



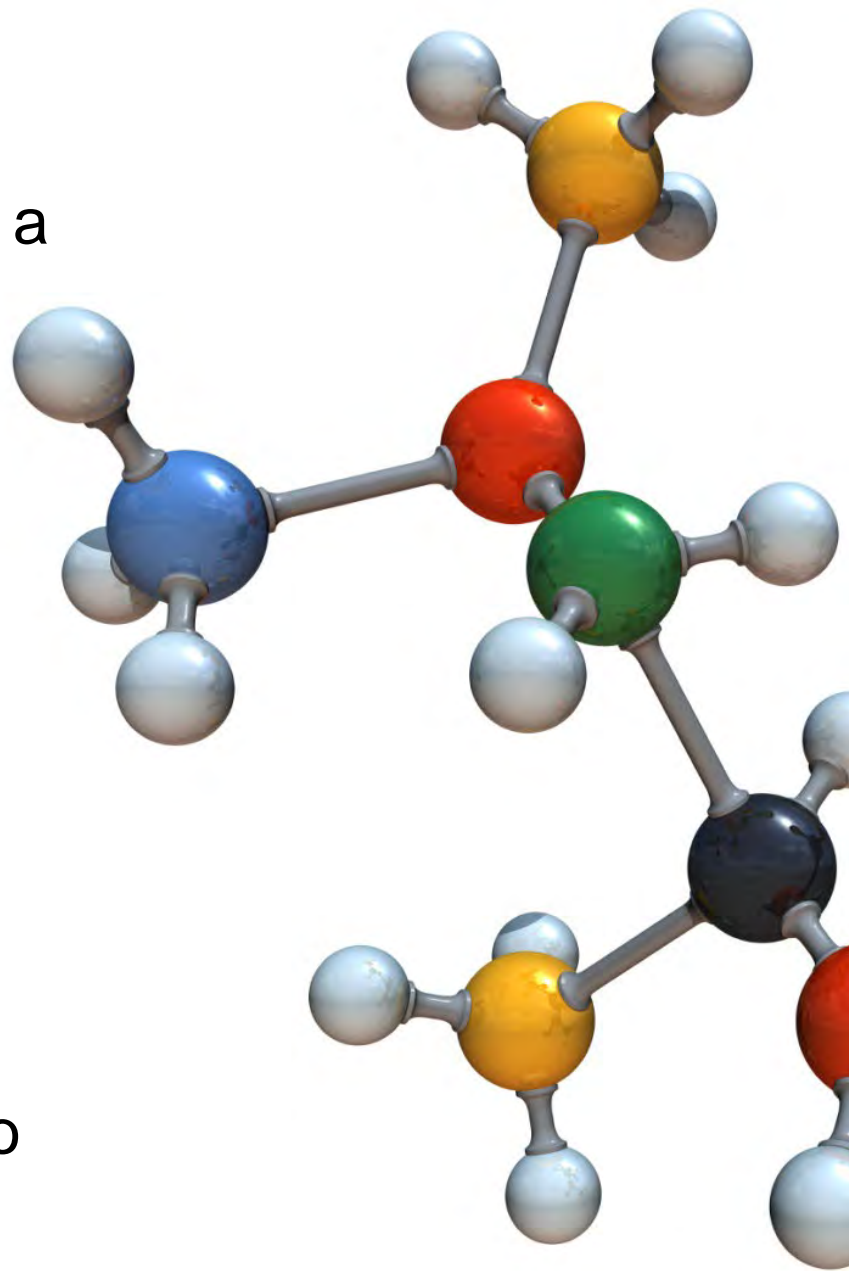
# Moving towards global harmonisation & standardisation

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20th August 2011  
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Photos: <http://www.pbse.com/lambsfeathers/image/>

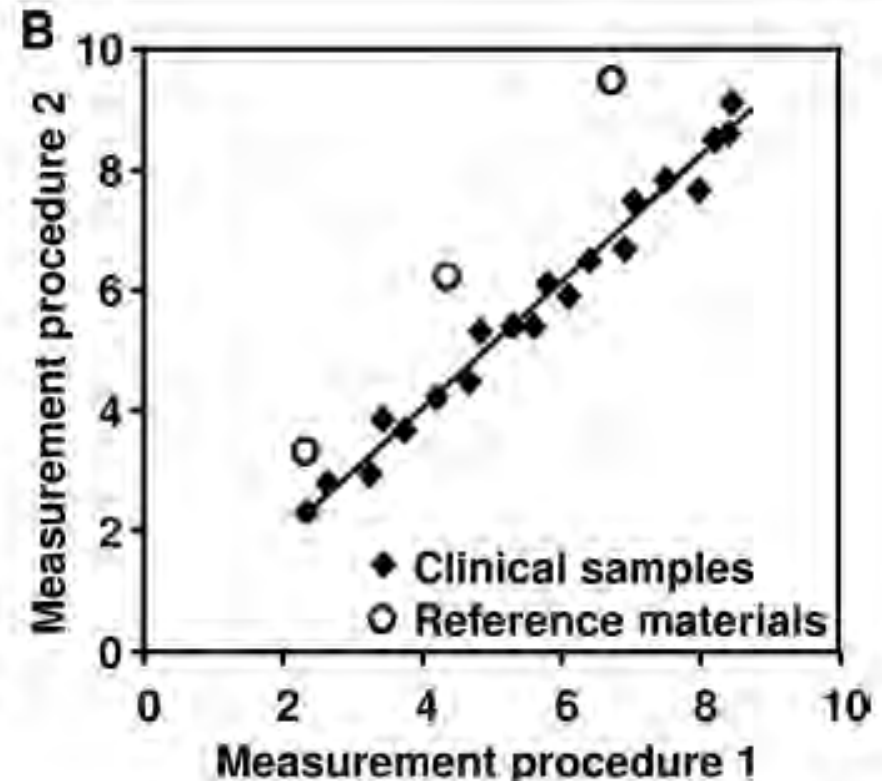
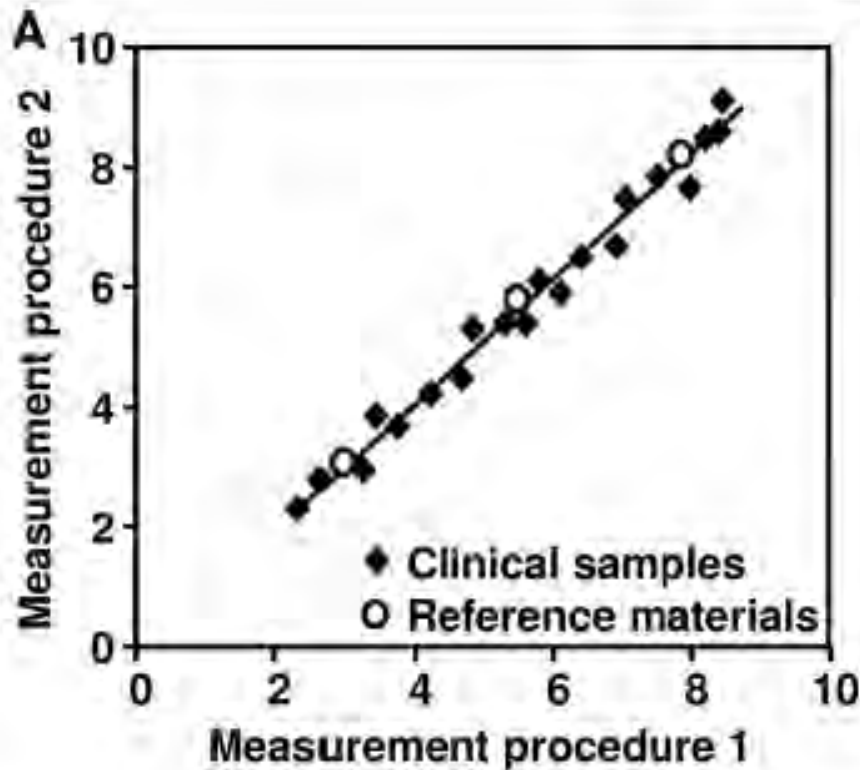
# Overview

- In recent years there has been a concerted effort to improve assay results, particularly in relation to:
  1. Commutability
  2. Traceability
  3. Standardisation
  4. Harmonisation
- This presentation aims to provide an insight into current thinking and activities related to improving result commutability





# 1. COMMUTABILITY



Not all reference materials have proven commutability

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# 2. Traceability

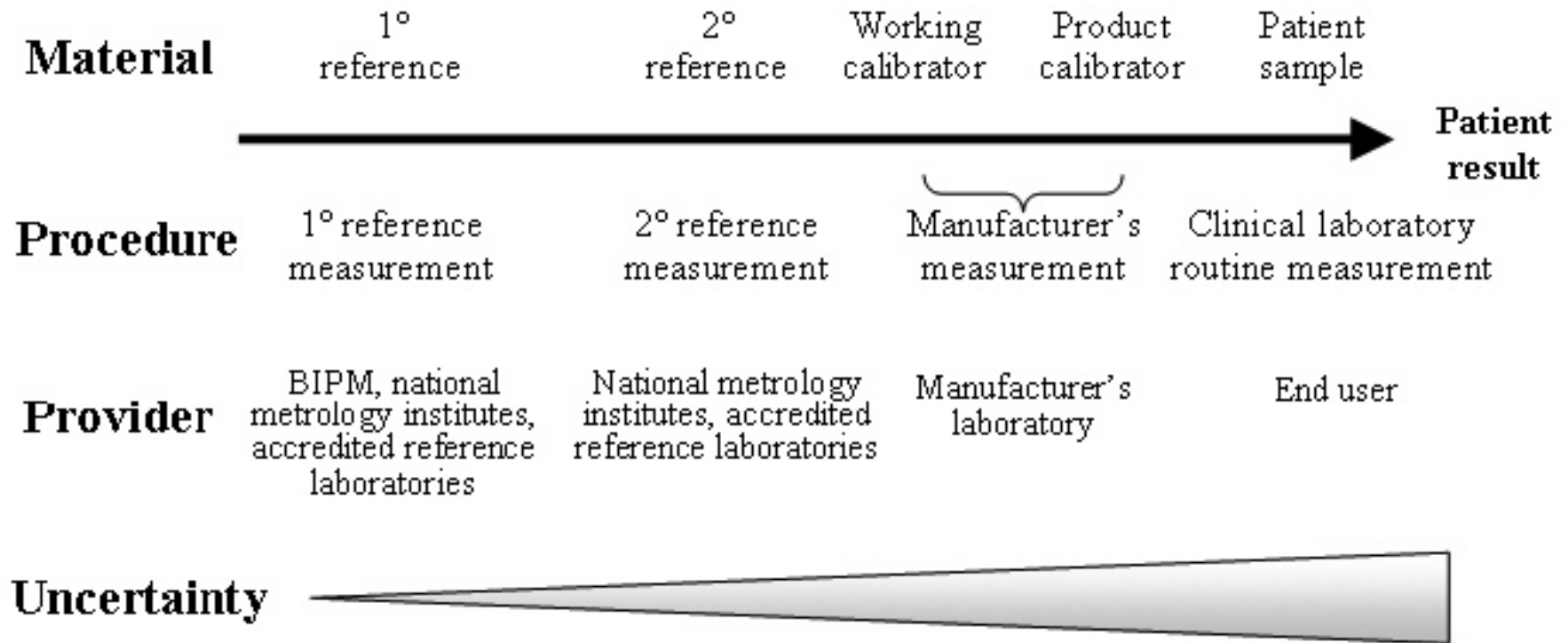
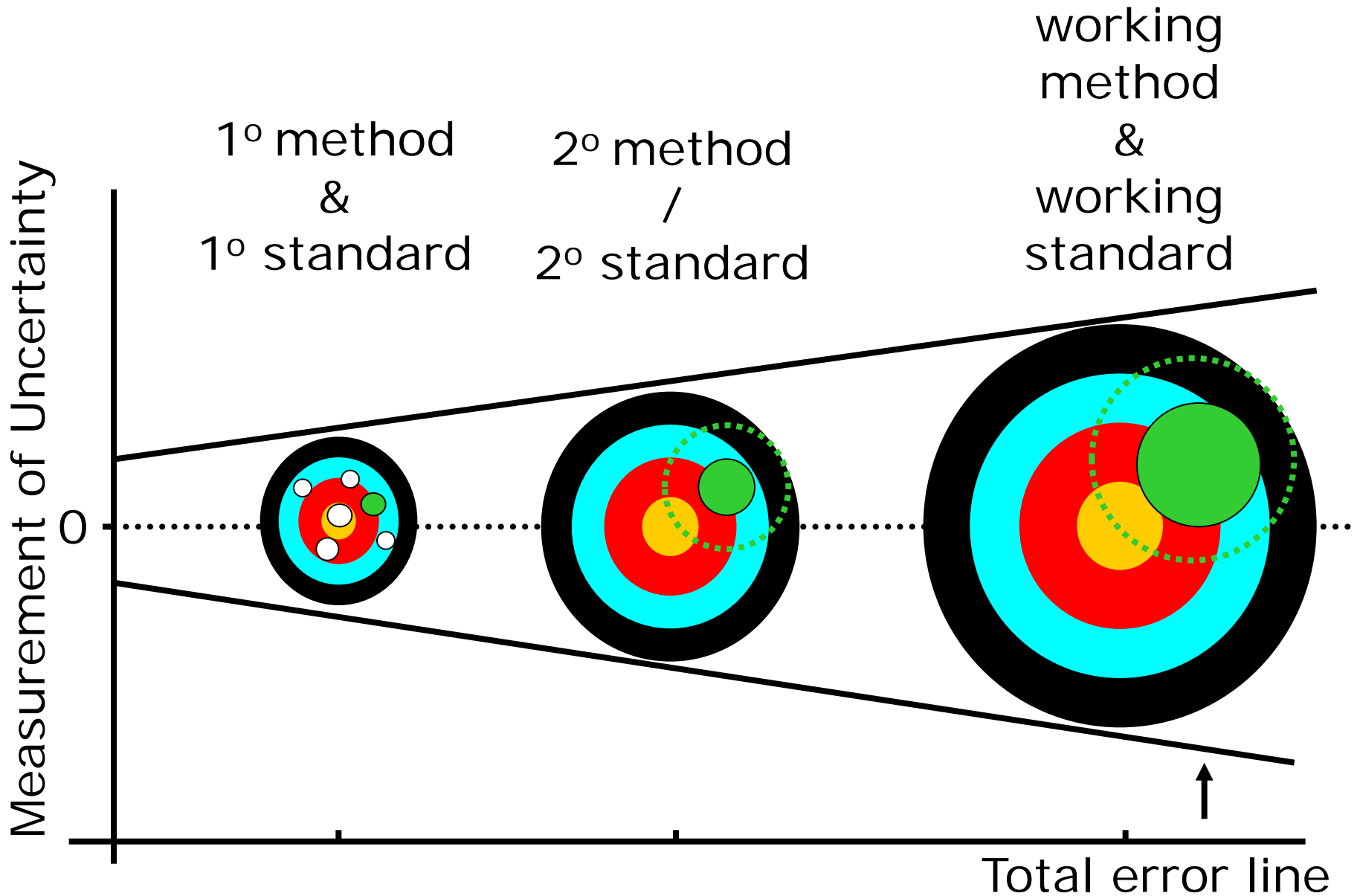


Figure. A generic calibrator traceability flowchart. Based on ISO 17511:2003 Fig 4.2.2.

# 2. TRACEABILITY



## 2. Joint Commission for Traceability in Laboratory Medicine - (JCTLM)

- EU Directive on Vitro Diagnostic measurements requires traceability to standards of “higher order”
- JCTLM Established by BIPM, IFCC and ILAC
- In co-operation with all stakeholders
- Traceability to SI, but if not (yet) possible to other internationally agreed references (e.g. WHO units for biological activity)
- Aim of JCTLM is to realise and support worldwide reliable comparability and traceability of measurement results in laboratory medicine

# 2 and 3. JCTLM Database

The screenshot shows the JCTLM Database website. At the top left is the BIPM logo (Bureau International des Poids et Mesures). The main header reads "Database of higher-order reference materials, measurement methods/procedures and services". On the right is the JCTLM logo and the text "JCTLM Database Laboratory medicine and *in vitro* diagnostics". A navigation bar contains "T+", "T", and "T-". A search bar is partially visible. A left sidebar contains a menu with items like "List of reference laboratories", "JCTLM Database", and "Contact us". The main content area has a "Refine search" section with a dropdown menu set to "All" and a "Refine search by matrix category" section also set to "All". Below these are three radio buttons, all of which are selected (indicated by green dots): "Higher-order reference materials", "Reference measurement methods/procedures", and "Reference measurement services". At the bottom of the search section are "Reset" and "Search" buttons.

Reference Laboratories and Methods is developing criteria for reference measurement laboratories

Reviewing reference materials and methods nominated as being of higher order

<http://www.bipm.org/jctlm/>

### 3. Examples of Standardisation

<b>Measurand</b>	<b>Method</b>	<b>Standards</b>	<b>Laboratories</b>
Cholesterol	Yes x 3	Yes x 5	Yes x 13

Based on JCTLM database search 10<sup>th</sup> August 2011



# 4. Harmonisation

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Special Report

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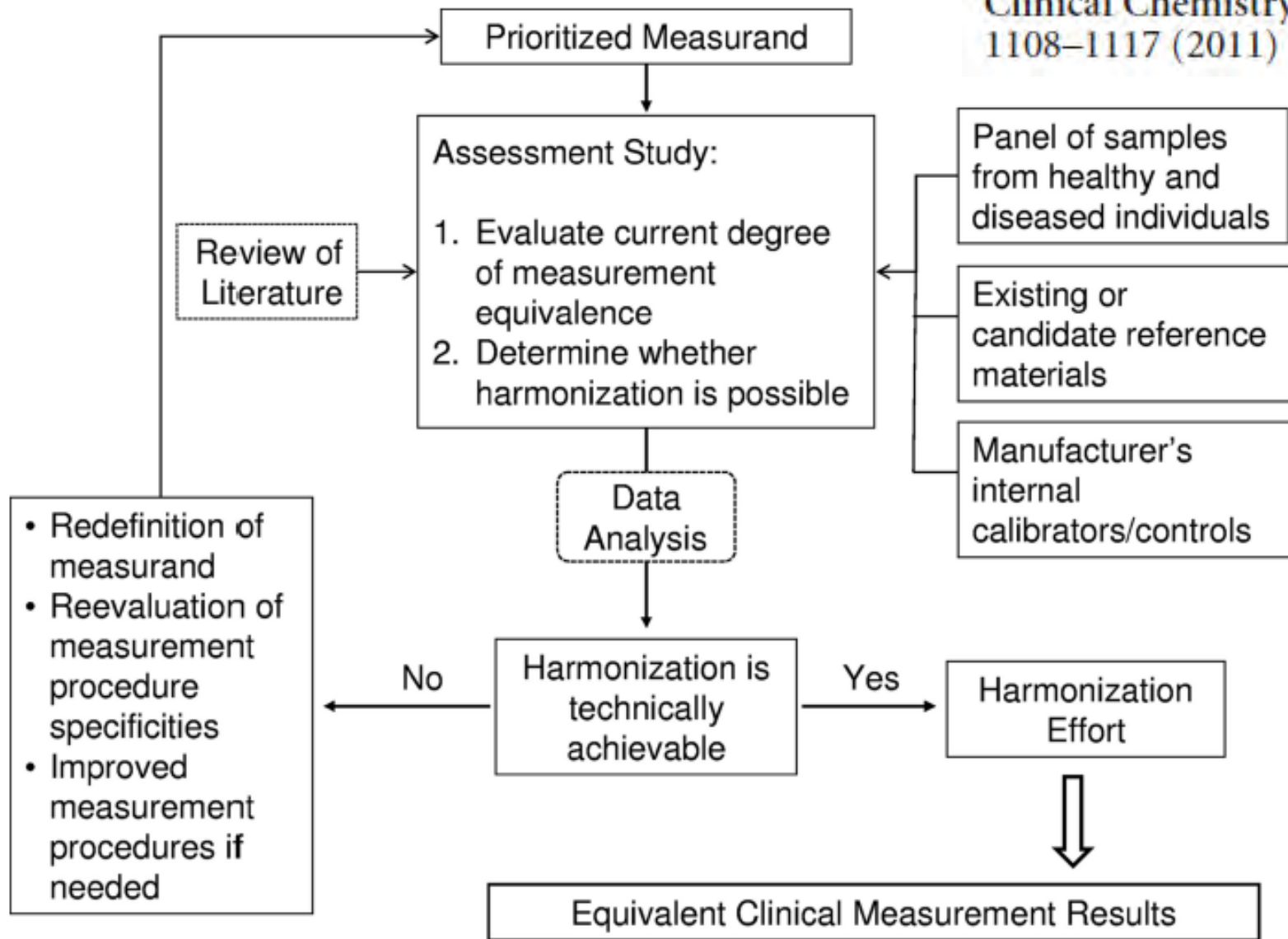
## Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,<sup>1\*</sup> Gary L. Myers,<sup>2</sup> Mary Lou Gantzer,<sup>3</sup> Stephen E. Kahn,<sup>4</sup> E. Ralf Schönbrunner,<sup>5</sup>  
Linda M. Thienpont,<sup>6</sup> David M. Bunk,<sup>7</sup> Robert H. Christenson,<sup>8</sup> John H. Eckfeldt,<sup>9</sup> Stanley F. Lo,<sup>10</sup>  
C. Micha Nübling,<sup>11</sup> and Catharine M. Sturgeon<sup>12</sup>

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# 4. Harmonisation: General Process

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# 4. Harmonisation: A practical application

- Conference:

Asia Pacific Chromatography Mass Spectrometry Meeting

- Chairs:

Danny Sampson & CS Ho

- Date:

2010 January Hong Kong

- Discussion:

Need for agreement b/w MS assays

- Inaugural meeting:

Saturday 16th January 2010



•“Mass spectrometry has become one of the most important tools in the analytical laboratory, with a wide range of applications” Spectrophotometry March 9, 2011

•Many applications relevant to Clinical Biochemistry

•Ideal to develop reference methods

# 4. APFCB MS harmonisation WG

APFCB

APFCB – Scientific Committee


APFCB – MSHWG

Testosterone Project group

Next project group

# Launched – Seoul 2010

ASIAN AND PACIFIC FEDERATION OF CLINICAL BIOCHEMISTRY



**MASS SPECTROMETRY  
HARMONISATION  
WORKING GROUP  
(MSHWG)**

**Serum Testosterone  
Project**

ASIAN AND PACIFIC FEDERATION OF CLINICAL BIOCHEMISTRY

**MASS SPECTROMETRY  
HARMONISATION  
WORKING GROUP  
(MSHWG)**

**TESTOSTERONE  
METHODS OF REFERENCE  
PROJECT**

## Asian and Pacific Federation of Clinical Biochemistry Mass Spectrometry Harmonisation Working Group


Kiyoshi ICHIHARA<sup>1</sup> and Chung Shun HO<sup>2</sup>

<sup>1</sup>Prince Alfred Hospital, Australia; <sup>2</sup>Murdoch Children's Research Institute,  
at Prince Alfred Hospital, Australia; <sup>3</sup>Yamaguchi  
University, Yamaguchi, Japan; <sup>4</sup>Prince of Wales Hospital, Hong Kong SAR,  
China; <sup>5</sup>RMIT University, Melbourne, Australia  
[ronda.greaves@rmit.edu.au](mailto:ronda.greaves@rmit.edu.au)

Reference intervals is of high importance for the future  
clinical laboratories. The proposal to establish a  
"Mass Spectrometry Harmonisation Working Group"  
(MSHWG) was put forward at an inaugural  
Pacific Conference of Chromatography and Mass  
Spectrometry. The first MSHWG meeting included members from the  
Hong Kong Society of Clinical Chemistry and industry, it  
under the Asian and Pacific Federation of Clinical

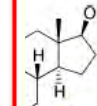
### Objectives:

1. Develop a reference interval document that  
has been sequentially endorsed by the  
MSHWG. The MSHWG is a Working  
Group of the APFCB. Scientific  
Secretary (Executive Secretary) and a  
Project Group will be established.  
2. Develop a reference interval document for  
the Executive Secretary for a  
document that include scientific  
initiatives.



**MASS SPECTROMETRY  
HARMONISATION  
WORKING GROUP  
(MSHWG)**

**Serum Testosterone  
Project**



Testosterone

1. Development of serum testosterone concentrations in clinical  
laboratories. The first project is the development of  
reference intervals on the serum testosterone LCTMS methods  
and harmonise serum testosterone results through  
harmonise LCTMS reference intervals for serum

2. Development of harmonisation  
reference intervals. The first project  
is the development of reference intervals  
on the serum testosterone assays.  
3. Participate in this project by  
contacting Dr Ronda Greaves

[ronda.greaves@rmit.edu.au](mailto:ronda.greaves@rmit.edu.au)

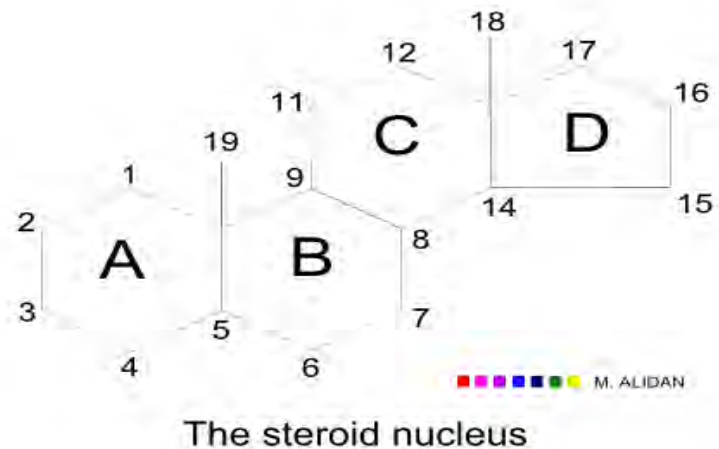
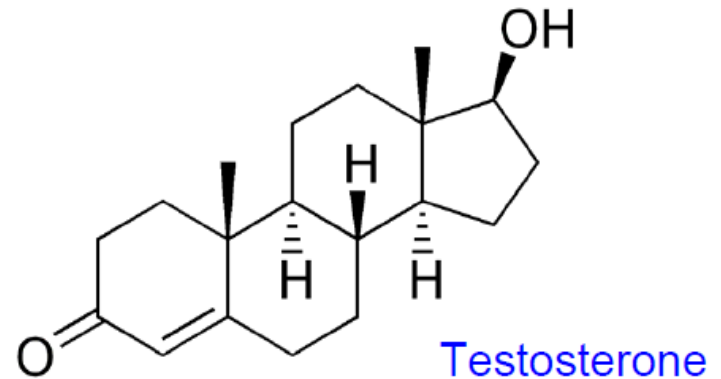


School of Medical Sciences, RMIT University



# 4. Why Testosterone?

- Initially steroids
- Simplified to one analyte
- Small number of labs
- Easier to control as the pilot
- No other group currently looking at testosterone
- Difficult analyte to measure in children and females
- Specific interest of three of the core group



## 4. Definition of Testosterone project

**“This project is to harmonise the measurement of serum testosterone concentrations in clinical samples using liquid chromatography isotope-dilution tandem mass spectrometry (LCTMS) methods”**

## 4. Harmonisation Goals

1. To provide detailed information on the different serum testosterone LCTMS methods used in Asian Pacific clinical biochemistry laboratories
2. To harmonise the serum testosterone results through the use of a set of common secondary serum calibrators that have been validated by a reference method
3. To harmonise reference intervals for serum testosterone of different sexes and age groups in the Asian Pacific region

# 4. Harmonisation Strategies

- A. Formation of the Project Working Group
- B. Recruitment of participating laboratories
- C. Documentation of serum testosterone LCTMS methods of participating laboratories
- D. Initial assessment of performance – Stage I
- E. Harmonisation of accuracy performance – Stage II
- F. Harmonisation of reference intervals – Stage III

# A. Formation of the Project Working Group

## Corresponding:

1. Trish Anderson - ASE
2. Brian Cooke – Royal Perth Hospital
3. Jan Gill – RCPA QAP
4. Ronda Greaves – RMIT University
5. Dr CS Ho – Prince of Wales Hospital
6. Kirsten Hoad – Royal Perth Hospital
7. Kiyoshi Ichihara - Yamaguchi University
8. John Joseph – QE2
9. Katsuhiko Kuwa – Japan Meteorology
10. Tze Ping Loh – National University Hospital
11. Brett McWhinney – Royal Brisbane
12. Michael Rennie – PM separations
13. Danny Sampson - RPA
14. Prof Junghan Song – Seoul National University Bundang Hospital
15. Trevor Walmsley - Canterbury Health

## Location:

- **Hong Kong**
- Japan
- **South Korea**
- NSW
- **New Zealand**
- **Queensland**
- Singapore
- Victoria
- **Western Australia x 2**

## Company Support:

- Agilent Technologies
- ASE
- PM Separations
- RCPA QAP Chemical Pathology Program



## B. Recruitment of participating laboratories

### 7 Labs currently with methods:

- **Hong Kong**
- **Korea**
- **Melbourne**
- **New Zealand**
- **Queensland**
- **Western Australia x 2**

## C. Documentation of serum testosterone LCTMS methods of participating laboratories

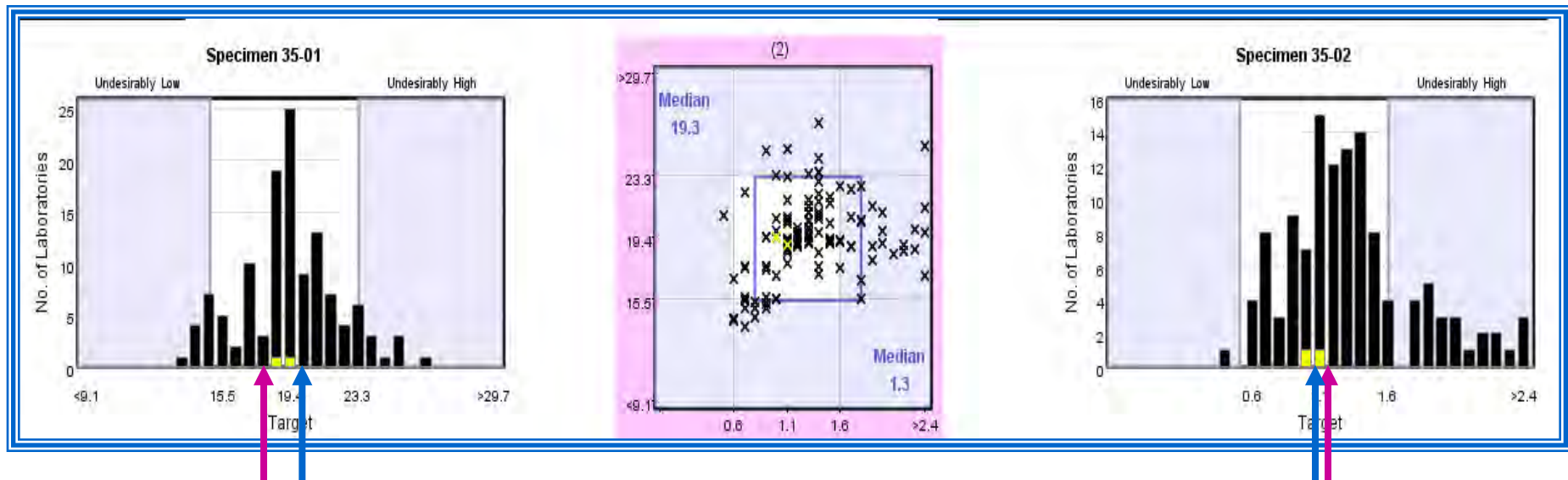
<b>Question</b>	<b>Response Summary</b>
<b>Testosterone standard material:</b>  <b>Source</b>  <b>Purity</b>	1: Lipomed, 2: WEQAS, 3-4: Sigma  1: > 98.5 %, 2: 99%, 3: >98%
<b>Isotope-labelled testosterone:</b>  <b>Source</b>  <b>Purity</b>  <b>Labelling positions</b>	D2 Testosterone  Cambridge Isotope Laboratories Inc.  98%  1,2
<b>Calibrator matrix</b>	Stripped plasma Foetal Bovine or stripped serum
<b>Source</b>	1:Sigma, 2:WEQAS, 3:Sera Care Life Sciences, 4:In-house

## C. Documentation of serum testosterone LCTMS methods of participating laboratories

<b>Question</b>	<b>Response Summary</b>
<b>MRM for quantitation</b>	289 > 109 or 97
<b>MRM for confirmation</b>	289 > 109 or 97
<b>MRM for labelled testosterone</b>	291 > 111 or 99

# D. Initial assessment of performance – Stage I

Accuracy, between-batch precision and linearity performance will be evaluated via the RCPA QAP Endocrine program over a 12-month period i.e. 2011



## D. MS-HWVG: Testosterone Results umol/L

Level	1	2	3	4	5	6
<b>TARGET</b>	<b>1.1</b>	<b>4.8</b>	<b>8.4</b>	<b>12.1</b>	<b>15.8</b>	<b>19.4</b>
lab A	0.9	4.8	8.4	12.1	16.9	19.4
	1.0	5.2	8.4	11.2	16.4	18.7
lab B	1.0	5.3	8.7			21.5
	1.1	5.2	9.0	12.5	17.5	19.4
lab C	1.0	4.8	8.6	12.0	16.9	19.6
	1.1	4.8	8.8	12.6	15.4	19.1
lab D	1.2	5.0	8.8	12.3	16.2	18.7
	1.2	5.0	8.3	12.1	16.2	19.4
<b>mean</b>	<b>1.06</b>	<b>5.01</b>	<b>8.63</b>	<b>12.11</b>	<b>16.50</b>	<b>19.48</b>
SD	0.11	0.20	0.24	0.46	0.67	0.88
<b>CV %</b>	<b>10.0</b>	<b>4.1</b>	<b>2.8</b>	<b>3.8</b>	<b>4.1</b>	<b>4.5</b>

### RCPA QAP Cycle 35

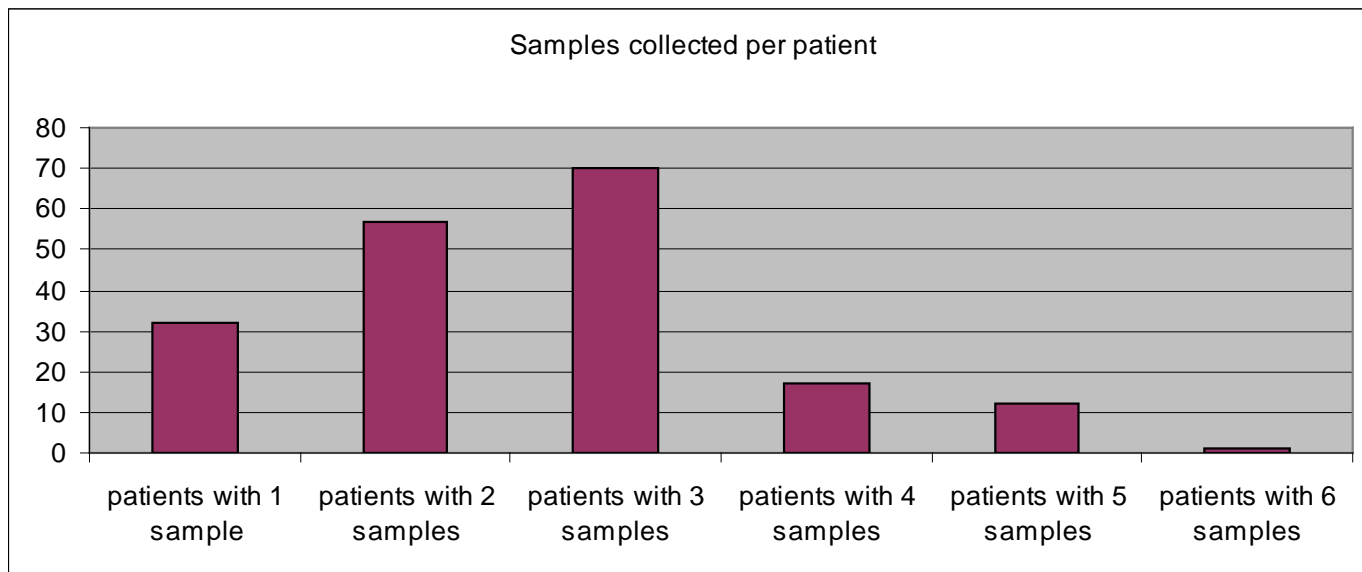


## 4. Update of Project Status

1. Formation of the Project Working Group ✓
2. Recruitment of participating laboratories ✓
3. Documentation of serum testosterone LCTMS methods of participating laboratories ✓
4. Initial assessment of performance – Stage I ✓
5. Harmonisation of accuracy performance – Stage II
6. Harmonisation of reference intervals – Stage III

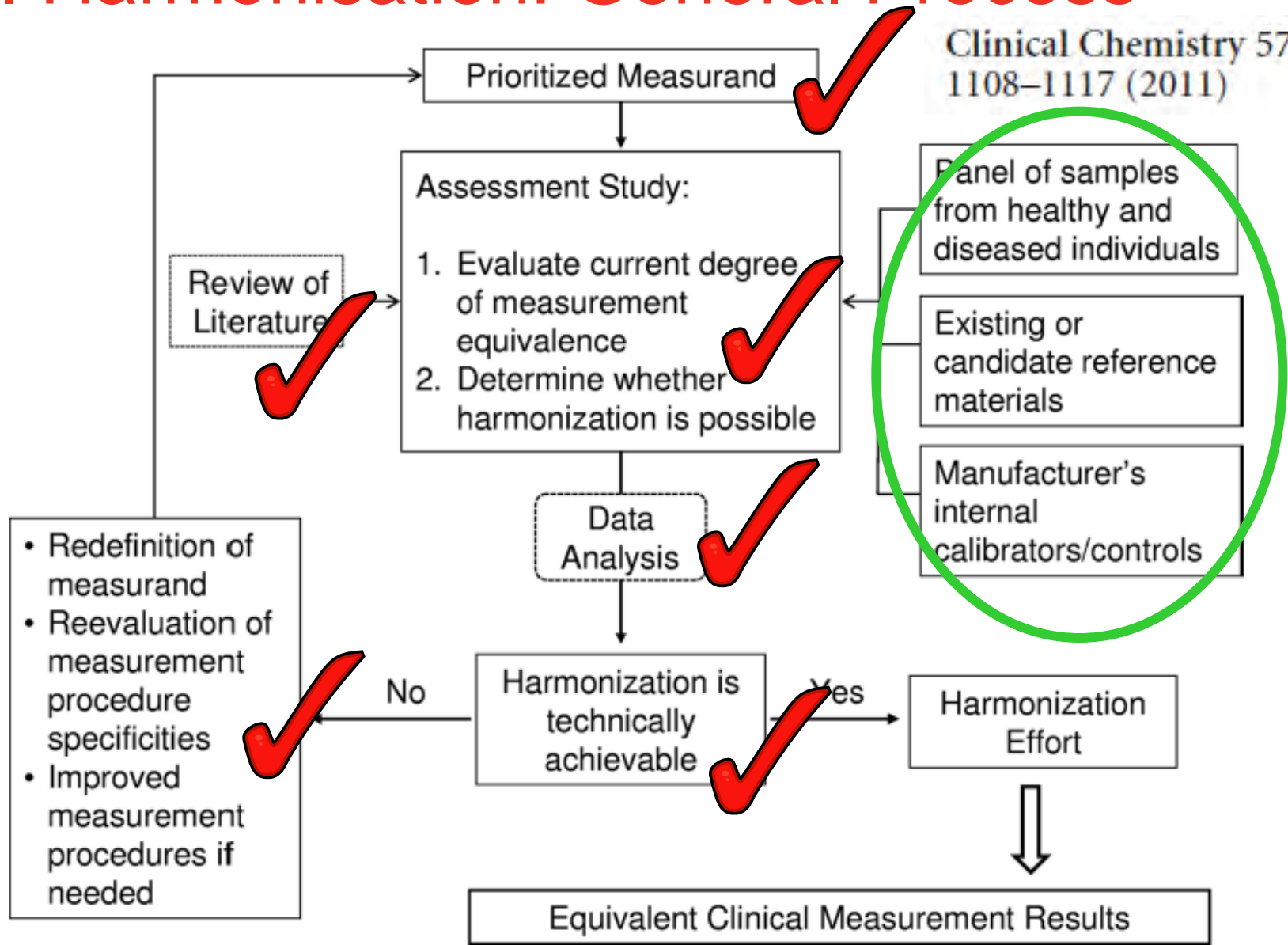
# F. Harmonisation of Reference Intervals

- Specific studies developed or tapped into e.g.:
- **PREMATURE INFANTS HORMONE STUDY**
  - Parents of infants born < 32 weeks gestation were approached for consent either antenatally or soon after delivery - 192 (56.1%) have agreed
  - Whole blood collected from babies on approximately days 1, 4, 7, 14, 21, 28 and 42, coinciding with routine blood sampling
  - 490 samples collected to April 2011 audit



# 4. Harmonisation: General Process

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# Harmonisation in Vietnam

## Some suggestions:

- Check package inserts for traceability of standards
- Choose material that is commutable
- Compare internal and external QC results between labs and instruments
- Ask your industry for information
- Form local QC subcommittees within e.g. VACB and /or Technologist societies

# In Conclusion



- **Achieving harmonisation and standardisation of clinical assays will provide commutability of results between laboratories**
- **This will produce improved ease of result interpretation for the doctor and patient**