

## TIGERS – supplemental statistical tables (in response to peer review)

**Table 1. Operating characteristics for 1000 simulated trials for each endotype sub-trial for certain scenarios (assuming 1.5 patients/site/month over 42 months), assuming a mortality rate of 15% in each subphenotype**

Scenario	Average/Expected sample size (range)	Expected duration in months (range)	Prob declare efficacy treatment 1	Prob declare efficacy treatment 2	Prob efficacy declared for at least one intervention*	Prob early stop treatment 1 for efficacy	Prob early stop treatment 2 for efficacy	Overall prob of inconclusive result in subtype**
<b>SRS 1</b>								
<b>Null: POR1=1, POR2 = 1</b>	1033 (376-1160)	44 (26-44)	0.1034	0.0974	0.1714	0.142	0.125	0.2373
<b>Both work: POR1 = 1.37, POR2 = 1.37</b>	743 (371-1144)	36 (25-44)	0.7787	0.7706	0.9046	0.7894	0.7753	0.0873
<b>SRS 2</b>								
<b>Null: POR1 = 1, POR2 = 1</b>	1209 (445-1287)	38 (23-41)	0.0706	0.0850	0.1372	0.1066	0.1147	0.2170
<b>Both work: POR1 = 1.37, POR2 = 1.37</b>	836 (423-1278)	31 (23-40)	0.7907	0.7639	0.9227	0.7342	0.7536	0.0711

POR1 = proportional odds ratio for investigational treatment 1 (e.g., tocilizumab);

POR2 proportional odds ratio for investigational treatment 2 (e.g., infliximab)

\*Proportion of simulated trials that the efficacy rule was met for at least one of investigational treatment 1 or treatment 2

\*\*An inconclusive result occurs if neither the efficacy or futility rules have been met (in either investigational arm)

**Table 2. Estimand framework**

Estimand attribute	Primary estimand
<b>Population</b>	Patients meeting the inclusion criteria and no exclusion criteria
<b>Treatment conditions</b>	(Active treatment + usual care) vs usual care
<b>Outcome variable</b>	An ordinal outcome: composite of organ support-free days up to 28 days and death
<b>Population-level summary measure</b>	Proportional odds ratio comparing each active treatment vs usual care
<b>Intercurrent event: strategies</b>	<p><b>Death:</b> Composite strategy (included in the outcome)</p> <p><b>Protocol non-adherence:</b> Treatment policy strategy</p> <p><b>Use of other effective/rescue medications:</b> Treatment policy strategy</p>