Overview and update of ICSH activities in haematology standardization

JCTLM meeting, Paris
2nd December 2019

Dr. Paul Harrison, University of Birmingham
ICSH Board Member & JCTLM representative
What is the ICSH?

• The International Council for Standardization in Haematology (ICSH) was initiated as a standardization committee by the European Society of Haematology (ESH) in 1963 and officially constituted by the International Society of Hematology (ISH) and the ESH in Stockholm in 1964.

• The ICSH is recognised as a Non-Governmental Organisation with official relations to the World Health Organisation (WHO).

• The ICSH is a not-for-profit organisation that aims to achieve reliable and reproducible results in laboratory analysis in the field of diagnostic haematology.

• The ICSH coordinates Working Groups of experts to examine laboratory methods and instruments for haematological analyses, to deliberate on issues of standardization and to stimulate and coordinate scientific work as necessary towards the development of international standardization materials and guidelines.

• The ICSH has published 25 Publications and guidelines since reforming in 2007 – seven more in draft form.
<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Country</th>
<th>Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>Samuel J. Machin</td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>Vice-Chair</td>
<td>Szu-Hee Lee</td>
<td>Australia</td>
<td>Website &amp; Haematology</td>
</tr>
<tr>
<td>Vice-Chair</td>
<td>Steve Kitchen</td>
<td>UK</td>
<td>Haemostasis Chair</td>
</tr>
<tr>
<td>Scientific Secretary</td>
<td>Gina Zini</td>
<td>Italy</td>
<td>Haematology</td>
</tr>
<tr>
<td>Treasurer</td>
<td>Alexander Kratz</td>
<td>USA</td>
<td>Finances &amp; Haematology</td>
</tr>
<tr>
<td>Member</td>
<td>Paul Harrison</td>
<td>UK</td>
<td>Platelets and Flow cytometry</td>
</tr>
<tr>
<td>Member</td>
<td>Wendy Erber</td>
<td>Australia</td>
<td>Haematology &amp; Molecular</td>
</tr>
<tr>
<td>Member</td>
<td>Kees Harteveld</td>
<td>Netherlands</td>
<td>Haemoglobinopathies</td>
</tr>
<tr>
<td>Member</td>
<td>Bob Gosselin</td>
<td>USA</td>
<td>Haemostasis</td>
</tr>
<tr>
<td>Member</td>
<td>Richard McCafferty</td>
<td>Ireland</td>
<td>Haematology</td>
</tr>
<tr>
<td>Administrator</td>
<td>Terry Fawcett</td>
<td>Australia</td>
<td>Administration</td>
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ICSH General Assembly Meetings

• 2007 – Amsterdam Netherlands
• 2008 – Sydney Australia
• 2009 – Rome Italy
• 2010 – Bangor USA
• 2011 – Montpellier France
• 2012 – Chicago USA
• 2013 – Gerrards Cross UK
• 2014 – San Francisco USA
• 2015 – Shenzhen China
• 2016 – Lucerne Switzerland
• 2017 – Kobe Japan
• 2018 – Miami USA
• 2019 – Lund Sweden
• 2020 – Singapore
AFFILIATE ORGANIZATIONS

NCCL CHINA
SCCL CHINA

UK NEQAS
International Quality Expertise

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

HSANZ NZ BRANCH

IEQAS
Irish External Quality Assessment Scheme

The Japanese Society for Laboratory Hematology

RCPAQAP
RCM Quality Assurance Program

KSLH
Korean Society for Laboratory Hematology

SEQC ML
Sociedad Española de Medicina de Laboratorio

World Health Organization

International Federation of Clinical Chemistry and Laboratory Medicine

JCTLM

CAP

Corporate Members

- Abbott Diagnostics
- Beckman Coulter
- BD
- BIT
- Cellavision
- Dako
- Instrumentation Laboratory
- Leica Biosystems
- Mindray
- Nihon Kohden
- Roche
- RR Mechatronics
- Siemens
- Sysmex
- Stago
- Ventana
ICSH GUIDELINES & RECOMMENDATIONS

2019 - Digital morphology analyzers in Hematology Review: ICSH review and recommendations

2018 - Laboratory Measurement of Direct Oral Anticoagulants (DOACS)

2017 – ESR Methods Guideline

2016 - Haematology Reporting
<table>
<thead>
<tr>
<th>Project</th>
<th>Project Lead</th>
<th>Status</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCTLM Traceability</td>
<td>Dr Paul Harrison</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>Immunoplatelet - JCTLM</strong></td>
<td>Dr Paul Harrison</td>
<td>Ongoing</td>
<td>Ongoing</td>
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<tr>
<td>Digital Morphology</td>
<td>Dr Alexander Kratz</td>
<td>Paper accepted</td>
<td>May 2019</td>
</tr>
<tr>
<td>Immunodifferential</td>
<td>Dr Brent Wood</td>
<td>Multi-centre trial</td>
<td>September 2019</td>
</tr>
<tr>
<td>Internal QC for analyzers</td>
<td>Mr Richard McCafferty</td>
<td>First Draft done</td>
<td>September 2019</td>
</tr>
<tr>
<td>MPV Standardization</td>
<td>Dr Paul Harrison</td>
<td>Retesting new material</td>
<td>May 2020</td>
</tr>
<tr>
<td>IRF Standardization</td>
<td>Dr Amrom Obstfeld</td>
<td>Retesting new material</td>
<td>May 2020</td>
</tr>
<tr>
<td>CD34 IHC Standardization</td>
<td>Dr Emina Torlakovic</td>
<td>First draft</td>
<td>September 2019</td>
</tr>
<tr>
<td>HbA2 Standard</td>
<td>Dr Kees Hartveld</td>
<td>In conjunction with IFCC</td>
<td>Uncertain</td>
</tr>
<tr>
<td>HbA Standard</td>
<td>Mr. Terry Fawcett</td>
<td>Need to retest old Eurotrol standard</td>
<td>December 2019</td>
</tr>
<tr>
<td>WCC Standardization by flow cytometry**</td>
<td>Mr. Vuong Nguyen</td>
<td>Evaluation of candidate methods</td>
<td>September 2019</td>
</tr>
<tr>
<td>WHO Liaison</td>
<td>Dr Gina Zini</td>
<td>Ongoing</td>
<td>Ongoing</td>
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<tr>
<td>Project</td>
<td>Project Lead</td>
<td>Status</td>
<td>Completion</td>
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<td>----------------------------------------------</td>
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<tr>
<td>Preanalytical Variables Guideline</td>
<td>Dr Steve Kitchen</td>
<td>Draft near completion</td>
<td>December 2109</td>
</tr>
<tr>
<td>FVIII/FIX Inhibitors Guideline</td>
<td>Dr Piet Meijer</td>
<td>Draft near completion</td>
<td>December 2019</td>
</tr>
<tr>
<td>Mixing Studies Guideline</td>
<td>Dr Dot Adcock</td>
<td>Draft near completion</td>
<td>December 2019</td>
</tr>
<tr>
<td>POC Guideline</td>
<td>Dr Dave Fitzmaurice</td>
<td>Draft near completion</td>
<td>May 2020</td>
</tr>
<tr>
<td>ADAMST13 guideline</td>
<td>Dr Ian Mackie</td>
<td>Draft near completion</td>
<td>September 2019</td>
</tr>
<tr>
<td>DOACS guideline update</td>
<td>Mr Bob Gosselin</td>
<td>Draft near completion</td>
<td>January 2020</td>
</tr>
<tr>
<td>Critical Results in Haemostasis</td>
<td>Mr Bob Gosselin</td>
<td>Just published</td>
<td>September 2019</td>
</tr>
<tr>
<td>Coagulation Analyzers Evaluation Guideline</td>
<td>Dr Chris Gardiner</td>
<td>Project has started</td>
<td>October 2020</td>
</tr>
<tr>
<td>Coagulation Reagents Evaluation Guideline</td>
<td>Mr Bob Gosselin</td>
<td>Project approved</td>
<td>October 2020</td>
</tr>
</tbody>
</table>
ICSH and JCTLM (Joint Committee for Traceability in Laboratory Medicine)

• Important Collaboration
• Very few Laboratory Haematology entries in JCTLM Database
• Both organizations have identified the need to collaborate
Expand JCTLM Executive Member organizations to include other disciplines in laboratory medicine

Outreach to ICSH as peer Lab Haem organization

- Reps from JCTLM and ICSH met 22 June 2015 @ EuroMedLab Paris
- Sam Machin gave a Webex presentation @ 2015 JCTLM Members & Stakeholders Meeting
- Graham Beastall attended ICSH General Assembly, 26 October 2016 Lucerne
- Bruce Davis & George Cembrowski attended 2017 JCTLM Members & Stakeholders Meeting, BIPM
- JCTLM and ICSH convened a meeting 14-15 May 2018, BIPM
- Gary Myers attended 2018 ICSH General Assembly, Miami USA
- ICSH Submitted Reference Method for Platelet Counting in 2018
- ICSH accepted as Executive Member in January 2019
- Ian Young attended 2019 ICSH General Assembly, Lund, Sweden
- Dr Paul Harrison, UK, appointed ICSH Board Member liaising with JCTLM
In 2019, the Joint Committee for Traceability in Laboratory Medicine accepted ICSH as an executive member of JCTLM. ICSH will assist with Haematology and Haemostasis traceability. This will encompass the sciences of metrology, laboratory medicine and laboratory quality management to help the IVD industry meet traceability requirements of the EC IVD Directive.
JCTLM Database: Entries as of March 2018

- 26 measurands with complete reference systems
- 293 Certified Reference Materials
- 184 RMPs that represent 83 different measurands in 9 categories
- 161 reference measurement services delivered by 17 reference labs

NOTE – VERY SMALL NUMBER OF BLOOD CELL COUNTING AND HAEMOSTASIS ENTRIES – HENCE NEED FOR ICSH LIAISON WITH JCTLM
Immuno-platelet counting

ICSH/ISLH (Late 1990’s) - proposed that the immunocount derived from the platelet:RBC ratio should become the new reference method

• Requirements of Platelet:RBC ratio method

  Optimal resolution of platelets from noise and other cells
  Antibody must specifically recognise all platelets
  Elimination of Coincidence events (platelet:RBC or RBC:RBC) by optimisation of dilution
  Sufficient platelets must be counted for accuracy

• Main Advantage

  Independent of pipetting and dilution artefacts
PLATELET/RBC RATIO

For full method see Harrison et al, 2001, AJCP, 115, 448-59
& ICSH/ISLH, 2001, AJCP, 115, 460-4
In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures
Reference measurement procedures for the accurate determination of cell concentrations: present status and future developments

Referenzmessverfahren für die genaue Bestimmung von Zellkonzentrationen: Status und zukünftige Entwicklungen

Abstract

Accurate determination of cell concentrations serves as a valuable tool to support medical diagnosis and therapy control, e.g., in haematology, immunology and transfusion medicine. Intra- and inter-laboratory comparability of measurement results is essential for patient safety. To derive the so-called “conventional quantity value” of a measurand as target value for intra- or inter-laboratory quality assurance and to establish a traceability chain to the international System of Units (SI), a primary reference measurement procedure is needed, defined as a procedure which includes a complete analysis of influence quantities and perturbing factors and a complete description of measurement uncertainties. We describe a primary reference measurement procedure for the determination of erythrocyte concentration, based on flow cytometric cell counting by impedance measurements. To correct for instrument- and sample-dependent counting loss due to random coincidences, dilution series are prepared. The reference quantity value of the cell concentration is derived by extrapolation to vanishing volume fraction of the sample in the measurement suspension. Typically, for erythrocyte and leucocyte concentrations respective uncertainties of approximately 0.75% and 2% are reached. Future developments concern the extension of the procedures validated for erythrocyte and leucocyte counting by including immunological staining and microscopic techniques.
List of reference measurement methods/procedures

This file was created on 27 April 2018 from the JCTLM-DB website (https://www.bipm.org/jctlm)
Your search criteria: Reference measurement methods/procedures, Analyte: thrombocyte, Analyte category: - Matrix category: -

Flow cytometry methods for thrombocyte in whole blood

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Applicable reference(s)</th>
<th>Full description of technique(s)</th>
<th>Applicable range</th>
<th>Expected uncertainty (level of confidence 50%)</th>
<th>Reference(s)</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFB reference method for blood cell counting</td>
<td>Fresh whole blood</td>
<td>Flow cytometry, cell differentiation by fluorescence detection of antibody stained platelets and light scattering, coincidence correction by dilution series</td>
<td>50 x10^3 to 1500 x10^3</td>
<td>10 % relative</td>
<td>J. Lab. Med., 2012, 36(1), 28-35; German National Standard DIN 58922-5</td>
<td>Validation of the reference method described in DIN 58922-5 is presently accomplished. Procedures used to derive the thrombocyte concentration by determining the platelet/erythrocyte ratio (Am J Clin Pathol., 2001, 115, 486-494 and references therein) are not suited as primary reference procedure, since coincidence correction has not been proved to yield correct results for particle subpopulations exhibiting dramatically different concentrations (e.g. 10 platelets / nl compared to 4000 erythrocytes / nl).</td>
</tr>
</tbody>
</table>
N = 480 (160 in triplicate)  
Platelet counts 1.4 – 738 x 10^9/L  
RBC counts 1.83-5.75 x 10^12/L

N = 90 (30 in triplicate)  
Platelet counts 4 – 50 x10^9/L  
RBC counts 2.04-3.98 x10^12/L

UKNEQAS PH Reference Lab Data (2001 – 2019)  
With and Without Coincidence Correction at 1:1000 final dilution
ICSH Platelet Counting Reference Method – Ongoing work

- Reference Method papers sent to JCTLM for feedback/approval?

- Update ICSH method to be compliant with new ISO standard and after JCTLM feedback

- Attend JCTLM meeting in Paris in December

- Possible comparison with the PTB method?
ICSH & JCTLM – In Summary

- Traceability in laboratory medicine is a requirement of the IVD Regulation
- JCTLM has been established to provide global support to IVD manufacturers and regulators on traceability in lab medicine
- Currently there are very few haematology entries in the JCTLM database
- ICSH is the organization producing standards and guidelines in Laboratory Haematology
- ICSH and JCTLM are collaborating on Haematology Projects
- ICSH has been accepted as an Executive Member of JCTLM
- Dr Paul Harrison is the ICSH Liaison Officer to JCTLM