PSA Test Harmonisation Outcomes Agreed at the NCCP PSA Harmonisation Board Workshop

Held on 3rd December 2014

NCCP PSA Harmonisation Board,
National Cancer Control Programme (NCCP),
Kings Inn House, 200 Parnell Street, Dublin 1
Tel 01 8287100  www.cancercontrol.hse.ie

2nd February 2015
The following PSA test harmonisation outcomes were agreed by the laboratories of the NCCP-designated cancer centres:

[1] The unit of measurement of PSA concentration in serum or plasma shall be μg/L and at least one decimal point is required.
Notes, additional information and references in Appendix 1, page 5.

[2] Assay details (calibration followed by manufacturer) shall be specified with the test name on PSA reports.
Notes, additional information and references in Appendix 2, page 6.

[3] Whole blood specimens for PSA measurement shall be drawn, transported, logged-in, and serum/plasma separated and ready for analysis in less than 24 hours. Requesting doctors shall be advised of this requirement. A warning shall accompany results on specimens exceeding this agreed time limit.

PSA testing shall not be performed on an un-centrifuged blood specimen received more than 48 hours after it was drawn, unless conclusive evidence indicates that longer contact times do not contribute to result error.
Notes, additional information and references in Appendix 3, page 7.

[4] Only PSA assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) shall be used.
Notes, additional information and references in Appendix 4, page 14.
[5] All NCCP-designated cancer centres shall participate in an ongoing external quality assessment scheme for PSA operated by IEQAS. The types of EQA samples used in the scheme will include pooled residual serum and occasionally donor serum samples. EQA results shall be returned for each analytical system from which patient PSA results are generated.

Notes, additional information and references in Appendix 5, page 19.

[6] Each NCCP-designated cancer centre shall:

(a) Set IQC limits for PSA using existing IQC material so as to achieve realistic concordance with coefficients of variation currently attained;

(b) Run a common IQC two-level product for the intensive quality management of PSA measurement. The common IQC material is not intended to replace or displace a centre’s existing IQC material.

(c) Set agreed common acceptance/rejection criteria for this material with the aim of improving the quality of results reported across all the centres.

Notes, additional information and references in Appendix 6, page 20.

Approaches to achieving harmonisation of clinical laboratory results.

Appendix 7 (page 22).
Appendix 1

The unit of measurement of PSA concentration in serum or plasma shall be μg/L and at least one decimal point is required.

References


Notes:

Change from ng/mL to μg/L does not change the numerical value, however it has implications for:
- Laboratory Information Systems;
- Laboratory user manuals;
- Healthlink (The National Healthlink Project) and primary care practice IT systems;
- However, the change is manageable.

When making the change, we suggest using ‘L’ as symbol for litre. CIPM approves both ‘l’ and ‘L’.

The litre and its symbol l were adopted by the CIPM in 1879. The alternative symbol for the litre, L, was adopted by the CGPM in 1979 in order to avoid the risk of confusion between the letter l and the number 1. Thus, although both l and L are internationally accepted symbols for the litre, to avoid this risk the preferred symbol for use in the United States is L.

Use of script letters: neither a lowercase script letter l nor an uppercase script letter L is an approved symbol for the litre.

Representation of the character ‘μ’ in laboratory information systems with limited character sets:
When the Greek lowercase character ‘μ’ is not included in the character repertoire of a laboratory information system, it is customary to use the Latin lower case ‘u’ in those circumstances.

http://unitsofmeasure.org

CIPM = International Committee for Weights and Measures (Comité International des Poids et Mesures).
CGPM = General Conference on Weights and Measures (Conférence Générale des Poids et Mesures).
Appendix 2

Assay details (calibration followed by manufacturer) shall be specified with the test name on PSA reports.

References:


NACB PROSTATE CANCER PANEL RECOMMENDATION 11:

Postanalytical requirements for PSA - information to be included in clinical reports

Clinical reports should include the name of the assay, relevant clinical decision limits, and a reminder that a single screening blood test result should not be used as the sole evidence of the presence or absence of malignant disease.

EUROPEAN GROUP ON TUMOUR MARKERS (EGTM), a European-Based Expert Group on Tumour Markers:

“Every laboratory report should contain the name of the assay used and a valid reference range, specifically generated for this assay to enable the physician in charge of interpreting the results to draw correct conclusions.”

www.egtm.eu

Notes:

Recommendation: the manufacturer’s analyser model name need not be specified unless significant differences in results are observed for different analyser models from the same manufacturer.
Appendix 3

Whole blood specimens for PSA measurement shall be drawn, transported, logged-in, and serum/plasma separated and ready for analysis in less than 24 hours. Requesting doctors shall be advised of this requirement. A warning shall accompany results on specimens exceeding this agreed time limit.

PSA testing shall not be performed on an un-centrifuged blood specimen received more than 48 hours after it was drawn, unless conclusive evidence indicates that longer contact times do not contribute to result error.

**Recommendation:**

Laboratories should advise GPs that patients requiring a PSA test should attend the practice for phlebotomy on the morning of a day on which there will be scheduled specimen transport to the regional laboratory.

**Notes on the evidence base underpinning some national and international recommendations on the stability of PSA in specimens of whole blood.**

(1) Stability has been defined (ISO Guide 30, 1992) as the capability of a sample material to retain the initial property of a measured constituent for a period of time within specified limits when the sample is stored under defined conditions. Instability is present when there are important changes in one or more of these measurements. (Draft ISO Technical Report entitled “Quality practices in collection, transport, receipt, and handling of samples for medical laboratory examinations”; January 2014).

(2) Some of the recommendations and studies referred to in this document use the term analyte when the correct term consistent with current international usage and in the context in which it is used is measurand.

[Analyte = the name of a substance or compound; Measurand = the quantity of the substance or compound intended to be measured].
[a] Prostate Cancer Risk Management Programme (PCRMP) for England, 2010


Recommendation: “Evidence indicates that PSA is stable in whole blood for up to 16 hours at room temperature. When taking blood you should ensure that the specimen will reach the laboratory and be separated within this time frame. The quality of PSA testing can vary between laboratories, depending on the type of PSA test employed. To reduce the effects of this variation, samples should be sent only to laboratories which employ a method for PSA assay which is equimolar (measures free and complexed PSA equally) and has calibration traceable to the World Health Organisation international standard. Such laboratories should also participate in the UK National External Quality Assessment Service (UK NEQAS) for PSA testing. In addition, samples from each individual patient should always be sent to the same laboratory.”

Evidence for recommendation:
Note that the recommended time frame of 16 hours for a specimen for PSA measurement to reach the laboratory and be separated is not explicitly stated in the three papers cited by the PCRMP. It is likely that the 16 hours target is a pragmatic choice made by the PCRMP to guide primary care practitioners in ensuring that specimens are drawn, transported, logged-in, separated and ready for analysis in less than 24 hours.

References cited:

“Stability in whole blood
The stability of PSA is most relevant to a screening programme in which many samples have to be posted to the laboratory. More work is required on the effect of storage over 24-72 h. Woodrum et al. 98 drew blood from 11 patients and allowed clotting to proceed at room temperature, preparing serum at 1, 3, 5 and 8 h. Approximately 1% of free PSA was lost per hour of clotting time, but no loss was noted for total PSA. These results are similar to those of Piironen et al., 99 who stored blood at room temperature for 1-6 h prior to separation. Total PSA, free PSA and complexed PSA were measured using separate immunofluorometric assays (IFMA). After 5.5 h, a statistically significant mean decrease was observed only for free PSA (mean decrease 3.5%).”


http://www.who.int/iris/handle/10665/65957
This document is based on the Recommendations of the Working Group on Pre-Analytical Quality of the German Society for Clinical Chemistry and the German Society for Laboratory Medicine, which were published in 2001.

Recommendation:

<table>
<thead>
<tr>
<th></th>
<th>Stability in whole blood at room temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PSA</td>
<td>1 day</td>
</tr>
<tr>
<td>Free PSA</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

Evidence cited for recommendations

Nine references are listed in relation to PSA. Please note that the references are cited incorrectly in the WHO document.


[c] NACB Laboratory Medicine Practice Guidelines: Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers; 2009.

Website: www.aacc.org (Follow link to NACB).
Recommendation:
“NACB Prostate Cancer Panel Recommendation 8:
Pre-Analytical Requirements for PSA: Sample Handling Samples should be centrifuged and refrigerated within 3 hours of phlebotomy; this recommendation is particularly relevant for fPSA, which is more labile than total PSA. Samples may be stored at refrigerated temperatures for up to 24 hours, but samples that will not be analysed within 24 hours of collection should be stored frozen (at least at -20°C and preferable at -30°C or lower). For long-term storage, samples should be frozen at -70°C or lower [LOE, not applicable; SOR, B].”

Notes:
LOE = Level of Evidence
SOR = Strength of Recommendation; (B = Moderate: Further research is likely to have an important impact on the Panel’s confidence in the estimate of effect and is likely to change the estimate).

Evidence cited for recommendations


Reference:

CLSI terminology: “Serum or plasma that has been completely separated from any contact with cells or clot.
Note: the serum or plasma has either been removed by pipette from the cells or contact has been interrupted by a chemical/physical barrier through the use of a serum/plasma separator device”.

Recommendations: (Note: recommendations made only for Total PSA)
(1) Uncentrifuged specimen stability for PSA at Room Temperature (20-25°C) in serum tube

| Whole blood in serum tube | PSA stability up to 24 hours |

Notes:
“The change produced by the storage conditions was considered to be clinically significant if it exceeded a clinically acceptable limit (CAL) and was statistically significant when compared with control samples. ... A clinically acceptable limit was based on analytical variation from laboratory data, biological variation and the minimal change considered clinically relevant. Although these values were subjective, they were similar to or exceeded calculated significant change intervals based on analytical variation.”

(2) Uncentrifuged specimen stability for PSA at Room Temperature (20-25°C) in heparinised plasma tube

| Whole blood in heparinised plasma tube | PSA stability up to 6 hours |


Notes:
“To determine the changes in analyte concentrations of plasma with and without prolonged contact with cells, the mean from 50 volunteers for each respective analyte was obtained. Clinically significant changes were determined by the significant change limit (SCL) approach defined as: SCL = Initial value ± 2.8 usual SD. It is based on the assumption that the usual SD (USD) is representative of the inherent day-to-day variability of the method. In this study, the calculated mean for each analyte at 0.5 h represented the initial value. USD was obtained by averaging the SD of the quality control data (target mean most closely matched the 0.5 h mean) observed for the last 12 months for each respective analyte. SCL was calculated by establishing the range (±2.8 USD) from mean at 0.5 h.”

CLSI general recommendations on uncentrifuged blood specimens (subject to the specific recommendations set out by CLSI concerning individual measurands):

“Within 48 hours of collection, if a blood sample has not been centrifuged, testing can be performed if the measurand is stable uncentrifuged for 24 to 48 hours and centrifugation can occur within the allowable time frame of 24 to 48 hours.

When a blood specimen is received more than 48 hours after it is collected and it has not been centrifuged, testing should not be performed unless conclusive evidence indicates that longer contact times do not contribute to result error. Therefore, stability of the specimens for different tests should be defined for reliable results.”
“These are the delivery times on GP specimens received in September 2013. Of 12,589 specimens received, 9,438 (75%) had collection times recorded on the request form. The time of delivery is recorded as the difference between the time of collection and the time of receipt in the laboratory. This data doesn’t take into account that some of our GP’s have centrifuges and will spin down their samples before sending. However, even amongst the spun specimens, many are inadequately spun and this has therefore not been considered in this analysis.”

<table>
<thead>
<tr>
<th>Time to Delivery</th>
<th>Number of Specimens</th>
<th>% of Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8h</td>
<td>6368</td>
<td>67.5</td>
</tr>
<tr>
<td>&lt; 16h</td>
<td>6829</td>
<td>72.4</td>
</tr>
<tr>
<td>&lt; 24h</td>
<td>7360</td>
<td>78.0</td>
</tr>
<tr>
<td>&lt; 48h</td>
<td>9305</td>
<td>98.6</td>
</tr>
<tr>
<td>&lt; 72h</td>
<td>9423</td>
<td>99.8</td>
</tr>
<tr>
<td>&lt; 96h</td>
<td>9432</td>
<td>99.9</td>
</tr>
</tbody>
</table>
Appendix 4

Only PSA assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) shall be used.

Notes:

WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670)

This consists of a batch of vials (coded 96/670) containing seminal plasma-derived prostate-specific antigen (PSA), 90% bound to 1-antichymotrypsin (PSA-ACT) and 10% in the free form, analysed by international collaborative study and established as the First International Standard for Prostate-Specific Antigen (90:10) by the Expert Committee on Biological Standardization of the World Health Organisation.

The assigned content is 1μg total PSA per vial. The International Unit of 96/670 is assigned without uncertainty.

Each vial contains the residue, after freeze-drying, of 2ml 20mM PBS, pH 7.4 solution that contained:

- Bovine serum albumin 10g/L
- Prostate-specific antigen (bound) 450μg/L
- Prostate-specific antigen (free) 50μg/L

Estimates of the contents of 96/670 by immunoassay were similar and consistent with local standards, giving a geometric mean estimate of 1.11μg/vial (95% confidence limits: 1.04 – 1.18). Therefore the preparation coded 96/670 was established as the First International Standard for PSA (90:10) with a defined content of 1μg per vial.”

Cautionary Notes:

(a) The commutability of the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) is not proven.

(b) PSA is an example of quantities for which results of measurements are not metrologically traceable to SI.

“These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization’s International Standards, such as protein hormones, some antibodies, and tumour markers.” [ISO 17511]

“One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure.” [ISO 17511].

(c) ISO 17511 states: “The WHO Expert Committee on Biological Standardization (ECBS) establishes international biological reference materials called "International Standards (IS)". For the first batch of such a material, an "international unit" is defined as an arbitrarily specified amount of the material and characterized by its specified biological activity. ... ..."  

The assigned value of such a reference material, even when it is highly purified, is related to a dedicated biological measurement procedure without metrological traceability to SI units. Such a material, therefore, cannot be called a primary reference material.”
Cautionary Note on availability of current WHO Standard (NIBSC Code 96/670):

Minutes of ICHCLR Council/Harmonization Oversight Group (HOG) Meeting, 10-11 February 2014:

“Dr Young stated in regards to PSA that there is a WHO reference material that is held by NIBSC. NIBSC approached IFCC because they are running out of material. He said there is a working group established and a chair to determine a new reference material.”

ICHCLR = International Consortium for Harmonisation of Clinical Laboratory Results.

The introduction of the WHO International Standard for Prostate-Specific Antigen has led to very significant improvements:

“Following establishment of the 1st International Standard for PSA in 2000, and its adoption as primary calibrator by most providers of PSA assays, the mean CVs observed in the UK NEQAS for PSA decreased by approximately two, from more than 20% in 1995 to approximately 9.5% in 2005. Recovery of added standard (1st IS for PSA) is near quantitative (106% in 2005), but individual method recoveries vary from 93% to 123%.”

Reference:
Calibration hierarchy and metrological traceability appropriate for PSA assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) according to ISO 17511.

ISO 17511:2003 Categories for Reference Systems

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Measurement Procedure</th>
<th>Primary (pure-substance) reference material</th>
<th>Secondary (value-assigned) reference material</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, Cortisol, HbA1c</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Haemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Tumour markers, proteins, HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Epstein-Barr virus, varicella zoster virus</td>
</tr>
</tbody>
</table>
The Pillars of Metrological Traceability

1) Primary Reference Measurement Procedure

“Reference measurement procedure having the highest metrological qualities, whose operation can be completely described and understood, for which a complete uncertainty statement can be written down in terms of SI Units, and where results are, therefore, accepted without reference to a measurement standard of the quantity being measured.” [ISO 17511]

2) Primary Reference Material

“Reference material having the highest metrological qualities and whose value is determined by means of a primary reference measurement procedure.” [ISO 17511]

3) Reference measurement services for IVDMD manufacturers and National EQA Schemes

These enable the adoption of common reference intervals and EQA surveillance of the integrity of the metrological traceability chain in the field.

Adapted from work of Dr Gary L Myers, AACC, Washington, USA

The NCCP expects its designated cancer centre laboratories to each play an active leadership role within its hospital group to ensure that PSA assays used across the hospital group are calibrated to the WHO International Standard and that IQC of PSA assays across the group are demonstrably sufficiently robust and sensitive to detect any significant shift in assay performance.

Important warning:

A change from the traditional Hybritech calibration of PSA assays to assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) has important consequences for reference limits, clinical decision points and age-related reference values.

Recalibrating a prostate-specific antigen (PSA) assay from an original Hybritech calibration to the new WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) by a manufacturer, in order to assure assay traceability to this higher-order material, results in approximately 20% lower PSA values for patient samples.

While a change in the range of 20 – 25% is reported in numerous published papers, the extent of the change may also be influenced by (a) differences in the commutability characteristics of Hybritech and WHO calibrators with respect to the assay, (b) the degree of equimolarity for bound and free PSA displayed by the assay and (c) other assay characteristics and design features.

Please consult with the assay system manufacturer for the exact evidence-based change to be expected.
The UK Prostate Cancer Risk Management Programme (PCRMP) advises medical practitioners requesting PSA tests that:

“The quality of PSA testing can vary between laboratories, depending on the type of PSA test employed. To reduce the effects of this variation, samples should be sent only to laboratories which employ a method for PSA assay which is equimolar (measures free and complexed PSA equally) and has calibration traceable to the World Health Organisation international standard.

Such laboratories should also participate in the UK National External Quality Assessment Service (UK NEQAS) for PSA testing. In addition, samples from each individual patient should always be sent to the same laboratory.”

The PCRMP has issued referral values based on assays whose calibration is traceable to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670).

<table>
<thead>
<tr>
<th>Age</th>
<th>PSA referral value (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>≥ 3.0</td>
</tr>
<tr>
<td>60-69</td>
<td>≥ 4.0</td>
</tr>
<tr>
<td>70 and over</td>
<td>&gt; 5.0</td>
</tr>
</tbody>
</table>

- As PSA levels rise with age, the PCRMP recommends the use of age-related referral values.
- These levels should be used for all men regardless of their weight.


The PSA assay used in the Oesterling et al study was the Hybritech Tandem-R PSA assay (FDA approved in 1986).

The next revision of the NCCP’s National Prostate Cancer GP Referral Guidelines is planned for the second quarter of 2015.

It is expected that the consequences for reference limits, clinical decision points and age-related reference values of the change to PSA assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) will be addressed in this revision.
The NCCP Prostate Cancer Referral Guidelines and the electronic GP referral system need to be updated to reflect these changes. Dr V Crowley, Chairman, NCCP PSA Harmonisation Board, will formally advise the Interim Director of the NCCP of this requirement.

The following table compares the current Irish NCCP Guidelines based on Oesterling et al. 1993 with the UK PCRMP Total PSA referral value using assays calibrated to WHO IS 96/670. It also includes, in column 3, the total PSA age-specific ranges according to Oesterling et al. 1993 recalculated to WHO IS 96/670 based on 20% reduction in value.

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Total PSA (μg/L) Oesterling et al. 1993</th>
<th>Total PSA (μg/L) Oesterling et al. 1993 recalculated to WHO IS 96/670 (based on 20% reduction in value)</th>
<th>UK PCRMP Total PSA referral value (μg/L) Using WHO IS 96/670</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 49</td>
<td>0.0 – 2.5</td>
<td>0.0 – 2.0</td>
<td>No values given</td>
</tr>
<tr>
<td>50 – 59</td>
<td>0.0 – 3.5</td>
<td>0.0 – 2.8</td>
<td>≥ 3</td>
</tr>
<tr>
<td>60 – 69</td>
<td>0.0 – 4.5</td>
<td>0.0 – 3.6</td>
<td>≥ 4</td>
</tr>
<tr>
<td>70 - 79</td>
<td>0.0 – 6.5</td>
<td>0.0 – 5.2</td>
<td>&gt; 5</td>
</tr>
</tbody>
</table>

Reference:
Appendix 5

All NCCP-designated cancer centres shall participate in an ongoing external quality assessment scheme for PSA operated by IEQAS. The types of EQA samples used in the scheme will include pooled residual serum and occasionally donor serum samples. EQA results shall be returned for each analytical system from which patient PSA results are generated.

Notes:

The laboratory of each NCCP-designated cancer centre will be expected to provide in rotation a 20 mL pooled residual serum specimen (with a total PSA value in the range 2 – 9 μg/L) once a year, so as to ensure a continuing supply of material for the scheme.

It is anticipated that IEQAS will also occasionally assess the EQA performance at low PSA concentrations, i.e. close to the functional sensitivity of the assay.

Each of the manufacturers providing PSA assay systems to the NCCP Designated Centres has agreed to participate in the EQA Scheme.

Regular formal reviews of performance with manufacturers whose systems are represented in the EQA Scheme will be undertaken.

The use of single donor serum in the occasional EQA distribution was perceived to be burdened by recruitment, consent, ethical and practical issues, however these difficulties are not insurmountable and require further attention.

It was agreed that IEQAS will introduce individualised EQA reports for this scheme. These EQA reports will show the original PSA data as reported by the participating laboratory and “EQA adjusted PSA data” computed to compensate for systematic differences between analyser groups thus allowing for the easier comparison of all three platforms over time. The computation of “EQA adjusted PSA data” is solely for the comparison of the EQA performance of the three PSA methods in use in the NCCP Designated Centre laboratories over time.

It was agreed that the calibrators of each of the three analytical systems used in the NCCP Designated Centres will be assayed on all three analytical platforms.

Reference:

Appendix 6

Each NCCP-designated cancer centre shall:

(a) Set IQC limits for PSA using existing IQC material so as to achieve realistic concordance with coefficients of variation currently attained;

(b) Run a common IQC two-level product for the intensive quality management of PSA measurement. The common IQC material is not intended to replace or displace a centre’s existing IQC material.

(c) Set agreed common acceptance/rejection criteria for this material with the aim of improving the quality of results reported across all the centres.

The common IQC material is Seronorm Immunoassay Lyophilised Control, Level 1 (Cat No 206005, Lot 1312558, Expiry date 2018-02) and Level 3 (Cat No 206205, Lot 1312564, Expiry date 2018-02). Reconstitution, storage conditions, and assay of these control materials will be in accordance with the IEQAS procedure to be issued in advance of the common IQC programme commencement date of the first week of March 2015.

Notes:

The manufacturers of the PSA assay kits used in the laboratories of the NCCP-designated cancer centres have agreed to fund the purchase of the common IQC material.

Each NCCP-designated cancer centre’s laboratory should inform IEQAS of its common IQC materials requirement. IEQAS is coordinating the reservation of the material with the Irish distributer, Cruinn Diagnostics.

Setting target CV (%) for IQC

It was agreed to set as target that which is consistently attained by 80% of the participants that is an IQC CV of 4%.
**IEQAS Survey (2013) of tPSA IQC in the NCCP Designated Centres (n = 9) CV (%)**

<table>
<thead>
<tr>
<th>IQC CV (%)</th>
<th>Number of values</th>
<th>Percent of all values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>23</td>
<td>79</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>26</td>
<td>90</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

**NCRI Survey (2008-2010) of tPSA IQC in all Irish laboratories performing PSA tests (n = 37) CV (%)**

<table>
<thead>
<tr>
<th>IQC CV (%)</th>
<th>Number of values</th>
<th>Percent of all values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>55</td>
<td>80</td>
</tr>
<tr>
<td>&lt; 8</td>
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<td>91</td>
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<td>68</td>
<td>97</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>69</td>
<td>99</td>
</tr>
<tr>
<td>&lt; 14</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

**Rationale for common IQC material:**

- It will provide an early alert to deterioration in assay quality / performance, whether this due to local circumstances or shared across all centres using the same analytical system.
- It will provide an indication of the performance of PSA assay across the designated centres on a week-to-week basis.
- It will assist in the investigation of changes in EQA performance.
- It will allow for the incremental narrowing of IQC performance limits as quality improves.
- It may identify exemplary quality management practices relating to the PSA assay that could be shared across the designated centres.
- The active management of IQC across the designated centres will require people talking, setting standards and doing and this is likely to increase the sense of collegiality amongst the designated centres.
Appendix 7

Notes on approaches to achieving harmonisation of clinical laboratory results

Background:

“Results between different clinical laboratory measurement procedures (CLMP) should be equivalent, within clinically meaningful limits, to enable optimal use of clinical guidelines for disease diagnosis and patient management.

When laboratory test results are neither standardized nor harmonized, a different numeric result may be obtained for the same clinical sample. Unfortunately, some guidelines are based on test results from a specific laboratory measurement procedure without consideration of the possibility or likelihood of differences between various procedures. When this happens, aggregation of data from different clinical research investigations and development of appropriate clinical practice guidelines will be flawed.

A lack of recognition that results are neither standardized nor harmonized may lead to erroneous clinical, financial, regulatory, or technical decisions.”

“Standardization of CLMPs has been accomplished for several measurands for which primary (pure substance) reference materials exist and/or reference measurement procedures (RMPs) have been developed.

However, the harmonization of clinical laboratory procedures for measurands that do not have RMPs has been problematic owing to

- inadequate definition of the measurand,
- inadequate analytical specificity for the measurand,
- inadequate attention to the commutability of reference materials,
- and lack of a systematic approach for harmonization.

To address these problems, an infrastructure must be developed to enable a systematic approach for identification and prioritization of measurands to be harmonized on the basis of clinical importance and technical feasibility, and for management of the technical implementation of a harmonization process for a specific measurand.”


Note:

Analyte = the name of a substance or compound;
Measurand = the quantity of the substance or compound intended to be measured.

The International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) has set out an approach to harmonisation.

The ICHCLR has its origins in a conference convened by the American Association for Clinical Chemistry in October 2010 on how to improve the harmonisation of test results for which there are no higher-order
reference measurement procedures and for which it is unlikely that such procedures will be developed in the foreseeable future.

The aim of the ICGCLR is:

a) To achieve harmonisation of reported results across multiple routine measurement procedures for the same measurand when there are no reference measurement procedures available;

b) To develop practical solutions for establishing the equivalence of reported values from different measurement procedures that are not traceable to SI.

c) Once attained, the harmonisation of results in this way would enable the implementation of common cut-off values and reference intervals.

ICHCLR approach to harmonisation

There are two main approaches to harmonisation. These are compared and summarised in the Table on page 18.

**Method 1 Harmonisation** relates to measurements that have full metrological traceability in accordance with ISO 17511 only. It is a “top down” approach passing ‘trueness’ to lower order measurement procedures and calibrators. Please note that for this method to be valid, the commutability of reference materials used to transfer calibration values must be understood and suitable for their intended uses at each level throughout the hierarchy of traceable calibration steps.

**Method 2 Harmonisation** is a “bottom-up” approach using commercial measurement procedures with no SI traceability. Essentially, it involves inter-method comparison studies coupled with mathematical recalibration for removal of systematic differences between values from routine commercial measurement procedures. The method’s weakness relates to how the harmonised calibration is sustained over time and commercial calibrator lot number changes.

Refer to Table on page 24 for further details.

The ICHCLR has developed a “toolbox” of technical procedures to be considered when developing a process to achieve harmonization for a measurand. These procedures and guides are comprehensive and may be accessed at [http://harmonization.net/Resource/Documents/Tool_Box_2013.pdf](http://harmonization.net/Resource/Documents/Tool_Box_2013.pdf).
Achieving harmonisation of measurement results by two methodologies.

Note only Method 2 (inter-method comparison) is relevant to PSA measurements.

This table is adapted from that of Dr Neil Greenberg in Clin Chem Acta 2014; 432: 49-54.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Method 1 – full metrological traceability</th>
<th>Method 2 – inter-method comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme</td>
<td>Hierarchical standardisation according to ISO 17511:2003. Top down approach passing ‘trueness’ to lower order measurement procedures and calibrators.</td>
<td>Inter-method comparison as described by ICHCLR Harmonisation Initiative (<a href="http://www.harmonization.net">www.harmonization.net</a>). Bottom up approach among routine (commercial) measurement procedures, with no SI traceability.</td>
</tr>
<tr>
<td>Reference materials</td>
<td>Certified purified reference materials and/or commutable secondary reference materials with associated uncertainties assigned to material value, preferably fulfilling requirements of ISO 15194:2009. (<a href="http://www.bipm.org/en/committees/c/i/cl">http://www.bipm.org/en/committees/c/i/cl</a>). Non-commutable reference materials without proven commutability may hinder achieving equivalence of results.</td>
<td>No higher order reference materials available. Panel(s) of commutable human samples may be available, to be assigned consensus values and associated uncertainties (not traceable to SI) via harmonisation studies (see <a href="http://www.harmonization.net">www.harmonization.net</a>). Some International Conventional Calibrators may be available (e.g. WHO materials), but usually not proven for commutability and may hinder achieving equivalence of results.</td>
</tr>
<tr>
<td>Calibration traceability</td>
<td>Commercial calibrators and reported results for routine measurement procedures traceable to SI unit via a metrological reference system (hierarchy of higher order reference measurement procedures and reference materials).</td>
<td>Commercial calibrators and reported results of routine measurement procedures not traceable to SI unit. Traceability linked via inter-method comparison studies of available commercial measurement procedures coupled with mathematical recalibration for removal of systematic differences among reported values.</td>
</tr>
<tr>
<td>Sustainability</td>
<td>Inbuilt sustainability via hierarchy of well-characterized and reproducible higher order and lower order reference measurement procedures and reference materials. (<a href="http://www.bipm.org/en/committees/c/i/cl">http://www.bipm.org/en/committees/c/i/cl</a>).</td>
<td>Risk for non-sustainability of harmonised calibrations over time as routine methods and commercial calibrator lots change. Panels of patient samples used as “calibrators” in harmonisation studies to be renewed over time (consumption and/or stability concerns.) Second and subsequent patient sample panels with values traceable to initial sample panel; presumes well-defined specifications for panel member selection. See ICHCLR Toolbox of Technical Procedures available at: <a href="http://harmonization.net/Resource/Documents/Tool_Box_2013.pdf">http://harmonization.net/Resource/Documents/Tool_Box_2013.pdf</a></td>
</tr>
<tr>
<td>Harmonisation goals</td>
<td>Equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical performance goals.</td>
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</tr>
</tbody>
</table>

ICHCLR = International Consortium for Harmonisation of Clinical Laboratory Results.