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REVIEW

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ICSH review of internal quality control policy for blood cell counters

Richard McCafferty[1] | George Cembrowski[2] | Barbara de la Salle[3] | Mingting Peng[4] | Eloisa Urrechaga[5]

[1]St James's Hospital, Dublin, Ireland

[2]University of Alberta, Edmonton, Alberta, Canada

[3]UK NEQAS, Watford, UK

[4]NCCL, Beijing, China

[5]Hospital Galdakao Usansolo, Bizkaia, Spain

Correspondence
Richard McCafferty, Haematology Department, St James's Hospital, James's Street, Dublin D08 K0Y5, Ireland.
Email: richard.mccafferty@stjames.ie

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Abstract

Introduction: This paper is a report of an ICSH review of policies and practices for internal quality control (IQC) policy for haematology cell counters among regulatory bodies, cell counter manufacturers and diagnostic laboratories. It includes a discussion of the study findings and links to separate ICSH guidance for such policies and practices. The application of internal quality control (IQC) methods is an essential pre-requisite for all clinical laboratory testing including the blood count (Full Blood Count, FBC, or Complete Blood Count, CBC).

Methods: The ICSH has gathered information regarding the current state of practice through review of published guidance from regulatory bodies, a questionnaire to six major cell counter manufacturers (Abbott Diagnostics, Beckman Coulter, Horiba Medical Diagnostic Instruments & Systems, Mindray Medical International, Siemens Healthcare Diagnostics and Sysmex Corporation) and a survey issued to 191 diagnostic laboratories in four countries (China, Republic of Ireland, Spain and the United Kingdom) on their IQC practice and approach to use of commercial IQC materials.

Results: This has revealed diversity both in guidance and in practice around the world. There is diversity in guidance from regulatory organizations in regard to IQC methods each recommends, clinical levels to use and frequency to run commercial controls, and finally recommended sources of commercial controls. The diversity in practice among clinical laboratories spans the areas of IQC methods used, derivation of target values and action limits used with control materials, and frequency of running commercial controls materials.

Conclusions: These findings and their implications for IQC Practice are discussed in this paper. They are used to inform a separate guidance document, which proposes a harmonized approach to address the issues faced by diagnostic laboratories.

KEYWORDS
cell counters, general haematology, ICSH, policy, quality control

1 | INTRODUCTION

This paper is a report of an International Council for Standardization in Haematology (ICSH) review of policies and practices for internal quality control (IQC) policy for haematology cell counters among regulatory bodies, cell counter manufacturers and diagnostic laboratories. It includes a discussion of the study findings and links to separate ICSH guidance[1] for such policies and practices. Historical methods for use of IQC materials included preparation of in-house material made from human donor or animal blood[2] preserved using various forms of

fixation to provide stability and extended life and tested using reference methods to assign target values and acceptable ranges. Today there is a reliance on commercially produced control materials due to staff time constraints, convenience and the need to have an IQC material that will assess all the parameters of the extended blood count.

There is a modern need for accreditation of clinical laboratories to international standards such as International Standards Organization (ISO) 15189[3] or the Clinical Laboratory Standards Institute (CLSI)[4,5] and enforcement with regulatory agencies such as the College of American Pathologists (CAP)[6] deemed status enforcer of Clinical Laboratory Improvement (CLIA) '88[7] and subsequent amendments with frequent revisions of these standards. This has increased focus and scrutiny of laboratory practice for IQC. In the absence of clear and considered policy guidance in this area, the application of the standards may be open to interpretation leading to variation in practice. In addition, there have been trends towards the application of universal IQC policies for clinical analyses across disciplines, for example between clinical chemistry and haematology.[4] However, these may not be appropriate or applicable to the field of cell counting which has key differences and specific issues that may not apply to the analysis of a traceable chemical entity.

1.1 | Historical perspective

The concept of quality control as part of the production process was developed in the in the decades between the first and second world wars (Shewhart, 1931[8]), with the introduction of mass production methods in industry. The introduction of laboratory automation and patient data management systems facilitated the application of the same concepts to the management of imprecision in diagnostic testing using control materials, "best practice" methods and statistical procedures.

The haemoglobincyanide (HiCN) standard introduced in 1967[9] markedly improved the accuracy of haemoglobin (HGB) measurement and at the time of writing, remains the only certified reference material (CRM) applicable to the blood count (full blood count, FBC, or complete blood count, CBC) and being evaluated by the Joint Committee for Traceability in Laboratory Medicine (JCTLM).[10] The JCTLM lists certified reference procedures (CRPs) in their database for total HGB measurement (since 2021).[11] The ICSH and other professional organizations have previously recommended testing methods that represent the best laboratory practice for cell counting and measurement of HGB concentration at the time.[12,13]

IQC materials for the blood count (FBC/CBC) were traditionally prepared within the laboratory[2]; however, the challenges associated with these procedures mean that commercially prepared controls are now the control materials of choice. In-house preparations may continue to have an application in resource-limited situations.[2]

The application of statistical analysis of both IQC data and patients' data was first applied in clinical chemistry by Levy and Jennings[14] as a means to monitor instrument performance and are now widely used in haematology. Duplicate tests on patients' specimens provide another way of checking the precision of routine work.[15] Bull[16] introduced a computerized algorithm to estimate the daily patient means of absolute values for mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC). This provided a means to detect drift in blood cell counters based on patient sample results, independent of the use of IQC material. The method is now incorporated in automated blood counters. However, this method cannot be applied in small volume laboratories as the method assumes numeric sampling will compensate for the expected inter-patient variation in these parameters. The introduction of automated blood cell counters from the 1960s and laboratory information systems (LISs) in the 1980s allowed the use of "delta" checking of individual patients' results by direct comparison with previous results for parameters of the blood count that are stable over time.[17] An overview of IQC methods applicable to cell counters is shown below.

IQC for haematology cell counters encompasses various methodologies and procedures, which can include the following. It is an essential prerequisite that cell counters must be calibrated before use and periodically thereafter, to ensure accuracy of measurement:

1. Use of IQC material to assess precision of the results generated and to detect malfunction or drift in the analyser
2. Use of moving averages of patient results to asses drift (Bull's algorithm $\bar{x}$)[16]
3. Use of retained fresh patient specimens (<12 h old) to assess precision and detect drift[15]
4. "Delta-check" comparison with previous patient results[17]
5. Verification of blood count results by reference to information obtained from blood film examination
6. Inter-instrument comparisons where possible, for example using retained patient specimens.[17]

Participation in external quality assessment (EQA) Schemes is a supplementary component of a quality management system (QMS) currently required by regulatory bodies.

1.2 | Purpose of this study

The ICSH perceived that a confused message exists in the practice of IQC for blood cell counters worldwide due to differences in the guidance of regulatory bodies and in the instructions for use of commercial IQC materials from cell counter manufacturers. The ICSH therefore carried out a study of the practice in the field as well as the published guidance available in order to issue a guidance that will bring clarity and to harmonize practice worldwide.

2 | METHODS

The methods employed in this study included:

1. A review of the published literature including recommendations and requirements of international quality standards including ISO and CAP.

2. Information gathering from all major cell counter manufacturers by questionnaire, which included the following questions:
   a. Their recommendation to customers for IQC of their instruments, to include all QC methods they recommend (such as $\bar{x}$ analysis of patient mean values) and recommendation for frequency of running the QC materials they supply
   b. Their policy for validation of their supplied IQC material, if possible
   c. To indicate whether their IQC material is supplied by a third-party manufacturer and if so to identify that manufacturer
   d. Their policy for ensuring traceability of their IQC materials to reference methods and determining uncertainty measurement of such IQC material(s)
   e. Their recommended or supplied statistical method to determine whether control results are out of range or require action, for example, use of Westgard rules or other method.
3. An international survey of quality practices across 191 laboratories in 4 countries to gather information on quality control practices in diagnostic laboratories The survey gathered information on the following:
   a. Instrument, instrument age, environment (type of hospital)
   b. Normal control: Means and standard deviation (SD) (60 days)—from which the distance of quality control error limits from the mean for each parameter is calculated.
   c. Number of samples run per day including frequency of running QC material
   d. Whether retained specimens are used in quality control and number of patient repeats daily
   e. What quality control (error) limits the laboratory uses
   f. Derivation of limits—whether derived from statistical limits calculated by the local laboratory or manufacturers-supplied limits are used.
   g. Use of patient means for QC
   h. Opinions:
      i. Usefulness of quality controlling the analyte
      ii. Intra-laboratory and extra-laboratory bias
4. From the above international survey of diagnostic laboratories, an analysis of the differences between upper and lower action limits for IQC failure used in responding laboratories, expressed in SDs from the observed mean.

3 | RESULTS

3.1 | Review of the published literature including recommendations and requirements of international quality standards

The recommendations from ISO[3] and CAP[6] regarding IQC were reviewed, along with the CLSI-approved standard H26-A2.[5] The findings are summarized in Table S1 provided with this paper.

ISO 15189 (Standards for the Medical Laboratory) states that "The laboratory shall design quality control procedures that verify the attainment of the intended quality of results." In particular, it states under subheading 5.6.2.2 that "The laboratory shall use quality control materials that react to the examining system in a manner as close as possible to patient samples. Quality control materials shall be periodically examined with a frequency that is based on the stability of the procedure and the risk of harm to the patient from an erroneous result." ISO further states in "Note 1" that "The laboratory should choose concentrations of control materials, wherever possible, especially at or near clinical decision values, which ensure the validity of decisions made"; and in "Note 2" that "use of independent third-party control materials should be considered, either instead of, or in addition to, any control materials supplied by the reagent or instrument manufacturer."

CAP[6] states that "longitudinal process quality control procedure for individual instruments may include: (1) Use of preserved of stabilized whole blood controls, (2) Moving average monitoring, (3) Retained patient specimens or (4) Some combination of the above." It further states that "At least two different controls must be assayed and evaluated every 24 h. For each QC procedure employed, the laboratory must have appropriate QC ranges. For example, expected recovery ranges for commercial control materials are NOT the same as between-run SD ranges, and are probably too wide for daily QC of a single instrument. The laboratory should calculate its own imprecision statistics for each instrument." It is of interest that under heading HEM.25850 Stabilized Controls, CAP expresses the following view "Stabilized control materials must be at two different analytic levels (i.e., 'normal' and "high'). (the use of) Three levels of control is a conceptual carryover from clinical chemistry, and does not apply to hematology particle counting. Dilute, 'low-level' (e.g., leucopenia and thrombocytopenia) 'oncology' controls are less informative indicators of calibration status and are neither required nor recommended."

In regard to commercially assayed controls, CAP states "control values correspond to the methodology and target values (mean and QC ranges) and are verified or established by the laboratory… each laboratory must assign its own initial target value, based on initial analysis of the material; this target value should fall within the recovery range supplied by the manufacturer, but need not exactly match the package insert mean. The laboratory must establish specific recovery ranges that accommodate known changes in product attributes, assuming that calibration status has not changed."

On the subject of the use of moving averages, the CAP guidance states that this is "acceptably sensitive to drifts or shifts in analyzer calibration if a supplemental QC routine (stabilized control material or retained patient specimens) is employed"; it also states that "laboratories analyzing fewer than 100 CBC specimens daily (long term average) should not use moving averages as the primary method for process control, as this would not generate sufficient data within a day to be of value."

CAP expresses the view that the use of retained patient specimens alone is inadequate for routine QC of the primary CBC instrument and must be considered as a supplemental procedure in combination with another QC system. It states that statistically defined limits should be used to determine agreement of sequential

assays of a given retained patient specimen to allow for time-dependent alterations in data from such labile samples.

The CLSI document "Validation, verification, and Quality Assurance of Automated Hematology Analyzers," approved standard—Second edition H26-A2[5] stipulates similar requirements to those of CAP. Appendix E "Establishing Laboratory-Specific Quality Control Means and Ranges" states that "As noted by Westgard, Means, standard deviations ranges and other data from outside your laboratory does not reflect the individual, particular conditions of your lab. The use of data supplied from outside the laboratory…is meant to be a temporary workaround." It states that "each laboratory must establish its own commercial control means and ranges, using a cumulative approach to calculations." It also states, however, that calculated mean values for each level should fall within the range specified on the manufacturer's package insert. The main guidance and recommendations given by regulatory bodies are summarized in Table S1.

3.2 | Survey of major cell counter manufacturers

Cell counter manufacturers were invited to provide the advice they give to users of their equipment, as detailed in the methods section above:

Replies were received from the following cell counter manufacturers:
Abbott Diagnostics, Abbott Park, Illinois, United States;
Beckman Coulter, Brea, California, United States;
Mindray Medical International, Shenzhen, China;
Siemens Healthcare Diagnostics, Erlangen, Germany;
Sysmex Corporation, Kobe, Hyogo, Japan;
Horiba Medical Diagnostic Instruments & Systems, Kyoto, Japan.

The following is an abridged summary of the key information in the replies received. A more complete description of the manufacturer replies is given in a Appendix S1 attached to this paper.

3.2.1 | Answers to question A: Manufacturer recommendation to customers for IQC of their instruments, to include all QC methods they recommend

The manufacturer replies to question A are summarized below.

- All manufacturers consider that their commercially supplied control material should be run at least daily.
- Four of the six manufacturers recommend that "multi-level controls" be run, some recommend this should include three levels daily (low, medium and high); one recommends "minimum basic two levels every 24 h."
- All recommend the use of patient moving average analysis, although some consider this optional as an IQC method.
- All recommend the use of delta-checks of previous patient results, although two of six consider this optional.
- All recommend the use of retained patient specimens, although two of six consider this optional to monitor performance trends.[15]

3.2.2 | Answers to question B: Manufacturer policy for validation of their supplied IQC material

The answers to this question varied between manufacturers. One stated that this requirement differs between manufacturers versus customers. Another stated that validation is carried out by their third-party IQC supplier. Two of the six suppliers stated that cross-over (overlap) studies should be performed when implementing a new kit or lot of control material, by running old and new lots concurrently to allow comparison with the existing lot. Two suppliers stated that the local laboratory should establish their own mean values, or verify the manufacturer's mean. Interestingly, one supplier stated that in this regard "requirements differ based on geography." Several cell counter suppliers offered no specific guidance or requirement to their laboratory users in this regard.

Three of the six replied that they offered an online inter-laboratory comparison program, which allows laboratories to submit IQC results online and receive real-time peer-group statistical reports. They consider this a form of validation of the supplied IQC material.

3.2.3 | Answers to question C: To indicate whether IQC material is supplied by a third-party manufacturer

All manufactures indicated that their commercial IQC are sourced from a third-party supplier, who in all cases was one of the following: Streck Laboratories, Omaha, Nebraska, USA, or R&D Systems of Bio-Techne, Minneapolis, MN, USA.

All manufacturers indicated that they provide detailed purchasing specifications specific to each product to the product manufacturer, who in some cases also provide the target values for each parameter.

3.2.4 | Answers to question D

Your policy for ensuring traceability of your IQC materials to reference methods and determining uncertainty measurement of your IQC material(s):

All manufacturers replied that reference methods are used to test the IQC material received from the third-party manufacturer. All stated that all assigned target values for calibrators and controls are traceable to National Institute of Standards and Technology (NIST),[18] ICSH or CLSI recommended procedures or approved reference procedures and materials. The reference methods cited include those to test for and assign target values for: WBC and RBC counts,[12] HGB,[13,19] haematocrit (HCT),[20,21] platelets (PLT),[22] reticulocytes (RET).[23]

3.2.5 | Answer to question E: Manufacturers recommended or supplied statistical method to determine whether control results are out of range or require action

Five of the six suppliers recommended using Westgard[24] rules, a system of using a shorthand notation for expressing quality control rules

as "NL," where N represents the number of control observations to be evaluated and L represents the statistical limit for evaluating the control observations; thus 1–3s represents a control rule that is violated when one control observation exceeds the ±3s (SDs or SD away from the mean) control limits. However, one stated "there is no current recommendation for IQC with regards among to performing multi-rule analysis on individual instrument systems." One cited the CLSI-H26[5] recommendation that multi-rules best apply only to WBC, RBC, Hb, Hct and PLT parameters. All manufacturers provide their own "middleware solutions." Levy—Jennings charts[14] are commonly used in such middleware or instrument software. One manufacturer stated that data can be evaluated using manufacturer or third-party supplied target values and ranges (at a minimum) or customer-established means and ranges, or a combination of both.

As above, three manufacturers have developed web-based "consensus" programs for comparison of IQC results among users.

3.3 | International survey of quality practices across over 191 laboratories in four countries to gather information on quality control practices

The ICSH issued a survey to clinical diagnostic laboratories in the four countries stated above and detailed below, in order to gather further information on their IQC practices and also to assess the IQC performance of cell counters by all manufacturers by using IQC data derived from the results from commercially supplied control materials.

4 | RESULTS OF THE SURVEY OF LABORATORY PRACTICES

4.1 | Results from the international survey of quality practices

Results were obtained from 191 institutions in China, the Republic of Ireland, Spain and the United Kingdom that had different testing capacity, different geographical distribution and different manufacturer's instruments. The results from survey questions 1 and 3–7, in regard to instrument type by manufacturer and quality control practices, are given in Tables 1 and 2.

Figure 1A,B (and Figure S1c–e) shows frequency histograms of the differences, expressed in SDs, between the high and low acceptable normal level quality control limits for UK laboratories that responded to the survey for HGB, MCV, HCT, MCH and MCHC, respectively. The UK laboratories were studied in detail because they showed the greatest diversity in practice of using manufacturer-supplied versus locally calculated action limits. One half of an individual difference yields the number of SDs that the control measurement needs to be away from the control mean to define an error condition. A difference of 6 thus implies that that a QC measurement needs to

TABLE 1 Results from the survey of laboratory practices by country.

Country	China ($N = 100$)	Ireland ($N = 20$)	Spain ($N = 10$)	United Kingdom ($N = 61$)	Totals
Cell counters used by manufacturer in each country					
Abbott	1	2	3	3	9
Horiba Medical	1			2	3
Beckman Coulter	17			8	25
Mindray	19				19
Siemens	9	3	1	15	28
Sysmex	53	15	6	33	107
Derivation of control targets and limits in each country					
Manufacturer supplied	17	18	8	38	81
Locally calculated	60	2	2	18	82
Combination of both	4			5	9
Other	19				19
Number of laboratories using patient moving averages in their IQC					
Used	35	10	2	30	77
Not used	65	10	8	31	114
Percentage use	35%	50%	20%	49.1%	40.3%
Use of retained patient specimens in QC in each country					
Used	7	3	0	9	19
Not used	93	17	10	52	172
Percentage use	7%	15%	0%	14.7%	9.9%
Total laboratories responding in each country					
	100	20	10	61	191

	China			Ireland			Spain			United Kingdom		
Control level	L	M	H	L	M	H	L	M	H	L	M	H
Low level control	0	1	3	1	2	3	1	3	4	1	1	8
Normal level control	0	1	3	1	2	12	1	3	4	1	2	7
High level control	0	1	3	0	1	2	0	3	4	0	1	6

TABLE 2 Reported daily frequency of running commercial IQC material, showing the lowest reported frequency for each control level (L), the most commonly used frequency (M) (mode) and highest frequency (H) in each country.

Note: The colour shaded column illustrates the most commonly used frequency (the mode) for running commercial IQC material.
Abbreviations: H, highest; L, lowest; M, mode.

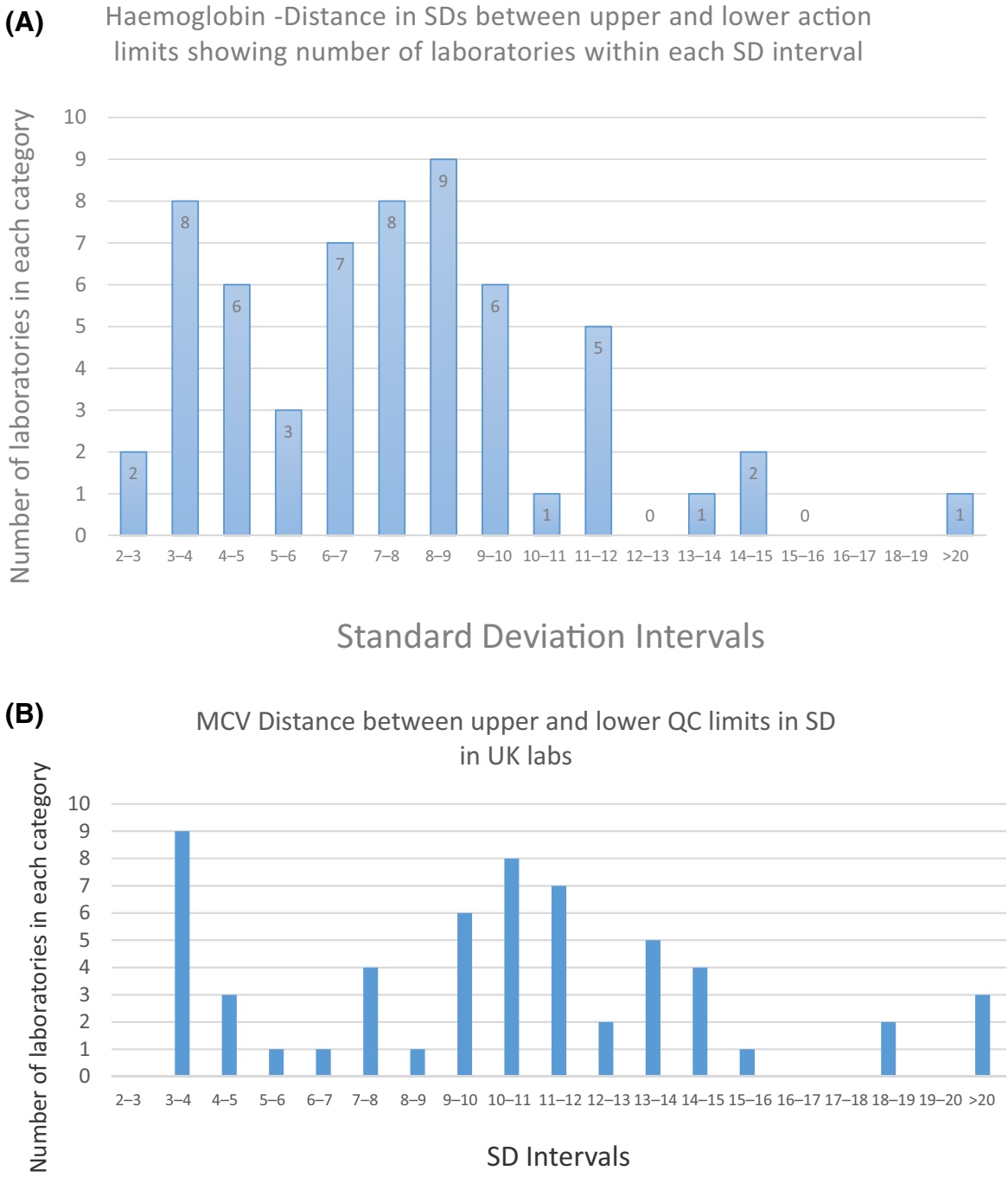

FIGURE 1 (A) Differences in SD of haemoglobin between the high and low acceptable normal level quality control limits in UK laboratories (Median = 8; $n = 58$). (B) MCV, Frequency histogram of differences, expressed in standard deviations, between upper and lower quality control limits (median = 10.7; $n = 57$).

be at least 3 SDs from the mean to indicate an error condition. This would be equivalent to applying the 1–3s control rule (Westgard nomenclature).[24] Looking at Figure 1A, the HGB frequency histogram which details the participating laboratory's differences between the high and low QC limits, most of the differences are less than 12 and generally range from 3 to 12 (meaning that deviations from 1.5 to 6 SD will indicate error). The median deviation is 8 SD which indicates that the typical laboratory does not flag a HGB error unless the control observation is more than 4 SD from mean.

The MCV graph shown in Figure 1B is somewhat different than the HGB graph in that there is a relatively high frequency of differences between 4 and 5 (corresponding to use of the 1–2s or 1–2.5s rules) and the median is 10.7, corresponding to a 1–5s or the 1–6s rule or even the 1–5.5s rule. Some laboratories are using very sensitive rules to detect errors in MCV and other labs respond only to much larger errors. The HCT graph (shown in Figure S1c) is shifted to the right with a median difference of 10.6 SD indicating that HCT needs to shift by more than 5 (10.6/2) SD to indicate an error (1–6 s control rule).[24] HCT is a noisier analyte than HGB and strangely, the limits for detecting error in HCT have been expanded compared to HGB.

The MCH and MCHC graphs shown in Figure S1d,e, respectively, show even greater tolerance of shifts and outliers with the median difference between the high and low control values being 12 (corresponding a Westgard rule of 1–6s).[24] The >20 difference bar encompasses a relatively large number of laboratories indicating these laboratories tolerated a 10s shift in MCHC. Table 3 shows the average differences from the mean of upper and lower QC limits for HGB, HCT, and MCV, in laboratories using manufacturer-supplied QC limits versus laboratories establishing their own limits by statistical calculation. This shows that that for certain parameters, these differences are larger when the laboratory used manufacturer-supplied action limits, than when the laboratory calculated the limits from statistical analysis.

Table 4 summarizes the medians of the differences, expressed in SDs, between the normal level control upper and lower quality control

TABLE 3 Average differences from the mean of upper and lower QC limits for haemoglobin, Hct, and MCV, in laboratories using manufacturer-supplied QC limits versus laboratories establishing their own limits by statistical calculation in the United Kingdom ($N = 61$).

FBC/CBC parameter	Haemoglobin (Hb) Difference in SD	Haematocrit (Hct) Difference in SD	MCV Difference in SD
Average for statistical limits laboratories	6.6 (±3.3 from mean)	8.2 (±4.1 from mean)	8.5 (±4.25 from mean)
Average for manufacturer limits laboratories	8.6 (±4.3 from mean)	12.1 (±6.05 from mean)	12.2 (±6.1 from mean)

TABLE 4 Medians of differences, expressed in standard deviations (SDs) between the normal level control upper and lower QC action limits for the four countries that participated in the survey, China ($N = 100$), Ireland ($N = 20$), Spain ($N = 10$) and the UK ($N = 61$), N (total) = 191.

Medians of difference in SD between normal control lower and upper QC action limits						
FBC/CBC parameter	All Region average	All region median	China median	UK median	Ireland median	Spain median
RDW	4.1	3.6	6.2	3.3	3	4
WBC	6	6.1	5.2	7	7.9	3.8
Haemoglobin	6.4	7.1	3.3	7	7.9	3.8
MPV	6.7	7.1	3.3	8	8	6.2
Basophil #	7.2	6.7	10.5	5.1	5.9	7.5
RBC	8.6	9.2	9.3	9.2	9.3	6.7
MCV	8.7	8.3	6.1	10.5	12.4	5.8
Eosinophil #	9	9.2	5.4	12	11.4	7
Monocyte #	9.3	9.1	8.7	15.2	3.9	9.5
Neutrophil #	9.9	10.7	10.7	11.2	10.7	7
Haematocrit	9.9	11	10.3	11.7	11.8	5.8
PDW	10.2	11.5	4.9	11.2	12.7	11.8
Platelets	10.6	10.3	9.7	10	10.5	12.3
Lymphocyte #	10.7	10.8	11.4	10.2	12.5	8.9
MCHC	11.1	11.1	9	13.3	12.3	9.8
Reticulocyte	11.1	12.3	4.1	14.1	15.8	10.5
MCHC	12.4	12.6	13.2	13.2	13.2	11.1
Median	9.3	9.2	8.7	10.5	11.4	7
Average	8.9	9.1	7.9	10	10.3	7.7
Comment	>12: little importance; <4 too much care; 4–8 optimal care; 8–12 less care					

limits for four regions that participated in the survey, China, UK, Ireland and Spain. The tests have been ordered by the average of the median regional scores. We attempted to categorize the tests depending on their median differences: <4 (red colour: very stringent QC); 4–8 (pink colour): adequate QC; 8–12 (yellow colour) less QC; >12 (green colour) far less QC. For individual medians that are less than 4, an equivalent control rule might be the 1–2s control rule which has a very high sensitivity to error but exhibits a high probability of false rejection, approximately 5% with a single observation, as described by Westgard.[24]

5 | DISCUSSION

IQC practices for blood cell counting have evolved since the era when IQC materials were routinely prepared and tested within the local laboratory. Today there is a reliance on commercially produced IQC materials supplied by the cell counter manufacturer or by third-party suppliers. A survey conducted as part of this study of eight laboratories in Malaysia (data not shown) indicated that even in remote regions, all laboratories use commercial control materials supplied by the cell counter manufacturer and have temperature control available to store these materials. An effective IQC policy should also incorporate many other lower cost or zero-cost methodologies. The ICSH survey shows there continues to be variation in practice worldwide and even within countries, variation in manufacturer recommendations, sometimes depending on the geographical area, and even some divergence in guidance on best practice among leading regulatory bodies and agencies. The separate ICSH guidance based on this study aims to propose a harmonized guidance to manufacturers on information they should issue to cell counter customers, and to recommend a policy for IQC procedures that diagnostic laboratories should adopt.

There is a general consensus among the regulatory bodies and instrument manufacturers regarding methodologies that should be employed as part of an IQC policy for cell counters, as shown in Table S2 and described above, although not all are considered mandatory by them. These include the daily use of stabilized whole blood controls at a minimum of two clinical levels, retained patient specimens for intra-laboratory comparisons to check precision, delta checks of previous patient results, verification by blood film analysis and the use of patient moving averages. Every method has some limitations and should be applied appropriately in each type of laboratory, for example the use of patient moving averages is not recommended when daily patient samples tested are less than 100 samples daily.[25,26]

There is a divergence of guidance from regulatory bodies in some respects, which has possibly led to confusion and variation in practice among diagnostic laboratories worldwide. For example, ISO alone states that "Independent third-party control materials should be considered, either instead of, or in addition to, any control materials supplied by the reagent or instrument manufacturer.[3]" The information gathered in this study from the cell counting industry suggests that commercial stabilized controls for cell counting are manufactured by a limited number of suppliers worldwide (only two were cited by six cell counter manufacturers). It is therefore possible that so-called independent third-party controls are manufactured by the same primary suppliers, for use with various cell counter types as specified on the product information. Such materials, if similarly produced, are therefore not inherently superior to commercial materials supplied by the cell counter manufacturer, but may be more economical. There may be a concern that the upper and lower result tolerance limits provided by the cell counter manufacturer may be too broad, however, that could be assessed by the local laboratory by analysis of the data, as prescribed by CLSI Standard H26-A2.[5] In addition, some parameters of the extended blood count may be specific to the particular manufacturer's instrument and technology; so the diagnostic laboratory needs to have an IQC material that will assess all such parameters used to make diagnostic decisions. Indeed, it is also a requirement of ISO 15189 that some form of quality control should be applied to any result or parameter that is reported clinically. Commercial quality control materials are expensive, so each laboratory is entitled to factor cost considerations into its internal policy, while considering all relevant requirements. It would also be useful to the diagnostic laboratory if more information regarding the manufacturer, source, and value assignment testing of the commercial control material were available.

In regard to the target values and QC ranges that should be used with commercially supplied controls; both the CAP[6] and CLSI H-26[5] prescribe that these should be "verified or established by the laboratory" and that each laboratory must assign its own initial target value, based on initial analysis of the material, but that this should fall within the recovery range supplied by the manufacturer. This guidance is based partly on the view that recovery ranges should "accommodate known changes in product attributes" and that "Means, standard deviations ranges and other data from outside your laboratory does not reflect the individual, particular conditions of your lab.[5]" There is a need for consensus and clarity in this area, since the ICSH survey found that there is considerable variation around the world and within countries as to the assignment of target values and ranges. In all countries surveyed (see Table 1), some laboratories established their own means and limits (42.9% of 191 laboratories), whereas others used the manufacturer-supplied values (42.4% of the total). In China, the majority (60% of 100 labs) established their own targets and limits, while in Ireland and Spain the majority used manufacturer's values (87% of 30 laboratories), while in the United Kingdom there was a more even split between each practice, with 38% of labs calculating their own limits for all or some parameters. This may be due to a difference in geographical area where each guidance is adopted and also to a lack of indication issued with commercial control material as to options for its optimal use. For example, in the European Union, CE-marking of in-vitro diagnostic materials[27] indicates that it should be used exactly as described by the supplier. This may influence the diagnostic laboratory in its choice to use manufacturer-supplied targets and ranges for each parameter. It is important that laboratories at a minimum should carry out verification of commercial control materials before use. This is a requirement of both of CLIA[7] and ISO 15189.[3] Our survey of 100 labs in China revealed that 64% of responding laboratories carry out such a verification of the control material.

Our survey data showed that there is variation in the adoption of upper and lower action limits for action with commercial QC materials. These are often greater distances from the mean or target than the theoretical 2 SDs that will encompass 95% of results when the system is in control, or 3 SDs that will encompass 99% of results (illustrated in Figure 1A,B and in Figure S1c–e). Importantly, we found that for certain parameters, these differences are larger when the laboratory used manufacturer-supplied action limits, than when the laboratory calculated the limits from statistical analysis (shown in Table 3). This suggests that the local laboratory should assess the action limits by measuring the SD locally and would be justified in tightening the limits in practice. It would significantly add to clarity in this area, if in addition to providing limits for the expected results for their control material, the manufacturer should transform and provide these limits as multiples of the usual SD for their common analysers.

All six cell counter manufacturers indicated that they employ reference methods in the testing and assignment of values to their control materials, as they do for calibrators, which are traceable to NIST,[18] ICSH[9,12,13,20,22] or CLSI recommended[19,20] procedures. It therefore seems incongruous in an era when traceability is important, that local diagnostic laboratories should be advised to replace assigned target values derived using reference methods with their own target values derived using non-reference methods from their own cell counters. However, changes in product attributes do need to be considered. Some cell counter manufacturers indicated in their replies to the ICSH, that they don't generally recommend that assay sheet targets and limits be used because "the range is larger to account for serial number specific biases." They commented that they do recommend the use of assay sheet limits only where there is a very low patient sample numbers and so statistical calculation of limits is not practical. Some also commented that they use users' data from the field, collected during the life of control and calibrator lots, to verify the performance of the material. It is not clear, however, that such considerations expressed by manufacturers are being communicated to users of their cell counters or included with control material inserts. As above, it would greatly help clarify practice if the manufacturers supply information regarding the derivation of limits in multiples of SD, and indicate clearly that the diagnostic laboratory can or should tighten these limits as prescribed by CLSI H26.[5]

Haematology laboratories primarily employ two different approaches in creating a statistical quality system. One is to use the manufacturer's suggested limits for allowable deviation from the control mean (documented in the control's package insert). There may be large inter-manufacturer differences in these limits when they are expressed as multiples of the usual instrument variation. In the other approach, the laboratory derives the average quality control imprecision for each of its analytes.

The FBC or CBC consists of at least 12 separate tests, with HGB, white cell count and platelets contributing enormously to patient diagnosis, monitoring and optimizing therapy. Other tests like RDW might only be inspected by the clinician if it is flagged as abnormal or to clarify a diagnosis. If an FBC/CBC component is regarded as very clinically important, it would be advantageous if this measured component is more carefully controlled, using action limits that will readily detect a problem.

There are important recent developments in IQC practice whereby the end-user lab can sign up to a manufacturer's scheme to collect their IQC data online and compare it to other users. The diagnostic laboratory's results are compared either to a consensus value or manufacturer's target value and they receive email notification if they are out of consensus. This trend, facilitated by more readily available IT connectivity between suppliers and the software or middleware supplied with the cell counter system, may well impact on which targets and limits the local laboratory adopts. This could result from a pressure to avoid IQC results being out of consensus with the peer group, even if they are within the targets and limits being used in the laboratory itself. This relatively new development has not yet been addressed by regulatory or guidance bodies and has the potential to have a significant impact on IQC practice.

An effective policy for IQC of cell counters should also include additional methodologies to the use of commercially supplied control materials. This is particularly relevant in the context of laboratory running costs, because commercial materials are expensive and furthermore, each commercial control run can consume expensive reagents to assess more specialized parameters that may only be used with a minority of patient samples. The use of patient means[16,26-28] for selected indices of the blood count even in small-volume medical laboratories, and of retained fresh patient samples to assess precision,[26] are well-established methods that have little or no ongoing material costs. It is surprising therefore that our survey of IQC practices revealed that a significant proportion of diagnostic laboratories are not using patient means as part of IQC (65% of Chinese laboratories, 50% of Irish laboratories, 80% of Spanish and 51% of UK laboratories, shown in Table 1). It was also of note that the laboratories not using this method included all sizes and workloads, for example processing up to 1500 patient samples daily. Similarly, the majority of respondents indicated that they don't use retained patient samples as part of IQC, only 19 of 191 laboratories or 10%, use these inexpensive but robust methods which are particularly useful for inter-analyser comparisons.

The use of delta checks[29] for comparison with previous patient results, now widely available through LISs, is an important form of in-house IQC that should not be overlooked. It is a post-analysis check that is particularly effective in detecting mis-labelled patient samples and "wrong-blood-in- tube" events, which are pre-analytical errors, not detectable at the analysis stage. Certain parameters of the blood count that do not exhibit rapid change without a blood transfusion, such as the MCV, are particularly useful tools that can be used in delta-checking. The comparison of blood count results with information available from blood film examination similarly represents an important post-analytical form of quality control and should form part of any well-balanced laboratory IQC policy.

6 | CONCLUSION

This ICSH study has shown existing diversity both in guidance and in practice exists in the area of internal quality control of cell counters.

One limitation of the study is that the detailed analysis of IQC practice was limited to four countries represented by the co-authors; nevertheless, this has confirmed the diversity in practice that exists and also highlighted the diversity that exists even within countries which have informed the ICSH Guidance. Future studies would help add further perspectives to the trend towards online comparison between IQC results among participating diagnostic laboratories. It is important that a diagnostic laboratory formulates a policy for IQC of cell counters that is both effective in ensuring that errors in patient results are minimized and is cost-effective.

The ICSH proposes guidance for such a policy for both cell counter manufacturers and for diagnostic laboratories in the related publication "ICSH Guidance for Internal Quality Control Policy for Blood Cell Counters." This guidance is based on the findings of the ICSH study described in this paper.

AUTHOR CONTRIBUTIONS

Richard McCafferty, George Cembrowski and Barbara de la Salle wrote the paper. Mingting Peng gathered data from China for for the international survey of clinical diagnostic laboratories, Eloisa Urrechaga gathered data from Spain, Barbara de la Salle gathered data from the United Kingdom and Richard McCafferty gathered data from the Republic of Ireland. All authors read, requested edits and agreed to the wording of the final paper.

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CONFLICT OF INTEREST STATEMENT

The co-author George Cembrowski declares the following: "G.S. Cembrowski and M.A. Cervinski are co-owners of patent number 10338085, "Devices and Methods to Determine Whether to Calibrate a Laboratory Analyzer." G.S. Cembrowski, "Altering Patient Care Based on Long Term SDD," publication number: US-2019-0035490 (with Junyi Mei), "Method And Apparatus For Calibration And Testing Of Scientific Measurement Equipment," United States Patent numbers: 8538727 and 10 332 621 (with David Tran)." The co-author Barbara de la Salle declares that she has received an honorarium from Abbott Diagnostics for speaking at a meeting within the past two years. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding author.

PATIENT CONSENT STATEMENT

Not required for this study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not required for this study. All statements quoted from other sources are from published scientific papers in the public domain. All data given in the paper are original to this study, gathered from clinical diagnostic laboratories and from cell counter manufacturers who gave permission for it to be used in this ICSH study.

CLINICAL TRIAL REGISTRATION

Not required for this study.

ICSH STATEMENT

Whilst the advice and information in this guidance is believed to be true and accurate at the time of going to press, the authors, ICSH and the publishers do not accept any legal responsibility for the content of this guidance.

ORCID

Richard McCafferty https://orcid.org/0000-0002-4916-2452
Barbara de la Salle https://orcid.org/0000-0002-2926-7441
Eloisa Urrechaga https://orcid.org/0000-0002-9610-7392

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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