Received: 22 September 2022 | Accepted: 17 February 2023

DOI: 10.1111/ijlh.14051

REVIEW

ISLH International Journal of Laboratory Hematology WILEY

ICSH guidance for INR and D-dimer testing using point of care testing in primary care

David A. Fitzmaurice[1] | Geert-Jan Geersing[2] | Xavier Armoiry[3] | Sam Machin[4] | Steve Kitchen[5] | Ian Mackie[4]

[1]Warwick Medical School, University of Warwick, Coventry, UK

[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[3]Claude Bernard University Lyon 1, Lyon School of Pharmacy (ISPB), Lyon, France

[4]Research Haematology Department, University College London, London, UK

[5]Sheffield Haemophilia and Thrombosis Centre, Sheffield, UK

Correspondence
Steve Kitchen, Sheffield Haemophilia and Thrombosis Centre, Sheffield, UK.
Email: steve.kitchen1@nhs.net

Abstract

This guideline has been written on behalf of the International Council for Standardisation in Haematology (ICSH) and focuses on two point of care haematology tests used within primary care, namely International Normalised Ratio (INR) and D-dimer. Primary care covers out of hospital settings and can include General Practice (GP), Pharmacy and other non-hospital settings (although these guidelines would also be applicable to hospital out-patient settings). The recommendations are based on published data in peer reviewed literature and expert opinion; they should supplement regional requirements, regulations or standards.

KEYWORDS
D-dimer, INR, point of care testing, primary care

1 | INTRODUCTION

This guideline has been written on behalf of the International Council for Standardisation in Haematology (ICSH) and focuses on two point of care (POC) haematology tests used within primary care, namely International Normalised Ratio (INR) and D-dimer. Primary care covers out of hospital settings and can include General Practice (GP), Pharmacy and other non-hospital settings. This guidance is intended for use by health care professionals performing INR or D-dimer tests in those locations (although these guidelines would also be applicable to hospital out-patient settings).

The recommendations are based on published data in peer reviewed literature and expert opinion; they should supplement regional requirements, regulations or standards.

Professor Sam Machin helped to draft this guidance document and critically commented on each draft, as well as approving the manuscript for publication. However, he sadly died on 2nd October 2021, before the final submission. This document is submitted with the approval of his wife, Jean Machin.

Disclaimer: While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the ICSH nor the publishers accept any legal responsibility for the content of this guidance.

2 | METHODS

A literature review was undertaken to identify published studies that could inform evidence-based practice on primary point of care testing related to INR and D-dimer. Our eligibility criteria were: systematic review/guideline describing the use of INR and/or D-dimer tests as part of primary POC and assessing INR and/or D-dimer POC equipment/device in terms of health service, staff training (frequency of use/learning curve), monitoring of quality (quality control), accreditation and safety. Only systematic review/guideline of high methodological quality were retained based on quality assessment. Studies reporting only diagnostic performance of INR and/or D-dimer POC were not included.

English language studies were searched in two electronic databases (EMBASE and PUBMED) from January 2005 to May 2017. A combination of free-text and thesaurus terms for 'POC', 'D-dimer', 'INR' were used to identify related literature. Two reviewers independently screened all titles/abstracts and examined full-text publications of potentially relevant citations (DF and GG). Disagreements were discussed and resolved through consensus. The quality of potentially relevant studies was assessed using the checklist published by the National Institutes of Health[1] for systematic reviews, and the AGREE II checklist for guidelines.[2] Quality assessment was performed

independently by two reviewers. Any disagreement between reviewers was resolved by consensus. The overall quality of each study was rated as poor, fair, or good, accounting for each study's limitations as emphasized by the items within the checklists. Only studies rated as good were deemed of high methodological quality and were therefore retained for final inclusion.

Of the 396 identified records, we removed 343 not meeting our inclusion criteria at title/abstract stage, leaving 53 articles to be examined at full-text. Based on screening at full-text, 22 fulfilled our eligibility criteria, but only four,[3–6] all systematic reviews, were rated of good quality. The Sharma paper[6] was included even though it primarily related to self-monitoring. We therefore concluded that there were no recent systematic reviews to inform evidence-based practice on primary POC testing related to INR and D-dimer.

Given the paucity of high-level quality evidence, a non-systematic targeted search was undertaken using the same electronic databases as described above and the same eligibility criteria except that we widened the search to primary research studies. This further search confirmed the paucity of available studies published as original papers on INR and D-dimer primary POC. Hence, the guideline was mainly based on expert's opinions and also used, where relevant, the studies identified in previous stages.

3 | RELIABILITY OF POC INR AND D-DIMER RESULTS

Ideally, INR and D-dimer devices intended for use in primary care should be assessed for accuracy and precision in clinical studies performed in a primary care setting. However, the INR has mostly been studied in terms of clinical efficacy and by measuring the time in therapeutic range. D-dimer studies have focussed on clinical outcomes since the measurement of accuracy and comparability with hospital laboratory methods is hampered by the lack of standardisation of D-dimer measurement. D-dimer represents a range of molecular species rather than a single entity, there is no International Standard plasma and methods use a variety of calibrants and monoclonal antibodies, so that they vary in sensitivity and measurement range.

POC device evaluations should include assessment of reproducibility (i.e., precision) and accuracy. The latter is determined in some regions by comparing the POC with a hospital laboratory measurement using a 'split' sample[7] or paired fingerstick and venous blood sample. However this is not always straightforward; there are several reasons why the POC and laboratory results might demonstrate poor agreement. Good correlations for INR can only be expected for patients whose INR results have stabilised and are within the therapeutic range. For INR values above 4.5, the INR system is no longer comparable between methods for reasons inherent in its calculation. Differences between POC and laboratory results may be due to inaccuracy in one or both of the methods being compared.

POC devices are considered acceptable if their performance is comparable to that achieved by standard laboratory methods using coagulometers. An alternative approach could also include, in addition to agreement with laboratory devices, a favourable comparison with reference methods on clinical outcomes, such as, for example, bleeding or thrombotic complications for POC INR devices. In most health economies it would be expected that oversight of any POC programme would be through a hospital laboratory, this would include responsibility for evaluation of any device alongside training documentation and responsibility for implementation of any quality assurance programmes.

> We recommend that POC INR and D-dimer tests performed in primary care should have the oversight of an accredited hospital laboratory.

4 | QUALITY ASSURANCE

It is well accepted by healthcare professionals that quality assurance (QA) must be used to ensure the accuracy and reliability of tests. In the POC setting, the the approach to QA suggests this is not always well understood,[7] although several national and international guidance documents and review articles have stressed the requirement.[8–11] The concept of QA and its importance should be included in the continuing primary care training process.

QA includes both internal quality control (IQC) and external quality assessment (EQA), which are detailed below. Both IQC and EQA should be performed if suitable materials for the POC device are available, at a minimum as required by regulatory authorities and manufacturer's recommendations. Manufacturers IQC materials provided by the device manufacturer are suitable for IQC testing and material from an organisation accredited against ISO 17043 for provision of POC INR or D-dimer testing is suitable for EQA testing.

5 | QUALITY CONTROL FOR INR TESTING IN PRIMARY CARE

5.1 | Internal quality control (IQC)

IQC is performed by the user with materials having a target value and acceptable range. Three different types of IQC are available for POC, depending on the individual device: electronic, on-board and liquid.[8] For electronic IQC a special cartridge is inserted instead of a test strip and this simulates test performance confirming adequate function of the optical or mechanical system. Where available, electronic IQC should be carried out every time the device is used, but does not replace the need for other forms of IQC, since only part of the system is being tested. Some devices utilise integral IQC within the test strip and this is useful to validate each individual test strip. Where possible, liquid IQC material (plasma or whole blood, as appropriate) should also be used. This should have a target within 2.0–4.0 INR units. Results should not only be within the manufacturer's target range, but also within an appropriate range for the use of the device (i.e., 2.0–4.0 for monitoring vitamin K antagonists, VKA). Repeated values should be

within 0.5 INR units of each other since this difference is not predicted to affect patient management; this is very important if the manufacturer provides a wide target range.

It is difficult to be prescriptive regarding the frequency of undertaking IQC tests however users should adhere to any regulatory requirements for their region, and to manufacturers' instructions for use. We recommend that IQC using liquid material should be performed as per recommendations below.

5.1.1 | Recommendations for POC INR IQC

Many of these recommendations are consistent with specific recommendations in previously published guidance.[8,10]

IQC should be performed.

- at the start of each clinic or day if the device is used in a domiciliary setting.
- after 20 tests have been performed.

Remark: The choice of 20 is pragmatic given that all patients seen prior to an out of range test would have to be recalled.

- when starting a new batch/lot of test strips.
- when beginning to use a new pack of test strips even if it is the same Lot number as before.
- if there is any doubt about the storage conditions of the test strips.
- if an unexpectedly high or low patient result occurs.
- if IQC results are outside the target range, a second IQC sample should be tested. If this is also outside the acceptable range, testing should be suspended and the health care professional should contact the manufacturer of the device.
- Record keeping should include the lot numbers of IQC material and any test materials used, the date and time of testing, the serial number of the device and the identity of the operator in addition to the IQC result obtained.

5.2 | External quality assessment (EQA) for POC INR

EQA for INR POC test devices has been recommended[12,13] and is available to healthcare professionals for a number of POCT devices[7,11,14,15] through organisations including UK NEQAS,[14] RCPAQAP[15] and others. This usually takes the form of the service provider sending lyophilised or liquid samples to the healthcare provider, who performs the test on their device and returns the result. Their proficiency is checked and a performance report is subsequently returned to them. Some authors have assessed use of native patient samples for EQA of POC[16,17] and applied this to POC INR testing when commutable EQA materials are not available[18] although the utility of comparison to a laboratory result depends on the accuracy of the laboratory method.

5.2.1 | Recommendations for POC INR EQA

- all users of POC INR testing should enrol in an EQA programme accredited against ISO 17043 where available, with the external quality assessment material provided directly to the health care professional for testing.
- in the absence of a formal EQA scheme, results from a fingerstick sample using POC and a paired venous sample collected at the same time tested using a laboratory coagulometer system should be compared.

Remark: This should be done in patients stabilised on VKA with therapeutic INR values. The results on paired samples should be within 0.5 INR units.

It is important to consider that INR results vary between analysers and reagents; causes of poor INR comparability have been reviewed.[19]

- EQA testing should be undertaken at least every 3 months or as per any regional regulatory requirements, whichever has the shorter interval between EQA testing.
- Where liquid IQC is not available/appropriate, more frequent EQA checks may be required.
- Record keeping should include the lot numbers of any test materials used, the date and time of testing, the serial number of the device and the identity of the operator in addition to any EQA results obtained.

5.2.2 | Recommendation concerning high INR values

- If INR values between 4.5 and 8.0 are obtained for a patient using a POCT device, the test should be repeated immediately. Such abnormal results could in principle be due to poor sample quality. If the repeat test confirms the result (i.e., within 0.5 INR units) and is between 4.5 and 8 the result can be used for patient management. If an INR result is >8 on initial or repeat testing the patient should seek medical advice promptly. In the case of any confirmed result above INR 8.0, a venous sample should be collected and sent to the laboratory for testing, since clinical intervention may be required depending on the degree of INR prolongation.[20]
- Remark: In some countries a venous sample would be sent for all INRs above the therapeutic range.

6 | TRAINING FOR POC INR METHODS

INR POC testing should only be performed by health care professionals (HCP) who have undertaken formal accredited training where available, this could include GPs, pharmacists and practice nurses. Health care assistants are also being utilised more within primary care in some countries. Training should include a basic understanding of

coagulation, the principles of oral anticoagulation with VKA, and INR monitoring. It should also ensure that the HCP demonstrates the ability to reliably measure the INR using a suitable POC device and where appropriate to recommend the correct warfarin dose (where regional regulations permit this for the particular HCP category). Detailed information about training programmes has previously been reviewed.[8]

7 | ADDITIONAL RECOMMENDATIONS FOR INR POC TESTING

- The POC device should have demonstrated acceptable performance in an evaluation independent of the manufacturer, ideally by an expert body approved by any regional regulatory process.
- All HCP using INR POC tests must demonstrate appropriate competencies through an accredited training scheme where available.

8 | POINT-OF-CARE D-DIMER TESTING

D-dimers are a heterogeneous group of proteins generated by the breakdown of cross-linked fibrin and provide an indirect marker of coagulation activity. It is widely appreciated that when combined with a clinical probability assessment, D-dimer can be used to exclude suspected cases of venous thrombo-embolism (VTE). Although the majority of patients enrolled in studies had a diagnosis of deep venous thrombosis,[4] similar strategies also appear to work in primary care for pulmonary embolus.[21] Laboratory based assays rely on ELISA techniques or automated immunoturbidometry and are generally considered to be high sensitivity assays for exclusion of VTE, and thus to rule-out the condition. Importantly, each D-dimer method uses different sets of monoclonal antibodies with varying specificity and reactivity, thus measuring a different population of cross-linked fibrin degradation products. No international standard for D-Dimer is presently available and assays are reported in different types of unit. Clinically validated cut-off values for VTE exclusion are therefore required for each test system. As such, different D-dimer assays are difficult to compare with each other in terms of laboratory precision and sensitivity. Nevertheless, many laboratory D-dimer assays use a cut-off of 500 μg/L to define the upper limit of the normal reference range. However, for some products, the value for negative exclusion of VTE may be different to the upper limit of the normal range. The current interpretation of D-dimer testing often incorporates patient age or pre-test risk to define the threshold.

For laboratory based D-dimer assays, it has been suggested that the negative predictive value should be ≥98%, which is equivalent to the sensitivity of ultrasonography for proximal vein thrombosis.[4,22] POC D-dimer methods can be either qualitative or quantitative. As a general rule, the validity of test results is compared with clinical diagnoses rather than with results from laboratory assays, which in fact also can be difficult given the aforementioned issues related to between test comparisons. This clinical validity of point-of-care D-dimer tests was meta-analysed by Geersing et al.[4] demonstrating that sensitivity of these tests is somewhat lower than laboratory assays, stressing the need that they can only be used in a low-risk population and thereby emphasizing the need to combine results with a clinical probability assessment. The latter should preferably be performed with an objective clinical decision rule, such as the rules proposed by Wells et al.[23,24] Combining a low to moderate (i.e., non-high) clinical probability with a negative (POC) D-dimer (either fixed threshold or adjusted for age or pre-test risk) can safely rule-out VTE in primary care.[25,26]

8.1 | Quality assurance for POCT D-dimer testing

In contrast to POC for INR, no formal studies have evaluated the obvious need for quality assurance for POC D-dimer methods, despite this being a regulatory requirement in some regions. In particular, the use of qualitative POC D-dimer assays is associated with quality issues regarding the actual performing of the test (e.g., not obtaining enough blood, air collection in the capillary tube, etc.). Thus, although the use of some qualitative assays was demonstrated to be safe in the context of controlled clinical trials, where participating GPs received continuous support and training, performance may be different in daily clinical practice. Novel qualitative assays are under development and are currently evaluated in clinical research settings, and will need continuous quality control.

Variability between imprecision of POC D-dimer has been reported with between day variation in D-dimer results obtained using five POC devices in the range 1.8%–15.3% at a D-dimer level close to cut-off for VTE[27] which confirms that quality control is required.

Some specific recommendations are given below and quality assurance for quantitative assays should follow a similar pattern as that described for point-of-care INR testing.

8.2 | Recommendations for point-of-care D-dimer testing

- POC D-dimer assays should only be used in patients with a low to moderate clinical probability assessment for VTE, stressing the need to combine them with a validated clinical prediction model.
- The use of qualitative POC assays should be restricted to strictly controlled settings where regular quality control is implemented and where regulatory requirements permit their use.

8.2.1 | Recommendations for POC D-dimer IQC

IQC should be performed.

- when starting a new batch/lot of test strips.

- when beginning to use a new pack of test strips even if it is the same Lot number as before.
- if there is any doubt about the storage conditions of the test strips.
- after a maximum of 20 tests have been performed.

If IQC results are outside the target range, a second IQC sample should be tested. If this is also outside the acceptable range, testing should be suspended and the health care professional should contact the manufacturer of the device.

8.2.2 | Recommendations for POC D-dimer EQA

All users of POC D-dimer tests should enrol in an EQA programme accredited against ISO 17043 where available.

If IQC and/or EQA are unavailable it is more difficult to confirm that the POC results are safe to release for patient management. In such cases the POC site should liaise closely with an accredited laboratory performing D-dimer to assess the feasibility of using paired samples tested on both the POC and laboratory methods as a form of quality assessment, although D-dimer results are not yet harmonised between different methods[27] so numerical equivalence between results of any two methods is rare.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

ORCID

Steve Kitchen https://orcid.org/0000-0003-4790-1159
Ian Mackie https://orcid.org/0000-0002-7393-2365

REFERENCES

1. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
2. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182:E839-E842.
3. Connock M, Stevens C, Fry-Smith A, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess*. 2007;11:iii-iv, ix-66.
4. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009;339:b2990. doi:10.1136/bmj.b2990
5. Gialamas A, St John A, Laurence CO, Bubner TK, PoCT Management Committee. Point-of-care testing for patients with diabetes, hyperlipidaemia or coagulation disorders in the general practice setting: a systematic review. *Fam Pract*. 2010;27(1):17-24. doi:10.1093/fampra/cmp084
6. Sharma P, Scotland G, Cruickshank M, et al. The clinical effectiveness and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy, compared with standard UK practice: systematic review and economic evaluation. *Health Technol Assess*. 2015;19(48):1-172. doi:10.3310/hta19480
7. Kitchen DP, Kitchen S, Jennings I, Woods TA, Walker ID, Preston FE. Point of care testing by health care professionals: current practice amongst the UK National External Quality Assessment Scheme Participants. *Br J Haematol*. 2005;130:320-321.
8. Jennings I, Kitchen D, Keeling D, Fitzmaurice D, Heneghan C, the BCSH Committee. Patient self-testing and self-management of oral anticoagulation with vitamin K antagonists: guidance from the British Committee for Standards in Haematology. *Brit J Haematol*. 2014;167:600-607.
9. Perry DJ, Fitzmaurice DA, Kitchen S, Mackie IJ, Mallett S. Point-of-care testing in haemostasis. *Br J Haematol*. 2010;150:501-514.
10. Briggs C, Guthrie D, Hyde K, et al. Guidelines for point-of-care testing: haematology. *Br J Haematol*. 2008;142:904-915.
11. Tripodi A, Bressi C, Carpenedo M, Chantarangkul V, Clerici M, Mannucci PM. Quality assurance program for whole blood prothrombin time-international normalized ratio point-of-care monitors used for patient self-testing to control oral anticoagulation. *Thromb Res*. 2004;113:35-40.
12. MHRA (Medicines and Healthcare Products Regulatory Agency). *Management and Use of IVD Point of Care Test Devices*; 2013. https://webarchive.nationalarchives.gov.uk/ukgwa/20141205150130/http://www.mhra.gov.uk/home/groups/dts-bi/documents/publication/con071105.pdf
13. Fitzmaurice DA, Gardiner C, Kitchen S, et al. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol*. 2005;131:156-165.
14. Kitchen DP, Kitchen S, Jennings I, et al. Point of care INR testing devices: performance of the Roche CoaguChek XS and XS plus in the UK NEQAS BC external quality assessment programme for healthcare professionals: four years' experience. *J Clin Pathol*. 2012;65:1119-1123.
15. Bonar R, Mohammed S, Favaloro EJ. International normalised ratio monitoring of vitamin K antagonist therapy: comparative performance of point-of-care and laboratory- derived testing. *Semin Thromb Haemost*. 2015;41:279-286.
16. Sølvik UØ, Stavelin A, Christensen NG, Sandberg S. External quality assessment of prothrombin time: the split-sample model compared with external quality assessment with commercial control material. *Scand J Clin Lab Invest*. 2006;66:337-349.
17. Stavelin A, Petersen PH, Sølvik U, Sandberg S. Internal quality control of prothrombin time in primary care: comparing the use of patient split samples with lyophilised control materials. *Thromb Haemost*. 2009;102:593-600.
18. Stavelin A, Petersen PH, Sølvik UØ, Sandberg S. External quality assessment of point-of-care methods: model for combined assessment of method bias and single-participant performance by the use of native patient samples and noncommutable control materials. *Clin Chem*. 2013;59:363-371.
19. Kitchen DP, Kitchen S, Jennings I, Woods T, Walker I. Quality assessment in point-of-care coagulation testing. *Semin Thromb Hemost*. 2008;34:647-653.
20. Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin – fourth edition. *Br J Haematol*. 2011;154:311-324.
21. Geersing GJ, Takada T, Klok FA, et al. Ruling out pulmonary embolism across different healthcare settings: a systematic review and individual patient data meta-analysis. *PLoS Med*. 2022;19:e1003905. doi:10.1371/journal.pmed.1003905
22. Keeling DM, Mackie IJ, Moody A, Watson HG, British Committee for Standards in Haematology. The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging. *Br J Haematol*. 2004;124:15-25.
23. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798.

24. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *NEJM*. 2003;349:1227-1235.
25. Oedega R, Moons KGM, Hoes AW. Ruling out deep vein thrombosis in primary care. *Thromb Haemost*. 2005;94:200-205.
26. Toll DB, Oudega R, Vergouwe Y, Moons KGM, Hoes AW. A new diagnostic rule for deep vein thrombosis: safety and efficiency in clinically relevant subgroups. *Fam Pract*. 2008;25:3-8.
27. Heerink JS, Gemen E, Oudega R, Hopstaken R, Geersing G-J, Kusters R. Analytical performance and user-friendliness of five novel point-of-care D-dimer assays. *Scand J Clin Lab Invest*. 2020;80:433-440.

How to cite this article: Fitzmaurice DA, Geersing G-J, Armoiry X, Machin S, Kitchen S, Mackie I. ICSH guidance for INR and D-dimer testing using point of care testing in primary care. *Int J Lab Hematol*. 2023;1-6. doi:10.1111/ijlh.14051