DRAFT Recommendations for public comments:
The annual bleeding rate (ABR) in hemophilia – Harmonizing definition, recording and reporting: Recommendations of ISTH – SSC FVIII / IX Sub-committee Working Group

Defining the problem

The sites, severity and frequency of bleeding have been used to assign etiology and severity of disorders of hemostasis, including hemophilia.(1) It is indeed the most critical patient reported outcome (PRO) by people with hemophilia (PWH) but individual perceptions of bleeding, particularly in the joint, vary significantly. This can result in variance and skewing of this data among cohorts. The number of bleeds over a defined period of time or 'bleeding rate' not only correlates with disease severity but the efficacy of therapeutic interventions have also been evaluated by this outcome parameter.(2) The 'annual bleeding rate', (ABR) a seemingly simple and straight forward patient reported outcome measure has been the primary / secondary endpoint for assessment of efficacy of all categories of therapeutic products – clotting factor concentrates (CFC), both standard and extended half-life (SHL / EHL) as well as a range of non-CFC products including gene therapy. However, the ABR is a subject of considerable interest due challenges in achieving harmony in its recognition and reporting in clinical trials and practice. Standardization of recording and reporting of ABR is therefore essential for both clinical trials and practice, including counselling and shared decision making. A detailed description of the heterogeneity of ABR has been recently compiled by this working group. (3)

The key aspects which need harmonization are mentioned below:

1.Recognition and recording of bleeds:

Described below are the clinical features and terms used for recognizing and reporting bleeding episodes.

i.The joint bleed: As the commonest site of bleeding among males with congenital hemophilia, the criteria by which to recognize a joint bleed was historically left to individual perception, both of patients with lived experience and that of the health care professional (HCP) evaluating them. The literature is therefore replete with examples of heterogeneity of clinical parameters used to report annual joint bleeding rates or AJBR.(4) Adding to this challenge is the differentiation of chronic arthropathic pain from a new bleed in such joints.(5) To help harmonize the recording of these events, the ISTH SSC had provided definitions for the joint bleed.(6) However, over the decade since its publication, adoption of this definition has been limited.(2) A limitation of the definition that has been noted in clinical trials is the ***mandatory*** requirement of aura along with the other clinical features to define a bleed. (7) This symptom is not always experienced

or described by patients even with obvious joint bleeds, particularly when more severe or traumatic. This lack of consistency in how joint bleeds are reported therefore leads to inaccuracies, limits comparisons and allows bias in recognition and reporting of clinical outcomes of therapeutic interventions as well as the individual clinical profile of the patient.

Of note is that other sites of bleeding can be more consistently confirmed and counted because they are either clinically obvious or can be radiologically confirmed.

ii.Aggregate bleed numbers: *Annual / annualized bleed rate (ABR)* - The number of bleeds reported over an observation period of 12 months or more has been called the 'annual bleeding rate' (ABR). When the number of bleeds is extrapolated to 12 months through model-based statistics from shorter durations of assessment, it has been reported as 'annualized bleeding rate' (also ABR).(4) While traditionally, *all bleeds* would make up the reported ABR, more recently, the concept of *'treated bleeds'* was introduced with the advent of non-CFC products to selectively consider those bleeds which warranted therapeutic interventions to be counted for efficacy assessment.(8) While semantically straight forward, given the lack of harmonization in clinical approach to what would be reported by patients and treated or not treated by health care professionals, this can enhance inconsistencies in reporting ABRs as well as the comparison of efficacy. Differentiation of bleeds into *spontaneous and traumatic* is another area which has lacked consistency in the absence of definitions. With increasing efficacy of therapeutic products, an important parameter now being reported is percentage of patients who have no bleeding at all, or the *rate of 'zero' bleeding,* but there is again lack of clarity and consistency in the duration of observation for reporting this outcome.

With increasing focus on women and girls with hemophilia for inclusion in clinical studies, there is need to standardize assessment and reporting of menstrual bleeding and peri-partum hemorrhage as well as the response to specific therapeutic interventions.

2.Reporting of bleeds

Apart from the issues mentioned above with regard to detection and recording of bleed events, there is also immense variation in several aspects of reporting of these data as practice outcomes or study endpoints. (2)

These include the following:

i. Efficacy period. As most interventional studies for new therapeutics have less than one year of efficacy period for primary endpoint assessment, the ABRs noted during this time are 'annualized' by different model-based statistical methods and reported as 'estimated' ABRs as opposed to the 'observed' ABR during the actual study period. (9,

10) The duration of observation is a significant variable in determining ABR and requires harmonization.

ii.Reported measures of central tendency. There is lack of harmonization in whether aggregate ABRs are reported as means or medians which can make major differences in of the interpretation of efficacy of interventions.

iii.Bleeding sites. Apart from joints, bleeding at other important sites such as muscle and central nervous system, which are not uncommon, are not consistently reported in data from clinical trials.

iv.All bleed vs treated bleed reporting and outcome determinant. With increasing use of 'treated bleeding' as primary efficacy outcome criteria, without defining or standardizing the treatment policies even within that particular study as different sites, practice variations can affect reported 'treated' bleeding rates. Joint bleeds have also sometimes been excluded from reporting if not treated. (11)

v.Absolute bleed rates or ranges. The reporting of absolute bleed rates at the lower end to show highest efficacy of therapeutic interventions are also not consistent in reports with different parameters being used in studies of different products – rates or percentage zero bleed, 0-1, <1, 1-3, <3 bleeds during the efficacy period, which, as mentioned above, is also variable.

vi.Supplementary details inadequate. The details provided in the supplementary documents of methods and protocol also often do not provide adequate details of the definitions in the protocol for assessing and capturing bleed events.

vii.Even though it is well known that bleeds are related to quantum and intensity of activities, a major lacuna in the field is the lack of any measurement of activities and correlating ABRs with them. This is possible as was reported many years ago while comparing two types of prophylaxis protocols in practice. (12) With increasing availability of easily usable devices that can quantify activity, this should be considered more regularly in both clinical trials and practice. (13)

Proposals for harmonization of recording and reporting of bleed events:

1.Definition of a bleed: The definitions used in the study to recognize specific bleeds must be clearly described. For pivotal trials of new therapeutics, it should be mandatory to use ISTH SSC recommended bleed definitions or other widely accepted standardized bleeding assessment criteria including those for menstrual bleeding, as relevant. With increasing efforts to include females with hemophilia in clinical studies, this is particularly relevant.

2.Recognition of a joint bleed: The original ISTH SSC definition of the joint bleed is to be retained with one modification – as 'aura' may not be perceived by all patients in all bleeds, its mandatory requirement to define a bleed should be replaced by aura being included with the other three criteria, (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline, in determining a joint bleed. In this context, 'aura' may be defined as 'any feeling of additional discomfort in the joint beyond baseline'. Any two of these criteria may be used to define a joint bleed event. In infants and young children, reluctance to use the limb alone may be considered indicative of a joint/muscle bleed.

The use of ultrasound to arbitrate on joint bleeds is not advisable given the technical challenge in detecting very small quantities of blood which may still be enough cause clinical effects and inflammation mediated joint damage. (14,15) There is no evidence that a 'microbleed' in a joint, being asymptomatic by definition, can be detected by ultrasonography.

3.Classification of a bleed:

i.Bleed events should be classified as 'spontaneous' unless reported by the patient to be associated with an obvious trauma, even during accustomed activity, or if associated with unaccustomed activities.

Bleeds in multiple locations but from a single trauma episode should be counted as one bleed from the ABR perspective.

ii.The use of the term 'treated bleeds' is not recommended unless accompanied by clear descriptions of treatment policies for bleeds and hemostasis products used but must still be accompanied by clearly reported data on number and location of untreated bleeds. It is total bleed rate at different locations which should be used for efficacy assessment.

4.Calculation of bleed rate:

i.In clinical studies of hemostasis products, the efficacy observation period with ABR as the endpoint, should at least for 12 months after achieving steady state therapeutic

levels, including extension phase follow-ups, given the well-known seasonal variation in activities among in many parts of the world

ii.If shorter durations of follow-up are used for regulatory approvals, the 12-month ABR data should be reported subsequently and considered more definitive for efficacy assessment.

iii.For reporting annualized ABR, it is recommended that the acronym EABR be used when extrapolating data from <12 months of planned efficacy observation period and OABR when calculating from ≥12 months observation period.

iv.For all ABRs, both mean (95%CI) and median (IQR) of the data should be reported for the observed and estimated numbers. The modelling method used for estimation of ABRs should be specified and justified for that data set.

5.Reporting of bleeds:

i.All bleeds should be reported in study reports and publications – with specific mention of number of joint, muscle and CNS bleeds and classification of spontaneous or traumatic.

ii.Rates of 'zero' bleeding should always be accompanied by observation period at which it was assessed. It is recommended that zero bleeding rates may be initially reported with a minimum of 6 months observation (zero ABR6) and but must also subsequently be reported at 12 months (zero ABR12) and beyond which will imply the percentage of patients with zero bleeds at those time points of follow-up.

iii.Given the clinical significance of ABR at the low end, apart from the rate of zero bleeding, data on low numbers of bleeds should be reported more specifically as 0, <1, 1-3 or rate of 1, 2, 3 bleeds individually, and >3 ABR and AJBR.

iv.Effort should be made to document levels of activity using suitable devices and correlate them with the reported ABRs.

v.For females with hemophilia, normalization of menstrual blood flow to physiological levels could qualify for being counted as 'zero' abnormal bleeding. This is a subject that needs further data and deliberation for standardization.

For all other aspects of assessment and reporting of bleeds in congenital hemophilia, the previous ISTH SSC recommendations will continue to apply. (6)

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