Review

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Recent initiatives in harmonization of hemostasis practice

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Abstract: Accepting that standardizing and harmonizing laboratory practice has considerable value within laboratory medicine, including within the field of hemostasis, this paper concentrates on some recent and important initiatives in harmonizing hemostasis practice. Harmonization of hemostasis practice to improve clinical diagnosis and management is best driven by evidence and, in the absence of evidence, by consensus and expert opinion. To such end, there are various groups involved in such initiatives, and recent initiatives by these groups are highlighted in this review.

Keywords: coagulation; guidance; guidelines; harmonization; hemostasis; standardization.

Introduction

This paper is complimentary to another in this issue of the Journal [1]. In order to avoid duplication, the reader should refer to that paper for introductory discussion around the value of harmonization and the role of external quality assessment (EQA)/proficiency testing in facilitating harmonization of test practice. Accepting that standardizing and harmonizing laboratory practice therefore has

considerable value within laboratory medicine, including within the field of hemostasis, this paper will concentrate on some of the recent and important initiatives in harmonizing hemostasis practice other than as covered in the earlier EQA paper [1].

Most modern laboratories are required to be accredited in order to perform testing or to receive public financial compensation for services, and this requirement is overseen by certain regulatory authorities. For example, within Australia, medical laboratories are required to meet ISO 15189 standards, and accreditation is overseen by the National Association of Testing Authorities. In Europe and the UK, laboratories are also required to meet ISO 15189 standards. In the US, the College of American Pathologists (CAP) acts in the capacity of accrediting laboratories, although participation is “voluntary”. However, Centers for Medicare and Medicaid Services (CMS) (through Clinical Laboratory Improvement Amendments [CLIA] regulation) requires all clinical laboratories to be accredited. CMS grants several organizations deemed status; thus, accreditation with the CAP also qualifies to meet the CMS regulation. Additional information regarding EQA and accreditation is provided in the earlier paper [1].

Thus, first and foremost, harmonization in hemostasis practice is partially driven, as in other fields of laboratory medicine, by documented standards of laboratory practice, such as ISO 15189, as well as associated stakeholders, including EQA providers and accreditation authorities [1]. Also involved are regulatory agencies, such as the CMS and Food and Drug Administration (FDA) in the US, the Therapeutic Goods Administration in Australia and organizations such as the Medicines and Healthcare Products Regulatory Agency and European Medicines Agency in Europe [2, 3]. These regulatory agencies essentially drive the technology and methods permitted to be used within a particular jurisdiction, and thus in part drive local “harmonization” practice. Conversely, lack of harmonization between regulatory agencies will create barriers to international harmonization. Irrespective, regulatory agencies are focused more on risk avoidance than “best clinical practice”, and so, harmonization driven by regulatory agencies may or may not actually enhance or improve test

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practice, depending on perceived risk. Several examples of regulation actually stifling innovation in hemostasis practice, or preventing oversight of hemostasis tests by EQA, have been highlighted previously [1–4].

Irrespective, lack of guidance detail in these regulations also contributes to poor testing quality. For example, in the US, the Code of Federal Regulations dictates the requirements for laboratory validation of a clinical laboratory method (e.g. precision, accuracy and reference interval) but fails to provide guidance for statistics or acceptable criteria to verify the performance of a test [5]. Additionally, using guidance documents for method validation for specific assays (e.g. FDA guidance for drug measurement using mass spectrometry) may not be suitable or sufficient to verify the performance of screening assays that have multiple functionality (e.g. prothrombin time [PT] and activated partial thromboplastin time [APTT]) [6]. Identification of best coagulation laboratory practices may be identified during EQA assessment [1], but ultimately the creation of guidance documents is required that address: (1) verification of performance or method validation (for laboratory developed assays) and (2) the three analytical phases (preanalytical, analytical and postanalytical) of coagulation testing.

One difficulty associated with laboratory testing is the lack of clinical evidence to warrant guideline anointment. Use of GRADE, or equivalent [7] measures, is nearly impossible for laboratory tests, but interestingly enough, it is typically used as surrogates for evidence-based guidelines.

Harmonization of hemostasis practice to improve clinical diagnosis and management is best driven by evidence and, in the absence of evidence, by consensus and expert opinion. To such end, there are various groups involved in such initiatives.

Clinical and Laboratory Standards Institute (CLSI)

The CLSI (<https://clsi.org/>) was in the past one of the foremost drivers of harmonization of laboratory practice within hemostasis. Importantly, CLSI developed laboratory guidelines using both evidence and expert opinion and drew committee membership from a wide variety of sources, including clinicians, laboratory scientists, industry and government (e.g. FDA) representatives. A summary of the more relevant guidelines produced by CLSI as related to hemostasis is listed in Table 1. Unfortunately, potentially based on commercial considerations, CLSI has

recently decided to cease production of certain types of guidelines (e.g. “specialized”), although CLSI continues to produce general purpose laboratory guidelines. With regard to documents specifically related to hemostasis test practice, the revision for the von Willebrand factor (VWF) testing document (H51) was essentially completed in 2015, but CLSI opted not to publish the document. Another document then in progress, for solid phase antiphospholipid antibody (aPL) testing to potentially compliment the lupus anticoagulant (LA) test guidelines then in production, and recently finalized [8], was also abandoned. CLSI has also been criticized for being too US centric in some of the guidelines it has produced, and the process has also been described as slow and cumbersome (guidelines may take several years to produce), with some documents being very lengthy (e.g. H61, LA testing [8]), and some recommended approaches are not readily achievable in laboratories from developing countries, or may counter-regional recommendations. CLSI guidelines also need to be purchased, and so are not free for all to use. CLSI hemostasis related guidelines in particular are perhaps also limited in terms of updates or continued relevance. For example, the guidance for international normalized ratio (INR) remains a first edition document published in 2005 [9] that has never been updated. It is also probably reasonable to say that the chair of any “expert committee”, not necessarily limited to CLSI, often has the strongest voice in the group, and may drive a particular point of view should they have strong feelings for same. In this way, sometimes “eminence” rather than “experience” or “evidence” may drive the decision-making process [10]. In any case, CLSI has become increasingly irrelevant to harmonization of hemostasis test practice over recent years.

International Council for Standardization in Haematology (ICSH)

Given the void created by CLSI’s perceived “disinterest” in continuing to pursue development of laboratory hemostasis guidance documents, the ICSH group (<http://icsh.org/>) has recently embarked on the progression of several guidance documents related to hemostasis, thereby aiming to improve standardization and harmonization of test practice in this field, and a newly formed “Haemostasis Group” has been tasked with this objective.

The documents intended to be produced over the next few years are listed in Table 2. These guidance documents are expected to be of considerable value to laboratory practice in the field of hemostasis and will complement

Table 1: A summary of the more relevant guidelines produced by CLSI as related to hemostasis.

Document	Summary ^a	Edition	Date of publication	Number of pages
H30 Procedure for the Determination of Fibrinogen in Plasma, 2nd edition	This document provides general guidelines for performing the fibrinogen assay in the clinical laboratory. It also includes reporting of results and <i>in vivo</i> and <i>in vitro</i> conditions that may alter results	Second	November 1, 2001	16
H54 Procedures for Validation of INR and Local Calibration of PT/INR Systems, 1st edition	This document describes the use of certified plasmas to enhance performance of the prothrombin time (PT)/International Normalized Ratio (INR) system test; reviews limitations of the INR systems that may occur when a manufacturer-determined ISI is used without local verification or calibration; and provides a rationale for performing local ISI verification with recommendations as to when PT calibration may be indicated. Part I is a detailed, expanded account for manufacturers and Part II is an abbreviated version useful for the clinical laboratory	First	August 19, 2005	64
H21 Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays, 5th edition	This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests	Fifth	January 23, 2008	48
H57 Protocol for the Evaluation, Validation, and Implementation of Coagulometers, 1st edition	This document provides guidance and procedures to the end user and manufacturer for the selection, evaluation, validation, and implementation of a laboratory coagulometer	First	January 23, 2008	48
H47 One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test, 2nd edition	This document provides guidelines for performing the PT and APTT tests in the clinical laboratory, for reporting results, and for identifying sources of error	Second	May 30, 2008	48
H58 Platelet Function Testing by Aggregometry, 1st edition	This document provides concrete, standard procedures for using aggregometry to assess platelet function in patient specimens with the intent to achieve greater uniformity of results	First	November 24, 2008	56
H59 Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease, 1st edition	This document provides guidelines regarding the use of D-dimer in exclusion of venous thromboembolism (VTE) including a description of the value of clinical determination of the pretest probability of VTE; the proper collection and handling of the specimen; assays used for D-dimer analysis; determination of the threshold for exclusion of VTE; interpretation of test results; and aspects of regulatory and accreditation requirements	First	March 31, 2011	44
H60 Laboratory Testing for the Lupus Anticoagulant, 1st edition	This document provides guidance and recommendations regarding the proper collection and handling of the specimen; descriptions and limitations of screening and confirmatory assays, and mixing tests used to identify lupus anticoagulant (LA); determination of cutoff values and calculations associated with the various assays; and interpretation of test results in an LA panel	First	April 4, 2014	116
H48 Determination of Coagulation Factor Activities Using the One-Stage Clotting Assay, 2nd edition	This guideline provides recommendations regarding the proper collection and handling of specimens, reagents, controls, calibrators, and materials needed to optimize factor assay testing. It includes recommendations for good laboratory practices related to analyzer and reagent performance, reference intervals, lot-to-lot validation, and quality control. Assay limitations and sources of errors and variability are also included	Second	March 30, 2016	60

^aAs per the CLSI website (<https://clsi.org/>) summaries.

Table 2: A summary of hemostasis related guidance documents in development by ICSH.

- Primary Care Point of Care testing in Haemostasis
- Guidance on Pre-analytic Variables in Haemostasis
- ICSH Guidance for the Laboratory Assessment of Direct Oral Anticoagulants (DOACs)^a
- ICSH Guidance for Laboratory testing of FVIII and FIX inhibitors

^aRecently completed and accepted for publication [11].

the many guidance documents already available from ICSH in other areas of hematology and also in other disciplines. Those interested in the past achievements of ICSH and other future plans are directed to the website and elsewhere [12–14].

One guidance document from ICSH, in the area of direct oral anticoagulants (DOACs), is already completed and has recently been published [11]. The recommendations for this DOAC guidance document are based on (1) information from peer reviewed publications about laboratory measurement of DOACs (i.e. “evidence”), (2) contributing author personal experience/expert opinion and (3) good laboratory practice. The document primarily addresses the laboratory assessment of dabigatran, rivaroxaban, apixaban and edoxaban. Consensus recommendations in the document indicate agreement by all contributing authors, who themselves are considered expert clinicians and scientists working in the field. Indeed, the writing group has cumulatively published over 100 papers in the field of DOACs. The document was also vetted by pharmaceutical and *in vitro* diagnostic industry representatives to permit their input and comments to be addressed in the laboratory recommendations. These are important considerations for guidance document development and assures these additional stakeholders are in agreement with laboratory recommendations, especially when based on expert opinion and conflicts of interest may be present.

International Society on Thrombosis and Haemostasis (ISTH)

The ISTH is recognized as the premier international group within the field of thrombosis and hemostasis (<http://www.isth.org/>). Most guidance documents related to hemostasis practice are produced by working parties/committees of the ISTH called “Scientific and Standardization Committees” (SSCs). Many SSC groups have been formed over the many years of the ISTH (http://www.isth.org/?page=ssc_bibliography), and current SSCs are listed in Table 3. According to the ISTH website, the SSCs draw their “strength and credibility from the hundreds of clinicians, researchers, and educators who volunteer to participate in its activities. The SSC’s programs reflect the strong scientific skill of its members as they create projects that respond to a variety of challenges in the fields of thrombosis and hemostasis. The SSC has 20 subcommittees in addition to one standing committee and the executive committee. Each subcommittee has a chairman and several co-chairmen. However, many participants contribute to the work of each group”. Further information on the SSC structure and function can be found on the ISTH website.

These SSCs have produced many guidance documents in the past 10 years, and indeed well over 100 ISTH SSC reports have been published in the ISTH journal (currently *Journal of Thrombosis and Haemostasis*) at last count. Given the broad makeup of the SSCs, it should be emphasized that many of the official communications do not relate to laboratory practice. Indeed, official communications can relate to any activities of the respective SSCs (Table 3), including definitions (e.g. bleeding severity), nomenclature (e.g. test analytes), specific projects or surveys, guidance on patient management or therapeutics (use or development), advice on clinical trial design/development, advice on animal models, guidance on clinical assessments, instrument and test evaluations, value assignments for coagulation standards, disease diagnosis, and so on. Some of the more relevant recent documents related to laboratory practice in hemostasis, with particular potential to hemostasis practice harmonization, can be highlighted, as summarized in Table 4. It should be noted that for some of these reports, laboratory practice only represents a small, albeit important, portion of the report/guidance document. This listing also identifies that some SSCs appear to be more active than others, and that sometimes different SSCs collaborate to produce combined reports. Sometimes, the pertinent SSC is not easily identified from the report. Particularly active have been the “Control of Anticoagulation” and “Factor VIII, Factor IX and Rare Coagulation Disorders” SSCs, each publishing six guidance documents in the past 6 years (Table 4).

Although these documents are generally of considerable value, inclusive of harmonization potential, the current requirement to have these published as “short communications” (maximum of 1500 words) in the ISTH society journal sometimes compromises their utility. For example, a large study of VWF testing that would have informed on test practice related to von Willebrand disease diagnosis, including benefits and limitations of

Table 3: A summary of hemostasis related ISTH SSCs.

SSC	Purpose ^a
Animal, Cellular and Molecular Models	This subcommittee is focused on animal and other models of thrombosis and hemostasis and parameters of coagulation and fibrinolysis
Biorheology	This subcommittee is focused on all blood flow related issues in thrombosis and hemostasis: from clinical blood flow assays of hemostasis to basic research models
Coagulation Standards Standing Committee	The SSC Coagulation Standards Standing Committee oversees the Secondary Coagulation Plasma Standard
Control of Anticoagulation	This subcommittee is focused on laboratory and clinical issues related to the use of anticoagulant drugs. It incorporates internists, hematologists, cardiologists, laboratory scientists and is addressed to a large spectrum of specialists
Disseminated Intravascular Coagulation	This subcommittee is focused on clinical syndromes of thrombosis and hemostasis, parameters of coagulation and fibrinolysis, and the pathology or etiology, diagnosis and treatments by physicians. This information is provided for experimental researchers, physicians for critical care medicine, hematology gynecology and oncology, and for laboratory scientists, and epidemiologists
Factor VIII, Factor IX and Rare Coagulation Disorders	The Factor VIII, Factor IX and Rare Coagulation Disorders Subcommittee has the mission of providing a forum for consideration of practical issues related to hemophilia and other rare bleeding disorders, provide state of the art knowledge regarding the diagnosis and management of these disorders, and conduct projects that aim to standardize and harmonize available laboratory evaluation and clinical care measures for the assessment of therapeutic products and clinical outcomes
Factor XI and the Contact System	This subcommittee is focused on basic research, physiology, diagnostics and pharmacology of blood coagulation factor XI and the plasma contact system
Factor XIII and Fibrinogen	This subcommittee is focused on all aspects of Factor XIII and fibrinogen with respect to thrombosis and hemostasis: from standardization issues to basic research and clinical relevance
Fibrinolysis	This subcommittee is focused on basic research concerning factors that upregulate/downregulate fibrinolysis as well as on clinical research involving the analysis of fibrinolysis-related parameters
Genomics in Thrombosis and Hemostasis	The aim of the group is to develop an approach to assist in reducing the time to diagnosis of rare platelet and bleeding disorders, by taking advantage of advances in Next generation sequencing (NGS) and selective capture technologies. For this potential to be fully realized, it is essential to develop a publicly accessible database that will provide stable reference DNA sequences with respect to which sequence variants that are known to be associated with rare inherited disorders can be mapped
Hemostasis and Malignancy	This subcommittee is focused on the spectrum of clinical disorders of hemostasis in malignancy, including venous and arterial thromboembolism, and bleeding. The Subcommittee comprises of members from diverse backgrounds and disciplines including hematologists, oncologists, surgeons, pulmonologists, epidemiologists, and translational and basic scientists
Lupus Anticoagulant/Antiphospholipid antibodies	The subcommittee has its focus on the standardization of existing assays that detect antiphospholipid antibodies, evaluating newly developed assays, and advising on the diagnostic criteria for the antiphospholipid syndrome
Pediatric/Neonatal Thrombosis and Hemostasis	The subcommittee is focused on addressing clinical issues in pediatric and neonatal thrombosis and hemostasis
Perioperative and Critical Care T&H	This subcommittee is focused on the perioperative management of patients on new anticoagulants who require an elective surgery, the interpretation of laboratory coagulation tests and scrutiny of platelet function laboratory tests in the perioperative setting
Plasma Coagulation Inhibitors	This subcommittee is focused on clinical and laboratory issues related to natural inhibitors of coagulation and factors associated with heritable thrombophilia, including but not restricted to Antithrombin, protein C, protein S and activated protein C resistance with or without factor V Leiden
Platelet Immunology	The activities of this Subcommittee are focused on immune disorders of platelets including fetal/neonatal alloimmune thrombocytopenia, primary immune thrombocytopenia (ITP), drug-induced thrombocytopenia and heparin-induced thrombocytopenia
Platelet Physiology	This subcommittee is focused on all aspects of the biology and function of platelets and their role in thrombosis, hemostasis and normal physiology. The SSC incorporates hematologists, cardiologists, laboratory scientists, health professionals and academics
Predictive/Diagnostic Variables	This subcommittee is focused on promoting knowledge translation and facilitating collaborative research relating to the diagnostic and predictive utility of clinical and biochemical markers of cardiovascular disease and thrombosis
SSC Executive Committee	This committee will be responsible for all functions normally assigned to an Executive/Nominating Committee, including matters relating to nominations, to long-range planning, programming, and finance. It should maintain a close relationship with the Scientific Subcommittees. The Executive Committee will function in all essential capacities as needed in the interim between meetings of the SSC

Table 3 (continued)

SSC	Purpose ^a
Vascular Biology	This subcommittee is focused on basic and translational research related to vascular biology and related (athero)-thrombotic disorders, through the development of biomarkers that require standardization
von Willebrand Factor	The von Willebrand factor (VWF) subcommittee is focused on the genetics, biology and function of VWF and its protease ADAMTS13, its relationship with cells and other molecules and all laboratory and clinical issues related to these processes, with special emphasis on von Willebrand Disease (VWD). This subcommittee incorporates hematologists and laboratory professionals promoting and facilitating collaborative basic and clinical research projects
Women's Health Issues in T&H	This subcommittee is focused on clinical syndromes of thrombosis and hemostasis and parameters of coagulation and fibrinolysis that are influenced by hormones and incorporates hematologists, obstetricians and gynecologists, laboratory scientists, and epidemiologists

^aAs per the ISTH website (http://www.isth.org/?page=ssc_bibliography) summaries. ISTH, International Society on Thrombosis and Haemostasis; SSCs, Scientific and Standardization Committees.

tests and test panel approaches, which could then have helped harmonize laboratory practice in this field, was reduced to such a shallow shell as to no longer be particularly useful for laboratories [15]. Also, the last “comprehensive” ISTH SSC guidance on LA testing, published in 2009 [16] was later criticized for some lack of clarity, particularly around the requirement for mixing studies [17, 18]. This likely arose because of the inability of this ISTH SSC to document the complexities of LA testing in the four pages of text “permitted” by their publication, and which in part probably helped to drive the formation of the much larger CLSI document (at 116 pages) ([8]; Table 1). However, to also be fair to the society journal, the 1500-word limit was probably imposed to ensure ISTH SSC communications were succinct and focused, and given the sheer number of such publications, that the journal had sufficient space to also publish on other aspects of thrombosis and hemostasis.

British Committee for Standards in Haematology (BCSH)

The BCSH is another group visibly represented in providing guidance and helping to drive harmonization of test practice in the area of thrombosis and hemostasis. The BCSH guidelines are now more simply known as BSH Guidelines and are written by expert consultants and clinical scientists currently practicing in the UK (<http://www.b-s-h.org.uk/guidelines/>). The BSH Guidelines provide up-to-date evidence-based guidance on the diagnosis and treatment of hematological diseases, not limited to thrombosis and hemostasis. There are three styles of guideline currently available: (a) BSH Guidelines (previously known as BCSH Guidelines): evidence-based

guideline developed following a professional literature search and a review of the evidence by the writing group. (b) BSH Good Practice Paper: used to recommend good practice in areas where there is a less robust evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care. (c) BSH Position Paper: the adoption and adaptation of a non-UK evidence-based guideline for use in the UK. Recent relevant publications related to the area of thrombosis and hemostasis and its harmonization of test practice are listed in Table 5. Some BSH Guidelines are prepared in collaboration with the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO), who themselves also prepare independent guidelines on hemostasis practice. Importantly, although many of the BSH Guidelines are directed towards clinical practice, several make specific recommendations on laboratory practice and, thus, provide a focus for harmonization between laboratories adopting the principles of these guidelines.

Regional thrombosis and hemostasis societies

Depending on locality, regional thrombosis and hemostasis societies may also be actively involved in development of guidance documents to help drive harmonization, although this is often only achieved at a regional level. For example, the Thrombosis and Haemostasis Society of Australia and New Zealand (<https://www.thanz.org.au/>), formally known as the Australasian Society for Thrombosis and Haemostasis, has been involved in developing such guidance documentation, most recently for DOACs [19], with a guidance document on heparin-induced thrombocytopenia in development. The society is also

Table 4: A summary of recent (last 10 years) ISTH SSC reports related to hemostasis practice.

SSC	Report	Year (Reference) ^a
Biorheology	Flow-dependent thrombin and fibrin generation <i>in vitro</i> : opportunities for standardization	2014 (T4-12)
Control of Anticoagulation	Recommendation on the nomenclature for oral anticoagulants	2015 (T4-6)
Control of Anticoagulation	Methods to determine apixaban	2014 (T4-10)
Control of Anticoagulation	Measuring oral direct inhibitors of thrombin and factor Xa	2013 (T4-19)
Control of Anticoagulation	Methods to determine rivaroxaban	2012 (T4-22)
Control of Anticoagulation	Towards a recommendation for the standardization of the measurement of platelet-dependent thrombin generation	2011 (T4-26)
Control of Anticoagulation and Lupus Anticoagulant/ Antiphospholipid Antibodies	Monitoring patients with the lupus anticoagulant while treated with vitamin K antagonists	2016 (T4-3)
Disseminated Intravascular Coagulation	Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines	2013 (T4-18)
Factor VIII, Factor IX and Rare Coagulation Disorders	Proposal for standardized preanalytical and analytical conditions for measuring thrombin generation in hemophilia	2017 (T4-1)
Factor VIII, Factor IX and Rare Coagulation Disorders	Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity	2012 (T4-21)
Factor VIII, Factor IX and Rare Coagulation Disorders	Measurement of factor VIII pharmacokinetics in routine clinical practice	2013 (T4-20)
Factor VIII, Factor IX and Rare Coagulation Disorders	Definitions in hemophilia	2014 (T4-9)
Factor VIII, Factor IX, and Rare Coagulation Disorders	Recommendations for performing thromboelastography/ thromboelastometry in hemophilia	2014 (T4-13)
Factor VIII, Factor IX, and Rare Coagulation Disorders	Towards standardization of clot waveform analysis and recommendations for its clinical applications	2013 (T4-15)
Factor XIII and Fibrinogen	Diagnosis and classification of factor XIII deficiencies	2011 (T4-27)
Factor XIII and Fibrinogen	Factor XIII: recommended terms and abbreviations	2007 (T4-32)
Factor XIII and Fibrinogen	Recommendations for nomenclature on fibrinogen and fibrin	2009 (T4-31)
Lupus Anticoagulant/ Antiphospholipid antibodies	Testing for Antiphospholipid antibodies with Solid Phase Assays	2014 (T4-11)
Lupus Anticoagulant/ Antiphospholipid antibodies	Update of the guidelines for lupus anticoagulant detection	2009 (T4-30)
Perinatal and Paediatric Haemostasis	Developmental hemostasis: recommendations for laboratories reporting pediatric samples	2012 (T4-23)
Perinatal and Paediatric Haemostasis	Recommendations for developing uniform laboratory monitoring of heparinoid anticoagulants in children	2012 (T4-24)
Platelet Immunology	Heparin-induced multi-electrode aggregometry method for heparin-induced thrombocytopenia testing	2016 (T4-2)
Platelet Immunology	Recommendations for standardization of laboratory testing for drug induced thrombocytopenia	2015 (T4-7)
Platelet Immunology	Laboratory testing for heparin-induced thrombocytopenia: a conceptual framework and implications for diagnosis	2011 (T4-25)
Platelet Physiology	Diagnosis of inherited platelet function disorders	2015 (T4-8)
Platelet Physiology	Recommendations for the standardization of light transmission aggregometry	2013 (T4-17)
Predictive Variables	Periprocedural antiplatelet therapy: recommendations for standardized reporting in patients on antiplatelet therapy	2013 (T4-14)
Vascular Biology	Standardization of preanalytical variables in plasma microparticle determination	2013 (T4-16)
Vascular Biology	Standardization of platelet-derived microparticle enumeration by flow cytometry with calibrated beads	2010 (T4-29)
Von Willebrand Factor/von Willebrand Disease	Platelet-dependent von Willebrand factor activity. Nomenclature and methodology	2015 (T4-5)
von Willebrand Disease and Platelet Physiology	Platelet type von Willebrand disease and registry report	2016 (T4-4)
Working group on nomenclature	Nomenclature of genetic variants in hemostasis	2011 (T4-28)

Table 4 (continued)

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Table 4 (continued)

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active by running an annual workshop, which is well attended and covers an array of topics but largely focused on hemostasis test practice.

Other drivers for harmonization in hemostasis practice

There are many other drivers of harmonization in hemostasis practice, including a variety of special interest groups involved in specific projects. For example, the Australasian Working Party on anticardiolipin antibody testing developed a consensus guideline on testing and reporting over a decade ago [10, 20]. Of relevance, the key recommendations of this guidance document were further recently developed and incorporated into subsequent international guidelines on anticardiolipin and anti- $\beta(2)$ glycoprotein I testing, produced under the auspices of an international antiphospholipid (APL) task force [21].

Harmonization of hemostasis test practice can also be achieved through large pathology networks. For example, the lead author on this paper works within a large public pathology network called New South Wales Health Pathology (NSWHP). This author has been involved in many standardization and harmonization initiatives, initially within small pathology networks, and then evolving to larger and larger groups. For INR testing for monitoring of vitamin K antagonist therapy, for example, initial harmonization involved a network of local metropolitan laboratories [22], which was eventually broadened to a network of 27 metropolitan and regional/rural laboratories [23], with corresponding improvements in test practice evidenced by lowered inter-laboratory variation in test results according to EQA data. NSWHP now represents an organization comprising more than 60 laboratories within the state of NSW in Australia and is the largest provider

of public pathology services within Australia (<http://www.pathology.health.nsw.gov.au/>), and the intention is to now progress INR harmonization practices across all laboratories in the organization. Another recent attempt at harmonization of internal quality control practice for routine coagulation across the network of 27 laboratories was also recently reported [24].

Other initiatives have also been planned by the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) in conjunction with the Italian Committee for Standardization of Laboratory and Hematology methods (CISMEL). A document has also been published aiming to improve national standardization of D-dimer usage in the emergency room, and also covering the many varied aspects of this measurement in clinical laboratories (i.e. sample collection, analysis, result reporting) [25]. Another document has been published to provide guidance to caregivers for harmonizing testing for DOACs in both routine and urgent settings [26]. Finally, a more recent document has been published in conjunction with the Academy of Emergency Medicine and Care, for harmonizing panels of tests (including hemostasis) and requesting patterns in the emergency setting at a national level [27].

Conclusions

This overview has provided several examples whereby various initiatives have helped drive harmonization of hemostasis practice. As highlighted in an accompanying paper [1], EQA organizations are also important contributors of laboratory harmonization. Moreover, it is possible for EQA organizations to interrogate laboratories about their practice for hemostasis assays, and to correlate this with guideline recommendations, as provided by expert groups such as ISTH, ICSH and BCSH, thereby highlighting

Table 5: A list of recent BCSH (BSH) publications related to guidance in hemostasis practice.

Title of publication	Year (Reference) ^a
The diagnosis and management of von Willebrand disease	2014 (T5-1)
Patient self-testing and self-management of oral anticoagulation with vitamin K antagonists	2014 (T5-2)
Guideline for the diagnosis and management of the rare coagulation disorders	2014 (T5-3)
Measurement of non-coumarin anticoagulants and their effects on tests of hemostasis	2014 (T5-4)
Diagnosis and management of acquired coagulation inhibitors	2013 (T5-5)
Diagnosis and treatment of factor VIII and IX inhibitors in congenital hemophilia	2013 (T5-6)
Guidelines on the diagnosis and management of heparin-induced thrombocytopenia	2012 (T5-7)
Guidelines on the laboratory aspects of assays used in hemostasis and thrombosis	2013 (T5-8)
Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies	2012 (T5-9)
Guidelines on the investigation and management of antiphospholipid syndrome	2012 (T5-10)
Guidelines for the laboratory investigation of heritable disorders of platelet function	2011 (T5-11)
Clinical guidelines for testing for heritable thrombophilia	2010 (T5-12)
Guidelines for the diagnosis and management of disseminated intravascular coagulation	2009 (T5-13), 2012 (T5-14)
Guidelines on fibrinogen assays	2003 (T5-15)

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areas of harmonization, as well as areas where laboratory practice diverges from the guidelines.

Another influencer of laboratory test practice harmonization, namely regulation, can have both positive and negative effects. Using the United States as an example, when the issue of laboratory testing has become an issue

of interest to legislators, the process of the development of rules for governing EQA organizations, EQA testing and indeed laboratory testing can become very prescriptive and, at times, onerous. Legislators and their advisors do attempt to create laws and regulations that provide for safe and effective outcomes, but the process often interferes

with attempts to create a system of best test practice. Over-arching legislation significantly impacts many “interest groups” (e.g. patients, small and large laboratories, manufacturers of instruments and reagents and consideration of the costs and funding for oversight and penalties for poor performance). Much of this was covered in the previous paper [1]. Of relevance to this paper, there will be harmonization of the process to the extent that the law requires. Thus, in the case of the CLIA in the USA, the law has defined some criteria for 83 analytes that are regulated. In the field of hemostasis, only three analytes (PT [not INR], APTT and fibrinogen) are regulated. However, the regulations fall short by not defining what must constitute a peer group, how many are required to analyze a group or the cascade that might be used to achieve an adequate number in the group for analysis. Thus, there develops a considerable lack of harmonization among providers regarding the analysis, and there is no harmonization for the analytes that are not regulated, namely all other tests of hemostasis. Finally, should privately/professionally developed guidelines or standards be developed, the result for their application in a country with such laws would be the necessity to change the law, a very difficult process that would, again, raise all of the political issues alluded to above. As a case in point, the list of 83 analytes regulated by CLIA was developed implemented in 1992, and despite several efforts, there has been no change to the list in more than 25 years.

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