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Updated guidance for efficacy and safety outcomes for clinical trials in venous thromboembolism in children: Communication from the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis

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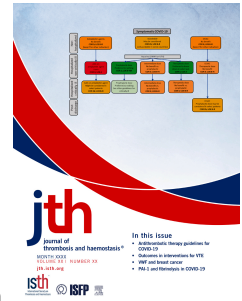
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Title: Updated guidance for efficacy and safety outcomes for clinical trials in venous thromboembolism in children: Communication from the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis

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ABSTRACT

Despite the growing number of pediatric antithrombotic clinical trials, standardized safety and efficacy outcome definitions for pediatric venous thromboembolism (VTE) clinical trials have not been updated since 2011. Many recent trials have adapted the recommended definitions, leading to heterogeneity in outcomes and limiting our ability to compare studies. The International Society on Thrombosis and Haemostasis Scientific and Standardization Subcommittee (SSC) on Pediatric and Neonatal Thrombosis and Hemostasis organized a Task Force to update the efficacy and safety outcome definitions for pediatric VTE clinical trials. The outcome definitions used in recent pediatric antithrombotic trials, definitions recommended for adult studies, and regulatory guidelines were summarized and reviewed by the Task Force as the basis for this updated guidance. Major updates to the efficacy outcomes include the removal of VTE-related mortality as a part of a composite primary outcome and explicit inclusion of all deep venous anatomic sites. Safety outcomes were updated to include a new bleeding severity category: patient important bleeding, no intervention, which encompasses bleeding for which a patient seeks care but there is no change in management. Menstrual bleeding can now be included in any bleeding category when those criteria are met. We hope these updated outcome definitions allow investigators to focus on clinically relevant and patient important outcomes and provide standardization to facilitate continued high-quality evidence for the use of antithrombotic therapies in children.

KEYWORDS: anticoagulants, pediatrics, venous thromboembolism, clinical trial, outcome assessment

INTRODUCTION

In the last decade, there have been several high-quality clinical trials for the treatment and prevention of pediatric thrombosis. The direct oral anticoagulant (DOAC) investigational programs in pediatrics have evaluated the pharmacokinetics, pharmacodynamics, safety, and efficacy of several DOACs and are either completed or nearly completed [1–8]. These studies, as well as clinical trials evaluating optimal duration of anticoagulant therapy in children with provoked venous thromboembolism (VTE), and VTE prevention in children with congenital heart disease, critical illness, malignancy, and COVID-19, have greatly improved the quality of evidence in pediatric thrombosis [5–12].

Primary outcomes of VTE clinical trials focus on prevention of new (recurrent and/or progressive) VTE and VTE-related mortality (efficacy) and bleeding (safety). In 2011, the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Subcommittee (SSC) on Pediatric and Neonatal Thrombosis and Hemostasis (hereinafter referred to as the “Pediatric SSC”) published guidance that included, for the first time, standardized outcome definitions for clinical trials in pediatric VTE [13]. These definitions have been widely used in pediatric anticoagulation trials, as well as in retrospective and prospective pediatric thrombosis observational studies. However, it has been more than a decade since the guidance was published, and several of the recent trials used adapted versions of these outcome definitions to meet their needs [1,2,6,7,9,10,12,14]. In addition, the categorization of menstrual bleeding, which was previously defined as minor bleeding in the 2011 guidance, required an update [13]. For these reasons, the Antithrombotic Trials Working Group of the Pediatric SSC empaneled an inter-SSC Task Force on Outcome Definitions for Pediatric VTE Trials to develop updated guidance.

METHODS

This multidisciplinary Task Force was comprised of the following members: Antithrombotic Trials Working Group of the Pediatric SSC representatives (E. Amankwah, M. Betensky, N. Goldenberg, C. Male, L. Raffini, H. Whitworth, A. Zia); Control of Anticoagulation SSC representatives (L. Castellucci, A. Cuker); a pediatric radiologist (E. Rinzler). The group discussed and modified recommendations through consensus.

Review of pediatric thrombosis clinical trial literature

We reviewed the safety and efficacy outcomes as defined in 13 pediatric thrombosis clinical trials identified via a search of PubMed and clinicaltrials.gov from 2019 – 2022. We selected these trials as the most prominent pediatric antithrombotic trials since publication of 2011 guidelines to represent the current outcomes used in the field. Information on outcome definitions was extracted from manuscripts reporting trial findings, study design manuscripts, available supplements including study protocols, and available information from clinicaltrials.gov [1–12,14–17]. These definitions were compared to the 2011 guidance [13] and deviations were tabulated by two members (H.W., L.R.; Supp Tables 1,2) and subsequently discussed by the Task Force in virtual meetings and via email.

Review of ISTH recommendations for outcome definitions in adult antithrombotic studies

We reviewed the published outcome definitions for bleeding in adult antithrombotic studies, including surgical and non-surgical patients, as recommended by the Control of Anticoagulation SSC of the ISTH [18–20]. Special focus was given to differences in the definition of clinically relevant non-major (CRNM) bleeding between the adult and pediatric guidance [13,18]. We also reviewed the adult definitions for pulmonary embolism (PE) related death and cause of death in VTE [21].

Review of regulatory agency guidance

There were no pediatric-specific recommendations for anticoagulation clinical trials available from the United States Food and Drug Administration or the European Medicines Agency (EMA). Guidance for VTE treatment studies in adults was available online from the EMA [22] and considered by the Task Force in the development of these definitions.

RECOMMENDATIONS

These updated recommendations apply primarily to clinical trials of pediatric VTE treatment and prevention but may be used or adapted for observational studies. Anticoagulants are also frequently used for non-VTE indications in children, including treatment of peripheral arterial thrombosis and arterial ischemic stroke, and prevention of thromboembolic complications of mechanical circulatory support (extracorporeal membrane

oxygenation and ventricular assist devices) and implanted intracardiac devices. While specific efficacy outcomes for these indications were outside the scope of this update, the bleeding definitions may be more readily adapted to these indications.

Here, we present updated guidance on primary and secondary efficacy and safety outcomes by indication (treatment or prevention), and definitions for the components of these outcomes. Optimal selection of outcomes for a specific trial must be aligned with study aims and hypotheses and may therefore differ from those recommended here for general application.

Efficacy outcomes

Updated efficacy definitions are provided in Table 1 and efficacy outcomes are summarized in Table 2.

The proportion of children with VTE in non-extremity/pulmonary locations is >10% [23]. Thus, efficacy outcomes should include all VTE sites (PE, lower and upper extremity DVT, cerebral sinovenous thrombosis, and non-extremity DVT including neck, vena cava, cardiac, and abdomen/pelvis). The primary efficacy outcome for VTE treatment studies (symptomatic recurrent and/or progressive VTE) differs from that of primary prevention studies (all incident VTE, including both clinically unsuspected and symptomatic events), given the potential importance of clinically unsuspected VTE in primary prevention studies. Clinically unsuspected VTE may also be a relevant primary outcome in certain treatment and secondary prevention studies that utilize surveillance imaging (e.g., ultrasound) in at-risk populations. These updated definitions replace the term “asymptomatic VTE” with “clinically unsuspected VTE” as per separate guidance from the Pediatric SSC [24].

The updated primary efficacy outcome no longer includes VTE-related mortality. Since VTE-related mortality is a very different clinical outcome from recurrent VTE, we felt these should not be combined in a composite outcome. VTE-related mortality is often not reported and is rare in pediatrics (0-0.4% in recent trials) [1,2,6,9,11]. Attribution of deaths to underlying VTE events may be challenging, given co-morbidities. The Predictive and Diagnostic Variables in Thrombotic Disease SSC of the ISTH recommends a classification system for cause of death in adult VTE studies, which may also be applied to pediatric studies [21]. VTE-

related mortality should be reported as a secondary outcome and when identified, we recommend these events be summarized in detail.

Similar to the 2011 guidance, this Task Force continues to recommend central adjudication in pediatric VTE clinical trials (blinded, in the case of comparative trials) [13]. Central radiology review of all VTE events should clarify persistent and new thrombus burden (VTE progression and/or recurrence) as well as resolution of prior thrombus. The time to VTE recurrence or progression should also be reported. Clinician judgment and adjudication should be utilized to classify an additional VTE as recurrent or concurrent when it occurs in a close temporal relationship (i.e., <7 days) to the index event.

To facilitate adjudication, standardized imaging protocols and consensus guidelines for evaluation of venous thrombosis should be utilized [25,26]. When possible, thrombus resolution should be a secondary outcome, ideally with pre-defined degrees of resolution similar to what was used in the EINSTEIN-Jr program, such as: resolved, improved, no change, deterioration [1]. Radiologic signs of post-thrombotic change should also be included as a secondary outcome, ideally assessed by the same imaging modality as the index event, and using pre-specified definitions, as outlined in consensus radiology guidance [25]. If definitions of VTE recurrence, symptomatic VTE, or VTE progression vary from these recommendations, they should be defined *a priori* in the study protocol and described in detail in published manuscripts.

Site-specific post-thrombotic sequelae are important long-term secondary outcomes. This includes post-thrombotic syndrome in extremity DVT evaluated by validated outcome instruments [27–30], as well as loss of vascular access, post-PE syndrome [31], and other rare complications including decreased renal function, neurologic complications, and portal hypertension. Updated guidance on these secondary outcomes and their definitions is being addressed separately by the Post-Thrombotic Sequelae and PE Working Groups of the Pediatric SSC.

Safety outcomes

Updated safety outcome definitions are provided in Table 3 and updated safety outcomes are summarized in Table 4.

Primary safety endpoints in antithrombotic clinical trials focus on bleeding events. It is important to capture bleeding severity in order to inform indication and population-specific risk-benefit assessment of anticoagulation. Given low rates of major bleeding in pediatric clinical trials (0 – 0.9% in recent prevention trials [6,7,11,12] and 0.4 – 2.3% in recent treatment trials [1,2]) and the clinical importance of additional non-major bleeding scenarios, we recommend a composite primary safety outcome of major and CRNM bleeding, as was done in several recent pediatric trials [1,4,6,8–12,14]. However, each bleeding severity category should be individually reported as a secondary outcome to allow for comparison of bleeding across studies and in meta-analyses. In regard to CRNM bleeding, we recommend that this classification include any bleeding episode for which a change in treatment regimen was made or endorsed by the treating clinician (e.g., discontinuing anticoagulant; withholding or reducing anticoagulant doses; adding antifibrinolytic agents; adding or escalating hormonal therapies for menstrual bleeding on anticoagulation).

Furthermore, we recommend that menstrual bleeding no longer constitute an exception from classification as major or CRNM bleeding when the defining criteria are met. Investigators should consider using specific menstrual bleeding tools, such as the Pictorial Bleeding Assessment Chart (PBAC), to capture heavy menstrual bleeding as an independent, secondary outcome in addition to classifying heavy menstrual bleeding in these recommended outcomes [32]. Given that not all study subjects are at risk for menstrual bleeding, it is important to report bleeding by anatomic site, including menstrual bleeding, so that the rate of clinically relevant menstrual bleeding can be reported as a proportion of the subjects at risk (i.e., only subjects who have started menses) for accurate reporting on the rate of heavy menstrual bleeding.

In order to capture bleeding events that may be important to patients, yet do not meet criteria for CRNM bleeding, we also recommend utilization of a new bleeding category: patient important bleeding, no intervention (PIBNI). This applies to events that result in a patient (or guardian) seeking medical care or advisement (emergency room, office visit, telephone, electronic message, or virtual/telehealth call) due to a bleeding episode, but do not prompt a change in management. The 2011 ISTH pediatric definitions classified this type of bleeding as minor bleeding; however, it was classified as CRNM bleeding in some of the recent investigational programs, in accordance with the 2015 ISTH adult definitions of CRNM bleeding [13,18]. We

propose this category to standardize the classification of these bleeding events. As this category of bleeding has not previously been used, we recommend that efforts be made to engage patient/parent advisory committees to inform the inclusion of PIBNI among outcomes in the design of future trials.

DISCUSSION

These outcome definitions for pediatric VTE clinical trials are meant to serve as an update to the 2011 definitions [13], taking into consideration the actual outcomes used in the most recent pediatric antithrombotic clinical trials [1-12, 14]. There are three major updates. First, the primary efficacy outcome is no longer a composite including VTE-related mortality and we clarified the definition of VTE sites to include non-extremity DVT including intracardiac and intra-abdominal/pelvic, as well as CSVT. While VTE in these locations were captured in several clinical trials, they were not explicitly listed in the prior outcome guidance [13].

Second, we have added a new classification of bleeding severity: patient important bleeding, no intervention (PIBNI) as a way to report bleeding that is troubling to patients but does not reach the threshold of clinically relevant bleeding. It is critical to include and understand these patient-important outcomes since they may affect clinical care and adherence. An improved understanding of patient-important outcomes will help providers counsel patients on expected bleeding and may help guide the choice of anticoagulant. Furthermore, access to care and clinician availability vary by study, location, and patient population; thus, including PIBNI in the primary outcome may overrepresent clinically relevant bleeding in certain populations and make study comparison more challenging. We recommend PIBNI be included as a secondary outcome to collect data more consistently on this type of bleeding.

Third, menstrual bleeding is now included in major, CRNM, and PIBNI bleeding, when those criteria are met. There are increasing data regarding heavy menstrual bleeding with anticoagulation, particularly DOACs, which may differ across drugs, and it is important to collect these data in a systematic and standardized way [33–36].

The outcomes included here do not capture all the outcomes that are relevant to children and adolescents with VTE. The new category of PIBNI bleeding is a step toward recognizing patient important

outcomes which should be captured in clinical trials. Future research should investigate simple, evidence-based, pediatric-specific tools to capture other patient reported outcomes including quality of life, activity limitations, and mental health, in addition to bleeding and thrombosis. This includes the ongoing and future projects by other Pediatric SSC Working Groups focused on Post-Thrombotic Sequelae and PE to define long-term outcomes. The addition of thrombus resolution as a secondary efficacy outcome may allow long-term studies to investigate the effect of persistent thrombus burden on these post thrombotic outcomes. The outcomes and definitions recommended here will require ongoing updates and re-evaluation as new pediatric antithrombotic clinical trials are developed and results made available. We hope future pediatric investigational programs utilize these definitions to allow for accurate and meaningful comparison between different drugs and indications for the growing number of available anticoagulants in pediatrics.

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Conflict of Interest: LAC's research institution has received honoraria from Bayer, BMS-Pfizer Alliance, The Academy for Continued Advancement in Healthcare Education, Amag Pharmaceutical, LEO Pharma, Sanofi, Valeo Pharma, and Servier. AC has served as a consultant for Synergy and the New York Blood Center and

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Table 1: Efficacy definitions for pediatric VTE treatment or prevention clinical trials

	2011 Definitions (13)	2022 Update
VTE sites	DVT affecting venous drainage from limbs (including caval thrombosis), right atrial thrombosis, and PE	PE, extremity DVT, non-extremity DVT including neck, vena cava, intracardiac, intra-abdominal/pelvic, and CSVT
VTE progression	Either an increase in longitudinal extent of thrombosis or a change from non-occlusive to occlusive. (Exact criteria to be determined a priori in each study)	Either an increase in thrombus burden or a change from non-occlusive to occlusive, interpreted by a radiologist. Exact criteria to be determined <i>a priori</i> in each study and adjudicated by a central committee
Post-thrombotic syndrome	Recommend use of one of two published scores (27,28)	Updated definitions to be addressed in future guidance by Post-Thrombotic Sequelae working group
Asymptomatic VTE <i>to be replaced by</i> Clinically Unsuspected VTE	Radiologically defined as adherent to the vessel wall and obstructing $\geq 1/3$ of the venous segment diameter	Clinically Unsuspected VTE, as defined by Betensky et al.(24): VTE radiologically confirmed by imaging performed either as surveillance for risk of VTE, or for non-VTE-related clinical issues, in the absence of any VTE-associated signs and symptoms
Symptomatic recurrent VTE	<i>Not defined</i>	Objective radiological evidence of recurrent VTE, including new site and VTE progression, relative to the study-qualifying imaging study for index VTE, accompanied by signs or symptoms corresponding to (and in temporal association with) the site of VTE

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism, CSVT: cerebral sinovenous thrombosis

Table 2: Efficacy outcomes for pediatric VTE treatment and prevention clinical trials

VTE treatment and secondary prevention clinical trials			
	2011 Definitions (13)	2022 Update	Comments regarding changes
Primary	Composite of: 1. All recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including DVT, PE and paradoxical embolism (asymptomatic and symptomatic) 2. VTE-related mortality	Composite of: 1. Symptomatic, recurrent VTE and/or VTE progression	1. Broader definition of VTE beyond only DVT, PE, paradoxical embolism 2. Include only symptomatic VTE in treatment/ secondary prophylaxis trials 3. Moved VTE-related mortality to secondary outcome
Secondary	1. Each individual component of primary outcome 2. All-cause mortality 3. New symptomatic DVT (including DVT progression) 4. New symptomatic PE 5. New paradoxical embolism 6. New asymptomatic DVT (including DVT progression) 7. Post thrombotic syndrome	1. VTE-related mortality* 2. All-cause mortality 3. Clinically unsuspected VTE 4. Symptomatic recurrent VTE, by location 5. Site-specific post-thrombotic sequelae 6. Thrombus resolution	1. Broader definition of VTE beyond only DVT, PE, paradoxical embolism 2. Symptomatic VTE no longer secondary outcome since it is primary outcome 3. Clinically unsuspected VTE moved to secondary outcome 4. Broader definition of post thrombotic sequelae 5. Addition of thrombus resolution
Primary VTE prevention clinical trials			
Primary	Composite of: 1. All incident VTE including DVT, PE and paradoxical embolism and 2. VTE-related mortality	Composite of: 1. All incident VTE, including both clinically unsuspected and symptomatic events	1. Broader definition of VTE 2. "Asymptomatic" changed to "clinically unsuspected" 3. Moved VTE-related mortality to secondary outcome
Secondary	1. Each individual component of primary outcome 2. All-cause mortality	1. VTE-related mortality* 2. All-cause mortality 3. Clinically unsuspected VTE 4. Symptomatic VTE	1. Symptomatic and clinically unsuspected VTE are separate secondary outcomes

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism

*VTE-related mortality is challenging to define and rare. Recommend these events be summarized with relevant details in manuscripts.

Table 3: Safety definitions for pediatric VTE treatment or prevention clinical trials

	2011 Definitions (13)	2022 Update	Comments regarding changes
Major bleeding	Composite of: 1. Fatal bleeding 2. Clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/ dL) in a 24-hour period 3. Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system 4. Bleeding that requires surgical intervention in an operating suite	Composite of: 1. Fatal bleeding 2. Clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/ dL) in a 24-hour period 3. Critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involves the central nervous system 4. Bleeding that requires an intervention via an invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy 5. Overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine, andexanet alfa, idarucizumab)	1. Addition of “critical” to bleeding sites to delineate significant (not trivial) bleeding in these locations and expansion of included sites 2. Additional invasive procedures added as interventions for major bleeding 3. Menstrual bleeding included in major bleeding if criteria met 4. Addition of bleeding for which a reversal agent is administered <i>Consider sub-categorization of major bleeding based on the development of disability or significant sequelae</i>
Clinically relevant non-major bleeding	Composite of: 1. Overt bleeding for which a blood product is administered, and which is not directly attributable to the patient’s underlying medical condition 2. Bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite	Composite of: 1. Bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication) Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, LARC placement 2. Bleeding that results in hospitalization or increased level of care 3. Overt bleeding for which a blood product is administered, and does not meet criteria for major bleeding	1. Removal of “intervention to restore hemostasis” 2. Examples of interventions included 3. Addition of bleeding that results in hospitalization or increased level of care 4. Menstrual bleeding included in CRNM if criteria met 5. Phone calls or in-person visits for bleeding do not qualify unless there is a change in treatment
Patient important bleeding, no intervention	N/A	1. Bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team (see above for examples of medical interventions)	1. New subclassification of bleeding to highlight bleeding that is relevant to the patient but does not meet the threshold of CRNM bleeding 2. Menstrual bleeding included in PIBNI if criteria met
Minor bleeding	1. Any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding 2. Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event	1. Any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding or patient important bleeding without intervention	1. Menstrual bleeding can now be classified as any severity of bleeding if criteria are met

VTE: venous thromboembolism; Hgb: hemoglobin; CRNM: clinically relevant non-major; TXA: tranexamic acid; LARC: long-acting reversible contraception; ED: emergency department

Table 4: Safety outcomes for pediatric VTE treatment or prevention clinical trials

	2011 Definitions	2022 Update	Comments regarding changes
Primary	Major bleeding	Clinically relevant bleeding, defined as a composite of: 1. Major bleeding 2. Clinically relevant non-major bleeding	1. Updated definitions of major and CRNM bleeding summarized in Table 3 2. Include CRNM bleeding as part of composite primary outcome
Secondary	1. Clinically relevant non-major bleeding 2. Minor bleeding	1. Each component of the primary outcome (Major and CRNM bleeding) 2. Patient important bleeding without intervention 3. Minor bleeding 4. All bleeding	1. Includes all bleeding and each category of bleeding reported individually 2. New bleeding category created (see Table 3)

VTE: venous thromboembolism; CRNM: clinically relevant non-major