SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT:

Guidance for evaluation and reporting of medication adherence for clinical trials of anticoagulants in children: Communication from the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis

Subcommittee:

SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis/Anticoagulation Adherence Working Party

Person responsible (Chair / Principal Investigator): Lori Luchtman-Jones

Description Abstract:

In response to growing recognition that non-adherence to anticoagulant medication prevents children, adolescents, and young adults from achieving the therapeutic benefits of anticoagulant medication, the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis convened a working group on medication adherence. The primary aim of this manuscript is to synthesize recommendations from the larger adherence science literature to provide guidance regarding the classification, collection, and interpretation of anticoagulation adherence data. The secondary aim of this manuscript is to evaluate the degree to which trials published from 2013 to 2023 adhered to these guidelines. As less than half of all trials reported on adherence and none included all recommended elements, the proposed guidelines have the potential to significantly enhance the rigor and reproducibility of pediatric anticoagulant research.

Achieving the therapeutic benefits of anticoagulant medication requires adherence, or that patients and families demonstrate medication-taking behavior that aligns with the agreed-upon prescribed medication regimen. Specifically, anticoagulation adherence requires that patients and/or families: 1) start the anticoagulant as prescribed (initiation adherence); 2) demonstrate day-to-day medication-taking behaviors that align with the prescribed regimen dose, number of doses per day, and dose timing (implementation adherence); and 3) stop the anticoagulant when directed (discontinuation adherence). Patients and families face numerous barriers to medication-taking at the patient- (i.e., side effects, burden, motivation, forgetting, pain), family- (i.e., caregiver involvement), community- (i.e., social stigma), and healthcare system- (i.e., access, cost) levels. As a result of these and other barriers, 3-42% of children and young adults demonstrate non-adherence to anticoagulants. Among older adults, anticoagulation non-adherence has been linked to both hemorrhagic and thrombotic complications and we hypothesize that children and young adults who are non-adherent are at risk for similar significant and potentially preventable consequences. Medical teams recognize the critical nature of preventing these potentially devastating consequences. In previously published survey of 251 clinicians involved in the anticoagulation management of children and/or adolescents and young adults (administered last year at the SSC meeting), the majority worried about non-adherence and made regimen modifications (e.g., changed prescriptions) to promote adherence.

In addition to impacting patient outcomes, anticoagulation non-adherence has the potential to affect the outcomes of clinical trials. While rates of pediatric anticoagulation non-adherence within clinical trials have not been well-characterized, data from other populations suggest that even within the tight confines of clinical trials, non-adherence is present. A study including 16,907 patients with various medical conditions enrolled in 95 clinical trials found that 4% of patients never started the medication (initiation non-adherence) and by day 100, 20% of patients had discontinued treatment and 12% were not taking the medication as recommended. By the end of 12 months, only 45% of patients were still taking the medication as prescribed. When non-adherence is not assessed or accounted for, trials erroneously assume that the novel agent was received at the intended dose, as opposed to the actual, lower or less frequent, dose. When novel agent dosing is overestimated, it can result in type 2 errors in judging efficacy, underestimates of dose-dependent adverse effects, overestimated dosing requirements, and inappropriate dose escalations. In sum, the effects of novel anticoagulants cannot be accurately estimated without understanding daily medication adherence. As a result, many regulatory bodies, including the Food and Drug Administration, recommend assessing medication adherence in clinical trials.

Design and methodology (Data expected to collect, sample size and statistical analysis):

This manuscript represents the efforts of the Anticoagulation Adherence Working Party (established in 2020) of the Pediatric and Neonatal Thrombosis and Hemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC). Working party members (co-authors) include experts in adherence science, anticoagulation, and pediatric hematology.

This group generated guideline content from the published literature and expert feedback. First, the first author extracted recommendations for assessing and reporting adherence within clinical trials from manuscripts identified via a literature review (PubMed/MEDLINE search using the terms “clinical trial” AND “medication adherence” AND pharmaceutical; forward and backward searches of included articles). Second, working party members (co-authors) provided additional recommendations. Third, the first and senior author synthesized recommendations into guidance related to clinical trial design, implementation, analysis, and reporting. Fourth, guidelines were presented at the ISTH 2023 Congress in Montreal to the audience attending the subcommittee session on Pediatric and Neonatal Thrombosis and Hemostasis. Attendees provided feedback via an anonymous survey administered via REDCap to inform refinements. Finally, the working group developed exemplar materials to supplement the agreed-upon guidelines.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

NA: this is a literature review and guidance paper, supplemented by results from a REDCap survey administered at the 2023 ISTH SC meeting.

Expected timeline:

Project stage/set up 2022
Launch July 2022
Duration ongoing
Finalization/analysis We are reviewing the REDCap survey data and almost ready to submit manuscript

Reporting (as above)

Expected outcomes (ie. publications): hoping for publication in JTH

Publication type (SSC Communication, Guidance document or original article): Guidance document

Description of project set/up and management, needed infrastructure and resources (summary): It's pretty much done. No needs, other than ongoing virtual working group meetings.

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