# 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

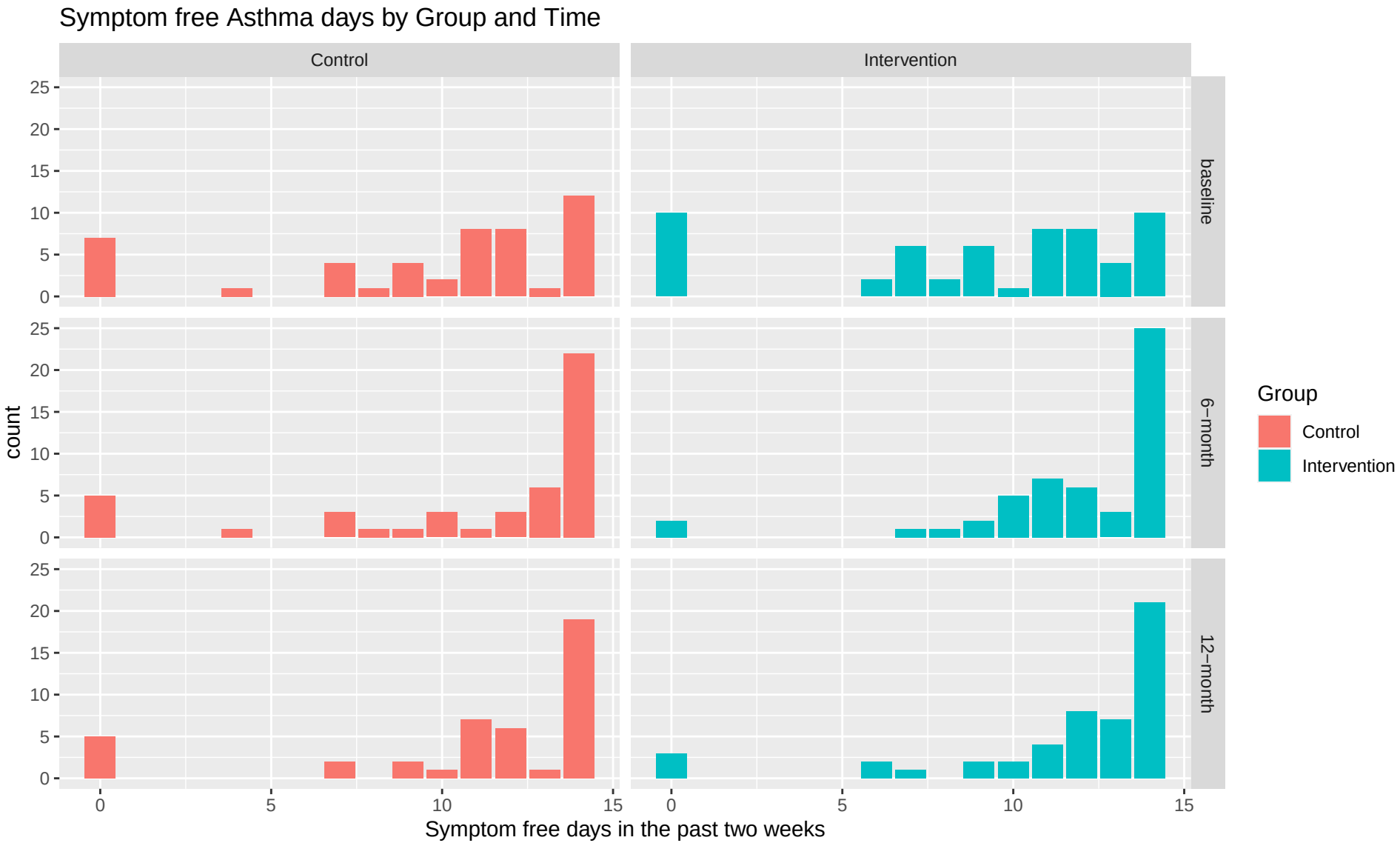
1. Data Overview
2. Exploration into Pilot Study data
   - Model Specifications
   - Results
3. Phase III Proposal
   - Model Specifications
   - Sample Size Suggestions

# Data Overview

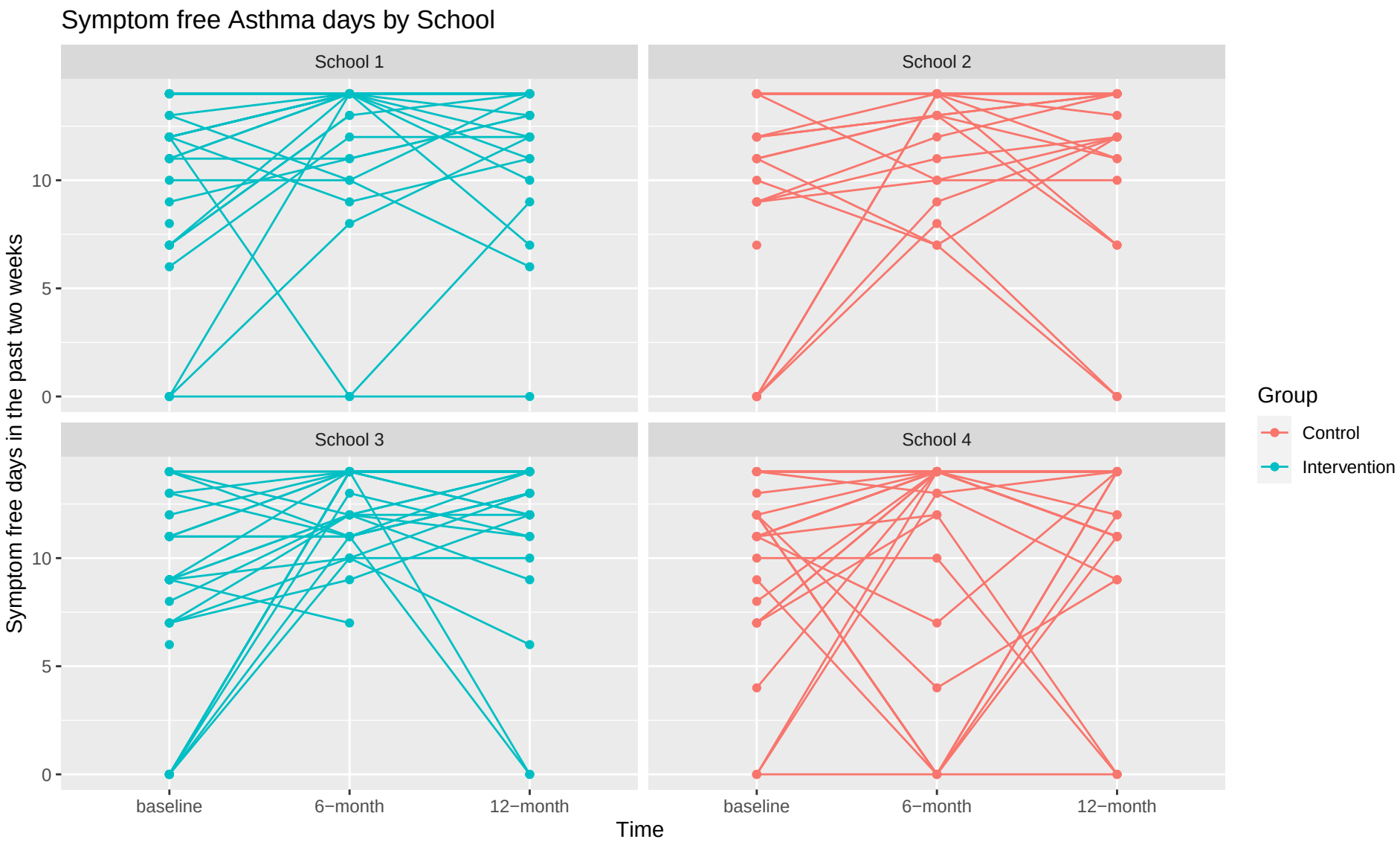
| Variable | Definition |
|---|---|
| ID | Participant's ID |
| Time | Follow up time (Baseline, 6 months, 12 months) |
| Group | Intervention group (control or Intervention) |
| SFD | Symptom free days in the past two weeks |
| School | School recruited for the study |

*Table 1:* Data Descriptions

# Data Exploration



# Data Exploration



# Data Exploration

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

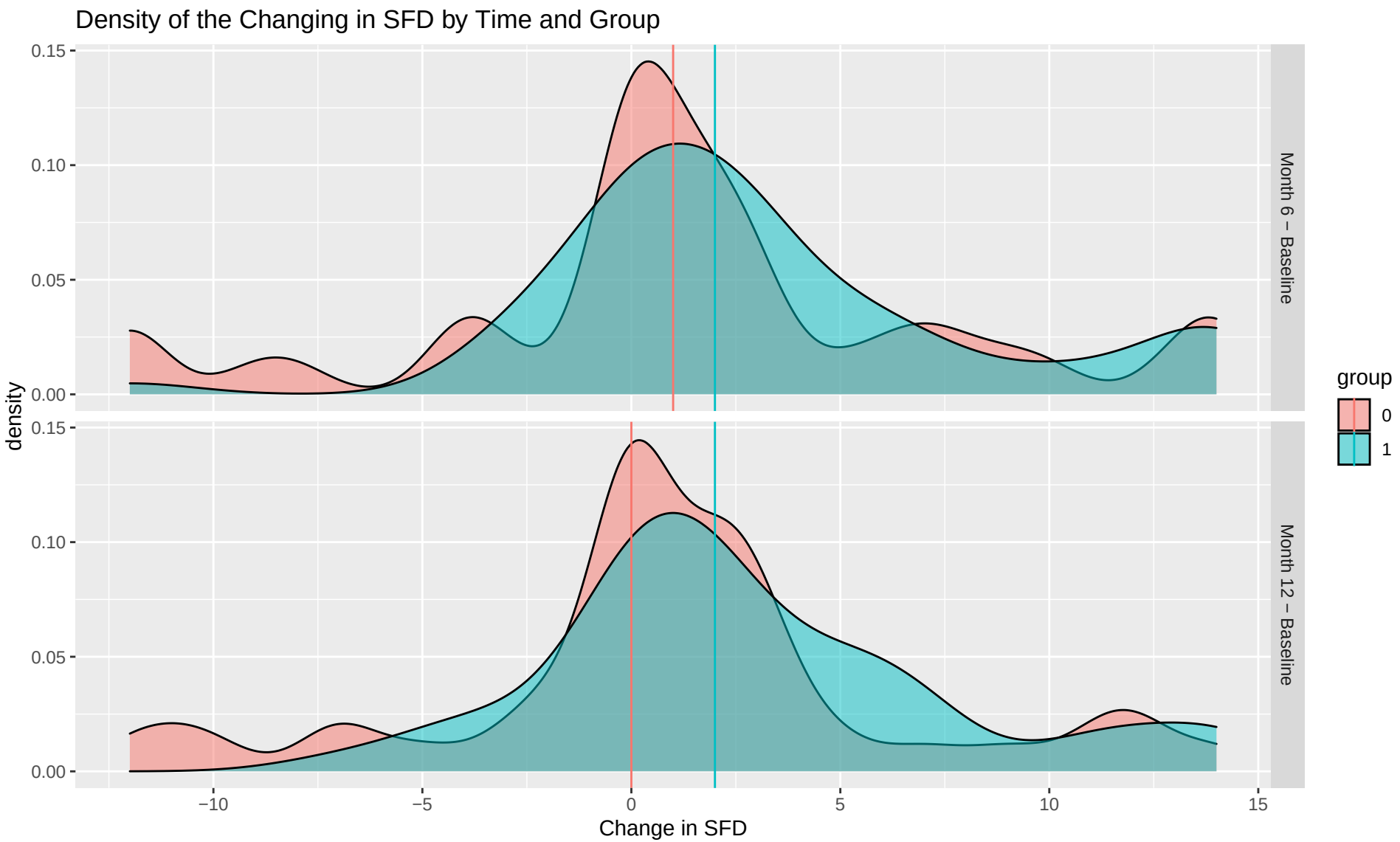
- Due to the skewed distribution towards higher values a poisson model will not fit our data well
- Outcome does not seem linear over the time observations.

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

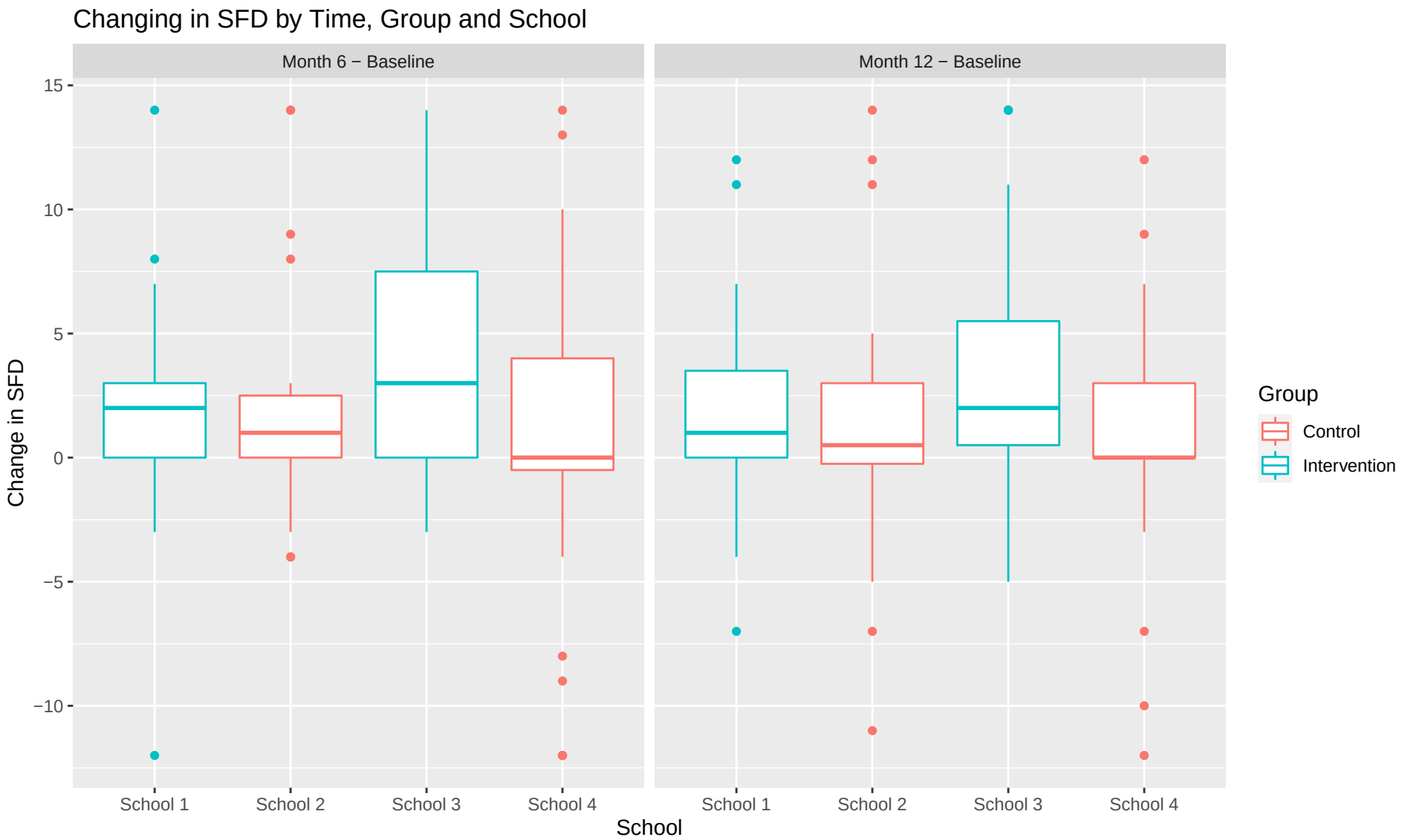
**New outcome:** Change in SFD (Continuous Data)

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

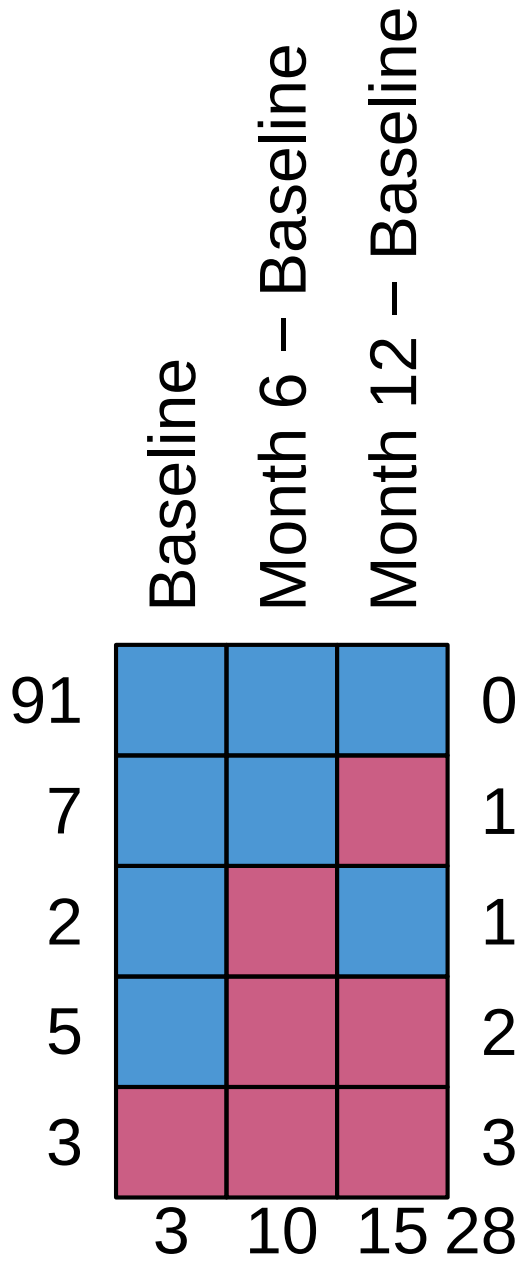
# New Continous Outcome



# Exploring variation between school and within school



# 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.

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

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:

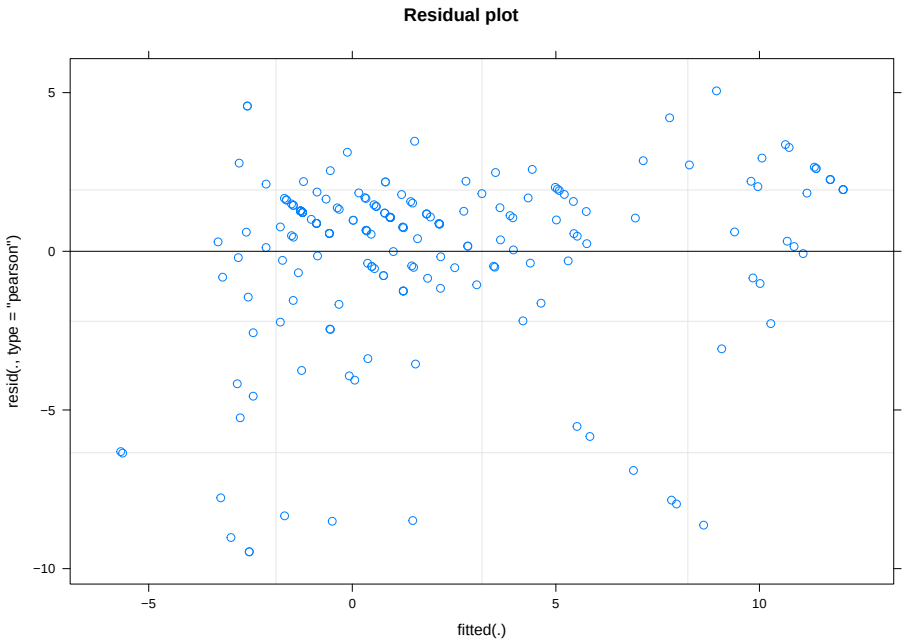
| group | Std.Dev | Variance |
|---|---|---|
| id | 2.055 | 4.221 |
| school | 0.000 | 0.000 |
| Residual | 3.250 | 10.560 |

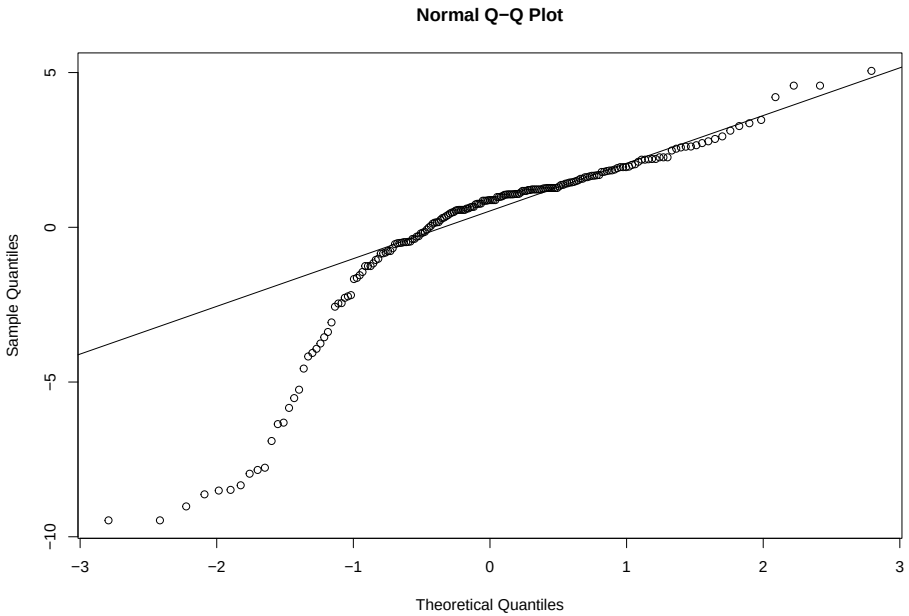
## Model Interpretations:

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

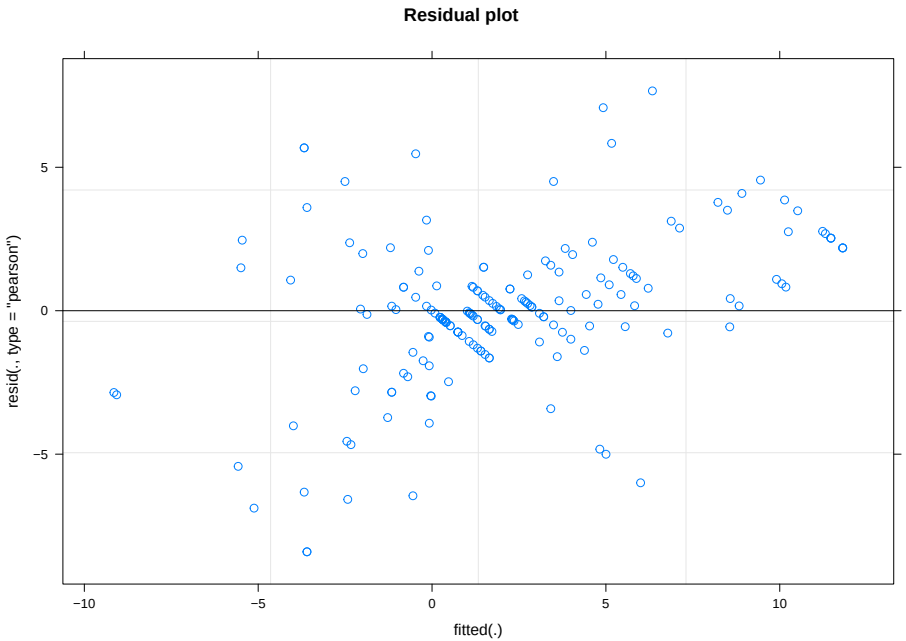
## Random Effects Estimates:

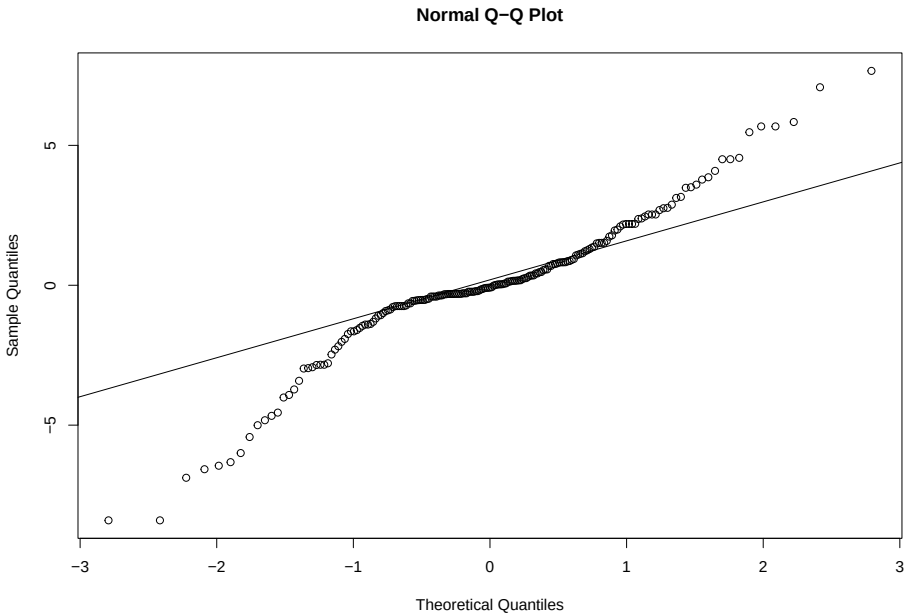
| group | Std.Dev | Variance |
|---|---|---|
| id | 4.384 | 19.215 |
| school | 0.597 | 0.357 |
| Residual | 3.275 | 10.726 |

## 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.

# Analysis for the pilot study

- Paired proportion test (binomial) / Paired T test (continuous, normal)
- For 6 months v.s. baseline, compair pass v.s. control
- For 12 months v.s. baseline, compair pass v.s. control
- Multiple adjustment
- Describe and comment on the effect sizes.
- Estimate intra class variation
- with bonferroni adjustment: $\alpha^* = \alpha/4$ for the 4 comparison