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# Adapting adaptive design methods to accelerate adoption of a digital asthma management intervention

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## Abstract

Investigators conducting translational research in real-world settings may experience changes that create challenges to the successful completion of the trial as well as post-trial adoption and implementation. Adaptive designs support translational research by systematically adapting content and methods to meet the needs of target populations, settings and contexts. This manuscript describes an adaptive implementation research model that provides strategies for changing content, delivery processes, and research methods to correct course when anticipated and unanticipated circumstances occur during a pragmatic trial. The Breathewell Program included two large pragmatic trials of the effectiveness of a digital communication technology intervention to improve symptom management and medication adherence in asthma care. The first trial targeted parents of children with asthma; the second targeted adults with asthma. Adaptations were made iteratively to adjust to dynamic conditions within the healthcare setting, informed by prospectively collected stakeholder input, and were categorized retrospectively by the authors as proactive or reactive. Study outcomes demonstrated improved treatment adherence and clinical efficiency. Kaiser Permanente Colorado, the setting for both studies, adopted the speech recognition intervention into routine care, however, both interventions required numerous adaptations, including changes to target population, intervention content, and internal workflows. Proactive and reactive adaptations assured that both trials were successfully completed. Adaptive research designs will continue to provide an important pathway to move healthcare delivery research into practice while conducting ongoing effectiveness evaluation.

## Lay summary

Health care research often moves slowly and consequently important results may take a long time to reach the patients they are intended to help. Implementation studies conducted in routine clinical practice are intended to accelerate the process of delivering new discoveries into settings where they can be more quickly put to use. However, conducting research in real-world settings can be challenging if changes occur in those settings during the course of the study. Therefore, an adaptive implementation approach that allows researchers to make changes during the course of a study can facilitate study completion and improve likelihood of intervention adoption into routine care. This report demonstrates the use of an adaptive implementation model in two large studies of asthma in children and adults. In both studies, communication technology including computerized phone calls, texts, and email helped improve treatment consistency and efficiency.

**Keywords** Asthma, Pragmatic trials, Adaptive implementation research

**Implications**

**Practice:** Digital technology communication can improve practice efficiency but to the extent it can be adapted to fit provider and patient needs.
**Policy:** Effective asthma programs should consider input from multiple sources including patients, institutional leadership, pharmacists, nurses, and physicians.
**Research:** Future research is needed to understand the "sweet spot" between digital and human delivered health care.

## INTRODUCTION

Implementation science aims to decrease time from discovery to clinical practice by creating a bridge from efficacy to adoption of evidence-based interventions. While randomized controlled trials have long been considered the "gold standard" for establishing the efficacy of interventions, adaptive design approaches are increasingly used within clinical

trials in an effort to accelerate research progression. Adaptive designs also support translational research by systematically adapting content and methods to enhance adoptability of interventions. Adaptive designs often consist of adjustments based on interim analyses of data and/or contextual changes. Such adjustments may be planned in advance or occur in response to unanticipated changes, and may involve adaptation of study protocols, hypotheses, sampling and randomization methods, and even treatment assignment, thus avoiding the need to conduct a series of separate trials [1, 2]. Implementation research studies may also use elements of adaptive research to further hasten real-world uptake of various interventions [3–8]. The elements of study design that may be modified over time in an adaptive implementation trial include study aims, randomization schemes, sample size, study objectives or endpoints, or changes in the setting personnel, study population, and intervention sequence or content [3–5, 9–16]. Adaptations may be *proactive* prior to randomization or *reactive* when unexpected circumstances impact the delivery setting and/or target population, necessitating changes to the methods, intervention, or target population [17]. An example of the proactive adaptation is seen in a trial that allows for re-randomization of participants mid-study [12], while reactive adaptation may occur in response to organizational or setting changes, such as resource reprioritization or healthcare delivery changes [13]. Proactive and reactive adaptations are not mutually exclusive. For example, even proactive adaptations may encounter unanticipated changes in the study environment. An ongoing program of adaptive implementation research can include a series of pragmatic trials which continue to inform routine practice (Fig. 1).

Research into health and communication technologies, an area undergoing rapid evolution, is particularly well suited for adaptive implementation studies [18]. Digital communication technology (DTC) may include speech recognition software, text messaging, and email. In some cases, efforts to study Electronic Health Record (EHR)-based DTC to improve adherence to health behaviors may yield outcomes that are outdated before the study is published. Recognizing this challenge, we used several adaptive strategies to test an EHR-based DTC program, Breathewell, to improve treatment adherence and increase care efficiency for patients with asthma. This adaptive research approach facilitated full implementation from pragmatic controlled trial into routine care. The purpose of this manuscript is to describe the adaptive design model as reflected in the Breathewell program.

## METHODS

### Overview of the Breathewell Program

The Breathewell Program included two randomized pragmatic trials and a phase of implementation of the Breathewell 1 intervention into routine care (Fig. 2). The two implementation studies were funded sequentially by the National Heart, Lung and Blood Institute (NHLBI) under an R01 funding mechanism. Both studies engaged digital health interventions. The first study was focused on improving child adherence to asthma medication, while the second study sought to reducing nursing burden and cost in the care of adults with asthma. Both studies were conducted at Kaiser Permanente of Colorado (KPCO), an integrated healthcare organization serving approximately 600,000 members in the Denver-Boulder area. The following is a description of the development of the Breathewell Program through the lens of adaptive design.

#### Breathewell 1

The objective of the first Breathewell study was to improve adherence to inhaled corticosteroid (ICS) medication in pediatric patients with persistent asthma. The DTC intervention was centered on speech recognition (SR) software with content populated from the KPCO EHR database to provide a tailored, computer generated, interactive discussion encouraging parents to refill their child's ICS when it was more than 30 days overdue for a fill [19]. This was a pragmatic clinical trial within which families were randomized to the SR intervention or usual care and followed for 24 months.

#### Breathewell 2

A second Breathewell study, also funded by the NHLBI, addressed utilization of health and communication technology in adult asthma care at KPCO (Fig. 2). The study expanded utilization of technology-enabled communication used in Breathewell 1 to include speech recognition, texting, and email. Within the intervention group, risk factors for asthma exacerbations were to be identified in the EHR database and included underfilling of inhaled corticosteroid, overfilling of

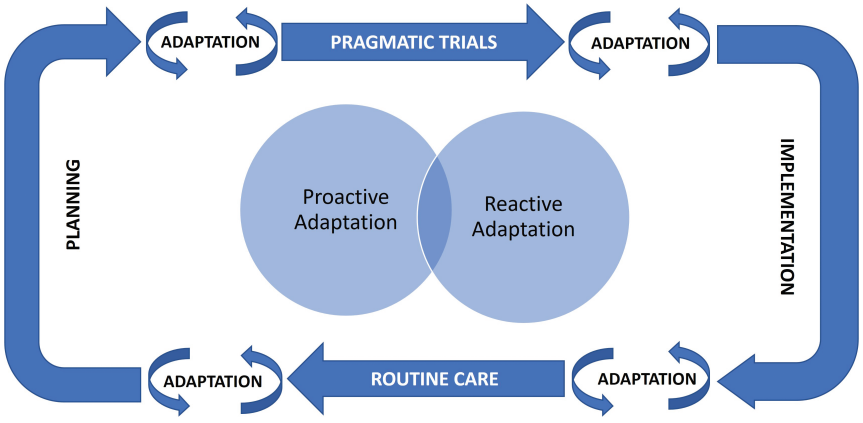


**Fig 1** | Adaptive implementation research model.

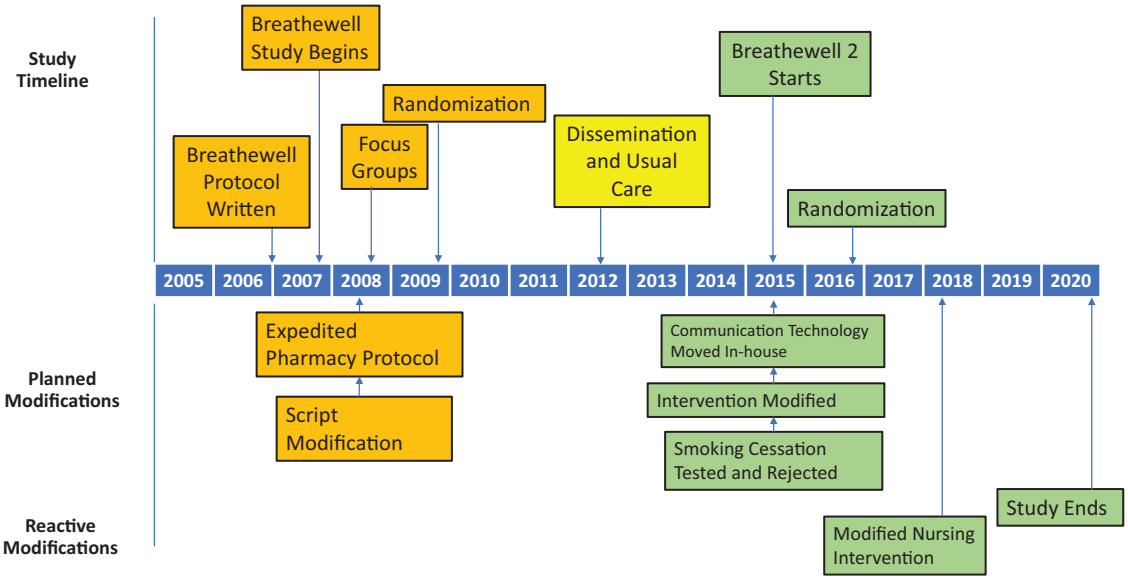


**Fig 2** | The Breathewell Program.

beta$_2$agonist, and history of asthma exacerbation. Medication overfilling or underfilling were to be addressed through the DTC intervention. Where elevated exacerbation risk was determined, an asthma risk report was to be sent to asthma care managers, a panel of nurses who routinely reach out by email and telephone, to support asthma patients. They would then determine whether to escalate care or arrange a follow up appointment with a KPCO allergist or primary care provider.

### Stakeholder engagement

The Breathewell Program included stakeholder, researcher, and oversight groups. Stakeholders included patients who participated in focus groups at the beginning of the initial study and provided feedback during key informant interviews following the introduction of the intervention and again after completion of the Breathewell 1 study. Other stakeholders included members of the research team, physicians, nurses, communication technology specialists, and organizational leadership. Stakeholder meetings occurred prior to the commencement of the trials. The research team was comprised of the principle and co-investigators, research coordinators, statisticians, and representatives from the allergy, nursing, and pharmacy departments. The research team met weekly initially, and then biweekly through the entire duration of the study. Topics for discussion included problems identified and whether adaptations to protocols or intervention content were necessary and appropriate. Information from meetings with stakeholders was recorded and included in weekly and biweekly study team meetings. Minutes from those meetings included documentation of any adaptive changes made in the course of the studies. Most adaptations in both trials were made prior to randomization, although one *reactive* adaptation in Breathewell 2 was made 18 months after randomization. The research team additionally worked closely with the oversight committee, which much like a data safety and monitoring board was charged with maintaining patient safety and improving asthma population management at KPCO. The oversight committee was comprised of asthma care managers and representatives from pharmacy, family medicine, allergy, and pediatrics. The research team and oversight committee remained in place for both Breathewell I and 2.

## RESULTS

### Breathewell 1

#### Adaptations

*Proactive adaptations prior to randomization.*

At the time when the study protocol was written and funded, the planned SR intervention included use of the primary care physician's own voice, a series of symptom questions, and branching options dependent on the parents' responses that could provide information about the medication, discussion of potential side effects, and other educational messages. Parents wishing to refill their child's medication were then to be transferred to the KPCO pharmacy. Several adaptations to the study protocol were made in the pilot phase based on stakeholder feedback. Parent focus groups and pilot testing brought responses necessitating re-writing of the speech recognition scripts. Parents preferred shorter telephone calls than originally planned, without prolonged educational content, that clearly identified the call as coming from KPCO. Further, parents preferred an expedited refill protocol that did not require transfer to a pharmacy line where they might have to wait on hold for a prolonged period of time [19]. These changes were made to the intervention with further programming that allowed immediate ordering of a refill during the speech recognition conversation without transfer to a pharmacy line. Providers and information technology staff advised against attempting to record each provider's voice, opting instead for a single standardized speech recognition voice. Programming was expanded to interface with the electronic pharmacy program and allow for immediate order of a refill in response to a parent voice confirmation of the request. Beyond tailoring the content of the speech recognition intervention, no changes were made to study aim, setting, personnel, or patient population (Table 1).

**Table 1** | Proactive and reactive adaptations to the Breathewell Program

| Trial phase | Research phase | Adaptation type | Adaptation |
|---|---|---|---|
| BW1 | Pre-implementation | Proactive | Protocol refinement based on stakeholder and parent input |
| | Pre-implementation | Proactive | Focus groups resulted in shortened messaging, eliminating educational content, and clearly identifying caller of incoming call |
| | Pre-implementation | Proactive | Pilot testing with parents resulted in elimination of transfer to pharmacy and development of an automated system to reorder medication |
| | Pre-implementation | Proactive | Pilot testing with asthma clinical providers and internal technology experts resulted in one singular voice rather than a tailored provider voice |
| Dissemination | Dissemination into usual care | Proactive | Transition to in-house technology system for outreach; outreach target population expanded to adults; use of internal administrative data to tailor the message to the patient |
| | Post-implementation into usual care | Reactive | Minor technology adaptations were made to accommodate asthma clinical guidelines and internal diagnostic code and medication changes |
| BW2 | Pre-implementation | Proactive | Continued use of in-house technology system for outreach |
| | Intervention modification | Proactive | Adaptation of primary intervention given the success of BW1 to usual care; transition focus to beta agonist overfill intervention using technology and reduce human resources |
| | Pilot intervention component | Proactive | Pilot test smoking cessation intervention component for feasibility and acceptability—tested and rejected |
| | Implementation adaptation | Reactive | Technology modification to enhance in-basket numeration for clinical nurse outreach team within 2 weeks of trial implementation |
| | Implementation adaptation | Reactive | Asthma nursing care management services discontinued by institution; moved to primary care clinical outreach |

*BW1* Breathewell 1 randomized clinical trial; *BW2* Breathewell 2 randomized clinical trial.

**Reactive adaptations. No reactive adaptations were made after commencement of the study.**

*Study outcome.*

SR telephone calls to parents in the intervention condition, which were triggered when an inhaled corticosteroid refill was 30 days overdue, improved adherence by 25.4%. Adherence, measured as proportion of days covered (PDC) based on refills, remained significantly higher in the intervention group than in the usual care group over a period of 24 months [19].

*Moving from pragmatic trial to real-world implementation (Fig. 2).*

The Breathewell 1 study offered evidence that the DTC intervention worked successfully in a pragmatic clinical trial to improve treatment adherence. That outcome opened the door to permanently embedding the intervention into routine care at KPCO. To move Breathewell 1 from the pragmatic trial to implementation into routine care [6], many elements of the original SR program were adopted as standard operating procedure in KPCO. While the SR program in Breathewell 1 was built and run by an outside vendor, adoption into standard operating procedure was accomplished by internal KPCO technology systems. Stakeholders determined that the target audience would be KPCO adults with asthma and parents of children with asthma. Calls fell into two categories: a brief reminder 5–11 days before the medication was due for a refill, and a more extended call for patients more than 30 days overdue for a refill. An automated exchange of information between the EHR and SR program included the patient's name, telephone number, name of medication, and refill history, and the last 4 digits of the patient's credit card, allowing for a tailored conversation with the patient or parent. The voice generated by the SR program could address the patient by name, identify the medication as well as the date of last refill, offer more information about how to manage asthma symptoms, connect them to the pharmacy refill line or automatically place a mail-order refill.

*Post-implementation outcomes.*

A total of 4,510 adults with persistent asthma received 24,599 automated Breathewell contacts. Patient adherence, measured as PDC, improved slightly, from 39.5 to 41.7% from the year before to the year after introduction of the technology-assisted communication intervention in routine care. Rates of oral steroid prescriptions decreased while emergency department visits and hospitalizations did not change [20].

## Breathewell 2

### Adaptations

*Proactive adaptations before randomization.*

The original study protocol included contracting with an outside vendor specializing in technology-enabled communication. However, as commencement of the study approached, internal growth in KPCO technology capability led to the decision not to utilize the outside vendor but instead utilize the internal technology team. This decision was made in part in recognition that adoption of the implementation study intervention into usual care after completion of the study would be expedited if the technology were developed and owned within KPCO (Table 1).

*Proactive adaptations after randomization.*

Four potential adaptations to the study were considered prior to randomization. (i) Organizational changes in use of digital communication technology necessitated a change in the intervention. Due to the success of the Breathewell 1 study and incorporation of the SR protocol into standard care [20], potential for further adherence improvement resulting from the Breathewell 2 intervention was diminished. Therefore, the primary intervention was adapted instead to address beta$_2$agonist overfilling, which is a predictor of asthma exacerbations [21]. In standard care at KPCO, when a beta$_2$agonist refill was requested more frequently than every 60 days, patients received a call from an asthma care nurse to determine whether the patient was experiencing more frequent asthma symptoms and, if so, to arrange an office visit with a prescribing provider. To reduce the nursing load, the Breathewell 2 intervention leveraged DTC outreach, triggered by the beta$_2$agonist refill request, with a screening question about recent symptoms. Patients were randomized to telephone, email, or usual care. If the technology-enabled communications determined that the patient was not experiencing increased symptoms, no referral to the asthma care managers was required, which accomplished the goal of reducing nursing staff time and creating greater clinical efficiency. (ii) Stakeholder feedback from asthma patient interviews and KPCO technology staff lead to the decision to make the first attempted outreach for patients randomized to telephone by text message. If the patient did not have a texting enabled phone, outreach switched to an SR call. If they did not respond to 3 text/SR attempts, or if they had an exacerbation in the last year or had not filled their ICS within the last 90 days, the patient was referred to the asthma care manager team. (iii) The smoking cessation intervention component was targeted at asthma patients recorded in the EHR to be current smokers and included a brief message about the importance of stopping tobacco use to their asthma and overall health. The smoking cessation component also included an offer to assist the patient in signing up for the KPCO sponsored Quitline smoking cessation program. In the initial phase, this communication technology intervention was tested with 121 asthma patients who were known smokers. The intervention had no impact on enrollment in the smoking cessation program. This outcome and recognition that patients prefer shorter calls resulted in a decision to exclude it from the overall Breathewell intervention (Table 1).

*Reactive adaptations.*

One significant change in the organization of care-delivery in KPCO occurred during the Breathewell 2 study. In a move toward cost containment, KPCO leadership eliminated the asthma care nurse program. Hence, the hand-off of patients with a positive technology-enabled symptom screening to the asthma care nursing team could no longer happen. The responsibility of contacting symptom-positive patients in the intervention groups was therefore instead transferred to primary care clinic nurses.

*Study outcome.*

Of 2,874 beta$_2$agonist refill requests, 1,188 (41%) were resolved through technology-enabled communication, thus eliminating the need for a nursing intervention. Asthma medication use and exacerbations over the following year did not differ between the usual care or intervention groups [22]. Further, the changes were cost-saving. Nursing care costs were reduced by $16,278. Once implemented, the cost to maintain the technology-assisted communication program was under $2000/year [23]. Patients who wished to receive technology-assisted communications also expressed a clear preference for text messaging [24]. The Breathewell 2 DTC intervention has not yet been implemented in standard care and, due to reorganization of KPCO asthma care management, will require further planning and adaptation of DCT information flow, as well as input from primary care stakeholders to maximize its utility and successful implementation (Table 1).

## DISCUSSION

The Breathewell Program used proactive and reactive adaptations across two pragmatic clinical trials, employing an adaptive implementation research approach to improve asthma medication adherence and care efficiency. Evidence from Breathewell 1 led to adoption of the DCT into routine care at KPCO. While overall study objectives remained the same, changes were made to intervention sequence, content, and technology pre- and post-randomization [6]. From an adaptation perspective, an intervention designed for, and shown effective with, a pediatric population was then adapted to assist an adult population. That change in turn required a planned, post-randomization change in intervention content in Breathewell 2. Specifically, the decision to change the Breathewell 2 intervention followed an organizational decision to fully implement the speech recognition program into asthma population-based usual care. The decision to move to digital technology created internally within KPCO, rather than to continue to utilize an external technology vendor, facilitates sustainability and likely contributed to the cost-saving documented in Breathewell 2.

The need to make adaptations was driven both by the nature of implementation research and the rapidly evolving technology at the center of the interventions. Recognizing that results from randomized clinical trials are frequently slow to disseminate into healthcare, implementation research is often conducted through pragmatic trials in real-world settings, with interventions delivered in multiple sites by existing clinical staff to a heterogeneous population of patients to answer clinically important questions [25]. In such settings, organizational challenges may threaten fidelity of the intervention and success of the trial. Some adaptive changes are *proactive*. For example, adaptive implementation studies have allowed for re-assignment of interventions that are not proving successful. Sequential Multiple Assignment Randomized Implementation Trials (SMART) utilized multistage randomizations with an adaptive approach during a trial if an intervention strategy was failing. One example of the use of the SMART adaptive approach is seen in a sequence of studies, the first of which failed because fewer than half of assigned study sites maintained the assigned intervention [26]. In a subsequent study, community-based outpatient clinics that did not respond were re-randomized to a modified intervention that included support from an external facilitator, internal facilitator, or both. Clinics unresponsive to the external facilitator were then randomized to a different facilitator [11]. Other adaptive changes are *reactive* where implementation research is susceptible to organizational and system changes in financial priorities, clinical structures, providers and care-delivery

protocols. Staff turnover and changes in existing programs have necessitated adaptations during other implementation trials [27, 28]. The capacity to adaptively modify the trial during the trial, consequently, becomes essential. At the same time, such course corrections during an ongoing trial must maintain the fidelity of the intervention [13]. As seen in the Breathewell program, adaptive implementation research can facilitate the translational process by allowing more rapid, real-world uptake of evidence-based interventions.

One challenge to the introduction of adaptive research designs is the establishment of an understanding with the funding organization and oversight committees that the adaptive approach, both *proactive* and *reactive*, may require changes in study protocols, hypotheses, sampling and randomization methods, and even treatment assignment. A written plan for the adaptive approach should be included in the study proposal. When the research is funded by the National Institutes of Health, frequent communication with the project officer as well as the data safety monitoring board is necessary to help assure that the proposed changes are consistent with the overall study goals and plan.

Limitations in this single example of the adaptive implementation model should be considered. While the Breathewell Program illustrated how sequential pragmatic trials, stakeholder input and multi-level adaptations can result in practice change, this research program is limited by its representation of one type of DCT within one type of setting, constraining the generalizability of our findings. Descriptions of the adaptations made also relied on retrospective review of project documentation and agreement among authors of whether they were prospective or reactive examples. Not included was a measure of the extent that specific adaptations improved or detracted from intended outcomes during the trials, nor their impact post-implementation. Comparison of adapted and non-adapted interventions, and the impact of specific types or levels of adaptations on the process indicators associated with implementation success (e.g., extent an adaptation impacted reach, adoption, fidelity, or maintenance) is a suggested area for future research [29].

Adaptive research designs will continue to provide an important pathway to move healthcare delivery research into practice while conducting ongoing effectiveness evaluation. Development of health and information technologies, and the systems and structures with which they interface, may outpace the clinical trials needed to test them. Fortunately, adaptive research designs allow for more rapid testing and implementation into healthcare. Studies that explicitly collect and analyze multilevel data iteratively to respond not only to treatment indicators but also to changes in policies, structures and systems, are increasingly essential to balance the pull of market, competitive and other pressures, with the need for rigorously tested, safe, effective, and adaptable digital health interventions.

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## Compliance with Ethical Standards

**Conflict of interests:** Bruce Bender, Peter Cvietusa, Glenn Goodrich, Diane King and Jo Ann Shoup declare that they have no conflicts of interest.

**Human Rights:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent:** This study involved human participants and a waiver of informed consent for a data-only study was granted by KPCO IRB.

**Welfare of Animals:** This article does not contain any studies with animals performed by any of the authors.

**Transparency Statements:** (1) Study registration: This study was registered both trials of Breathewell with clinicaltrials.gov (Breathewell 1 Identifier: NCT00958932; Breathewell 2 Identifier: NCT02761837). (2) Analytic plan registration: The analysis plan was not formally pre-registered. (3) Availability of data: De-identified data from this study are not available in a public archive. De-identified data from this study will be made available (as allowable according to institutional IRB standards) by emailing the corresponding author. (4) Availability of analytic code: Analytic code used to conduct the analyses presented in this study are not available in a public archive. They may be available by emailing the corresponding author. (5) Availability of materials: Materials used to conduct the study are not publicly available.

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