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

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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

Overview

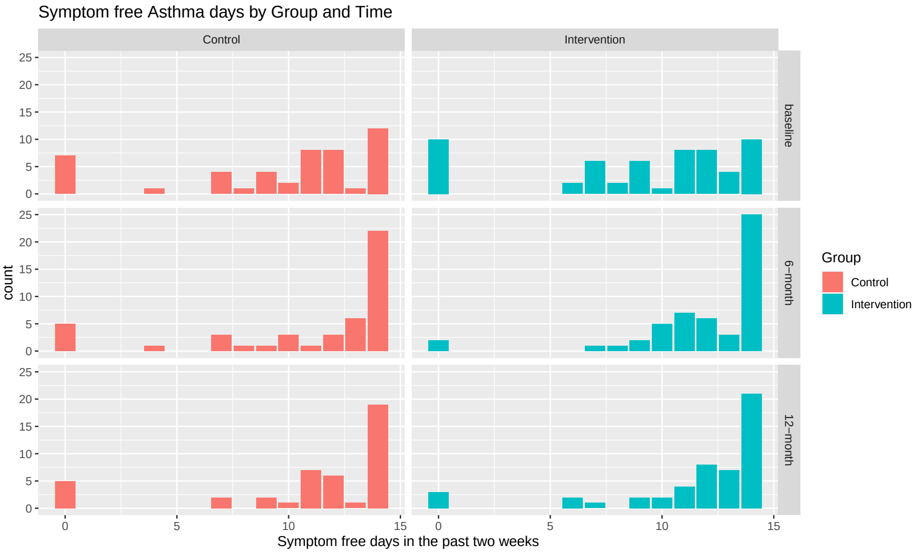
1. Data Overview
2. Exploration into Pilot Study data
   - Model Specifications
   - Results
3. Phase III Proposal
   - Model Specifications
   - Sample Size Suggestions

Data Overview

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

Data Exploration



Data Exploration

Current outcome: SFD (Count data)

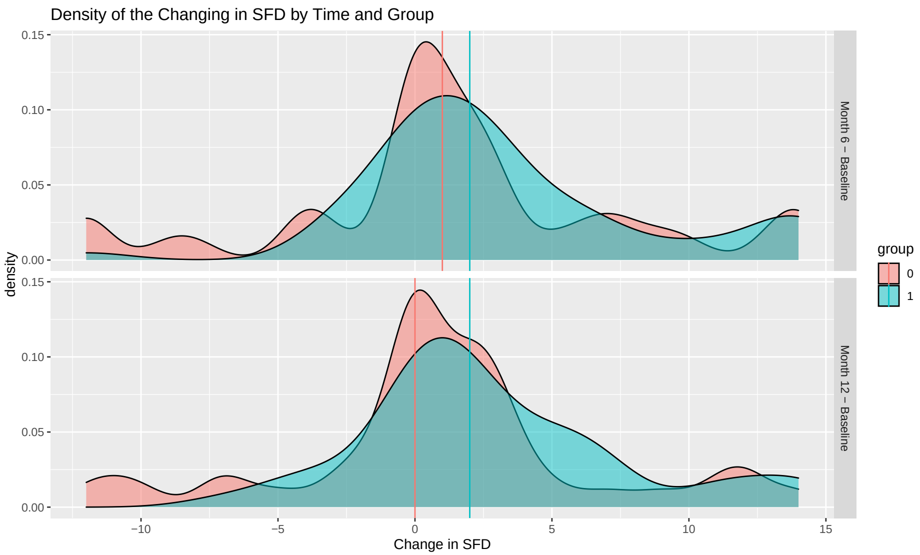
- Due to the skewed distribution towards higher values a poisson model will not fit our data well
- Outcome does not seem linear over the time observations.

Interested in the change from baseline to observation times.

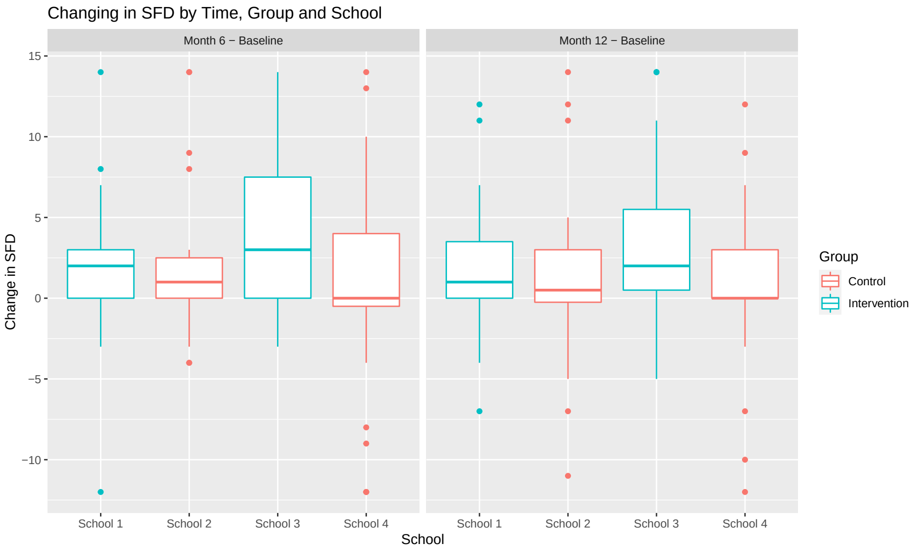
New outcome: Change in SFD (Continuous Data)

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

New Continous Outcome



Exploring variation between school and within school

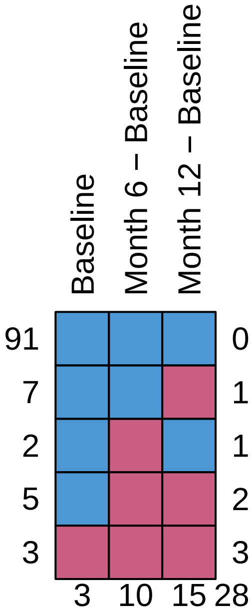


Data Description

Characteristic	Overall, N = 108[1]	Group Control: School 1, N = 28[1]	Group Control: School 3, N = 31[1]	Group Intervention: School 2, N = 21[1]	Group Intervention: School 4, N = 28[1]	p-value[2]
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	

[1] Median (IQR)
[2] 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 used mixed effect model.

$$
\begin{aligned}
Y_{ijk} &= \beta_0 + \beta_1 Baseline_{ij} \\
&\quad + \beta_2 Group_{ij} + \beta_3 Compare_{ijk} \\
&\quad + \beta_4 Group_{ij} \times Compare_{ijk} \\
&\quad + \alpha_{0i} + \alpha_{0j} + \epsilon_{ijk}
\end{aligned}
$$

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

Missing Data Assumptions

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

- MAR assumption: $R \perp\!\!\!\perp Y_{mis} | X, Y_{obs}$
- Separable parameter assumption
- Ignorability condition

$$
\begin{aligned}
L_i^{\mathrm{O}}(\theta, \psi) &\propto f_{\theta, \psi}\left(Y_{\mathrm{obs}, i}, R_i, X_i\right) \\
&= f_{\psi}\left(R_i \mid Y_{\mathrm{obs}, i}, X_i\right) f_{\theta}\left(Y_{\mathrm{obs}, i} \mid X_i\right)
\end{aligned}
$$

Model Result

Fixed Effects Estimates:

Characteristic	Beta	95% CI[1]	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

[1] CI = Confidence Interval

Random Effects Estimates:

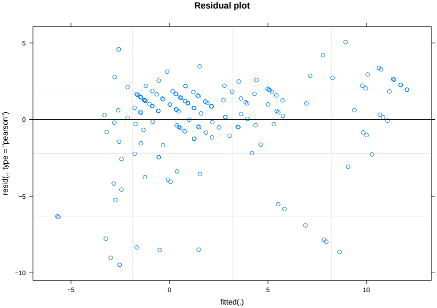
group	Std.Dev	Variance
id	2.055	4.221
school	0.000	0.000
Residual	3.250	10.560

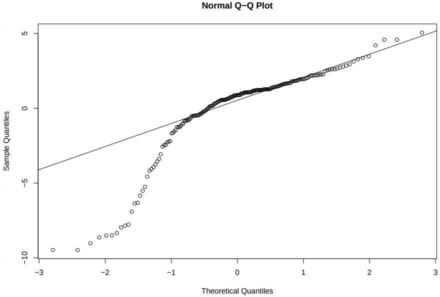
Model Interpretations:

1. interpretations
2. interpretations
3. interpretations

Note: This model is singular

Model Quality





Model without Baseline

Fixed Effects Estimates:

Characteristic	Beta	95% CI[1]	p-value
group			
0	—	—	
1	1.7	-2.5, 5.8	0.3
compare			
m6_m0	—	—	
m12_m0	-0.08	-1.5, 1.3	>0.9
group * compare			
1 * m12_m0	-0.26	-2.2, 1.7	0.8

[1] CI = Confidence Interval

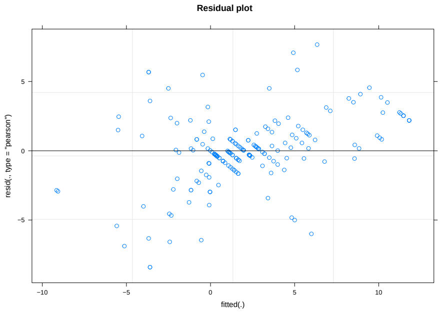
Random Effects Estimates:

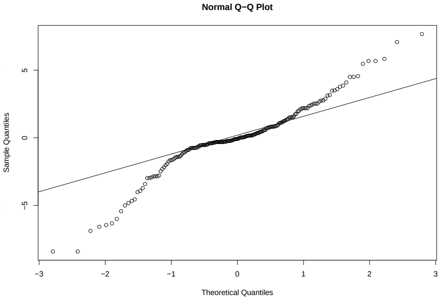
group	Std.Dev	Variance
id	4.384	19.215
school	0.597	0.357
Residual	3.275	10.726

Model Interpretations:

1. interpretations
2. interpretations
3. interpretations

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:

3 level structure[2]:

$$y_{ijk} = \beta_0 + \delta_{(3)} X_{ijk} + \mu_i + \mu_j + e_{ijk}$$

- i for school, j for subjects, k for measures
- $\mu_i \sim N(0, \sigma_b^2)$ random intercept between schools
- $\mu_j \sim N(0, \sigma_w^2)$ random intercept for subjects within schools
- $e_{ijk} \sim N(0, \sigma^2)$ random error term

Intraclass Correlation Coefficient

$$\rho_1 = \frac{\sigma_b^2 + \sigma_w^2}{\sigma_b^2 + \sigma_w^2 + \sigma^2} \qquad \rho_2 = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2 + \sigma^2}$$

Hypothesis Set Up

Hypothesis: $H_0 : \delta_{(3)} = 0$, $H_1 : \delta_{(3)} \neq 0$

- *Clinical Interest*: $H_1 : \delta_{(3)} > 0$?
- Calculate N based on normal distribution
- Interested in when $\beta = 0.20$, $\alpha^* = 0.05/2$ and $\Delta = 1/3$

Three levels of Sampling

- N_1: Number of Observation looks (4 in our case)
- N_2: Number of Indiviuals in each School *(What we want to estimate)*
- N_3: Number of Schools for one treatment arm (15 in our case)

Sample Size Calculation

Sample Size formula

$$N_2 = \frac{2(1 + (\rho_1 - \rho_2)N_1 - \rho_1) z^2_{\alpha^*,\beta}}{N_1 N_3 \Delta^2 - 2\rho_2 N_1 z^2_{\alpha^*,\beta}}$$

Where z is calculated based on the normal distribution.

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

Intra Class Correlation in our Models

Model 1 Random Effects:

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

1. $\rho_1 = 0.286$
2. $\rho_2 = 0.000$

Model 2 Random Effects:

group	Std.Dev	Variance
id	4.384	19.215
school	0.597	0.357
Residual	3.275	10.726

1. $\rho_1 = 0.646$
2. $\rho_2 = 0.012$

Sample Size Suggested

label	rho1	rho2	class_size	group_size	total_samp
Est w/ Baseline	0.286	0.000	4.372	65.580	131.160
Average	0.466	0.006	5.918	88.766	177.532
Est w/0 Baseline	0.646	0.012	7.656	114.846	229.692

Resources

[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.