Appendix A
Rationale for modified futility rule for Favipiravir & Ivermectin
1 June 2022

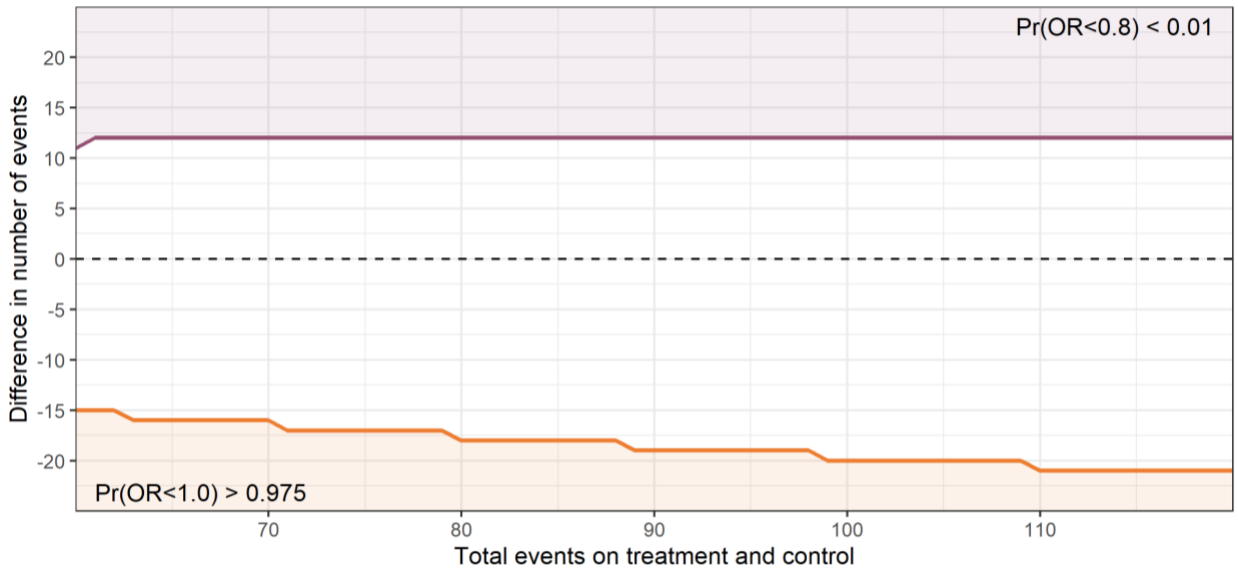
Overview

The PRINCIPLE TMG is revising the futility rule for Favipiravir and Ivermectin in order to ensure that the study reaches a swift conclusion for the interventions in the trial. Currently, both arms have met success on the time to recovery endpoint. As per the protocol, enrollment to these arms will continue until a determination can be made on the hospitalization / death endpoint. For each intervention, enrollment will stop when the treatment is found to be superior to usual care (success) or there is sufficient evidence that a clinically meaningful benefit is unlikely (futility). In the current Adaptive Design Report (ADR version 4.3), futility is declared if the probability of a clinically meaningful benefit is less than 1%. This rule was appropriate for smaller sample sizes, where there is increased risk of a mistakenly dropping an effective intervention. However, this rule is too conservative given the sample sizes that are anticipated in the current study. In particular, enrollment to an intervention may continue even if the data favor usual care over the treatment. The TMG is proposing that the futility threshold by raised to 25%. This rule would ensure that a decision is reached for interventions with a minimal benefit on hospitalization while continuing to enroll arms where there is promising evidence of efficacy on the rate of hospitalization/death.

Current Hospitalization Futility Rule

Currently, futility on the hospitalization endpoint is declared if the probability of a clinically meaningful benefit is less than 1%. A clinically meaning full benefit is defined as an odds ratio of 0.8 or better. This is approximately a 20% relative reduction in the rate of hospitalization (i.e., 4% on treatment vs. 5% on control). Figure 1 shows the approximate hospitalization/death data that would lead to a decision of success or futility with the current futility rule.

Figure 1: Hospitalization stopping rules in the PRINCIPAL trial. The y-axis is the difference between the number of events (i.e., hospitalization/death) on a single treatment and the Usual Care. Negative values indicate that the data favor the treatment. The purple shaded region show data sets that lead to a futility decision. The orange shaded region show data sets that lead to a decision of success.



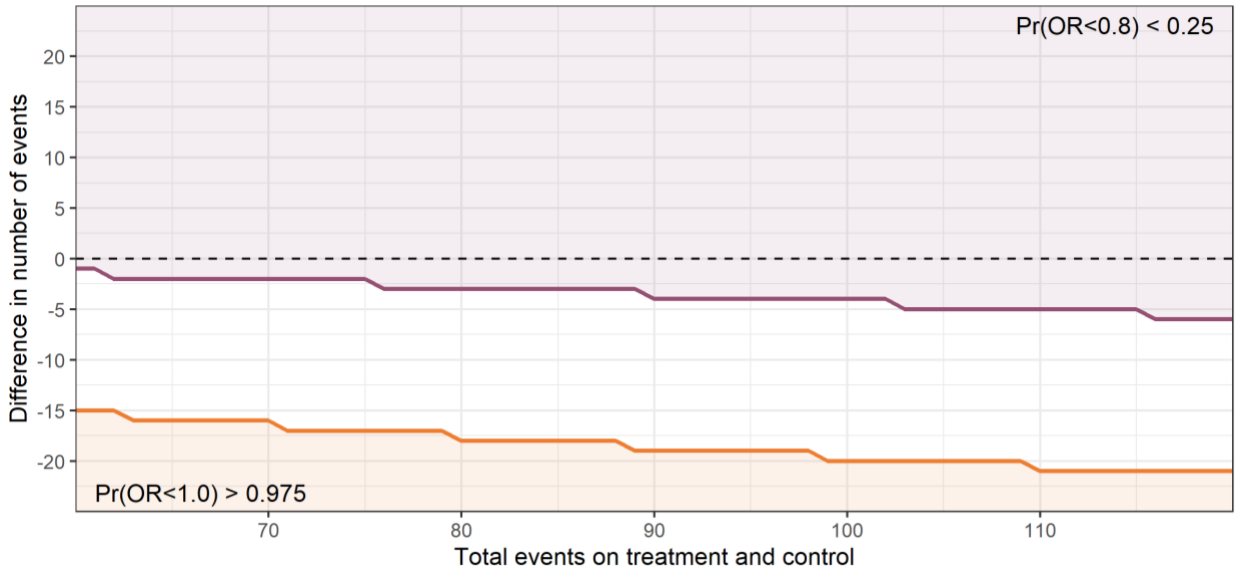
For the interim analysis of a treatment arm vs. Usual Care, the decision to declare success or futility depends on the overall sample size (x-axis) and the difference in the number of events (y-axis). For example, if there are currently 70 events in total distributed between treatment and Usual Care, and there are 16 fewer hospitalization/deaths on treatment (y-axis = -16, treatment = 27, Usual Care = 43) would lead to a decision of success. Alternatively, 12 more hospitalization/deaths on treatment (y-axis = +12, treatment = 41, Usual Care=29) would lead to a futility decision.

Based on the aggregate number of observed hospitalization events since Ivermectin and Favipiravir have begun randomization (N~90), we expect that each interim analysis has between 60 and 70 events. To declare success on the hospitalization endpoint for a given intervention, approximately 15 more hospitalizations/deaths need to be observed on the Usual Care arm than the treatment arm (orange line). To declare futility, approximately 12 more hospitalization/deaths need to be observed on the *treatment* arm (purple line). Given that neither success or futility has been declared, it is likely that the difference between treatment and Usual Care events ranges from -14 to 11 (unshaded white region). This means that randomization may continue to a treatment arm even if the study data indicate that the usual care arm is favored.

Revised Hospitalization Futility Rule

The PRINCIPLE TMG is changing the futility threshold for these two interventions from 1% to 25%. The success stopping rule remains unchanged. Figure 2 shows the hospitalization data that would lead to a decision of success or futility with the revised futility rule.

Figure 2: Proposed hospitalization stopping rule. The y-axis is the difference between the number of events on a single treatment and the control. Negative values indicate that the data favor the treatment. The purple shaded region show data sets that lead to a futility decision. The orange shaded region show data sets that lead to a decision of success.



The revised futility rule is more stringent than the previous rule. For example, if there are currently 70 events distributed between one treatment and Usual Care, a difference of -2 (treatment = 34, Usual Care = 36) would lead to a futility decision (ignoring impact of covariates in the primary analysis model).

Under the revised futility rule, data that favor the treatment by 2 or fewer events could lead to a decision of futility (purple line). This means that only arms with promising data would remain randomizing in the study. Treatments with negative results would be stopped for futility, allowing more patients to be randomized to promising treatments and increasing the efficiency of the study. The revised futility rule is documented and applied to Favipiravir and Ivermectin in the new Adaptive Design Report version 5.0.

Technical Consideration

The analysis in Figures 1 and 2 was performed using a model that does not include covariates. The PRINCIPLE primary analysis adjusts for baseline covariates (age, comorbidity, vaccination status) and temporal changes is the hospitalization rate. The impact of this adjustment is difficult to quantify; we anticipate that they may slightly change the size of the event-difference needed to trigger success or futility.