Title: Childhood asthma and household exposures to nitrogen dioxide and fine particles: A triple-crossover randomized intervention trial

Online Data Supplement

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METHODS

Study Participants

The target population for this intervention study was school-aged children (5 to 11 years old) with persistent asthma living in homes with high levels of NO_2. The Children's Air Pollution Study (CAPS) enrolled 126 children recruited from September 2015 through April 2019, using a variety of methods including flyers distributed to schools in cities and towns with gas lines in Connecticut and the Springfield area of Massachusetts; social media (Facebook); Craigslist advertisements; letters to selected families of the University Hospital's pediatric patients admitted for asthma; letters to our former study subject families; and flyers placed in doctors' offices and community centers. Interested families were invited to provide us with their contact information by phone, e-mail or by taking a brief online survey. Families were then contacted by trained research assistants and invited to participate in a brief screening questionnaire. Disease severity for study eligibility was determined during the brief screening questionnaire by asking for the total number of months the asthmatic child had any symptoms or any asthma controller medication use during the past year. Children were eligible for the study if they had more than 6 months of either symptoms OR medication use OR 4 or more months of both symptoms and medication. For potential subjects satisfying initial screening criteria and agreeing to participate in household NO_2 screening, a passive NO_2 monitor (1, 2) was sent to the home for placement in the main living space for one week. Families living in homes where the one-week integrated average NO_2 concentration was 15 ppb or higher were invited to participate.

Study Design

The intervention protocol was a block-randomized, double blind, triple crossover design involving three air cleaner configurations ("treatments"). Each randomization was blocked so that for every 18 families randomized there would be three in each sequence. A randomization scheme to accommodate enrollment of 630 families was created by one of the unblinded staff using PROC PLAN in SAS (version 9.4, SAS Institute, Inc.). A numbered list using letters to represent air cleaner types and their delivery sequence for each family was kept in a book accessible to the scheduler. Families were *randomized* in order from the list by the scheduler at the time an enrollment home visit for equipment installation and home interview was confirmed. Families (and their eligible child(ren)) were *enrolled* into the study at the time of the home visit once the child's caregiver signed the consent form and accepted delivery of the equipment. All enrolled families, all four CAPS principal investigators and all but three support staff were blind as to the nature and sequence of air cleaner treatment assignments. The three exceptions included two staff members whose responsibilities included quality control and assurance of air cleaner assignments based on the family randomization list and a laboratory technician whose responsibilities included working with the two other unblinded staff to assure that all air cleaner maintenance and preparation protocols for home deliveries were followed. The project supervisor, study scheduler, field research assistants and data entry staff were blind as to individual machine configuration and treatment sequence. Figure S1 shows the timeline for subject participation including three, 5-week treatment periods beginning with a one-week washout; timing of equipment deliveries and pick-ups (including passive air quality monitors), and data collection interviews.

Environmental Intervention Protocol

Description of air cleaners. The air cleaners (n=60, 20 for each intervention treatment condition) included three custom configurations of the IQAir® (Goldach, Switzerland) GC model made by the company's design engineering staff. All air cleaners were fitted with a riser on locking casters and an outflow stack to enhance airflow into the bottom of the machine, through the filtration/scrubbing system and out the top. All had a custom, tamper-proof control panel which maintained flow rate and resulted in similar noise levels for all three conditions. All machines had locking lids and were configured to remain on until they were replaced (or removed) at the end of each treatment period and were equipped with a counter that recorded the number of hours the machine was plugged into a power source (Figure S2). From the initial order of 60 machines, three were reserved, one for testing purposes in the equipment lab, and two to be used for spare parts as needed. Thus, the study was launched with 19 air cleaners in each of the three configurations. The number of air cleaners in rotation at any given time, even accounting for machines out of deployment for maintenance and repair, was always sufficient to meet the rate of enrollment.

Air cleaner type 1 was the NO_2-reduction machine configured to provide sham particle filtration (<10% particle filtration efficiency at 0.3 µm) and real NO_2 scrubbing. For this machine, the four gas-phase scrubbing canisters that come with the GC model were filled with Purafil® media (Doraville, GA) (3). Purafil®-containing canisters for the NO_2-reduction configuration were fitted with HEPA sleeves to filter fine particles resulting from machine transport. Air cleaner type 2 was the particle reduction machine configured to provide real particle filtration (with a HEPA filter - approximately 99.5% particle filtration efficiency at 0.3 µm) and sham NO_2 scrubbing. For sham NO_2 scrubbing, the canisters were filled with inert media (a mixture of aquarium gravel and baked clay). Sham canisters for the HEPA configuration were fitted with HEPA sleeves. Air cleaner type 3 was the placebo/control machine configured to provide sham particle filtration and sham NO_2 scrubbing. For the control configuration, the canisters were each fitted with a sham filter sleeve to filter any coarse particles coming from the filter media as a result of machine transport. All machines came with a transport lid that could be exchanged for the lid with outflow stack. All machine types were identical in appearance and weight, measuring 1.4 m from floor to top of stack, and weighing approximately 24 kg.

Field equipment placement protocol. At the initial home visit, the air cleaner was installed in the main living area by a trained research assistant. Once the research assistant locked the outflow lid into place and plugged the machine into an outlet, the respondent was instructed to leave the machine on (i.e., not unplug it) until it was replaced with the next assigned machine. The research assistant placed two NO_2 monitors, one in the main living area and one in the child's bedroom, and one nicotine badge monitor in the main living area (4, 5); administered a structured interview to the child's primary caregiver (the study "respondent," usually the mother) to collect demographic information and the child's asthma and allergy history; and provided the respondent with a calendar diary to record the child's daily asthma symptoms, medication use, physician visits, respiratory illnesses, days of restricted activity and missed days of school. At the end of each treatment period, a research assistant replaced the air cleaner with the next one assigned ("swap visit") or collected the air cleaner at the end of the final treatment arm. At the air cleaner swap visits, the research assistant collected the passive air monitors (NO_2 monitors and nicotine badge) and placed new ones.

Air cleaner and gas detector set-up (from p37-40, Children's Air Pollution Study (CAPS) Research Assistant Manual):

Parameters for placement of the air cleaner (best scenario):

- Minimum of 6 feet from kitchen entry
- Minimum of 2 feet from walls or furniture
- Minimum of 6 feet from forced hot air intake or vent
- Minimum of 6 feet from windows that may be opened during study
- Minimum of 6 feet from air conditioner

Air cleaner deployment and maintenance protocols. Data collected at the end of each treatment period included: health data during a phone interview at which time the respondent was prompted to refer to the symptom collection calendar; a machine maintenance record completed when the air cleaner returned to the lab; an equipment placement record completed at the time of machine "swap" or removal. Study protocol prohibited the same research assistant from both installing (or swapping) equipment for a household's treatment period then subsequently collecting health data at the end of that same period.

Information collected at the end of each treatment period was used to determine adherence to study protocol: 1) the child slept in the home for 5 out of every 7 nights; 2) the air cleaner was running continuously for 90% of the 35-day monitoring period (31.5 days total) according to the machine hours of operation counter; 3) the air cleaner was in a protocol-acceptable location for 90% of the monitoring period.

Air cleaner set-up and baseline measurements of efficiency, field use records, and maintenance schedules were tracked by an Access database, with scheduled maintenance orders routinely transmitted to the lab technician based on the number of times any individual air cleaner had been deployed. The air cleaners were randomly assigned identification numbers by one of the unblinded data management staff so that blinded study personnel would not be able to identify configurations by machine number.

Initial set-up: The lab technician initially readied each air cleaner for use according to the specifications for each experimental configuration, then recorded the configuration, filter type, and filter sleeve type in the database. For the NO_2 reduction machines, a barcoded identification number was affixed to each of the four gas-phase canisters and recorded in the database. Baseline measures of pressure and flow rate were used to establish an acceptable range of performance parameters, with upper and lower limits conforming to the minimum and maximum readings taken at this time within each configuration.

Deployment order: In order to ensure that all of the air cleaners received approximately the same amount of use, and to minimize the impact of any unforeseen machine-level differences in performance, the 19 air cleaners in each configuration were randomly assigned to a deployment order schedule which was provided to the lab technician. As each air cleaner was returned to the lab after a deployment, any scheduled maintenance was performed, after which it was returned to the end of the line to await its next deployment. Machines that required non-routine maintenance or repair were removed from rotation until such repairs were made. All of the machines cycled through the deployment order in this fashion and the number of deployments by configuration are displayed in Table S1.

Routine maintenance and quality control measurements: After each field deployment, the external parts of the air cleaner were wiped down with a mild cleaning solution and the internal parts vacuumed. The lab technician measured both air flow and pressure after each deployment

to assess efficiency and recorded the counter reading for hours of use. Figure S3 shows the machine readiness protocol.

At the beginning of the study the air cleaner filters and canister sleeves were replaced on the following schedule:

NO_2 reduction:	Sham filter replaced after every three deployments Purafil®-containing canisters replaced after every four deployments
Particle reduction:	HEPA filter and canister sleeves replaced after every three deployments
Control:	Sham filter replaced after every three deployments; canister sleeves vacuumed after each deployment

In November of 2017, routine air flow measurements taken after field deployment indicated that filters in the particle-reduction machines were clogging sooner than expected, resulting in air flow readings below the range of acceptable values established empirically at the beginning of the study. Given that the machines were custom-built and non-standard configurations, there were no objective acceptable operating ranges against which to measure machine performance.

A consultation with IQAir assured investigators that an overall 10% reduction in efficiency over time was within normal operating parameters; thus, the acceptable operating range for each configuration was reduced by 10% at its lower bounds. The maintenance schedule for the particle-reduction configuration was modified so that the filter and canister sleeves were replaced after every two deployments instead of every three, and we also decided to replace the filters on the control machines after every two deployments as well. These changes became effective on November 17, 2017. Machine efficiency continued to be measured after each deployment and all air cleaners operated within acceptable ranges throughout the remainder of the study. Table S2 displays the normal operating ranges and mean (SD) flow rate and pressure measurements at the beginning and end of the study.

Over the course of the study there were a few unforeseen issues that arose which required resolution outside of the normal maintenance protocol. Eleven machines came back from field deployment smelling strongly of cigarette smoke; in these cases, in addition to performing the routine vacuuming and cleaning, the lab technician replaced all of the filters and filter sleeves regardless of where the machines were in their maintenance calendar. Routine maintenance dates for these machines were adjusted accordingly.

Two machines in the NO_2 reduction configuration sustained some water damage from a ceiling pipe leak. The machines were taken out of service, cleaned and dried thoroughly, and had their canisters, filters, and sleeves replaced with new ones. The lab technician subjected these machines to testing by running them continuously for several days and monitoring air flow and pressure. Once it was determined that each machine was operating normally, they were returned to service.

Three machines (two NO_2 reduction and one control) were permanently removed from service due to breakage of the plastic arms that secure the top of the machine to the body. Machine transport lids were removed for machine home placement and removal, then again after every field deployment so that the interior components could be vacuumed, and also for filter replacement as necessary; therefore these arms experienced more wear and tear than they would have under normal household use. The locking arms proved to be a vulnerable part of the design of these otherwise reliable machines.

RESULTS

Study Recruitment

From October, 2015 through April, 2019, nearly 2,000 inquiries were generated by our recruitment efforts which included 158,798 study flyers distributed to 490 schools (flyers were distributed up to three times to schools in the most populous districts); 17,700 letters sent to families of children hospitalized with asthma in the University's Hospital (including two mailings to selected towns in the Hospital's catchment area); 312 letters sent to previous study families; over three years of advertisements on Craigslist, and nearly two years advertising on Facebook. The source of study information for enrolled families is shown in Table S3.

Asthma-related Adverse Events

Asthma-related adverse events are shown in Table S4. None of the asthma-related adverse events reported were deemed to be study-related.

Household NO_2 measurements

Passive NO_2 monitors (Palmes tubes) were placed in the main living area of each home at the beginning of each 5-week treatment with the assigned air cleaner. Palmes tubes were collected at the end of each treatment period when one air cleaner was replaced with the next one assigned or was removed at the end of the study. Laboratory analysis of the NO_2 monitors produced a 5-week integrated average concentration (in ppb's). Table S5 shows the results of the repeated measures linear mixed model analysis of the effect of treatment arm on measured NO_2 concentration. The particle-reduction treatment was associated with significantly lower concentrations, by approximately 3 ppb, than either of the other two treatments.

Covariates included in adjusted analyses

Table S6 shows effect estimates from compliance analyses for pairwise contrasts showing differences in symptom days between covariate categories. Note that results are for all covariates included in adjusted compliance analysis (see main text, Table 4, model B) and compliance analysis also including measured NO_2 as a factor (see main text, Table 6).

References

1. Belanger K, Holford TR, Gent JF, Hill ME, Kezik JM, Leaderer BP. Household levels of nitrogen dioxide and pediatric asthma severity. Epidemiol 2013;24:320-330.
2. Palmes ED, Gunnison AF, DiMattio J, Tomczyk C. Personal sampler for nitrogen dioxide. Am Ind Hyg Assoc J 1976;37:570-577.
3. Purafil Inc. Safety Data Sheet. Product Specifications For Purafil SP Media. 2009 [cited 2020 April 29]. Available from: https://www.purafil.com/wp-content/uploads/2015/08/Purafil-SP-Media-SDS-GHS-v1.02.pdf.
4. Hammond SK, Leaderer BP. A diffusion monitor to measure exposure to passive smoking. Environ Sci Technol. 1987;21(5):494-497.
5. Leaderer BP, Hammond SK. Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. Environ Sci Technol. 1991;25:770-777.

Table S1. Number of field deployments by experimental configuration.

	No. of deployments						
Configuration	2	3	4	5	6	7	8
NO_2 reduction	0	2	1	4	5	5	2
Particle reduction	1	0	0	3	12	3	0
Control	0	1	1	3	10	4	0

Note. Every time a particular machine was installed in a home, it was recorded as a "deployment" in the machine maintenance data base. See details of deployment order assignment protocol, above (page 6).

Table S2. Normal air cleaner operating ranges and mean (SD) flow rate and pressure measurements at the beginning and end of the study.

Configuration	Normal operating range[a]		Beginning		End	
	Flow rate[b]	Pressure[c]	Flow rate[b]	Pressure[c]	Flow rate[b]	Pressure[c]
NO_2 reduction	133-160	0.25-0.32	155.6 (6.9)	0.29 (0.03)	150.5 (4.3)	0.27 (0.02)
Particle reduction	122-192	0.18-0.23	130.9 (8.2)	0.20 (0.01)	129.5 (3.5)	0.19 (0.01)
Control	163-192	0.35-0.40	176.5 (8.2)	0.38 (0.02)	171.0 (4.3)	0.37 (0.01)

[a]Lower limit of range reflects a 10% reduction from initial values to accommodate an expected decrease in efficiency over time

[b]Flow rate is reported in cubic feet per minute

[c]Pressure measured by magnehelic gauge and reported in pounds per square inch

Table S3. Source of study recruitment for enrolled families (n=116).

Source	N (%)
Study brochure to elementary school	57 (49.1)
Letter to selected hospital[a] patients	22 (19.0)
Facebook	17 (14.7)
Craigslist	7 (6.0)
Letter to previous study subjects	5 (4.3)
Doctor's office	3 (2.6)
Word of mouth	2 (1.7)
Flyer from public event	1 (0.9)
Does not know	1 (0.9)
Community site	1 (0.9)
Total	116

[a]The University Hospital

Table S4. Asthma-related adverse events by treatment arm.

		Treatment Arm		
		NO_2-reduction	Particle-reduction	Control
Asthma-related adverse events[a]	Total	N (%)	N (%)	N (%)
Hospitalizations	5	1 (20.0)	1 (20.0)	3 (60.0)
ER Visits	20	7 (35.0)	8 (40.0)	5 (25.0)
Unscheduled doctor or clinic visits	61	19 (31.1)	23 (37.7)	19 (31.2)
Prednisone burst	18			
Asthma diagnosis	12	6 (50.0)	1 (8.3)	5 (41.7)
No asthma diagnosis[b]	6	2 (33.3)	2 (33.3)	2 (33.3)
Total number of events (N [%])[c]	104	35 (33.7)	35 (33.7)	34 (32.6)

Note. Adverse events reported in all experimental observations (n=332) completed by study subjects (n=126).

[a]Includes asthma-related events listed as ICD10 codes J40 - J47 for hospitalizations, ER visits, unscheduled doctor or clinic visits, and Prednisone burst (with and without asthma diagnosis).
[b]Includes diagnoses of ear infection and croup (n=1), croup (n=2), pneumonia (n=1), and none (no doctor interaction reported) (n=2).
[c]104 adverse events reported for 51 out of 126 (41%) children. Percentages in body of table represent the total number of a particular adverse event reported in each treatment, e.g., of all adverse events reported (n=104), approximately one-third of them were reported in each arm.

Table S5. Effect of treatment arm on household NO_2.

Factors	Treatment arms N (Ss)	N (obs)	df	Estimate (SE)	p-value[a]
Treatment Arm	106	267	2, 105	(Mean [SE])	<0.0001
NO_2-reduction				17.40 (1.25)	
Particle-reduction				20.90 (1.26)	
Control				20.98 (1.27)	
Contrasts				(Mean Diff [SE])	
NO_2-reduction vs Control			105	3.83 (0.77)	<0.0001
NO_2-reduction vs Particle-reduction			105	3.76 (0.74)	<0.0001
Particle-reduction vs Control			105	-0.07 (0.77)	<0.0001

Note: N=106 subjects in the compliance analysis completed 267 treatment arms with non-missing NO_2 measurements. Laboratory analyses of passive NO_2 monitoring in the main living area resulted in three, 5-week integrated averages for each subject - one for each study treatment arm completed (NO_2-reduction, particle-reduction, and control).
[a]p-values from repeated measures linear mixed model.

Table S6. Effect estimates from compliance analyses for pairwise contrasts showing differences in symptom days between covariate categories.

	Compliance Analysis					Compliance including measured NO_2				
Covariates	**N (%) (Ss)**	**N (obs)**	**df**	**Estimate (SE)**	**p-value**	**N (%) (Ss)**	**N (obs)**	**df**	**Estimate (SE)**	**p-value**
Total	109	270				106	267			
Age (yrs)			1, 98		0.29			1, 95		0.13
5-7 vs 8-10				-0.70 (0.66)					-1.00 (0.66)	
Gender			1, 98		0.31			1, 95		0.27
Male vs Female				-0.68 (0.66)					-0.74 (0.66)	
Hispanic			1, 98		0.30			1, 95		0.23
No vs Yes				0.92 (0.85)					1.02 (0.84)	
Race			3, 98		0.19			3, 95		0.51
Black vs White				1.05 (0.99)					0.92 (1.00)	
Multi-racial, Other vs White				0.98 (0.88)					0.55 (0.89)	
Respondent's Education (yrs)			2, 98		0.76			2, 95		0.81
<12 vs ≥16				0.61 (1.30)					0.85 (1.31)	
12-15 vs ≥16				0.56 (0.84)					0.39 (0.86)	
Allergies (report of MD dx)			1, 98		0.97			1, 95		0.91
Yes vs No				-0.03 (0.73)					0.08 (0.73)	
Enrolled child number			1, 98		0.52			1, 95		0.64
1 vs 2				-0.80 (1.24)					-0.60 (1.30)	
Smoking in the home during treatment arm			1, 98		0.25			1, 95		0.44
Yes vs No				0.76 (0.66)					0.51 (0.65)	
Season of treatment arm			3, 98		0.44			3, 95		0.49
Summer vs Winter				0.36 (0.79)					0.56 (0.78)	
Fall vs Winter				-0.87 (0.74)					-0.64 (0.74)	
Spring vs Winter				-0.07 (0.73)					0.32 (0.73)	

Note. Results are for all covariates included in adjusted compliance analysis (see main text, Table 4, model B) and compliance analysis also including measured NO_2 as a factor (see main text, Table 6).

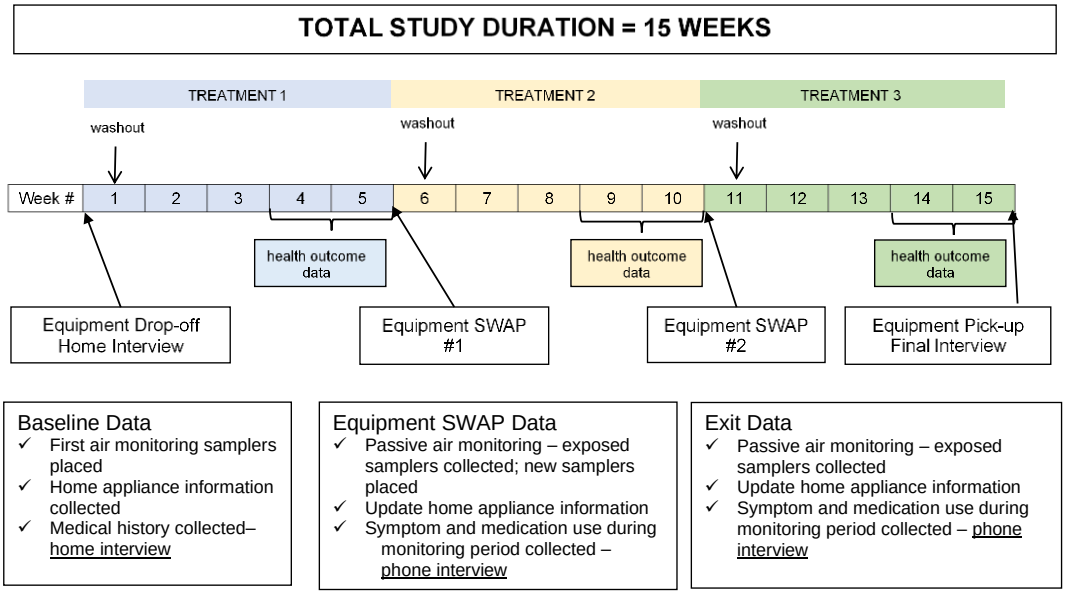

Figure S1. Subject participation timeline. Each treatment period was 5-weeks in duration beginning with a one-week washout period. Health outcome data used in analyses included number of days of symptoms during the final 14-days (2 weeks) of the treatment period.

Figure S2. IQAir® GC model shown with locking outflow top, riser, and locking casters. (The photo is from IQAir, with permission to use for publication.)

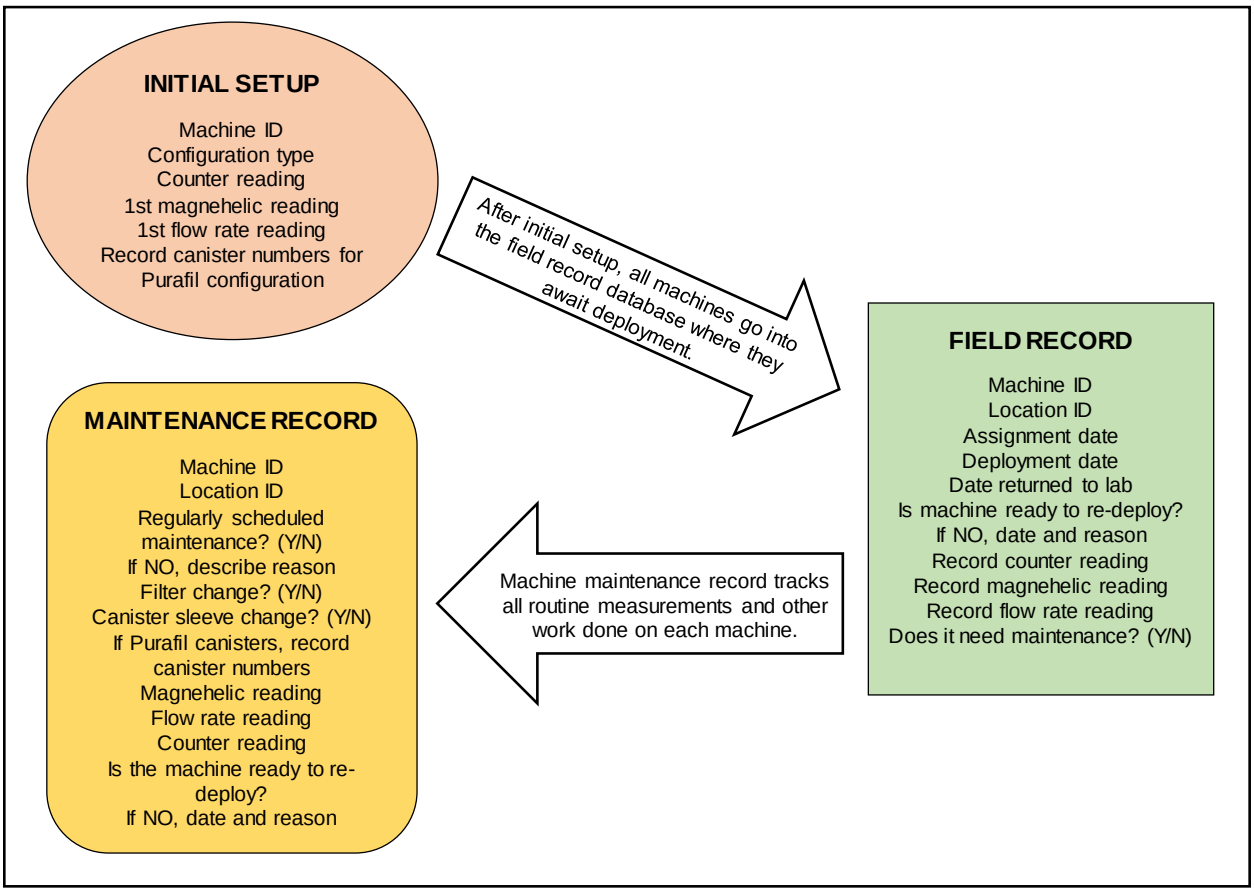

Figure S3. Machine maintenance protocol.