduate faculty of Danylo Galyttzky's Lviv National Medical University located at Thrombosis and Hemostasis Centre at West Ukrainian Specialized Children's Medical Centre. Professor Leonid Dubey will manage whole project and team. Mykhailo Kuziuk will lead the project (coordinate, collect and compile all data, provide them to statistical analysis).

The project will consist from few stages:

1. Baseline and follow up anonymous assessments (questionnaires) of knowledge among HCPs (attendees of Hemophilia course) regarding Ultrasound examination and HEAD-US as well will be provided before, after and in 3 month after training. The frequency of usage of the HEAD-US at the

end of the project implementation will be possible to evaluate based on analysis the assessments (questioners, mentioned above).

The questionnaires will be developed by our team. Preliminary, the following questions may be included in the questionnaires (as example).

- a) How often performed ultrasound of the joints in a child with hemophilia?
- b) Who performs the USE?
- c) Did they hear something about HEAD-US?
- d) If it is a fast protocol, whether to incorporate it into routine clinical practice as part of a routine check-up?

2. Develop educational and informational materials:

- a) Educational materials of the necessity of using of HEAD-US for physicians.
- b) Educational materials of the necessity of using of HEAD-US for parents.
- c) Special Checklist for physicians in usage of HEAD-US protocol.

3. Articles in medical press of the necessity and recommendations of usage of HEAD-US for physicians, analysis of the results of the implementation program.

Preliminary plan of medical journals in which these articles will be published:

- Hemophilia journal
- Ukrainian Journal "Child's health"

4. Provide trainings, competency evaluation and certification in the use of this HEAD-US protocol by initiating the introduction to the program of training of hematologists:

- Lecture "Hemophilia arthropathy. New way in early diagnostic" will include next parts:
 - Hemophilia arthropathy;
 - Methods of detection;
 - Methods of early detection;
 - Development and definition of a simplified scanning procedure and scoring method for Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US);
 - Necessity of early joint assessment with joint sonography for physicians and parents in order to improve quality of life and management children with hemophilia;
 - Barriers of implementation of HEAD-US in routine practice;
 - Theoretical training of using of HEAD-US in routine practice;
 - Deontological aspects of working with patients parents.
- Practical trainings for:
 - Input and output testing;
 - Examining of hemophilia children on prophylaxis without visual changing's in joints by using Joint sonography of elbow, knee and ankle;
 - Improving practical skills.

5. Identify barriers of implementation of HEAD-US protocol in the clinical practice during study timeline and develop recommendation of their overcoming.

These barriers will be identified in real clinical practice. Approximately 50 children, aged 5-18 with Hemophilia A,B from the west part of Ukraine, will be examined in the Thrombosis and Hemostasis center according to Clinical Guidelines and HEAD-US protocol. We will evaluate how the protocol helps in routine clinical practice, how long it lasts, what prevents routine using and what different between clinical and visual joints changes.

All patients and their parents will sign Informing concern form to participate in this program. This forms will be approved by the Ethics Committee of West Ukrainian Specialized Children's Medical

Centre. All personal information will be encrypted and would be storage only at the project center (for details, see section Target audience).

In case of examination we will:

- Develop clinical forms of patient’s examination which help us to detect cartilage changes. We will also collect number and dose of factor and other results to conduct it into the analysis;
- Develop questionnaires for parents of Hemophilia children in order to estimate subclinical joint bleed;
- Adapt the questionnaires of quality of life for children with hemophilia in order to evaluate health-related quality of life, depending on joint status;
- Measure of joint function by using Hemophilia Joint health score 2.1;
- Developing and collecting this data will give us understanding of changing’s in the stain of the patient and it quality of life;
- Develop special Checklist for physicians in usage of this ultrasound protocol.

6. To develop clinical recommendation of implementation in clinical routine practice the fast track protocol for large joints (elbow, knee and ankle). This recommendation will help healthcare professionals on usage the HEAD-US protocol in daily clinical practice as a part of routine examination children with Hemophilia.

7. Inclusion HEAD-US protocol in Clinical Guidelines of Hemophilia Management (unified clinical protocols of primary, secondary (specialized), emergency and tertiary (highly specialized) care for children suffering hemophilia A and adapted clinical guideline (based on evidence) on the subsequent revision.

8. Present at the National children oncohaematologists association meeting (05.2017, 12.2017) the Implementation HEAD-US in daily clinical practice.

5. Evaluation Design

To assess the effectiveness of the implementation of HEAD-US protocol in routine clinical practice we will conduct a prospective and post-hoc analysis of the assessments of physicians before the start of the project and on its completion.

Based on the analysis, it will be possible to evaluate the frequency of use of HEAD-US at the end of the project implementation.

Developing of a unified clinical recommendation on usage in clinical routine practice the fast track protocol (HEAD-US) for large joints (elbow, knee and ankle), educational materials regarding necessity of early joint assessment with joint sonography for physicians and parents helps to make a standard routine management for children with hemophilia.

6. Detailed Work plan and Deliverables Schedule

	Activity	Deadline
1.	Elaborate the educational materials of the necessity of using of HEAD-US for physicians.	03/2017
2.	Elaborate the educational materials of the necessity of using of HEAD-US for parents.	03/2017
3.	Elaborate the of special Checklist for physicians in usage of this ultrasound protocol	03/2017
4.	Publish articles in medical press of the necessity of using of HEAD-US for physicians and parents, analysis of the results of the work and trainings, recommendation on usage HEAD-US	03/2017-12/2018

5.	Print of all educational materials for trainings	08/2017
6.	Provide trainings, competency evaluation and certification in the use of this HEAD-US protocol by initiating the introduction to the program of training of hematologists: Lecture "Hemophilia arthropathy. New way in early diagnostic	09/2017-12/2017
7.	Outside trainings	09/2017 -12/2018
8.	Develop the questionnaires for physicians	02/2017
9.	Evaluate how the protocol helps in routine clinical practice, how long it lasts, what prevents routine using and what different between clinical and visual joints changes. Examination of patient suffering Hemophilia in the Thrombosis and Hemostasis center according to Clinical Guidelines and HEAD-US protocol.	01/2017-06/2018
10.	Develop inform concern form for patients and their parents and get approval in the Etic Committee.	03/2017
11.	Develop clinical recommendations of implementation in clinical routine practice the fast track protocol for large joints (elbow, knee and ankle)	06/2017
12.	Present at the National children oncohaematologists association meeting	05/2017 12/2017
13.	Include HEAD-US protocol Clinical Guidelines on Hemophilia Management (unified clinical protocols of primary, secondary (specialized), emergency and tertiary (highly specialized) care for children suffering hemophilia A and adapted clinical guideline (based on evidence) on the subsequent revision.	No time limit
14.	Develop clinical forms of patient's examination which help us to detect cartilage changes. We will also collect number and dose of factor and other results to conduct it into the analysis.	02/2017
15.	Develop questionnaire for parents of haemophilia children in order to estimate subclinical joint bleed.	03/2017
16.	Adapt the questionnaires of quality of life for children with hemophilia in order to evaluate health-related quality of life, depending on joint status.	03/2017

E. References (no page limit)

1. W. Foppen et al. Value of routine ultrasound in detecting early joint changes in children with haemophilia using the 'Haemophilia Early Arthropathy Detection with UltraSound' protocol. *Haemophilia* (2016), 22, 121–125
2. Leslie, R. and Catherine, M. (2007), Modern management of haemophilic arthropathy. *British Journal of Haematology*, 136: 777–787. doi: 10.1111/j.1365-2141.2007.06490.x
3. Hemophilia, Musculoskeletal Complications by Ray F DECKilcoyne from [medicines.com](http://www.medicines.com). [Hemophilia, Musculoskeletal Complications/](http://www.medicines.com/Hemophilia_Musculoskeletal_Complications/).

4. M. Sigl-Kraetzig et al. Ultrasonography of joints and correlation with function in Haemophilic Arthropathy - interim results of a clinical pilot trial (HämarthroSonoPilot). European Society of radiology. www.myESR.org
5. Martinoli C. et al. «Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)» <http://www.ncbi.nlm.nih.gov/pubmed/23571706>
6. Martinoli, C., Di Minno, M. N. D., Pasta, G. and Tagliafico, A. (2016), Point-of-care ultrasound in haemophilic arthropathy: will the HEAD-US system supplement or replace physical examination?. Haemophilia, 22: 20–21. doi: 10.1111/hae.12840
7. Order of the Ministry of Public Health of Ukraine from 30.07.2010 #647 Clinical protocol of medical care of patients suffering haemophilia.