APPLICATION NOTE

Exhaled Breath Condensate (EBC) in Early-Phase Respiratory Drug Development

A framework for evaluating when and how EBC collection adds value to an early-phase program — and when it does not.

Respiratory Research, Inc. · RTube™ Platform

01 · THE ARGUMENT

The Lung Biology Most Programs Never Examine

Ambiguous Phase II results produce a question that is almost always unanswerable: did the drug fail, or did the measurement fail? The two failure modes have entirely different implications — one warrants stopping, the other warrants redesign — but without biology collected from the lung, they are indistinguishable. That is not a data quality problem. It is a collection problem. The tables below show what that gap costs, and what closing it provides.

The Decision Risk

Outcome	What it means without airway data
Weak or negative results	Cannot determine whether the drug failed to engage airway biology or whether the biology changed but was not captured. Two failure modes with different implications become indistinguishable.
Positive results	Biological responses at the airway level are invisible. Patient stratification and Phase III endpoint selection proceed without the mechanistic data that would make them more precise.
Heterogeneous results	The source of heterogeneity cannot be located. Without local biological context, there is nothing to compare.

What EBC Provides

EBC does not resolve ambiguity independently. Its value is directional context at the airway level — context that differs meaningfully by outcome, and that cannot be reconstructed after the trial closes.

Situation	What EBC adds
Weak or negative results	Without airway data, a weak result has two equally plausible explanations: the drug didn't work, or the drug worked but no one was watching the right biology. EBC makes those two explanations distinguishable.
Positive or heterogeneous results	Airway-level data supports responder analysis that blood markers do not provide. Correlation with clinical response creates the basis for stratification, biomarker hypothesis generation, and dosing rationale.
Null EBC signal	A null airway result alongside a positive clinical outcome is a finding — provided collection, biomarker selection and laboratory analyses were sound. It can locate where the drug's mechanism is not operating, which is different from a failed measurement.

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Situation	What EBC adds
Any outcome	Banked samples. This cohort, at this timepoint, is a fixed resource. As new biomarkers are validated, only programs that collected EBC can reanalyze.

The Risk of Not Collecting Lung Biomarkers

The central risk is reaching a high-stakes development decision — stop, advance, or redesign — without having examined the biology where the drug is expected to act. That gap, once the trial completes, cannot be closed.

EBC addresses this risk directly: non-invasive, approximately 12 minutes per visit, no additional safety considerations, and no regulatory exposure provided data are pre-specified and clearly designated as exploratory in the protocol and statistical analysis plan. Its contribution is contextual — biological resolution added to a picture that clinical and systemic data draw in broad strokes. It will not provide validated biomarkers and is not powered to drive standalone decisions. Known pre-analytical variability requires standardized collection and processing protocols. These are scope conditions, not disqualifying ones.

Whether EBC belongs in a given program follows from these criteria:

EBC Is Appropriate When

- The PD question is lung-compartment specific
- It involves pathways FeNO cannot measure — oxidative stress, neutrophilic inflammation, pH, cytokines, leukotrienes, or multi-pathway biology beyond Th2/eosinophilic
- A pre-specified exploratory analysis plan exists
- The team has accounted for known analyte variability in the sample size calculation

EBC Is Not Appropriate When

- Blood or FeNO can adequately answer the PD question
- The program requires endpoint-level evidence, not mechanistic context
- No analysis plan exists for handling between-day variability
- The goal is to generate data without a defined downstream use
- Remote collection is assumed without site-equivalence validation for labile analytes

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Example: What This Looks Like in Practice

A 12-week Phase II proof-of-concept trial in moderate-to-severe COPD with 80 subjects across 4 sites. The EBC sub-study enrolls 60 of those subjects under a separate consent. RTube™ EBC is collected at baseline, week 4 — where early pharmacodynamic signal would indicate target engagement ahead of the primary endpoint readout — and week 12, aligned with existing visit schedules, adding approximately 12 minutes per visit.

The pre-specified biomarker panel is 8-isoprostane (oxidative stress), LTB4 (neutrophilic inflammation), and EBC pH, with FeNO and blood IL-6 collected at the same timepoints as validated co-measures. The analysis plan defines directional hypotheses for each biomarker based on the drug's mechanism, specifies within-subject change as the primary metric, and pre-specifies that all results including null findings will be reported. Bioanalytical work is contracted to a single central lab to eliminate inter-site variability.

If the drug advances, the data inform Phase III endpoint selection and patient stratification — replacing indirect proxies with directly measured airway biology. If it does not, the data do something harder to replace: they characterize what the drug did and did not engage at the site of action, which is the one analysis that can distinguish a failed drug from a failed measurement and support three concrete downstream uses: responder enrichment criteria for the Phase III population, exposure–PD modeling for Phase III dose selection, and a defensible salvage analysis if the primary endpoint is missed but airway PD is positive.

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The Airway PD Gap in Early Respiratory Programs

The measurement problem is structural, not incidental. Most early-phase programs have access to the same set of tools, and each has a constraint that prevents it from answering the lung-compartment pharmacodynamic question directly.

The result is a consistent structural gap: early-phase programs make dose selection, go/no-go, and Phase III endpoint decisions based on indirect or infrequent measures, without serial, non-invasive data from the tissue where the drug is supposed to work. When results are clean, that gap goes unnoticed. When results are equivocal, it becomes the problem.

Modality	Lung Specificity	Invasiveness	Serial Feasibility	Limiting Constraint
BAL / Bronchoscopy	High	Very High	1–3x per study	Invasiveness, procedural risk, cost, and specialist requirement make it difficult to justify for exploratory endpoints; impractical for serial use
Blood / Serum	Low	Low	Feasible	Does not reflect lung compartment biology
Induced Sputum	High	Moderate	Limited	Patient and investigator burden; alters airway environment.
FeNO	High	None	Excellent	Single pathway (Th2/eosinophilic only)
EBC (Exhaled Breath Condensate)	High	None	Excellent	Biomarkers are exploratory only (no formally-qualified Drug Development Tool (DDT) status
EBA (Exhaled Breath Aerosol)	High	None	Excellent	Very early stage, small body of evidence, no ERS/ATS methodology, no scalable trial-deployable commercial standard platform, biomarkers are exploratory only (no DDT qualification)

> *EBC or EBA? EBA is a promising emerging modality with neither ATS/ERS methodology standards nor a validated trial-deployable platform and therefore not a candidate for trial inclusion today.*
>
> *The question is not EBC or EBA. It is EBC now — or no airway PD data at all.*

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What EBC Is — and What It Is Not

Exhaled breath condensate is collected by having a subject breathe tidally through a chilled collection device. Aerosolized airway lining fluid droplets and vapors condense on the cooled surface and are recovered for analysis. The resulting sample contains measurable concentrations of inflammatory mediators, oxidative stress markers, cytokines, leukotrienes, nucleic acids, pH, and volatile organic compounds.

Two things about EBC should be held separately, because conflating them leads to both overclaiming and underclaiming.

The RTube™ EBC Collection Platform

The RTube™ is the most extensively validated EBC collection device in the published literature. Over 230,000 collections across 25+ years, zero adverse events attributed to device use, 400+ peer-reviewed publications, and ISO 13485 manufacturing establish its collection track record. Its performance is not in question.

EBC as a Biomarker Matrix

EBC biomarkers are a separate matter. The evidence base is substantial — 2,500+ peer-reviewed publications with demonstrated treatment-response signal across multiple disease areas and ATS/ERS methodology standards — but study results vary across analytes and settings, reflecting an active standardization effort rather than evidence that the biology is absent. Formal regulatory qualification of individual EBC biomarkers as Drug Development Tools has not been completed.

> *EBC biomarkers are classified as exploratory under the FDA-NIH BEST framework: biological plausibility and published supporting evidence exist, but formal qualification for a specific context of use in drug development is not complete. In practice, exploratory status carries no requirement for statistical powering, no impact on primary endpoint strategy, and no added regulatory risk — provided data are pre-specified and clearly designated as exploratory in the protocol and statistical analysis plan. See Section 07 for the three questions that determine whether EBC belongs in a given program.*

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Signal From the Airway: What the Evidence Shows

The question most programs never answer is whether the drug reached and altered the biology at the target site. The studies below document that EBC can detect that biology — repeatedly, non-invasively, and in populations where other measures cannot. None of them prove that EBC data changed a development decision. They prove that the signal exists and can be captured. Which means its absence in any given trial is not inevitable — it is simply what happens when no one asks the question.

The category has a track record. Sputum-eosinophil enrichment in the Haldar and Nair Phase II studies (NEJM 2009) reset the trajectory of the IL-5 class and the severe-asthma biologics that followed. EBC's positioning is to extend that logic — biomarker-enriched trial design at the airway level — to soluble mediator pathways where cell-counting endpoints have less to say.

Indication	Key Biomarkers	Biological Signal, Feasibility Evidence, and the Specific Gap Addressed
COPD	*8-isoprostane, H_2O_2, IL-6, IL-8, PDGF-AA, oxidized phospholipids*	Airway oxidative and inflammatory signal detectable and reproducible (r = 0.93–0.96 within-sample; PDGF-AA ρ = 0.59–0.72 vs. clinical scores). Gap: blood markers do not reflect lung compartment biology.[6,7]
Asthma (non-eosinophilic / pediatric)	*LTB4, cysteinyl leukotrienes, 8-isoprostane, EBC pH, TBARS*	Oxidative stress signal elevated in status asthmaticus vs. controls (14.3 vs. 5.2 pg/mL; p < .001); 100% collection feasibility in pediatric ICU. Gap: FeNO is not elevated in neutrophilic or paucigranulocytic asthma and does not reflect non-Th2 inflammatory mechanisms.[11,12]
Asthma / Pathway Stratification	*LXA4, LTB4*	EBC LTB4 distinguished asthma from health with 100% sensitivity and specificity (AUC 1.0); LXA4 achieved AUC 0.96 — exceeding FeNO or blood eosinophils. The LXA4/LTB4 ratio fell 41% in severe versus moderate asthma (P=0.034), correlating with FEV1 impairment. Severity reflects a deficit in pro-resolving mediators, not merely excess inflammation — a pathway-level insight cell-counting endpoints cannot resolve.[14]
ARDS / Mechanically Ventilated	*IL-2, TNF-α, oxidative stress panel, EBC pH*	IL-2 and TNF-α correlated independently with radiograph severity and pneumonia (OR 1.68 and 3.20; p = 0.02). Gap: BAL requires bronchoscopy in critically ill patients.[8]
Cystic Fibrosis / Pediatric (<7 yrs)	*pH, sialic-acid:urea, LTB4, IL-8, glutathione metabolites*	Collection feasible and reproducible across visits (PROMISE ETI sub-study). Null EBC result after ETI initiation rules out a hypothesis: ETI acts on mucociliary clearance, not the inflammatory mediators EBC measures. Gap: spirometry unreliable under age 7; sputum induction poorly tolerated.[10]
Oncology / CRT Monitoring	*TGF-β1, IL-1α, IL-6, IL-10*	95.4% biomarker measurability across a 10-week chemoradiotherapy course, comparable to serum (97.8%). Establishes serial collection feasibility in active oncology treatment.[13]

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FEATURED STUDY — RTube™ EBC in the NHLBI Severe Asthma Research Program

Kazani et al. Exhaled breath condensate eicosanoid levels associate with asthma and its severity

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DOI: 10.1016/j.jaci.2013.01.058

Conducted at Brigham and Women's Hospital within the NHLBI's Severe Asthma Research Program (SARP), this study tested whether EBC measurements of opposing arms of arachidonic acid metabolism — pro-resolving lipoxin A4 (LXA4) and pro-inflammatory leukotriene B4 (LTB4) — could non-invasively characterize asthma and its severity. Investigators (Kazani, Wechsler, Levy, Israel and colleagues) enrolled 81 adults: 12 healthy controls and 69 asthmatics across mild, moderate, and severe (ATS refractory criteria). EBC was collected via RTube™ (10 minutes tidal breathing, sleeve pre-chilled to −20°C, immediate freezing at −80°C under inert gas), extracted by C18 Sep-Pak, and quantified by enzyme immunoassay.

LXA4 and LTB4 were each elevated tenfold in asthmatics versus controls. An LXA4 cutoff of 7 pg/mL gave AUC 0.96; LTB4 at 11 pg/mL gave AUC 1.0 with no asthmatic-control overlap. The LXA4/LTB4 ratio fell 41% in severe versus moderate asthma (P=0.034), with LXA4 correlating with FEV1. Head-to-head, FeNO at 25 ppb misclassified 32% of moderate and 61% of severe asthmatics; EBC cutoffs misclassified essentially none.

This stands out for three reasons. First, the RTube™ was the collection device. Second, the work was conducted within SARP, the NIH-funded severe asthma network whose investigators (Israel, Levy, Wechsler) are recognized scientific advisors to multiple severe-asthma development programs. Third, the operating characteristics are diagnostic-grade, not exploratory in spirit — illustrating the potential of EBC to move beyond exploratory status in the future.

> *What the evidence establishes: airway-level biological signal is detectable by EBC across multiple disease states, is collectable without adverse events at rates comparable to serum, and correlates with validated clinical measures in COPD and ICU populations. What it does not establish: that programs have been designed to act on the signals EBC can provide. That is a design gap, not a biological one.*

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What Well-Designed EBC Sub-Studies Account For

EBC has a substantial and growing evidence base. Realizing its value depends on study designs that account for the specific characteristics of EBC as a matrix. Three design requirements apply to any EBC sub-study and determine whether the data will be interpretable.

1. Pre-Specify the Analysis Plan Before Collection Begins

This is the single most common failure mode. Between-day within-subject variability for some analytes — LTB4, 8-isoprostane — is substantial in disease populations, and group-level treatment effects require appropriate sample sizing to detect. Defining what a meaningful signal looks like, how variability will be managed statistically, and what decision the data could influence before collection begins is not optional — it is what separates interpretable pharmacodynamic data from noise that gets filed away. Within-subject designs (baseline, peak exposure, washout) are substantially more interpretable than cross-sectional comparisons given known inter-subject variability.

2. Structure EBC as a Decoupled Sub-Study

EBC collection should be a separate sub-study with its own informed consent, not embedded as a primary or secondary endpoint. This insulates the primary trial from any operational issues on the EBC side and signals to regulators that no qualification claims are being made. EBC data will be exploratory, and the protocol should reflect that explicitly.

3. Standardize Collection and Anchor to a Validated Co-Measure

The RTube™ is the most validated EBC collection platform available. Whatever device is selected, it must be held constant throughout a study — inter-device comparability for analytes other than pH cannot be assumed. Standardized breathing protocol, fixed cooling conditions, and consistent sample handling are prerequisites for interpretable data across sites.

EBC data should also be collected alongside a validated co-measure: FeNO in eosinophilic or mixed-mechanism indications, blood eosinophils, or sputum differential depending on the program. This is not a substitute for EBC — FeNO answers only the Th2/eosinophilic question and cannot address the broader airway inflammatory, oxidative stress, or cytokine biology that EBC captures — but it provides the interpretive reference point that makes EBC signals credible and comparable to something the field already trusts.

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What This Justifies Spending — and What It Does Not

The incremental cost of a properly executed EBC sub-study in a Phase II proof-of-concept trial is modest relative to the overall trial budget. The more important question is what the data will actually be used for.

Cost Dimension	Estimated Range	Notes
Site training and SOP development	$15,000 – $30,000	One-time; reusable across sites
Device and consumables	$20,000 – $50,000	50–100 patient sub-study, 2–4 sites
Sample handling, storage, shipping	$10,000 – $20,000	
Bioanalytical assays	$50,000 – $150,000	Depends on panel size and lab
Data management and statistics	$20,000 – $50,000	
IRB sub-study amendment	$10,000 – $20,000	
Total realistic range	**$125,000 – $320,000**	**Scale depends on panel size, site count, and bioanalytical lab selection**

A Phase II proof-of-concept trial in a respiratory indication typically costs $5M–$20M fully loaded. A $150K–$300K sub-study represents 1–3% of that budget. The relevant comparison is not the sub-study cost against the trial cost. It is the sub-study cost against the cost of the decision the sub-study informs. A go/no-go call that sends a program into Phase III, or terminates one that could have been redesigned, is worth orders of magnitude more than $300K to get right. EBC does not make that decision. It provides the one piece of proximal biological context that might prevent the decision from being made in the dark — but only if the sub-study is designed to produce interpretable data.

A sub-study without a pre-specified analysis plan and defined downstream use will not produce that context. It will produce data that cannot be used — which means the program reaches a stop, advance, or redesign decision having collected airway biology it cannot act on. That is not a minor inefficiency. It is the same gap the sub-study was added to close, reproduced at cost. Implementation discipline is what determines whether the biological window the device opens actually closes the evidentiary gap — and what determines whether a null result is interpretable data or an unexplained gap in the dossier.

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Three Questions That Determine Whether EBC Belongs in Your Program

EBC is a specialized tool. Its inclusion should follow from clear answers to three questions — each evaluated before the protocol is written. A yes to all three is the signal that EBC belongs in the program. A no to any one means the tool may not fit the question.

Q1	**Is the pharmacodynamic question lung-specific?** If blood biomarkers, FeNO, or spirometry can answer it, EBC adds cost without unique value. Compartment specificity must be the reason for choosing it.
Q2	**Does that question require a non-invasive airway measure that FeNO cannot provide?** FeNO answers one question: is there Th2-driven eosinophilic airway inflammation? If that is the PD question, FeNO is the appropriate tool. If the question involves oxidative stress, non-Th2 mediators, pH, cytokines, leukotrienes, or multi-pathway biology, EBC is the appropriate non-invasive choice — with the understanding that it does not match BAL's analytic fidelity.
Q3	**Is there a pre-specified analysis plan with a defined downstream use?** Define what a meaningful signal looks like, how variability will be managed, and what decision the data could influence. Without this, the sub-study will not produce interpretable data and will not justify its cost.

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08 · CONCLUSION

The Decision Is Made Once

Every trial that closes without lung biology collected has answered the collection question by default. That default is not neutral. The program that produced ambiguous results and stopped has foreclosed the one analysis that might have distinguished a failed drug from a failed measurement. The program that advanced without airway data is making Phase III endpoint and stratification decisions on systemic and indirect measures alone. In both cases, the biology where the drug was expected to act was never examined. The cost of that gap is not visible at the time the decision is made. It becomes visible later, when the question cannot be reopened.

The option to collect it exists once, at the design stage. The decision to collect or not is made once, by default if not by choice, and it is irreversible.

Evaluating EBC for Your Program

If you are considering whether non-invasive airway pharmacodynamic measurement addresses a gap in your early-phase program, contact Respiratory Research, Inc. to discuss study design, collection standardization, and biomarker selection.

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Contact Us

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