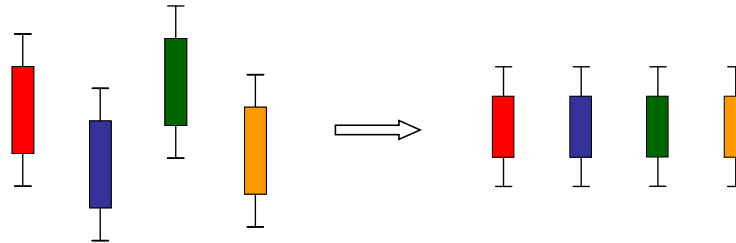


The AACC Concept of Method Harmonization

Harmonization.net



Gary L. Myers, PhD
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Outline

- Why harmonized results are needed
- Barriers to harmonized results
- AACCC's global harmonization initiative

Primary reasons for testing

- To develop epidemiologic data from which to establish clinical practice guidelines for disease management
- To identify individuals at increased risk of disease and/or to manage a disease in an individual

Good laboratory medicine requires:

- Total error of measurement small enough that a result reflects a patient's biological condition
- Comparable results independent of
 - ◆ where and when a test was performed
 - ◆ the measurement procedure used

How to achieve comparable results

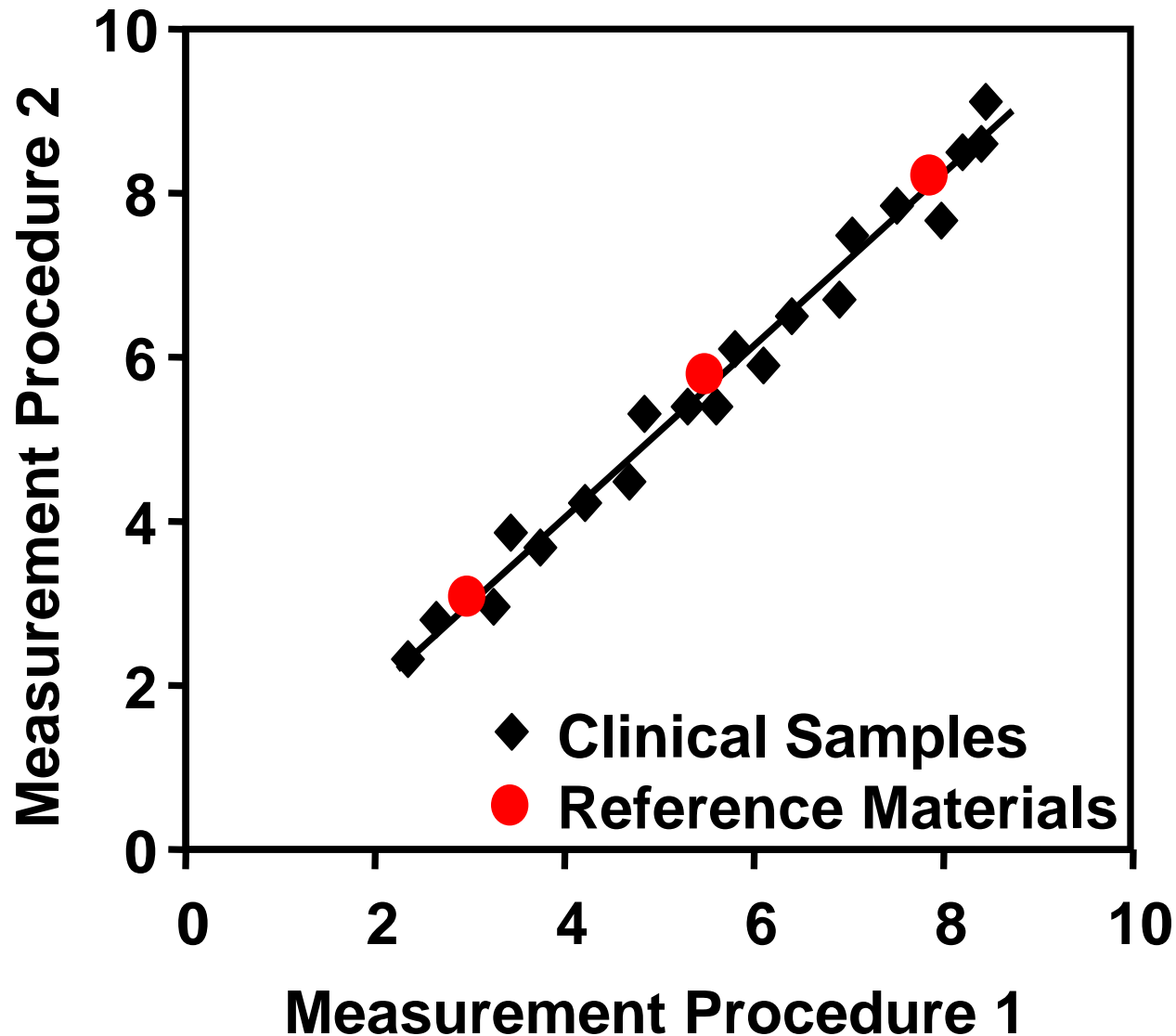
- Calibration traceable to a common reference system
- Surveillance (PT or EQA) to monitor and maintain consistent performance

Problem

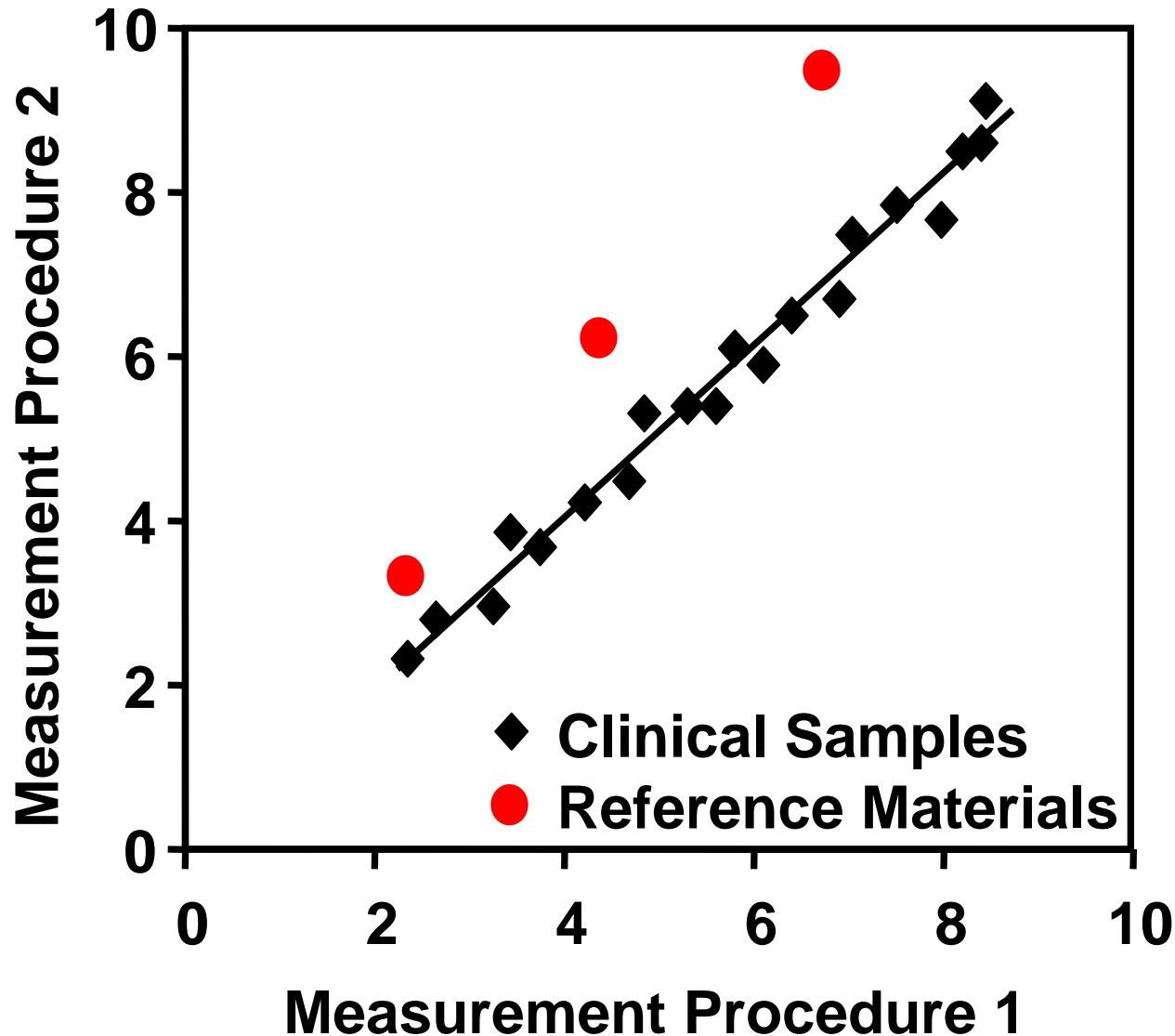
Many reference materials and EQA/PT survey materials are not commutable with native clinical samples for routine clinical laboratory procedures

- Intended for use to calibrate higher order reference measurement procedures
- Commutability has not been validated for use with routine measurement procedures

Commutable: same relationship for clinical samples and reference materials



Non-commutable: different relationship for clinical samples and reference materials



Use of a non-commutable material for calibration traceability will cause:

- Incorrect value assignment for a calibrator
- Incorrect results for patient samples

EQA/PT materials are usually not commutable with patient samples

- Magnitude of a matrix-related bias is unknown
 - ▶ Observed bias = calibration bias + matrix-related bias
- Cannot compare a lab's result to:
 - ▶ Another method's mean value
 - ▶ An all methods' mean value
 - ▶ A reference method assigned value
- Cannot compare mean values between different methods

Traceability of Laboratory Results

Standardization and harmonization are based on traceability principles described in ISO standard 17511. Differences between standardization and harmonization

- Standardization: all measurement procedures get the same result for a sample and the result is traceable to SI with a reference measurement procedure
- Harmonization: all measurement procedures get the same result for a sample when there is no reference measurement procedure

Traceability of Laboratory Results

The standard includes 5 categories of reference systems. There are well established procedures to address standardization of measurands in categories 1, 2 and 3. Category 4 includes measurands for which reference materials are available for calibration, but there is no RMP. Category 5 includes measurands for which neither RMPs nor reference materials for calibration are available.

Standardization

Category	Reference measurement procedure	Primary reference material (pure substance)	Secondary reference material (value assigned)	Examples
1	Yes	Yes	Possible	Electrolytes, glucose, cortisol
2	Yes	No	Possible	Enzymes
3	Yes	No	No	Hemostatic factors
4	No	No	Yes	Proteins, tumor markers, HIV ^a
5	No	No	No	EBV ^b , VZV ^c

Harmonization

^a Human Immunodeficiency virus

^b Epstein Barr virus

^c Varicella zoster virus

Progress has been made!

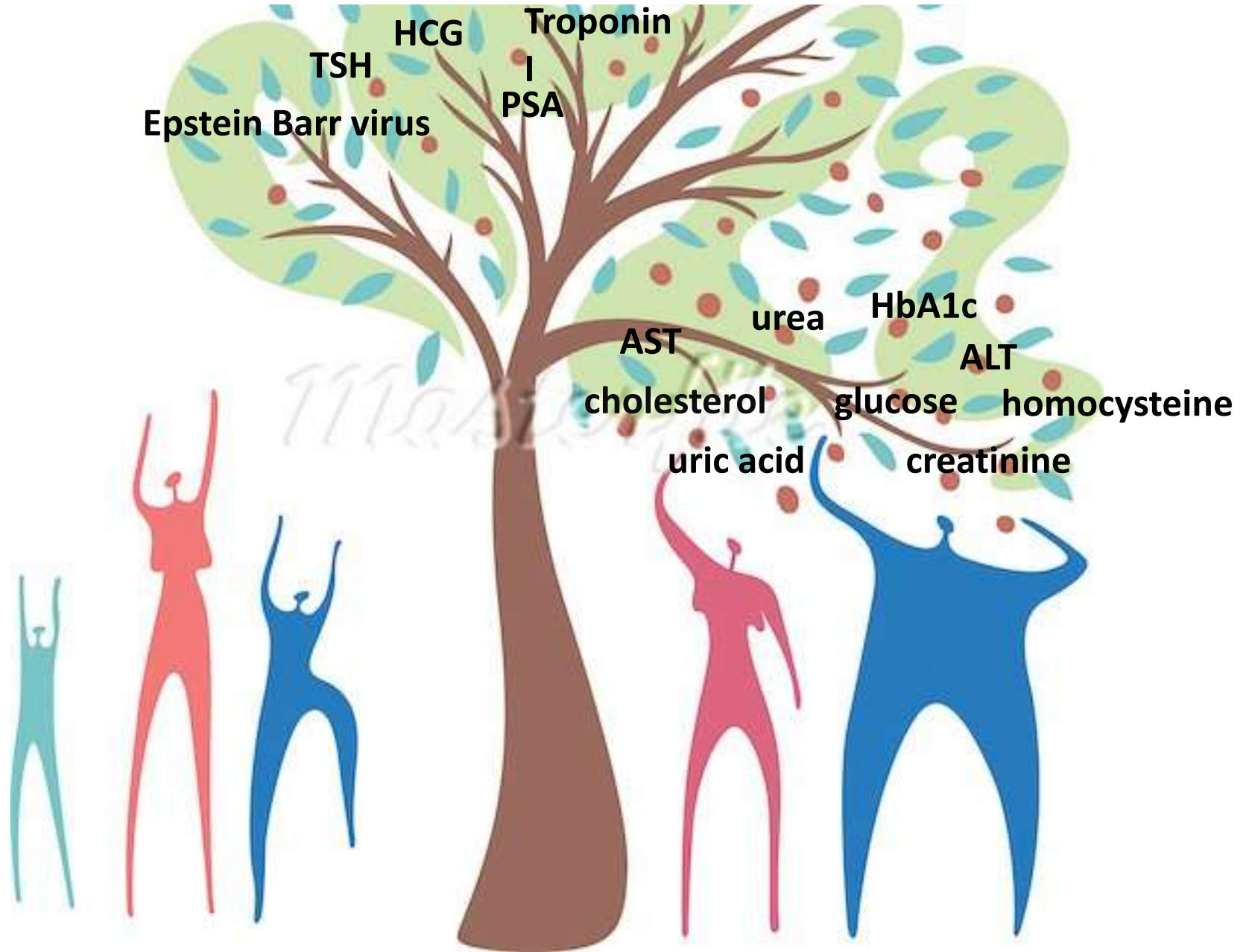
ISO categories 1-3 are being addressed by a number of existing organizations, for example:

- Centers for Disease Control and Prevention
- College of American Pathologists
- Institute for Reference Materials and Measurements
- International Federation of Clinical Chemistry
- Joint Committee on Traceability in Laboratory Medicine
- National Institute for Standards and Technology
- National Glycohemoglobin Standardization Program
- World Health Organization

Progress has been made!

- However, the approach has been ad-hoc based on individual interests
- There has not been a systematic approach to focus on high priority measurands
- ISO categories 4 and 5 are technically more difficult

Picking the low-hanging fruit !



An iceberg floating in a blue sea under a blue sky with clouds. The visible tip of the iceberg is labeled with various organizations and entities. The labels are: CLSI, CAP, IRMM, JCTLM, IFCC, NIST, Industry, NGSP, CDC, and ISO.

CLSI CAP IRMM JCTLM IFCC NIST Industry
CDC ISO NGSP

Measurands for which
reference procedures
exist or can be developed

Barriers to harmonization

- Lack of a systematic process to identify and prioritize measurands
- Lack of commutable reference materials
- Materials labeled as “reference materials” that have not been validated to be commutable
- Inadequate definition of the measurand
- Inadequate analytical specificity for the measurand
- Lack of systematic procedures to implement harmonization when there is no reference measurement procedure

What do we do?



Opinion Paper

Accuracy in clinical chemistry – who will kiss Sleeping Beauty awake?

Linda M. Thienpont*

Challenged clinical laboratories to address the issues associated with harmonization



Prince Harmonization finds the Sleeping Beauty

Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,^{1*} Gary L. Myers,² Mary Lou Gantzer,³ Stephen E. Kahn,⁴ E. Ralf Schönbrunner,⁵ Linda M. Thienpont,⁶ David M. Bunk,⁷ Robert H. Christenson,⁸ John H. Eckfeldt,⁹ Stanley F. Lo,¹⁰ C. Micha Nübling,¹¹ and Catharine M. Sturgeon¹²

**Report from the AACC Leadership Forum, October, 2010:
Improving Clinical Laboratory Testing through
Harmonization: An International Forum**

The Roadmap

Develop processes and procedures for:

1. Prioritization of analytes
2. Gap analysis for what needs to be done
3. Technical process to achieve harmonization
4. Surveillance of success of harmonization

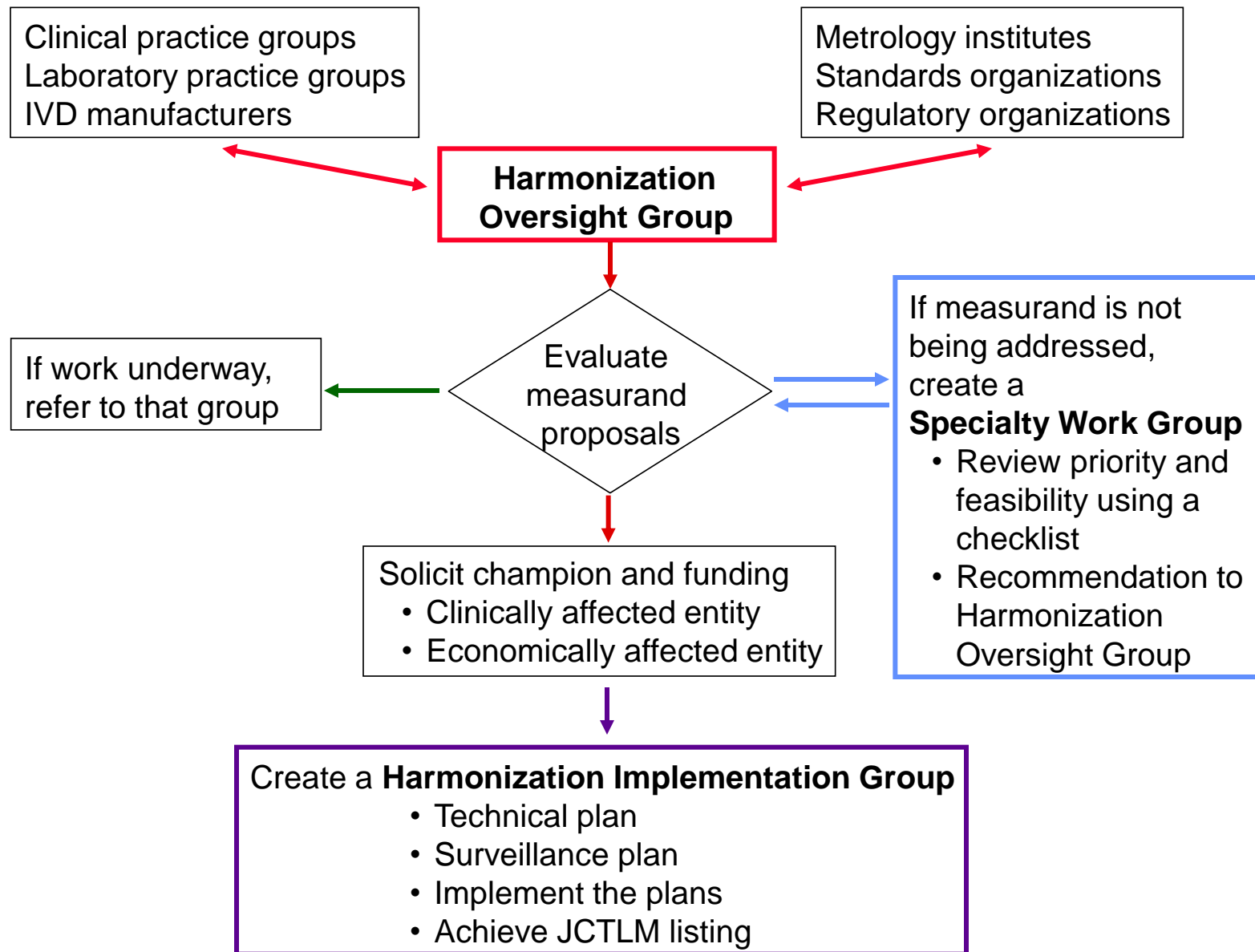
Focus on measurands for which no reference method exists

Measurands in categories 4 and 5 have been technically more difficult to address, thus there have been few effective procedures implemented for harmonization in these categories.

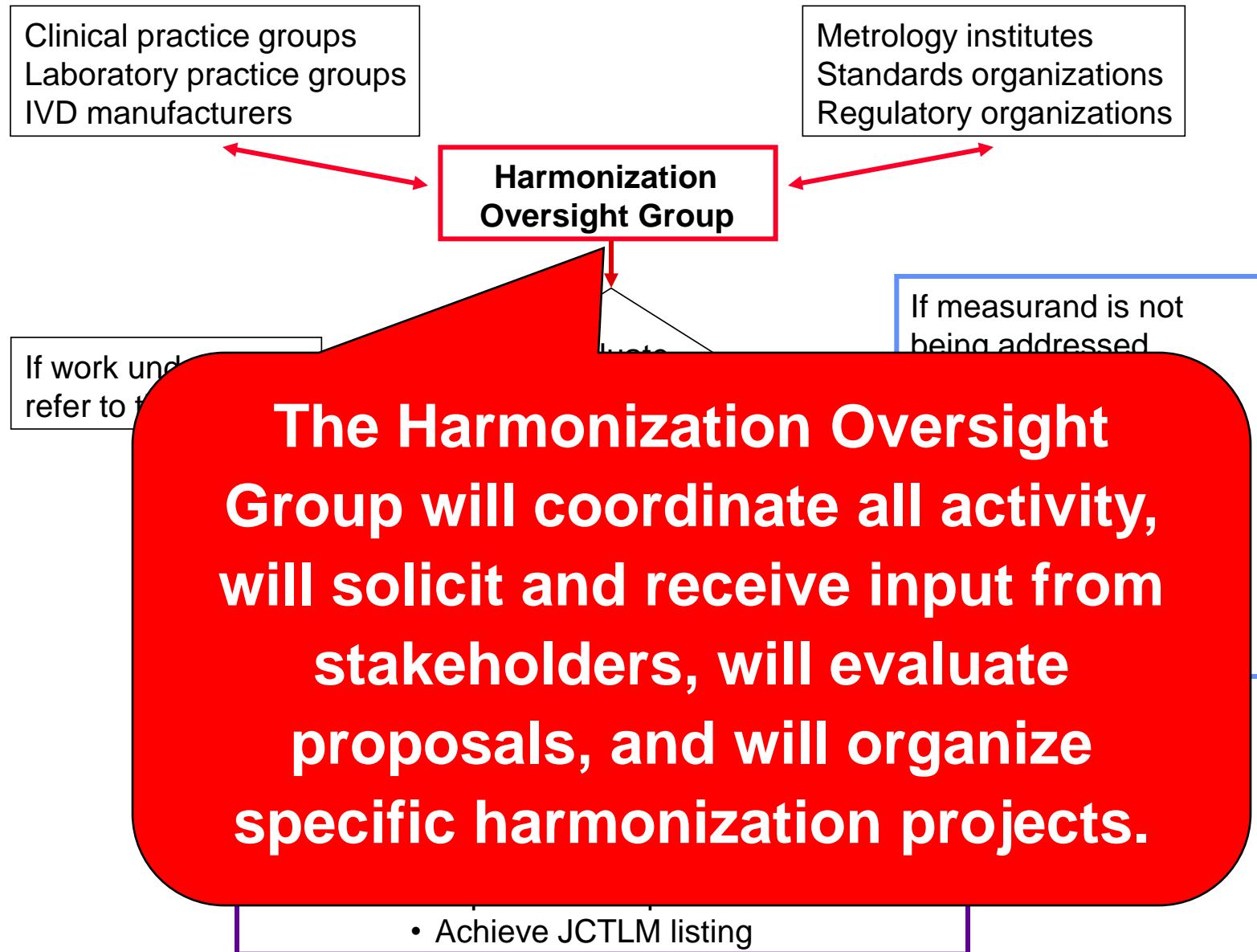
Examples of category 4 and 5 measurands

- Thyroid stimulating hormone
- Troponin I
- Prostate specific hormone
- Human chorionic gonadotropin
- Natriuritic peptides
- Carcenoembryonic antigen
- Leutenizing hormone
- Hydroxylated vitamin D vitamers
- Epstein Barr virus
- BK virus
- Varicella zoster virus

AN INFRASTRUCTURE FOR HARMONIZATION



AN INFRASTRUCTURE FOR HARMONIZATION



AN INFRASTRUCTURE FOR HARMONIZATION

The Specialty Work Group includes experts in clinical use and laboratory measurement of the measurand and will evaluate the clinical importance of a measurand, evaluate the gap between clinical requirements and current practice, and assess the technical feasibility to harmonize the measurand.

Metrology institutes
Standards organizations
Regulatory organizations

If measurand is not being addressed, create a

Specialty Work Group

- Review priority and feasibility using a checklist
- Recommendation to Harmonization Oversight Group

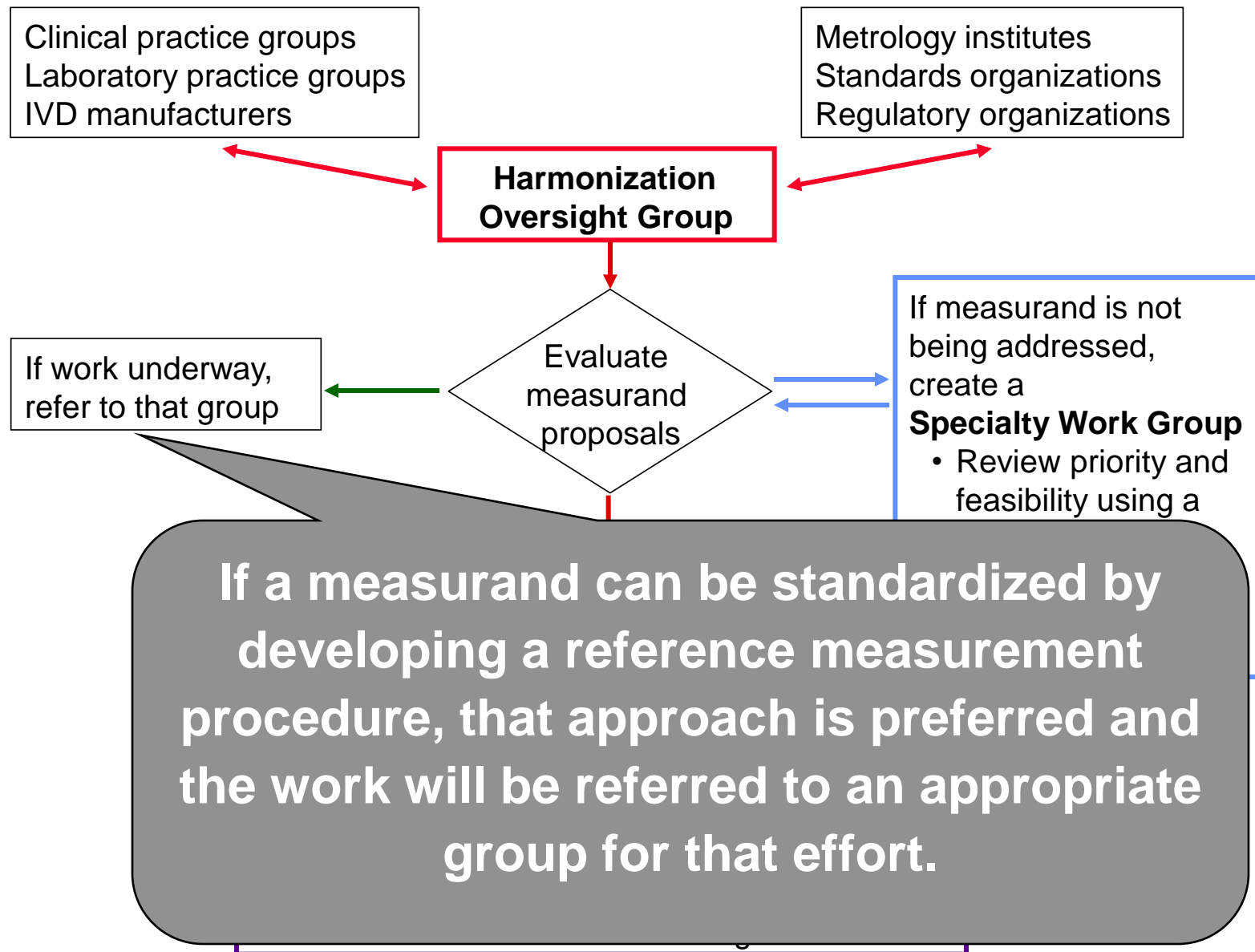
Harmonization Group

- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

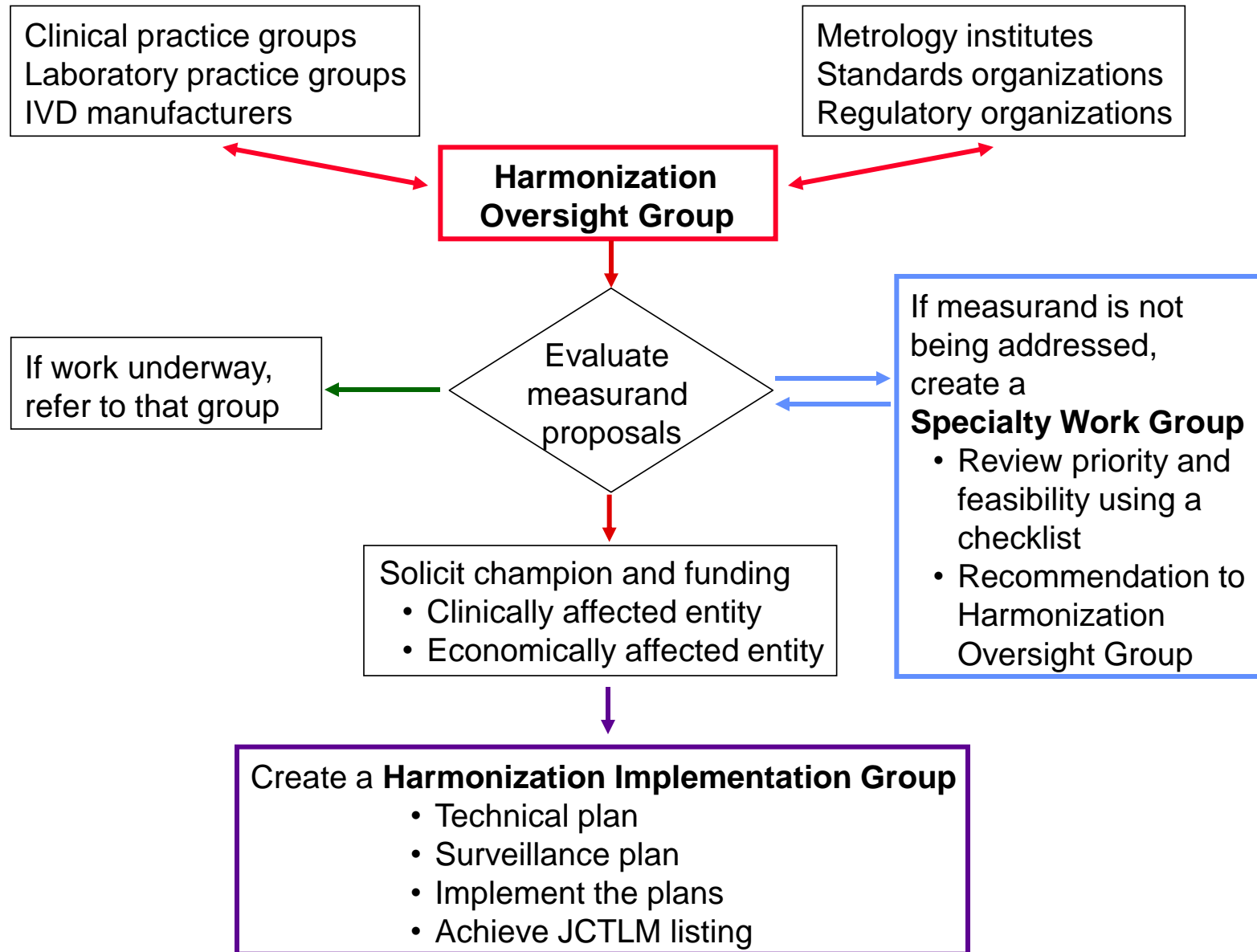
Domains of a Harmonization Assessment Checklist

- What is the clinical need for measurand measurement?
- Do evidence based clinical practice guidelines include the measurand?
- Do clinicians or other stakeholders express concern about the measurand?
- Is the measurand measured in clinical trials?
- Is more than one measurement procedure available for the measurand?
- Do inter- measurement procedure performance characteristics for the measurand fail to meet clinical requirements?
- Is harmonization technically achievable?

AN INFRASTRUCTURE FOR HARMONIZATION



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A Harmonization Implementation Group will manage the technical implementation of a harmonization process for a specific measurand. This group will develop the criteria for acceptable agreement among clinical laboratory measurement procedures, the technical plan for harmonization, any needed reference materials, implement procedures to achieve harmonization, and ensure a process to assess the success of harmonization.

• Economically affected

Oversight Group



Create a **Harmonization Implementation Group**

- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

Role of EQA/PT in Harmonization

Clinical practice groups
Laboratory practice groups
IVD manufacturers

Metrology institutes
Standards organizations
Regulatory organizations

If you are involved in the process, using commutable survey materials, EQA/PT programs will play a key role in providing a mechanism to assess the success of harmonization.

• Economically affected entities
• Oversight Group



Create a **Harmonization Implementation Group**

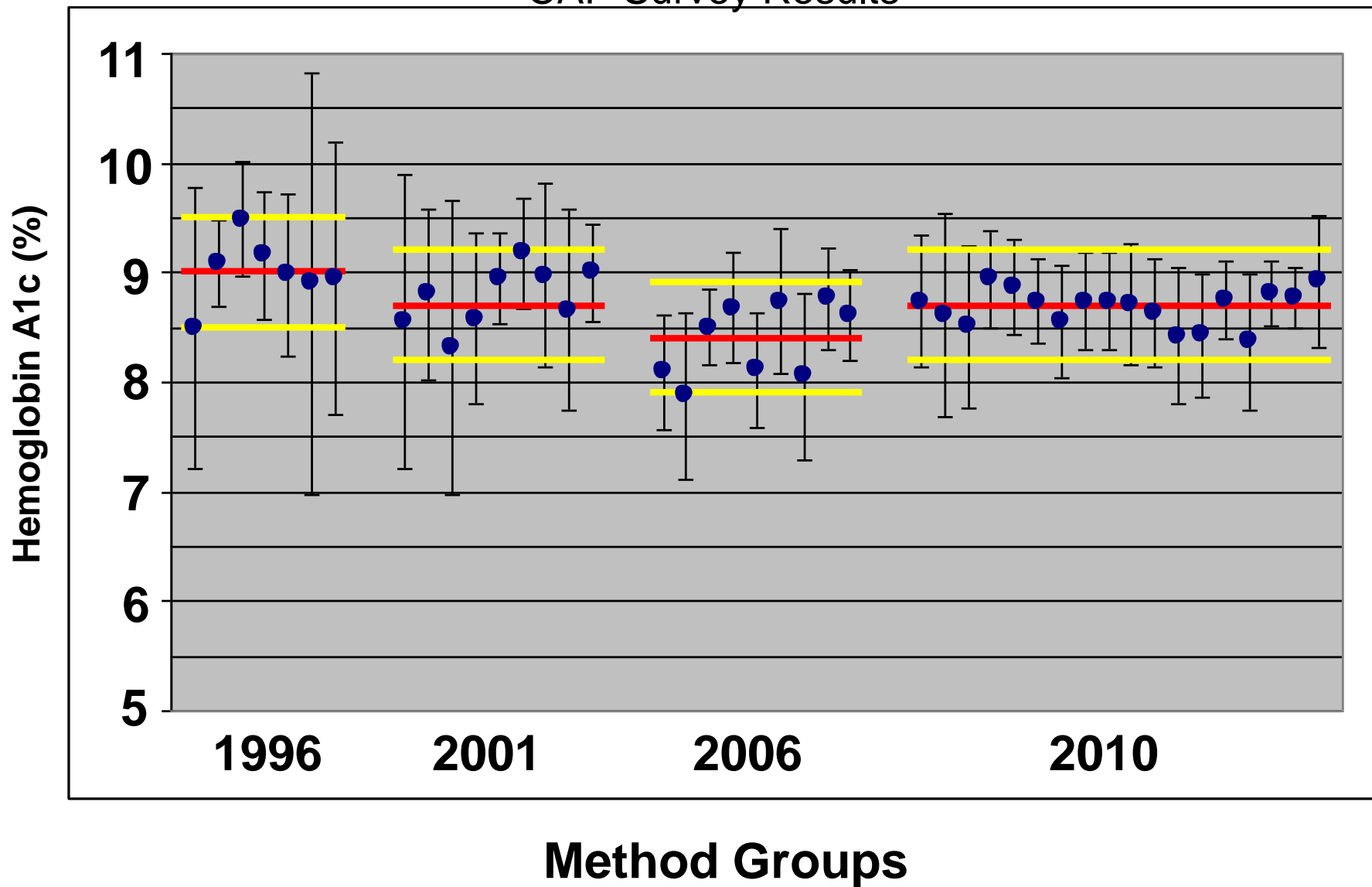
- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

Some EQA/PT programs use commutable samples

- ▶ Samples are typically prepared from freshly collected and minimally processed human samples
- ▶ May be limited to one or a small number of analytes due to availability of samples with appropriate concentrations
- ▶ Can compare results across assay systems
- ▶ Can evaluate success of harmonization and standardization

HbA1c Measurement

CAP Survey Results



Next steps

- A Steering Committee is responsible to implement the infrastructure for harmonization
- 3 Task Forces have been formed to develop operating procedures for the major components
 1. Planning the harmonization oversight group
 2. Developing checklists for prioritization and gap analysis
 3. Developing a tool box of technical processes for assessment and harmonization of measurands

Guiding principles

- Implementation of the harmonization process will require the involvement of international clinical and medical organizations, IVD manufacturers, clinical laboratories, metrology institutes, standards setting organizations, regulatory agencies, and EQA/PT providers.
- An open and transparent process is essential for success.

Guiding principles

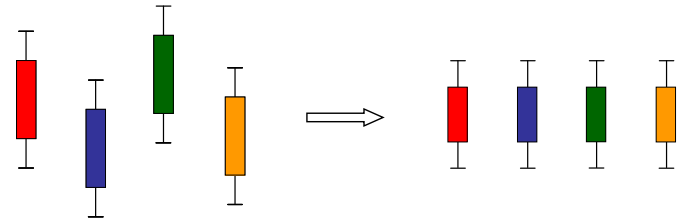
- Long term success will depend on collaboration among stakeholders committed to improving patient care and to providing financial resources required for implementation of harmonization processes.
- The goal is harmonized results that are fit for the intended clinical purpose. Pragmatic approaches will be needed.

www.harmonization.net

- Communication center for the project
 - ❖ Status reports
- General information portal for global standardization/harmonization activities
 - ❖ Useful technical information
 - ❖ Information on all global initiatives
 - ❖ Links to other organizations

Conclusions

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- A global infrastructure and systematic approach for harmonization (and standardization) for all measurands is needed.
- The goal for the Steering Committee and Task Forces is to have an operational harmonization process in place by the end of 2012.
- Implementation of a comprehensive harmonization process will require the involvement and cooperation of all interested stakeholders.

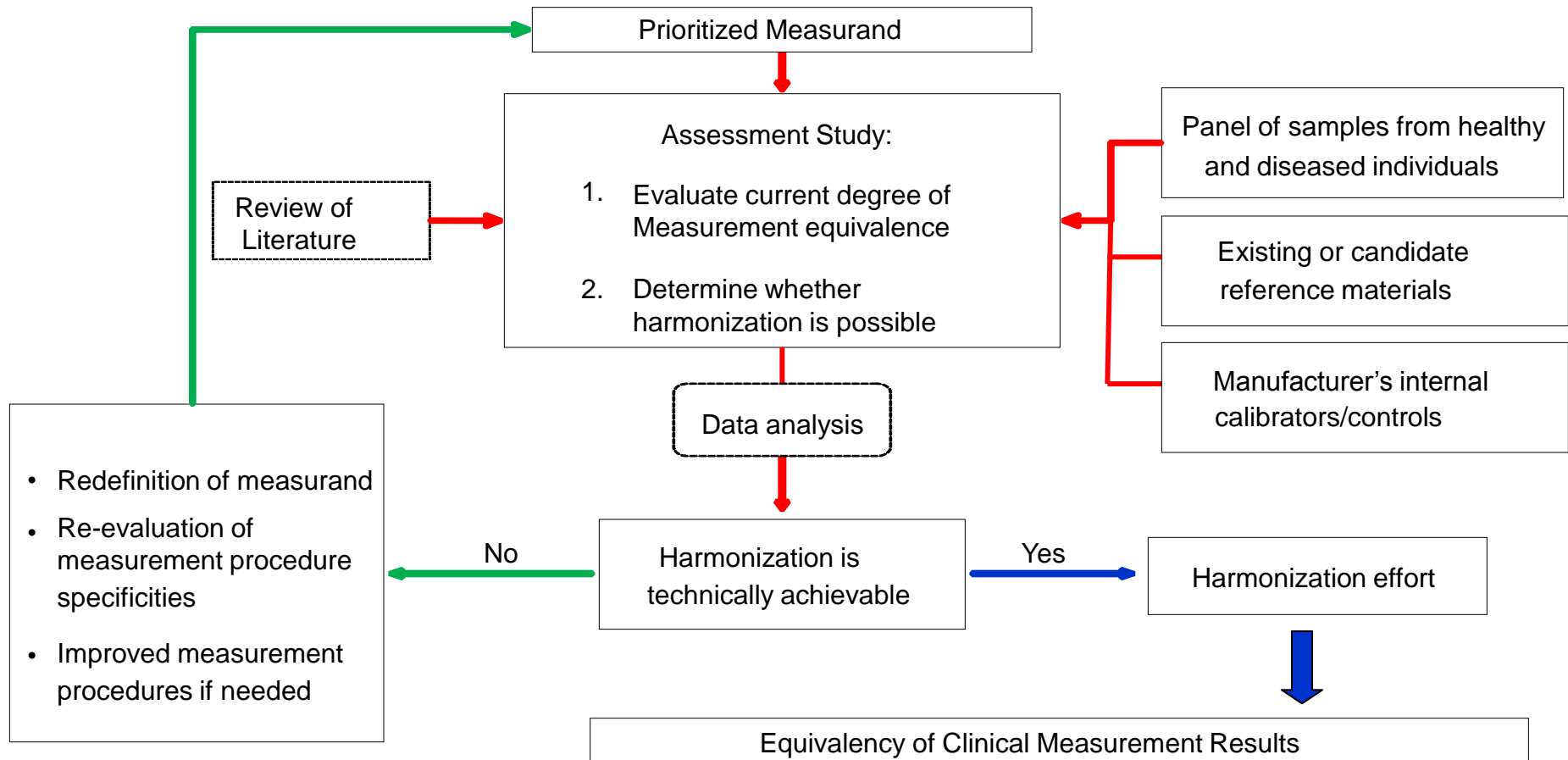
Thank You !

Questions or Comments

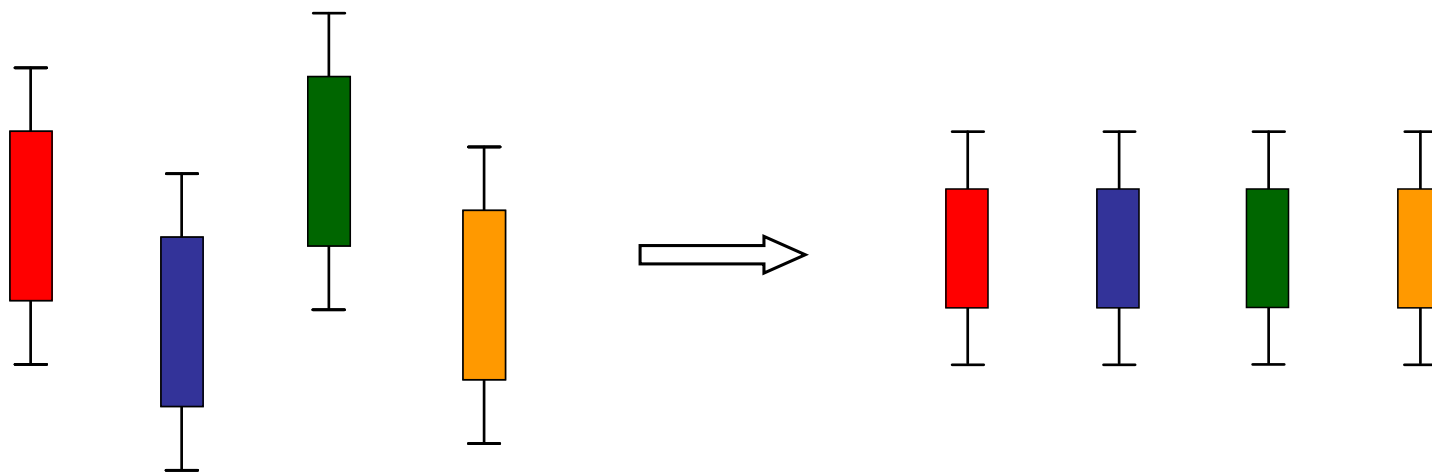


A Strategy for Harmonization of a Measurand

The specifics of any harmonization effort will vary for different measurands. However, a general strategy provides a framework for developing measurand specific protocols.



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Traceability to Système International

