Statistical Analysis Plan – part 2

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2 Introduction

2.1 Preface

During the COVID-19 pandemic, school closures were implemented to safeguard students, teachers, and their families from the airborne transmission of SARS-CoV-2. However, these closures brought potential issues of disrupted learning, social isolation, and well-being challenges, highlighting the need for alternative measures. This pilot study aims to explore the feasibility and potential impact of integrating air purifiers equipped with HEPA filters into school classrooms to enhance infection control.

2.2 Research Questions

1. Is it acceptable and feasible to deploy air purifiers into classrooms?
2. Is air purification superior to no air purification in lowering the concentration of particulate matter (PM2.5) in classrooms (irrespective of whether ceiling-mounted or portable air purifiers are used)?
3. Are portable air purifiers noninferior to ceiling-mounted air purifiers in lowering the concentration of PM 2.5?

The study consists of two parts, referred to as part 1 and part 2, which are further described in the protocol. Question 1 is addressed in parts 1 and 2. Questions 2 and 3 are addressed in part 2. This SAP focuses on part 2 because part 1 uses information collected from interviews that will not be analyzed statistically. Unless otherwise stated, all data and analyses discussed herein pertain to part 2. While this pilot study is mainly concerned with acceptability and feasibility, the primary outcome from the perspective of this SAP is air quality.

3 Study Methods

3.1 General Study Design and Plan

Population	School students and staff.
Interventions	1. Ceiling-mounted air purifier. 2. Portable air purifier.
Control	No air purifier.
Primary outcome	Air quality.
Design	Three-arm randomized crossover.
Blinding	N/A
Treatment allocation	Each of three classrooms were randomized to one of the three treatment sequences as in Table 1.

3.2 General Study Populations and Inclusion-Exclusion Criteria

See published protocol at Zenodo (1)

3.3 Treatment Allocation

Each of three classrooms was randomly assigned to one of the three treatment sequences shown below (Table 1).

Table 1—Randomization schedule

		Classroom		
Week	**Date**	*1*	*2*	*3*
1	29.Jan to 4.Feb	Both OFF	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF
2	5.Feb to 11.Feb	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF	Both OFF
3	12.Feb to 18.Feb	Ceiling Mounted ON Portable OFF	Both OFF	Ceiling Mounted OFF Portable ON
4	19.Feb to 25.Feb	Both OFF	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF
		Winter Holiday		
5	4.Mar to 10.Mar	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF	Both OFF
6	11.Mar to 17.Mar	Ceiling Mounted ON Portable OFF	Both OFF	Ceiling Mounted OFF Portable ON
7	18.Mar to 24.Mar	Both OFF	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF
		Easter Holiday		
8	1.Apr to 7.Apr	Ceiling Mounted OFF Portable ON	Ceiling Mounted ON Portable OFF	Both OFF
9	8.Apr to 14.Apr	Ceiling Mounted ON Portable OFF	Both OFF	Ceiling Mounted OFF Portable ON

Note that while it would be possible in principle for both the ceiling-mounted and portable air purifier to be on at the same time, this treatment combination will not be used.

3.4 Blinding/Masking

Blinding was not employed, as it would not be sensible for this small pilot study.

4 Outcomes

4.1 Primary outcome

The primary outcome is air quality as assessed by particular matter concentration ($PM_{2.5}$ with units $\mu g/m^3$; a count variable). This will be measured using two different optical sensors (Airthings and Digiref) placed at two different locations in each classroom. Air quality will be measured at 5- to 10-minute intervals, defining a time series. Rather than aggregate data from the two sensors, we will treat the measurements as being clustered within classroom. An excess of zero counts of $PM_{2.5}$ is possible.

4.2 Secondary outcome

The secondary outcome is air quality as assessed by volatile organic compounds (VOC, with units of ppm; a count variable). This will be measured in the same way as for the primary outcome.
The study will also assess adverse events (defined as students or staff needing any medical attention or experience any injury or other harm), but we will not statistically analyze adverse event data.

5 Sample Size

The sample size was calculated as follows. We set a non-inferiority margin and stated that portable air purifiers are as good as ceiling-mounted air purifiers if there is a non-significant difference of 10 percentage points in particle density. For these calculations, particle density without air purification is assumed to be 10 $\mu g/m^3$ (2) Assuming that ceiling-mounted air purifiers remove 50%, and portable air purifiers remove 45%, the measured particle density after purification is 5 and 5.5 $\mu g/m^3$, respectively. Given these assumptions, and a one-sided power calculation, we calculated that we would need 28 measurements in each group. Thus, we planned to run part 2 of the trial for 6 weeks, measuring at least once daily in each classroom during the weekdays when the classrooms are in use, to get 30 measurements.

6 General Analysis Considerations

6.1 Timing of Analyses

We performed an interim analysis for the purpose of gathering data for the REK application (deadline of 19th March 2024), before all data were collected. We will use data from all 9 weeks of the study period for the final analysis. No follow-up analyses are planned.

6.2 Analysis Sets

6.2.1 Anticipated format of the data

Table 2 shows the anticipated form that the data will take to permit the planned analyses. Note that it is not anticipated that the data will be exactly as shown, or that the variables have the names shown, but that the format will be very similar or can be easily transformed into this form. The data are arranged with one set of outcome and covariate measurements, for a given sensor, per row. The Week variable identifies the week in which the measurements we made. The Room variable identifies the classroom. The Start Time and End Time variables specify the time period during which the measurements were made and allow the period of exposure to be calculated for the count outcomes. The values XX/XX/XX XX:XX merely indicate that a sufficiently precise date and time will be available, but these variables will be used to calculate exposure, so if this information is available directly, it should be used instead. The Treatment variable indicates treatment assignment. The Sensor variable identifies the sensor type used to measure the air quality outcomes. The $PM_{2.5}$ and CO_2 variables specify the outcomes. The other outcomes and covariables are indicated by "…".

Table 2—Anticipated format of the data

Week	Room	Start Time	End Time	Treatment	Sensor	$PM_{2.5}$	CO_2	…	Indoor Temp.
1	1	XX/XX/XX XX:XX	XX/XX/XX XX:XX	Ceiling	Airthings	9	…	…	18
1	2	XX/XX/XX XX:XX	XX/XX/XX XX:XX	Portable	Digiref	6	…	…	21
…	…	…	…	…	…	…	…	…	…
2	3	XX/XX/XX XX:XX	XX/XX/XX XX:XX	None	Digiref	20	…	…	20
…	…	…	…	…	…	…	…	…	…

6.2.2 Intention to treat analysis set

An intention to treat (ITT) analysis set will include measurements of the outcomes and covariates, as described above, from all three classrooms made during school hours for the whole study period. We may need to remove erroneous measurements and will report if and how this was done. The ITT set will be used for the main analyses of the primary and secondary outcomes.

6.2.3 Per protocol analysis set

A per protocol (PP) analysis set will be defined by restricting the ITT set to exclude measurements made when the air purifiers were not running as planned (defined using reports from the school). The PP set will be used for exploratory analyses of the primary and secondary outcomes.

6.3 Covariates and Subgroups

Figure 1 shows a directed acyclic graph (DAG) that presents possible causal pathways for several time-varying covariates (defined in Table 3) that may affect the outcome variables.

Figure 1—Directed acyclic graph

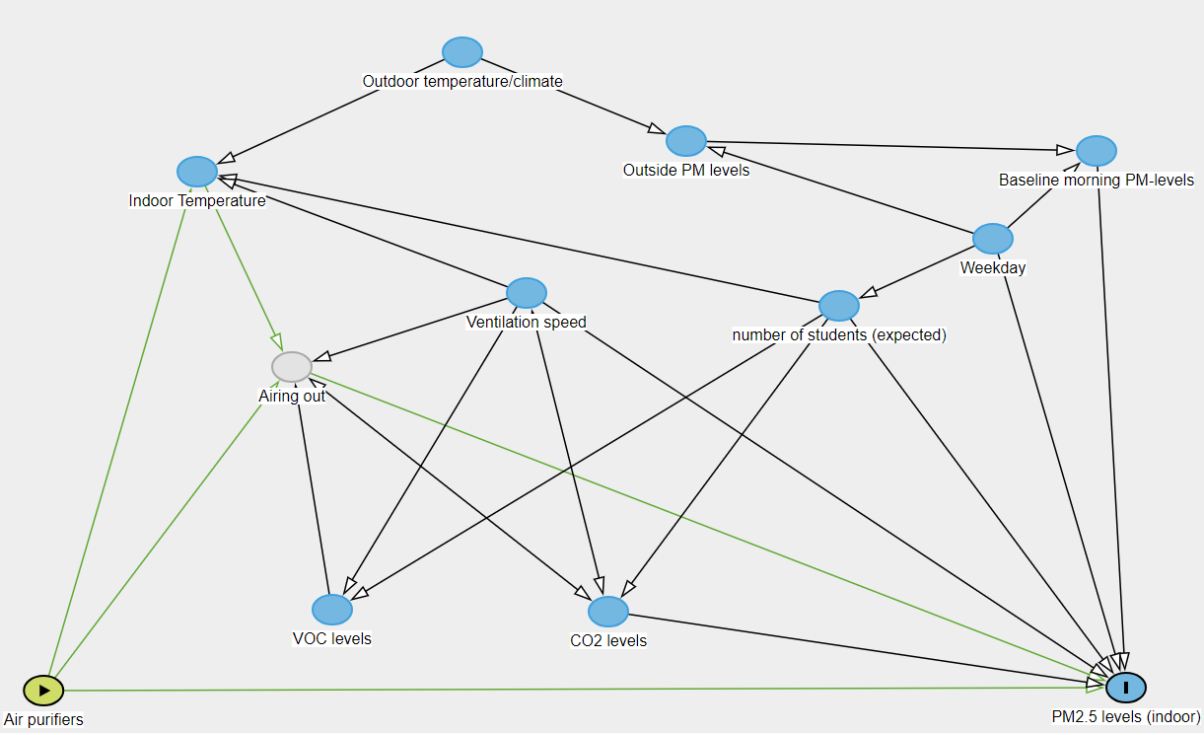


Table 3—Time-varying covariates

Time-varying Covariate	Units	Type
Ventilation level	Low/high	Categorical
Number of students expected	Students	Count
Weekday	N/A	Factor
Baseline morning $PM_{2.5}$ level	$\mu g/m^3$	Count
CO_2 level	ppm	Count
VOC level	ppb	Count
Indoor temperature	°C	Continuous
Outside $PM_{2.5}$ level	ppm	Count
Outdoor temperature	°C	Continuous
Airing out	N/A	Dichotomous (unobservable)

This pilot randomized only three classrooms to one of three treatment sequences. It is therefore very unlikely that the randomization will facilitate strong causal inferences to be made, because any observed differences in outcomes between the treatment sequences may plausibly be explained by a covariate (which may or may not be observable). However, there may be insufficient data to account for the effect of the covariates and also obtain sufficiently precise estimates of treatment effect. The main analyses will be performed without adjusting for covariates, but we will also perform exploratory analyses that attempt to account for the covariates (see section 8.5).

6.4 Missing Data

We anticipate that no data will be missing. However, because this is a pilot, we will treat any missing data as missing completely at random (MCAR) and perform complete case analysis.

6.5 Intercurrent Events

We will address lack of adherence using per protocol analyses. We will address the possible effect of time-varying covariates using the approach described in section 8.5. Because this is a pilot, we will not consider other covariates that could be considered as intercurrent events.

7 Summary of Study Data

7.1 Figures

We plan to present the following figures:

1. Room plans showing the locations of the air purifiers and air quality sensors.
2. Six boxplots summarizing the distributions of the primary outcome ($PM_{2.5}$ counts) by sensor type (Airthings and Digiref) and treatment (both air purifiers off, ceiling-mounted air purifier on, portable air purifier on).
3. Six boxplots summarizing the distributions of the noise level measurements by sensor type (Airthings and Digiref) and treatment (both air purifiers off, ceiling-mounted air purifier on, portable air purifier on).
4. Four time series plots showing air quality, one for each of the following parameters: $PM_{2.5}$ CO2, VOC, and humidity. Each graph will contain five lines, with each line representing the data collected from one of the five classrooms with ceiling-mounted or portable air purifiers from part 1 of the study.
5. A line graph showing the weekly rate of questionnaire response among students/legal guardians in part 1.

7.2 Tables

We plan to present tables like those in the following subsections.

7.2.1 Study timeline

A table like Table 1 will be presented to explain the study timeline and randomization schedule.

7.2.2 Baseline characteristics

A table like the following (Table 5) will be presented to describe key baseline variables across the three classrooms, as measured in week 0 (i.e., the week before treatment commencement):

Table 4—Baseline characteristics

		Classroom 1	**Classroom 2**	**Classroom 3**
Date built or last renovated		DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY
Floor area (m^2)		XX.X	XX.X	XX.X
Ceiling height (m)		X.X	X.X	X.X
Classroom volume (m3)				
Openable window area (m^2)		XX.X	XX.X	XX.X
Declared number of students*		XX	XX	XX
Orientation of classroom (direction/view)		East/schoolyard	West/street	..
Surroundings		Rural	Urban	Suburban
Temperature (°C)	Mean (SD)	XX.X (X.X)	XX.X (X.X)	XX.X (X.X)
	Median (IQR)	XX.X	XX.X	XX.X
		(XX.X to XX.X)	(XX.X to XX.X)	(XX.X to XX.X)
Relative humidity (%)	Mean (SD)	XX.X (X.X)	XX.X (X.X)	XX.X (X.X)
	Median (IQR)	XX.X	XX.X	XX.X
		(XX.X to XX.X)	(XX.X to XX.X)	(XX.X to XX.X)
VOC (ppb)	Mean (SD)	XX.X (X.X)	XX.X (X.X)	XX.X (X.X)
	Median (IQR)	XX.X	XX.X	XX.X
		(XX.X to XX.X)	(XX.X to XX.X)	(XX.X to XX.X)
CO_2 concentration (ppm)	Mean (SD)	XX.X (X.X)	XX.X (X.X)	XX.X (X.X)
	Median (IQR)	XX.X	XX.X	XX.X
		(XX.X to XX.X)	(XX.X to XX.X)	(XX.X to XX.X)
$PM_{2.5}$ (µg/m^3)	Mean (SD)	XX.X (X.X)	XX.X (X.X)	XX.X (X.X)
	Median (IQR)	XX.X	XX.X	XX.X
		(XX.X to XX.X)	(XX.X to XX.X)	(XX.X to XX.X)

SD: standard deviation; IQR: interquartile range; *Number of students in the class using the classroom.

7.2.3 Air purifier specifications

A table will be presented to describe the specifications of the air purifiers in terms of their size (length, width, height), noise level, coverage area, Clean Air Delivery Rate (CADR), and power rating.

7.2.4 Estimates of treatment effect for the primary and secondary outcomes

A table like the following will present estimates of treatment effect for the primary and secondary outcomes (ITT analysis set). Superiority of air purification to no air purification (see section 2.2) will be assessed by testing the joint null hypothesis of no treatment effect for ceiling-mounted and portable air purifiers (see section 8.2). Noninferiority of portable air purifiers to ceiling-mounted air purifiers (see section 2.2) will be assessed by testing one-sided null hypotheses (see section 8.4).

Table 5—Estimates of treatment effect for the primary and secondary outcomes

	Crude summaries[1]			Treatment effects with 95% CIs[2]		p-values	
	None	Ceiling	Portable	Ceiling vs None	Portable vs None	Superiority of air purification	Noninferiority (portable vs ceiling)
Primary outcome							
$PM_{2.5}$	XXX	XXX	XXX	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)	0.XXX	0.XXX
Secondary outcome							
VOC	XXX	XXX	XXX	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)	0.XXX	0.XXX

1. Crude summaries are aggregated over sensor type and classroom. Count and dichotomous outcomes are summarized as totals. Continuous outcomes are summarized as means (SDs). 2. Treatment effects are estimated by accounting for treatment sequence and repeated measures.

Note that due to the design of the study (crossover with repeated measures), it is not possible to present crude summaries of the outcomes by treatment, as is common in parallel RCTs, without breaking randomization. (i.e., to report crude summaries, it is necessary to aggregate over sensor type and classroom).

7.2.5 Results of the exploratory analyses of the primary and secondary outcomes

A table like the following will present results of the exploratory analyses of treatment effect for the primary and secondary outcomes (PP analysis set).

Table 6—Results for the exploratory analyses of the primary and secondary outcomes

	Crude summaries[1]			Treatment effects with 95% CIs[2]		p-values	
	None	Ceiling	Portable	Ceiling vs None	Portable vs None	Superiority of air purification	Noninferiority (portable vs ceiling)
Primary outcome							
$PM_{2.5}$	XXX	XXX	XXX	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)	0.XXX	0.XXX
Secondary outcome							
VOC	XXX	XXX	XXX	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)	0.XXX	0.XXX

1. Crude summaries are aggregated over sensor type and classroom. Count and dichotomous outcomes are summarized as totals. Continuous outcomes are summarized as means (SDs). 2. Treatment effects are estimated by accounting for treatment sequence and repeated measures.

7.2.6 Results of the exploratory covariate-adjusted analysis of the primary outcome

A table like the following will present results of the exploratory covariate-adjusted analyses of treatment effect for the primary outcome.

Table 7—Results for the exploratory time-varying covariate-adjusted analysis

	Crude summaries[1]			Treatment effects with 95% CIs[2]		p-values	
	None	Ceiling	Portable	Ceiling vs None	Portable vs None	Superiority of air purification	Noninferiority (portable vs ceiling)
Primary outcome							
$PM_{2.5}$	XXX	XXX	XXX	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)	0.XXX	0.XXX

1. Crude summaries are aggregated over sensor type and classroom. Count and dichotomous outcomes are summarized as totals. Continuous outcomes are summarized as means (SDs). 2. Treatment effects are estimated by accounting for treatment sequence and repeated measures.

7.3 Derived Variables

There are no derived variables. Because imputation will not be used, no consideration of derived imputed variables is necessary.

7.4 Protocol Deviations

Any deviations from the original protocol or this SAP will be reported and justified.

8 Estimation and Analyses

8.1 Main statistical concerns

The main statistical concerns for this pilot are:

1. The crossover design with multiple crossovers and repeated measures. Outcomes measured by a given sensor in a given classroom are therefore likely to be autocorrelated.
2. Use of two sensors in each classroom.
3. Possible overdispersion and zero-inflation of count outcomes.
4. A research question concerning noninferiority.
5. Competing exposures (time-varying covariates) and the very limited number of classrooms.
6. Multiplicity issues arising from estimating treatment effects and testing superiority and noninferiority hypotheses for each outcome.

This pilot uses a crossover design, in which classrooms cross over from one treatment to another each week. We therefore assume that weekends and holidays act as washout periods and sufficiently eliminate any carryover effects such that these do not need to be addressed in the analyses.

It is not possible to prespecify a “correct” model for a given outcome variable because very little can be assumed about the data generation mechanism. While data-driven model choices could be made at the analysis stage, there is a risk that these choices could be made to obtain “convenient” results. We will therefore prespecify relatively simple models that attempt to address the main statistical challenges. However, given the nature of this study, the results of these analyses should not be overinterpreted.

The effects of ceiling-mounted and portable air purifiers (compared to no air purifiers, the reference) will be estimated using fixed effects.

We will account for the likely autocorrelation within classroom and sensor using first order autoregressive models. Due to the assumed nature of the primary outcome and the limitations this poses on estimator choice, we will implement autoregression by including lagged log rate as a fixed effect (i.e., we assume that log event rate in a given time period depends on the log of the observed event rate in the previous time period for the same classroom and sensor). Because we do not know *a priori* that accounting for first-order autocorrelation will be sufficient, we will perform exploratory sensitivity analysis of the primary outcome using higher order autocorrelations. We will report this narratively (e.g., in a discussion section), but the main results will use first-order autocorrelation as prespecified.

We will account for the use of two sensors as a fixed effect (i.e., we assume there may be a systematic difference in readings from the two types of sensors). Because measurements are clustered within classroom, we will compute cluster robust standard errors with classroom as the cluster variable. We will not treat classroom as a random effect in this pilot, given there are only three.

We will account for possible overdispersion, and zero-inflation of count outcomes as described in section 8.2.

We will address the noninferiority issue as described in section 8.4.

We will address the issue of time-varying covariates by performing an exploratory analysis for the primary outcome as described in section 8.5 (see also sections 6.3 and 7.2.6).

There are possible multiplicity issues that arise from estimating treatment effects and testing superiority and noninferiority hypotheses for each outcome. Because this is a pilot, we will not formally adjust for multiplicity, but will avoid overinterpreting "significant" results given the multiplicity issue and the other study limitations.

8.2 Treatment effect estimation for count outcomes

As described in section 8.1, possible first order autocorrelation will be modelled by including lagged log rate as a fixed effect. These will be computed as:

$$\log \rho_{s,c,i} = \log y_{s,c,i-1} - \log t_{s,c,i-1}$$

where the lagged logged rate $\log \rho_{s,c,i}$ for sensor type s in classroom c for time period i is the difference on the log scale between the outcome (y) and exposure (t) for that sensor and classroom in the preceding time period. Note that $\log \rho_{s,c,i}$ is undefined for the initial time periods where there is no preceding time period and may not have an interpretation that is consistent with the other values of $\log \rho_{s,c,i}$ at the start of the school day (which includes after weekends and holidays). We will treat undefined values as latent (i.e., missing) values that can be predicted due to the assumed autocorrelation, and estimate them using maximum likelihood using the approach described by Allison 2012 ("Handling missing data by maximum likelihood", SAS Global Forum. Vol. 2012. No. 312.). Briefly, undefined values of the lags will be set to zero and a factor variable created with a base level for well-defined lags and each of the undefined lags will be identified by a unique level. This variable will then be included as a fixed effect such as to estimate the values of the undefined lags.

We will estimate treatment effects for count outcomes as rate ratios. We will report treatment effects using a zero-inflated negative binomial model that accounts for possible overdispersion and

anticipated zero-inflation, or a negative binomial model that accounts for possible overdispersion, or a Poisson model that accounts for neither, selected based on the Akaike information criterion. The model selected for a primary or secondary outcome using the ITT analysis set will then be used in subsequent analyses of the same outcome. The three analyses can be implemented using the Stata syntax:

```
zinb  y lr i.tr i.sen i.undef, exp(exp) inf(_cons) irr vce(cl class)
nbreg y lr i.tr i.sen i.undef, exp(exp)            irr vce(cl class)
poisson y lr i.tr i.sen i.undef, exp(exp)          irr vce(cl class)
```

where **y** is the outcome variable, **lr** is the variable containing the lagged log rate for corresponding values of **y**, **tr** is the treatment variable (None [the reference level], Ceiling, or Portable), **sen** indicates sensor type, **undef** is the factor variable that identified undefined lags, **exp** specifies exposure (the length of time over which the outcomes were measured and can be omitted if the periods are identical), and **class** identifies classroom (1, 2, or 3). The actual variable names used in the analysis may differ.

The treatment effects columns of Table 5 and similar will be populated using the coefficients and confidence intervals estimated for the non-base levels of the **tr** variable. The p-value for the superiority hypothesis column of Table 5 and similar will be computed using syntax like:

```
local port = "Portable" : `: value label tr'
local ceil = "Ceiling"  : `: value label tr'
test _b[count:`port'.tr] = _b[count:`ceil'.tr] = 0
```

8.3 Treatment effect estimation for continuous outcomes

We will estimate treatment effects for continuous outcomes as differences in means. The analysis can be implemented using the Stata syntax:

```
regress y ly i.tr i.sen i.undef, vce(cl class)
```

where **y** is the outcome variable, **lr** is the variable containing the lagged outcome for corresponding values of **y**, and the other variables are as defined in section 8.2. Continuous outcomes and lags will not be log-transformed. The treatment effects and superiority p-value columns of Table 5 will be populated as described in section 8.2.

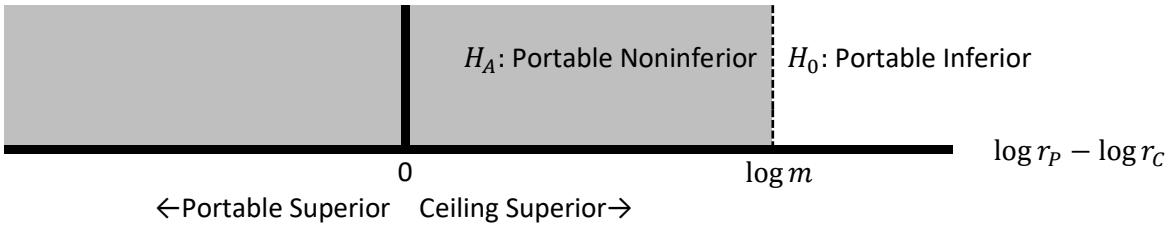
8.4 Assessing noninferiority

Figure 2 illustrates how we will assess noninferiority of portable versus ceiling-mounted air purifiers. A p-value for the noninferiority hypothesis column of Table 5 and similar will be computed by testing a one-sided null hypothesis H_0 that the effect of portable air purification compared to ceiling-mounted air purification is greater than or equal to a noninferiority margin $\log m$:

$$H_0: \log r_P - \log r_C \geq \log m$$
$$H_A: \log r_P - \log r_C < \log m$$

where $\log r_P$ and $\log r_C$ are the log rates for portable and ceiling-mounted air purifiers, respectively, and lower rates are preferable. Rejecting H_0 corresponds to accepting the alternative hypothesis H_A that portable air purifiers are noninferior to ceiling-mounted purifiers.

Figure 2—Assessing noninferiority of portable versus ceiling-mounted air purifiers



The test can be implemented in Stata using syntax like:

```
nlcom _b[count:`port'.tr] - _b[count:`ceil'.tr] , post
local sign = sign(_b[_nl_1])
test _b[_nl_1] = margin
display "H_0: coef >= " margin " p = " normal(`sign'*sqrt(r(chi2)))
```

where **margin** is the margin on the log scale and the other variables and macros are defined in section 8.2.

Noninferiority margins are chosen using the "fixed" approach on the basis of a confidence interval on an effect estimate comparing a reference intervention to a control (see the US FDA guidance (3)). Han et al. (4) compared $PM_{2.5}$ levels in classrooms with and without air purifiers. Using FDA terminology, their air purifier treatment is an active comparator, and the no air purifier treatment is an inactive comparator.

Han et al. estimated mean $PM_{2.5}$ levels of 22.1 μg/m³ (inactive comparator) and 7.3 μg/m³ (active comparator), corresponding to a rate ratio of around $7.3/22.1 = 0.33$, or -1.1 on the log rate ratio scale, in favor of the active comparator (air purifiers). While statistical uncertainty on mean outcomes was reported, a confidence interval on treatment effect was not reported, so cannot be used to choose a noninferiority margin. While it would be possible to impute this from the reported information, it should be sufficient for a pilot study to choose a noninferiority margin using a point estimate of effect. A noninferiority margin for a rate ratio preserving a proportion p of the absolute effect of an active verses inactive comparator can be calculated as:

$$m = \frac{E_{\text{inactive}}[Y] - p(E_{\text{inactive}}[Y] - E_{\text{active}}[Y])}{E_{\text{active}}[Y]}$$

where $E_{\text{active}}[Y]$ and $E_{\text{inactive}}[Y]$ are expected outcomes for the active and inactive comparators, respectively. Using the averages reported by Han et al. for the $PM_{2.5}$ outcome ($E_{\text{active}}[Y] = 7.3$ μg/m³ and $E_{\text{inactive}}[Y] = 22.1$ μg/m³) and aiming to preserve at least $p = 80\%$ of treatment effect gives a noninferiority margin of $m = 1.4$, which is $\log m = 0.34$. Note that this margin meets the FDA recommendation that the margin is not larger than the expected difference between <u>active</u> control and no treatment (i.e., $|\log 1.4| < |\log -1.1|$).

In other words, if Han et al. had found that another type of air purifier was noninferior to the purifier used in their study with respect to this margin, the expected $PM_{2.5}$ value for this other type of air purifier would have been less than $22.1 \times 0.33 \times 1.2 = 10.2$ μg/m³.

For simplicity, we will also use the same noninferiority margin for the secondary outcomes.

8.5 Exploratory covariate-adjusted analyses of the primary outcome

There are around 10 time-varying covariates that may explain the primary outcome. This will

correspond to a larger number of variables once factor variables have been expanded (e.g., weekday has five levels). We will perform exploratory model selection for the primary outcome to identify which time-varying covariates are associated with the primary outcome and estimate treatment effects that are adjusted for these covariates. Estimation will be performed using cross-fit partialing-out lasso Poisson regression. Lagged log rate and sensor type will be forced into the model. Time-varying covariates will be selected via the lasso. Experimentation suggests that it may not be feasible to account for undefined lags using maximum likelihood (see section 8.2) by forcing the corresponding variables into the model, so we will allow them to be selected via the lasso or omit them if necessary. We will use 10 cross-fitting folds. The analysis can be implemented in Stata using syntax like:

```
xpopoisson y i.tr, cont((ly i.sen) i.undef $cov) exp(exp) vce(cl class)
```

where **`$cov`** is a global macro that expands to the names of the time-varying covariates, and the other variables as are defined in section 8.2.

We will report the time-varying covariates selected, but the above model does not estimate coefficients for "control" variables. Because these coefficients are unlikely to have reliable causal interpretations, we will not run subsequent analyses to estimate them.

The model above will not be able to account for overdispersion or zero-inflation, but to the author's knowledge Stata does not provide a model selection approach for zero-inflated negative binomial regression or a suitable alternative. This limitation is probably reasonable for an exploratory analysis, however if estimation cannot be reliably performed (e.g., nonconvergence, poor model fit) we will either explore an alternative approach at analysis time or report why these analyses could not be performed.

9 Estimands

This section presents all estimands in terms of the objective, a statement of the estimand in plain language, the target population (i.e., who or what the estimate can be applied to), the analysis set (i.e., what subset, if any, of the full analysis set will be used to perform the analysis), the outcome variable, strategies for handling ICEs and missing data, the effect measure that will be estimated, and the estimator used to perform the analysis.

9.1 Primary Outcome Estimands

Objective To estimate the effects of ceiling-mounted and portable air purifiers (interventions) versus no air purifiers (control), and to assess the superiority of air purifiers (ceiling-mounted or portable) to no air purifiers, and the noninferiority of portable to ceiling-mounted air purifiers, all with respect to air quality.

Estimands Rate ratios for ceiling-mounted and portable air purifiers versus no air purifiers.

Target population School students and staff.	**Analysis sets** ITT (main and covariate-adjusted analyses) and PP (exploratory analysis)
Outcome Variable $PM_{2.5}$	
ICE Strategy None	**Missing Data Strategy** Complete case analysis
Effect Measure(s) Rate ratios	**Estimator** Zero-inflated negative binomial regression

9.2 Secondary Outcome Estimands

9.2.1 Volatile organic compounds (VOCs)

Objective To estimate the effects of ceiling-mounted and portable air purifiers (interventions) versus no air purifiers (control), and to assess the superiority of air purifiers (ceiling-mounted or portable) to no air purifiers, and the noninferiority of portable to ceiling-mounted air purifiers, all with respect to VOCs.	
Estimands Rate ratios for ceiling-mounted and portable air purifiers versus no air purifiers.	
Target population School students and staff.	**Analysis sets** ITT (main and covariate-adjusted analyses) and PP (exploratory analysis)
Outcome Variable VOCs	
ICE Strategy None	**Missing Data Strategy** Complete case analysis
Effect Measure(s) Rate ratios	**Estimator** Zero-inflated negative binomial regression

10 Reporting Conventions

In general, percentages in the table of baseline characteristics will be rounded to whole numbers, and summaries of continuous variables will be presented to one decimal place.

Statistical estimates will be presented as points with two-sided 95% confidence intervals and *p*-values (one- or two-sided, as appropriate). Point estimates and confidence intervals will be reported to 2 decimal places, and *p*-values will be reported to three decimal places or as $p < 0.001$. The conventional 95% significance criterion will be used throughout.

11 Quality Assurance of Statistical Programming

Because this is a pilot, we will not write and test the statistical code prior to analysis. Analysis code and data will be versioned using an appropriate system to be chosen by the analyst and may be published alongside the results of the pilot.

12 Summary of Changes to the Protocol and/or SAP

This section is to be completed to document and justify any changes to a published version of this SAP.

13 Acknowledgements

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14 Reference List

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