## Appendix A: Standard Operating Procedure for Spirometry

Baseline and final visit lung function assessment will be performed at the UCLA Exercise Physiology Research Laboratory. All subjects performed forced spirometry maneuvers on Vmax spirometry to assess baseline and final lung function and all subjects were asked to perform both forced and slow spirometry including inspiratory capacity (IC) maneuvers using SpiroPro® (eResearch Technology. Philadephia, PA).

Spirometry will be performed in accordance with the new ATS/ERS standards. Testing will be performed by a certified pulmonary function technologist with the patient in the seated position with a nose clip applied after the subject has rested for at least 10 minutes. Forced expiratory maneuvers will be performed at least in triplicate with the minimal requirement that at least three maneuvers are “satisfactory”. The best two maneuvers will meet criteria for repeatability for forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), i.e. both the FVC and the FEV1 measurements agree within 150 ml. Spirometric measures will be repeated, if necessary, up to a maximum of eight times in an attempt to achieve both satisfactory and repeatable results.

In programmable portable spirometry device, SpiroPro®, the acceptability and repeatability of the tests will be graded according to table below. Subjects will be informed by these messages to improve their next maneuver.

Slow inspiratory maneuvers will be performed using the criteria described in Figure 1 aiming for three acceptable tests with the difference between the two best IC values being ≤100 ml. The acceptability and repeatability of the tests will be graded according to Tables 1 and 2.

**Table 1**. Quality control messages (acceptability criteria) for forced vital capacity maneuvers

|  |  |  |
| --- | --- | --- |
| **For Acceptability criteria** | | |
| Message | Criteria | Recommendation |
| Don’t hesitate | Back‐extrapolated volume >150 ml or 5%  of FVC whichever is greater | The patient must exhale all air at once and  not exhale in short bursts. |
| Blast out faster | Time until peak flow >120 ms | The patient must exhale more explosively  and as firmly and quickly as possible. |
| Blow out longer | Expiration time ‘volume‐time curve shows  no change in volume (<0.025 L) for ≥1 sec | The patient stopped exhaling too early.  The patient must exhale still further and  force as much air as possible out of his or  her lungs. |
| General quality control messages | | |
| Good effort, do next | Test meets above criteria | Good test. Only one to two more  good tests and the test is complete. |
| Deeper breath | FEV1 or FVC not reproducible. Difference  with respect to best test >150 ml or 100ml  if FVC is < 1.0L. | The test differs greatly from previous  tests. The patient can inhale even more  deeply and exhale even more air. |
| Test complete | QC grade A or B reached after 3 trials.  After 4 trials loosened to include QC  grade C. Or after 5 trials automatically no  matter the grade. | The test is complete. An adequate number  of good tests is available. |

**Table 2.** Quality control messages (acceptability criteria) for slow vital capacity maneuvers

|  |  |  |
| --- | --- | --- |
| For Acceptability criteria | | |
| Message | Criteria | Recommendation |
| Breathe easy | EELV stability not met (±200 ml for 3  consecutive breaths) | The patient must relax and breathe  normal |
| Slow down | Respiratory rate > 20 bpm | The patient must relax and breathe  slower |
| Bigger breath | IC maneuver <1L or 2x tidal volume | The patient must inhale a full, deep breath following the ‘BEEP’ |
| **General quality control messages** | | |
| Good effort, do next | Test meets above criteria | Good test. Only one to two more  good tests and the test is complete. |
| Deeper breath | IC repeatability not met (±10% of largest  acceptable IC) | The test differs greatly from previous  tests. The patient can inhale deeper. |
| Test complete | QC grade A or B reached. After 5 trials  loosened to include QC grade C. See QC  grade documentation. | The test is complete. An adequate  number of good tests is available. |



**Figure 1**. Method for measurement of inspiratory capacity.

## Appendix B: Standard Operating Procedure for Statistical Process Control

We use statistical process control to pick up the deviation of all measures from baseline during monitoring time. There were 4 steps programmed on the portable hand-held spirometry & electronic questionnaires.

**Step 1**: 7-day rolling averages were used as the baseline of daily measurement s. Values recorded on subsequent days were judged acceptable if they lay between pre-defined upper and lower limits assuming normal distribution.

**Step 2:** The higher cut-off value identified the highest 2.5% of normally distributed values (P=0.975). If the measured value was higher than this, subjects were asked to repeat the maneuver and the lowest of the two measures was accepted (technical acceptability). (see Figure 1).

**Step 3**: The lower cut-off value identified the lowest 5% of normally distributed values (P=0.050). If the measured value was lower than this, subjects were asked to repeat once. If the repeated value was above the threshold, then that value was accepted. If lower again, a clinical event was marked and sent as an alarm to the research center (clinical event detection). (see Figure 2).

**Step 4**: Alarms on 2 consecutive days were counted as an exacerbation.



**Figure 1**. Technical acceptability



**Figure 2.** Clinical event detection

## Appendix C: Statistical Method for Concordance Analysis

For each pair of a predictor and an outcome a 2 by 2 table was constructed and Cohen’s kappa was calculated as follows:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Outcome** |  |  |
|  |  | Exacerbation | None | Total |
| **Predictor** | Positive | a | c | a + c |
|  | Negative | b | d | b + d |
|  | Total | a + b | c + d | N |

observed proportion of agreement: Po = (a + d)/N

expected proportion of agreement: Pe = ((a + b) \* (a + c) + (c + d) \* (b + d)) / (N\*N)

Cohen’s Kappa = (Po-Pe) / (1-Pe)

Values for Cohen’s kappa are interpreted as follows:

|  |  |
| --- | --- |
| <0 | No agreement |
| 0-0.20 | Slight agreement |
| 0-21-0.40 | Fair agreement |
| 0.41-0.60 | Moderate agreement |
| 0.61-0.80 | Substantial agreement |
| >0.80 | Almost perfect agreement |

Values of Cohen’s kappa can be adjusted for prevalence and bias as follows:

proportion of positive agreement: P\_pos = 2 \* a / (N + a - d)

proportion of negative agreement: P\_neg = 2 \* d / (N – a + d)

prevalence index: P\_index = (a - d)/N

bias index: B\_index = (b - c)/N

prevalence-adjusted-bias-adjusted Kappa: Kappa\_adjust = 2 \* Po - 1

This calculation adjusts the kappa value for imbalances caused by differences in prevalence and bias (Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol.* May 1993;46(5):423-429).

## Appendix D: Statistical Method for Missing Data

The application of statistical process control relies on tracking a 7-day rolling average for each variable of interest. The sequence of steps used to identify the upper (P<0.975) and lower (P<0.05) boundaries of acceptability are described in detail in Appendix A. We developed a standardized approach for handling these missing data as shown below.

When data for a particular day were missing and yet data for the preceding 7 days were within acceptable boundaries according to statistical process control, then the confidence intervals established using the preceding 7 measurements were carried forward to the next day of measurement.

Panel A (below) shows FEV1 falling below the 7-day rolling average minus 1.645 SD on two consecutive days commencing Day 24 but the event appears to have ended by Day 29 due to data missing on Days 27 and 28.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **A** |  |  |  | **B** |  |  |
| **Day** | **FEV1 < Threshold\*** | **FEV1 Event Count** |  | **Day** | **FEV1 < Threshold\*** | **FEV1 Event Count** |
| 23 | 0 | 0 |  | 23 | 0 | 0 |
| 24 | 1 | 0 |  | 24 | 1 | 0 |
| 25 | 1 | 1 |  | 25 | 1 | 1 |
| 26 | 1 | 1 |  | 26 | 1 | 1 |
| **27** | **missing** |  |  | 29 | 1 | 1 |
| **28** | **missing** |  |  | 30 | 1 | 1 |
| 29 | 1 | 0 |  | 31 | 0 | 0 |
| 30 | 1 | 1 |  | 32 | 0 | 0 |
| 31 | 0 | 0 |  | 33 | 0 | 0 |
| 32 | 0 | 0 |  | 34 | 0 | 0 |
|  |  |  |  |  |  |  |

Panel B (above) shows the elimination of missing data revealing that event criteria continue to be met until Day 30. \*Threshold is below the 7-day rolling average minus 1.645 SD.

## Appendix E: Event Counts for Individual Patients

We examined the distribution of events for each of the 11 subjects who contributed to the 2,618 patient-days of monitoring. Given that individual subjects contributed varying numbers of days of monitoring, we have calculated annualized rates for each predictor for each patient. Interestingly, this approach enables us to identify those subjects with greater clinical instability (e.g. Subjects 1006 and 1017 highlighted in red) compared with those who are more stable (e.g. Subjects 1002 and 1027 highlighted in green).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ID** | **Total days monitor-ed** | **O1** | **Annualized event rate for each subject** | **O4** | **Annualized event rate for each subject** | **FEV1** | **Annualized event rate for each subject** | **FVC** | **Annualized event rate for each subject** | **PEF** | **Annualized event rate for each subject** | **IC** | **Annualized event rate for each subject** | **In-activ** | **Annualized event rate for each subject** | **MRx** | **Annualized event rate for each subject** | **Quick BD** | **Annualized event rate for each subject** |
| 1002 | 85 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 | 4.29 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 | 4.29 | 2 | 8.59 |
| 1004 | 351 | 1 | 1.04 | 1 | 1.04 | 1 | 1.04 | 2 | 2.08 | 2 | 2.08 | 3 | 3.04 | 0 | 0.00 | 0 | 0.00 | 1 | 1.04 |
| 1006 | 363 | 5 | 5.03 | 2 | 2.01 | 1 | 1.01 | 3 | 3.02 | 3 | 3.02 | 2 | 2.03 | 8 | 8.04 | 1 | 1.01 | 1 | 1.01 |
| 1009 | 62 | 1 | 5.89 | 1 | 5.89 | 1 | 5.89 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| 1010 | 350 | 0 | 0.00 | 0 | 0.00 | 2 | 2.09 | 2 | 2.09 | 0 | 0.00 | 2 | 2.03 | 0 | 0.00 | 0 | 0.00 | 18 | 18.77 |
| 1013 | 149 | 0 | 0.00 | 0 | 0.00 | 1 | 2.45 | 0 | 0.00 | 1 | 2.45 | 1 | 1.01 | 1 | 2.45 | 0 | 0.00 | 1 | 2.45 |
| 1015 | 366 | 4 | 3.99 | 1 | 1.00 | 3 | 2.99 | 1 | 1.00 | 1 | 1.00 | 1 | 1.01 | 9 | 8.98 | 0 | 0.00 | 2 | 1.99 |
| 1017 | 382 | 15 | 14.33 | 1 | 0.96 | 2 | 1.91 | 2 | 1.91 | 5 | 4.78 | 5 | 5.07 | 0 | 0.00 | 0 | 0.00 | 27 | 25.80 |
| 1024 | 237 | 0 | 0.00 | 0 | 0.00 | 2 | 3.08 | 1 | 1.54 | 1 | 1.54 | 2 | 2.03 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| 1026 | 139 | 0 | 0.00 | 0 | 0.00 | 2 | 5.25 | 1 | 2.63 | 3 | 7.88 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| 1027 | 134 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |