Platform trials enroll broad patient populations over long periods of time. Maintaining comparability across time and patient heterogeneity can be challenging. Careful allocation is one solution.

MOTIVATION

- Platform trials are rapidly gaining popularity by allowing multiple treatments to be tested at the same time with greater efficiency and cost-effectiveness than traditional clinical trials.
- However, systematic bias may occur, particularly in platform trials utilizing a shared control arm, due to therapy availability between sites, inclusion/exclusion criteria with some patients ineligible for certain therapies; and time-related bias.

METHODS

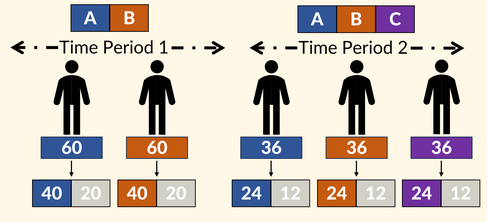
- A general allocation and analysis plan for creating comparable active and control arms in which the active arm has the same breakdown (in expectation) of time/ eligibility groups as the control arm is illustrated below.
- Viele[1] shows that allocating patients in two stages, first equally among cohorts (an active arm combined with a set of controls) and then K:1 between active:control where K is the number of eligible cohorts, maintains comparability across time and eligibility when the analysis is restricted to concurrent, co-eligible controls. Viele[1] also generalizes this to unequal randomization if more patients are desired on certain arms.
- Comparability is maintained if unequal weights are chosen as the number of active patients in each time/eligibility group would be a constant multiple of the number of control patients in that time/eligibility group.

DISCUSSION

- The randomization scheme is easy to implement and flexible to allow for arms entering and leaving the trial, eligibility restrictions, and can be employed in platform trials which utilize re-randomization.
- Using non-concurrent controls or advanced allocation methods such as response adaptive randomization requires alternative modeling approaches.
- The scheme has limitations in comparing two active arms to each other. For comparability, the analysis must be restricted to times when both active arms are enrolling and to patients eligible for both arms.

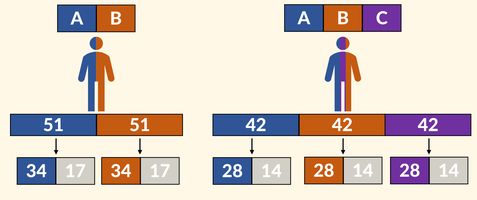
STRATEGIES FOR NON-COMPARABLE GROUPS MAY STILL INCUR BIAS

TIME BIAS: Analysis based on concurrent controls

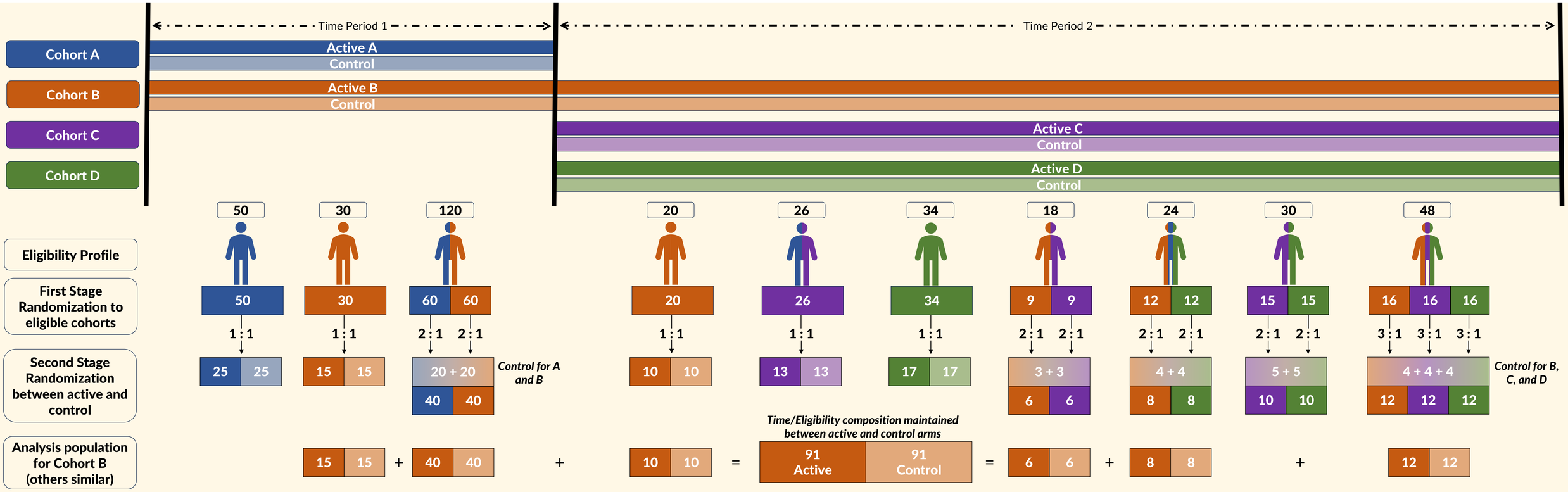


In the example above, patients are equally allocated to active cohorts within time period and randomized 2:1 within cohorts. All patients are assumed eligible for all arms. All controls are concurrent to arm A and the analysis compares 64 patients on active arm A to 76 on control. Although there are 40 time period 1 patients in both active arm A and control, there are 24 time period 2 patients on active arm A and 36 on control. Any differential effect between time periods will result in bias.

ELIGIBILITY BIAS: Analysis is restricted to eligible controls



In the example above, patients are equally allocated to active cohorts they are eligible for and randomized 2:1 within cohorts. There are no distinct time periods here. An analysis on arm A including all controls eligible for arm A would compare 62 patients on active arm A to 76 on control. Although there are 34 patients eligible for A and B in both active arm A and control, there are 28 patients eligible for A and B in active arm A and 14 on control. Any differential effect between eligibility subgroups will result in bias.



Example allocation (in expectation) of a platform trials with 200 patients enrolled per time period. The shade of the figures indicates the active cohorts to which the participant is eligible. The method produces an analysis population for each cohort that equates the control and active arms under comparison over time and eligibility. For example, in Cohort B 60% of active patients come from time period 1 and 60% of control patients come from time period 1. Additionally, 27% in each of the active and control arms come from patients eligible for only Cohort B, 44% in each arm comes from patients eligible for A and B, 7% in each arm comes from patients eligible for B and C, 9% in each arm comes from patients eligible for A, B, and D; and 13% in each arm comes from patients eligible for B, C, and D.

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This work is based on the recent publication:
[1]Viele, K. Allocation in platform trials to maintain comparability across time and eligibility. *Statistics in Medicine*. 2023; 84(16): 8411– 8436.