

WHITE PAPER

5 WAYS TO IMPROVE SPIROMETRY QUALITY IN A CLINICAL TRIAL

Spirometry data is pivotal to assessing primary or secondary outcomes in most respiratory trials, but the methodology for data acquisition and data collection is rarely published.

In the experience of the authors of this review, a significant portion of spirometry data in clinical trials is of inadequate or questionable quality. Data variability induced by suboptimal spirometry quality necessitates increasing the size of the study population and can even undermine the trial results. The aim of this whitepaper is to describe and explain the main quality issues encountered in clinical trials and to explore mitigation actions that can reduce these issues.

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Many different values are used to evaluate lung function but in this review we will only cover the measures from the forced expiratory maneuvers: Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) as they are, by far, the most universally used values in respiratory trials such as asthma, COPD, idiopathic pulmonary fibrosis, interstitial lung diseases, bronchiectasis and cystic fibrosis.

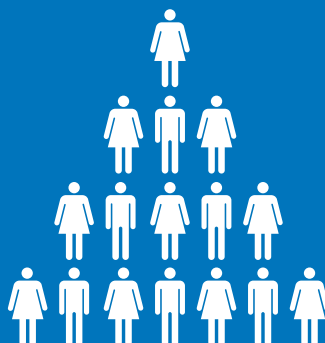
Since 2005, nearly 3,000 respiratory trials have included spirometry in the protocol¹. Spirometry is an instrumental gauge of respiratory health that can provide information not detected in other areas of examination. Moreover, spirometry is not limited to respiratory trials but valuable in trials that have known pulmonary toxicity associations such as oncology, musculoskeletal and neurology.

In recent years, an annual average of 150 to 250 trials used spirometry data as a study outcome (www.clinicaltrial.gov - accessed on April 11 2016)

POOR QUALITY SPIROMETRY DATA CAN LEAD TO:



**INCREASED DATA
VARIABILITY**



**AN INCREASE IN THE NUMBER
OF SUBJECTS IN A TRIAL**



ADDITIONAL TRIAL COSTS

IMPORTANCE OF SPIROMETRY IN CLINICAL TRIALS

Spirometry is a safe and non-invasive test. During the critical patient onboarding stage of a trial, spirometry testing helps ensure that the right patients are diagnosed, staged, and placed into the right trials. Proper patient enrollment is critical to trial success and evaluating response to therapy.

Additionally, the proper classification of airflow obstruction, identified through the performance of spirometry testing, allows investigators to stratify patients into the most suitable drug arm or trial. In a recent study, spirometry testing led to the correction of 48% of patients' being diagnosed². Spirometry is also used to evaluate a patient's lung function to ensure that the patient is not experiencing an adverse event such as the deterioration in lung function due to treatment or disease progression.

In most cases, forced manoeuvres are needed in spirometry tests and they present a number of inherent challenges. Typical challenges encountered when acquiring spirometry data in a clinical trial include:

- Patients who are unable to produce an optimal maneuver because they may not understand the instructions, be too tired to produce a sufficient forced expiration maneuver, or are unable to stop coughing during the test.
- Errors in data reporting or lack of understanding of basic spirometry rules for example, FEV1>FVC Non-valid flow volume loops, despite repeatability of the values. This combined with overly strict interpretation of the guidelines can lead to an unacceptable rate of rejection of spirometry data.
- Technicians using a predicted set of lung volumes outside of the specific protocol guidelines.

- Incorrect collection of demographic information for predicted calculations.
- Substantial variation of FEV1 across study visits (> 500 ml or 20 % of the predicted FEV1) that is not clearly associated with any clinical adverse event. Unstable asthma can lead to abnormal volumes and flow volume loop patterns; however a certain amount of correlation between the clinical pattern and the spirometry pattern of the subject is expected.

Having systems and processes in place that are designed around preventing and mitigating the quality issues that arise from these challenges is critical in order to conduct a successful trial.

SIMPLIFYING YOUR JOURNEY

Spirometry is well standardized and easy to perform with the proper training and experience. When conducted appropriately spirometry provides consistent and reproducible results across different pulmonary function laboratories.

Investigator sites participating in clinical trials may have varying levels of experience with spirometry. Additionally, technical proficiency may be limited at sites with infrequent enrollment, changing study personnel or delays between training during study start-up and the onset of patient enrollment. In PAREXEL's experience, most spirometry trials we have included the provision of standardized devices to all sites in order to eliminate any possible sources of variation across sites. Most modern spirometers meet or exceed ATS guidelines and are capable of producing high-quality and reproducible data, as long as the device has been calibrated appropriately and the trained pulmonary technician follows proper testing procedures.

Therefore, the quality of spirometry is most significantly affected by the level of skill the technician has and not the device itself.³

CENTRAL SPIROMETRY SERVICES IMPROVE DATA QUALITY

Traditionally, in clinical trials where a central lab is not contracted, spirometry data is uploaded to an electronic data capture (EDC) application from the investigator or study coordinator. Clinical monitors evaluate repeatability of the values according to guidelines and confirm that a calibration check of the spirometer device was performed on the day of the spirometry session.

This method is most commonly used when spirometry data is not contributing to the primary endpoint as it has inherent risks. The most common of these risks is that clinical monitors are not adequately trained in pulmonary function testing, which makes it very difficult to properly assess value repeatability and the shape of the flow volume loop.

Limitations in the quality assessment of spirometry tests can be improved by systematic computerized analysis followed by central review, by experienced and registered respiratory therapists.

On a recent PAREXEL phase IV trial without centralized control, over 40% of spirometry tests performed at specialized sites did not meet ATS/ERS Guidelines until corrective actions were implemented. The most important benefit of centralized spirometry is that it helps to mitigate this expensive and potentially catastrophic risk.

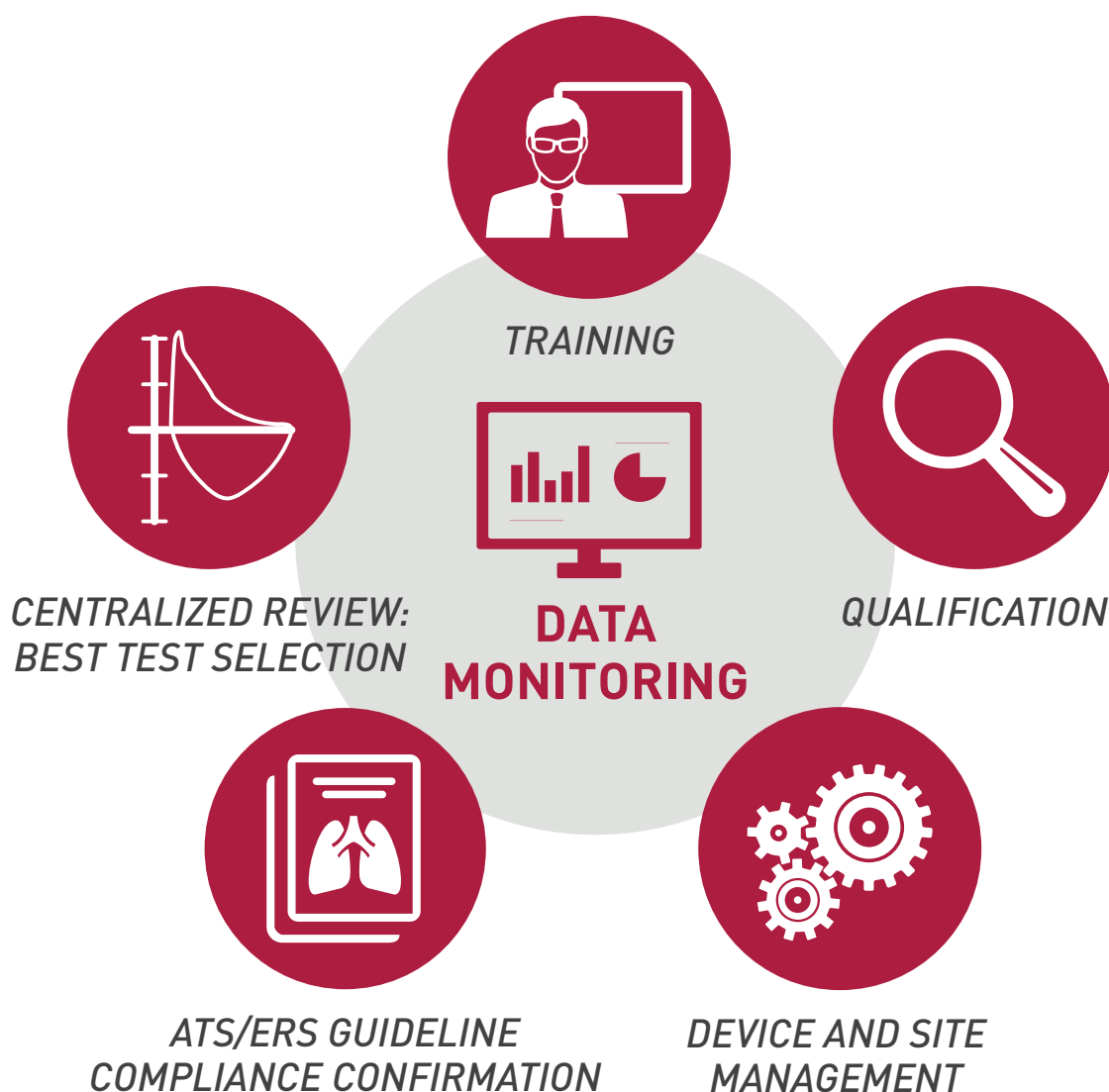
CENTRALIZED SPIROMETRY CAN IMPROVE CLINICAL TRIAL QUALITY BY:



- Reducing the amount of data that is non-usable, ensuring a more appropriate patient population and, reducing overall enrollment (**see note above**). Often non-centralized studies may have data that is not acceptable; therefore increasing the cost to repeat those studies, plus the time and cost to potentially enroll more patients.
- Reducing cost and time by utilizing a single vendor across central reviews.
- Providing more comprehensive site training that includes directions for use of the spirometry device and software, best practices, coaching techniques, ATS/ERS Guideline review, protocol-specific requirements, and an operational overview.
- Centralizing data monitoring to provide an overall view of data quality, performance trends, and standardization results and impact.
- Providing consistency in best-test selection by utilizing centrally trained reviewers.
- Providing more complete site support as centrally trained reviewers are working directly with the site data for guideline review and best test selection. Data can continuously be monitored to identify patterns across sites and determine when re-training may be necessary.
- Leveraging advanced centralized systems that mirror clinical practice and grant reviewers easy access to previous test results for a given patient.
- Reducing variability and bias as data amongst central readers will inherently, due to small pool size and blinding to other clinical data, be more consistent and less partial than the investigator sites.
- Instituting procedures that require each user across sites to be trained and qualified before being allowed to capture test results.

5 STEPS TO IMPROVE SPIROMETRY RESULTS

In order to ensure the best quality results of spirometry efforts on a clinical trial, we recommend implementing the following five centralized procedures. Central standardization across all testing and data review processes, from end to end, ensures that conditions for each patient, test, QC and review are acceptable.





1

TRAINING

Training is a critical component in driving consistency across sites and to ensure that test results are repeatable. Without centralized training, sites will default to administering tests according to their specific guidelines and not internationally recognized ones like ATS' (The American Thoracic Society) and ERS' (European Respiratory Society). Inconsistent device calibration and methods of coaching lead to non-reproducible test results. Teaching sites reliable methods for conducting spirometry tests gives each technician across patients and sites, the ability to produce consistent results, which ensures patients are treated appropriately according to their disease pathology.

Good patient coaching is essential in obtaining the best effort by the patient. Without proper coaching, the patient may not understand how to perform the test with maximal effort, resulting in poor representation of data. Obtaining accurate results may be extremely difficult with certain patients who suffer from severe diseases, but with a properly calibrated device and a well-trained technician, inaccurate results can be minimized through personalized coaching techniques.

Finally, it is equally critical to ensure that clinical monitors are carefully trained on the basics of spirometry testing in a clinical trial, as well-trained monitors are excellent tools for reducing site burden and improving overall data quality.

Sites are responsible for:

- Identifying testing errors and rectifying them
- Performing assessments of repeatability
- Identifying the 2 highest volume loops for each result
- Performing calibration checks and verification of the spirometer log

Competency should continuously be monitored throughout the lifecycle of the trial and retraining of site staff should be offered when deficiencies are identified or when there are long delays between subject enrollments.



2

QUALIFICATION

The spirometry core lab should conduct a proactive assessment of the site and technician's experience and competency in performing spirometry testing. This assessment should evaluate:

- Length of experience performing spirometry testing
- Relevant education and certification
- Training history
- Clinical trial experience
- Device and software experience
- General familiarity with ATS/ERS Guidelines

Identifying this information in advance will allow the core lab to identify strengths and weaknesses of the site, in advance of on-study patient testing. The training and start-up activities can then be tailored specific to that site's needs.

A site's competency for performing high quality spirometry testing should be evaluated through the collection of volunteer tests or a test transfer, whenever possible. A series of tests on a healthy volunteer (likely a co-worker at the facility) can be collected and submitted to the core lab for review. This process allows for the core lab to ensure that the site is properly adhering to ATS/ERS Guidelines and that there is a sufficient understanding of the device and associated software by the user. Any deficiencies

in the test transfer should be reported back to the site and depending on the severity, may require re-training or corrective action prior to performing on-study patient testing.



3

DEVICE AND SITE MANAGEMENT

Sites will default to their standard device management, which can be incorrect and certainly inconsistent when evaluated across sites. According to a recent NIH publication (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4314842/>), it is essential to “ensure that a site is using spirometry on a regular basis, has a trained spirometry technician, is well-versed with ATS/ERS 2010 requirements, understands the need for calibration and performs and interprets acceptable, reproducible graphs. High level oversight is needed during the trial to ensure good quality spirometry reports. Retraining of site staff is the key to avoid major spirometry quality issues.” Software should be configured carefully to provide clear user instruction, ATS/ERS Guideline prompts and error messages that are easily understood by technicians. Basic reference materials should be provided to the sites that include simple step-by-step instructions for set-up and use, representative flow volume loop examples, error message explanations, acceptability criteria guidelines troubleshooting tips. These tips should include instructions for coaching the effort and liaising with sites’ IT departments in advance of patient visits to ensure that data transfers are able to occur securely and efficiently prior to any patients’ participation in the study.



4

ATS/ERS GUIDELINE COMPLIANCE CONFIRMATION

An important consideration when reviewing spirometry data, is the ability to detect quality concerns early and to provide meaningful feedback to the sites quickly so that corrective actions can be taken. When spirometry test data is reviewed in isolation, it is difficult to make the distinction between quality issues due to a patient’s inability to follow instructions and quality issues related to a lack of proficiency on the part of the technician. Therefore, grouped quality review of multiple tests coming from a single site should be implemented to help minimize risk. These reviews should be programmed at predefined study visits for example, the screening visit for the initial patient enrollment in a trial at a site). When performing a quality check of a patient’s spirometry test data, the core lab should always ensure that the following conditions are reviewed for compliance and accuracy:

- Acceptability of the measure: using guidelines to check the acceptability of the flow volume loop.
- Reproducibility in at least 2 out of 3 acceptable maneuvers (the two highest volumes are used as long as they are <150 ml difference).
- Appropriate and accurate demographics have been used.
- Flow volume loops are of high quality and demonstrate maximal effort.

Performance of calibration in accordance with ATS/ERS Guidelines is also critical in ensuring that the spirometer at the site is accurate and functioning properly. The core lab should monitor and collect this data regularly and should work with the site to ensure the following:

- Equipment is being calibrated with a three liter syringe daily prior to any patient testing.
- The syringe must be certified to be accurate by the manufacturer; this test is typically performed annually unless otherwise indicated by the manufacturer.



5

CENTRALIZED REVIEW: BEST TEST SELECTION

A central spirometry reviewer is blinded to the testing circumstances that occur during the spirometry data collection. Centralized services enable blinded reviews to be conducted independently from sponsors and the conduct of other trial activities. Independent reviewers must be registered respiratory experts who are trained to review in a clinical trial environment where the objective is to ensure consistent results across all patients, sites, and timepoints.

Independent spirometry reviewers will be trained on interpretation and quality assessment. The core lab should monitor the consistency of both quality review and spirometry interpretation between reviewers at the start of the trial and whenever a new reviewer joins the team. Discrepancies and variability in the way that spirometry tests are assessed between reviewers should be discussed to establish an ongoing and improving level of consistency.

The primary objective when conducting a central review is to establish precise rules for both the computerized analysis and the central reader's assessment. Clearly defined rules, that are applied to all data, in the same way, result in better data quality overall. Feedback on the central assessment results should be shared with the sites in order to advance their understanding of central review criteria, which will help to improve the data being collected by the site, one patient at a time.

It is critical that sites are informed whether the test was acceptable or not after each assessment is made. "Quality grades serve as a guide to judge the reliability of the test" (<http://www.spirometry360.org/spiro360resources/>) and centralized spirometry vendors can provide the following quality grade information:



Acceptable

Submitted test met all the
ATS/ERS Guidelines.



Borderline
acceptable

All criteria are not met but the data is judged usable by the central reviewer after applying a predefined set of rules. In the research setting, some maneuvers yielding flow-volume loops that do not meet all ATS/ERS Guidelines for acceptability may still be adequate for the purposes of data collection.



Unacceptable
and
unusable

Data will be handled on a project basis with sponsor input. Generally, sponsors will opt to discard unacceptable data or set up a threshold for acceptability of unusable data.

The study protocol should describe how the unacceptable spirometry data will be used and whether it is acceptable to repeat the test in cases of unacceptable data.

Finally, data monitoring is the foundation supporting the prior five steps. The results of data monitoring are presented to the core lab's medical team to evaluate the evolution of key data points across time, sites, and patients. The analysis allows detection of data variance and negative performance trends which may result in queries, corrective actions and re-training for the site. For example, the core lab should have the ability to easily monitor the FEV1 data within a patient for any values inconsistent with what might be expected. FEV1 values

can also be monitored across the site to look for consistent poor performance, a clear reflection of inadequate coaching techniques by the site technician. Similarly, trending and monitoring of calibration results, as outlined in step four, should be evaluated as part of overall data monitoring to ensure ATS/ERS compliance.

Data quality can be compromised if there is a shift from standard practices. Data inconsistencies can be quickly identified and remedied by leveraging data monitoring processes. Identifying issues early, before they become systemic, is critical in ensuring overall data quality.

CONCLUSION

Spirometry testing provides important and unique data on the functioning of the respiratory system and there are no surrogate markers for these values. Spirometry tests are complex and it has been a challenge to reach an acceptable level of quality in the context of a drug trial.

Starting a study without a detailed action plan to contain, control and prevent quality issues related to spirometry tests, are considered a thing of the past. Those actions are potentially costly and should be tailored for the trial. Neglecting quality control and using qualified pulmonary lab technicians for spirometry testing jeopardizes the validity of study results and may impact subject safety. Data reviewers are unable to effectively identify important trends in lung function when the spirometry data quality is substandard. The most critical aspect to ensuring quality spirometry data begins and ends with supporting sites and easing their burden. Additionally, engagement between monitors and spirometry core lab staff is fundamental to supporting sites. The goal for all parties is to improve data quality and drive endpoints, by creating simple processes and requirements that a site can easily follow; ultimately helping sponsors, sites, and most importantly, patients, breathe easier.

We are always available for a conversation.

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