RAPID local ischemic postconditioning in acute ischemic **S**troke p**A**tients recei**VE**d successful thrombectomy reperfusion (**RAPID-SAVE**)

STATISTICAL ANALYSIS PLAN

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BOIN12 Study Design and Statistical Analysis Plan

This study employed the Bayesian optimal interval phase I/II (BOIN12) trial design[1] find the optimal biological dose (OBD). The BOIN12 design used utility to quantify the desirability of a dose in terms of toxicity-efficacy trade off and adaptively allocated patients to the dose that has the highest estimated desirability. The utilities ascribed to each possible efficacy-toxicity outcome were as follows: (No Toxicity, Efficacy) = 100; (Toxicity, Efficacy) = 60; (No Toxicity, No Efficacy) = 40; and (Toxicity, No Efficacy) = 0. A higher value indicated a more desirable outcome (0 and 100 present the least and most desirable outcome, respectively).

Let $u1,\cdots,u4$ denoted these utilities. Given a dose j, let $p1,\cdots,p4$ denoted the corresponding probabilities of observing each of the possible toxicity-efficacy outcomes. Then, the mean utility of dose j is

$$uj=p1u1+p2u2+p3u3+p4u4.$$

A higher value of uj indicated a higher desirability of dose j in terms of risk-benefit tradeoff. To safeguard patients from toxic and/or futile doses, two dose acceptability criteria were used by BOIN12 to decide which doses might be used to treat patients. A dose was deemed as admissible and eligible for treating patients if it satisfied the following safety and efficacy criteria.

$$\text{(Safety)}\quad \Pr(\ (\pi T > 0.15\ |\text{data}))< 0.95,$$

$$\text{(Efficacy)}\quad \Pr(\pi E < 0.6\ |\text{data})< 0.9.$$

where πT and πE were the true DLT rate and efficacy rate, respectively. These two conditions ensured that the admissible dose could not be overly toxic or futile. Doses that were not admissible would be eliminated from the trial. If a dose was eliminated due to toxicity, all doses higher than that dose would also be eliminated. The objective was to identify the OBD, defined as the dose that was admissible and had the highest desirability.

We planned to enrol a maximum number of 60 patients with a cohort size of 5. When the current dose's observed toxicity rate fell within the stay interval of BOIN, we would stop exploring higher doses if its number of patients $\geq N*$, where $N*= 5$. The BOIN12 design is depicted in Supplemental Figure 1 and it was implemented according to the following 3 steps via the BOIN12 shiny app[2].

1. Treat the first cohort at dose level 3.
2. Suppose that the current dose level is j, choose one of the following three cases to determine the dose for treating the next cohort of patients:

   Case A: determine the desirability of dose levels $j-1$, j, and $j+1$ using the rank-based desirability score (RDS) table (Table 1), and choose the one that has the highest desirability to treat the next cohort. If the RDS of all three doses are "E," stop the trial and no dose should be selected. In the case that dose level $j-1$ (or $j+1$) does not exist, then apply the above rule to dose levels j and $j+1$ (or j and $j-1$).

   Case B: determine the desirability of dose levels j and $j-1$ using the RDS table (Table 1), and choose the one that has the higher desirability to treat the next cohort. If the RDS of the two doses are "E," stop the trial and no dose should be selected. If the current dose level j is the lowest dose, treat the next cohort of patients at the lowest dose unless the RDS of the lowest dose is "E," at which point terminate the trial.

   Case C: determine the desirability of dose levels j and $j-1$ using the RDS table (Table 1).

   - If the current dose level j is the lowest dose, treat the new patients at the lowest dose unless the RDS of the lowest dose is "E," at which point terminate the trial.

- If the current dose level j is not the lowest dose and the RDS of dose level $j-1$ is not "E," de-escalate the dose to level $j-1$ to treat the next cohort of patients.

If the current dose level j is not the lowest dose and the RDS of dose level $j-1$ is "E," stay at the current dose level j to treat the next cohort of patients unless the RDS of dose level j is "E," at which point terminate the trial. In the event of **Case A** or **Case B**, to prevent getting stuck in a local dose, an extra dose exploration rule is implemented to escalate to the next higher untried dose if the following two conditions are met:

- The number of patients treated at the current dose is ≥ 15.
- The next higher dose is not eliminated and has never been used for treating patients.

3. Repeat step 2 until the maximum sample size of 60 is reached or if the number of patients treated on any dose reaches 20. Then, use the isotonic estimation method described in Lin et al.[1] to select the OBD as the dose that is admissible and that has the highest estimated utility.

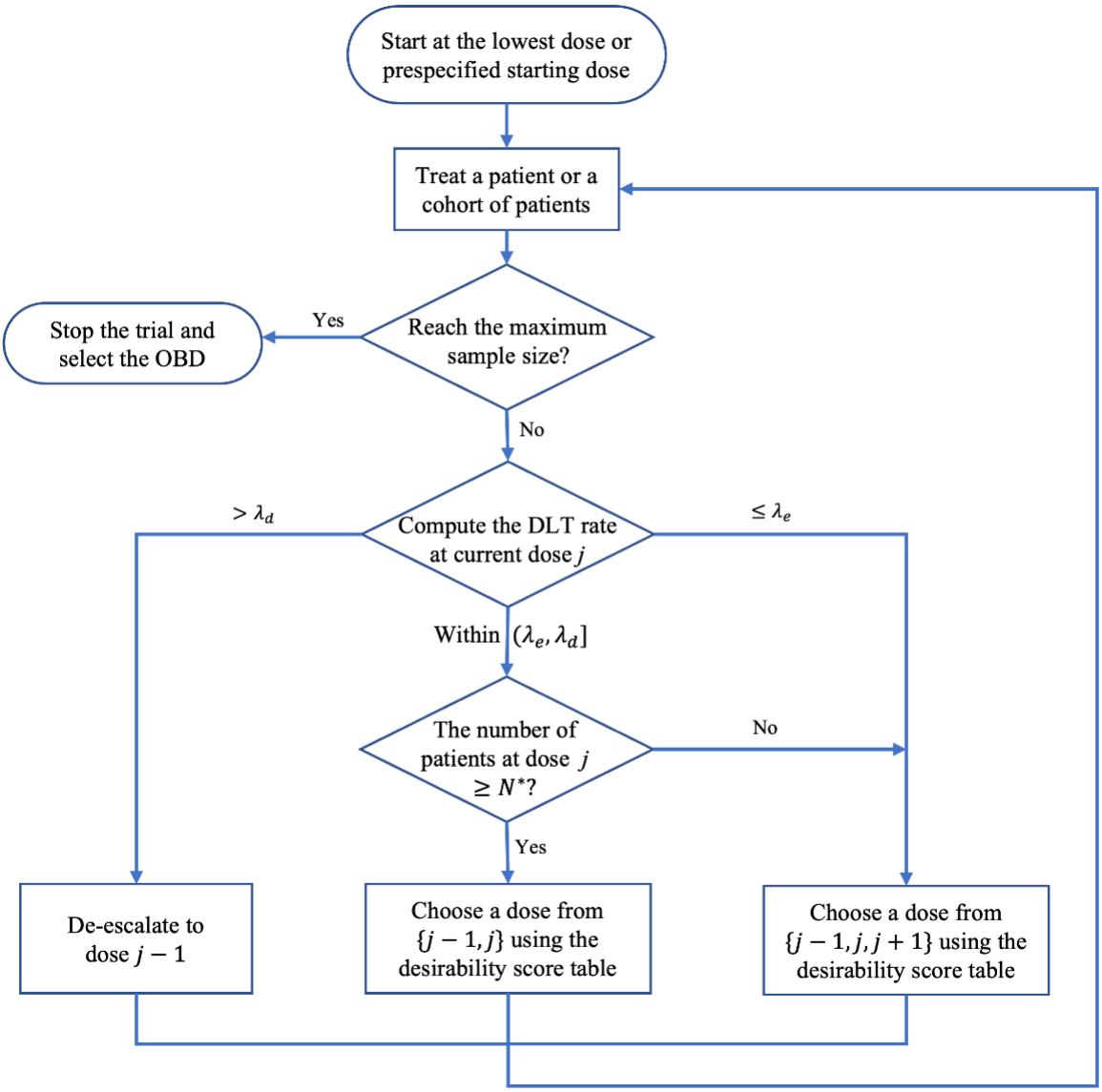

Figure 1. Flowchart for trial conduct using the BOIN12 design, where $N*$= 5, and (λe,λd)= (0.118, 0.179).

eTable 1. Rank-based desirability score (RDS) table for the BOIN12 design, where "E" means elimination. A larger value of RDS means higher desirability, and any value of RDS is deemed higher than "E". **#Pts** denotes the number of evaluable patients treated at current dose; **#Tox** denotes the number of evaluable patients who experience toxicity; **#Eff** denotes the number of evaluable patients who experience efficacy.

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
0	0	0	262	15	0	7	96	15	4	9	61	20	2	19	528
5	0	<= 1	E	15	0	8	159	15	4	10	115	20	2	20	556
5	0	2	169	15	0	9	232	15	4	11	183	20	3	<= 9	E
5	0	3	268	15	0	10	297	15	4	12	256	20	3	10	19
5	0	4	377	15	0	11	366	15	4	13	321	20	3	11	47
5	0	5	483	15	0	12	435	15	4	14	389	20	3	12	90

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
5	1	<= 1	E	15	0	13	497	15	4	15	457	20	3	13	147
5	1	2	101	15	0	14	542	15	>= 5	Any	E	20	3	14	213
5	1	3	199	15	0	15	565	20	0	<= 9	E	20	3	15	264
5	1	4	308	15	1	<= 6	E	20	0	10	90	20	3	16	328
5	1	5	413	15	1	7	61	20	0	11	147	20	3	17	391
5	>= 2	Any	E	15	1	8	115	20	0	12	213	20	3	18	448
10	0	<= 4	E	15	1	9	183	20	0	13	264	20	3	19	501
10	0	5	172	15	1	10	256	20	0	14	328	20	3	20	539

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
10	0	6	250	15	1	11	321	20	0	15	391	20	4	<= 9	E
10	0	7	330	15	1	12	389	20	0	16	448	20	4	10	8
10	0	8	414	15	1	13	457	20	0	17	501	20	4	11	27
10	0	9	492	15	1	14	514	20	0	18	539	20	4	12	59
10	0	10	545	15	1	15	550	20	0	19	561	20	4	13	109
10	1	<= 4	E	15	2	<= 6	E	20	0	20	571	20	4	14	170
10	1	5	117	15	2	7	31	20	1	<= 9	E	20	4	15	227
10	1	6	196	15	2	8	75	20	1	10	59	20	4	16	287

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
10	1	7	286	15	2	9	136	20	1	11	109	20	4	17	351
10	1	8	360	15	2	10	204	20	1	12	170	20	4	18	410
10	1	9	444	15	2	11	276	20	1	13	227	20	4	19	468
10	1	10	513	15	2	12	347	20	1	14	287	20	4	20	515
10	2	<= 4	E	15	2	13	412	20	1	15	351	20	5	<= 9	E
10	2	5	69	15	2	14	478	20	1	16	410	20	5	10	2
10	2	6	141	15	2	15	529	20	1	17	468	20	5	11	12
10	2	7	220	15	3	<= 6	E	20	1	18	515	20	5	12	34

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
10	2	8	306	15	3	7	16	20	1	19	549	20	5	13	73
10	2	9	387	15	3	8	46	20	1	20	566	20	5	14	129
10	2	10	467	15	3	9	96	20	2	<= 9	E	20	5	15	192
10	3	<= 4	E	15	3	10	159	20	2	10	34	20	5	16	243
10	3	5	37	15	3	11	232	20	2	11	73	20	5	17	312
10	3	6	94	15	3	12	297	20	2	12	129	20	5	18	371
10	3	7	172	15	3	13	366	20	2	13	192	20	5	19	430
10	3	8	250	15	3	14	435	20	2	14	243	20	5	20	488

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
10	3	9	330	15	3	15	497	20	2	15	312	20	>= 6	Any	E
10	3	10	414	15	4	<= 6	E	20	2	16	371				
10	>= 4	Any	E	15	4	7	6	20	2	17	430				
15	0	<= 6	E	15	4	8	23	20	2	18	488				

Reference

1. Lin R., Zhou Y., Yan, F., Li D., and Yuan, Y. (2020). BOIN12: Bayesian optimal interval Phase I/II trial design for utility-based dose finding with immunotherapy and targeted therapies, *JCO Precision Oncology 4*, 1393-1402.
2. Zhou, Y., Lin, R., Kuo, Y., Lee, J. J, & Yuan, Y. (2021). BOIN suite: a software platform to design and implement novel early phase clinical trials. *JCO Clinical Cancer Informatics 5*, 91-101.