9 July 2021

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Harmonization Study Data Review Update & Roadmap Manuscript

Tim Mercer and Marc Salit
Coronavirus Standards Working Group

What should a Coronavirus Standards Working Group do?

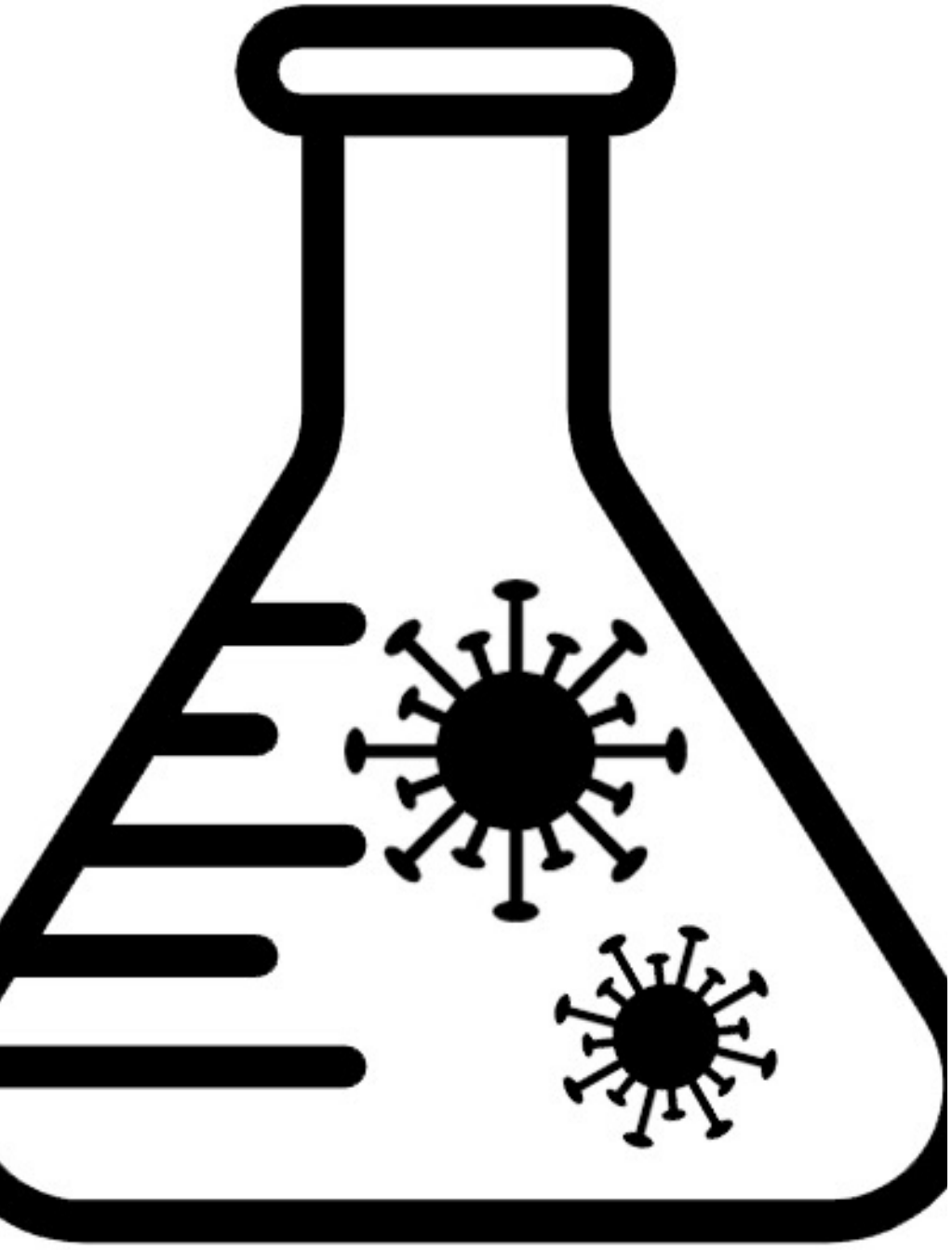
Assure development and availability of standards, controls, interlab testing, knowledge to support successful rollout & scaling of 2019-nCoV testing

Identify and develop critical infrastructure to support…

- confidence in test results
- interoperability
- scale-up
- long-term capacity

Identify best practices that should be institutionalized

Learn what we need to so next time we have a global network in place ready to make standards.



Agenda

Harmonization Study Results

- Value Assignment
- Consistency
- Plan to publish

Roadmap Manuscript

- Outline
- Recommendations
- Plan to publish

Viral RNA Harmonization Study Dashboard Complete!

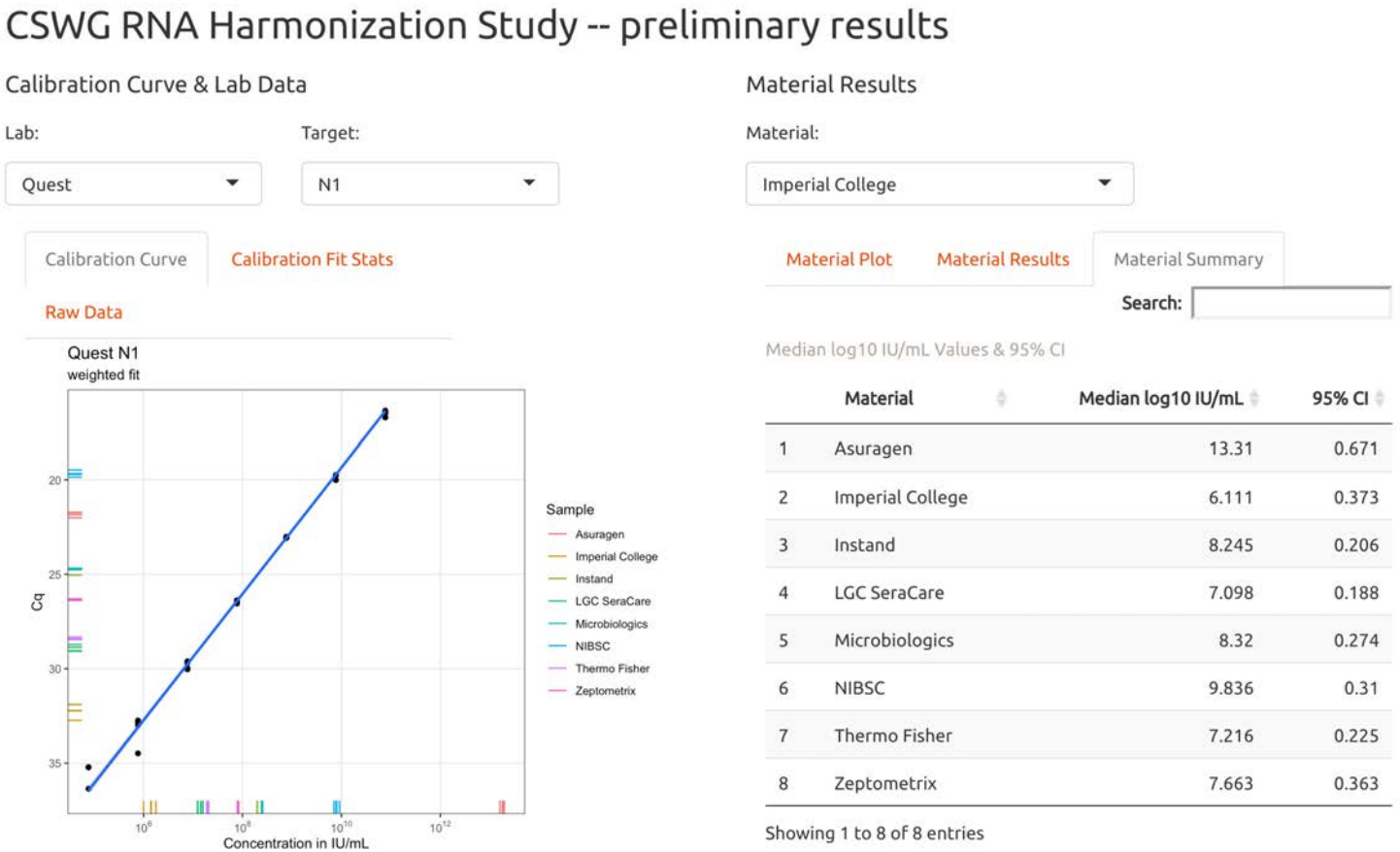
- Data in from 14/14 labs
- Analysis Dashboard refined
- Unitage resolved
- Preliminary value assignment
- Need to review anomalies, establish takeaways, develop manuscript

CSWG Viral RNA Harmonization Study Status

	NIST	NML/LGC	NIB (Slovenia)	Bio-Rad	Western	MUSC	Mayo	Labcorp	Quest	Biogazelle	MassCPR Diagnostics	Stanford Medicine	Los Alamos	biodesix
Panel Received	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Lab Metadata Entry Initiated	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Lab Metadata Entry Complete	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Lab Data Received	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Data Summarized	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Data Analyzed	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑

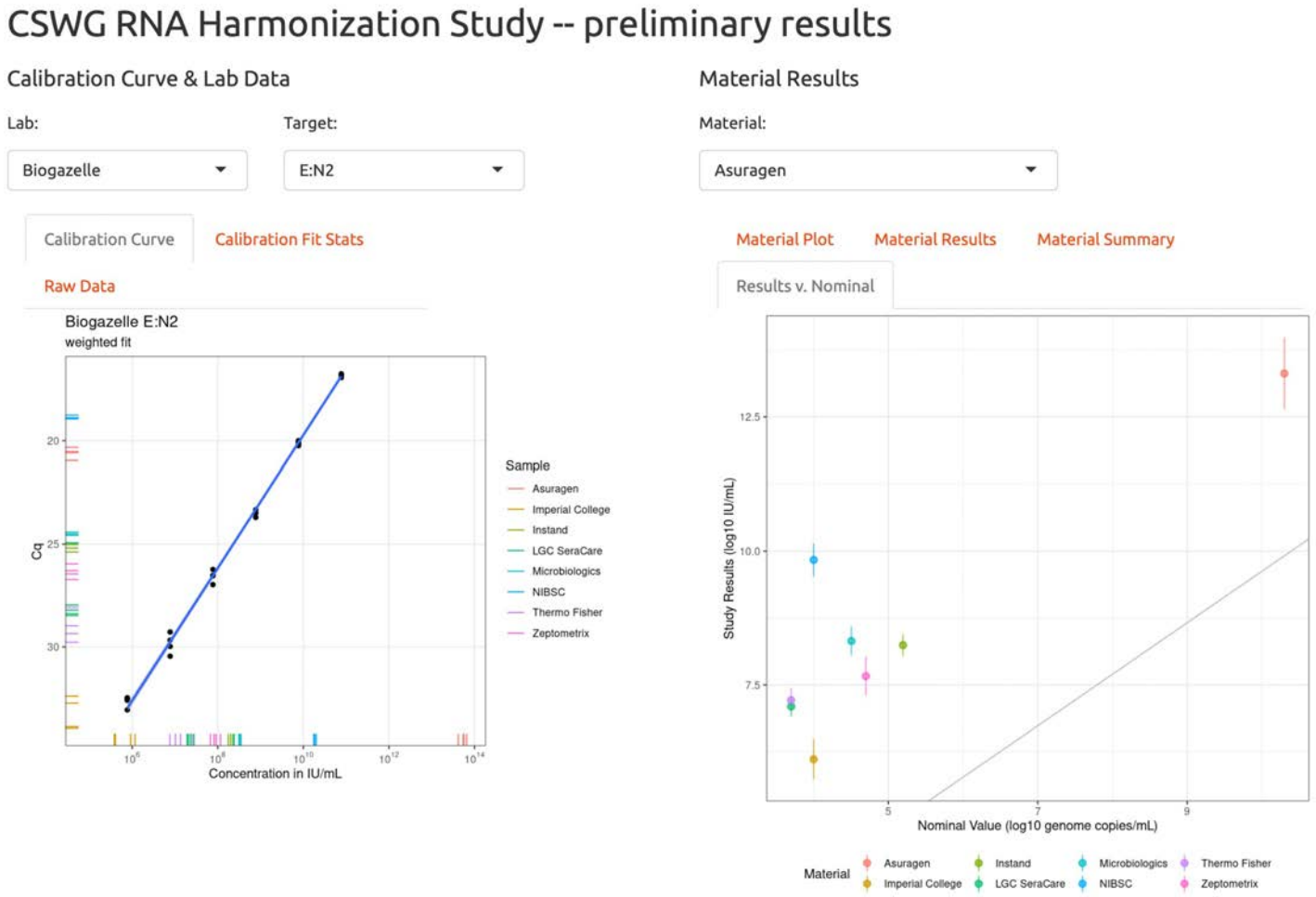
Harmonization Dashboard Updates

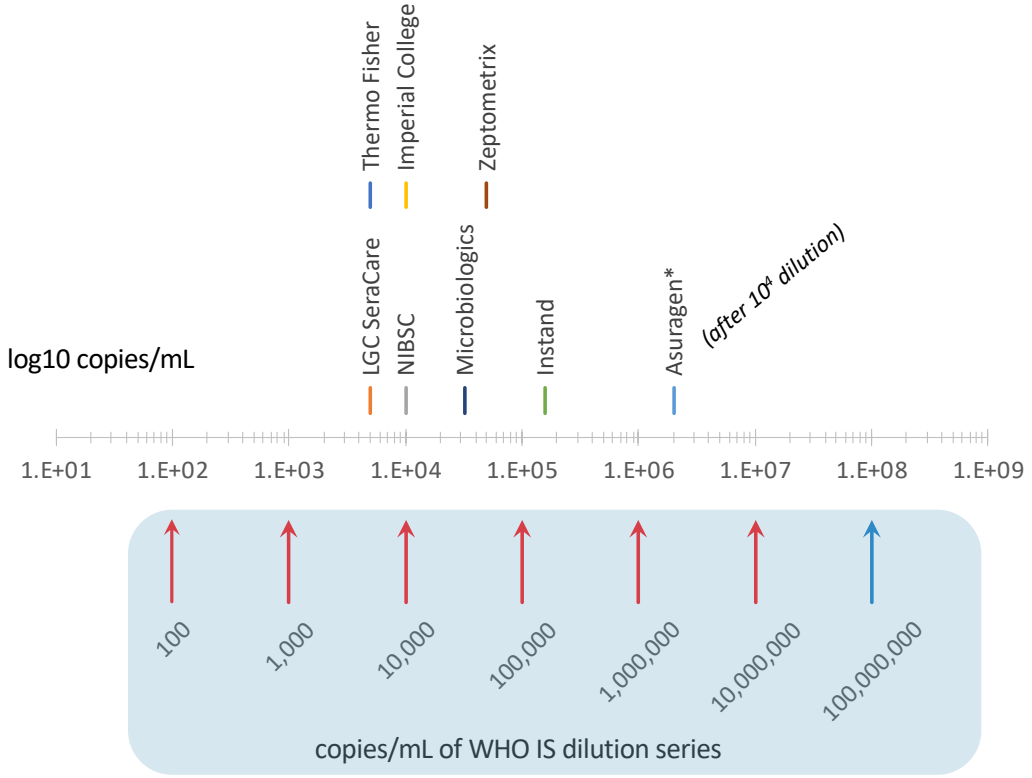
- added data tables for calibration panel
  - calibration results
  - all raw data
- added material summary tab
  - robust ”value assignment” estimates
- fixed unitage
- fixed 2x dilution problem with International Standard value

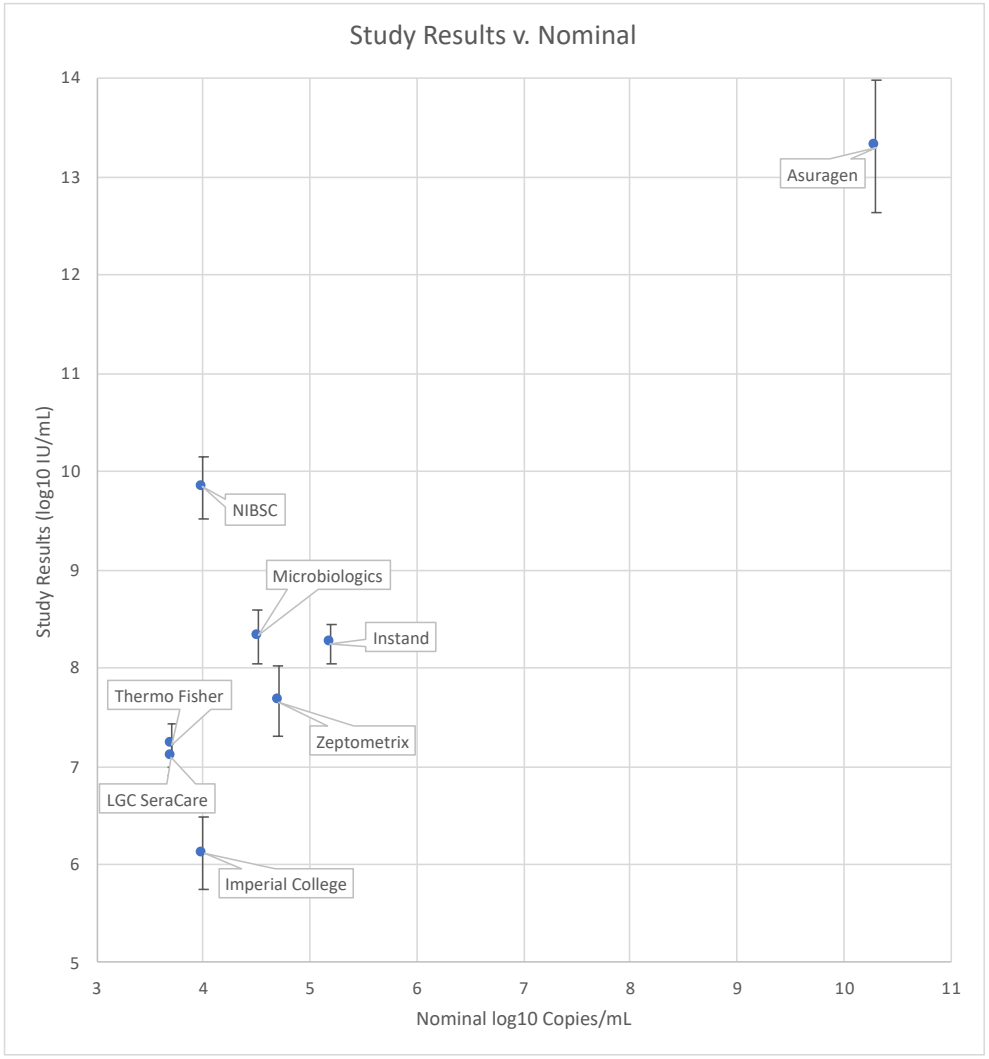


Comparison to nominal values

- added tab with graph of log results v. log nominal
- line has slope 7.7/8, intercept = 0







Nominal material values and study results

Conversion from copies/mL to IU/mL

Medicines & Healthcare products Regulatory Agency

WHO International Standard
First WHO International Standard for SARS-CoV-2 RNA
NIBSC code: 20/146
Instructions for use
(Version 2.0, Dated 05/01/2021)

3. UNITAGE

The assigned potency of the WHO International Standard for SARS-CoV-2 RNA for NAT-based assays is 7.40 Log10 IU/ampoule. After reconstitution in 0.5mL of molecular grade water or PBS, the final concentration of the preparation is 7.70 Log10 IU/mL.

World Health Organization

WHO/BS/2020.2402
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 9 - 10 December 2020

Collaborative Study for the Establishment of a WHO International Standard for SARS-CoV-2 RNA

Emma Bentley[1], Edward T. Mee[1], Stephanie Routley[1], Ryan Mate[2], Martin Fritzsche[2], Matthew Hurley[3], Yann Le Duff[3], Rob Anderson[3], Jason Hockley[4], Peter Rigsby[4], Mark Page[1], Nicola Rose[1], Giada Mattiuzzo[1#] and the Collaborative Study Group[*]

was detected. The inactivation procedure was approved by the NIBSC Biological Safety committee.

To prepare the bulk material, quantification of the SARS-CoV-2 genome copies within the inactivated material was determined relative to a plasmid standard curve by in-house real-time RT-PCR using primer/probe targeting the E-gene [9]. The material was prepared to contain $1x10^8$ genomes per mL and as with the chimeric LVP, was formulated in universal buffer containing a background of $1x10^5$ copies/mL of human genomic DNA.

Next steps on Viral RNA Harmonization Study

review anomalies

identify trends in results

extraction effects from different labs?

develop key conclusions and takeaways

disseminate values

suggest preprint publication

plan to publish manuscript

build a team to develop

- need a lead to do Methods section

Tim and Marc's recent review is on the cover of this month's *Nature Reviews Genetics*

- bringing the band back together again to lead development of the ***CSWG Roadmap*** paper

“A roadmap to better COVID-19 testing from the Coronavirus Standards Working Group”

Introduction

Standards needed for COVID-19 testing

- **Reference materials**
- **Proficiency testing schemes**
- **Information standards**
- *Are we missing anything?*
- *Stories, studies, findings specific to COVID-19 pandemic.*

The COVID-19 testing process.

- **Molecular testing**
- **Antigen testing**
- **Serology testing**
- *What standards are needed used to measure vaccine performance, immune protection in population? - needed for safe recovery*

Genome surveillance

- *What standards are needed for genome surveillance of SARS-*
- *Foresee new standards for the future?*

Concluding recommendations.

- *What did we get right? What did we get wrong?*
- *What can we improve testing/standards now? In the future? The next pandemic?*
- *We want bold, fair and thoughtful recommendations.*

Develop consensus on draft recommendations

Materials

- bring attention to developing standards that underpin *reliability of tests*
  - ***"X-Prize for Pandemic Pathogen Standards"***
- scalable distribution of widely-available calibration materials, controls, and standards of *trusted* quality
- rapid studies to establish traceability to International Unit
- recommend EUA for Standards
- EUAs for Tests should be comparable by using comparable standards to calibrate

Proficiency Tests/EQA

- establish/identify coordinating body for EQA schemes
- recommend ongoing demonstration of EUA test comparability with EQA
  - address limitation of EUA by demonstrating field performance of authorized tests

Minimum Information Standards

- about a control – standardize information on how to use this control accurately
- about a test – standardize information about a test and how to use and interpret results accurately

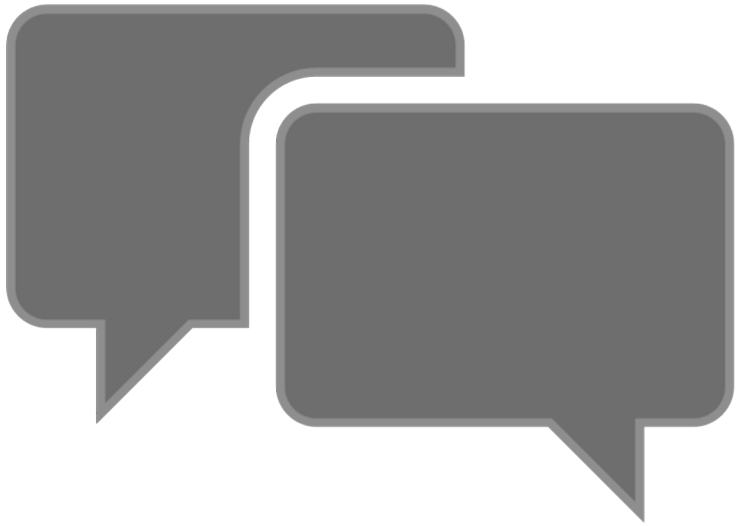
Develop consensus recommendations

- Scalable distribution of widely-available calibration materials, controls, and standards for tests
  - oversight/evaluation/authorization of these standards
    - this could be an “EUA” for standards
  - calibration of these standards against the International Standard when it becomes available from WHO

- EUAs for tests should be calibrated with standards that have a provenance
  - standards that can be compared across EUAs
  - this would be a way to make EUAs comparable

Next steps

Timeline	• share draft today • contributions by 26 July
Protocol for contributions	• shared Word Doc • shared Google Doc
Google sheet for authorship	• Name, Contributions, Affiliation(s), COI



Discussion