

# **P9185 - Project 3: Protocol of a Cluster-randomized trial for Asthma-PASS**

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2022-04-25

# Background

Our interest is in persistent asthma in minority children.

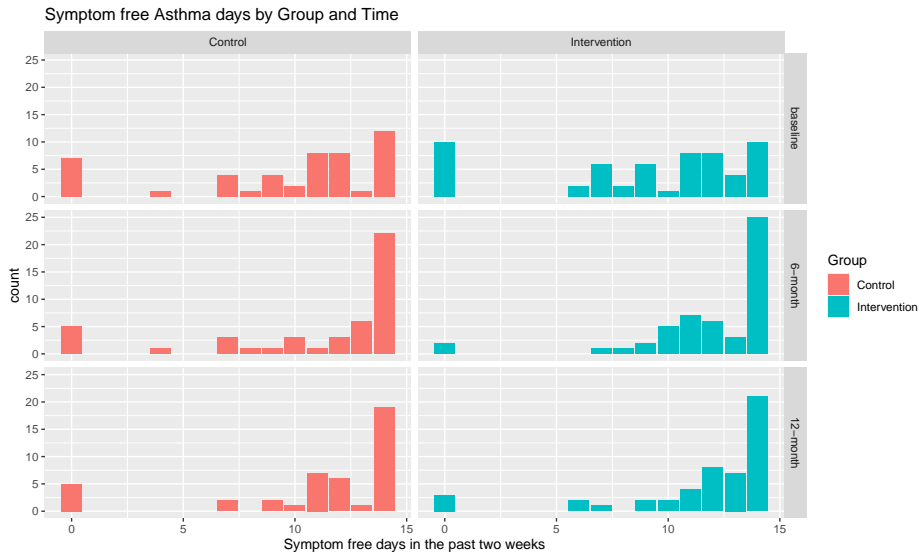
- Comprehensive school-based interventions in collaboration with communities to reduce asthma morbidity and promote physical activity in urban areas.
- A pilot cluster RCT was conducted exploring this intervention in Bronx elementary schools
  - **Goal:** whether Children in schools receiving Asthma-PASS intervention may experience a greater improvement in the number of SFD at 6 **or** 12 months follow up than the children in the comparison group.
  - 4 Bronx elementary schools were recruited into the pilot study.
  - A total of 108 children recruited including ages 4-11 years with physician-diagnosed persistent or uncontrolled asthma attending kindergarten to 5th grades

- ① Data Overview
- ② Exploration into Pilot Study data
  - Model Specifications
  - Results
- ③ Phase III Proposal
  - Model Specifications
  - Sample Size Suggestions

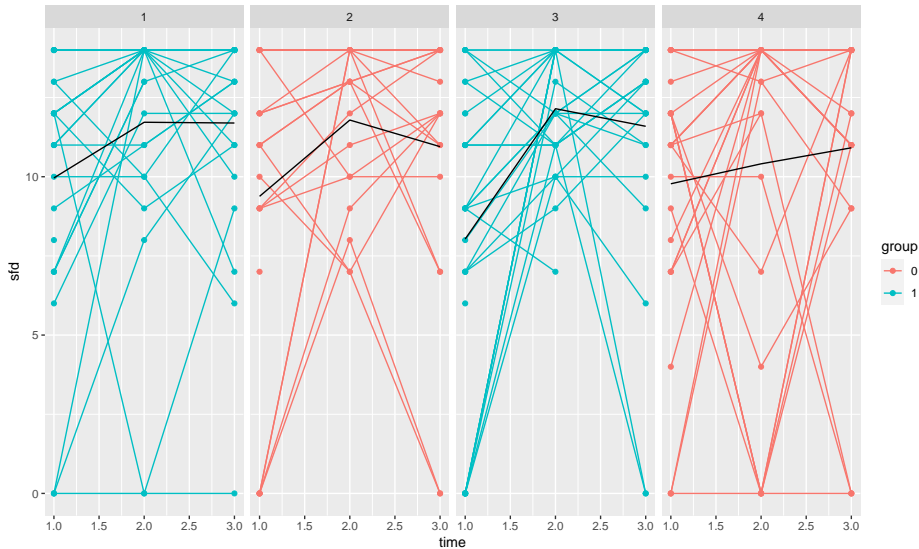
Variable	Definition
ID	Participant's ID
Time	Follow up time (Baseline, 6 months, 12 months)
Group	Intervention group (control or Intervention)
SFD	Symptom free days in the past two weeks
School	School recruited for the study

*Table 1: Data Descriptions of Pilot Study*

# Data Exploration



# Data Exploration



## **Current outcome:** SFD (Count data)

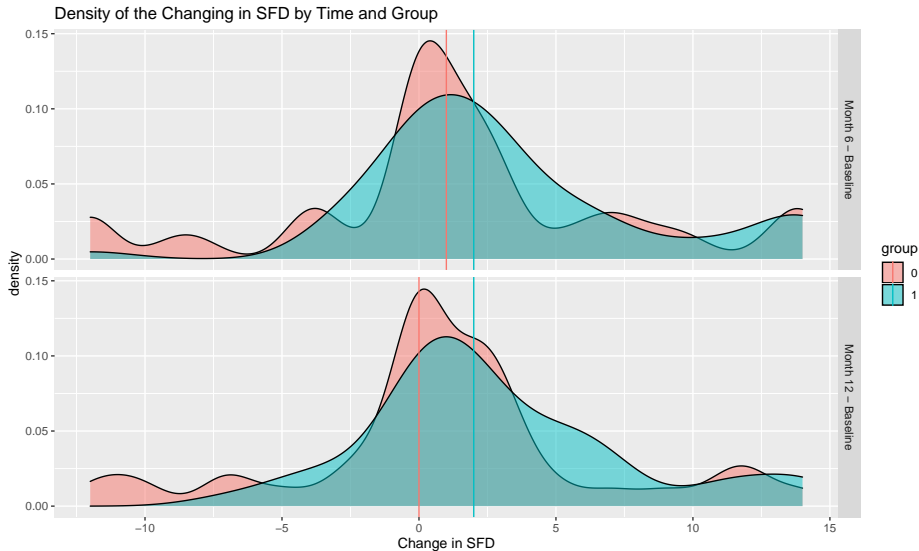
- Due to the skewed distribution towards higher values a poisson model will not fit our data well
- Outcome does not seem linear over the time observations.

*Interested in the change from baseline to observation times.*

## **New outcome:** Change in SFD (Continuous Data)

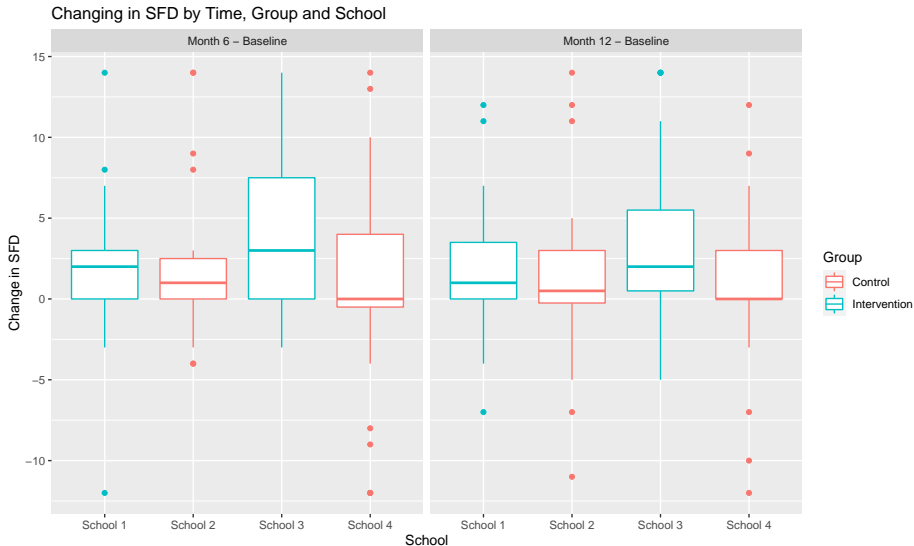
- Transform the SFD by calculated:
  - 6 month observation - baseline
  - 12 month observation - baseline
- Baseline with become covariate

# New Continuous Outcome





# Exploring variation between school and within school



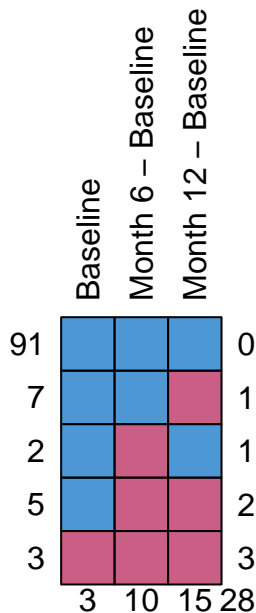
# Data Description

Characteristic	Overall, N = 108 <sup>1</sup>	Group Control		Group Intervention		p-value <sup>2</sup>
		School 1, N = 28 <sup>1</sup>	School 3, N = 31 <sup>1</sup>	School 2, N = 21 <sup>1</sup>	School 4, N = 28 <sup>1</sup>	
baseline	11.0 (7.0, 13.0)	12.0 (7.5, 13.0)	9.0 (6.2, 11.8)	11.0 (9.0, 14.0)	11.0 (7.5, 12.5)	0.3
Unknown	3	1	1	0	1	
Change_6months	2 (0, 5)	2 (0, 3)	3 (0, 8)	1 (0, 2)	0 (0, 4)	0.3
Unknown	10	3	4	2	1	
Change_12months	1.0 (0.0, 4.0)	1.0 (0.0, 3.5)	2.0 (0.5, 5.5)	0.5 (-0.2, 3.0)	0.0 (0.0, 3.0)	0.2
Unknown	15	5	4	1	5	

<sup>1</sup> Median (IQR)

<sup>2</sup> Kruskal-Wallis rank sum test

# Missing Data



# Model Specifications

To model change in SFD let  $i$  for school,  $j$  for subjects,  $k$  for measures.

We will use mixed effect model.

$$\begin{aligned} Y_{ijk} = & \beta_0 + \beta_1 \text{Baseline}_{ij} \\ & + \beta_2 \text{Group}_{ij} + \beta_3 \text{Compare}_{ijk} \\ & + \beta_4 \text{Group}_{ij} \times \text{Compare}_{ijk} \\ & + \alpha_{0i} + \alpha_{0j} + \epsilon_{ijk} \end{aligned}$$

where  $\alpha_{0i} \sim N(0, \sigma_1^2)$ ,  $\alpha_{0j} \sim N(0, \sigma_2^2)$ , and  $\epsilon_{ijk} \sim N(0, \sigma^2)$ .

We will be assuming data is missing at random (MAR)<sup>[1]</sup>.

# Model Result Fixed

## Fixed Effects Estimates:

Characteristic	Beta	95% CI <sup>†</sup>	p-value
baseline	-0.82	-1.0, -0.69	<0.001
group			
0	—	—	
1	1.1	-0.46, 2.6	0.2
compare			
m6_m0	—	—	
m12_m0	-0.05	-1.4, 1.3	>0.9
group * compare			
1 * m12_m0	-0.27	-2.2, 1.6	0.8

<sup>†</sup> CI = Confidence Interval

## Model Interpretations:

- 1 When comparing the 6 months and baseline, The increase of sfd in intervention group is 1.1 (-0.46, 2.6) more than the increase of sfd in the treatment group.
- 2 When comparing the 12 months and baseline, The increase of sfd in intervention group is 0.81 (-1.60, 2.12) more than the increase of sfd in the treatment group.
- 3 No significant improvement from intervention group.



# Model Result Random

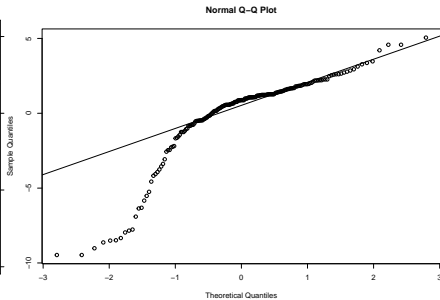
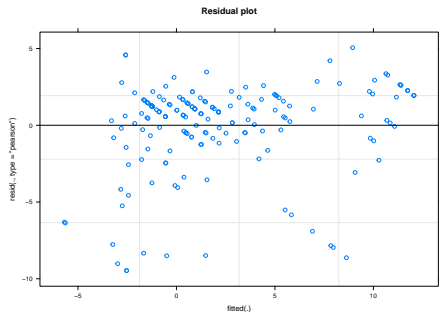
## Model 1 Random Effects:

group	Std.Dev	Variance
id	2.055	4.221
school	0.000	0.000
Residual	3.250	10.560

Calculating the Intraclass  
Correlation Coefficient

$$\textcircled{1} \rho = \frac{\sigma_2^2}{\sigma_2^2 + \sigma^2} = \frac{0}{0 + 10.560} = 0$$

# Model Quality



# Cluster RCT design

- The investigators wish to propose a **cluster-randomized clinical trial (RCT)** in 30 Bronx schools to evaluate the effectiveness of their intervention program.
- Primary hypothesis: compared to the control group, children in schools randomized to intervention group will experience a greater improvement in the number of SFD at **any of the 3, 6, 9, and 12 months** assessment.
- The investigators would like to have at **80% probability** to declare the trial is successful if the true effect size in **improvement of SFD over time** is **at least 1/3 standard deviation**.



# Study design proposal:

- The primary interest of the study: test whether there is difference at any of the 3,6,9,12 months;
- Consider 4 comparisons separately:
  - month3: sfd\_chage~group
  - month6: sfd\_chage~group
  - month9: sfd\_chage~group
  - month12: sfd\_chage~group

## Two levels of Sampling

- $N_1$ : Number of Individuals in each School (*What we want to estimate*)
- $N_2$ : Number of Schools for one treatment arm (15 in our case)

# Study design proposal:

## 2 level structure<sup>[2]</sup>:

$$y_{ij} = \beta_0 + \beta_1 X_{ij} + \beta_2 y_{0,ij} + u_i + \epsilon_{ij}$$

- i for school, j for subject,  $y_{ij}$  is the sfd\_change from tested time point to baseline
- within each comparison, there is only 1 measurement. So no consideration of the intra-subject correlation
- $u_i \sim N(0, \sigma_u^2)$ , random intercept between schools
- $\epsilon_{ij} \sim N(0, \sigma_e^2)$ , random error term

## Intraclass Correlation Coefficient

$$\rho = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_e^2}$$

# Hypothesis Set Up

**Hypothesis:**  $H_0 : \beta_1 = 0, H_1 : \beta_1 \neq 0$

- calculate N based on normal distribution, with multiple adjustment:  
 $\alpha^* = \alpha/4 = 0.025/4$
- $\beta = 0.2$
- $N_1 = N_0 = 15$
- Interested in when standardized effect size  $\Delta = 1/3$

# Sample Size Calculation

## Test statistics

$$D_2 = \frac{\sqrt{N_2 N_1} (\bar{Y}_1 - \bar{Y}_0)}{\sigma \sqrt{2(1 - \rho)}} \sim N(0, 1)$$

## Sample Size formula

$$N_1 = \frac{2(1 - \rho)z_{\alpha^*, \phi}^2}{N_2 \Delta_{(2)}^2 - 2\rho z_{\alpha^*, \phi}^2}$$

Where  $z$  is calculated based on the normal distribution.

$$z_{\alpha^*, \beta}^2 = (z_{\alpha^*/2} + z_{\beta})^2 = [\Phi^{-1}(1 - \alpha^*/2) + \Phi^{-1}(1 - \beta)]^2$$

# Sample Size Suggested

rho	class_size	group_size	total_samp
0.00	13.381	200.720	401.440
0.01	15.294	229.411	458.822
0.03	21.685	325.278	650.556

[1] Hogan, J. W., Roy, J., & Korkontzelou, C. (2004). Handling drop-out in longitudinal studies. *Statistics in Medicine*, 23(9), 1455–1497.

<https://doi.org/10.1002/sim.1728>

[2] Ahn, C., Heo, M., & Zhang, S. (2014). *Sample size calculations for clustered and longitudinal outcomes in clinical research*. CRC Press.