AI-powered cough counting: an objective and scalable endpoint

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Abstract

Cough is a ubiquitous health indicator whose global physical, psychological, and financial burden is extreme and underappreciated. As a disruptive, discrete, and information-rich symptom that is associated with a myriad of diseases, cough is also the ideal clinical endpoint. And yet, even in the age of mobile health, AI, and Big Data, cough continues to be assessed mainly through subjective surveys and brief acoustic recordings with bulky and expensive clinical devices. Half the world population now carries smartphones that, when combined with AI-powered software, can be used as clinical tools for quantifying cough endpoints objectively. Scalable mobile cough monitoring has the potential to transform clinical trials by increasing their success rate, decimating their costs, accelerating products to market, and improving health equity worldwide.

Keywords

clinical endpoints — clinical trials – cough monitoring — respiratory health

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Cough: a global burden, a clinical priority

Cough is everywhere. It is part of normal life; a healthy person coughs an average of once per hour [1, 2]. Cough is also a chronic symptom of dozens of diseases, from the common cold, asthma and COPD to lung cancer, tuberculosis and COVID-19 [3–5]. It is also a disease in itself. 40% of the population at any one time reports cough [6], and chronic cough, defined as cough lasting longer than eight weeks, is an illness that occurs in 10-20% of the world's population [7–10], though this is likely an underestimate [7, 10]. Chronic cough accounts for more than a third of outpatient clinic visits in the United States [7, 11, 12] and more than 27 million visits per year globally [10, 13]. Cough is an unusual symptom, in that it is observed by care providers and also self-reported by patients. The development of cough is the most common reason that people seek primary and specialty care [10, 13]. As such, cough is an important service pathway for all clinical products, even those not focused strictly upon respiratory health.

Cough is important. It diminishes quality of life, though the ubiquity and normalcy of cough can make its global burden easily overlooked [7, 10]. The human toll of cough is both physical and psychological [14, 15]. Physical effects of chronic cough include incontinence, chest pain, headache, syncope, vomiting, and sleep disturbance [15]. Sleep deprivation caused by nighttime cough results in fatigue, poor concentration and malaise, which hurts patients' professional and personal spheres [10]. Psychologically, chronic cough leads to anxiety and depression, particularly when the underlying cause of cough remains unknown [10, 16]. Socially, coughing bouts lead to embarrassment and social isolation, which exacerbate psychological effects [10, 15]. For these reasons, cough is regularly used as *both* a factor *and* a metric for quality of life [10, 17].

Cough is expensive. Its global financial burden is extreme. An astounding $250 million is spent on cough drops each year in the United States alone [18]. For COPD —a disease characterized by chronic cough and shortness of breath [3] —the global costs of treatment, morbidity and lost earnings are counted in the tens of billions [19]. Lost productivity caused by chronic cough and other respiratory diseases cost nations millions in GDP each year [20]. On the individual level, the cost of chronic cough can be debilitating. The total uninsured cost of care for a patient with complex chronic cough is typically more than $10,000 USD [21]. These costs disproportionately impact the lives of minorities, women, and marginalized families, exacerbating cycles of global poverty [22, 23].

For all these reasons, cough is common in clinical research and is increasingly used as a primary endpoint in clinical trials [15]. Cough is studied for various purposes: as a disease unto itself (e.g., chronic cough [8, 10, 24]), as a biomarker for other diseases of interest (e.g., tuberculosis [25] and COVID-19 [5]), or as an indicator of quality of life (e.g., asthma [9]). All of these studies look for changes in cough either as a reflection of the course of disease or as an indicator of the effectiveness of treatment. Cough is an obvious endpoint for trials of medications developed specifically for cough, e.g., antitussive drugs [9, 26, 27] (a $3 billion USD per year market and growing [28, 29]), and chronic cough remains an active field of research that requires tools for counting coughs as an endpoint [24]. But cough is also used as a surrogate endpoint for the response to therapy for a myriad of other diseases [9, 15, 26, 30–34].

Cough as an objective endpoint: missed opportunities

Cough is the perfect clinical endpoint. It is common, easily detected, information-rich, and widely recognized as an indicator of illness [7, 11, 15, 34]. In the last century, cough assessments have emerged as an increasingly important tool for screening, diagnostics and monitoring [34–39]. Another advantage of cough is its dimensionality; it can be assessed from many angles —cough reflex sensitivity, cough severity or intensity, cough impact on quality of life, and cough frequency [9, 15, 40] —and trends in these metrics over time are as valuable diagnostically as the metrics themselves [15, 34].

In practice, however, cough remains drastically underutilized. The vast majority of studies assess cough endpoints by asking patients about coughs —via questionnaires such as the Leicester Cough Questionnaire, the Visual Analog Scale, Cough-specific Quality of Life Questionnaire, the Cough Severity Score, the Cough Severity Diary, the Automated Device for Asthma Monitoring and Management, and the Asthma Control Questionnaire [15, 41–46] —instead of just *listening* to them. Several of these surveys are well-validated and of value, particularly in assessing impacts upon quality of life, but they are limited by their subjectivity and small sample size [9, 15]. If objective observations could be paired with the patient's self-reported experience, such questionairres would be even more informative and actionable [9, 15].

Far less progress has been seen in objective measures of cough frequency and severity. There is broad consensus among cough specialists that precise, objective evaluations are needed in order to study the impact of cough properly [9], and that the assessment of cough frequency is the gold-standard objective tool [15]. Cough counting monitors also reduce the sample size needed for clinical trials and provide an objective means of distinguishing between healthy and ill patients [15, 47, 48]. For these reasons, using acoustic cough counting as an endpoint is a top-priority recommendation of the CHEST Expert Cough Panel [9].

The cough counting devices currently available for clinical studies are expensive, obtrusive, time-limited, and labor-intensive. Though several devices have been developed over the years [47–53], the only validated cough counting devices in widespread use are the Leicester Cough Monitor and VitaloJAK [1, 15, 37, 48, 54, 55]. These are custom-built devices that record for a single 24-hour period, and the acoustic data they collect require between 5 and 90 minutes of manual verification for each day of recording [1, 15, 54, 56]. These devices are also cumbersome, which reduces patient retention and could potentially alter their cough behavior, thus undermining the reasons for their use [34]

These devices also constrain clinical research. The price, obtrusive equipment, and analysis burden of these devices force clinical studies that use them to be either more costly or smaller in scale, which generates statistical issues when endpoint variability is high, as is inherent in human cough [15, 34], and/or when effect sizes of treatments are inherently small [57]. Also, since these devices are designed to monitor patients for less than a day, the data collected may not be representative of general patterns in a patient's life [9, 48], nor can the data speak to long-term or emerging trends in cough behavior, which of themselves could be information-rich clinical endpoints that remain untapped and unexplored [34]. Furthermore, these cough counting tools are typically available only to patients of means with ready access to research clinics, since the devices are expensive when patients are uninsured and they must be returned after only a day of use.

But the parallel rise of smartphones and machine learning has unlocked a new market. Smartphones are in the pockets and purses of nearly half the world population [58], and there are now more phones than people in some Western developed nations [58, 59]. Most importantly, smartphones have distributed high-quality optical and acoustic sensors to at-risk populations worldwide. As these devices have proliferated, new AI technology has enabled the automated analysis of enormous volumes of data [60, 61]. The joint rise of smartphones and AI has the potential to improve healthcare equity for billions living in remote and low-income settings [62–66]. AI-enabled mobile-health apps are rapidly gaining use in clinical care and research [67], and they offer the ideal platform for an unobtrusive tool for monitoring cough objectively [34]. Once adopted as such and cough data are collected at an increasing rate, AI algorithms will become increasingly proficient at (1) distinguishing coughs from other percussive sounds [34], (2) associating certain cough attributes with particular diseases (e.g., [68, 69]), and (3) identifying individual-level characteristics in a patient's cough [60, 61, 70]. These tools will enable *real-time, long-term, continuous,* and *personalized* remote monitoring, with the potential to fundamentally change our approach to patient care, public health, emergency response, and clinical trial design [34, 57, 70–74].

Scalable cough counting with AI: the future of clinical trials

The delays and costs inherent to clinical trials have reached crisis levels [75]. The development cycle for bringing a new drug to market takes 10 to 15 years and \$1.5 to \$2.0 billion USD [76]. These costs have doubled in the last decade [57]. Clinical trials consume the latter half of this cycle [57], the majority of which fail [77, 78]. Each failed trial costs investors \$0.8 to \$1.4 billion USD [57, 79]. The two most common causes of trial failure are (1) low participant adherence / retention, and (2) poor infrastructure for monitoring clients and measuring clinical endpoints [57, 80]. Harrer and colleagues

[57] summarized the crisis as follows: *"A fundamental transformation of the underlying business and innovation model of the entire [clinical trial] industry is needed for a paradigm shift to a new sustainable trajectory of growth and progress"*.

Remotely monitored, AI-powered endpoints for cough can transform clinical trial design. AI techniques in combination with mobile device technology have the potential to develop innovative approaches to clinical research [57, 81–83]. Several researchers have highlighted the benefits of using smartphones and their notification functions for improving participant retention and adherence to treatment [57, 84, 85], and AI software could improve these efforts using dynamic predictions of drop-out risk [57]. Higher retention reduces the cohort size necessary for a trial, thus saving time and money [57]. These benefits apply to all clinical trials. But for those using cough as an endpoint, the most transformative advantages would come with the use of long-term, continuous, AI-powered cough counting software from unobtrusive smartphones, wearable devices, and Internet-of-Things products.

The key benefits of mobile, AI-powered cough counting in trials include the following:

1. No technological constraints on sample size or trial duration, since monitoring software is easily scaled and devices are already distributed in the population. The cough data stream can be tracked at nearly no cost during months of remote trial participant follow-up.
2. Broader and more equitable access to potential participants, since participants can be remote and need not visit or return to a clinic.
3. Access to many endpoints at once, since long-term cough monitoring can measure the characteristics of individual coughs, cross-sectional assessments of cough frequency, as well as continuous longitudinal trends in those metrics.
4. Exponential increase in sample size, since devices need not be returned and AI-powered cough detection algorithms can automatically analyze data.
5. Smaller detectable effect size, thanks to the increase in sample size.
6. Conversely, larger effect sizes can be expected from the many objective endpoints available, therefore allowing patient cohort size to be smaller for an identically powered study.
7. Extreme cost savings, higher rates of trial success, and expedited regulatory approval for new drugs, due to all of the above.
8. More effective and equitable health solutions for all.

Mobile, AI-enabled tools for cough counting will fundamentally disrupt the status quo for clinical trials in respiratory medicine. The benefits and cost savings of this sea-change will reshape systems of care and improve global health.

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