We are delighted to invite your participation in the Coronavirus Standards Working Group (CSWG) Harmonization Study. The CSWG has been working since March 2020 to ensure that the standards, controls, and validation tools are in place, so we rely on the accuracy of test results. We are an open, public group with participation from organizations building the testing technology, organizations making the standards and controls, professional societies representing the scientists and testing labs, public health agencies, regulatory agencies, national measurement laboratories, and international standards bodies. More information is at https://jimb.stanford.edu/covid-19-standards.

Our Harmonization Study will establish the equivalence of SARS-CoV-2 RNA target concentrations across a panel of materials and calibrate those results against the candidate WHO International Standard (IS) reference sample. Those materials included in the study will have a basis to assert traceability of their viral RNA concentration levels to the value of the WHO IS. All data and results will be made publicly available without embargo, as soon as the results are validated. Following studies from the CSWG will employ these materials to develop benchmarking and validation kits.

This study is not a comparison of tests or of labs. This study is not a survey of test or method performance for limit of detection, precision, repeatability; it is not a study of commutability. This study will not evaluate material homogeneity or stability.

The study will analyze measurement results from approximately 10 established laboratories representing leading clinical labs, test developer labs, and national measurement institutes. These labs will measure a panel of approximately 10 different SARS-CoV-2 viral RNA preparations that are widely available and used as standards and controls. The preparations will include inactivated virus samples, recombinant virus samples, and recombinant bacteriophage samples, all suitable as full-process controls that can be extracted as a mock clinical sample. Measurements will include RT-qPCR and digital PCR methods, and will employ standards (e.g. MIQE) and best practices in reporting protocols, conditions, experimental factors, and results.

We will establish an open, public repository for the data, annotation, methods, and analysis of the study. The design of this resource will accommodate distribution of information to, as well as collection of the study questionnaires and results from the participants.

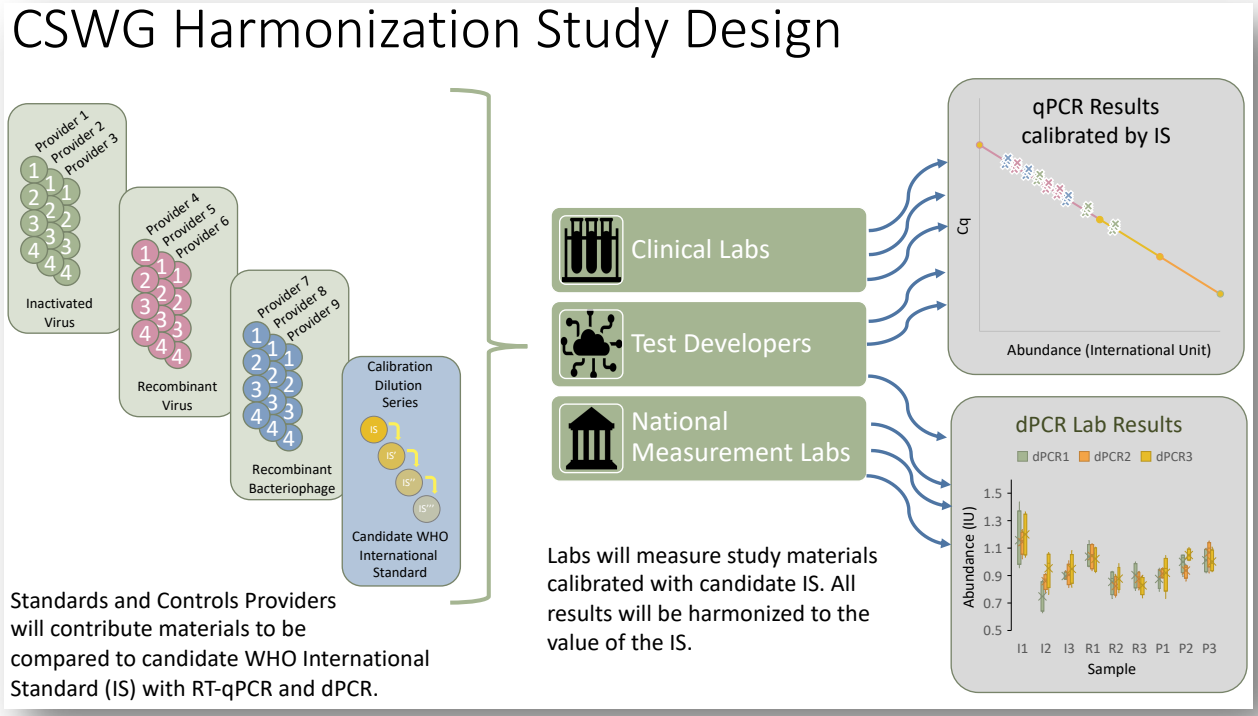
The CSWG has 3 teams developing and operating the study, supported by Marc Salit, Director of the Joint Initiative for Metrology in Biology (JIMB) who is the CSWG founder. The teams are:

- Sample Planning Team
    - Russell Garlick, LGC SeraCare
    - Hui Wang, ThermoFisher Scientific
- Lab Planning Team
    - John Sninsky, Stanford SPARK
    - Sebastien Fuchs, Western University of Health Science
- Design/Analysis/Reporting Team
    - Jim Huggett, CCQM Nucleic Acid Working Group
    - Sasha and Sarah Zaranek, Curii
    - Clare Morris and Mark Page, NIBSC

(all named, please check accuracy and affiliations!)

Study Design

Each laboratory will measure 4 samples from each participating material provider, each provided as a "catalog product" in the packaged vial as would be received by a typical user. *(do we want to include some sort of material-provider NTCs??).* Each lab will also measure a dilution series of the candidate WHO IS that will be provided by the National Institute of Biological Standards and Controls (NIBSC), who are developing the IS. *(what multiplicity will the calibration curve be measured with? triplicates?)*



The study protocol will include recommended replication design of measurements and plan to measure "no-template control" materials. (To Be Specified). A recommended dilution protocol will be included to assure sample levels are in range for the lab's method. (is this how we'll proceed??? clinical labs are doing qualitative "yes/no" tests)

Materials Providers

Participating material providers will provide free-of-charge 64 samples of a catalog SARS-CoV-2 standard or control material in Viral Transport Media matrix. Documentation will be provided in the style of a "Certificate of Analysis" and an "Instructions for Use" description to provide best guidance on handling and accurate use.

Please notify the study planning team if any details are inconsistent with your material or your ability to supply it as described – let's work out any inconsistencies!

Measurement Laboratories

Participating labs will receive the materials and documentation, will document all protocol elements, and measure the samples. Labs will provide results for each tube of each materials, and report both the measurement results and a MIQE-compliant, detailed description of the step-by-step protocol in a provided form and questionnaire (ideally on-line in the to-be-developed CSWG Data Repository).

Please notify the study planning team if any details are inconsistent with your ability to carry out the study as described – let's work out any inconsistencies!

Logistics

Logistics for this study will be managed and operated by the JIMB labs, with David Catoe leading. JIMB will receive the materials from the providers, assemble panels, and distribute the panels to the participating labs. Preliminary knowledge of the candidate panel materials indicates various recommended storage conditions; JIMB will develop a plan to manage this, and work with the participating providers and labs to assure feasibility and practicality.

What should the CSWG and the participating labs expect?

At its best, this study will build the bridge for traceability of measurement results to the WHO International Standard Unit for those materials studied. The scope of traceability would be straightforward to extend beyond the study materials by new comparisons. This will be valuable to the global SARS-CoV-2 molecular testing enterprise.

Our study design will yield knowledge of some of the sources of variability in viral RNA abundance measurements; while it is not a comprehensive quantitative assessment of all sources of bias and variability, our results will establish practical, fit-for-purpose, *useful* comparability amongst materials and establish traceability to the new IS.

Participating labs will get a sense of their performance in a small population of specialized labs, and may be able to identify artifacts or biases, and better be able to optimize methods and procedures.

The CSWG will have useful experience and demonstration of our ability to coordinate work across the working group, and we will have developed an "interoperable" suite of materials we can use to develop new kits to do test benchmarking and validation. We will have a model for further work in developing standards for molecular testing, and a basis to extend to antigen or serological testing as we proceed.