

Go-aHEAD - Implementation of the HEAD US Score into Standard of Care in Children and Adolescents with Hemophilia in Germany

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ABSTRACT

Overall Goal: Optimizing treatment in hemophilia care by systematic evaluation of therapeutic interventions on the basis of valid outcome parameters. To this end we will implement the HEAD US scoring system as routine outcome parameter into standard care of hemophilic children, adolescents and young adults in Germany and secure quality improvement.

Target Population: Age from 1-25 years of age, with moderate or severe hemophilia A or B treated in Hemophilia Centers in Germany.

Methods: Quality Improvement Study, Development of target intervention via PDSA cycling. Evaluation of success based on the following outcome parameters: (1) Success of implementation measured by number/ percentage of patients with severe to moderate hemophilia investigated by the HEAD US score in participating hemophilia centers. (2) Quality of ultrasound investigation assessed by intercomparison programmes including assessment of reliability.

Assessment: Currently no easily accessible and valid outcome parameters are available to (i) detect early joint damage and (ii) measure potential changes by repeated measurements. It is imperative to establish suitable noninvasive outcome parameters to compare different clinically relevant therapeutic strategies in children.

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A. Reviewer Comments

Comment 1: “Leasing of Ultrasound machines”

Your proposal includes funding to lease ultrasound machines. While this is acceptable, the panel would like you to provide information in your full proposal related to how you plan to sustain this project once the grant funding ends.

We understand that leasing of high quality machines for the majority of centers would exceed financial support via this grant. We decided not to include funding to lease machines upfront into this proposal as all participating centers have access to high quality equipment. After in depth discussions about which interventions are most needed to improve quality all members of the study group agreed, that personnel both on site and to finance a project coordinator are most important. We will critically investigate this topic during the study cycles.

Comment 2: “Sample Size”

Please explain how you will measure the goal of having 25% of children be investigated with ultrasound at the end of the study period.

4 of the 5 participating centers are level 1 Hemophilia Centers (Comprehensive Care Centers). We calculated around 500 patients treated in our centers and 1750-2000 patients in Germany who belong to the target audience. As we expect high acceptance rates for performing ultrasound, we plan to include referred patients from other centers in Step 2. Finally we aim to initiate up to 5 more centers in Step 3, hence 25% of all eligible patients, a total of 500 patients, is a realistic goal for a Germany wide project.

Comment 3: “MRI validation”

There was some confusion around the MRI validation noted in your submission. Please confirm that this project is separate to what you are proposing to do with this grant funding.

Reply: The MRI validation of the HEAD US score is the basis for this quality improvement project. The two projects address different research questions and are separate with regard to financing.

B. Research Proposal

1. Overall Goal & Objectives

Background: Despite prophylactic factor replacement recurrent joint bleeding occurs in hemophilia patients resulting in long term joint damage, chronic pain and chronic morbidity. Early intraarticular bleedings may be subclinical but may lead to hemophilic arthropathy by a chronic self-perpetuating cycle of hemarthros and synovitis. Detection of joint damage at an early stage is crucial to avoid progression to irreversible arthropathy¹.

Detection of early and subclinical joint damage has been hampered by a lack of methods to assess early joint changes. Given the social and economic challenges there is an urgent need for tools that can screen for the presence of early hemophilic arthropathy. Ultrasound is particularly suited to (i) investigate joint changes from early life on and (ii) perform repeated measurements to study treatment effects in observational studies. A scoring system, the HEAD-US score, has been developed by Martinoli et al. to evaluate joint damage in hemophilia patients by ultrasound following a standardized and simple protocol². Such standardized methods of data acquisition and image interpretation for ultrasound for all age groups are essential for its application in multicenter cohort studies evaluating disease progression and the effect of treatment in interventional studies as well as for early detection of joint damage to guide therapeutic interventions in standard clinical care³.

Alternative methods such as the assessment of pharmacokinetics have been promoted as proxy to assess optimal treatment. Factor levels do not necessarily correspond to joint damage, however, and individual differences in bleeding risk confound the relationship between pharmacokinetics and long term outcome. Therefore pharmacokinetics guided treatment cannot solve the problem.

During the last years educational programs have been established teaching this standardized ultrasound scoring system to healthcare providers in all major hemophilia centers in Germany. However despite the effort both in teaching and learning standardized ultrasound evaluation of arthropathy has not entered standard of care so far^{4,5}.

Goal: To improve the long term health of children and adolescents with hemophilia and optimize treatment efficacy screening for subclinical bleeds via regular ultrasound and herewith motivate treatment adjustments.

To this end we aim to successfully implement the HEAD US scoring system, a simple ultrasound joint score, into standard of care of hemophilic children and adolescents in Germany. We plan to establish it as an outcome parameter for repeated investigations, study its value and if appropriate adapt the method to optimize acceptance, reliability and validity.

Learning and teaching programmes on ultrasound assessment have been undertaken to promote this technique. Still, we need to systematically improve quality and evaluate the impact our interventions have on (i) frequency of children investigated by ultrasound and (ii) the quality of investigations achieved⁶.

This project perfectly fits into the guiding principles of the Charité University Center to “translate current knowledge not only to provide the best possible care and

support, but to meet the individual needs of our patients.”For the complete guiding principles see https://www.charite.de/en/the_charite/about_us/principles/ This project will be embedded in the National Cohort on PUP hemophilia curated by the National Society for Thrombosis and Hemostasis (GTH). The working group has defined the goal to thoroughly observe and critically evaluate different treatment strategies in children with hemophilia to optimize care and avoid unnecessary financial burden for society. This goal can only be achieved if we manage to implement valid and easy accessible outcome parameters into care.

Objectives

1. To assemble a consortium of interdisciplinary specialists in (i) ultrasound, (ii) pediatric hemostaseology and (iii) health services research dedicated to improve care in children with hemophilia.
2. To enhance a training and certification system to specifically train healthcare providers to use the head US scoring system in children.
3. To establish centers of expertise spread over Germany, using identical or comparable high standard equipment and techniques.
4. To establish a standardized blinded reading at a central site to supervise quality and reliability of the technique in different hemophilia treatment centers.
5. To implement the HEAD US scoring system into standard care of hemophilic children and adolescents.
6. To evaluate the suitability of the HEAD US scoring system for children of different age groups.
7. To adapt the scoring system for evaluation of arthropathy in children if appropriate to optimize validity and feasibility.
8. To translate the gain of knowledge and practical skills on ultrasound assessment of hemophilic arthropathy to improvement in clinical care.

2. Current assessment of need in the target area

During the last years training systems for healthcare providers have been developed in Europe. In Germany, until now, physicians of all major hemophilia centers have been trained in the HEAD-US ultrasound method by this training system. This means that both trainer and clinical physicians of the corresponding hemophilia centers have already made clear that there is strong need for objective and easy accessible methods to assess treatment efficacy and health in hemophilic patients. The training performed during the last years has been evaluated as excellent, participation of the workshops was high. Still, the transfer from learning to implementing the technique to clinical practice has not been successful so far. Michael Sigl Kreatzig (Principle Investigator), supported by trained colleagues as Natascha Marquardt (Coinvestigator) have performed ultrasound investigations in more than 200 children of all age groups by visiting hemophilia centers all over Germany, however they have not managed to turn the probe over to regional centers of expertise.

Michael Sigl Kraetzig, principal investigator of this study proposal, has performed interviews in 15 pediatric hemophilia centers in Germany from 2015-2016. Until now only one center has implemented the scoring system into routine assessment of patients so far (MSK, Ulm), two centers occasionally perform ultrasound (Bonn, Stuttgart). No repeated measurements in individual patients have been undertaken so far in pediatric hemophilia centers in Germany. Major reasons given in the qualitative interviews have been (i) lack of high quality ultrasound devices as point of care devices (3/15), (ii) no opportunity for feedback and regular training to improve the own skills resulting in low quality (13/15), (iii) time restrictions (14/15), (iiii) no prioritization for ultrasound investigations (12/15). Moreover centers criticized that until now there exists no framework, no observational studies to systematically evaluate efficacy of treatment interventions in Germany.

The gap widens even further when we look at the emerging field of treatment options. During the last years the treatment landscape has dramatically changed with half-life extended entering the market, products with alternative mode of action or gene therapy reaching clinics within the next years. Individualized therapy has become the magic formula of optimal treatment, also in hemophilia care. For treating children on the highest standard we need to know what we are doing. To this end we need to establish valid and standardized outcome parameters in German pediatric hemophilia centers to be able to compare different treatment strategies.

Traditionally hemophilia patients are treated all over Germany, both in private praxis and large academic centers. Expert opinion guides treatment decisions in most of the cases and places. Apart from major bleeds no outcome is systematically assessed in daily practice (personal communication working group on pediatric hemophilia, Pediatric GTH, 10/2016). Both academic opinion leader and health insurances become increasingly aware of the differences of treatment strategies between centers and support the idea to establish Centers of Excellence in Pediatric Hemophilia Care and critically analyze therapeutic interventions. This year a German wide working group on hemophilia care has been formed, curated by the German Society of thrombosis and hemostasis to increase quality of care of pediatric patients. CK is speaker, MSK and SH are active members of this working group, with a special focus on implementation of outcome parameters in this observational study.

Within this quality improvement project we first would establish and certify five centers of excellence for outcome assessment via ultrasound. Centers of excellence would need to fulfill defined quality standards both in clinical expertise as well as in technical equipment, would be obliged to participate in biannual intercomparison programmes to become a certified Center. We would distribute centers over Germany to avoid long distances to enable annual investigations of joint damage via ultrasound.

3. Target audience

Target audience are all children, adolescents and young adults from 0-25 years of age with moderate to severe hemophilia A or B treated in Hemophilia Centers in Germany.

(STEP 1, patients of Hemophilia Centers Bonn, Frankfurt, Heidelberg, Ulm-Blaubeuren, Berlin// Step 2 additional referrals from other hemophilia centers of the region// Step 3 certification of additional centers).



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Head Christoph Koenigs
Category Comprehensive Care Center

Hemophilia Center Blaubeuren-Ulm
Head Michael Sigl Kraetzig
Category Hemophilia Treatment Center

Participating Centers of Expertise

Standard of care includes quarterly to biannual assessment of bleeding history and clinical investigation. Compliance is high in general, clinical assessment is linked to the supply with factor products in the majority of treatment centers. Patients and their parents will be informed about the procedure in preparation of a routine visit.

We expect a significant direct benefit for patients and parents: The majority of parents or older children highly valued the systematic and objective examination of potential joint damage. Moreover thorough investigation of major joints might influence patient reporting on complaints or history of overt bleeds.

Treatment changes related to results of the HEAD US score should be handled with care as the predictive value of early joint changes and chronic joint morbidity have not yet been determined. We plan to implement regular outcome measurements to be integrated into routine assessment of hemophilia patients. Once established we will gain insights and experience, this will change treatment care in hemophilia allowing for earlier and individualized adjustment of treatment intensity. Therefore all children with moderate to severe hemophilia may benefit from the project.

4. Project design and methods

Our project is designed as a quality improvement study. To this end we plan to study the factors that influence the full and effective use of the HEAD US Scoring system in practice, to overcome the obstacles and to establish effective structures.

The outcomes analyzed are:

1. Implementation success rate: Number of patients in whom the HEAD US score is performed (relative to total number of patients of the target audience, absolute values per center).
2. Quality of standardization of the HEAD US method: Interrater reliability between investigators and centers.

We plan to supervise our implementation strategy by biannual cycling rounds of the study team to critically evaluate feasibility and appropriateness of the implementation strategy and adaption of the process. We follow the PDSA (Plan-Do-Study-Act) cycling strategy steps. PDSA steps are conducted over a minimum of 3 cycles designed to discover and solve problems and hence make the implementation process a success. Systematic evaluation of measures of agreement (Inter-rater reliability, intra-rater reliability). Performance of regular, at minimum biannual inter comparison programmes, between participating centers.

We address the pre-defined needs as follows:

Need for equipment will be addressed by defining quality standards for ultrasound devices and supporting financing via leasing contracts for the duration of the project. During the study period we plan to negotiate reimbursement with health insurance companies resulting in financing of ultrasound devices for routine practice.

Need for time capacity and financial resources to prepare for regular ultrasound investigations, training and supervision will be addressed by (i) refunding of the expenses for travel costs for group meetings. Moreover (ii) a lump sum will be paid to every center meeting the standards defined by our working group on requirements.

Need for comparability and standardization between centers will be addressed by development of standardized age dependent ultrasound protocols in the participating Centers of Competence and blinded assessment via a central reference center by a second set of eyes.

Need for regular training and feedback will be addressed by (i) regular in site training courses (ii) blinded assessment via a central reference center by a second set of eyes and (iii) regular, biannual, intercomparison programmes.

Need for sustainability to assess long term changes via repeated measurements. The consortium is responsible for the implementation of the HEAD US score as outcome parameter in the German Registry for Previously Untreated Patients (GEPHARD) and clinical trials evaluating new treatment strategies. We have the full support of the GEPHARD steering committee, see letter of commitment.

This project is original. For the first time a German wide network will be composed by an interdisciplinary team of clinicians, pediatric radiologists and clinical epidemiologists from major pediatric hemophilia centers with the specific focus on implementation and advancement of an objective outcome parameter into routine care of hemophilic patients.

We plan to implement standardized ultrasound assessment both as point of care method in daily routine and as an outcome parameter in research projects as the

German Pediatric Registry of PUP of the German Thrombosis association (GEPHARD) and clinical trials.

Previous work: (1) During the last years Michael Sigl Kraetzig and his team have continuously assessed hemophilic arthropathy in pediatric patients at all major hemophilia care centers in Germany and herewith have been able to optimize age dependent assessment. Moreover he has established a two-step teaching system for health care professionals on the HEAD-US score. All participating collaborators have already been trained by Michael Sigl-Kraetzig. (2) Natascha Marquardt and Peter Staritz are qualified to work on the level of an instructor for the HEAD US score. Natascha is currently preparing a manuscript on the single center experience in performing the HEAD US Score in hemophilic patients.

(2) Susanne Holzhauer and her team at the Charité, Children's Hospital are currently comparing the HEAD US score with MRI to validate the score to measure hemophilic arthropathy. This validation study is essential to implement the score to clinical practice and potentially replace MRI techniques.

5. Evaluation design

We will establish regular biannual meetings and a reporting system evaluating the success of the intervention and eventually adapting the programme using the following metrics:

- (1) Number of patients in whom the HEAD US has been performed per center related to patients treated in that center, data are reported to the study central at time point one.
- (2) Delta/amount of change of patient numbers investigated in 6 monthly intervals. We expect to investigate a minimum of 50% of patients treated at that center at 12 months duration of the study.
- (3) HEAD US score of patients investigated.
- (4) Reliability assessment via biannual ultrasound intercomparison programmes
- (5) Structured interviews with health professionals participating in the teaching programs on acceptance of teaching strategies and of the HEAD US Scoring system.

Project outcomes on implementation and teaching will be published as health service science project. Moreover, implementation of the scoring system as outcome parameter for research projects will enable publication of results in peer reviewed journals.

6. Detailed Workplan and Deliverables Schedule

	01-06/2017	07-12/2017	01-06/2018	07-12/2018
Standardization of technical devices per center				
Development of standardized protocols for HEAD US in different age groups				
Consensus on teaching and certification standards				
Teaching of 1-2 staff members per center				
Setup of a database with regular reporting of HEAD US score.				
Quality assessment via reliability testing/intercomparison programmes				
Collection of data , analysis of data Every 6 months				
Apply for financing via health insurance				

C. References

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