R-TPI: A NOVEL DESIGN FOR ACCELERATING DOSE FINDING TRIALS

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R-TPI: Rolling Toxicity Probability Interval Design to Shorten the Duration and Maintain Safety of Phase I Trials

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Joint work by Wentian Guo[1], Yuan Ji[1,2], and Daniel Li[3]

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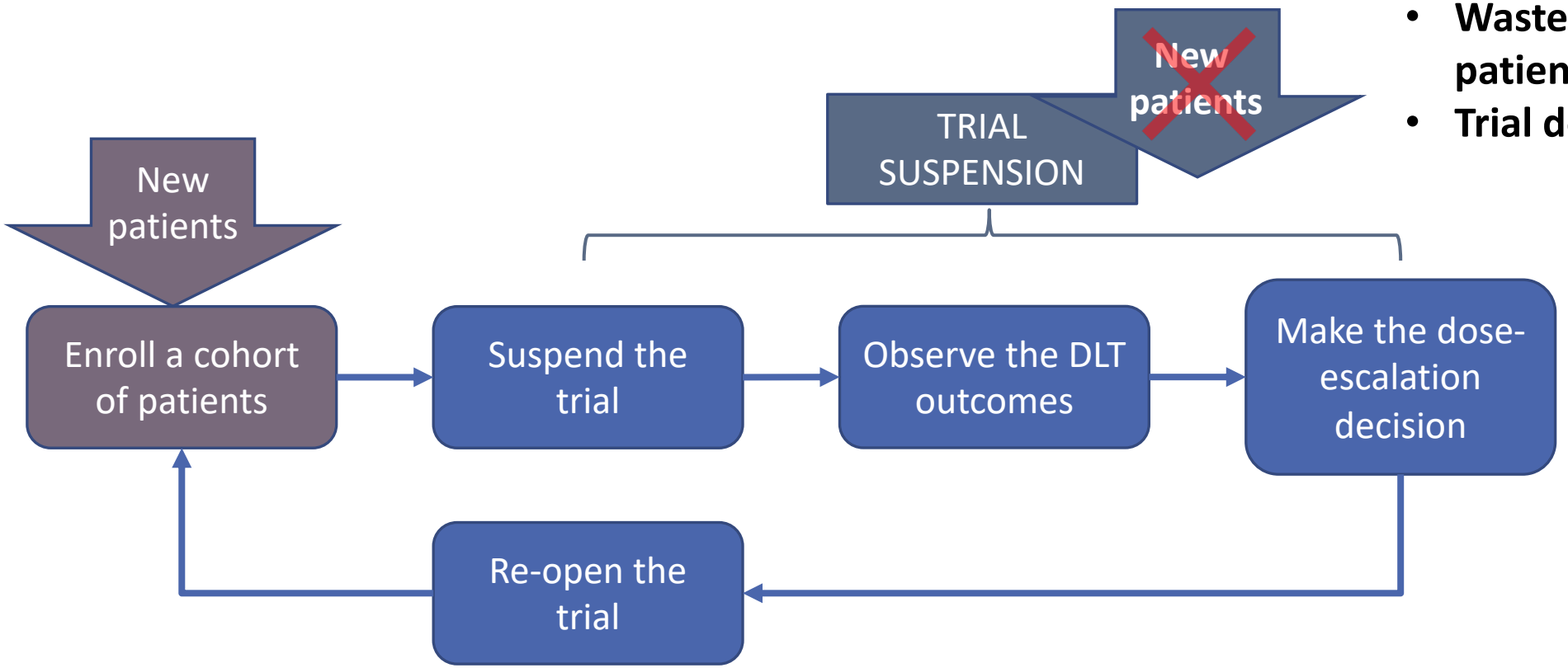
Background: Cohort-Based Phase I Trials



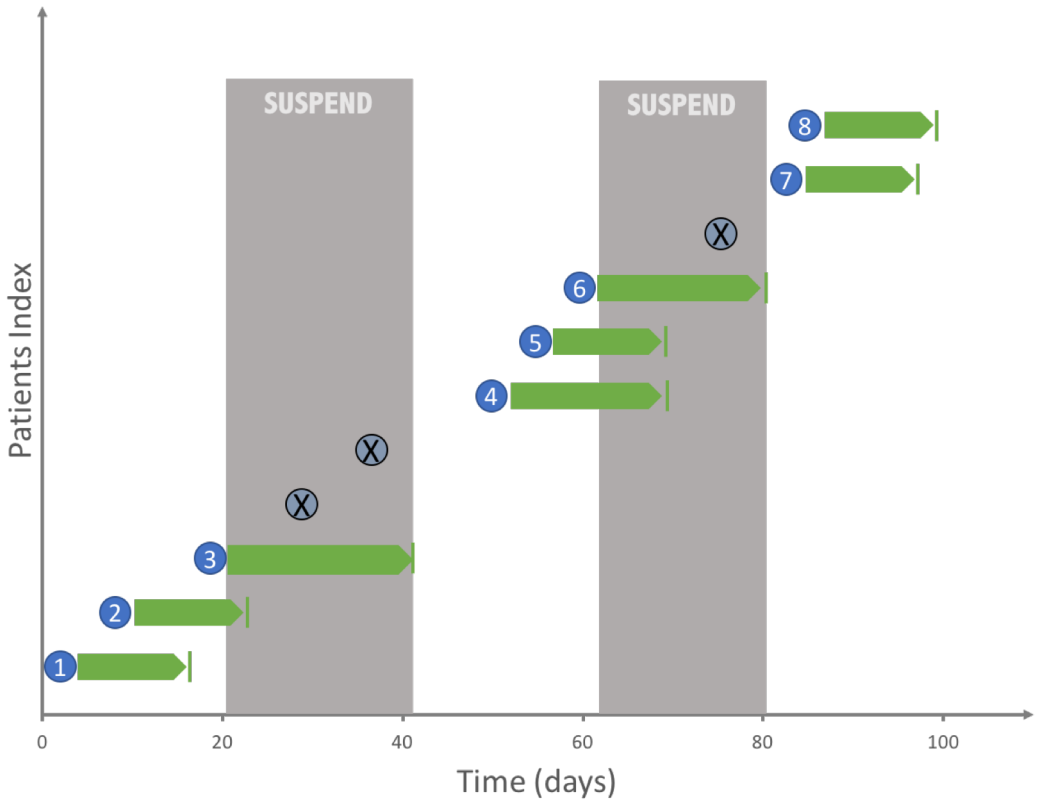
- **Waste of precious patient resources**
- **Trial delay**

A canonical cohort-based phase 1 trial: 3+3, CRM, BLRM, mTPI, mTPI-2, or BOIN

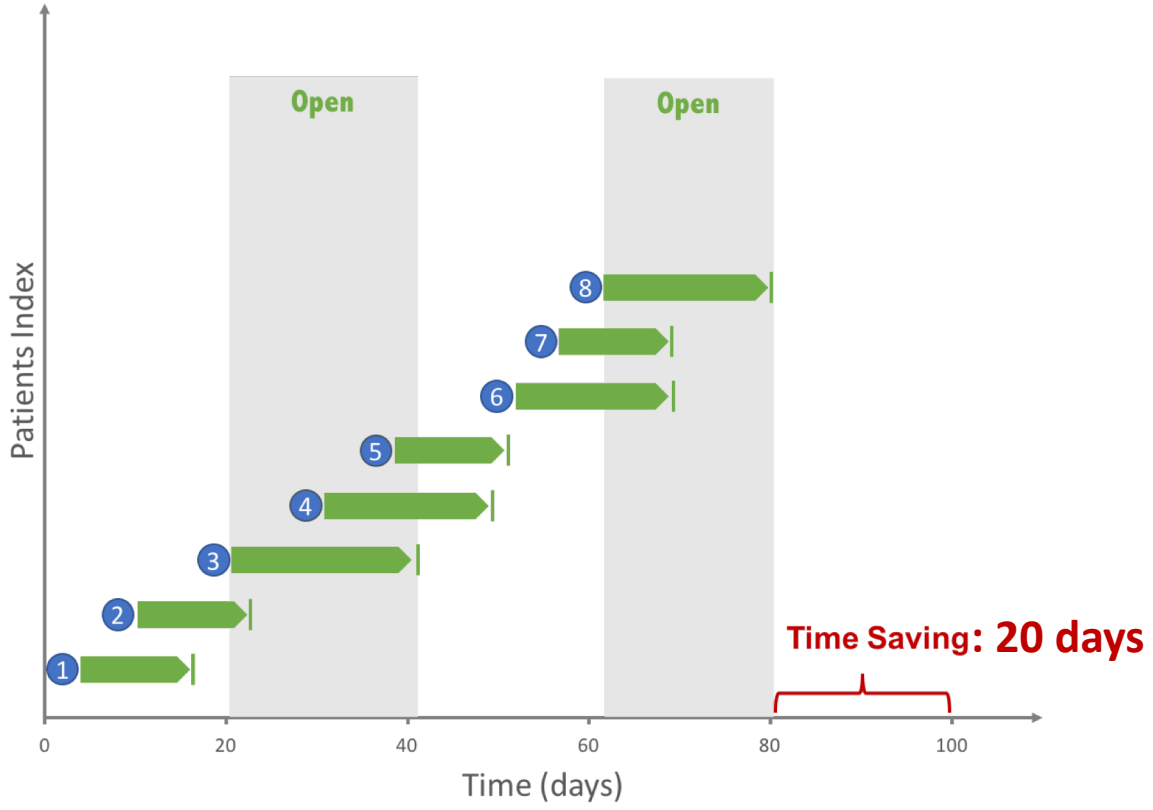
Cohort-Based vs Rolling-Based

Cohort-Based	The cohort-based enrollment is standard
Suspension	Patient accrual is often suspended

Rolling-Based	Ideally few suspensions
Rolling Six Design	Enroll up to six patients continuously



Timeline for a cohort-based trial



Timeline for a rolling-based trial

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The Rolling Six Design (RSD)

- Skolnik et al., 2008, JCO
- To accelerate the pediatric trial based on 3+3
- How? Sometimes no need to wait for the pending results to make a decision.

Debatable decisions:

- 0 DLT, 3 Non-DLTs, 1 pending: S
  Waste patient resources at low doses
- 0 DLT, 0 Non-DLT, 3 pending: S
  Somewhat aggressive

Other problems

- rule-based and by definition, cannot adjust to different pT values
- only rules for up to six patients

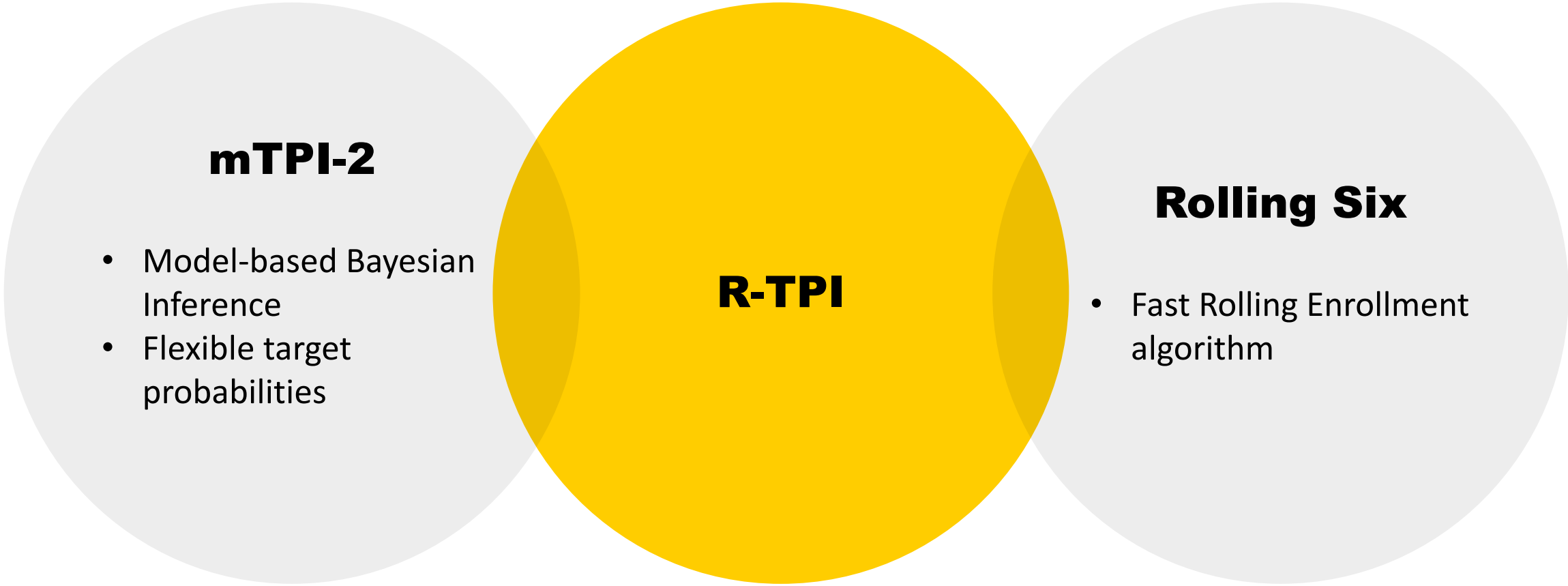
Rolling Six: an Algorithmic Design for Target toxicity probability

$p_T \approx 1/6$

Rolling Six can be summarized in a table.

	Observed data at dose d			Decision	
$\#Enrolled$	# DLTs	# Non-DLTs	# Pending	MTD Not Exceeded	MTD Exceeded
2	0, 1	any	any	S	-
2	2	0	0	D	-
3	0	0, 1, 2	3, 2, 1	S	-
3	0	3	0	E	-
3	1	0, 1, 2	2, 1, 0	S	-
3	≥ 2	any	any	D	-
4	0	0,1,2,3	4,3,2,1	S	S
4	0	4	0	E	S
4	1	0,1,2,3	3,2,1,0	S	S
4	≥ 2	any	any	D	D
5	0	0,1,2,3,4	5,4,3,2,1	S	S
5	0	5	0	E	S
5	1	0,1,2,3,4	4,3,2,1,0	S	S
5	≥ 2	any	any	D	D
6	0	0,1,2,3,4	6,5,4,3,2	Suspend	Suspend
6	0	5,6	1,0	E	MTD
6	1	0,1,2,3,4	5,4,3,2,1	Suspend	Suspend
6	1	5	0	E	MTD
6	≥ 2	any	any	D	D

R-TPI is a hybrid design



R-TPI aims to combine model-based inference with fixed rolling rules to achieve faster enrollment, safer trials, controlled sample size, and comparable "power" (in finding MTD).

How R-TPI Accelerates the Trial

By natural human thinking

Consider a given moment of a mTPI-2 driven trial:

y_d=1 (# of DLT),

n_d=2 (# of DLT + non-DLT),

m_d=1 (# of pending patients).

mTPI-2 Decision Table (pT=0.15)

	1	2	3	4	5	6
0	E	E	E	E	E	E
1	D	D	D	D	D	S
2		DU	DU	DU	DU	D
3			DU	DU	DU	DU
4				DU	DU	DU
5					DU	DU
6						DU

Column indicates the number of patients treated.
Row indicates the number of patients with DLTs

What if a new patient becomes eligible? Turn the patient away?

-The answer is no!

Why?

Because regardless of what outcome of the pending patient is, the decision is D.

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R-TPI Decision Rules

- R-TPI can enroll patient when some patients are still pending by logical rules.
- Decisions are made based on y_d, n_d, and m_d
- **$D(y_d,n_d) \triangleq$ the mTPI-2 decision for y DLT out of n patients**

	$D(y_d,n_d)$	$D(y_d+m_d,n_d+m_d)$	$D(y_d,n_d+m_d)$	R-TPI Decision
	Decision for current observation	Decision for the most toxic case scenario	Decision for the safest case scenario	
1	D	D	D	D
2	D	D	S or E	S
3	S	S or D	S	S
4	S	S or D	E	S or suspend*
5	E	E	E	E
6	E	S or D	E	S or suspend*

*If more than 3 continuous patients has been enrolled, suspend the trial to avoid over-enrolling patients on the current dose.

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Methods Overview

- R-TPI can enroll patient when some patients are still pending
- Decisions are made based on y_d, n_d, and m_d
- Decisions are made based on the current observed data and the possible outcomes of the pending patients.
- What is the maximum number of m_d, denoted as C, to be allowed in the trial?
  - For cohort-based design, C=3
  - For Rolling Six, C=6
- C is also an important threshold to control the enrollment speed for R-TPI. Recommend a value between 3 and 6.

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Rules for a Dose Never Used: Run-in Stage

- Two stages in R-TPI
- Run-in stage (when a dose d_0 is never tested before)
- R-TPI keeps enrolling new patients at dose d_0 until either
  1. $n_{d0} > 0$, i.e. there is at least one outcome at d_0 , or
  2. $n_{d0} = 0$ and $m_{d0} = C$, e.g., C = 3 .

- C is the maximum number of pending patients allowed in the trial.
  - For cohort-based design, C=3
  - For Rolling Six, C=6
- C is also an important threshold to control the enrollment speed.
- Recommend a value between 3 and 6.

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Rules for a Dose Never Used: Run-in Stage

- Two stages in R-TPI
- Run-in stage (when a dose d_0 is never tested before)
- R-TPI keeps enrolling new patients at dose d_0 until either
  1. $n_{d0} > 0$, i.e. there is at least one outcome at d_0 , or
  2. $n_{d0} = 0$ and $m_{d0} = C$, e.g., $C = 3$.
- If condition 1 is met, switch to rolling stage.
- Else, wait until $n_{d0} > 0$ and then switch to rolling stage.

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Rolling Stage

- Rolling stage: assume the current dose is d and we have at least one observation at dose d.
- Whenever a new patient becomes eligible:
  - If m=0, assign the new patient based on D(y,n);
  - If m=C, suspend the enrollment;
  - Otherwise, assign the new patient based on R-TPI decision table
- The decision table can be pre-tabulated based on the logical decision rules.

	$D(y_d,n_d)$	$D(y_d+m_d,n_d+m_d)$	$D(y_d,n_d+m_d)$	R-TPI Decision
	Decision for current observation	Decision for the most toxic case scenario	Decision for the safest case scenario	
1	D	D	D	D
2	D	D	S or E	S
3	S	S or D	S	S
4	S	S or D	E	S or suspend*
5	E	E	E	E
6	E	S or D	E	S or suspend*

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Transparent Decision Table for R-TPI

Table 2: R-PTI Decision Table with $p_T = 0.17$, $\epsilon_1 = \epsilon_2 = 0.05$ and $C = 3$. The last column is the corresponding decision of RSD (only showing decisions when MTD not exceeded in Table 1).

Observed data at dose d				Decision	
$n_d + m_d$	y_d	n_d	k_d	R-TPI	RSD
1	0	0	1	S	-
1	0	1	1	E	-
1	1	1	1	D	-
2	0	0,1	any	S	S
2	0	2	any	E	S
2	> 0	any	any	D	S or D
3	0	0,1,2	3	Suspend	S
3	0	1,2	< 3	S	S
3	0	3	any	E	E
3	> 0	any	any	D	S or D
4	0	1,2,3	3	Suspend	S
4	0	2,3	< 3	S	S
4	0	4	any	E	E
4	> 0	any	any	D	S or D
5	0	2,3,4	3	Suspend	S
5	0	3,4	< 3	S	S
5	0	5	any	E	E
5	1	any	any	S	S
5	> 1	any	any	D	D
6	0	3,4,5	3	Suspend	Suspend or E
6	0	4,5	< 3	S	-
6	0	6	any	E	E
6	1	any	any	S	Suspend or E
6	> 1	any	any	D	D
7	0	4,5,6	3	Suspend	-
7	0,1	5,6	< 3	S	-
7	0	7	any	E	-
7	1	5,6	3	Suspend	-
7	1	7	any	S	-
7	> 1	any	any	D	-

Table 3: R-PTI Decision Table with $p_T = 0.3$, $\epsilon_1 = \epsilon_2 = 0.05$, and $C = 3$. The last column is the corresponding decision of RSD (only showing decisions when MTD not exceeded in Table 1).

Observed data at dose d				Decision	
$n_d + m_d$	y_d	n_d	k_d	R-TPI	RSD
1	0	0	1	S	-
1	0	1	1	E	-
1	1	1	1	D	-
2	0	0,1	any	S	S
2	0	2	any	E	S
2	> 0	any	any	D	S or D
3	0	0,1,2	3	Suspend	S
3	0	1,2	< 3	S	S
3	0	3	any	E	E
3	1	any	any	S	S
3	> 1	any	any	D	D
4	0	1,2,3	3	Suspend	S
4	0	2,3	< 3	S	S
4	0	4	any	E	E
4	1	any	any	S	S
4	> 1	any	any	D	D
5	0	2,3,4	3	Suspend	S
5	0	3,4	< 3	S	S
5	0,1	5	any	E	E or S
5	1	3,4	≥ 3	Suspend	S
5	1	3,4	< 3	S	S
5	> 1	any	any	D	D
6	0	3,4	3	Suspend	Suspend
6	0	4	< 3	S	-
6	0	5	any	E	E
6	1	3,4,5	3	Suspend	Suspend
6	1	4, 5	< 3	S	-
6	0,1	6	any	E	E
6	2	any	any	S	D
6	> 2	any	any	D	D
7	0	4,5	3	Suspend	-
7	0	5	< 3	S	-
7	0	6	any	E	-
7	1	4,5,6	3	Suspend	-
7	1	5,6	< 3	S	-
7	0,1	7	any	E	-
7	2	6,7	any	S	-
7	> 2	any	any	D	-

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Simulation Studies

We conducted extensive simulation studies

- A bench mark study with RSD using the scenario in Skolnik et al., 2008, JCO.
- Simulation studies to compare R-TPI, mTPI-2, 3+3 and Rolling 6 under 60 scenarios under matching sample size of 3+3 with varing
  - Target toxicity probabilities
  - Number of doses
  - Location of true MTD
  - Enrollment speed
  - C, the maximum number of allowed pending patients

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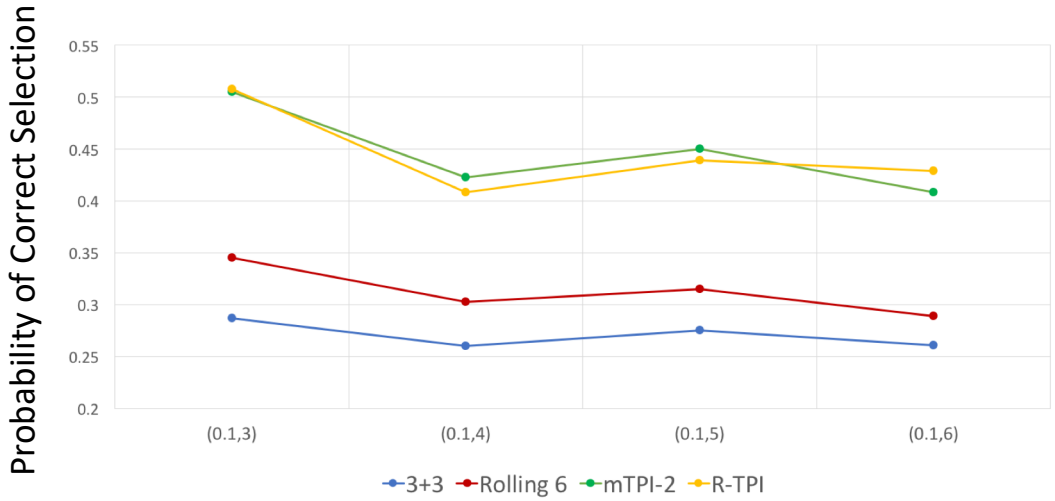
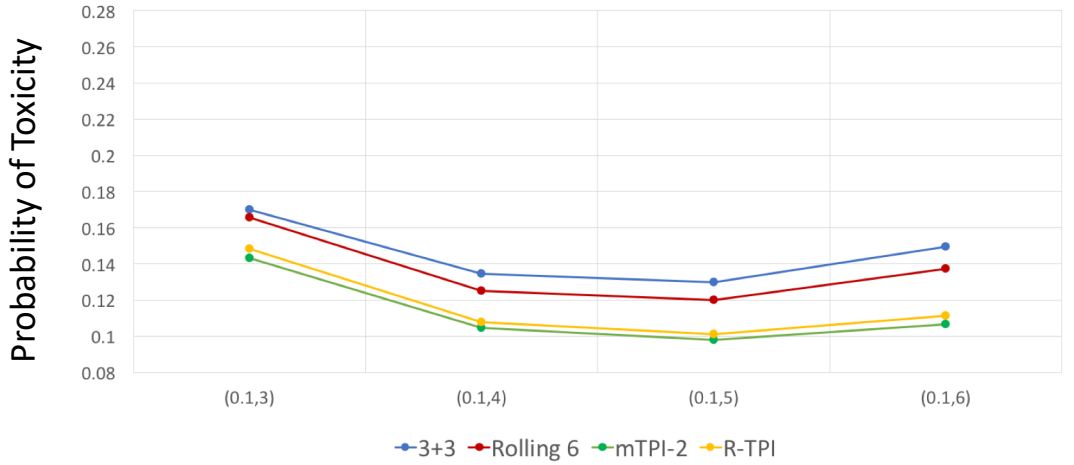
Simulation Results: Benchmark with RSD

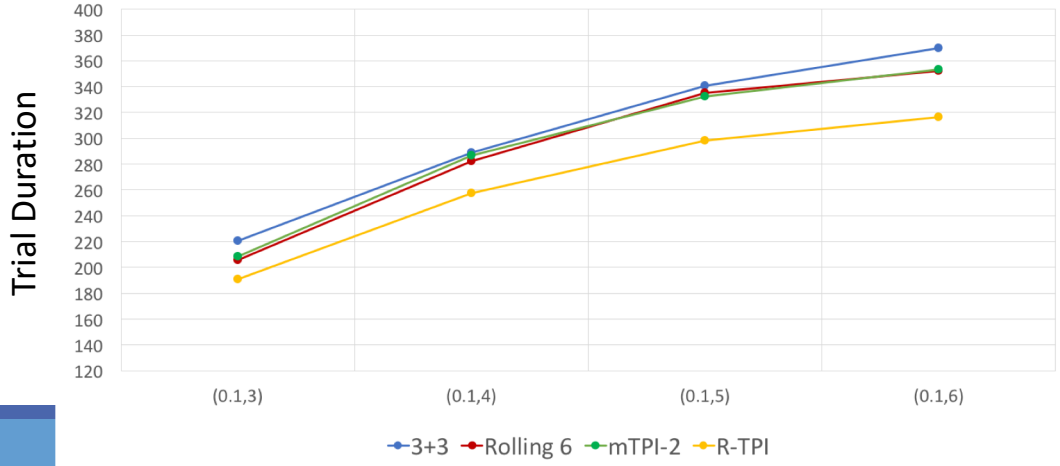
- The scenario used in Skolnik et al., 2008, JCO
- True probabilities of toxicity: (0.05,0.1,0.3,0.5,0.75,0.9,0.95,0.99,0.99)
- R-TPI results in about the same trial length as RSD: 287±40 vs 290±82
- R-TPI performs better in selecting the correct dose than RSD

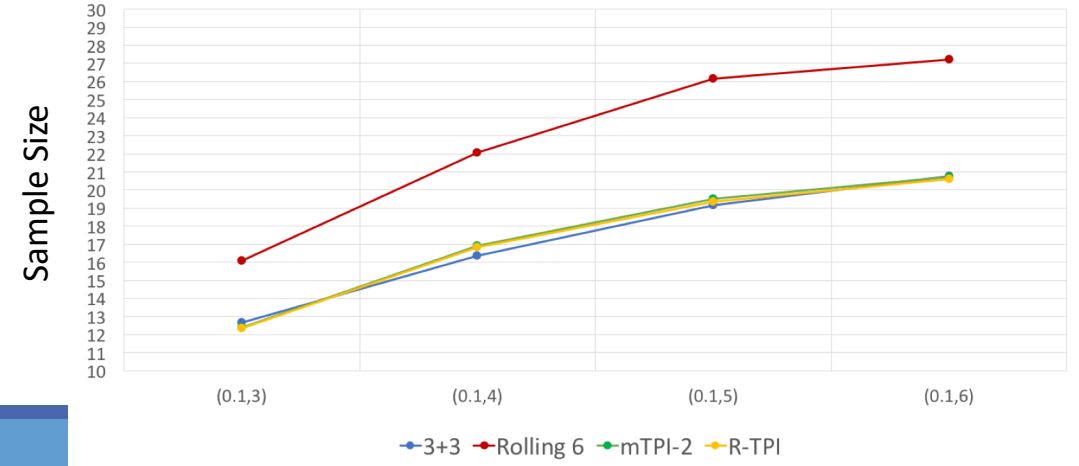
Selection probability	R-TPI	RSD
Dose 2: 0.1	0.54	0.51
Dose 3: 0.3	0.20	0.28

Comparison of Four Designs (pT=0.1, C=3)

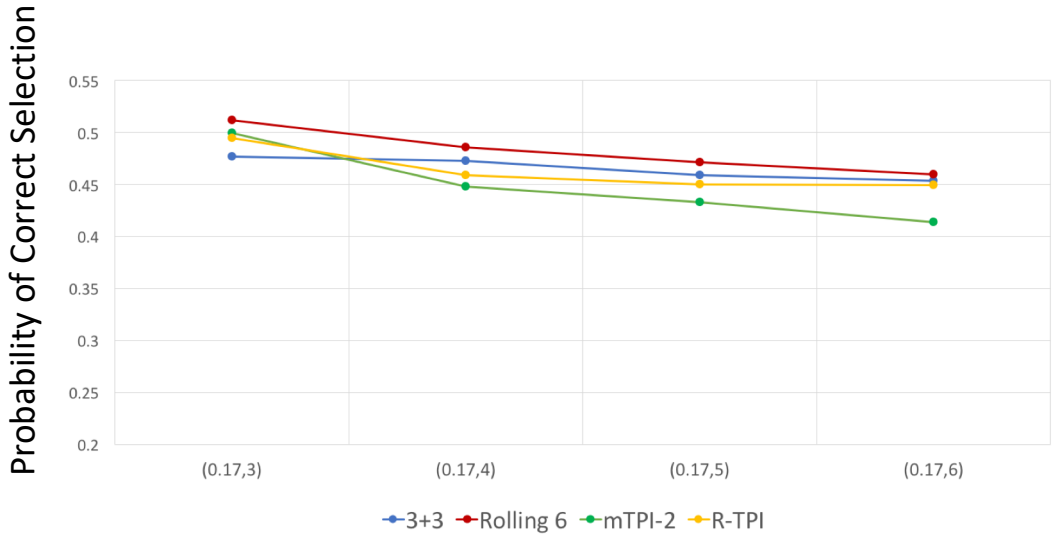


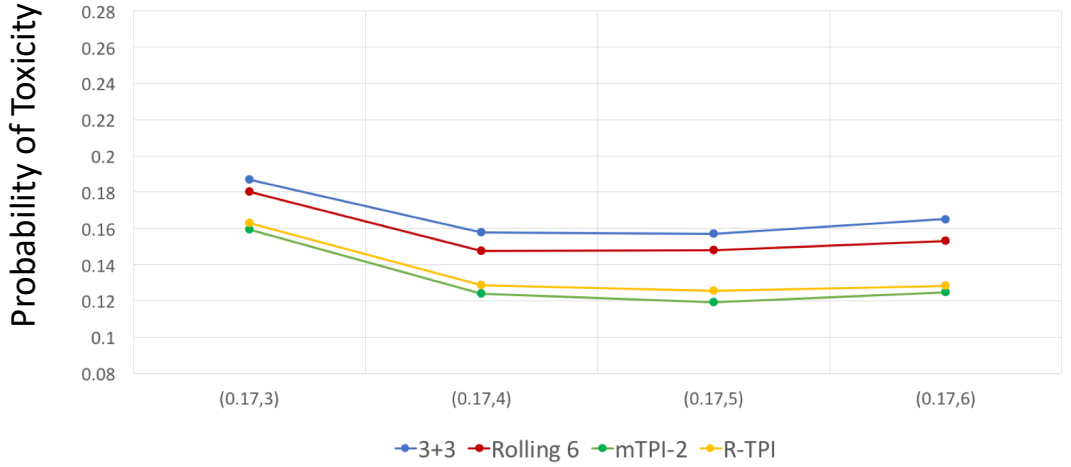


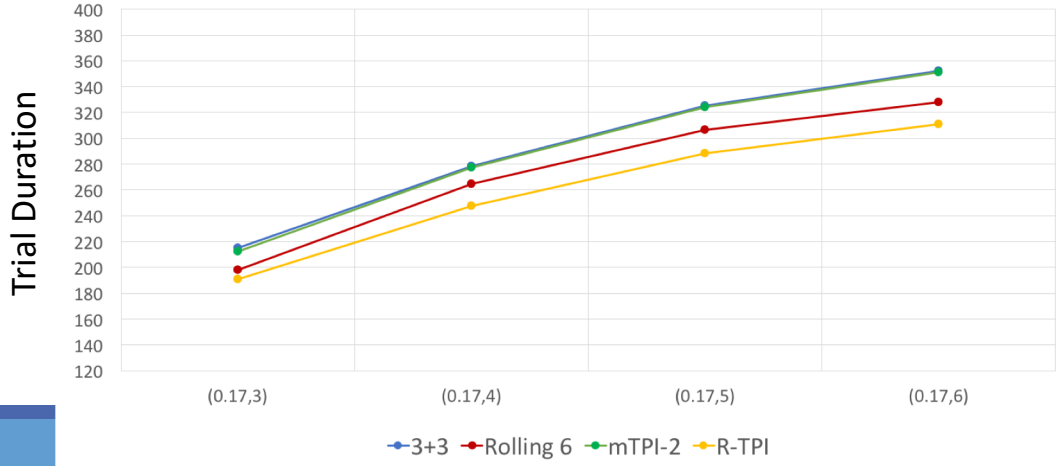


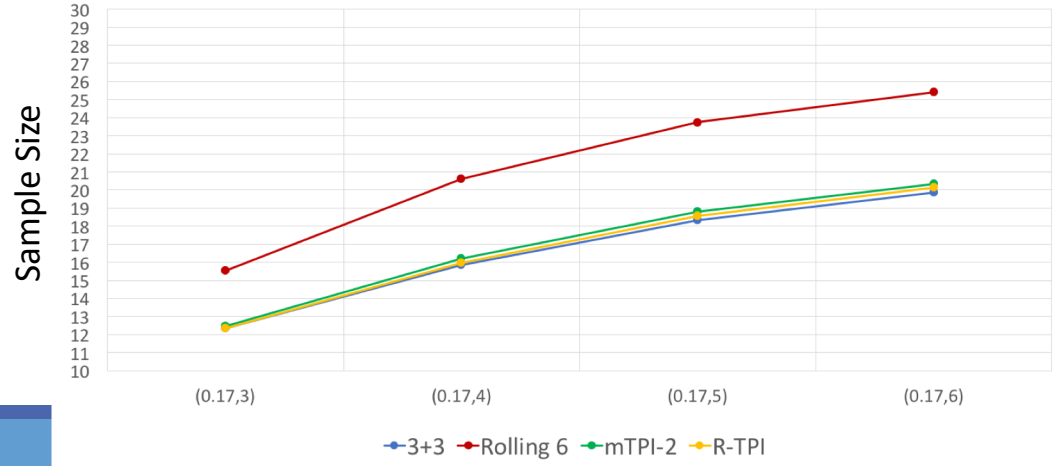


Comparison of Four Designs (pT=0.17, C=3)

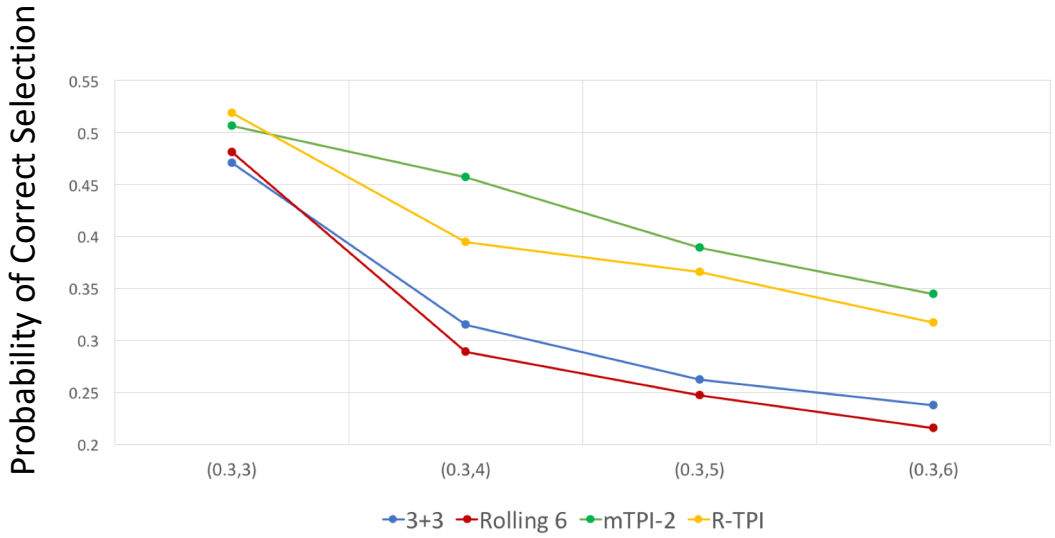


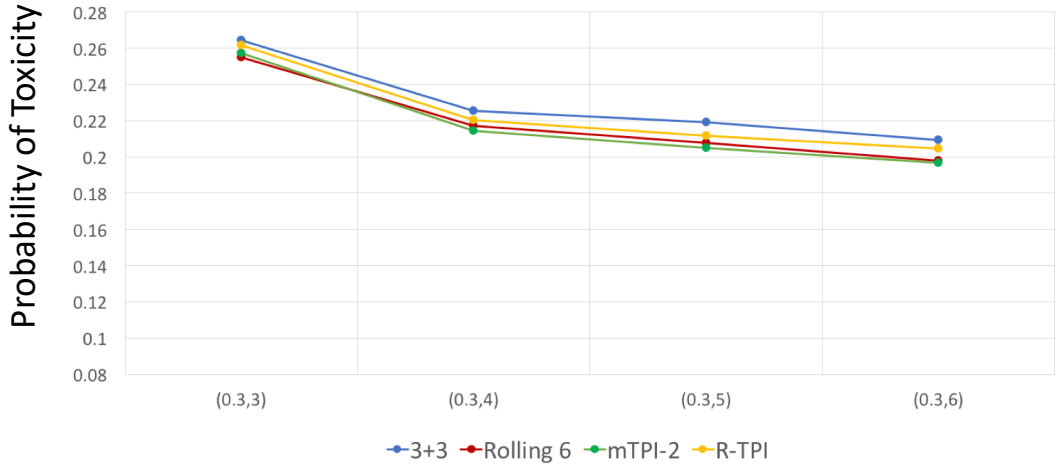


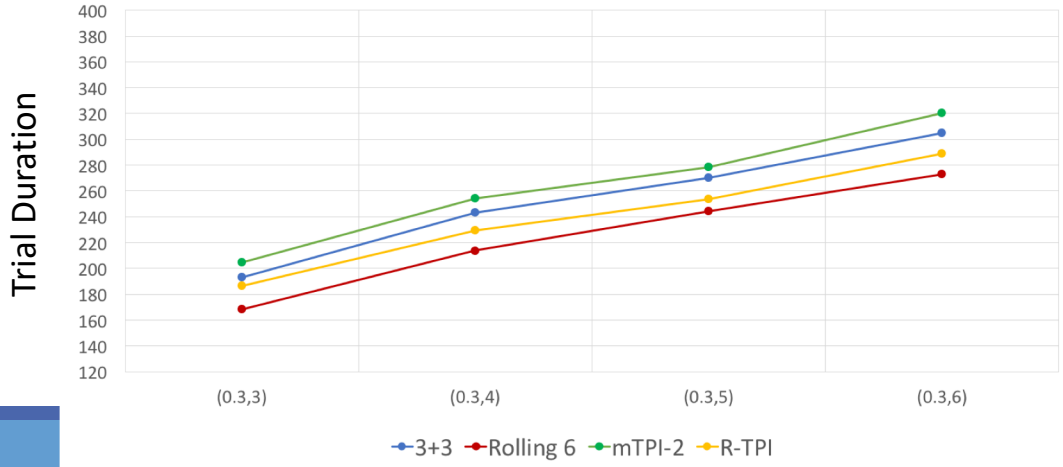


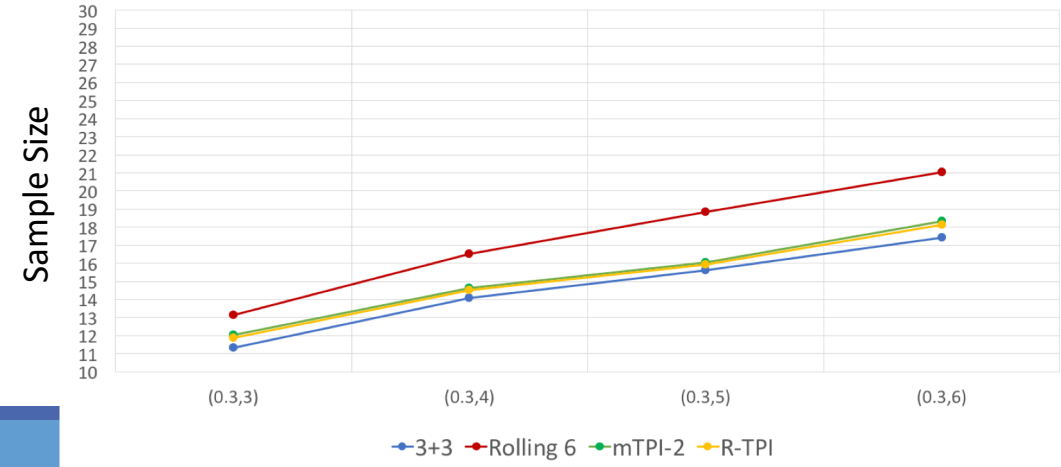


Comparison of Four Designs (pT=0.3, C=3)









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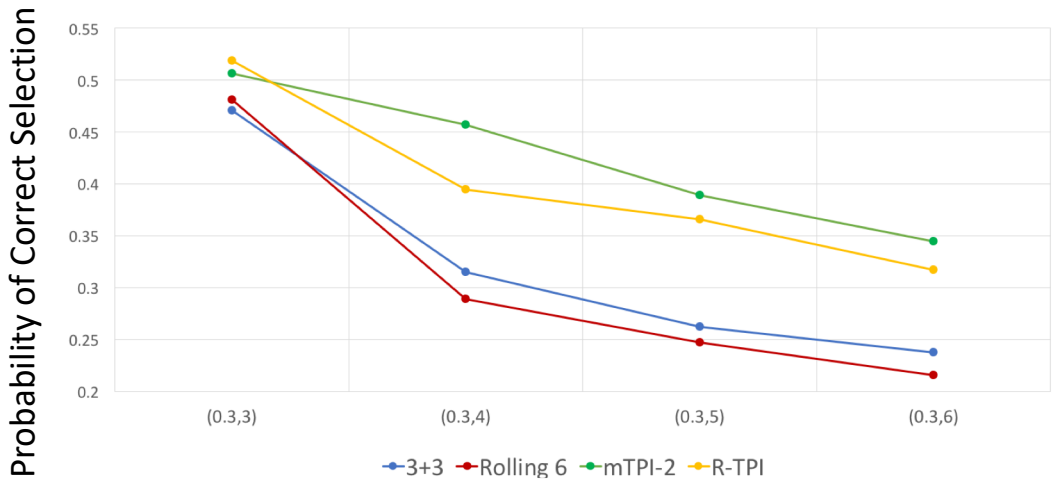
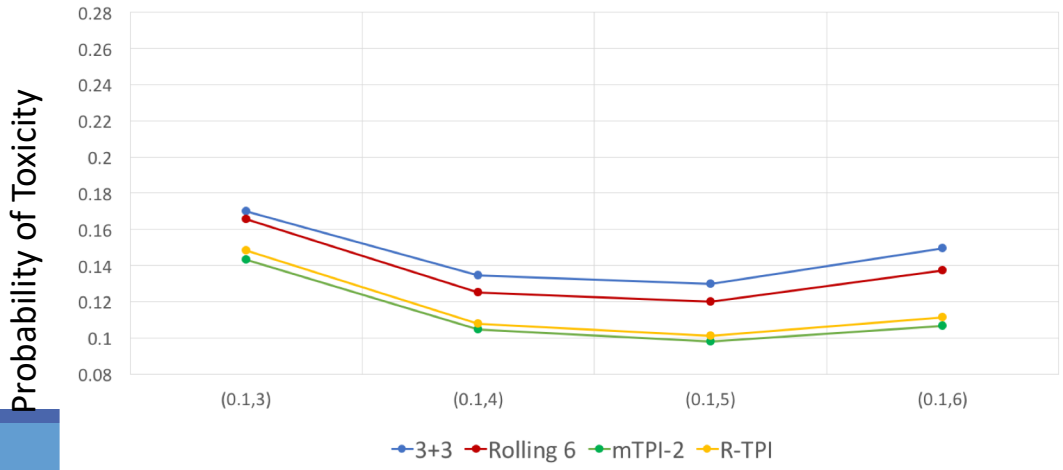
Simulation Results Summary (1)

- R-TPI tends to generate shorter trials compared to cohort-based designs, such as mTPI-2 and 3+3
- R-TPI has comparable power in selecting the true MTD as mTPI-2
  - Better than 3+3 and RSD when the target is not 0.17.
- R-TPI has similar toxicity probability as mTPI-2

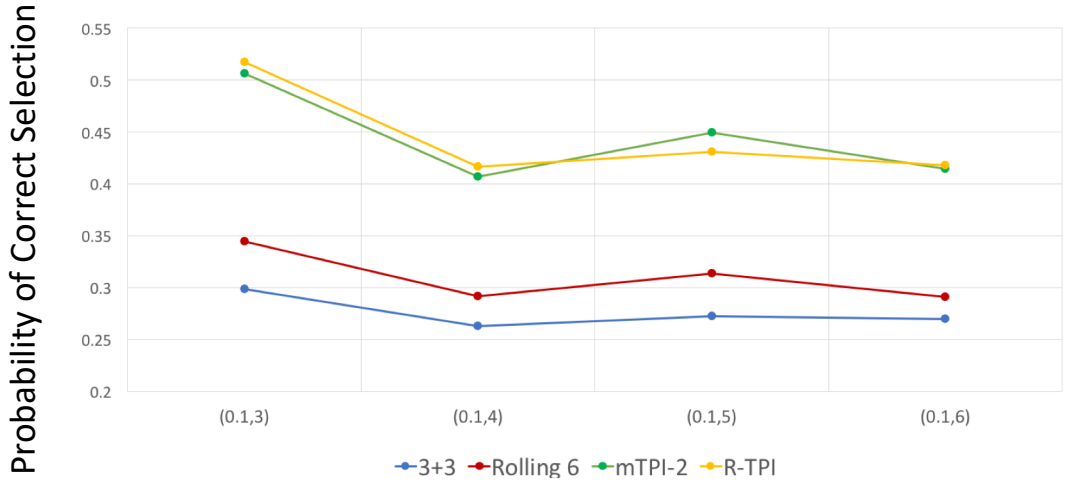
Performance under Varying Enrollment Speed

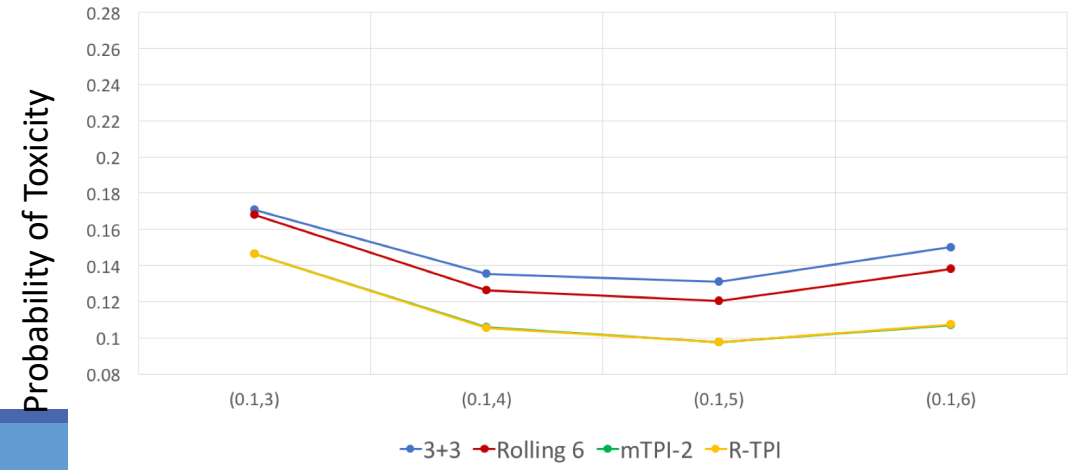
Three patients per month



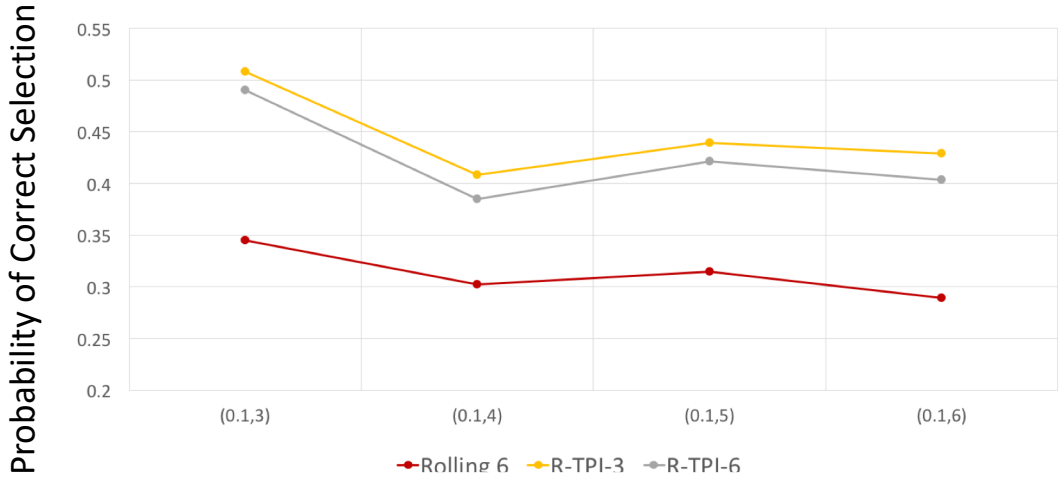


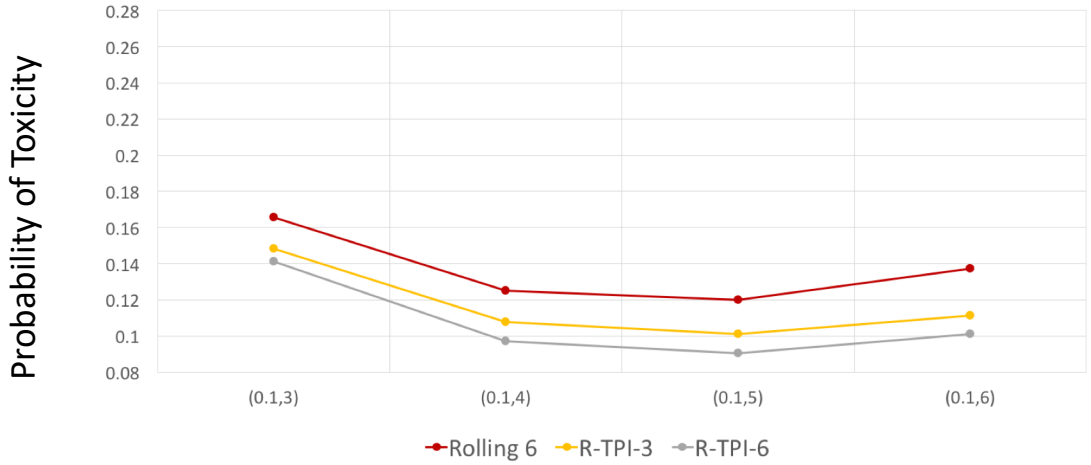
Six patients per month

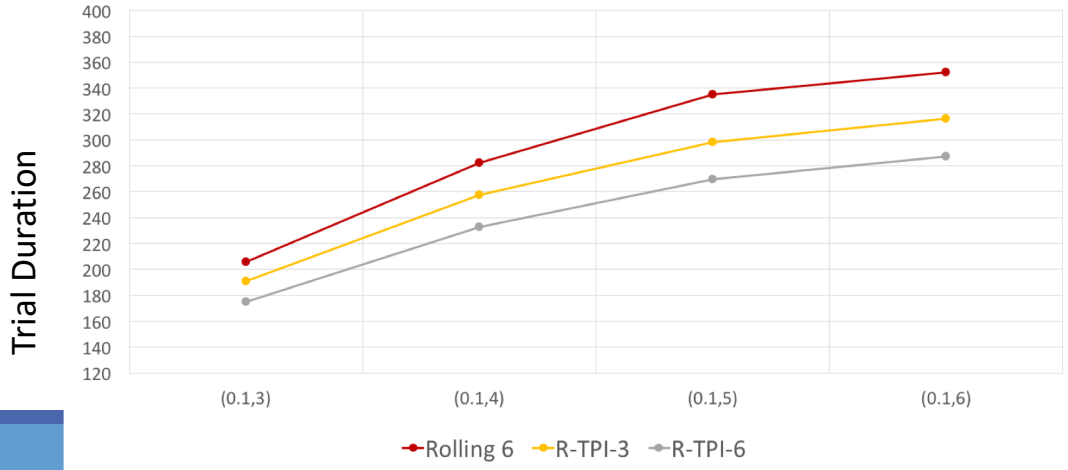




Performance under Different C Values







R-TPI-3: R-TPI with C=3
R-TPI-6: R-TPI with C=6

Simulation Results Summary (2)

- R-TPI's performance is robust from high to low enrollment speed.
- Larger C leads to faster trials.

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Summary and Remarks

- In a broad setting involving multiple scenarios, R-TPI is generally faster, safer, and more reliable than 3+3.
- R-TPI is faster than mTPI-2, while maintaining the similar toxicity profile and power with mTPI-2.
- R-TPI is a simple and transparent design.
- RSD tends to enroll too many patients on low doses.
- Use R-TPI with care if there is potential late-onset toxicity.
- Modeling time to DLT might improve R-TPI.