Reply: Be aware of legally required metrology and higher-order reference measurement services run in calibration laboratories: A report from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-Scientific and Standardization Committee (SSC)/ International Society on Thrombosis and Haemostasis (ISTH) working group on PT/INR standardization

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Letter to the Editor

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Reply: Be aware of legally required metrology and higher-order reference measurement services run in calibration laboratories

A report from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)–Scientific and Standardization Committee (SSC)/ International Society on Thrombosis and Haemostasis (ISTH) working group on PT/INR standardization

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To the Editor,

In 1795 the French revolutionary government with strong involvement from prominent scientists pioneered by introducing the metric system to unify measurements and replace confusing local units. Its adoption caused international debate due to differences in tradition and trade interests. To continue establishment of standards, the International Bureau of Weights and Measures (BIPM) was founded in 1875 after the Metre Convention. The BIPM maintained and refined measurement standards through global scientific collaboration, paving the way for the adoption of the International System of Units (SI) at the General Conference on Weights and Measures (CGPM) in 1960 [1]. Nowadays the SI system is the fundament for consistent and accurate global measurement in science and everyday life, ensuring data comparability to promote global exchange. Similarly, in laboratory medicine metrological traceability to the SI or higher-order Reference Measurement Procedures (RMP) or Reference Materials (RM) is crucial to ensure metrologically traceable medical test results [2, 3]. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Scientific Division (SD) (https://ifcc.org/ifcc-scientific-division/) has a pivotal role when it comes down to operationalization of the SI-system and prioritization of critical measurand's standardization in laboratory medicine (see Figure 2 in reference [4] for stakeholders involved in establishing and implementing metrological traceability). A metrological linkage with a Reference Measurement System (RMS) based on the SI is promoted and implemented where possible. Higher-order RMPs are established and run by calibration (reference) laboratories, who form the foundation for metrological traceability in laboratory medicine. According to ISO 15195:2018 they are referred to as "calibration laboratories" and according to ISO 17511:2020 "reference/calibration laboratories". RMPs are typically laborious and expensive methods not to be used for routine analysis, but in calibration laboratories. RMPs follow ISO 15193:2009 and are metrologically traceable according to ISO 17511:2020. RMPs can be IFCC, World Health Organization (WHO) and Scientific and Standardization Committee (SSC)/International Society on Thrombosis and Haemostasis (ISTH) endorsed. For calibration services additional adherence to ISO 17025:2018 and ISO 15195:2018 is required [5]. RMPs and RMs as part of an RMS are used for standardization in laboratory medicine. Successful examples include HbA1c [6–8], enzymes [9], apolipoproteins [10] and creatinine [11, 12] standardization. Global test standardization in the coagulation domain is, however, not yet accomplished, and the first globally standardized coagulation test with a complete calibration hierarchy compliant to ISO 17511:2020

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tests is yet to be adopted in 2026 and beyond: the PT/INR test [13–15].

Given this context, in the May 2025 issue of the journal of Clinical Chemistry and Laboratory Medicine (CCLM), Favaloro questions the contemporary relevance of the harmonized Manual Tilt Tube technique (MTT) for prothrombin time (PT)/International Normalized Ratio (INR) measurements [16], which is a WHO and an IFCC-SSC/ISTH endorsed RMP. As representatives of one of the calibration labs, i.e. the Coagulation Reference Laboratory (CRL) from Leiden University Medical Center (LUMC) within the newly recognized RMS for Global PT/INR Standardization (Figure 1 for calibration hierarchies), and on behalf of the IFCC-SSC/ISTH working group on global PT/INR Standardization, we consider it essential to reply to this Editorial article to avoid confusion about the place for the MTT in modern haemostasis diagnostics. At CRL, a WHO-endorsed calibration lab for decades and formerly known as "Netherlands Reference Laboratory for Anticoagulant Control", we have a long history of calibration assignments for industrial partners and the MTT is performed by skilled and well-trained operators. Within a network of four calibration laboratories, workshops were organized to harmonize the MTT procedure and optimize the performance across different calibration labs [14], reaching excellent between-operator variations [15]. The harmonized MTT in the newly endorsed RMS (see Figure 1 for calibration hierarchies for wet lab citrated plasma and point-of-care whole blood) forms the higher-order foundation for PT/INR measurements globally. Calibration labs perform the harmonized MTT for INR value assignment with the primary International Reference Preparation (IRP) for thromboplastin (human recombinant) characterized by established values for International Sensitivity Index (ISI) and Mean Normal PT (MNPT) [15]. The new calibration hierarchy is ISO 17511:2020 compliant and makes use of a single human recombinant IRP in contrast to the two higher-order IRPs (rabbit brain and human recombinant origin) historically.

The MTT is particularly suited as RMP, as it has been recommended by the WHO and used from the early beginning for the definition of the INR and ISI [18]. The MTT is also manufacturer independent and vital for the continuation of the INR system [19]. In comparison to the multiplicity of automated analysers, the MTT minimizes ISI bias and ensures long-term availability. Other than that, the harmonized MTT is essential for the preservation of the primary IRP stock, the method is cost-effective and available for interested laboratories at a global scale (following appropriate training of the operators) [15, 20–22]. To ensure the method RMP is fit-for-purpose, the MTT has been harmonized to reduce measurement uncertainty within 3.3 % (1/3 of maximum allowable measurement uncertainty (MAU)) among four calibration labs [15, 17]. The calibration labs will perform calibration services especially for the *In-vitro* Diagnostics (IVD)-industry. Additionally, value assignments of commutable samples for third parties (e.g. thrombosis service centers, External Quality Control (EQA)-organizers, …) will also be performed. The ultimate goal is that every PT/INR result is within the maximum allowable measurement uncertainty of 10 % of the reference value and becomes traceable to the primary RMP and IRP [13]. EQA organizer(s) should adapt their EQA-designs for trueness assessment of PT/INR in medical laboratories. In that context, the MTT is not at all recommended for the end-users, but is meant to be run by operational experts in calibration labs. It is important to realize that the MTT is on the top of the calibration hierarchy for PT/INR testing, according to ISO 17511:2020 clause model 5.3: with a higher-order reference reagent and measurement procedure (MP) defining the INR (measurand) [13]. As such, the combination of the primary IRP and harmonized MTT forms the metrological foundation for global PT/INR standardization and enables the end-user results to be metrologically traceable, establishing an unequivocal traceability chain for PT/INR test results. The need for global PT/INR standardization becomes evident when, for example, whole blood point of care INR device validation studies show systematic bias in particular devices compared to laboratory INR methods [23].

Following establishment and implementation of IRP coded 24/114, also known as the WHO 6th International Standard for Thromboplastin (human recombinant), in 2026 and beyond, the WHO, the Medicines and Healthcare products Regulatory Agency (MHRA), the IVD-industry, calibration labs and other stakeholders in the IFCC-SSC/ISTH working group are collaborating to facilitate a smooth adoption and implementation of the new RMS. As ISO 17511:2020 is a normative reference in IVDR 2017/746, the IVD-industry must produce kits that generate metrologically traceable results [24]. By applying the metrological traceability concept for the very first time for a coagulation test and by upgrading and harmonizing the WHO MTT PT/INR kits based on rabbit (-combined) thromboplastin will see the largest change in end-result. The IFCC and ISTH have an important role by endorsing the new RMS, while the IVD-industry is proceeding with the immediate implementation of the new RMS. Education in metrology in this context is essential [2, 3].

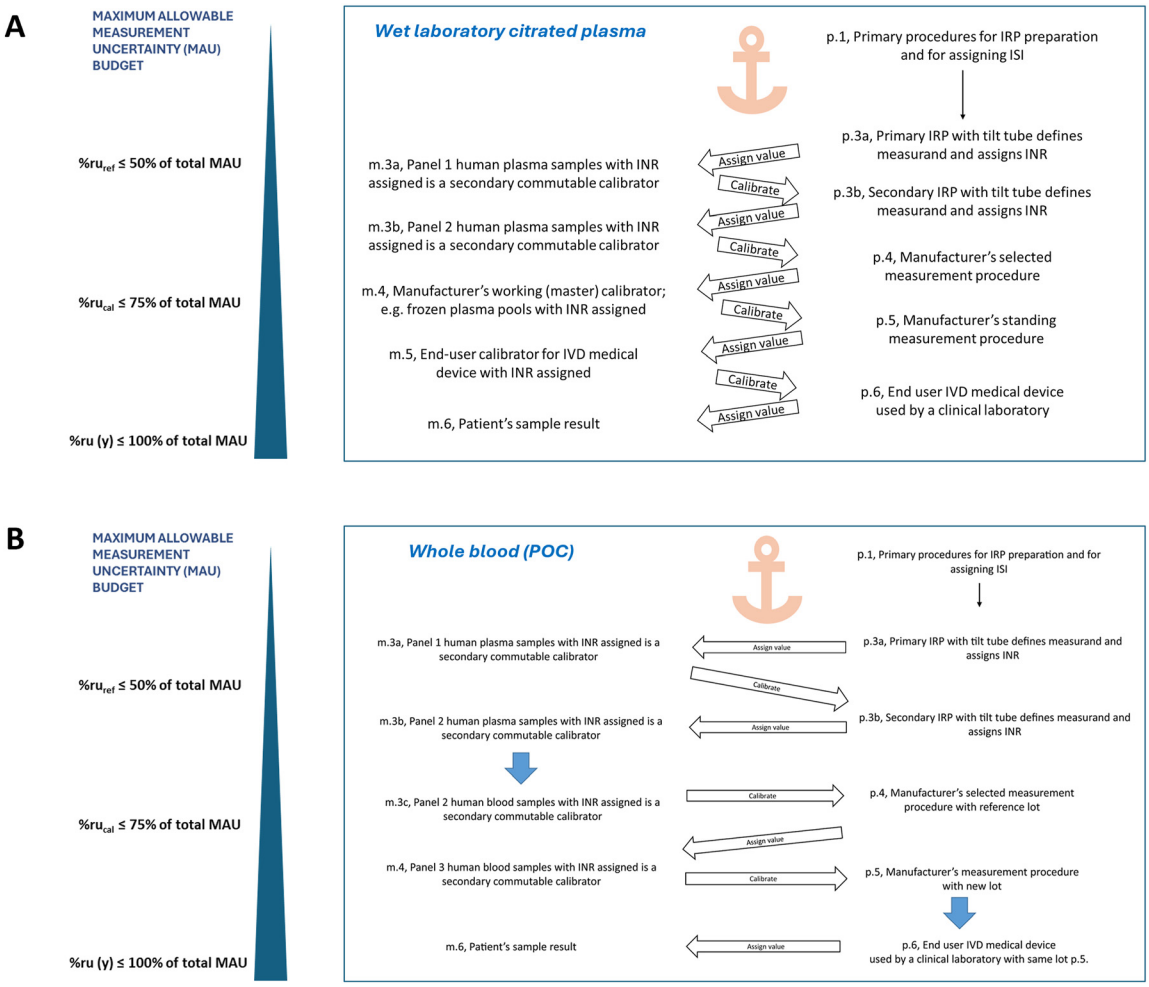

Figure 1: Complete calibration hierarchies for PT/INR according to ISO 17511:2020 for (A). Wet laboratory citrated plasma samples and (B). Point-of-care (POC) whole blood samples [13]. On the left side the maximum allowable measurement uncertainty (MAU) budget is shown, which has been recently updated [17]. Reprinted from Journal of Thrombosis and Haemostasis, Vol. 22, Issue 4, Antonius M. H. P. van den Besselaar et al., Defining a metrologically traceable and sustainable calibration hierarchy of international normalized ratio for monitoring of vitamin K antagonist treatment in accordance with International Organization for Standardization (ISO) 17511:2020 standard: Communication from the International Federation of Clinical Chemistry and Laboratory Medicine–SSC/ISTH working group on prothrombin time/international normalized ratio standardization, 1236–1248, Copyright 2024, with permission from Elsevier. License no. 6210640029620.

In conclusion, Favaloro should be aware of the legally required metrological traceability of test results, the relevance of ISO 17511:2020 and the importance of calibration laboratories accomplishing global test standardization. The MTT is a higher-order RMP, WHO and IFCC-SSC/ISTH endorsed, which together with the primary IRP for thromboplastin lays the foundation for the calibration hierarchy of PT/INR tests. Its intended use is only to be operated by internationally recognized calibration labs. The complete RMS for PT/INR is the anchor for enabling metrological traceability of PT/INR tests results within MAU in time and space [13–15]. Global adoption of the IFCC, WHO and ISTH endorsed PT/INR RMS is a must to ensure exchangeability of PT/INR results within 10 % for different methods, overall improving patient management and outcome.

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