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REVIEW ARTICLE

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International Council for Standardisation in Haematology (ICSH) recommendations for collection of blood samples for coagulation testing

Steve Kitchen[1] | Dorothy M. Adcock[2] | Ray Dauer[3] | Ann-Helen Kristoffersen[4,5] | Giuseppe Lippi[6] | Ian Mackie[7] | Richard A. Marlar[8] | Sukesh Nair[9]

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

[2]Laboratory Corporation of America Holdings, Burlington, NC, USA

[3]Melbourne, Australia

[4]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[5]Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway

[6]Section of Clinical Biochemistry, University of Verona, Verona, Italy

[7]Research Department of Haematology, University College London, London, UK

[8]Department of Pathology, University of New Mexico, Albuquerque, NM, USA

[9]Christian Medical College, Vellore, India

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

Abstract

This guidance document has been prepared on behalf of the International Council for Standardisation in Haematology (ICSH). The aim of the document is to provide guidance and recommendations for collection of blood samples for coagulation tests in clinical laboratories throughout the world. The following processes will be covered: ordering tests, sample collection tube and anticoagulant, patient preparation, sample collection device, venous stasis before sample collection, order of draw when different sample types need to be collected, sample labelling, blood-to-anticoagulant ratio (tube filling) and influence of haematocrit. The following areas are excluded from this document, but are included in an associated ICSH document addressing processing of samples for coagulation tests in clinical laboratories: sample transport and primary tube sample stability; centrifugation; interfering substances including haemolysis, icterus and lipaemia; secondary aliquots—transport and storage; and preanalytical variables for platelet function testing. The recommendations are based on published data in peer-reviewed literature and expert opinion.

KEYWORDS

coagulation, ICSH, sample collection

1 | INTRODUCTION

A number of preanalytical variables have been shown to have an impact on many laboratory tests, including those related to haemostasis and thrombosis.[1,2] The preanalytical phase is a major source of inaccurate laboratory test results,[3] with between one third and three quarters of laboratory errors being attributable to this phase,[4] and appears especially problematic in relation to coagulation tests. Many preanalytical errors are a consequence of inappropriate or problematic blood sample collection, handling, storage, transport or processing. In 2013, a study estimated the average cost of a preanalytical error to be around $200 in both European and North American institutions, representing an annual cost of $1.2 million for a 650 bed hospital in the USA Table 1.[5]

Preanalytical problems can be surprisingly common, occurring in around 5% of samples in one study where samples not arriving in the laboratory (49% of problems), haemolysis (20%), sample clotting (14%) and inappropriate blood-to-anticoagulant ratio (14%) were the most frequently encountered issues.[6] Analysing inappropriate samples and release of results which may be unsafe for informing clinical management decisions constitutes an important risk for patient safety. Some samples may not be easy to replace, and not all rejected samples are replaced within the relevant time frame. Samples with a high risk that results could be unsafe should not be analysed, but any acceptance/rejection protocols should balance the risks of releasing potentially unsafe or misleading results against the risks associated with rejection followed by delay, or sometimes failure in obtaining a replacement sample, leading to delay or absence of test results.

2 | ORDERING TESTS

The introduction of hospital integrated systems (HISs) and laboratory information systems (LISs) has led to integrated electronic medical records capable of sharing critical patient information, such as relevant medical history, previous surgery or treatments and laboratory results. Electronic medical record systems can include computerized provider order entry (CPOE) functionality and can support hospital wide integration of electronic and clinical databases. Laboratory clinicians and scientists need to understand both laboratory and hospital information systems and their integration,[7-9] as well as often managing or providing oversight for collection services. Electronic ordering directly affects central specimen reception data entry time, which has broader impact on turnaround times. Data entry time was found to be shortened after implementation of electronic ordering and was significantly faster compared with paper-based ordering.[10] The use of CPOE has also been shown to enhance decision support systems and can improve laboratory efficiency and its contribution to effective patient care, while proving to be also a repository for interrogating all orders that have been placed.[11] The introduction of electronic ordering systems (EOS) as part of an integrated electronic medical record is expected to eliminate legibility issues with interpretation of handwritten orders and should reduce errors in both the wards and the laboratory, thus improving/enhancing the quality of the information provided to the laboratory. Computerized provider order entry systems have been promoted for their potential to improve the quality of care through their potential to increase efficiency, effectiveness and accuracy.[12,13] Laboratory testing has a direct impact on the length of stay in short stay units, especially in emergency departments (EDs). The laboratory turnaround time (TAT), number of testing episodes and test volume have been shown to influence emergency length of stay.[14] EOS provide many potential benefits for improving the efficiency and effectiveness of healthcare delivery. They also have impacts for organizational and communication processes within the hospital. Georgiou et al[15] showed that EOS resulted in major alteration of the information management processes within the hospital which in turn impacted communication processes.

Electronic ordering systems must have robust process design that minimizes risk of error. The collection of samples using these systems can still result in error due to poor labelling, including the wrong patient's blood in the tube. Some systems are hybrids between HISs and LISs and may allow networked printers to be used for generation of labels at the point of collection. These systems may generate labels remotely from the point of collection, causing the collection staff to go to the printer, collect the label and return to the bedside or point of collection to label the blood tubes. This type of system has the potential for confusion and error. Moreover, multiple patient labels may be generated, and labelling mistakes may occur whether the wrong label is placed on the blood tube. Integrated systems are more robust and may allow for handheld devices to be used at the point of collection. These systems permit the phlebotomist to scan hospital in-patient's wrist band if these are in use, and generate appropriate labels at the point of collection. Other mobile devices such as computer on wheels systems may also be used, providing a facility with an integrated printer which can generate appropriate labels locally.

Introduction of CPOE poses a major challenge for pathology laboratories, which may experience major changes in organizational and work relationships. Pathology laboratories need to be proactive in planning and implementation of these systems. The importance of building strong organizational links and relationships with the users of these systems is crucial to their success.[13,16,17]

There are a number of important components that can facilitate adoption of a good paperless requesting system, including (i) establishment of an implementation committee to ensure seamless integration of EOS; (ii) processes and policies for positive patient identification must be in place; (iii) positive identification of collectors must be integrated into the system to ensure full traceability and auditing, especially with paperless requests; (iv) integration of dedicated printers at the point of collection, such as handheld printers or computers on wheels; (v) development of clear written procedures; (vi) establishment of healthcare professional training programmes, especially related to procedural requirements for blood collection; (vii) automated functions, both for supporting operations and executive operations; (ix) monitoring of quality indicators; (x) ongoing communication among healthcare professionals and fostering interdepartmental cooperation; (xi) user friendly software; and (xii) use of unambiguous test names and codes.

Recommendation 2.1: Laboratory management including experienced coagulation laboratory scientists should be involved in the process of developing institutional policies related to test ordering and collection of blood samples for tests being performed in the coagulation laboratory.

Recommendation 2.2: Electronic ordering of coagulation tests and electronic reporting of results are recommended, where possible.

Remark: The use of computerized systems for ordering coagulation tests is preferred over paper-based ordering.

Recommendation 2.3: Where wrist bands are in use, scanning and printing tube labels at the point of collection are recommended over centralized label printing.

3 | SAMPLE COLLECTION TUBE AND ANTICOAGULANT

The type of blood sample conventionally used for coagulation tests must possess particular physical and biological characteristics, which makes it unique in the entire framework of in vitro diagnostic testing. Unlike serum or certain other types of blood specimens (ie lithium-heparin or EDTA plasma), the plasma used for clotting tests should fulfil two basic requirements: (1) the sample should be anticoagulated immediately after collection, to maintain coagulation factors in the form of zymogens and to prevent activation and clotting and (2) blood coagulation should still be activatable

TABLE 1 Summary of recommendations

Section	Recommendations
Ordering tests	Recommendation 2.1: Laboratory management including experienced coagulation laboratory scientists should be involved in the process of developing institutional policies related to test ordering and collection of blood samples for tests being performed in the coagulation laboratory
	Recommendation 2.2: Electronic ordering of coagulation tests and electronic reporting of results is recommended, where possible
	Recommendation 2.3: Where wrist bands are in use scanning and printing tube labels at the point of collection is recommended over centralized label printing.
Sample collection tube and anticoagulant	Recommendation 3.1: Laboratories must have a written policy on acceptable blood collection systems/tubes for testing performed at their facility.
	Recommendation 3.2: When citrated blood is recommended for coagulation testing, it should be anticoagulated with 105-109 mmol/L (3.1%-3.2%) trisodium citrate, unless otherwise indicated
	Recommendation 3.3: We recommend against use of 129 mmol/L (3.8%) trisodium citrate for collection of blood samples destined for coagulation testing.
	Recommendation 3.4: Blood samples collected into trisodium citrate for monitoring unfractionated heparin therapy should not have a large air space after addition of blood sample to the tube is completed.
	Recommendation 3.5: When different blood tubes produced by different manufacturers are expected to be used with the same test system and reagents, the comparability of test results shall be tested and validated prior to their use.
Preparation of the patient prior to collecting a blood sample	Recommendation 4.1: In preparation for collection of a blood sample for coagulation tests, patients should avoid strenuous exercise and stress immediately prior to blood draw
Blood Sample collection device	Recommendation 5.1: Blood samples for measuring PT, APTT, fibrinogen and other coagulation tests for management of bleeding and clotting disorders should be collected using 19-21 gauge needles for adults with good venous access, and 22-23 gauge needles for others including small children.
	Recommendation 5.2: Blood samples for assessing some coagulation activation biomarkers should not be collected using indwelling catheters.
	Recommendation 5.3: There is no requirement to discard the first volume of blood collected prior to collecting coagulation samples via the same needle, except when blood is collected through butterfly needles or indwelling catheters or when the sample is collected for platelet function studies.
	Recommendation 5.4: The sample should be mixed promptly by multiple gentle inversions (3 or 4 times, or following blood tube manufacturer's indications) immediately after collection.
Venous stasis before collection	Recommendation 6.1: Venous stasis induced by the use of a tourniquet should not normally exceed 2 min during collection of blood for coagulation tests.
Order of drawing when different sample types are collected.	Recommendation 7.1: When multiple types of blood collection tubes are filled from the same venipuncture including when the blood in a single syringe is transferred to multiple tubes, the following order should be used: 1. Blood culture tube 2. Coagulation tube 3. Serum tube with or without clot activators, with or without gel 4. Heparin tubes with or without gel 5. EDTA tubes 6. Glycolytic inhibitor tubes 7. Other tubes (eg trace elements)
Sample labelling	Recommendation 8.1: Blood samples should be labelled immediately before blood collection or immediately after blood collection following the regulatory requirements or policies of the country, region or institution, with patient's first and last name, an identification number and/or date of birth, and the date and time of specimen collection. This should be completed before leaving the side of the patient.
Ratio of blood to anticoagulant	Recommendation 9.1: Blood tubes with <80% of nominal filling volume should be rejected by the laboratory and should not be analysed.
Influence of haematocrit	Recommendation 10.1: The ratio of blood to trisodium citrate anticoagulant should be adjusted for coagulation tests when patients have haematocrit >55% (>0.55) using the formula $C = (1.85 \times 10^{-3})(100\text{-Hct})(V)$ where C is the volume of citrate in mL that should be added to a volume of blood (V) in mL to form an anticoagulated blood sample.
Conclusions	Recommendation 11.1: All laboratories should establish a written policy on what samples can be accepted for coagulation testing and which must be rejected. This policy should be jointly constructed by the laboratory management and clinicians or healthcare providers who make use of that laboratory service.

when performing certain coagulation tests, since many of these analyses are based on measurement of clotting times. This means that the use of serum (in which clotting has already been triggered) or plasma anticoagulated with additives which are effectively irreversible (such as lithium-heparin or EDTA) is unfeasible for most coagulation tests, since blood clotting is inhibited in these biological matrices (1). The use of buffered sodium citrate for the temporary inhibition of blood coagulation is hence considered the best compromise. The concentration of citrate in the primary blood tube is standardized for binding a physiological amount of ionized calcium present in blood, so that blood coagulation cannot be triggered in the blood tube, after drawing blood. Nevertheless, the addition of a supraphysiological concentration of calcium (typically 20-25 mmol/L) during performance of clotting tests is sufficient to overcome the calcium-binding capacity of citrate, allowing blood coagulation to be triggered with various activators used for various clotting-based coagulation tests (eg tissue factor, silica, ellagic acid, kaolin, thrombin and snake venoms). Inherent to this concept is that the ratio between citrate and blood in the primary collection tube should be strictly standardized, preventing an excess of citrate that may impair sample recalcification upon testing, or else an excess of blood that may overcome the binding capacity of citrate (see sections 9 and 10).

There is currently no universally adopted system of colour coding for blood collection tube caps/stoppers, though many international manufacturers utilize light blue for sodium citrate for collection of blood samples for coagulation tests, as recommended by the International Standards Organisation (ISO).[18] Tubes differ in their tube composition (siliconized glass or different types of plastic), the composition of their stoppers, the anticoagulant concentration they contain and the air space in the tube after addition of blood to anticoagulant, as well as for the concentration of other substances which may interfere with the coagulation process (ie magnesium).[19] All of these can influence the results of screening tests such as prothrombin time (PT) and especially activated partial thromboplastin time (APTT), which can vary by up to 10% depending on the collection tube used.[20] A number of other tests may also be affected by the use of different blood sample collection systems.[21,22] Several different sodium citrate concentrations are in use. The Clinical Laboratory Standards Institute (CLSI) recommends[23] using 105 to 109 mmol/L trisodium citrate dihydrate (ie 3.1%-3.2%), and most commercial tubes contain citrate within this concentration range.

Another important and highly specific preanalytical problem in coagulation testing is the potential contamination of citrated plasma with other additives, such as irreversible anticoagulants (especially EDTA) or clot activators (eg thrombin). This may happen both inadvertently (eg cross-contamination from one tube to another during venipuncture) and voluntarily (eg filling a coagulation tube with EDTA blood).

Published evidence indicates that starting from ~30% contamination of citrate-anticoagulated blood with EDTA-anticoagulated blood, some clotting tests may be dramatically prolonged.[24]

Testing serum or EDTA plasma can yield grossly abnormal (spuriously low) factor activity results. EDTA plasma, in fact, may perfectly mimic a factor VIII inhibitor sample.[25] Serum samples can be characterized by evaluating APTT, PT and fibrinogen and looking for characteristic results. Fibrinogen, factor II, factor V and factor VIII are fully consumed during clotting of blood samples in vitro so PT and APTT do not give recordable clotting times and fibrinogen is not detectable if serum is tested. EDTA samples demonstrate prolonged APTT and PT and can be detected by EDTA-induced precipitation of sodium tetraphenylborate or calcium-based colorimetric analysis as calcium is essentially undetectable in EDTA plasma. Serum and potassium EDTA plasma can also be distinguished from citrate plasma using simple measurements of potassium, calcium and sodium.[26]

The collection tube used for samples used in relation to laboratory monitoring of vitamin K antagonist drugs can affect the accuracy of International Normalised Ratio (INR) results. The INR is derived using the International Sensitivity Index (ISI) of the reagent/instrument combination used in the analysis. The ISI of a thromboplastin may be affected by the strength of citrate anticoagulant used for sample collection during thromboplastin calibration.[27-30] The World Health Organization (WHO) recommends using 109 mmol/L trisodium citrate for ISI/INR work or a mixture of trisodium citrate and citric acid if the total citrate plus citric acid concentration is 109 mmol/L and the pH is ≥5.[31] Manufacturers of widely used thromboplastins comply with this guidance and use this lower strength anticoagulant when deriving ISI values; such values are however not valid for INR determination in patient samples collected into 129 mmol/L sodium citrate, since in this case the reported INR would be up to 20% higher than the correct value for results at the top of the therapeutic range.[27] When a centre is considering changing the type of blood collection tube, the alternatives should be checked against the existing tubes. A process to do this for use in vitamin K antagonist therapy has been published,[32] while more general recommendations for comparing and validating blood tubes have also been endorsed by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).[33]

As previously mentioned, magnesium contamination within the citrate anticoagulant of some collection tubes can have an impact on PT ratio.[34] The presence of magnesium can introduce differences in PT/INR determined with different reagents.[30] The source of the magnesium was thought to be the rubber stopper in the tube[34] and replacement of these by a new formulation low magnesium version improved the agreement between PT/INR results with different reagents.[35] The differences between INRs in different tubes were around 7%-8% with some recombinant tissue factor (TF)-based PT reagents (higher INRs in the low magnesium stopper tubes). No difference was found in INR when PT/INR was determined with a number of thromboplastins prepared as tissue extracts.

Platelet activation occurs over time in citrated blood after it has been collected. This leads to release of granular constituents including platelet factor 4 (PF4). If the sample contains unfractionated heparin (UFH), this leads to progressive neutralization

of heparin and APTT shortening.[36,37] An alternative anticoagulant that has been used is citrate, theophylline, adenosine and dipyridamole (CTAD). This mixture chelates calcium via the citrate but also prevents in vitro platelet activation via effects on cyclic AMP. Samples from patients receiving UFH collected into CTAD are stable for at least 4 hours,[36] whereas samples containing UFH should ideally be centrifuged within 1 hour of collection[23] and analysed within 4 hours if citrate alone is used as anticoagulant. CTAD tubes are also recommended for assessment of platelet activation markers such as PF4 or analytes related to other proteins stored in platelet granules, thus including plasminogen activator inhibitor-1 (PAI-1).[38]

A large air space in the tube after addition of blood to anticoagulant can affect test results. This is due to the additional available space for sample mixing during transport and the higher blood collection tube inner surface-to-blood volume ratio, which can lead to platelet activation, release of PF4 and neutralization of a proportion of any UFH present with loss of anti FXa activity and shortening of APTT if citrate is used as anticoagulant, at least when ~70% of the tube was airspace after addition of blood.[39] The use of CTAD abolishes this problem.[40] Collection tubes with other additives can be acceptable for specific coagulation tests after local validation, for example corn trypsin inhibitor[41]

Recommendation 3.1: Laboratories must have a written policy on acceptable blood collection systems/tubes for testing performed at their facility.

Recommendation 3.2: When citrated blood is recommended for coagulation testing, it should be anticoagulated with 105-109 mmol/L (3.1%-3.2%) trisodium citrate, unless otherwise indicated.

Recommendation 3.3: We recommend against use of 129 mmol/L (3.8%) trisodium citrate for collection of blood samples destined for coagulation testing.

Remark: Blood samples collected into 129 mmol/L (3.8%) trisodium citrate must never be used for INR determinations performed with thromboplastins that have been assigned an ISI in calibrations with samples collected into 105-109 mmol/L trisodium citrate.

Remark: While ever blood collection tubes containing 129 mmol/L trisodium citrate are commercially available manufacturers of thromboplastins should state what strength of trisodium citrate was used for assignment of ISI.

Recommendation 3.4: Blood samples collected into trisodium citrate for monitoring unfractionated heparin therapy should not have a large air space after addition of blood sample to the tube is completed.

Remark: Blood samples for monitoring unfractionated heparin therapy collected into citrate theophylline adenosine dipyridamole (CTAD) are unaffected by large air space in the tube after addition of blood sample to the tube is completed.

Recommendation 3.5: When different blood tubes produced by different manufacturers are expected to be used with the same test system and reagents, the comparability of test results shall be tested and validated prior to their use.

4 | PREPARATION OF THE PATIENT PRIOR TO COLLECTING A BLOOD SAMPLE

Fasting is not routinely requested and is not necessary before collection of blood samples for most coagulation tests, although high levels of lipids in plasma may affect the results of some clotting tests performed with optical coagulometers (see Kitchen S et al for recommendations on testing samples with lipaemia[42]).

Both factor VIII (FVIII) and von Willebrand factor (VWF) can be temporarily elevated by strenuous exercise[43] or by stress,[44] which could include the stress associated with blood collection in some subjects, particularly in children. Fibrinogen and fibrinolytic parameters can also be affected, and D-Dimer may be elevated by exercise.[45] Factor VIII/VWF levels increase during pregnancy and acute phase/inflammation.[46,47] These increases can be large enough to mask the presence of mild haemophilia or von Willebrand disease (VWD).

Results of coagulation tests may vary according to the time of day with approximately 2 seconds shorter APTTs and 0.6 g/L lower fibrinogen at 2 PM compared with 8 AM in one study.[48]

Patient posture immediately prior to blood sample collection may have a significant impact on the results of PT, APTT and fibrinogen testing. Differences between supine, sitting and standing for 20-25 minutes prior to venipuncture were less than 5% for PT and APTT but up to 10% for fibrinogen (highest concentration when the subject was standing).[49] For a recent detailed review of patient issues related to sample collection, see Gosselin and Marlar.[50]

The interval between treatment with some drugs and sample collection is important for interpretation of a number of coagulation test results including factor assays after replacement therapy in the management of bleeding disorders and drug monitoring during several types of anticoagulant therapy.[51]

Recommendation 4.1: In preparation for collection of a blood sample for coagulation tests, patients should avoid strenuous exercise and stress immediately prior to blood draw.

5 | BLOOD SAMPLE COLLECTION DEVICE

The device used for drawing blood plays a crucial role in safeguarding sample quality and generating reliable test results. General agreement has been reached that all the different materials necessary for blood collection (ie needles, holders and blood tubes) should be part of a fully integrated system.[33,52] As specifically regards the needle used for collecting blood, some studies performed in the past few years highlighted that the use of needle with calibre between 19 and 23 gauge does not impact the reliability of coagulation testing. The use of smaller needles (eg 25 or 27 gauge) may cause a partial activation of haemostasis, as reflected by a decreased platelet count and an increase in cross-linked fibrin degradation products (ie D-dimer).[53] According to this evidence, it seems cautionary to discourage the use of very small-bore needles, except when their use is unavoidable (eg in

infants or in patients with difficult venous accesses). There is also no contraindication for using the so-called butterfly needles (winged collection devices), since it was shown that these devices do not routinely cause enough spurious activation of platelets and blood coagulation to affect routine tests, although collecting from a central or intravenous line is not recommended when measuring prothrombin activation products such as thrombin–antithrombin complex and prothrombin fragment 1.2, as these parameters may be falsely elevated due to activation by the line.[54]

Whenever using these or similar devices (eg intravenous cannulas), it is advisable that the air or the infusion fluids contained in the tubing have been completely discarded (eg using an appropriate discard volume, typically larger than their dead space, ahead of that collected for coagulation testing).[55,56] Once collected, tubes must be promptly and gently mixed by 3-4 end-over-end inversions to avoid in vitro clot formation. As regards the use of the discard tube before the coagulation tube, this practice has been in place for decades in some countries based on the assumption that some prothrombotic substances (especially TF and phospholipids) released during venipuncture may be aspirated into the tube and may hence spuriously trigger blood coagulation. Published evidence confirms that this is not normally the case, so that the use of a discard tube is deemed unnecessary when collecting blood for conventional clotting assays.[56,57] The only exceptions are represented by samples collected through butterfly devices or intravenous cannula, and those used for platelet function testing.[58]

Recommendation 5.1: Blood samples for measuring PT, APTT, fibrinogen and other coagulation tests for management of bleeding and clotting disorders should be collected using 19-21 gauge needles for adults with good venous access, and 22-23 gauge needles for others including small children.

Recommendation 5.2: Blood samples for assessing some coagulation activation biomarkers should not be collected using indwelling catheters.

Recommendation 5.3: There is no requirement to discard the first volume of blood collected prior to collecting coagulation samples via the same needle, except when blood is collected through butterfly needles or indwelling catheters or when the sample is collected for platelet function studies.

Recommendation 5.4: The sample should be mixed promptly by multiple gentle inversions (3 or 4 times, or following blood tube manufacturer's indications) immediately after collection.

6 | VENOUS STASIS BEFORE COLLECTION

The use of the tourniquet is virtually unavoidable in the routine activity of phlebotomists, since it helps to better visualize the vein to be punctured and avoids the vein collapsing during the blood collection procedure. This can be basically accomplished by generating venous blood stasis (arterial flow should not be interrupted by excessively tightening the tourniquet). When blood stasis exceeds 2-3 minutes, then the number or concentration of corpuscular elements, larger molecules and protein-bound compounds gradually increase in parallel with the length of tourniquet placing, so affecting the results of some coagulation tests[59] including haemostatic proteins stored in vascular endothelium. This occurrence should hence be carefully prevented, by limiting tourniquet placing to a minimum and in any case for no longer than 2 minutes (the tourniquet can be released for 30 seconds and then eventually reapplied when the venipuncture is prolonged), or else using transillumination devices, which help visualizing the veins without concomitantly producing venous stasis.[60]

Recommendation 6.1: Venous stasis induced by the use of a tourniquet should not normally exceed 2 minutes during collection of blood for coagulation tests.

7 | ORDER OF DRAWING WHEN DIFFERENT SAMPLE TYPES ARE COLLECTED

It is convenient and common practice to collect several different blood samples consecutively through the same needle. This frequently includes tubes with different additives. This raises the possibility of cross-contamination of blood tubes during venipuncture. One rare example can occur when a blood gas syringe is connected to the port of a catheter leading to transfer of highly concentrated heparin onto the port. If a syringe is then used for collecting citrated blood without removal of residual heparin, there can be substantial contamination. Although it is undeniable that contamination may occur when drawing blood with syringes, the new generation of evacuated blood collection tubes has virtually eradicated this problem.[61] The debate about the need to follow a so-called "order of draw", entailing a specific sequence for drawing blood tubes, remains open. The current recommendations of the Working Group for Preanalytical Phase (WG-PRE) of the EFLM endorse that following a specific order of draw is not challenging and support the use of the order of draw for collecting venous blood[62] and recommends the sequence shown in recommendation 7.1 below.

Recommendation 7.1: When multiple types of blood collection tubes are filled from the same venipuncture including when the blood in a single syringe is transferred to multiple tubes, the following order should be used:

1. Blood culture tube
2. Coagulation tube
3. Serum tube with or without clot activators, with or without gel
4. Heparin tubes with or without gel
5. EDTA tubes
6. Glycolytic inhibitor tubes
7. Other tubes (eg trace elements)

8 | SAMPLE LABELLING

The issue of when to label a sample is still a matter of open debate.[63] Despite that some recommendations support the practice

of labelling blood tubes after and not before venipuncture,[64] others firmly discourage this practice, so supporting the suggestion that blood tubes should be labelled before and not after being collected.[65] Strong views in support of labelling before[66] or after[67] collection have been expressed by experts in different regions. Others argue that either practice is acceptable if properly performed.[68] As mentioned, no definitive consensus has been reached on this practice, and the WG-PRE of the EFLM has recently concluded that the policy of labelling blood tubes before or after collection should encompass a risk analysis of the entire local phlebotomy process, but one strategy has not unequivocally been shown to be clearly better than the other for preventing sample identification errors.[69] Notably, the position of the label on the tube is important and the label should never be placed on the cap of the tube, since it can easily be detached. Ideally, the label should not completely envelop the tube, at least if visual inspection is the method used to confirm adequate tube filling.

Recommendation 8.1: Blood samples should be labelled immediately before blood collection or immediately after blood collection following the regulatory requirements or policies of the country, region or institution, with patient's first and last name, an identification number and/or date of birth, and the date and time of specimen collection. This should be completed before leaving the side of the patient.

9 | RATIO OF BLOOD TO ANTICOAGULANT

The mixture of trisodium citrate anticoagulant with blood should be done in a standardized ratio of 1:9 (anticoagulant: blood) for coagulation testing. Collecting a lower amount of blood than that defined by blood tube manufacturers (ie tube underfilling) alters the ratio of plasma to anticoagulant which in turn alters the dilution factor of plasma proteins and the relative excess of citrate may impair the following processes of recalcification and activation of blood coagulation. If the collection tube contains between 80% and 90% of its target fill volume, there may be minor artefactual prolongation of PT and APTT. However, if the blood tubes are filled to less than 80% of their nominal filling volume, the PT and APTT are then spuriously prolonged and can generate an analytically and clinically significant bias.[70] The artificial prolongation of PT and APTT in underfilled tubes is more pronounced if blood is drawn into 129 mmol/L citrate compared with 109 mmol/L. It is possible that the effects of underfilling may depend on the blood collection tubes used, because of differences in the composition of tubes, the inner dimensions of tubes and the air space-to-surface area ratio in tubes after filling. It may not be safe to use the findings from studies on one type of tube to set sample filling acceptance criteria for use with other tube types.

The chance that the volume of blood may be larger than predicated is less likely, since the vast majority of commercial blood tubes are now evacuated (ie the aspiration force does not allow to introduce an excess of blood in the container) and have very little free air space between the upper layer of blood and the cap once the tube has been filled with blood. All blood collection tubes should have a labelled expiry date and must be used before this has been reached.

The final effect of fill volume on results of coagulation tests depends on reagents, size and type of the blood tube.[71] Spurious prolongation of PT and APTT may occur in samples from normal subjects, and the effects on some coagulation tests may be unpredictably biased.

Recommendation 9.1: Blood tubes with <80% of nominal filling volume should be rejected by the laboratory and should not be analysed.

Remark: Tubes with 80%-90% of nominal filling volume may be acceptable if local validation confirms that the impact on results would not affect patient management.

10 | INFLUENCE OF HAEMATOCRIT

Besides filling problems, an additional issue may compromise the balance between citrate and ionized calcium in the specimen. Haematocrit is conventionally defined as the ratio between the volume of red blood cells (RBCs) and the total volume of blood. The greater is the haematocrit value, the lower is the amount of plasma and its constituents in the total volume of blood. When the haematocrit value exceeds 0.55 (ie 55%), the concentration of ionized calcium in the blood tubes is so decreased that clotting tests may be ultimately impaired with possible spurious prolongation of PT and APTT.[72] Such samples have an altered anticoagulant-to-plasma ratio in a similar way to underfilled samples (ie anticoagulating the plasma component not the cellular component). This problem is avoided by altering the anticoagulant-to-blood ratio so that less anticoagulant is added. Clinical and Laboratory Standards Institute (CLSI) has released specific recommendation that a formula should be used for adjusting the final concentration of citrate in the blood tube whenever the haematocrit is >55% (>0.55) (eg [residual volume of citrate in the tube] = [100-haematocrit] × [sample volume]/[595-haematocrit in %])[64] which was a formula described in a study assessing the impact of citrate concentration on PT.[73] Adjustment of citrate-to-blood ratio when haematocrit is >55% is also recommended by the World Federation of Haemophilia for coagulation testing related to investigation of subjects with bleeding disorders.[74] An alternative formula has been described as follows[23]

$$C = (1.85 \times 10^{-3})(100 - Hct)(V)$$

where C is the volume of citrate in millilitres (mL) that should be added to a volume of blood (V) in mL to form an anticoagulated blood sample. Using an example Hct of 70% and 4.5 mL of collected blood prior to addition of anticoagulant, this gives the following calculation
that is, 0.25 mL of citrate is mixed with 4.5 mL of blood.

$$1.85 \times 0.001 \times 30\,(100 - 70) \times 4.5\text{mL} = 0.25\text{mL of citrate}$$

This formula has been validated for use with PT, APTT and other coagulation tests,[72] so should be preferred although the calculated citrate-to-blood ratio using the two formulas is practically identical.

If a patient is severely anaemic, there is an increased plasma volume so that there may be sufficient residual calcium after mixing with trisodium citrate in the tube for coagulation to proceed in the sample, leading to activation and possible shortening of APTT alongside consumption of clotting factors, including fibrinogen. However, it seems that low haematocrit has less effect on results so there is usually no requirement to adjust the citrate-to-blood ratio for samples from subjects with anaemia.[75]

Recommendation 10.1: The ratio of blood to trisodium citrate anticoagulant should be adjusted for coagulation tests when patients have haematocrit >55% (>0.55) using the formula.

$$C = (1.85 \times 10^{-3})(100 - Hct)(V)$$

where C is the volume of citrate in mL that should be added to a volume of blood (V) in mL to form an anticoagulated blood sample.

Remark: Once a tube has been specifically prepared for use in a particular patient, it should be labelled and handled in such a manner that will be only used for the intended patient.

11 | CONCLUSIONS

The institution should have written policies/procedures detailing all aspects of blood collection processes, and some preanalytical errors can be prevented by using protocols or checklists, aimed to provide short and simple messages for remembering the most critical activities of venous blood collection. One such tool has been recently proposed by the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC WG-EAV), in the form of a 12-item phlebotomist checklist.[76] The use of this checklist has been strongly encouraged in many national laboratories, and preliminary data confirm its real effectiveness for reducing the vulnerability of many preanalytical activities.[77]

Some blood samples may not be easy to replace, and not all rejected samples are replaced within the relevant time frame. This means that any citrated blood sample acceptance/rejection protocols taking account of the causes of bias in test results described above and in ICSH recommendations on sample processing[42] should balance the risks of releasing potentially misleading results against the clinical risks associated with rejection followed by delay or absence of coagulation test results. If a preanalytical change causes bias which has no impact on patient care, then the balance of risk may well favour release of those results. This type of approach has been considered in other areas of laboratory medicine.[78]

Recommendation 11.1: All laboratories should establish a written policy on what samples can be accepted for coagulation testing and which must be rejected. This policy should be jointly constructed by the laboratory management and clinicians or healthcare providers who make use of that laboratory service.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

SK, DA, RD, AHK, GL, IM, RAM and SN contributed to drafting the document and to review and finalization of recommendations.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Steve Kitchen https://orcid.org/0000-0003-4790-1159
Dorothy M. Adcock https://orcid.org/0000-0002-0182-6272
Giuseppe Lippi https://orcid.org/0000-0001-9523-9054
Ian Mackie https://orcid.org/0000-0002-7393-2365
Richard A. Marlar https://orcid.org/0000-0002-8223-2811
Sukesh Nair https://orcid.org/0000-0002-3760-0929

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