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RESEARCH LETTER

Reporting haemostasis assays in IU/dL—A recommendation for harmonisation from the British Society for Haematology Haemostasis and Thrombosis Task Force, UK NEQAS for Blood Coagulation and the UK Haemophilia Centres Doctors Organisation

To the Editor,

For many tests in clinical medicine, metrological traceability and standardisation of reported results using Système International (SI) units ensures health care professionals in different institutions can understand, compare and interpret test data on their patients. According to Hansen, 'a non-systematic use of measurement units can create errors in communication between health care professionals and become a risk to patient safety'.[1] Concentrations for many laboratory test parameters can be defined using SI units, established for a large number of parameters in haematology and chemistry.[1] However, in haemostasis, the variables involved in quantification of an enzymatic process such as a clotting factor assay may not be easily defined using a specific metrological assay. Furthermore, very few haemostatic parameters have units defined in the International Federation of Clinical Chemistry and Laboratory Medicine (IFCCLM) Nomenclature for Properties and Unit terminology list.[2] Plasma levels of procoagulant factors and natural anticoagulants in mass concentration vary by more than a 1000-fold (Table 1), so measurement and reporting of such absolute values for clotting factors would greatly complicate interpretation of the presence or degree of a factor deficiency.

In haemostasis, the standards against which most factors are compared are international standards (IS) adopted by the World Health Organization (WHO). Prior to the establishment of IS in haemostasis, clotting factor activity in a test sample was defined relative to the activity in a pool of normal plasma which was arbitrarily assigned a value of 100% activity. Factor deficiency could then be defined as a % activity (relative to this pool) that fell below an established reference range. However, the actual level of the specific factor in the normal pool could vary significantly.[4] This issue can be overcome by measuring factors in a test sample relative to a reference material or standard of known concentration. Using this standard, the concentration of activity (or antigen) in the test sample can be determined and compared to established reference ranges in the diagnosis of a bleeding or thrombotic disorder.

International units are defined as the amount of analyte (antigen or activity) in 1.0 mL of pooled normal plasma.[4] Subsequent IS and also secondary standards are traceable to the first IS for a factor through collaborative value assignment studies. The SSC/ISTH Secondary Coagulation Standard (produced under the auspices of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) through the Coagulation Standards Standing Committee), is available to manufacturers to calibrate commercial standards for a range of factor assays, and has assigned potencies for these factors in IU/vial.[5]

In the absence of a SI unit for haemostasis factor concentrations, a variety of units are currently used by haemostasis laboratories. For most assays, these include IU/mL or IU/dL, and U/mL or U/dL if the reference material is not calibrated to the IS. Additionally, % remains widely used, in part due to the labelling of calibration plasmas by diagnostic manufacturers. It should be noted that other units are also in use for some haemostasis assays, such as μg/mL, ng/mL, μg/mL fibrinogen equivalent units (FEU) and ng/mL FEU for D-Dimer assay.

In 2023, United Kingdom National External Quality Assessment Scheme (UK NEQAS) (blood coagulation) asked participants in the external quality assurance scheme which units they used for reporting factor assays. Although the majority (64%) of UK labs have moved to using a standard of known concentration, 69% of participants from outside the UK continue to report as % of a normal pool (Table 2).

There is also variable practice with respect to reporting in the literature. A review of peer-reviewed published papers reporting FVIII assay results revealed data reported in a range of different units—U/mL, U/dL, IU/mL, IU/dL and % (see Table 3). These data indicate a lack of standardisation in reporting units, even within a single journal, and within a single article.

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There is some guidance on units of reporting from expert groups, but there is a lack of consistency or specific recommendation for these seemingly interchangeable units. The British Society for Haematology (BSH) guidelines[13] state that standards, calibrators and controls with potencies traceable to an IS should be used (e.g. IU/mL or IU/dL for factors) when available. Of note, the authors describe factor levels of <1 IU/dL when describing a factor deficient plasma.

International Council for Standardization in Haematology (ICSH) guidelines[14] recommend use of IU/dL when the calibrated material is calibrated to the WHO standard. However, they state alternative units such as % are acceptable.

Clinical & Laboratory Standards Institute (CLSI) guidelines[15] state units can be reported in %, U/mL, U/dL, IU/mL or IU/dL, but do recommend IU is used in preference to U if the assay is calibrated against an IS.

The World Federation of Haemophilia (WFH) laboratory manual,[16] developed for guidance to laboratories in resource-limited countries, uses IU/dL where relevant—but stops short of making this a recommendation.

Given the wide variation in the practice of reporting units, the authors have a particular concern for the potential for diagnostic errors by clinicians presented with a haemostasis assay result, where a severely deficient result could be misinterpreted as normal or vice versa. Of note, in the NEQAS questionnaire, two centres indicated they do not use the same units for reporting all assays, and 5/71 centres indicated they do not provide local reference ranges when issuing patient reports, which could also contribute to misinterpretation. Even when laboratories provide consistent units for reporting, the variation between laboratories is a significant risk for clinicians and other health care professionals moving from one institution to another without knowledge of the local reporting units. The use of decimal places increases the risk of transcription errors while artificially increasing the apparent accuracy of the result since most one-stage assays reported in IU/dL are not sensitive to one decimal place. A survey of healthcare professionals found that results reported with decimal places were more likely to cause confusion and errors in interpretation than if the result was converted to a whole number.[17]

A questionnaire was distributed in September 2024 to members of the United Kingdom Haemophilia Centres Doctors Organisation (UKHCDO), BSH, British Society for Haemostasis and Thrombosis (BSHT) and HaemSTAR working in the field of haemostasis, with a request for clinicians and scientists to indicate any known incidents of errors related to reporting units. Among 97 respondents, 17 indicated they were aware of errors or near misses, including a case of 1 IU/mL FXIII being interpreted as '1%', and confusing 0.1 IU/mL with <1 IU/dL. 91% of responders to this questionnaire supported harmonisation of reporting units, with 87% preferring IU/dL.

Several commented that a value in IU/dL was comparable with % when discussing levels with colleagues and patients, although it should be noted that these units are not interchangeable.

TABLE 1 Mean plasma levels of key coagulation factors in the circulation (adapted from Moore et al.[3]).

Coagulation factor	Mean plasma level μg/mL
Fibrinogen	3000
Factor II	90
Factor V	10
Factor VII	0.5
Factor VIII	0.1
Factor IX	5
Factor X	8
Factor XI	5
Factor XIII	10
Antithrombin	140
Protein C	4
Protein S	10

TABLE 2 Reporting units used for factor assays by 71 laboratories in the UK NEQAS (Blood Coagulation) EQA programmes.

Reporting unit	UK, *n* (%)	Non-UK, *n* (%)	All, *n* (%)
IU/dL	15 (38)	3 (9)	18 (25)
IU/mL	10 (26)	7 (22)	17 (24)
%	14 (36)	22 (69)	36 (51)

TABLE 3 Units reported in selected articles from scientific journals.

Article	References	Factor assay units reported in article	Comments
Res Pract Thromb Haemost 2023: Lancellotti et al.	[6]	IU/mL, IU/dL	Variable units within a single article
Semin Thromb Hemost 2023: Bowyer & Gosselin	[7]	IU/dL, IU/mL	IU/mL was quoting a study
Ther Adv Hematol 2018: Lambert et al.	[8]	%, IU/dL	Variable units within a single article
J Thromb Haemost 2023: Constantinescu-Bercu	[9]	IU/dL, U/mL, %	Table 1 headed IU/dL but results in U/mL, fig uses % but data appear as U/mL
J Thromb Haemost 2023; issue 12 Goudemand et al.	[10]	IU/dL	Variable units within the same issue of a journal
J Thromb Haemost 2023; issue 12 Hamedani et al.	[11]	IU/dL	
J Thromb Haemost 2023; issue 12 Drop et al.	[12]	U/mL	

A standardised approach to reporting haemostasis assay results to either U/dL or U/mL is therefore required. Given that IS are available for the majority of factors, a reference preparation or standard used in the assay traceable to the IS should be used, and the preferred unit for reporting then becomes IU.

The following points support the recommendation to report assay results in IU/dL.

1. Reporting in IU/mL will lead to many results reported as values below 1.0 (i.e. between 0.01 and 0.99). The use of decimal places increases the risk of errors in interpretation among health care professionals, with potential consequences for patient care. Use of decimal points when reporting results can also be misleading, implying a level of accuracy in an assay which cannot be justified, and also could be misread.
2. From guideline document recommendations, IU/dL is supported.
3. Given the straightforward premise of 'normal plasma' containing 100% of a factor, IU/dL and % are effectively comparable in terms of understanding, but using IU/dL avoids the pitfalls and lack of standardisation when using % results.
4. Formulas for calculating doses of factor concentrate are based on increments of factor levels in U/kg. The resulting rise in factor levels equates to whole units per dL rather than fractions of units per mL. If on treatment levels are reported in IU/mL, an additional calculation step is required when assessing the response increasing the chance for error.

We acknowledge the restrictions that may be in place with existing laboratory information systems (LIS) for reporting assay units, and that updating systems may affect legacy data—any change in practice would need to manage such risks. However, to reduce potential errors in future, and to assist in the harmonisation of assay data, we therefore recommend the following:

- Laboratories should report assay results in IU/dL, rather than IU/mL, except where an IS is not available, in which case U/dL should be used.
- Laboratories should use these units consistently across all their assays (unless appropriate to report in alternative units—e.g. D-Dimer in ng/mL FEU).
- Results in IU/dL should be reported to the nearest whole number.
- Reference plasmas/standards used in assays should be traceable to IS wherever possible.
- Laboratories should report results for haemostasis assays with reference ranges.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing, revision and approval of this article.

KEYWORDS

coagulation factors, external quality assessment, haemostasis

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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