Harmonisation of Adult and Paediatric Reference Intervals for General Chemistry Analytes Across Australian Pathology Laboratories

A project funded under the Australian Government's Quality Use of Pathology Program

Delivered by the Harmonisation Committee of the Australasian Association of Clinical Biochemists (AACB)

towards pathology harmonisation

Final Performance Report – June 2014

Harmonisation of Adult and Paediatric Reference Intervals for General Chemistry Analytes Across Australian Pathology Laboratories

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Front Cover: Delegates who attended the first Harmonisation Workshop, Sydney, May 2012

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1.1 Abbreviations

AACB - Australasian Association of Clinical Biochemists

ARQAG - Auckland Region Quality Assurance Group

CALIPER - Canadian Laboratory Initiative on PEdiatric Reference Intervals

CRI - Common Reference Interval

HRI – Harmonised Reference interval

HRIWG - Harmonised Reference Interval Working Group

NACB - National Academy of Clinical Biochemistry

NATA – National Association of Testing Authorities, Australia

NORIP - Nordic Reference Interval Project

PITUS - Pathology Information, Terminology and Units and Standardisation

QUPP - Quality Use of Pathology Program

RCPA - Royal College of Pathologists of Australasia

SRAC - Scientific and Regulatory Affairs Committee

1.2 Glossary

Bhattacharya analysis – an analytical tool to identify normal Gaussian and non-Gaussian distributed data in the presence of other data. This data can then be used to determine or validate reference intervals[13]

Reference Interval – the upper and lower limits for a numerical pathology result usually derived from a reference / healthy population. Limits are typically set to represent 95% of a normal healthy population. The 95% interval is usually two-sided and defined by low and high cut-off values excluding 2.5% of the reference population on each side

HbA1c – Haemoglobin A1c – a glycated component of haemoglobin which reflects average circulating glucose

2 Executive Summary

2.1 Background- current situation

Appropriate pathology reference intervals that flag the need for clinical intervention are an essential component of good patient outcomes.

Reference intervals in Australian Laboratories are currently derived from a variety of sources[1]. These may range from clinical decision limits based on outcome studies (e.g. HbA1c levels for risk of retinopathy[2]) or published studies (e.g. NORIP[3]) to "in house" verification of manufacturers' package inserts.

The ideal reference interval is a balance between specificity and sensitivity (i.e. acceptably low false negative/positive rates) and should take account of any differences due to age and sex.

Koerbin et al have shown that different laboratories in Australia quote different reference intervals for the same tests, yet they are using the same analytical methods and platforms[3]. Further, he has shown that in many cases, labs obtain results for the same patient sample that are not significantly different.

2.2 Rationale for the Harmonisation Reference Interval (HRI) Program

The quest for common reference intervals for routine pathology tests has been impeded in the past by the lack of standardization between analytical methods and the perceived issues with recruiting a suitable cohort of "normal" healthy subjects[1].

Studies[4,5,6,7] have shown that advances in the standardization of many analytical methods now make it possible to harmonise reference intervals.

To date there has not been a nationally coordinated review of common reference intervals for routine pathology analytes for both the adult and paediatric population in Australia.

Given paediatric reference values change significantly in the first days, months and years of life, there is a particular need for reliable intervals to ensure timely treatment.

2.3 Methodology – development of the program

An evidence based methodology was used to develop the program. Data from classic reference

interval studies (analysis of samples from apparently healthy individuals) was combined with large databases of actual outpatient results.

Bias studies using human serum were used to demonstrate that results from different laboratories using different analytical platforms could be combined.

Laboratories across Australia "mined" their own patient data to verify the proposed intervals.

Clinical experts were asked to critically assess the ability of the intervals to appropriately detect where intervention and follow-up was required.

Workshops (3 in total) were convened with representatives from all Australian pathology networks and labs to discuss the intervals and agree on the HRI's.

2.4 Delivery of the overall program

The accumulated evidence was presented at 3 successive Workshops.

Consensus was sought at each stage and only those analytes with unanimous agreement were adopted.

2.5 Evaluation of the overall program

The final set of Harmonised Reference Intervals have been extensively evaluated by clinical experts and individual laboratories.

"Field" testing where the impact of HRI's on rates of normal/abnormal flags showed acceptable frequency consistent with predicted outcomes.

3 Introduction

In 2012, the AACB received a grant from the Department of Health's Quality Use of Pathology Program to assist with the implementation of Common Reference Intervals (CRI's) across Australian pathology laboratories. The AACB caters for the professional development and training of its members who mainly consist of medical scientists and pathologists from Australia and New Zealand. It is actively involved projects to improve the quality of healthcare both locally and globally.

This report outlines the activities and milestones that were enabled by the QUPP funding agreement which ran from June 2013 to June 2014.

3.1 Background to the project

Since 2011, a major strategy of the the Scientific and Regulatory Affairs Committee (SRAC) of the Australasian Association of Clinical Biochemists (AACB) has been to facilitate the adoption of harmonised reference intervals (HRI's).

A "Harmonisation" Committee was formed in late 2011 and comprised both Chemical Pathologists and Medical Scientists from large public and private pathology networks.

An evidence based approach was used to derive and validate the intervals with extensive data analysis.

Data was compiled by the committee from a range of sources:

- Dr Ken Sikaris shared the results from a large "data mining" exercise undertaken by Sonic Laboratories where over 5 million outpatient results were used to produce a set of reference intervals that had been adopted by their network across Australia.
- Gus Koerbin from ACT Pathology shared the data he had collected from his "Aussie Normal" study (in press) where over 1800 healthy individuals were screened and tested for a panel of routine pathology tests. Bias studies were also performed on this sample bank where specimens were sent around Australia for analysis across a variety of instruments[4].
- Dr Tina Yen also commenced a data mining exercise with paediatric laboratories across Australia and New Zealand to try and address the lack of local ranges covering birth to adulthood.

A workshop was organised in May 2012 to present the above data and propose a series of HRI's. This was attended by senior pathologists and medical scientists from across Australia and New Zealand. The evidence was clear as was the need to pursue consensus and verification of the proposed ranges.

Two sub-committees were subsequently formed, one to address adult HRI's and the other to focus on paediatric intervals.

It was determined that further work was required to ensure that the proposed intervals were appropriate for each laboratory and their associated network/ branch labs.

QUPP Funding was sought to allow additional data analysis and workshops as these were a key component to verifying the HRI's and achieving consensus for implementation across Australia.

3.2 Current practice for determining Reference Intervals

For those reference intervals where a decision limit has not been published (e.g. fasting glucose for diabetes) there are a variety of approaches that labs currently use to derive their intervals, these include:

- Historical – dating back to a source which may have not been fully documented.
- Local volunteers - usually where volunteer lab staff are bled and a mean and +/- 2 standard deviations used to calculate the reference interval
- Publications – a peer reviewed reference interval study, e.g. NORIP[3]
- Text books – e.g. Tietz[8]
- Manufacturer Kit package inserts
- Verification of published intervals – again usually from volunteer lab staff where a small number (around 10) are bled and their results checked against the proposed interval.
- Data mining of existing data – extraction and analysis of large databases of historical data is the ideal way to determine a reference interval as this also incorporates pre analytical "real life" factors. Large amounts of data are required to minimise any effects from non-healthy individuals. Hospital Laboratories would usually only use outpatient samples for this analysis.
- Clinical judgement – overlay of clinical judgement onto calculated/published/verified intervals – input by a pathologist in consultation with treating clinicians to ensure that the proposed intervals will meet their clinical needs.

Labs are required to document the source of their reference intervals for accreditation purposes. They are also required to verify that the interval continues to be appropriate if they change methods or calibrators[9].

More recently, an application of the Stockholm Heirarchy has been proposed as a guide to drive high quality reference1 intervals with gradations from 1 (best practice) to 5 (textbooks, package inserts) (Table 1). The AACB HRI approach was pitched at level 2.

3.3 Why is harmonisation of RI's needed

Most laboratories do not have ready access to the large amounts of data required to establish a valid reference interval and often use the "10 volunteer" approach to verify a published interval. This, in turn, can lead to sub-optimal intervals that can vary significantly between labs for no valid reason.

This variation was clearly demonstrated at the first Harmonisation Workshop, where most laboratories /instrument platforms showed no significant differences when analysing the same set of serum samples, yet there was wide variation in reference intervals being quoted[4].

3.4 World first achievement

Based on a review of the literature and feedback from our international colleagues, the evidence based / peer review approach adopted in Australia is unique (Figures 1A &B). By combining data from a large cohort of "healthy volunteers" (Aussie normals) and extensive data mining from pathology information systems, the Harmonisation Committee has compiled a unique "best practice" set of HRI's for adults and paediatrics.

Table 1. The Stockholm Hierarchy applied to reference intervals and clinical decision limits[1].

1. Clinical decision limit based on clinical outcome study e.g. HbA1c cut-off based on the presence of diabetes outcome (retinopathy)
2. Other methods of determining reference interval or clinical decision limit a. Reference intervals derived from apparently healthy populations e.g. NORIP, CALIPER. b. Clinical decision limits based on clinicians' opinions of disease e.g. thyroid-stimulating hormone (TSH) upper reference limit (2.5 mIU/L) from NACB.
3. Published professional recommendations a. National or international expert bodies e.g. national urine protein cut-offs. b. Expert local groups or individuals e.g. ARQAG,SONIC.
4. Reference limits set by a. Regulatory bodies e.g. prostate-specific antigen (PSA) cut-offs. b. Formal Reference Interval Survey e.g. UK Harmony Survey.
5. Reference interval based on the current state of the art a. Reference interval used in post-analytical external quality assurance e.g. pathology interpretation exercises. b. Current publications on methodology e.g. textbooks or kit inserts.

4 Project objectives

4.1 Primary Project objective

The overall objective of the project was to facilitate the adoption of HRI's (where possible) across Australia.

To achieve this objective by consensus required extensive data analysis and consultation with stakeholders – namely the key personnel in pathology practices across Australia.

4.2 Examination of current HRI methods

Most of the current activity for HRIs is based around routine chemical pathology testing. While the AACB is also collaborating with the RCPA to promote HRI's in other pathology disciplines (e.g. haematology, microbiology, immunology) these areas are not as advanced with implementation.

Internationally there are a number of organisations who have either implemented HRIs (e.g. UK Harmony[10]) or are actively pursuing by standardising calibrators and methods (e.g. USA[11], EU[7,12]).

The UK approach was to survey what intervals labs were quoting, compile to the most commonly reported and seek consensus.

4.3 Benefits of providing a consistent program for HRIs

Reference intervals are an ongoing challenge and while the traceability of calibrators should prevent change or drift, there is a signifcant benefit to providing a consistent approach to setting and monitoring.

- While individual laboratories or networks will still be required to verify the appropriateness of a reference interval for their method and setup[13,14,] they will now be checking against an optimised interval which has been derived from extensive data analysis that would normally be beyond their resources.
- There are significant patient safety benefits to a national HRI as clinicians will be able to more confidently compare results from different laboratories, moreover the flagging of abnormal results will be consistent across Australia.
- There are economic benefits to HRI's as the need to repeat tests as patients move between healthcare organisations is reduced. In addition, a high quality interval will be less subject to false positives and negatives which translates to more appropriate use of

healthcare funds

- The rollout of the national e-health program will also benefit from less lines of code as harmonised results can be combined from those institutions who report a HRI

We see this as a significant step forward in providing improved patient care and outcomes.

5 Methodology

5.1 Gathering the Evidence

Members of the HRIWP gathered evidence from 4 principal sources[15]:

Aussie Normals

- Blood samples were collected from 1876 "healthy" volunteers residing in the ACT.
- All subjects were selected based on their responses to a lifestyle absence of known conditions such as pregnancy, diabetes, renal or cardiovascular disease.
- The main analytical platform for the study were Abbott systems (ARCHITECT ci8200 and ci16200)

Sonic Data

- Results from Bhattacharya analysis of data mined by Sonic Laboratories

Paediatric Data

- Results from Bhattacharya analysis of data mined by Australian Paediatric Laboratories[16]

Bias Studies

- 33 matched samples from the Aussie Normal collection were sent to 24 laboratories. Two studies were performed (Bias 1 & 2). Coverage of 8 instrument platforms was achieved.
- Traceability of calibration
- Previous work by George Koumantakis (a member of the HRI Committee) had demonstrated that calibrators in use in Australia were all traceable to international standard material[17] (A table showing the full list of "Package Insert Reference Methods and Traceability" is available at http://www.aacb.asn.au/professionaldevelopment/methods).

5.2 Stakeholders – consultation

A list of principal stakeholders and decision makers was compiled by the HRI Committee. This list consisted not only of senior pathologists and medical scientists, but also industry representatives who sell and distribute instruments and reagents – the same platforms that were used to analyse the Aussie normal and bias samples.

This group was then invited to an initial workshop where they were presented with background information as well as the accumulated evidence.

Proposed refinements to the HRI's were extensively discussed at the 2 day workshop and incorporated in the next draft of HRI's.

Individual laboratories/networks were then invited to verify the proposed intervals using their own local data. They then fed back their results and comments to the HRI Committee via the spreadsheet tool.

Another 2 stakeholder workshops were then conducted to discuss the verification data as well as update on further bias studies where problem analytes had been identified.

The HRI Committee also invited prominent clinicians to the second Workshop for their input on analytes that were being proposed to change to decision limits rather than calculated intervals. ALT and Urate were specifically targeted for clinical debate.

The updated HRI's were again discussed one by one at the third workshop in May 2014 and a number were agreed (by "show of hands"). There is still more work to be done for those analytes where consensus was not achieved.

5.2.1 Paediatric HRI Working Group – meetings and outcomes

The Paediatric WG, chaired by Dr Tina Yen, was formed at the first Harmonisation Workshop (May 2012) and continued to meet both before and during the subsequent workshops.

The WG consisted of Chemical Pathologists from all the major paediatric laboratories in Australia (Qld 2, NSW 2, Vic 2, SA 1, WA 1) and New Zealand (1).

In 2012 they undertook a survey of the paediatric reference intervals in use across Australasia and found some 15 different versions[16].

An extensive data mining exercise with over 1.8 million results from 15 paediatric laboratories ranging from newborn to 22 years were compiled and analysed using Bhattacharya analysis.

The results of the Bhattacharya analysis were then reviewed by the Paediatric WG and modified where needed based on their extensive clinical experience.

5.2.2 Collaboration with RCPA on Pathology Information, Terminology and Units Standardisation (PITUS)

Jill Tate, chair of the AACB Harmonisation Working Group was also appointed to Chair the PITUS Harmonisation Working Group 4. The other members of this group were Robert Flatman (AACB), Michael Legg (PITUS), Donna Moore (PITUS), Graham Jones (AACB / RCPA) and Peter Graham (AACB).

This group have now completed the first draft of "Guidelines for Harmonisation in Pathology Reporting - Rendering of Reference Limits and Population Partitions, Formatting and Flagging of Test Results, and Non-combination messaging". This work also incorporates the HRI's and has defined a series of recommendations on how reference intervals should be reported and flagged. The Guideline also outlines a protocol for programming age ranges in days into laboratory information systems.

The draft document will be submitted to QUPP as part of the final report for the PITUS projects.

5.2.3 Stakeholder workshops – meetings and outcomes

The HRI Working Group had a series of meetings via teleconference and face-to-face from May 2012 to June 2014. The outcomes of these meetings were as follows:

- The preliminary results of the Aussie Normal study, the bias study and the Sonic Reference Interval study were reviewed and an initial set of HRI's were developed at a 1 day meeting at the AACB Sydney office in May 2012.

- Bias surveys of Australian laboratories (involving dispatch of sets of 33 serum samples to 24 public and private laboratories throughout Australia and New Zealand representing the 8 major chemistry platforms[4]) were subsequently completed and the results presented at the 1st Stakeholder Harmonisation Workshop in Sydney in May 2012. This workshop was attended by 57 delegates representing all the major laboratory networks as well as clinicians and industry. The Workshop achieved several outcomes including confirmation of a number of general chemistry adult and paediatric intervals. Further progress was also made on the more difficult analytes (e.g. ALT, Albumin, Lipase).
- A second stakeholder workshop was convened in July 2013 where further consultation resulted in agreement on a core set of analytes, but further data analysis was requested for some of the more difficult analytes. Clinicians were asked to attend this workshop to present their perspective on the proposed intervals, this generated considerable discussion on Urate as well as the liver enzymes ALT/AST.
- The HRI Working Group met again in December 2013 in Sydney to finalise the Paediatric Reference intervals and further review additional data on the Adult Reference Intervals including the potential impact on flagging rates as presented by Dr Ken Sikaris from Sonic Pathology, a major private pathology lab.
- HRIWG convened in February 2014 to finalise the program and speakers for the 3rd Stakeholder Harmonisation Workshop that was held in Sydney on 30 April and 1 May. 55 delegates representing all the major public and private pathology networks across Australia were presented. This meeting also coincided with a meeting attended by international harmonisation experts who kindly agreed to present at the workshop. Further analysis and group discussions achieved final consensus on the majority of adult and paediatric reference intervals under consideration

A full listing of all the Workshop presentations and related outcomes is available on the AACB website: http://www.aacb.asn.au/professionaldevelopment/harmonisation

See also: Project Activity Plan – Appendix 1

Figures 1A and 1B summarise the above evidence based methodologies employed by the Adult and Paediatric HRI Committees.

5.3 Analysis of proposed reference intervals with checklist/ spreadsheet tools and validation of proposed reference intervals

A spreadsheet tool (developed by Graham Jones) was disseminated to laboratories across Australia and New Zealand.

Laboratories were asked to extract their own data from their laboratory information systems and use the spreadsheet to analyse. The spreadsheet had embedded formulas to enable Bhattacharya analysis of the extracted laboratory data and proved to be a valuable tool for validating the proposed HRI's.[13]

The spreadsheet data was then compiled into a master document for further review by the HRIWG.

5.4 Flagging rates

An additional tool was introduced at the May 2014 Workshop by Ken Sikaris when he presented an analysis of the impact of the proposed HRI's on "flagging rates" for Sonic patients. In theory, a workable (95%) reference interval should only flag an abnormal result for 5% (2.5% low and 2.5% high) of the "normal" population.

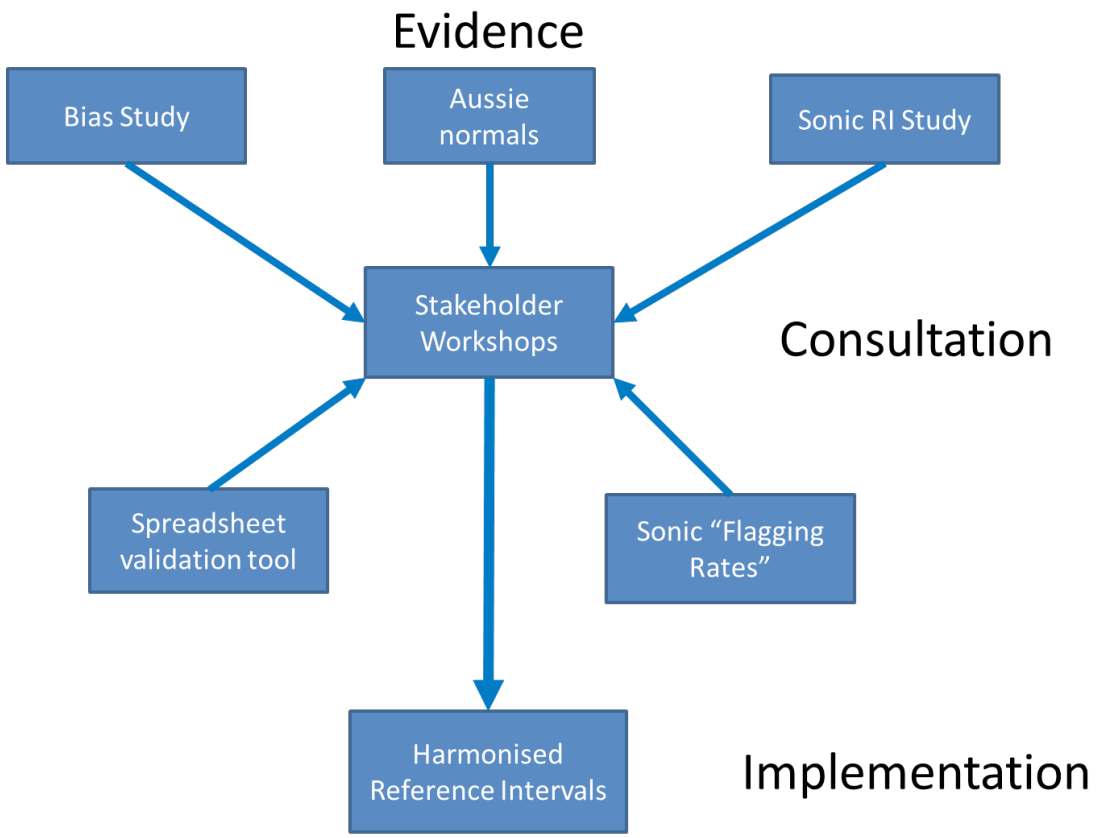

Figure 1A. AACB Evidence based / consultation approach for Harmonised Adult Reference Intervals

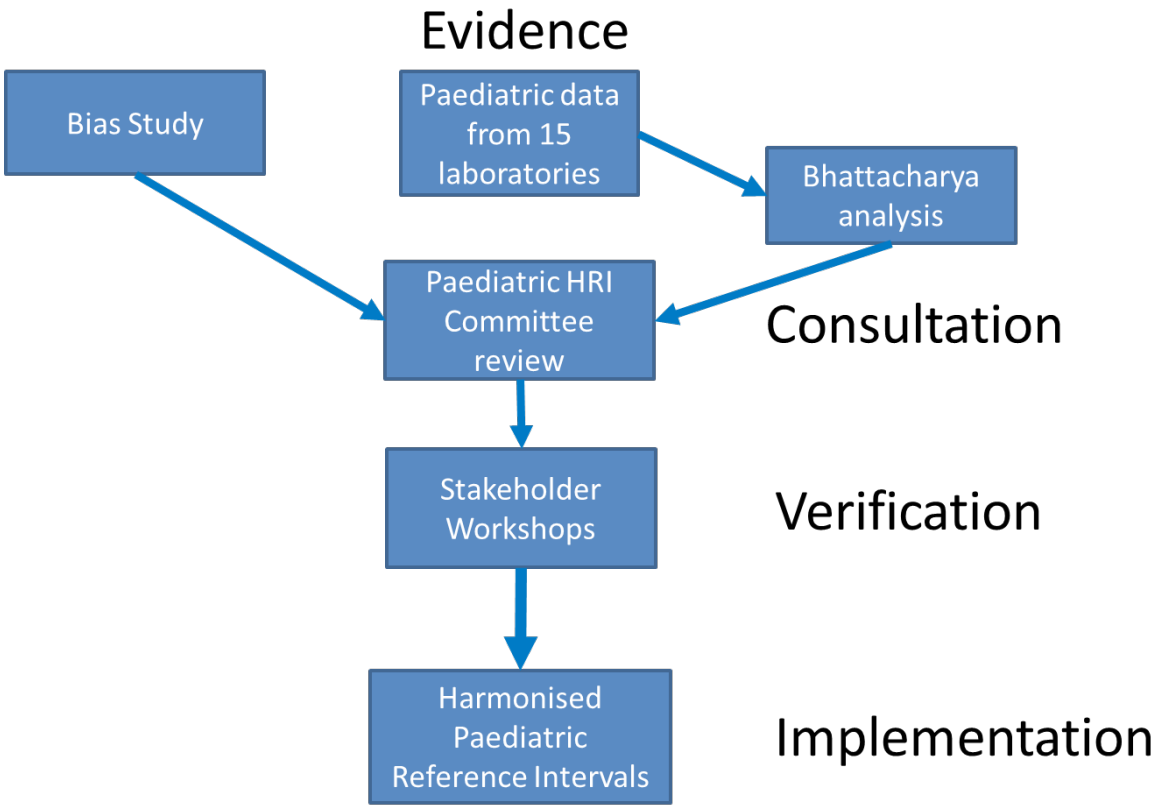

Figure 1B. AACB Evidence based / consultation approach for Harmonised Paediatric Reference Intervals

5.5 Bias surveys

Two Bias studies were undertaken covering multiple platforms using serum samples from the Aussie Normal sample bank and RCPA External Quality Assurance Program:

Platforms covered:

Abbott Architect, Roche Modular/Cobas, Roche Integra, Beckman Coulter (DxC/Dxi), Beckman Coulter (Olympus), Siemens Dimension, Siemens Advia, Ortho Clinical Vitros

Analytes covered – Bias 1 - 33 samples / 24 labs:

Na, K, Cl, Urea, Creatinine , Glucose , Bicarbonate, ALT , AST, CK , LD , GGT, ALP, TBil, Ca, Adj. Ca, Mg, PO4, TP, Alb, UA , Cholesterol, Triglycerides, HDL, CRP, Iron ,Transferrin, Lipase

Analytes covered – Bias 2 - 9 samples + 6 EQAP samples / 30 labs:

Na, K, Cl, Urea, Creatinine , Glucose , Bicarbonate, ALT , AST, CK , LD , GGT, ALP, TBil, Ca ,Mg, PO4, UA, Cholesterol, Triglycerides, HDL, CRP, Iron, Transferrin, Lipase, Ferritin, TSH, FT4, Tot PSA

Submitted Lab data was analysed by comparing the average platform result with the average of all results and calculating the difference between those concentrations.

The Allowable Limits of Error as listed in the RCPA Chemical Pathology Quality Assurance Programs (RCPA QAP) were then overlaid to define upper and lower acceptable differences[5].

6 Results

6.1 Bias studies and results of workshop discussions

The bias studies demonstrated that 19 of the 27 common analytes tested could potentially meet harmonisation requirements (Table 2)[4].

Six of these (e.g. glucose, cholesterol) already had recommended decision limits available, note however, that labs reporting those limits still need to ensure and monitor for acceptable bias.

A further 9 were subjected to the evidence based review process and accepted for HRI's.

The remaining 4 (urea, urate, CK and AP) were flagged during the review process for further investigation, mainly due to clinical reasons. It is interesting to note that the extensive data mining flagged clinical issues that would not normally be known to most laboratories

Examples of results for an acceptable bias (Sodium) and unacceptable (GGT, ALT) are shown in Appendices 2 ,3 and 6.

While Table 3 shows analytes where bias is an issue, it was still noted in a 2013 survey of reference intervals in use in Australian Laboratories that discrepancies in reference intervals were greater than could be attributed to a bias effect[18,19]. ALT is a good example of where upper limits varied from 30 to 55 U/L (Appendix 5) yet the bias between methods (and within methods) (Appendix 6) does not support the variation.

It is also worth noting that after discussion with clinicians at the 2nd Workshop, ALT, AST and Urate were flagged as analytes where a clinical decision limit may be more appropriate than a "healthy" population range.

6.1.1 Further assessment of certain analytical methods

As listed in Tables 2 & 3 there are still a number of analytes where further investigation is required. The analytes flagged in Table 2 require further clinical input as bias is not an issue.

The tests flagged in Table 3 are mainly due to method differences which contribute to unacceptable bias. While these tests still have the potential for harmonisation, more work is required. Where multiple methods exist for the same test (see examples in Appendix 4), the preferred option would be to standardise on one method across all platforms where possible e.g. Bromocresol Purple for Albumin, IFCC (L to P) for Lactate Dehydrogenase (LD). This will require negotiation with manufacturers and laboratories following a formal recommendation and endorsement from the AACB and RCPA.

Table 2. Analytes where bias is not an issue for harmonisation of adult reference intervals noting those which require further investigation for final approval[20]

Analyte	Approved for HRI (Y / N / NA)	Reason not approved
Sodium	Y	
Potassium	Y	
Chloride	Y	
Bicarbonate	Y	
Urea	N	Further investigation of age and sex specific intervals required
Creatinine	Y	
Total Protein	Y	
Urate	N	Further investigation of gout related decision point required
Calcium	Y	
Magnesium	Y	
Phosphate	Y	
Creatine Kinase (CK)	N	Further investigation on fall in CK levels as men age is required
Glucose	NA	NA
Alkaline Phosphatase	N	Further investigation – e.g. changes in postmenopausal women
Cholesterol	NA	NA
Triglycerides	NA	NA
HDL	NA	NA
Iron	NA	NA
Transferrin	NA	NA

Y= Yes, N= No, NA=Not Applicable as recommended clinical decision limits or published professional recommendations are already in use – still important for labs to show no bias for these tests.

Instrument Platforms tested: Beckman Dx series, Abbott Architect, Ortho Vitros, Roche Cobas, Roche Integra, Siemens RxL, Siemens Advia, Beckman AU series

Table 3. Analytes where bias is an issue

Analyte	Issue	Options to resolve
Albumin	Method differences (BCG vs BCP)	Recommend single method – Bromocresol Purple (BCP)
Globulin	Calculated test – albumin method difference impacts	Recommend single albumin method – (BCP)
ALT (P-5-P)	Method differences (P-5-P vs non P-5-P)	Recommend single method -Pyridoxal-5-phosphate (P-5-P)
AST (P-5-P)	Method differences (P-5-P vs non P-5-P)	Recommend single method -Pyridoxal-5-phosphate (P-5-P)
CRP	Problem with limit of detection for some methods	Investigate further
Total Bilirubin	Method differences and sample stability in bias studies	Investigate further, particularly for paediatrics
GGT	Method differences	Investigate further
LD	Method differences	Recommend single method – Lactate to Pyruvate
Lipase (Methods)	Method differences	Liaise with manufacturers for single method
Ferritin	Method differences	Investigate further
TSH	Method differences	Investigate further
FT4	Method differences	Investigate further
Total PSA	Method differences	Investigate further

6.2 Results of individual / network labs verification – achieving consensus

Agreement from all major pathology networks and most of the independent laboratories has now been achieved for the majority of the proposed reference intervals (Table 4).

Consensus was achieved by presenting the evidence and encouraging open discussion from Workshop participants – it is worth noting that the agreed HRI's were approved unanimously by all those attending the May 2014 workshop.

Several laboratory networks have already adopted the HRI's, others have scheduled for their next update.

Some labs have flagged that they will still use a local interval for some specific (HRI) tests and have provided valid reasons for doing so.

Appendices 7 and 8 show examples of verification data and the intervals that labs have accepted – 23 laboratories covering all the major networks in Australia are listed in this file. A full data set for all analytes is available at: http://www.aacb.asn.au/professionaldevelopment/harmonisation

Table 4. Overview of Australian Pathology Laboratories that have either adopted or plan to adopt the agreed HRI's

Laboratory Network	NSW/ACT	VIC	SA/NT	WA	QLD	TAS
*Sonic	✓	✓	✓	✓	✓	✓
*Primary	✓	✓	✓	✓	✓	✓
Healthscope	✓	✓	✓	✓	✓	✓
Public State Networks	✓	N/A	✓	✓	✓	✓
Non-network Laboratories	✓	✓	✓	✓	✓	✓

*Note Sonic and Primary Labs have flagged 1 -2 analytes where they will adopt minor variations e.g. upper end for potassium due to pre-analytical issues with GP collects.

6.3 HRI for paediatric patients – achieving consensus

The Paediatric HRI's were similarly impacted by the same bias and method differences as the adult intervals.

As the participating paediatric labs had already mined their data to produce the intervals which were then further refined by the Paediatric Working Party, the verification process undertaken by the adult labs was not required.

The proposed ranges were still presented for general discussion at the workshops to ensure that the interface from paediatric to adult intervals was consistent.

There are some notable differences with the paediatric intervals :

- Multiple age categories apply and these will require careful programming in laboratory reporting systems – this will also be defined in the PITUS report (Legg, 2014, in press)
- A plasma interval is quoted for potassium as many institutions collect plasma samples for their paediatric patients (mainly to minimise haemolysis)
- Enzymatic creatinine is the predominant (recommended) methodology for paediatrics
- Alkaline Phosphatase extends to age 22 years, whereas most adult ranges start at age 18.

6.4 Review of impact of HRI's on Flagging Rates

An analysis of flagging rates presented by Ken Sikaris at the May 2014 Workshop found most HRI's triggered a rate of 2-3% high/low which and was generally considered acceptable (Figure 2).

It was noted in discussions at the Workshop that pre-analytical issues will potentially impact on the flagging rate for potassium (Figure 3) and Sonic has elected to adjust their interval to reduce this issue.

Figure 4 shows an apparent high flagging rate for bicarbonate on an Abbott platform, this was conveyed to the manufacturer and a bias with a calibrator has since resolved the issue.

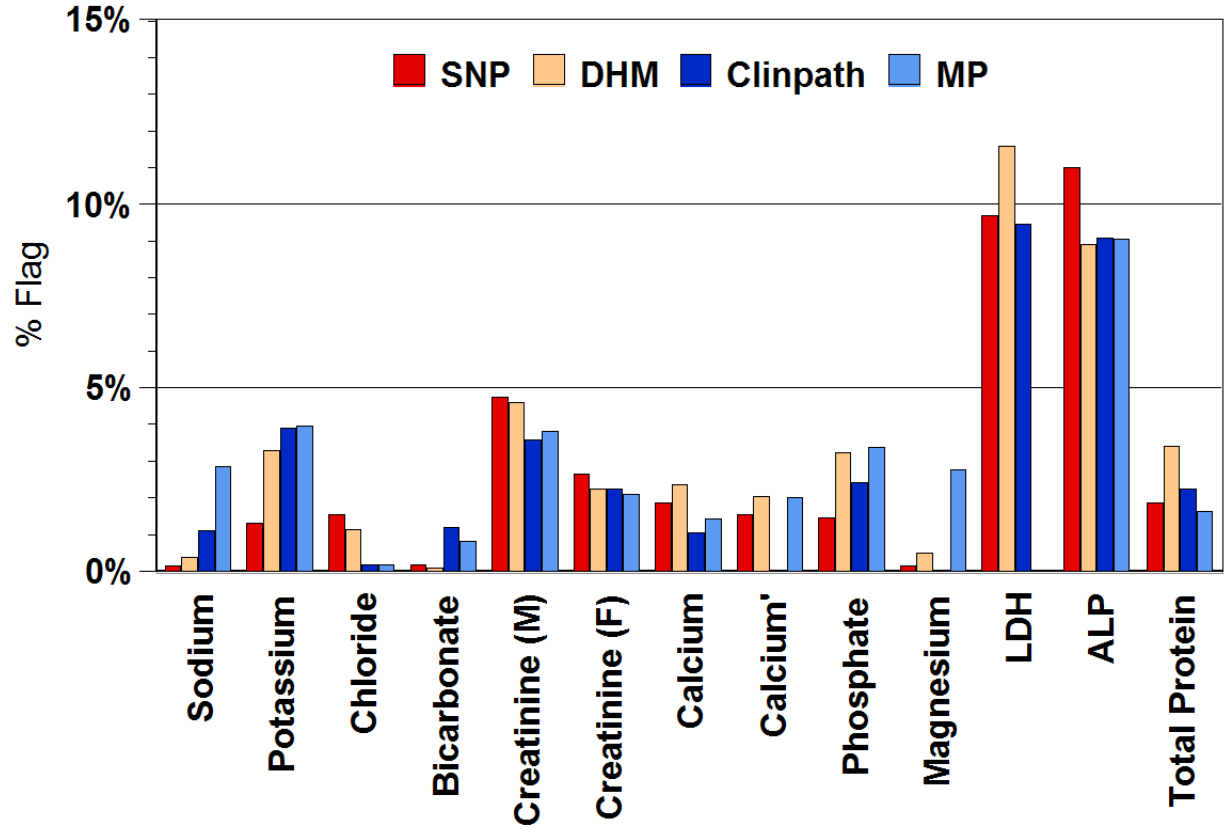

Figure 2. Flagging rates for HRI's for Sonic Labs (Sikaris, 2014)

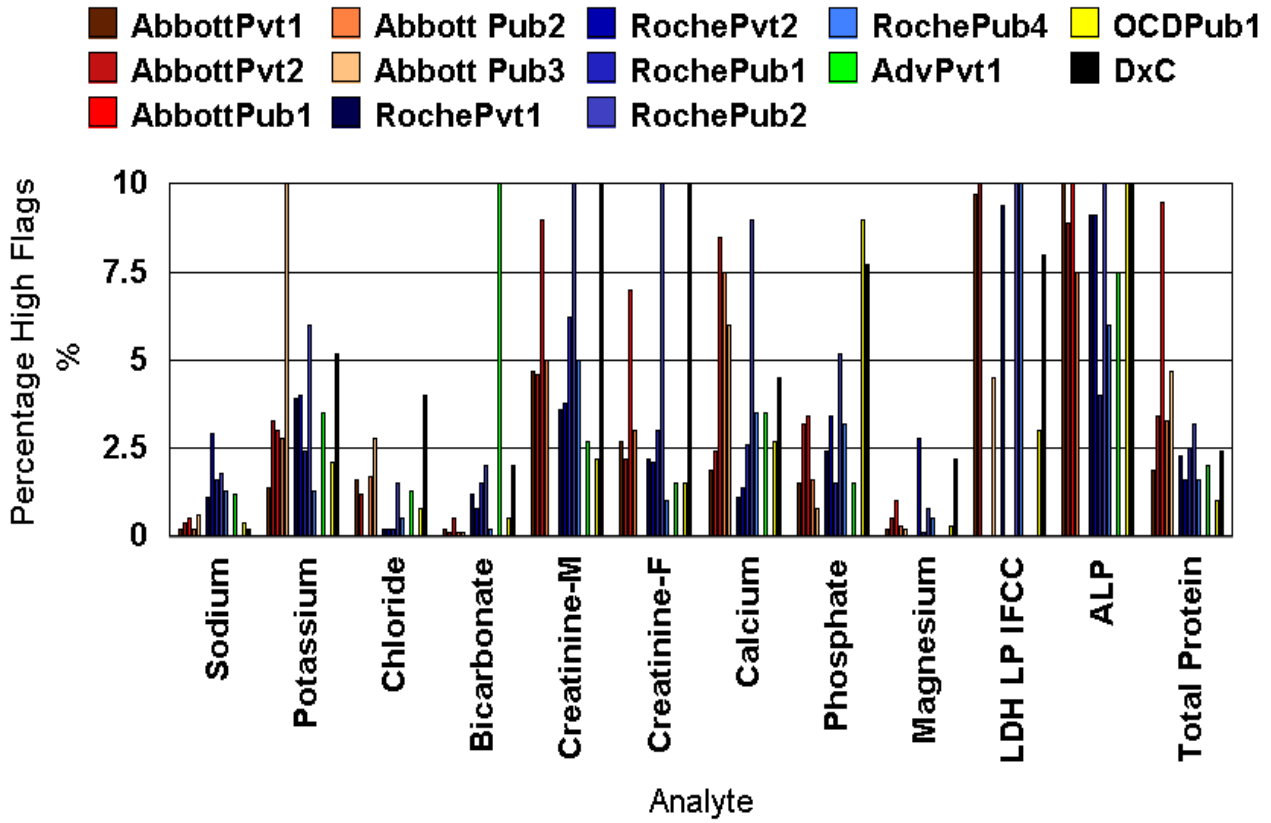

Figure 3. High flags obtained from various laboratories, public (Pub) and private (Pvt) using Abbott (5 labs), Roche (5 labs), Siemens Advia (1 lab), Ortho OCD (1 lab) and Beckman DxC (1 lab). (Sikaris, in press)

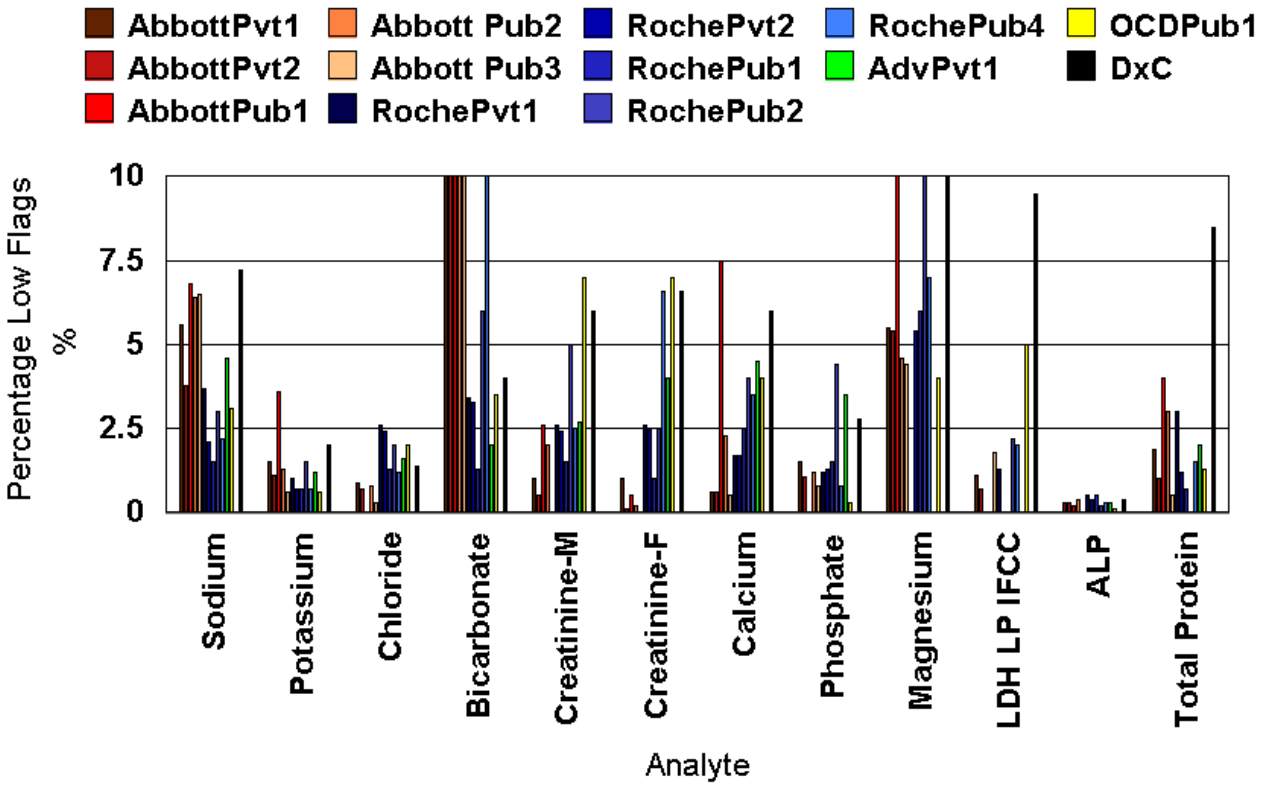

Figure 4. Low flags obtained from various laboratories. (Sikaris 2014, in press)

6.5 Australasian Harmonised Reference Intervals

It was resolved at the May 2014 Harmonisation Workshop to submit the agreed HRI's (Tables 4 & 5) for endorsement by the AACB and the RCPA. It was further resolved to accept that labs could still quote a local interval for a specific test provided they had suitable data to demonstrate their interval was valid.

Table 5 Australasian Harmonised Reference Intervals - Adult Intervals*

Analyte	Male	Female
Sodium	135 – 145 mmol/L	
Potassium (serum)	3.5 – 5.2 mmol/L	
Chloride	95 – 110 mmol/L	
Bicarbonate	22 – 32 mmol/L	
Creatinine *	60 – 110 umol/L	45 – 90 umol/L
Calcium	2.10 – 2.60 mmol/L	
Calcium (albumin adjusted)	2.10 – 2.60 mmol/L	
Phosphate	0.75 – 1.50 mmol/L	
Magnesium	0.7 – 1.1 mmol/L	
Lactate Dehydrogenase ** **[L to P] (IFCC)**	120 – 250 U/L	
Alkaline Phosphatase	30 – 110 U/L	
Total Protein	60 – 80 g/L	

***** Unless otherwise specified, the intervals are for serum or plasma for adults (18 years of age and older). The intervals are for use by laboratories using methods which are traceable to JCTLM-listed reference materials, methods and services (except bicarbonate where no references are listed).

****** This range is proposed for use for both serum and plasma. Laboratories testing only heparin plasma may choose to use a lower interval.

******* Creatinine has harmonised reference intervals for adults up to the age of 60 years. For older ages laboratories may elect to maintain these.

******** [L to P] (IFCC), lactate to pyruvate method (IFCC method)

Table 6 Australasian Harmonised Reference Intervals - Paediatric Intervals

Analyte	Age	Reference Interval
Sodium	0 - <1wk	132 - 147 mmol/L
	1wk - <18y	133 - 144 mmol/L
	≥18y	**135 - 145 mmol/L**
Potassium (serum)	0 - <1wk	3.8 - 6.5 mmol/L
	1wk - <6mo	4.2 - 6.7 mmol/L
	6mo - <2y	3.9 - 5.6 mmol/L
	2y - <18y	3.6 - 5.3 mmol/L
	≥18y	**3.5 - 5.2 mmol/L**
Potassium (plasma)	0 - <1wk	3.5 - 6.2 mmol/L
	1wk - <6mo	3.8 - 6.4 mmol/L
	6mo - <2y	3.5 - 5.4 mmol/L
	2y - <18y	3.3 – 4.9 mmol/L
Chloride	0 - <1wk	98 - 115 mmol/L
	1wk - <18y	97 - 110 mmol/L
	≥18y	**95 - 110 mmol/L**
Bicarbonate	0 - <1wk	15 - 28 mmol/L
	1wk - <2y	16 - 29 mmol/L
	2y - <10y	17 - 30 mmol/L
	10y - <18y	20 - 32 mmol/L
	≥18y	**22 - 32 mmol/L**
Calcium	0 - <1wk	1.85 - 2.80 mmol/L
	1wk - <6mo	2.20 - 2.80 mmol/L
	6mo - <2y	2.20 - 2.70 mmol/L
	2y - <18y	2.20 - 2.65 mmol/L
	≥18y	**2.10 - 2.60 mmol/L**
Magnesium	0 - <1wk	0.60 - 1.00 mmol/L
	1wk - <18y	0.65 - 1.10 mmol/L
	≥18y	**0.70 - 1.10 mmol/L**
Phosphate	0 - <1wk	1.25 - 2.85 mmol/L
	1wk - <1mo	1.50 - 2.75 mmol/L
	1mo - <6mo	1.45 - 2.50 mmol/L
	6mo - <1y	1.30 - 2.30 mmol/L
	1y - <4y	1.10 - 2.20 mmol/L
	4y - <15y	0.90 - 2.00 mmol/L
	15y - <18y	0.80 - 1.85 mmol/L
	18y - <20y	0.75 - 1.65 mmol/L
	≥20y	**0.75- 1.50 mmol/L**

Analyte	Age		Reference Interval	
Creatinine *	0 - <1wk		22 - 93 μmol/L	
	1wk - <4wk		17 - 50 μmol/L	
	4wk - <2y		11 - 36 μmol/L	
	2y - <6y		20 - 44 μmol/L	
	6y - <12y		27 - 58 μmol/L	
	Male		**Female**	
	12y - <15y	35 - 83 μmol/L	12y - <15y	35 - 74 μmol/L
	15y - <19y	50 - 100 μmol/L	15y - <19y	38 - 82 μmol/L
	≥19y - <60y	**60 - 110 μmol/L**	**≥19y - <60y**	**45 - 90 μmol/L**
Alkaline Phosphatase	**Male**		**Female**	
	0 - <1wk	80 - 380 U/L	0 - <1wk	80 - 380 U/L
	1wk - <1mo	120 - 550 U/L	1wk - <1mo	120 - 550 U/L
	1mo - <6mo	120 - 650 U/L	1mo - <6mo	120 - 650 U/L
	6mo - <2y	120 - 450 U/L	6mo - <2y	120 - 450 U/L
	2y - <6y	120 - 370 U/L	2y - <6y	120 - 370 U/L
	6y - <10y	120 - 440 U/L	6y - <10y	120 - 440 U/L
	10y - <14y	*130 - 530 U/L*	10y - <13y	*100 - 460 U/L*
	14y - <15y	*105 - 480 U/L*	13y - <14y	*70 - 330 U/L*
	15y - <17y	*80 - 375 U/L*	14y - <15y	*50 - 280 U/L*
	17y - <19y	*50 - 220 U/L*	15y - <16y	*45 - 170 U/L*
	19y - <22y	*45 - 150 U/L*	16y - <22y	*35 - 140 U/L*
	≥22y	**30 - 110 U/L**	**≥22y**	**30 - 110 U/L**

*****Reference intervals for patients <19y are specific for labs which use the Ortho Vitros enzymatic creatinine assay. For labs that do not use the Vitros enzymatic creatinine assay, the adult creatinine reference interval may be applied from age 18y[16].

7 Difficulties encountered and how they were resolved

Some of the delays encountered in the project were mainly due to the time availability of our volunteers serving on the Working Group; these have largely been overcome by scheduling regular teleconferences and workshops.

The more recent assessment of the impact on flagging rates has shown that potassium will flag more in some GP settings due to pre-analytical (delayed separation) issues. This may pose an undue burden on some laboratories. It was agreed at the May 2014 Workshop that individual labs can still choose to use an adjusted reference interval provided they have the data to support a local change.

As the evidence and validation data was collated, presented and discussed, it was apparent that this work should have been addressed before now.

It is only through a structured approach that consensus has been achieved. The Chemical Pathology community across Australia and New Zealand showed a commitment to the outcome, particularly once the evidence was highlighted at the Workshops.

The Workshops proved to be milestones for the project as participants took time out from their busy work schedules to focus and discuss the issues – all in the one room.

The real driving force for the project was the Harmonisation Committee, chaired by Jill Tate. Each member made a significant contribution and complemented the whole.

8 Future Directions

There is still a group of more "difficult" analytes. While proposed intervals have been determined for these, more work is required before they can be included in the recommended HRI's.

Examples are bilirubin both for neonatal and adults and urea where gender and age limits will likely apply. Some of the other tests (AST, ALT, GGT, and Lipase) where assay differences impact results may require a recommended method to move forward (e.g. BCP is now the recommended method for Albumin).

In December 2013 the RCPA QAP commenced a Liquid Serum Chemistry / Reference interval survey where frozen human serum was sent to 94 participating labs across Australasia. This survey will be repeated in 2014 and ideally continue thereafter. The 2013 reference interval results show some labs had started to adopt the proposed HRI's. This ongoing survey will provide further information on the uptake of HRI's as labs implement, moreover, it enables further assurance that bias is remaining at acceptable levels. HRI's will require constant monitoring to ensure that they remain relevant (Appendix 9).

A number analytes that are measured by immunoassay techniques also present a challenge, but are equally important to patient safety. The AACB plans to tackle these, initially to at least ensure that there is consistency within an instrument user group.

There are also other components of pathology requesting, testing and reporting that also require ongoing collaboration to harmonise, these include:

Critical Limits (AACB Critical Limits WP)

Report format (PITUS)

Panel profiles (e.g. LFT) (T Badrick surveys, in press)

Evidence based test requesting (T Badrick, in press)

The AACB has commenced work in all the above areas and progress updates were given at the May 2014 Workshop – http://www.aacb.asn.au/professionaldevelopment/workshop-2014

9 Conclusion

This project has demonstrated how a committed group from the AACB was able to gather the evidence and present the case for harmonised reference intervals. The consensus approach achieved active participation from the pathology community and ownership of the outcomes. This should facilitate the next phase of endorsement and full adoption across Australia.

The potential health and safety benefits are significant as further harmonisation activities are undertaken using the Australian evidence based model.

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11 Acknowledgements

This project owes much to the dedicated AACB HRI Committee under the guidance and leadership of Jill Tate whose passion to achieve an outcome inspired us all.

AACB Committee for Harmonised Common Reference Intervals

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[9] Roche Diagnostics, Sydney

[10] AACB, Alexandria, Sydney

P Graham

14/7/2014

11 Appendices

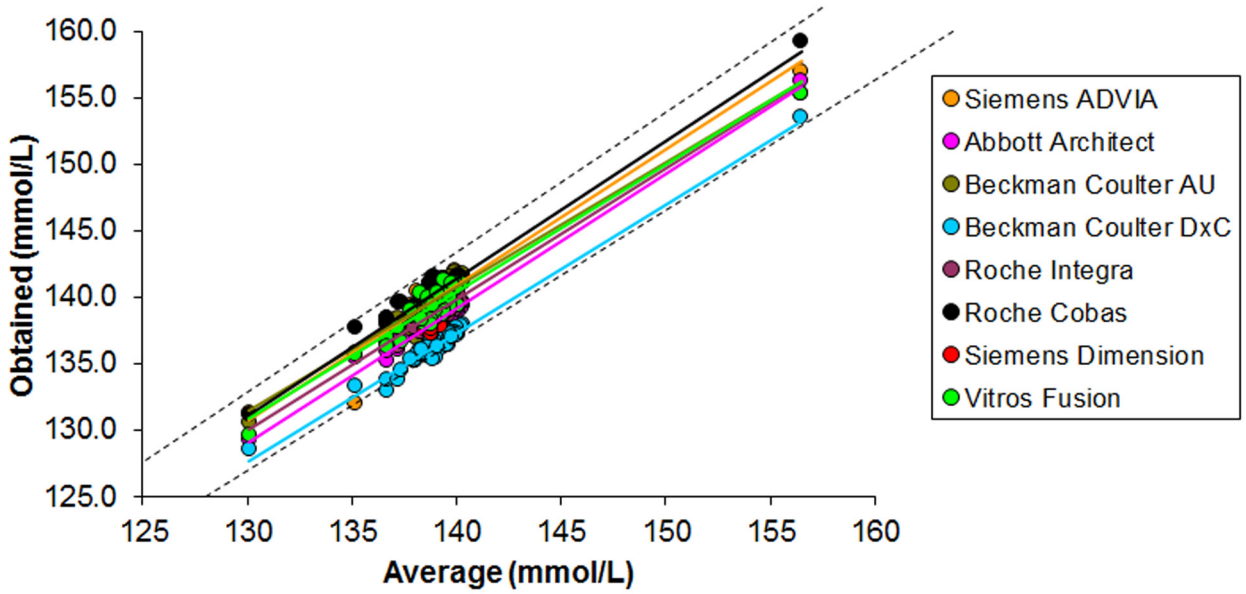
Appendix 1. HARMONISATION ACTIVITY PLAN June 2013 - June 2014

Objective	Activity	Milestone to achieve objective	Timeframe: expected duration for each activity
1. Assisting laboratories adopt HRIs using a prepared checklist/ spread sheet	The HRI checklist needs to be tested by laboratories using their own patient data and modifications made as necessary. To get uptake and adoption of this critical step small workshops will be run where representatives from laboratories can be shown how to analyse their own patient data and comparisons can be made between labs. We have budgeted for 3 such workshops to take place in Sydney and Melbourne. In addition we have also budgeted for travel by a relevant expert to individual laboratories	All major laboratory networks will have used the checklist to process their patient data and produced Reference Intervals which can be compared to others including current Sonic RIs. ***Update as at June 2014*** *All major laboratory networks have reviewed the checklist and their associated data* *Dr Tina Yen has completed the analysis of the paediatric data submitted by 31 laboratories located across Australia and New Zealand*	July – December 2013 – completed Completed April 2014 Third Workshop completed May 2014
2. Resolving remaining analytical biases that prevent adoption of HRI	Further survey work is being conducted to determine which analytes have analytical biases that might require analyser specific RIs. The results of this work need to be discussed at a face to face workshop similar to the one held by the AACB in 2012. The planned date for this workshop is in the 2nd half of 2013.	(i). Completion of bias surveys and collation of data by April 2013. - *done* (ii). Review of results by HRI Working Party of SRAC. - *done* (iii). Presentation of data and decision on HRIs at workshop with representatives of all major labs/networks. – *Presented at the 12 and 13 July Workshops in Sydney - 57 delegates (including clinicians) from major laboratory/ hospital networks across Australia and New Zealand attended.*	(i). July – September 2013 - done (ii) October 2013 - done (iii) December 2013 - done

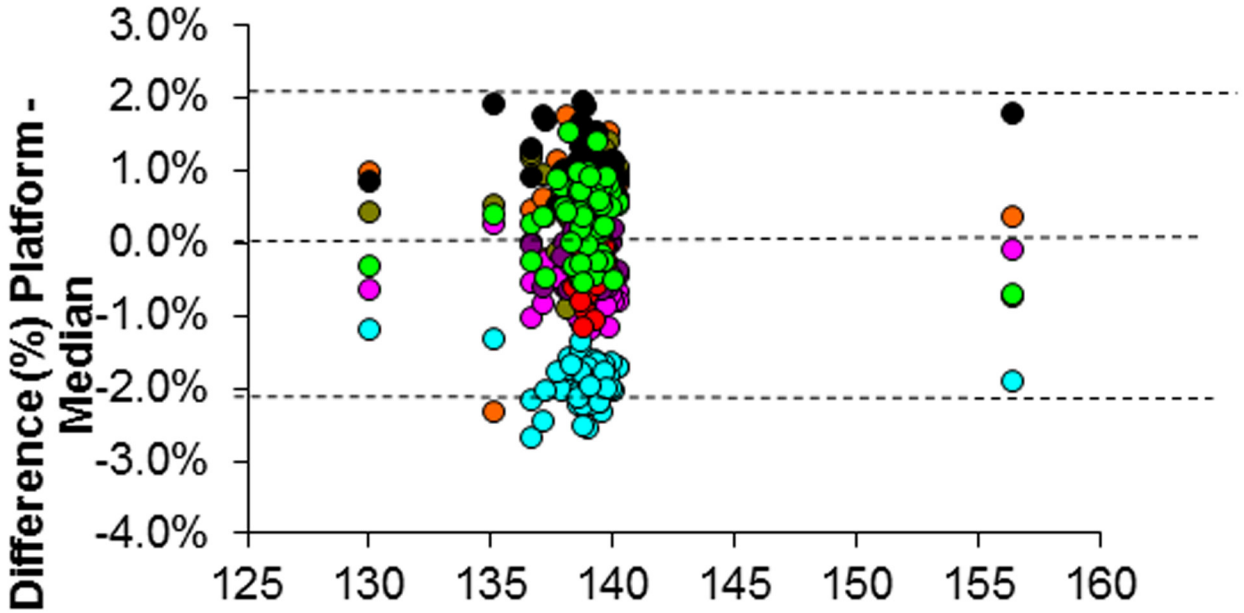
Objective	Activity	Milestone to achieve objective	Timeframe: expected duration for each activity
3. Collating and disseminating evidence to support adoption of HRI for each analyte	Work is proceeding on collation of the evidence for HRIs into a standard template including: laboratory RIs survey data, manufacturers' RIs, bias assessment results, literature, RI consensus data (e.g. ARQAG, SIQAG), RI formal studies (e.g. Aussie Normals), data mining data from Sonic Health. Once completed this data will need to be presented and reviewed at the HRI Workshop.	(i). Completion of HRI template data for each analyte. – *Completed, to be updated with December meeting outcomes* (ii). Review and discussion at HRI workshop by representatives of all major labs/networks. – *Actively discussed at the July HRI workshop – previously reported*	(i). July 2013 - done (ii). December 2013 - done
4. Review of existing RIs for paediatric patients and decisions on how to harmonise	The Paediatric HRI Working Group needs to meet face to face on two occasions in order to discuss the various issues that exist in this area and to make decisions on HRIs for various analytes.	(i). 1st meeting of the Paediatric HRI Working Group – *proceeded successfully on July 11, 2013* (ii). 2nd meeting of the Paediatric HRI Working Group (iii). Agreement on Paediatric HRIs - *data analysis complete*	(i). August 2013 - done (ii). November 2013- done (iii). May 2014 - done

Appendix 2. Example of bias assessment for Sodium – acceptable

Sodium Bias Data for 24 participating laboratories (Koerbin May 2013 Harmonisation Workshop[18])

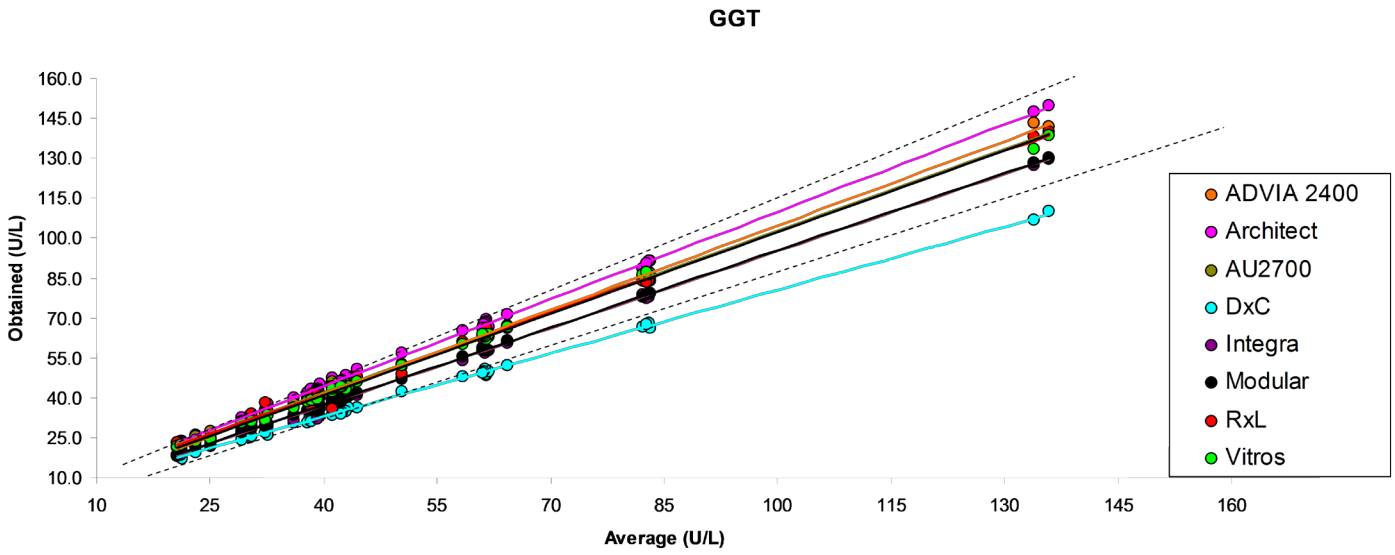


Difference Plot for Sodium

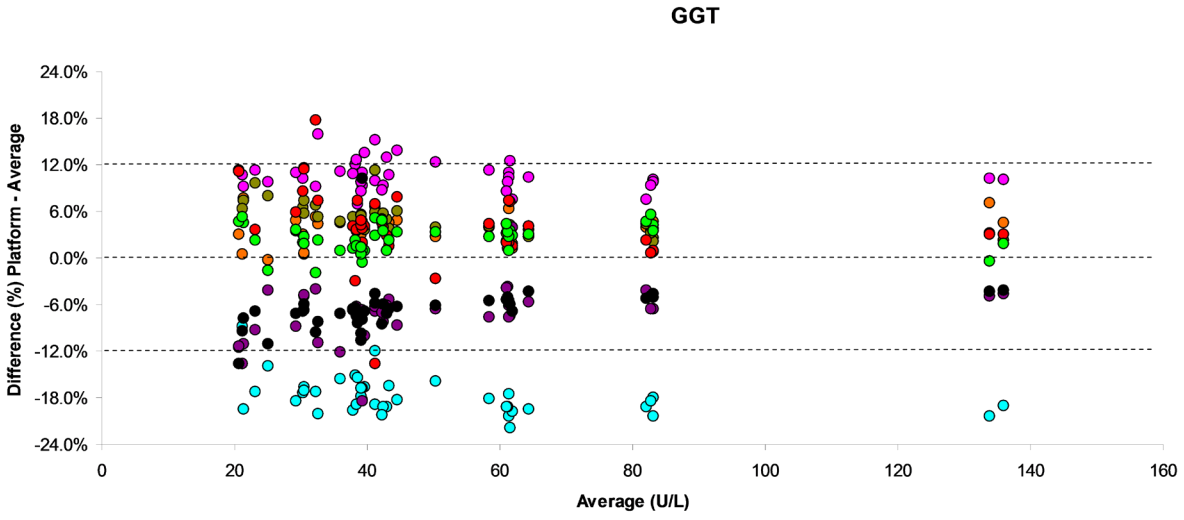


Appendix 3. Example of bias assessment for Gamma Glutamyl Transferase (GGT) – not acceptable due to method differences

GGT Bias Data for 24 participating laboratories (Koerbin 2013 Harmonisation Workshop)[18]



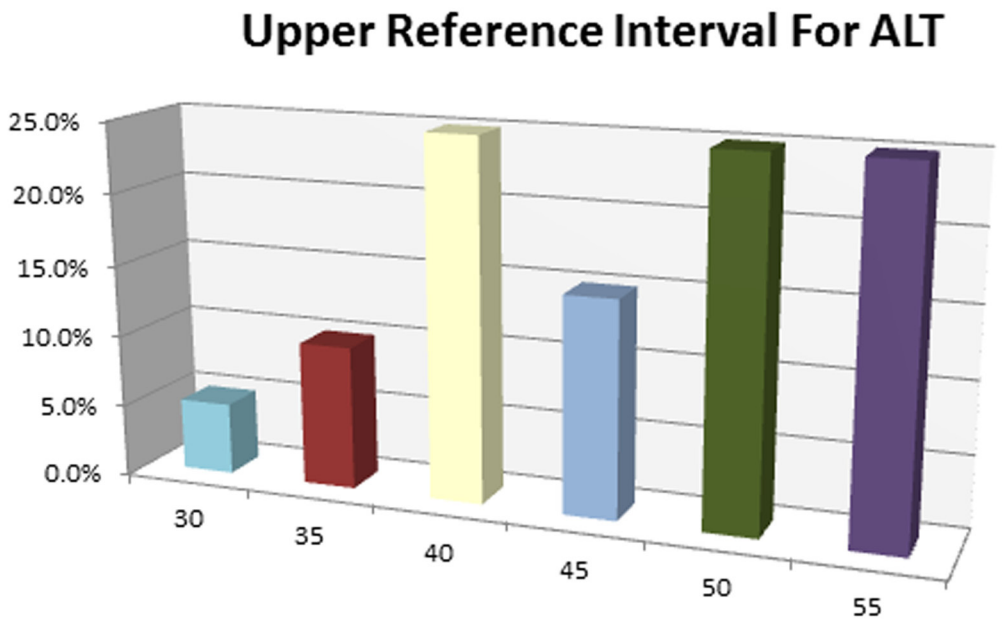
Difference Plot for GGT



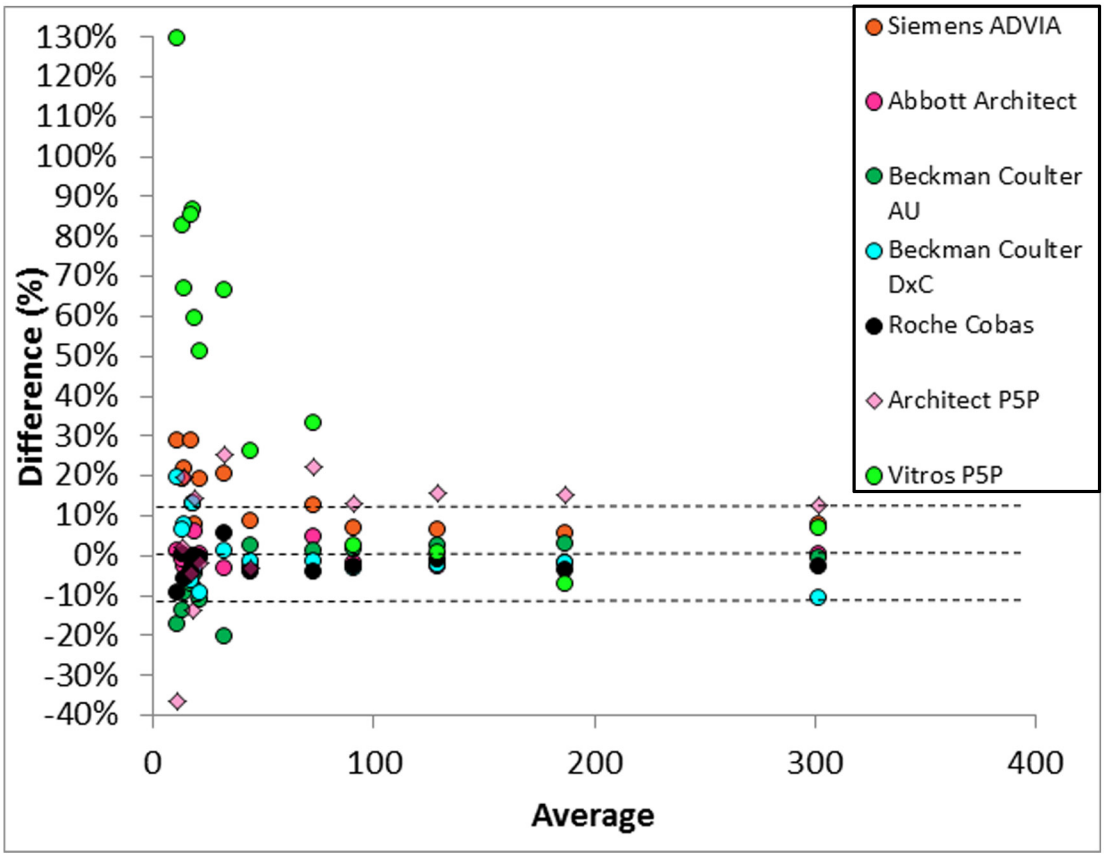
Appendix 4. Example of method differences that prevent harmonisation (Koerbin, July 2013 Harmonisation Workshop)[18]

	GGT	Lipase	LD
Modular	g-Glutamyl-3-Carboxy-Nitoanilide	Spectro - Glutaric Acid Ester	IFCC Recommended Method
Integra	g-Glutamyl-3-Carboxy-Nitoanilide	Spectro - Glutaric Acid Ester	IFCC Recommended Method
Vitros	g-Glutamyl-3-Carboxy-Nitoanilide	Spectro-diacetylglycerol	Pyruvate >0.7 mmolar (P-L)
Au2700	Mod IFCC (Szasz)	1,2-Diglyceride subst./co-lipase	Lactate to Pyruvate (NADH)
Abbott	g-Glutamyl-3-Carboxy-Nitoanilide	Quinone dye	Lactate to Pyruvate (NADH)
DxC	g-Glutamyl-3-Carboxy-Nitoanilide	Spectro - Glutaric Acid Ester	Lactate to Pyruvate (NADH)
Advia	g-Glutamyl-3-Carboxy-Nitoanilide	Spectro - Glutaric Acid Ester	Lactate to Pyruvate (NADH)

Appendix 5. Example of differences in reference intervals across Australian Laboratories (Ryan, May 2012 Harmonisation Workshop)[18]



Appendix 6. Example of effect of different methodologies on bias data – ALT (ALT Bias Data, Koerbin[18])



Appendix 7. Example of Bias Assessment for Sodium

Alternative name	(NA)			**Reported to (# DP)**	0		
Units	mmol/L			**Sample type**	Serum/ plasma		
Methods	Direct and Indirect ISE			**Paediatric intervals:**	Yes	See below for details	
LOINC				**Pregnancy intervals:**	No		
Reference interval survey data:		132 - 145 mmol/L					
Manufacturers intervals:		**Dimension**	136	145	**Vitros**	137	145
		Advia	136	146	**Modular**	133	145
		AU	136	146	**Integra**	136	145
		DxC/Dxi	136	144	**cobas 6000**	136	145
		Architect	136	145	**cobas 8000**	136	145
Manufactures traceable to:			**Traceability**	**Reference method**		**Traceability**	**Reference method**
-		**Dimension (RXL/EXL)**	NIST SRM 2201	Flame Atomic Absorption Photometry	**Vitros**	NIST SRM 919a	Flame atomic emission spectoscopy
-		**Dimension (Vista)**	NIST STM 9096	Flame photometry	**Modular**	NIST 909	Flamephotometry
		Advia	SRM 909b	CDC Flame Photometry reference Method	**Integra**	NIST 909	Flamephotometry
		AU	SRM 956a		**cobas 6000**	NIST 909	Flamephotometry
		DxC/Dxi	SRM 919a		**cobas 8000**	NIST 909	Flamephotometry
		Architect	NIST 909	Flamephotometry			
Analytical platforms assessed in Bias survey: Advia 2400, Architect, AU2700, DxC, Integra, Modular, RxL, Vitros							
Bias assessment outcome:		No sign. method bias					

Appendix 7 (Continued) Example of Evidence base data assessment for Sodium					
Sonic data	135 - 145 mmol/L Unisex Adult			**NORIP**	137 - 145 mmol/L Unisex ≥18y SERUM
	134 - 124 mmol/L Pregnancy				137 - 144 mmol/L Unisex ≥18y PLASMA
	132 - 147 mmol/L Paed ≥1wk - <12m			**Aussie Norms**	
	132 - 145 mmol/L Paed ≥12m - 15y			**UK Harmony**	133 - 146 mmol/L
ARQAG	135 - 145 mmol/L Unisex Adult				
	134 - 148 mmol/L Neonate				
SIQAG	135 - 145 mmol/L Unisex				
The Alfred	135 - 145 mmol/L Unisex				
WA ranges	134 - 146 mmol/L Unisex, 136 - 145 mmol/L Unisex, 135 - 145 mmol/L Unisex				
Proposed intervals from Workshop:					
Adult	**Unisex**	**135 - 145 mmol/L**			
Paediatric	Birth - <7d	132 - 147 mmol/L	Confirmed		
	≥7d - <2yr	133 - 145 mmol/L			
	≥2yr - <12yr	134 - 144 mmol/L			
	≥12yr - Adult	135 - 145 mmol/L			
RCPAQAP Reference Intervals Program (40 yo)					
LRL: 136 mmol/L most common (43labs), followed by 135 (42) and 134 (33)					
URL: 146 mmol/L most common (61 labs), followed by 135 (56)					

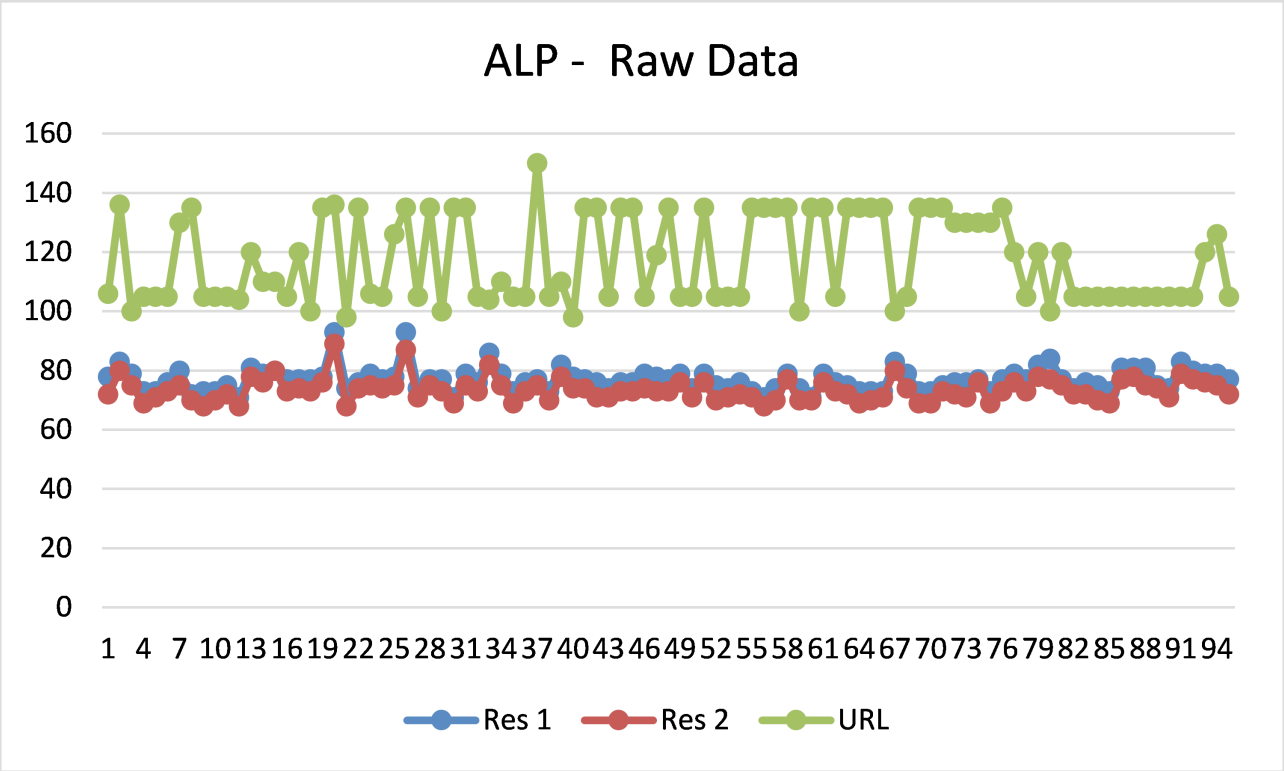
Note: Full list available at http://www.aacb.asn.au/professionaldevelopment/workshop-2014

Appendix 8 Example excerpt of Common Reference Intervals - Uptake Sheet for Sodium

PLEASE CONFIRM YOUR LABORATORY'S WILLINGNESS TO ADOPT PROPOSED CRI BY ADDING DATA IN SPREAD-SHEET					
Adult CRI (round 1)					
Note adult is from 18 years of age and above. Separate intervals may be indicated in pregnancy (not specified here).					
The following laboratories have agreed as follows:					
C - These intervals in current use A - The laboratory agrees to use these intervals following official endorsement N - The laboratory has evaluated the intervals and found them not suitable for use P - The laboratory is planning to introduce these intervals (irrespective of official endorsement)					
(#) - see comment relevant to number				**A or C**	24
Follow hyperlinks for additional data on analyte					
e.g. Bias study results, other CRI, manufacturer's ranges				**Analyte**	**Sodium**
QAP reference interval study				**Range**	135 – 145
				Units	mmol/L
				Further Data	Sodium
Laboratory	**State**	**Contact/email**	**Analyser**	**Limitations**	
SydPath	NSW	gjones@stvincents.com.au	Roche Modular		A
Pathology Queensland	QLD	jacobus_ungerer@health.qld.gov.au	Beckman-Coulter		C
Austin Pathology	VIC	que.lam@austin.org.au			A
Mater Pathology	QLD	janet.warner@mater.org.au	Ortho-CD		C
Royal Hobart Hospital	TAS	Michael.Smillie@dhhs.tas.gov.au	Architect		C
Northern Tasmania Pathology Service	TAS	Michael.Smillie@dhhs.tas.gov.au	Architect		A
DHM	NSW	ntaylor@dhm.com.au	Abbott and Roche		C
SNP	QLD	david_kanowski@snp.com.au	Abbott and Roche		C
MPS	VIC	alan.mcneil@mps.com.au	Roche		C
CAPITAL Path	ACT	paul.whiting@capitalpath.com.au	Roche		C
ClinPath	SA	mmetz@clinpath.com.au	Roche		C
CliniPath	WA	ssacks@clinipathpathology.com.au	Roche		C
Hobart Path	TAS	richard.hanlon@dspl.com.au	Roche		C
Southern.IML	NSW	gary.morris@southernpath.com.au	Roche Cobas		C
Pathology North (RNSH)	NSW	doug.chesher@health.nsw.gov.au	Abbott Architect		A
Pathology North (HAPS)	NSW	amanda.caswell@hnehealth.nsw.gov.au	Abbott Architect		A
ACT Pathology	ACT	heather.robins@act.gov.au	Abbott Architect		A
PathWest	WA	elizabeth.byrnes@health.wa.gov.au	Abbott Architect and OCD Vitros		A
SA Pathology	SA	penelope.coates@health.sa.gov.au	Siemens,Advia Roche,Beckman		A
SEALS	NSW	rita.horvath@sesiahs.health.nsw.gov.au	Roche Cobas 6000/8000		C
Monash Pathology	VIC				C
Dorevitch Pathology	VIC	Nilika.Wijeratne@dorevitch.com.au	Advia/Integra		A
Laverty Pathology	NSW	chris.farrell@laverty.com.au	Siemens Advia 2400		C

Note: Full list available at http://www.aacb.asn.au/professionaldevelopment/workshop-2014

Appendix 9. Example of data for Alkaline Phosphatase (ALP) submitted by 94 labs participating in the December 2013 RCPA QAP Liquid Serum Chemistry /Reference Interval survey (G Jones, May 2014 Workshop[20])



Blue bar = Serum sample 1 result (U/L)

Red bar = Serum sample 2 result (U/L)

Green Bar = Upper reference interval limit quoted by lab at time of survey (Dec 2013)