SCIENCE BRIEF

AI-enabled risk-based monitoring — respiratory

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Clinical overview — spirometry

Spirometry is a fundamental pulmonary function test designed to assess how well the lungs function by measuring the volume and speed of inhaled and exhaled air. This non-invasive diagnostic tool helps healthcare professionals evaluate respiratory conditions, such as asthma, chronic obstructive pulmonary disease (COPD) and other lung disorders.[1,2] During a spirometry test, individuals exhale forcefully into a device called a spirometer, producing essential data that aids in the diagnosis and management of various respiratory issues.

By measuring airflow and lung volumes, spirometry ideally provides objective and reproducible data that are essential for the evaluation of both therapeutic efficacy and safety. In trials of asthma, COPD, interstitial lung disease and other disorders that affect the respiratory system, spirometry-derived parameters such as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and the FEV_1/FVC ratio are routinely used as primary or secondary endpoints.

Because spirometry is a highly effort-dependent test, variability in technique and coaching can introduce risks to data quality and, consequently, the interpretability of trial outcomes. In multicenter studies, where measurements are collected across diverse sites and populations, these risks can be amplified. Risk-based monitoring (RBM) is therefore particularly important in spirometry-driven trials, as it enables sponsors to identify and focus on the sites, participants and/or datasets most vulnerable to errors or inconsistencies. By applying RBM principles, clinical teams can proactively safeguard data integrity, allowing early identification and intervention for emerging problematic data quality, ensuring endpoint reliability and maintaining confidence in spirometry results intended for regulatory submission.

Risk-based monitoring

RBM is an important tool to optimize efficiency and data quality in clinical trials. According to FDA's final 'Guidance for the industry' on RBM, drug sponsors are "required to provide oversight, including ensuring proper monitoring of the investigation."[3] The FDA guidance notes that such oversight helps to ensure "the integrity of the data submitted to the FDA" and recommends that "sponsors should implement a system to manage both risks to participants (e.g., a safety problem) and to data integrity (e.g., incomplete and/or inaccurate data)" and that "this system should include a risk-based approach to monitoring tailored to the potential risks for the specific clinical investigation." Finally, the guidance states that effective implementation of risk-based monitoring "should help maximize the quality of a clinical investigation."[3,4]

AI-enabled RBM

Clario offers RBM services for spirometry, not only focusing on ATS/ERS data quality but also considering data integrity and plausibility. This offering combines the strengths of interpretation by spirometry specialists with statistical techniques that are programmed into AI models to help identify data anomalies for rapid analysis and detection. Each individual's lung function exhibits a characteristic pattern derived from the shape, dynamics and key features of their spirometry curves. AI algorithms can analyze these distinctive patterns, creating a sort of personalized spirometry profile for each participant.

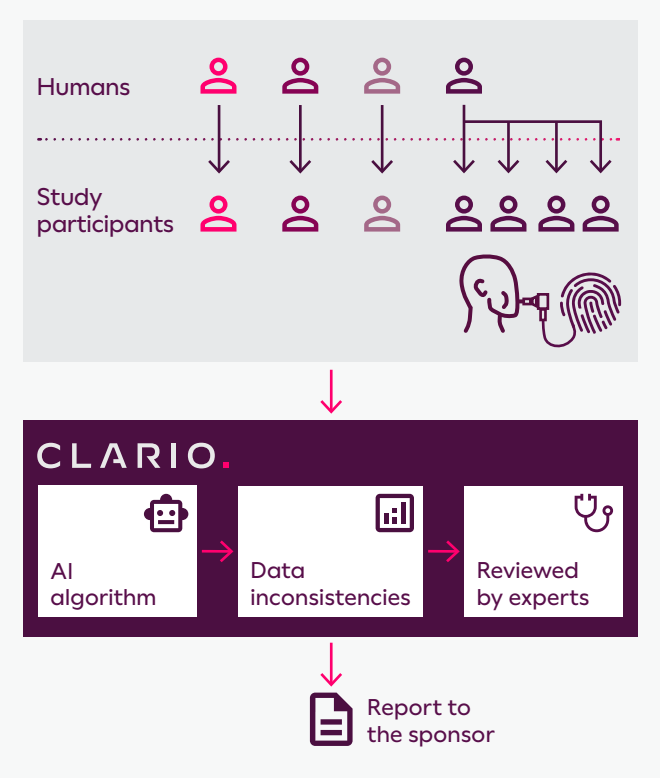
This innovative approach allows for the identification of anomalies in the data, serving as a robust tool to recognize potential data inconsistencies in clinical trials.

Additionally, aggregated spirometry data, when analyzed collectively through Clario's RBM AI algorithm, provides a powerful tool

for identifying specific study sites in clinical trials that are more consistently generating questionable data and that may benefit from additional support and/or intervention, including possible retraining of optimal spirometry techniques.

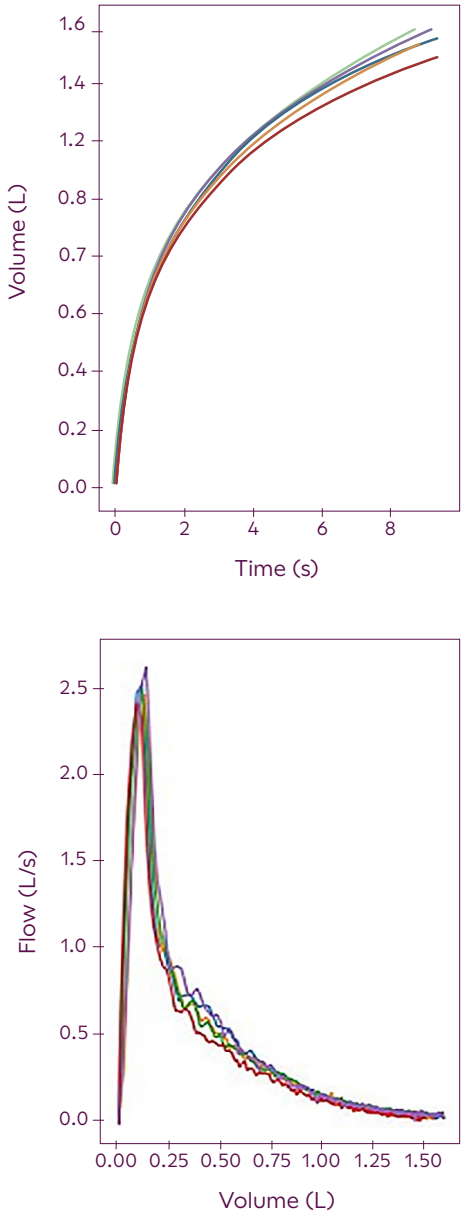
Spirometry mirror participants

The AI system compares the profiles of flow-volume loop geometries from each participant at a site to look for clusters of unusually similar data. This process can pick up potential duplicate or mirror participants who may represent a deviation from the protocol or mislabeling of visits by site. Specifically, the AI system clusters measurements from different participants at the same site for the same time point based on their **spirometry curve similarities**, flagging cases that might potentially suggest mirror participants.[5]



Data discrepancies identified can then be reviewed and validated by experts. This may lead to further investigation and comprehensive site review.

Figure 1. Examples of volume-time (seconds) and flow-volume (liters) curves for five different participants who are flagged by the AI system as mirror participants because of their high spirometry curve similarities and are validated by experts.



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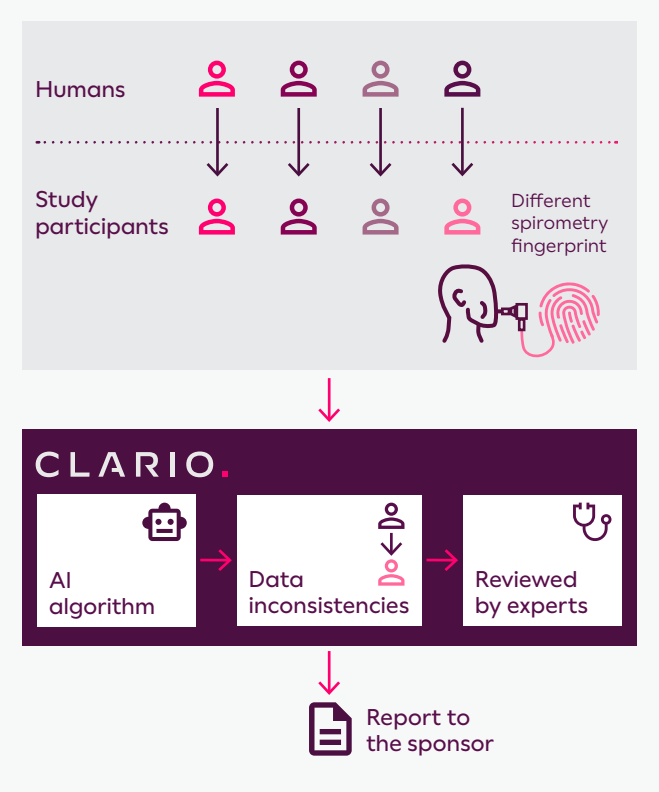
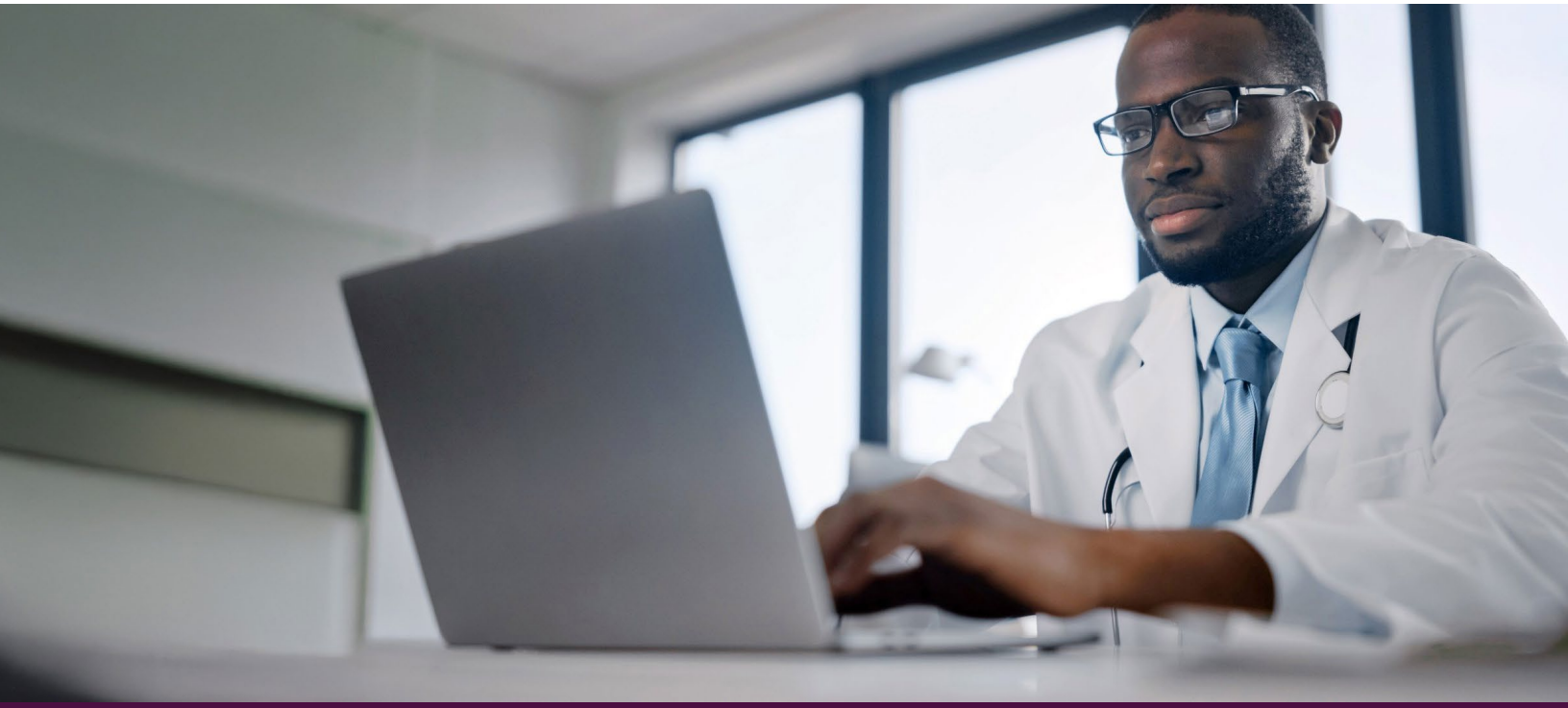
Longitudinal spirometry fingerprinting

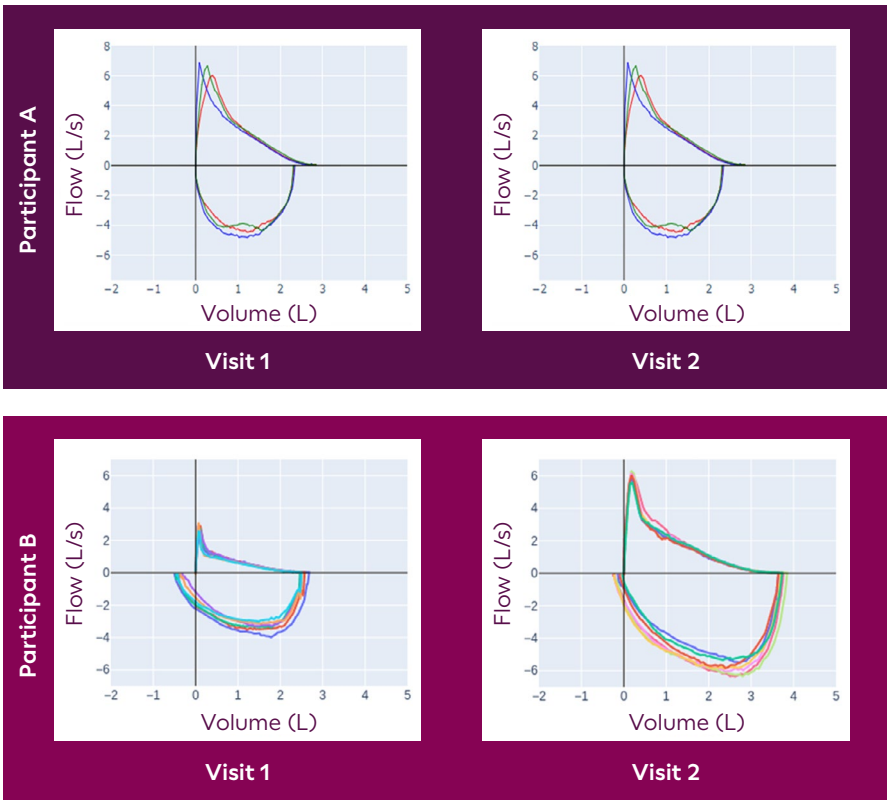
The use of AI can also facilitate the comparison of spirometry efforts from the same participant across multiple time points in a clinical study. The algorithm establishes a characteristic profile as described in the previous section, for an individual's respiratory pattern derived from the shape, dynamics and key features of their spirometry curves. By comparing efforts from the same participant over different timepoints, the model can **identify implausible or unexpected deviations** that may indicate technical errors, data irregularities, participant replacement or clinically meaningful changes in lung functions that require further review.





This longitudinal approach enhances traditional quality control by allowing recognition of implausible data deviation over time, offering opportunity for further investigation and optimizing both data integrity and the resulting reliability of trial outcomes.

Figure 2: Examples of analysis of flow-volume curves for Participants A and B across two visits. Participant A exhibits a similar pattern over time, but Participant B shows significant changes from Visit 1 to Visit 2, resulting in the AI model flagging this case.



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Main benefits

- AI-powered review enhances data quality and data integrity through an efficient and scalable approach, ensuring a more complete review and flagging data requiring further investigation by experts.
- Automation through AI helps support earlier detection of irregularities, allowing more timely intervention and corrective action to preserve data quality.
- Clario AI RBM tools seek to consider the limited data quality assessment offered through ATS/ERS 2019 standards, highlight implausible measurements that can critically affect data integrity for clinical trials and enhance confidence in the reliability of spirometry-based endpoint measures.
- The AI-based approach is an effective and efficient translation of the risk-based approach mandated by the FDA and EMA.
- The enhanced confidence in respiratory endpoints achieved through application of the AI-driven tools outlined in this brief results in more robust and defensible respiratory clinical trial results on which sponsors depend.

AI solutions can take RBM in respiratory trials a step forward by strengthening spirometry data integrity and improving the reliability of trial outcomes.

References

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About Clario

Clario is a leading provider of endpoint data solutions to the clinical trials industry, generating high-quality clinical evidence for life sciences companies. We offer comprehensive evidence-generation solutions that combine medical imaging, eCOA, precision motion, cardiac and respiratory endpoints.

For more than 50 years, Clario has delivered deep scientific expertise and broad endpoint technologies to help transform lives around the world. Our endpoint data solutions have been deployed over 30,000 times to support clinical trials in more than 100 countries. Our global team of science, technology, and operational experts have supported over 70% of all FDA drug approvals since 2012.