1. Organize data

Outcome: Y_{ijk} , i=subject, j=period, k=week

Covariates: ijk treatment, period, week, sequence, viral load, age, gender,

Three period Cross-over design sequences, we assume only carry over one period

	μ_A	$\mu_B + \rho_A$	$\mu_C + \rho_B$	Remaining effect	
(1)	Α	В	С	$ ho_A$	$ ho_B$
(2)	С	Α	В	$ ho_{\mathcal{C}}$	$ ho_A$
(3)	В	С	Α	$ ho_B$	$\overline{ ho_{\mathcal{C}}}$
(4)	В	Α	С	$ ho_{\scriptscriptstyle B}$	$ ho_A$
(5)	Α	С	В	$ ho_A$	$\overline{ ho_{\mathcal{C}}}$
(6)	С	В	Α	$ ho_{\mathcal{C}}$	$ ho_B$

Notice that $((1)+(4))-((2)+(5))=2(\rho_B-\rho_c)$

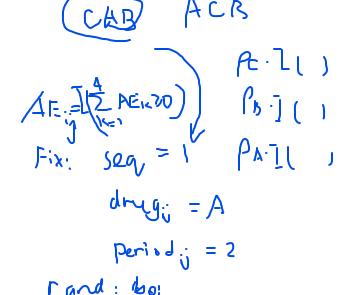
$$H_0$$
: $\rho_A = \rho_B = \rho_c \quad \Leftrightarrow \quad H_0$: $\rho_{AB} = \rho_{AC} = \rho_{BC}$

Generate 3 new sequence indicators:

AB, CA, BC

Sequence 2 =
$$\begin{cases} 0, & if \ seq = ABC \ or \ BAC \\ 1, & if \ seq = CAB \ or \ ACB \\ 2, & if \ seq = BCA \ or \ CBA \end{cases}$$

3. Time variable:



If you care about one pill is safer than another, only cumulate the 4 weeks in the period; If you want to know about specific week, need use week as time variable.

Treat week as categorical vs continuous?

€ategorical: model nonlinear trend

Continuous: linear trend

Bin (7, P) Binomial

Adhere:

fix: p, anus, reviod

random: boi + Chij

random: boi + Coij

You can plot before model it.

4. Adverse events: often rare events, may not converge.

To solve:

- 1) sum over 4 weeks or code =1 if adverse events occurred at least in one week;
- 2) use penalized logistic

Use mixed effects model for this project.