SSC Subcommittee Project/Collaborative Project

Hemophilia Carrier Nomenclature: Proposed terminology to improve communication

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- Person responsible (Chair / Principal Investigator)
    - Robert Francis Sidonio, Jr. MD, MSc.
- Design
    - Narrative review and expert opinion
- Aim/Objective/Rationale (Needs assessment / Reason)
    - Rationale: There is no formal terminology to apply to hemophilia A and B carriers regarding whether they have normal (>50% FVIII/FIX) or deficiency in the mild, moderate and severe range creating confusion in academic discussion and conveying data to the consumer population. Furthermore, there are limited guidelines on how to approach and manage those patients.
    - Objective: To propose terminology and a conceptual framework for categorization of hemophilia A and B carriers accounting for personal bleeding history, genetic determinants and baseline factor level which will ultimately improve communication between providers, researchers, payers and community members.
        - Aim 1: To characterize the bleeding tendency in hemophilia A and B carriers and challenges in receiving medical care and meeting the needs of this population.
        - Aim 2: To standardize terminology and categorization of hemophilia A and B carriers with and without normal factor levels.
        - Aim 3: To identify the strengths and limitations of proposed terminology and assess the potential impact of change in the nomenclature.
        - Aim 4: To determine the role of a bleeding assessment tool in the diagnosis and management in hemophilia A and B carriers.
- Methodology (Data expected to collect, sample size and statistical analysis):

- This will be a narrative review, thus we will gather and summarize empirical evidence and synthesize and harmonize with expert opinion to determine a rational conclusion. Because the level of evidence will be likely no higher than level IIa (well designed controlled study without randomization) and the majority will be level IIb (well designed quasi-experimental study) and level III (well designed non-experimental descriptive studies), a narrative review is appropriate. Statistical strength will be assessed but with limitations as this will be a narrative review.

- Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):
  - Utilizing the framework of the Cochrane Database of Systematic Reviews with aforementioned limitations, we will construct and execute a MEDLINE database search utilizing various MeSH terms for pediatric and adult hemophilia carriers limiting date search to 1980-2017 in English, Dutch, French and German evaluating RCTs, Meta-analyses, Controlled clinical trials, Epidemiologic studies, Prospective studies, Multicenter studies, Clinical trials, Practice Guidelines, Reviews, Multicase reviews, Technical reports, Validations studies, Case reports, Journal articles (Letters to the Editors, Communications, original articles). We will grade the level of evidence using the NHLBI system.

- Expected timeline:
  - Project stage/set up
    - Phase 1: Meet to discuss outline and agenda and goals and assign members work.
      - July 2017
    - Phase 2: Perform and synthesize literature systematic review
      - August - September 2017
    - Phase 3: Meet to propose terminology and nomenclature
      - October - November 2017
    - Phase 4: Draft proposed terminology and invite comments from payers, key community members and key researcher organization
      - December – Feb 2018
    - Phase 5: Draft manuscript and submit to ISTH SSC for approval and publication
      - March 2018 – May 2018
  - Launch
    - June 2018
  - Duration
    - 12 months
  - Finalization/analysis
    - May -June 2018
  - Reporting

- July 2018

- Expected outcomes (ie. publications):
  - Publication type (SSC Communication, Guidance document or original article):
  - We anticipate that after performing a narrative review harmonized with expert opinion, we will produce a guidance document suggesting nomenclature for hemophilia carriers, outlining and identifying the strengths and limitations of the proposed terminology which should improve the consistency in categorization and communication for providers, researchers, the community and payers. Furthermore we will outline the challenges of meeting the needs of this population in our current health care systems.

- Description of project set/up and management, needed infrastructure and resources (summary):
  - This project will require at least 2 in person meetings if possible that we will attempt to align with national and international meetings. In addition we will need administrative support to arrange for online web meetings and documentation of minutes. We request a research librarian or statistician to assist with the literature review and funding to pay for a meeting on phase 3 portion of the study and to pay for travel for those to present draft information at the HFA and NHF meetings.

- Possible references:
  - Mauser-Bunschoten, EP. World Federation of Hemophilia. Symptomatic Carriers of Hemophilia. Dec 2008. #46.
  - Plug I et al. Bleeding in carriers of hemophilia. Blood 2006;108(1):52-6. Epub 2006
  - DiMichele DM et al. Severe and moderate hemophilia A and B in US females. Haemophilia.2014;20:e136-43.
  - Paroskie et al. A cross-sectional study of bleeding phenotype in haemophilia A carriers. BJH.2015 Jul;170(2):223-8.
  - Olsson A et al. Clotting factor level is not a good predictor of bleeding in carriers of haemophilia A and B. Blood Coagul Fibrinolysis.2014 Jul;25(5):471-5.
  - James PD et al. Evaluation of the utility of the ISTH-BAT in haemophilia carriers: a multinational study.Haemophilia.2016 Nov 22(6):912-918