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Khorsand, Nakisa; Beyer-Westendorf, Jan; Sarode, Ravi; Schulman, Sam; Meijer, Karina

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RECOMMENDATIONS AND GUIDELINES

# Definition of haemostatic effectiveness in interventions used to treat major bleeding: Communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Nakisa Khorsand[1] | Jan Beyer-Westendorf[2] | Ravi Sarode[3] | Sam Schulman[4,5] | Karina Meijer[6]

[1]Department Pharmacy, OLVG, Amsterdam, the Netherlands

[2]Thrombosis Research Unit, Center of Vascular Diseases, Dresden University Hospital 'Carl Gustav Carus', Dresden, Germany

[3]Division of Transfusion Medicine and Hemostasis, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[4]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[5]Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

[6]Department of Hematology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

**Correspondence**
Nakisa Khorsand, OLVG Hospital, Department of Pharmacy, Oosterpark 9, 1091 AC, Amsterdam, the Netherlands.
Email: N.Khorsand@olvg.nl

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## 1 | BACKGROUND

A common challenge for studies investigating the hemostatic effectiveness of the reversal agents or any other treatment used to manage a major bleed, especially in patients on anticoagulants, is defining and measuring clinical outcome. Therefore, in 2016, the Scientific and Standardization Subcommittee (SSC) on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis (ISTH) proposed criteria to evaluate the hemostatic effectiveness of anticoagulant reversal in major bleeding management.[1]

This definition was adopted by several studies.[2-8] Additionally, in 2018, the applicability and reliability of this ISTH definition was assessed in a method agreement analysis.[9] These studies identified challenges in using the definition for visible bleeding versus non-visible bleeding and the actual timeline to use when hemoglobin levels are compared (including the situation in which red blood cells are transfused). Furthermore, for intracranial hemorrhage, some clarification in using validated scoring systems was needed.

In this revision, the working group aims to clarify the proposed definition as well as provide practical guidance and recommendation for a correct application of this standardized definition.

Furthermore, the definition is made suitable to have a broader applicability for evaluation of any treatment to manage a major bleed.

## 2 | METHODS

Key source materials include the results of recently conducted method agreement analysis.[9] Furthermore, the recommendations herein summarize expert consensus, including presentations and discussions at Control of Anticoagulation subcommittee meetings during the 62nd and 63rd SSC meetings of ISTH. Final recommendations are derived by consensus within the working group subjects.

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## 3 | REVISED GUIDANCE STATEMENT

**Visible bleed**

Definition of this bleeding type:
Bleeding site is visible to the naked eye, e.g., skin bleeding, visible mucosal bleed (oral, nose, anal) or active bleeding is located in a compartment in which blood cannot be occult (epistaxis, vaginal bleeding).

Good effectiveness is achieved when all below criteria are met:

- Visible bleeding has ceased within 4 hours from the end of the initial hemostatic management.
- By 48 hours from the end of the initial management, there is no need for further treatment with hemostatic agents or coagulation factors, or transfusion of other blood products.
- Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis.
- No unscheduled (re-)interventions are needed for bleeding management within 48 hours from initial management.

**Non-visible bleed**

Definition of this bleeding type:
All bleeds that do not classify as visible, musculoskeletal, or intracranial bleeds.
This includes gastrointestinal (GI) bleeds when the bleeding site is not visible to the naked eye, regardless of visible (e.g., melena) signs.

Good effectiveness is achieved when all below criteria are met:

- At 48 hours after presentation or at discharge (whichever is first) the hemoglobin level has not dropped more than 10% compared to the hemoglobin level measured after completing the initial management (including infusion of red blood cells).
- By 48 hours from the end of the initial management, there is no need for further treatment with hemostatic agents or coagulation factors, or transfusion of other blood products.
- Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis.
- No unscheduled (re-)interventions are needed for bleeding management within 48 hours from initial management.

**Musculoskeletal bleed**

Good effectiveness is achieved when all below criteria are met:

- Pain is stable or reduced, and swelling is stable or reduced within 24 hours from the end of initial hemostatic management or at time of discharge from the acute hospitalization (whichever is first).
- By 48 hours from the end of the initial management, there is no need for further treatment with hemostatic agents or coagulation factors, or transfusion of other blood products.
- Fasciotomy is either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis.
- No unscheduled (re-)interventions are needed for bleeding management within 48 hours from initial management.Annotation of effective hemostasis with excellent clinical outcome when also:

No neurologic dysfunction or limb loss is present at time of discharge from the acute hospitalization (at discharge can be replaced by “at day = 30,” whenever applicable).

**Intracranial bleed**

Good effectiveness is achieved when all criteria below are met:

- The hematoma volume is stable, or increased by <35% as compared to baseline volume, as assessed by a computed tomography (CT) scan within 12 hours (time window of 6–24 hours after the index CT).
- No deterioration of the Extended Glasgow Outcome Scale (GOS-E) or any validated scoring system as assessed at 24 hours compared to that at presentation.
- By 48 hours from the end of the initial management, there is no need for further treatment with hemostatic agents or coagulation factors, or transfusion of other blood products.
- Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis.
- No unscheduled (re-)interventions are needed for bleeding management within 48 hours from initial management.

Annotation of effective hemostasis with excellent clinical outcome when also:

- No neurologic deterioration/dysfunction is present at discharge from the acute hospitalization (at discharge can be replaced by “at day = 30,” whenever applicable) as assessed with any validated scoring system (e.g., GOS-E) compared to that at presentation.

## 4 | CLARIFICATION OF THE REVISED GUIDANCE STATEMENT

### 4.1 | General

The hemostatic effectiveness is a binary assessment, i.e., effective or ineffective. The treatment outcome is regarded as “effective hemostasis” only when all criteria within the relevant bleeding type are met. Furthermore, for musculoskeletal or intracranial bleeding, an annotation of “excellent clinical outcome” could be gained when all criteria of good effectiveness *and* the additional predefined clinical outcome are met.

### 4.2 | Initial management

The term “initial management” is used to indicate any treatment or strategy that is part of the initial bleeding management, including any studied treatment. This can also include infusion of blood products,

hemostatic agents, reversal agents, coagulation factors, and invasive interventions with diagnostic and therapeutic intention.

### 4.3 | At presentation

When the term "at presentation" is used, it indicates the time of presentation to the medical hospital where the initial management starts.

### 4.4 | Bleeding type

This item was discussed, and additional clarification was added to the criteria.

Bleeding is only classified as a visible bleed when the site of the bleeding is directly visible to the naked eye (e.g., skin surface, visible mucosal bleed [oral/nose/anal]) or when active bleeding is located in a compartment in which blood cannot be occult for longer time periods (e.g., epistaxis, vaginal bleeding). If blood can be seen, but not the actual site of the bleeding, and blood can be stored in a compartment (e.g., intestinal blood loss), this does not classify as a visible bleed.

Non-visible bleeding is any bleed that does not classify as visible, musculoskeletal, or intracranial bleeds (e.g., occult hemoglobin/blood loss). This includes GI bleeds, even when the bleeding site is visible during endoscopy. Generally, bleeds that are clinically evaluated by monitoring hemoglobin levels (as opposed to direct observation) qualify as non-visible bleeding.

### 4.5 | Hemoglobin levels

This item was discussed, and the criterion was further clarified and changed.

For non-visible bleeds, the outcome is defined by comparing the hemoglobin after initial management (T0 is immediately after completing the transfusion of red blood cells that was ordered at initial presentation of the bleed) with the hemoglobin measured at 48 hours after presentation. The bleeding outcome is defined as "good" when there is no drop of hemoglobin level of more than 10%. For patients who are discharged in a clinically stable situation before 48 hours, the hemoglobin at discharge can replace that at 48 hours.

This change allows patients who are discharged home early in stable condition to be classified as "good outcome" instead of "not evaluable."

### 4.6 | Pain and swelling

This criterion is adjusted whereby not only improvement, but also stable pain and swelling, is assessed as good clinical outcome of the bleeding management.

### 4.7 | Intracranial bleeds

For the intracranial bleeding type, it is allowed (as was erroneously missing in the first publication) to replace GOS-E with any validated scoring system to assess neurologic outcome if GOS-E is not routinely collected (especially in post hoc settings). We have used Glasgow Coma Scale as a valid alternative, but other scales could also be used.

### 4.8 | Additional invasive interventions

This item was discussed, and the criterion was further clarified and changed.

Invasive interventions are sometimes needed as part of the bleeding management. The fact that an intervention was performed initially does not change the criteria for outcome. However, if an intervention was complicated by bleeding, this signifies ineffective outcome. Similarly, an unscheduled (re-)intervention performed for bleeding control within 48 hours after initial bleeding management signifies ineffective outcome.

Of note, by invasive (re)intervention, all procedures with a clear therapeutic intention to manage the bleeding are meant. Diagnostic procedures, e.g., (second look) endoscopies, do not influence the hemostatic outcome, and are therefore not part of the assessment criteria.

### 4.9 | Time frame of 48 hours

For assessing hemostatic effectiveness, a time frame of 48 hours is maintained. If all criteria are met within this time frame, effective hemostasis is achieved. Any rebleed occurring after this time frame; requiring bleeding management with any treatment, e.g., an antidote, and/or transfusion of any blood product; and/or (unscheduled) re-intervention should be regarded as a new bleed and has no impact on the assessment of the hemostatic management of the index bleeding event.

## 5 | RECOMMENDATIONS

When validating the first definition of good clinical outcome, besides a few indistinctive parameters, some issues in applicability were identified. Most issues are solved by the revision of the criteria. In addition, problems were seen when data were missing. Also, as expected, adjudicators can make mistakes. Therefore, we additionally recommend the following:

- Prospective studies should be designed in a way that ensures the collection of parameters at the specified time points as required by the ISTH definitions.

- Two or more adjudicators should assess all cases independently with consensus forming after discussion.
- Verify that adjudicators read and understand definitions and assessment criteria.
- Collect and analyze data on additional pharmacological, coagulation, infusion, and intervention treatment used besides the data on the evaluated treatment.

## 6 | DISCUSSION AND CONCLUSION

The present article is a revised definition for rating clinical outcome and good effectiveness of hemostatic management of patients presenting with a major bleeding complication. Compared to the first definition that was published in 2016, the main adjustments concern clearly defined bleeding types and time frame. Clarifying the definition of bleeding types, especially regarding the visible and non-visible bleeds, will improve reproducibility of assessment, with no impact on average assessment. Most importantly, the definition can now be used for all bleeding management instead of only anticoagulant-associated bleeding.

The adjusted time frame allows patients who are discharged home early to be classified as "good outcome" instead of "not evaluable."

Additional interventions were discussed in the working group and unplanned interventions were added. The criteria describe good clinical outcome, without inferring a causal relation with any initial intervention. The main issue here is that patients might undergo several interventions at the same time, for instance a pharmacological intervention plus endoscopy for a bleeding ulcer. If these criteria are used for the assessment of effectiveness of antidotes or any other hemostatic treatment option, especially in uncontrolled studies, data on invasive interventions should be collected and additional analyses should be performed excluding patients undergoing additional interventions. Furthermore, unscheduled (re)interventions are added to the definition as consensus was reached that this signifies ineffective hemostatic outcome of the initial management.

Lastly, we added a recommendation paragraph to this revision to improve the applicability. This mainly involves using a committee of two or more adjudicators to assess the clinical outcome using this definition.

In conclusion, we recommend adoption of this revised ISTH-SSC standardized definition for any future studies addressing the hemostatic effectiveness of any treatment to manage a major bleed.

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### AUTHOR CONTRIBUTIONS

NK prepared the first draft of the manuscript; all authors contributed equally to the preparation and finalization of this manuscript.

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