MULTIPLE BREATH NITROGEN WASHOUT TESTING: SITE TRAINING AND QUALIFICATION REQUIREMENTS

The University of Queensland Child Health Research Centre, Brisbane, Australia

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MBW Central Training and Over-Reading Centre

The Centre at The University of Queensland Child Health Research Centre (UQ CHRC) is the Australasian hub of the existing central over-reading centre (CORC) network comprising additional sites in North America (based at Hospital for Sick Children, Toronto) and Europe (based at the Royal Brompton Hospital, London). The CORC has long-standing experience in MBW, as evidenced by the role of the Director (Prof Paul Robinson) in previously published international MBW standardization guidelines and the subsequently developed $MBWN_2$ Standard Operating Procedure (SOP) manual. Training for MBW occurs as an intensive training course and qualification process based on the procedure outlined in this document to facilitate standardized data collection for multi-centre clinical trials. It is delivered using an online platform and, if feasible at the time of training, a hands-on face-to-face training course, based on the approaches outlined in the current SOP testing manual. Given the previous challenges of travel restrictions during the period of heightened COVID concern, the ability to deliver the entire training using an online platform approach was also developed.

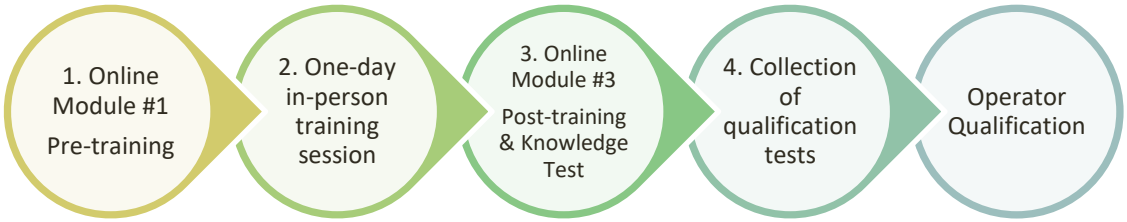
For qualification inquiries please contact: MBWCentre@uq.edu.au

$MBWN_2$ Training Session

Operators who will perform MBW measurements on clinical trial study participants should register to attend either an in person MBW training session or virtual MBW training session.

In-person Training:

An overview of the in-person training program is shown below.



Operators participating in in-person training will attend a one-day, hands-on training session held in Brisbane. Prior to attending in person, participants should complete the online MBW Pre-Training module. *Please note*: some of the material presented in the online module will **not be** covered again during the one-day training session. Operators will be given the link to complete the Post-training online module after attending in-person training.

Virtual Training:

In an effort to continue $MBWN_2$ training during the COVID-19 pandemic the North American, European and Australian MBW central over-reading centres (CORCs) developed a virtual alternative to in-person MBW training. An overview of the virtual training program is shown below.

Trainees participating in the virtual program must first complete the Pre-Training online module. In-lieu of the in-person training session operators will independently review a virtual MBW training online module and attend a live webinar hosted by their regional CORC (highlighted in red above). Operators will be given the link to complete the Post-training online module after attending the regional webinar. While most of the training can be conducted remotely, sites must also have in person access to their Exhalyzer® D MBW device.

Please Note: This virtual training format is NOT the standard for moving forward. In-person training will resume once regional travel is feasible.

$MBWN_2$ Post-Training Knowledge Test

Upon completion of the Post-Training online module all operators are required to complete the Post-Training knowledge test (80% pass mark required) within **2 weeks** of attending the in-person training session or webinar. The knowledge test should be completed before MBW qualification tests are collected.

$MBWN_2$ Qualification Tests

MBW test feasibility improves as operators gain experience testing the target study population. After attending the training session and completing the knowledge test, each operator should perform qualification MBW tests to demonstrate ability to collect technically acceptable MBW data. Each operator is required to submit *a minimum* of 5 qualification test occasions. *Qualification tests are required to be submitted within **3 months** of attending the training session.* To be certified, 80% of

submitted trials (i.e. 4/5) must be deemed successful tests, and the successful tests must include at least two subjects with Cystic Fibrosis and at least one subject in the age range being recruited for the study.

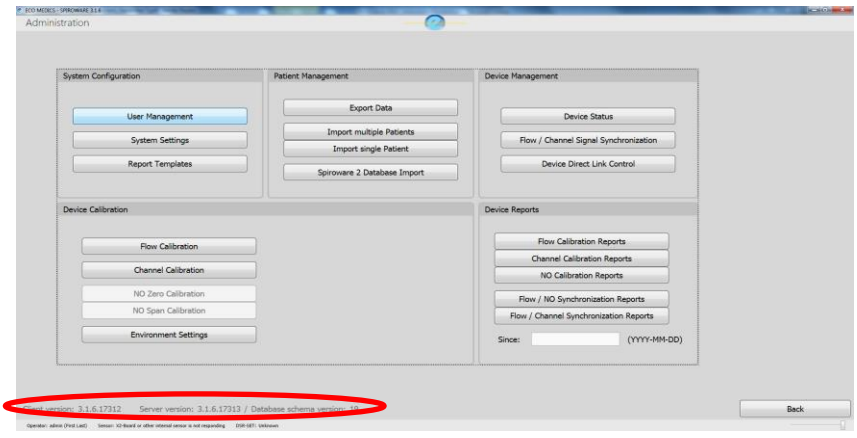
Qualification Subject Population – Who to test?

Sites should test both healthy volunteers and subjects with a confirmed diagnosis of CF. In general these subjects should include subjects representative of the study population (i.e. adult or pediatric). This ensures valuable experience in testing the age group being recruited for the intended study.

Protocol for Qualification Tests

1. $MBWN_2$ device operation and data collection should be performed according to the MBW working group SOP. Test occasions collected previously, and not tested to current SOP guidelines will not be accepted.
2. The Spiroware version specified in the study protocol must be used
    1. Version 3.1.6.17312/3 (May 2014) has been used in many studies to date
    2. Version 3.3.2 may be used in selected new studies
3. Each test occasion submitted should represent a discrete subject.
4. Sites should aim to collect 3 good quality trials per test occasion.
5. Poor quality trials should be excluded from summary results by the operator.
6. Data collected for studies that have been over-read by the CORC cannot be used as qualification test submissions

The Spiroware version can be found at the bottom of the Administration menu.



Successful Test Occasion

A successful $MBWN_2$ test occasion will consist of two acceptable trials. Acceptable trials are defined as trials having:

1. No evidence of leak
2. No evidence of coughing, laughing or talking
3. No evidence of signal misalignment
4. No evidence of inadequate time between trials
5. Clear satisfaction of end of test criteria
6. Grossly normal tidal breathing pattern*

*Sites should aim to demonstrate ability to encourage subjects into breathing in a relaxed tidal breathing pattern during the pre-washout and washout phase of testing. Only trials with grossly distorted breathing pattern will be deemed unacceptable for breathing pattern alone.

Site Feedback

Feedback to sites will include comments and suggestions aimed to emphasize and support good practice and offer suggestions on improvement. Feedback will be provided to the sites on the quality of each transmission **within two weeks (ten) business days of receiving files in the correct format (see Appendix 1).** The MBW Centre will request by email that sites re-transmit MBW data if data submitted requires correction. Reasons for data correction include 1) Signal misalignment 2) System settings are incorrect and 3) File naming is incorrect. The ten business day window will re-commence upon receipt and download of corrected data.

Unsuccessful Qualification

If the operator does not meet qualification requirements on the first attempt, they will be asked to submit 5 additional $MBWN_2$ qualification test occasions for evaluation. 4/5 additional $MBWN_2$ qualification test occasions must be successful for the operator to be qualified. The additional test occasions should be collected by the site operator whose original submissions were unsuccessful. Under circumstances where additional traces are also unsuccessful, further training may be required. This will be addressed on a case by case basis.

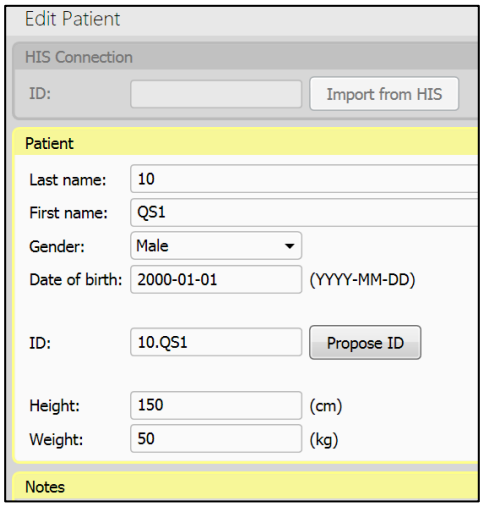
Training and Certification of additional operators:

Only certified operators will be qualified to perform MBW measurements for the subsequent clinical trial. Any new operator can register for an upcoming training session if subsequent ones for the study are scheduled to occur. Dissemination of training materials to new operators within a site is up to the discretion of the site. Additional operators may only be trained by a trained and certified operator, who is experienced in testing and has demonstrated thorough understanding of test procedure through a record of successful testing during subsequent clinical trial testing. New operators who are trained by an

existing operator at their site must submit 5 additional qualification test occasions with 4/5 successful test occasions in order to become certified for testing in the clinical trial. Qualification tests may be submitted to the central over-reading centre at UQ CHRC (by the process outlined above) at any time.

Appendix 1. Spiroware File Naming

Only de-identified subject files can be submitted to the central site for over-reading. Studies submitted as $MBWN_2$ qualification tests should use the following naming scheme:



- Last Name: Site Number
  - Site number will be assigned by the central over-reading centre if not already assigned by the study sponsor.
- First Name: Qualification Subject Study Number
  - Please assign each qualification subject a discrete study number (ie. QS1 – QS10)
- ID: Site Number.Qualification Study Number (e.g. 10.QS1)
- Date of birth: please enter as accurately as IRB allows.
- Height and weight: please enter accurate measurements from day of test
  - obtain measurements as you would for a study participant

If you do not have a Qualification Subject Study Number, please email the UQ CHRC MBW centre

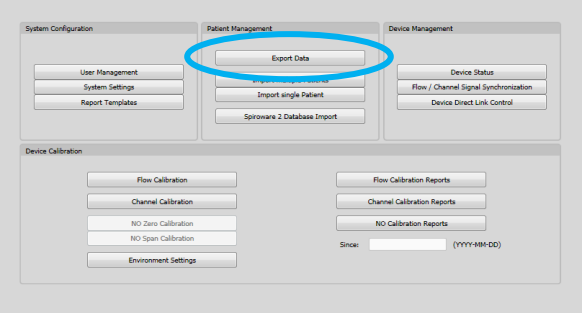
Appendix 2. Data Export

Sites must confirm Spiroware software version PRIOR to exporting subject files. (See Appendix 1)*

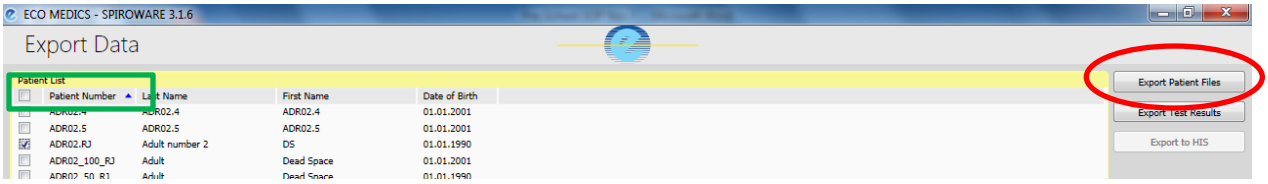
*Any site who does not have this software version should contact the Australian or New Zealand distributor for Ecomedics AG (Ascencia) for this software update.

*****Files must be saved as DRAFT prior to export*****

Select **Export Data** from the administration menu of SPW.



This will bring up the entire patient list; all files are selected by default. If you do not wish to export all patient files in the database uncheck **Patient Number** (square) and then select the files you wish to export.



- Select **Export Patient Files** in upper right corner of the Export Screen (circle).
- Select a pre-existing folder or make a new folder to store exported .spx files and press ok.
- Once complete a confirmation will appear in the **Export Log** at the bottom of the export data page.

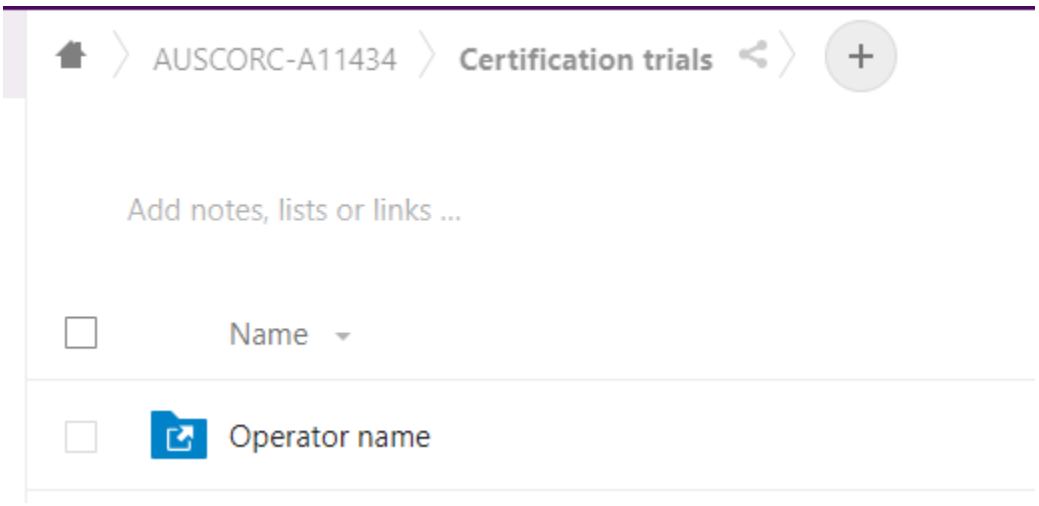
Once export is confirmed the operator should ***log out of local*** Spiroware account.

Appendix 3. Data Transfer

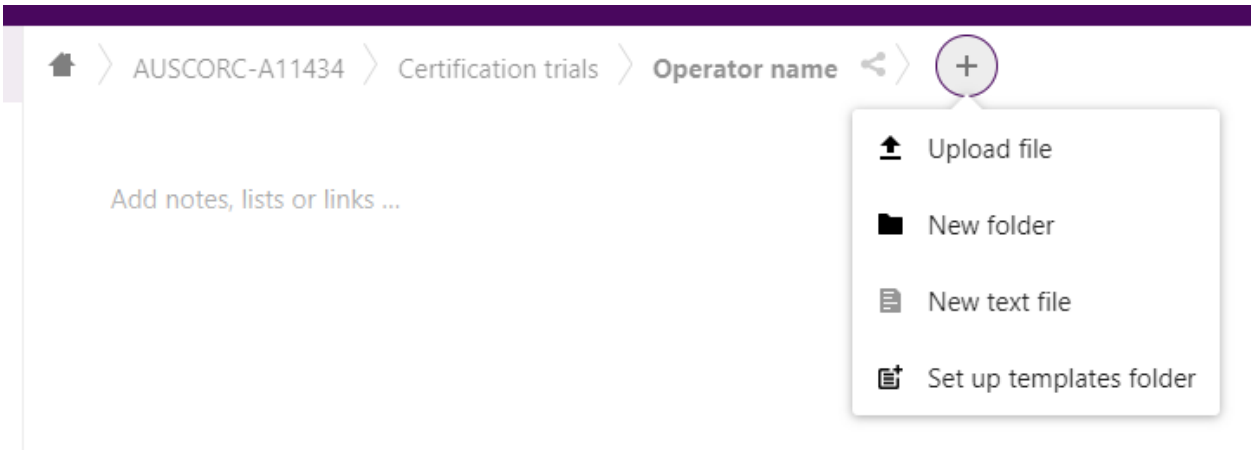
Exported .spx/.spe files from all sites will be submitted for over-reading via a secure Research Data Manager (RDM) site hosted by the Australian CORC at The University of Queensland.

Study Data Submission Process – UQRDM Record

- Please contact the AUS CORC to request the set up of a link to the RDM
    - The MBW Centre at The University of Queensland will set-up an RDM access for each operator.
    - This requires the e-mail address of the designated operator from each site. Please provide this to AUS CORC.
- Upon creation of access to the RDM, an email containing the link will be generated to the designated user. This email will be sent from the UQ Research Data Manager.
- Once accessed you will see the following



- Within this folder you will upload your certification .spe/.spx files as per the image below
- Files can be uploaded by clicking on the "+" button and then clicking "upload file"



Once you have uploaded the complete set of certification trials:

- Please send an email to the address below to notify the site of the file submission
    - mbwcentre@uq.edu.au