SUPPLEMENTAL MATERIAL:

Safety monitoring:
Administration of Study Drug
1. Assignment of tPA dose tier: The TIPS database will be accessed by the site PI. A study patient ID will be assigned by the Database. Confirmation of Inclusion and Exclusion criteria will be completed electronically by the site PI or designee prior to providing a tPA dose tier for a newly enrolled patient. TIPS will then require that the site PI contact the study PI, project manager or designee to confirm the correct dosage.
2. Administration of tPA: The 50 mg vials (Activase) will be prepared according to the manufacturer's recommendations.[1] There are three dose tiers (0.75, 0.9, 1.0 mg/kg) of IV tPA, with a maximum dose reached at 90 kg body weight. Ten percent of the dose will be given as a bolus over 5 minutes and the remaining 90% will be given over the remaining hour (5 min + 55 min or a total of 1 hour) . Dose level for a given patient will be determined using the adaptive safety dose finding method.[2]
3. General monitoring during administration of tPA: Patients will be admitted to the Pediatric Intensive Care Unit for the first 24 hours for treatment and for cardiac and respiratory monitoring. They must remain hospitalized for a minimum of 3 days following study drug intervention, which would be consistent with standard care of children with acute stroke with significant deficit.
4. Administration of tPA: As anaphylaxis has been reported with tPA administration, epinephrine, dopamine, diphenhydramine and hydrocortisone will be available at the time of tPA administration. Administration of tPA will be stopped immediately if any of the following occur: hypotension, tachycardia, hyperthermia, suspected anaphylactic reaction; suspected intracranial or serious hemorrhage or bleeding; need for emergency surgery; hypertension; the patient's parent or guardian withdraws consent; the investigator feels that the administration should be discontinued.

Angioedema has been reported, in association with ACE inhibitors. The tongue should be examined 30 minutes after start of tPA infusion and every 20 minutes x 3 in any patient on an Ace inhibitor. If angioedema is suspected, tPA must be discontintued, and the patient given diphenhydramine 1 mg/kg. Solumedrol, epinephirne and airway mangement may be indicated in severe cases.
5. Laboratory Studies: As standard of care for children with acute stroke, it is expected that CBC, PT, PTT, and D-dimer will be sent in a child with possible acute stroke and this data will be captured in CRF 11 – CRF 14 for laboratory tests.
Blood samples for PK:
Blood samples for PK will be obtained at baseline and at 6 timed intervals following IV tPA administration to construct individual patient plasma-concentration profiles for free tPA, tPA antigen (tPA-PAI-complex) and PAI-1. This will be documented in CRF 08: Activase Pharmacokinetics Sampling Log.
Timing of blood draw: There will be 7 time points for PK blood sampling:

1. Baseline prior to tPA infusion
2. 10 minutes after start of tPA (which is 5 minutes after end of the initial bolus of 10% total dose of tPA to be given over 5 minutes),
3. 60 minutes after the start of bolus (at the end of IV infusion),
4. 65 minutes after the start of the IV infusion (5 minutes after completion of infusion),
5. 70 minutes after start of IV infusion,
6. 120 minutes after start of IV infusion,
7. 24 hours after start of IV infusion.

The maximum amount of blood to be drawn is 21 cc.

Blood samples will be obtained from a heparinized venous catheter placed in the arm contralateral to tPA administration. Each time point will require a 3 mL sample. The first 1 mL will be discarded while the remaining 2 mL will be used for assay of unbound tPA, PAI-1, and tPA antigen. This remaining 2 mL will be placed in a Stabilite tube (DiaPharma) and labeled with the patient's study ID

number and the time and date the samples were obtained. All samples will be centrifuged at 1800g for 30 minutes at 4 C, then frozen at -80 C until analyzed.

Once all samples for a given patient have been collected, the samples will be mailed from local sites to the Pharmacokinetics Core.

Post-intervention care:

1. Monitoring during and following tPA administration

Guidelines for treatment of acute childhood stroke [3] will be followed:

1. Pediatric Intensive Care Unit admission for the first 24 hours for cardiac and respiratory monitoring.
2. Neurological status checks every 15 minutes for two hours after procedure, then every 30 minutes for 6 hours, then every 60 minutes for 16 hours, or until 24 hours following tPA administration. If bedside provider notes a worsening in neurological status of any type, the stroke neurologist should be recalled to the beside to perform an additional PedNIHSS and other neurologic assessments as clinically indicated.
3. NPO except for medication for 24 hours.
4. Ensure normal O_2, CO_2, pH, normothermia, normoglycemia.
5. Ensure normovolemia.
6. Titrate systolic blood pressure for minimum of 50th percentile for age and maximum of 15% above 95th percentile for age (See Blood Pressure chart below, from "Determination of blood pressure percentiles in normal-weight children: some methodological issues. Rosner B et al, Am J Epidemiol,167:653-666, 2008.). If there is persistent blood pressure elevation (more than 1 hour) of 15% or more above the 95th percentile based on age/gender/height norms in the child at rest at any time after tPA infusion, treatment to lower blood presure should be instituted. If blood pressure is more than 20% over the 95th percentile, blood pressure lowering should be instituted immediately upon verifying the reading. These treatment guidelines should be in place for the duration of the child's hospitalization.

   Consider treatment of significant hypertension with labetalol or angiotensin converting enzyme inhibitor to lower by ~25% over 24 hours. Avoid decreasing blood pressure by more than 25% in the first 2 hours of treatment. Blood pressures should be recorded at least every 15 minutes for the first 4 hours after tPA infusion begins,then at least every 30 minutes for the next 4 hours, then at least every hour for the first 24 hours after tPA infusion.

   From 24-48 hours, blood pressure should be monitored at least every 2 hours, and from 48-72 hours, blood pressure should be monitored every 4 hours. See below for Blood Pressure Guidelines.
7. Establish two large peripheral intravenous lines.
8. Bed rest with head of bed flat.
9. Treat all temperatures >38.5C with acetaminophen +/- external cooling if necessary.
10. Laboratory Studies: Will be obtained as part of treatment for AIS in childhood.

In addition, for patients in the study, care will include:

11. Intramuscular injections will be avoided.
12. Insertion of indwelling Foley catheter should be avoided during the tPA infusion and for as least 30 minutes after the tPA infusion ends.
13. Insertion of a nasogastric tube will be avoided during the first 24 hours.
14. Central venous access and arterial punctures will be avoided during the first 24 hours.

2. Blood Pressure Guidelines Post tPA

Titrate systolic blood pressure for minimum of 50th percentile for age and maximum of 15% above 95th percentile for age.

If there is persistent blood pressure elevation (more than 1 hour) of 15% or more above the 95th percentile based on age/gender/height norms in the child at rest at any time after tPA infusion, treatment to lower blood pressure should be instituted.

If blood pressure is more than 20% over the 95th percentile, blood pressure lowering should be

instituted immediately upon verifying the reading. These treatment guidelines should be in place for the duration of the child's hospitalization.

0-4 hours post tPA:
Blood pressure should be recorded prior to starting tPA infusion
Blood pressures should be recorded at least every 15 minutes for the first 4 hours after tPA infusion begins

4-8 hours post tPA:
Blood pressures should be recorded at least every 30 minutes for the next 4 hours,

8-24 hours post tPA
Blood pressures should be recorded every hour

24-48 hours post tPA:
Blood pressure should be monitored every 2 hours

48-72 hours
Blood pressure should be monitored every 4 hours

Elevated Blood Pressure Interventions

Consider treatment of significant hypertension with labetalol or angiotensin converting enzyme inhibitor to lower by ~25% over 24 hours. Avoid decreasing blood pressure by more than 25% in the first 2 hours of treatment. As always, clinical judgment about patient safety should be paramount.

Concomitant Medications: Concomitant Medications during the first 48 hours after study intervention will be recorded**.** No anticoagulant or antiplatelet medications should be administered for 24 hours (including heparin, aspirin, NSAIDS). The exception would be an intraluminal cardiac or carotid thrombus where the risk of re-embolization likely outweighs the risk of SICH. If there is no contraindication, aspirin at 3-5 mg/kg should be started 24 hours following tPA infusion, unless there is indication for another antithrombotic medication. Prophylactic H2 blockers or PPI prophylaxis will be used as clinically indicated.

Suspected or confirmed intracranial hemorrhage (ICH): Thrombolytic-related ICH generally occurs in the first 6 hours after thrombolytic therapy. All patients with suspected or confirmed ICH should be cared for in a Pediatric ICU. Urgent neurosurgery and hematology consults should be obtained. In TIPS, the acute management of intracranial hemorrhage will consist of the following:

1. Suspected Intracranial Hemorrhage

With any otherwise unexplained neurological deterioration, emergent investigations and interventions include:

1. Stop tPA or heparin infusion (if ongoing) immediately. Discontinue antiplatelet medications
2. Emergent Neuroimaging: CT Head (MRI if CT unavailable)
3. Stat Laboratory Studies: CBC, PT, PTT, fibrinogen, electrolytes, BUN, creatinine, glucose, type and hold for possible packed red blood cell transfusion.
4. Correction of Coagulopathy: Coagulopathy due to tPA is likely to consist of hypofibrinogenemia, elevated PT secondary to decreased factor V, and elevated PTT due to decreased factor VIII. Hypofibrinogenemia (fgn <100 gm/dL) should be corrected with 1 donor unit (bag)/5kg body weight cryoprecipitate; this can be expected to raise the fibrinogen level by 50 mg/dL. Cryoprecipitate also contains factor VIII (~100 units/donor unit) and can be expected to raise the factor VIII level approximately 40 U/dL (%). This dose of cryoprecipitate is thus likely to raise both fibrinogen and factor VIII into a hemostatic range.

Since the hemostatic level of factor V is about 30%, correction of factor V by the infusion of FFP is not likey needed unless the PT is above 20 seconds. In this case, give 10-15 ml/kg FFP.

An alternative to the use of cryopreciptate to replace fibringogen and factor VIII is the potential use of fibrnogen concentrate and factor VIII concentrate if available and if volume constraints are severe. Indications and dosing per instituional consulting hematologist.

If the platelet count is decreased <100/μL in addition to decreased fibrinogen and elevated PT and PTT, DIC should be suspected and both platelets (1 donor unit/5kg body weight) and FFP (10-15 mL/kg) may be administered in addition to cryoprecipitate. tPA also has an antiplatelet effect. Giving random

donor platelets may provide additional benefit.

If hemorrhage is severe and uncontrollable with replacement therapy with cryoprecipitate, FFP and platelets, consideration may be given to use of recombinant FVIIa at a dose of 30 mcg/kg in consultation with institutional consulting hematologist as recombinant FVIIa carries a thrombotic risk.

5. Treatment of Hypertension: BP should be maintained within normal parameters for age with a target of 50-95% according to age/height (chart included in study protocol). Labetolol 0.2 mg/kg IV push over 2-3 minutes, repeat every 15 minutes prn or nicardipine drip at 1mcg/kg/min are recommended to treat hypertension.
6. Management of Potential Volume Overload: Subjects who concomitantly receive cryoprecipitate, fresh frozen plasma, and platelets may be at risk of volume overload though this is less likely in children without cardiac disease. These subjects should be managed, as needed, with additional furosemide to prevent the development of acute respiratory failure due to pulmonary edema.

The hematologist caring for the child may individualize care for a specific patient based on their assessment and treatment plan.

2. Confirmed Intracranial Hemorrhage

Confirmed ICH will be treated based on fundamental principles of both adult hemorrhagic stroke (American Stroke Association [ASA] guidelines[4] and Pediatric Neurointensive care as adapted by the TIPS Executive Commitee) as follows:

1. Begin by following all of the directions for the "suspected ICH" section above.
2. Monitoring in the pediatric intensive care unit.
3. Urgent neurosurgical consultation.
4. Anti-convulsants for treatment of seizures. Load fos-PHT or Keppra for confirmed seizures. Consider EEG monitoring.
5. Fever should be treated with antipyretics.
6. Treatment of elevated ICP should include a graded approach with goal of maintaining cerebral perfusion pressure:
    a. Head of bed to 30 degrees.
    b. Ensure adequate analgesia and sedation.
    c. More aggressive therapies such as osmostic diuresis with mannitol and hypertonic saline, CSF drainage, neuromuscular blockade, and hyperventilation to be considered in consultation with pediatric neurosurgery and PICU.
7. Maintain normoglycemia.
8. Treat hypertension of > 90th percentile for age with labetolol 0.2 mg/kg IV push over 2-3 min, repeat every 15 minutes prn. Target BP between 50-95% for age/height and to maintain CPP. Contraindications include asthma, cardiac failure, and greater than first degree heart block.
9. Correction of coagulopathy as outlined above.

Systemic hemorrhage

Systemic hemorrhage is an uncommon complication of thrombolytic therapy, occurring in less than 0.5% of adult patients. Management is similar to ICH. If bleeding is superficial (e.g. nose bleed, IV site etc.), ice may be used to reduce regional blood flow. If ice and pressure are not successful in controlling superficial bleeding, the topical use of compression with gauze pads soaked in injectable anti-fibrinolytic agents such as epsilon amino-caproic acid (Amicar) or tranexamic acid should be applied. Specialty-specific assistance to be sought urgently (e.g. ENT for nose bleeding).

Orolingual angioedema

Orolingual angioedema is an uncommon complication of thrombolytic therapy, occurring in 1% or less of adults. Risk factors may include premorbid use of ACE inhibitors, β-blockers, and frontoinsular infarction. Management varies by severity. Most angioedema is mild and does not require treatment. H1 and H2 blockade management with IV diphenydramine, 5 mg/kg daily divided in 4 doses (maximum 300 mg daily) and IV ranitidine, 2-4 mg/kg/day divided every 6-8 hours (maximum 200 mg/day) may suffice. For more severe cases, IV hydrocortisone (1-5 mg/kg/day divided every 12-24

hours) may be administered. Racemic epinephrine is not advised for potential increased risk of intracerebral hemorrhage. Early consultation with anesthesia should occur for airway management in more severe cases.

Acute hypotension

Acute hypotension is an uncommon occurrence with thrombolytic therapy, occurring in 0.4% of adult patients. It may be related to release of bradykinin. Treatment is generally successful with simple volume expansion. Treatment will begin with boluses of normal saline 10cc/kg repeated up to 3 times over 15 minutes. Albumin may be protective in adult stroke and may therefore also be considered. Refractory cases may require use of inotropic agents at the discretion of the treating intensivist.

Consultation with PI, co-PI and Key Senior Personnel: The PI, co-PI and Key Senior Personnel can be contacted for consultation in the event of hemorrhage or other adverse event during TIPS.

Follow-up Head CT: Head CT will be performed for establishment of the primary endpoint and safety monitoring at 24 ± 6 hours following tPA administration. If a head MRI with GRE or SWI has been performed as part of routine care in the 24 ± 6 hours following tPA administration time interval, this may be substituted for the study CT scan.

Follow-up PedNIHSS: The pediatric version of the NIH stroke scale will be performed:

1. 50-75 minutes post initiation of tPA
2. 2 hrs post initiation of tPA
3. 12 hrs post tPA ± 6 hr
4. 24 hrs post tPA ± 4 hr
5. 36 hrs post tPA ± 4 hr
6. 48 hrs post tPA ± 8 hr
7. Day 7 or discharge, whichever occurs first.

The PedNIHSS will be performed by the site PI or site co-PI.

Assessment of toxicity:

Primary endpoint toxicity is defined as SICH or severe hemorrhage within 36 hours of tPA administration, defined as any of the following:

1. PH2 (parenchymal hemorrhage within 36 hours after tPA administration involving > 30% of the infarcted area)[5, 6], regardless of whether or not it is associated with clinical deterioration, OR,
2. Any intracranial hemorrhage which is judged to be the most important cause of neurological deterioration. Neurological deterioration is guided by a minimum of change of 2 or more points on the PedNIHSS from the lowest PedNIHSS. At the time of each PedNIHSS assessment, the site PI or co-PI will review the patient's course with the care team to ensure that all changes in neurologic status, including improvements since the last assessment by the study team, are captured, OR,
3. Any hemorrhage that results in the need for transfusion, need to discontinue study drug, surgical evacuation of hemorrhage, or death.

To ensure that all SICH are captured promptly, therefore optimizing safety within the trial, review by the Imaging Core and the Study Coordinating Center of the following situations is required prior to further dose escalation:

1. If a patient has had a worsening of 2 or more points on the PedNIHSS or deterioration in level of consciousness, further escalation of dose will not occur until the Imaging Core (IC) has confirmed absence of an intracranial hemorrhage.
2. If the Imaging Core (IC) reports an intracranial hemorrhage other than HI-1, the TIPS Safety Board will review study records to confirm that SICH has not occurred, prior to dose escalation.

Full Statistical Design of TIPS:

1 Overview

The Bayesian method of toxicity probability intervals[2] will be used to select one of the following three dose tiers (0.75, 0.9, 1.0 mg/kg) of IV tPA. The dose escalation for the two age groups (2-10, 11-17 years) will be performed independently.

Within each age group, patients will be treated in cohorts of 3 patients. The decision to escalate to the next dose tier, stay at the current tier, or de-escalate to the previous tier is made based on the posterior probability of the current dose being too high or too low given the outcome of all patients treated with this dose with a target acceptable toxicity level of p_T=0.1. No untried tiers will be skipped during the escalation process. A non-informative prior Beta(0.05,0.05) distribution on the probability of toxicity will be used for the posterior probability calculations at each dose level. The tuning parameters of k_1=1.2, k_2=0.3 which control the aggressiveness of the escalation and de-escalation decisions, were used to construct the final design. Additionally, the posterior probability of a given dose being above a level p_H=0.1 is monitored, and once this probability exceeds ξ=0.9, that tier and all higher tiers are closed for further recruitment. The next cohort is enrolled at the lower dose tier, if available. A total of 18 patients per study arm will be enrolled, unless toxicity stops the trial earlier.

2 Dose escalation and MTD selection procedures

The principles described above lead to the following dose modification rules:

- Three patients will be studied at the first dose level.
- At each of the dose levels after a cohort of three patients have been treated, a decision to move to the next higher dose level, stay at the current dose, or move to the next lower dose level will be made based on the number of dose limiting toxicity (DLT)s observed in all patients treated at the current level (i.e. including potential earlier cohorts) as shown in Table I.

Table I. Design targeting 10% toxicity.

Cumulative number of patients at the dose	Cumulative number of DLTs for each decision		
	Escalate to next tier	Stay at current tier	De-escalate and close tier
3	0	1	2+
6	0	1	2+
9	0	1-2	3+
12	0-1	2	3+
15	0-1	2-3	4+
18	n/a	n/a	4+

For example, if 6 patients (i.e. two cohorts) have already been treated at a given dose, then the next three patients will be enrolled at the next higher dose if no patients had a DLT, at the same dose if 1 had DLT, and at the next lower dose if 2 or more DLTs happened. In the latter case, the dose will also be declared unacceptable and closed for any future enrollment.

- If the highest dose level is reached or the next dose level has already been closed due to excessive toxicity, instead of escalation the same dose level is used.
- If a de-escalation decision is made at the lowest dose level, the study is stopped for excess toxicity, and no MTD is selected.
- A study arm will be stopped after 18 patients in the corresponding age-group have been treated. At the end of the data collection for an arm, the posterior mean probability of DLT will be estimated for each dose level, followed by isotonic regression to impose monotonicity with dose. The dose

which has not been declared unacceptable and whose estimated probability of DLT is closest to 10% will be selected as the MTD. In case of a tie, the highest tiered dose will be selected if the estimated probability of DLT is below 10%, and the lowest if it is above 10%. The DLT estimation will be performed separately for the two arms.

- If the dose that is selected as MTD after 18 subjects has had only one cohort of 3 subjects treated on it, another cohort will be enrolled at that dose, and the MTD re-estimated. If this re-estimation changes the MTD to a dose level that also had only one cohort treated on it, an additional cohort of 3 patients will be recruited for that level, and the MTD re-estimated again. No further extensions will be done, so the maximal number of subjects is 24. This procedure ensures that at least two cohorts have been evaluated at the dose declared as MTD.
- The DSMB and NINDS can stop the study at any time, as can the FDA by revoking the IND. The statistical design of the study also defines stopping points.
- *Study termination:* A study arm will be closed when the planned enrollment of at least 18 patients has been achieved and at least 6 patients have been treated at the MTD, or the lowest dose has been found to have unacceptably high toxicity that is 2 or more patients out of the first 3 or fewer treated at the lowest dose (denoted as 2/3) have dose-limiting toxicity, or 2/6, or 3/9 or 12, or 4/15 or 18. The study will be terminated when both arms have been closed.
- *Periods when further patients may not be enrolled:* If the next dose of IV tPA will be determined by the toxicity data at 36 hours, then further patients may not be enrolled in this arm until toxicity data has allowed the statistician to allocate the next dosing level.

3 Operating characteristics of the study

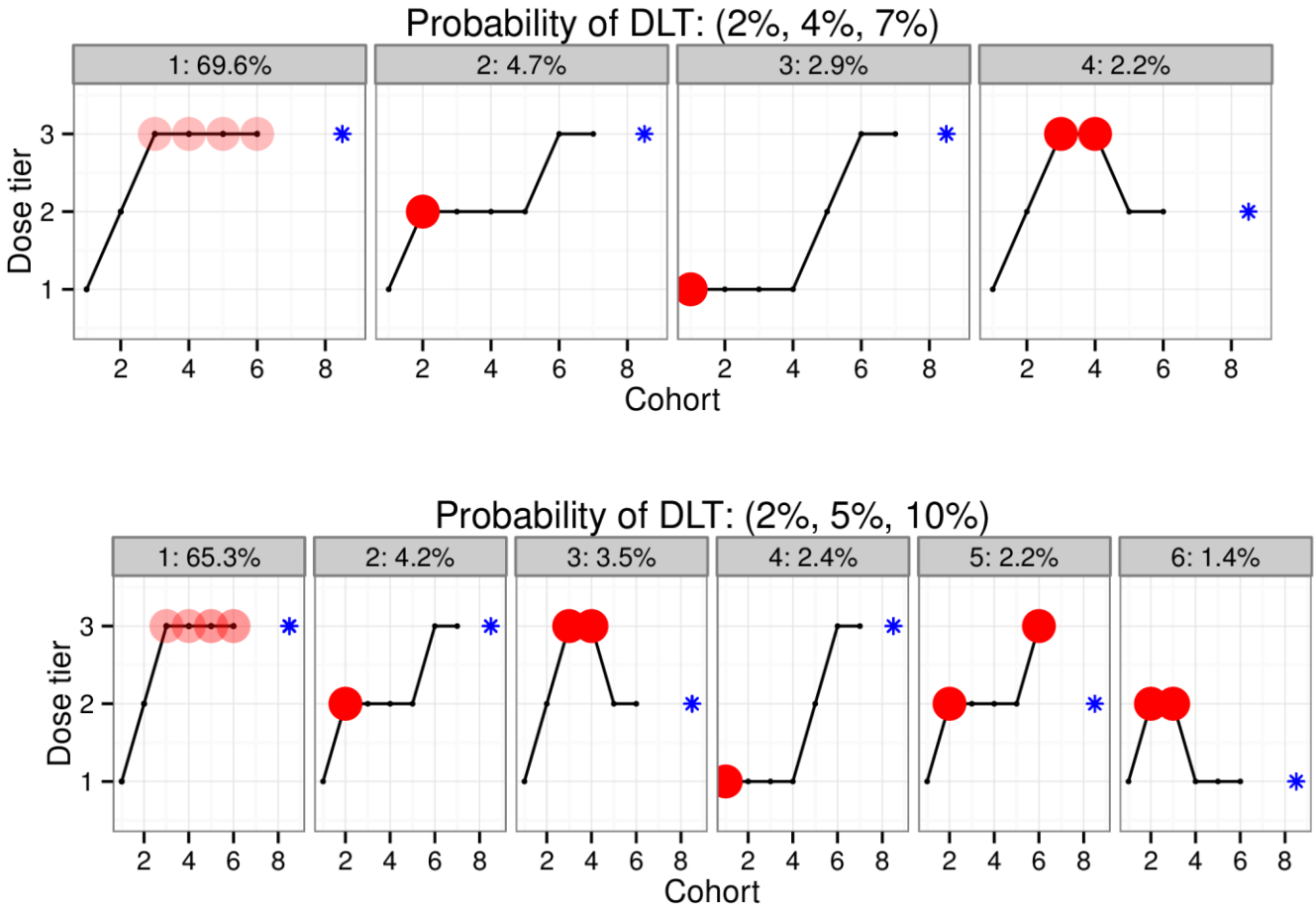
The operating characteristics of the design were evaluated via simulation (10,000 replicates)[1]. Table II shows the probability that a given dose will be selected at the end of the study for various scenarios for the true rate of DLT, the total expected number of patients, the expected number of patients with a DLT, and the probability that the trial will need to be extended with additional cohorts due to only one cohort treated at the current MTD. In the overwhelming majority of the extended trials, the MTD does not change as a result of the additional cohort. The first two rows represent scenarios considered to be most likely based on adult data.

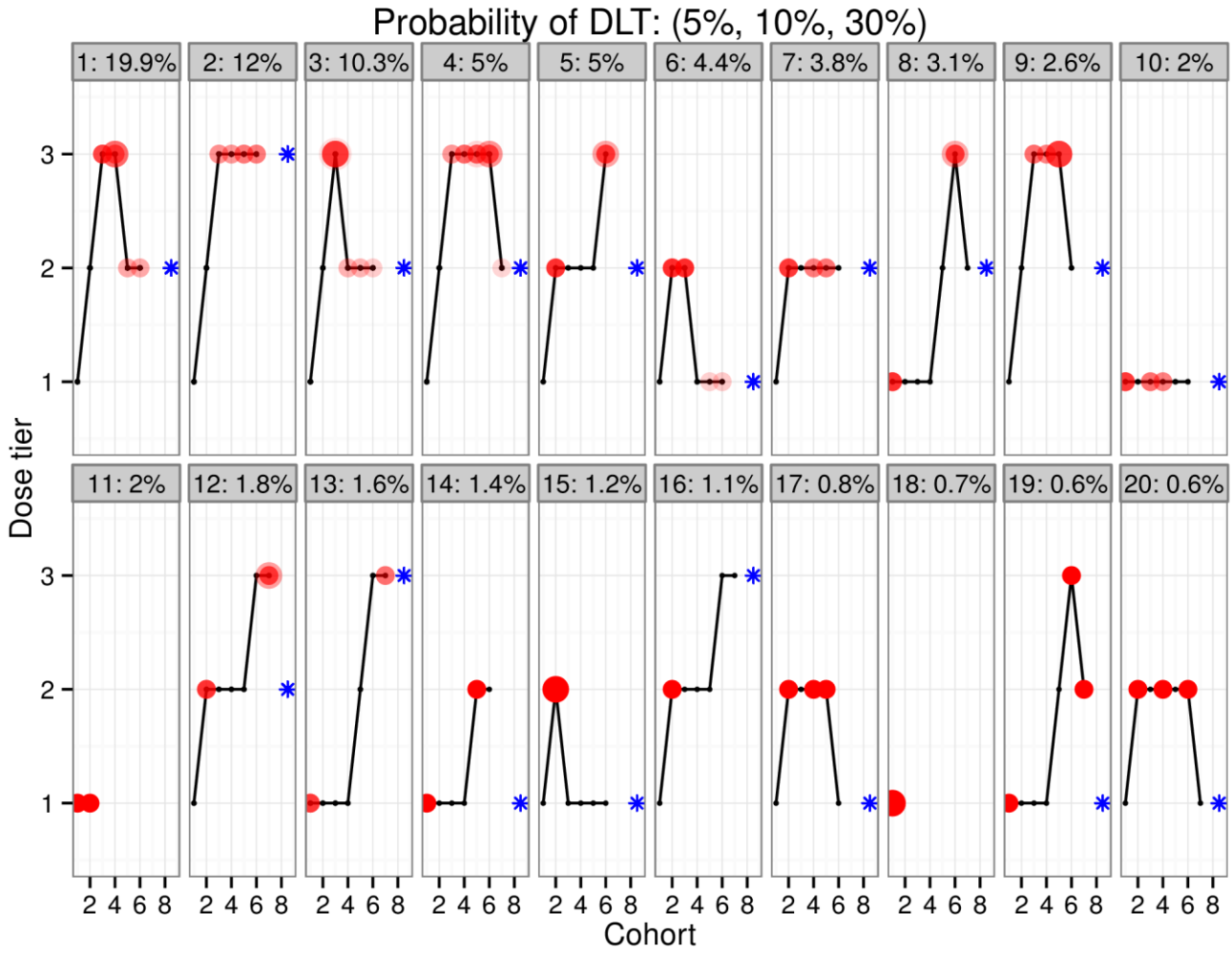
Table II. Operating characteristics of the design targeting 10% toxicity that is continued until at least two cohorts are treated at the MTD.

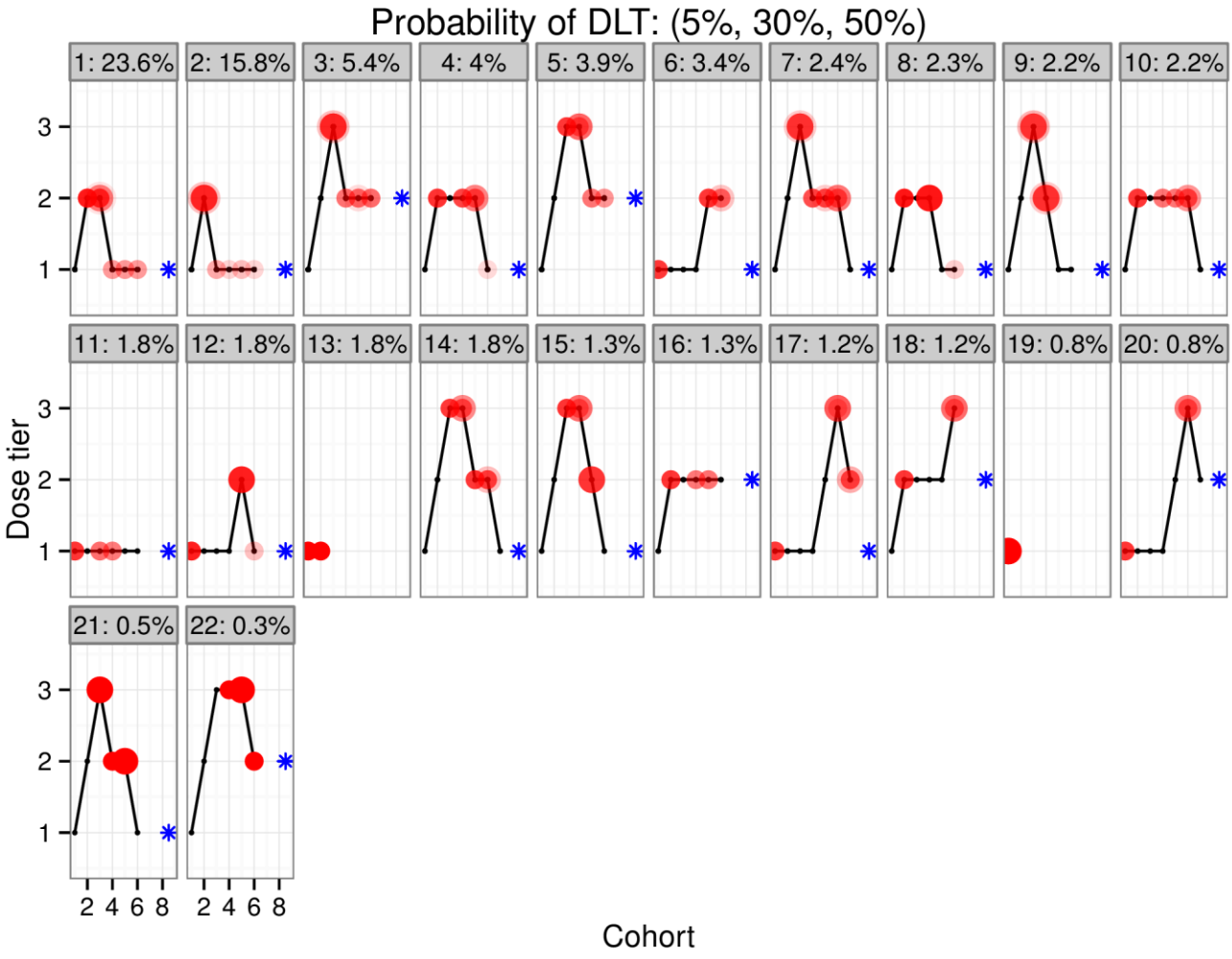
Prob. of DLT	Prob. dose selected MTD				Expected number of		Trial extension		
	No dose	1	2	3	patients	toxicities	prob.	MTD ↑	MTD ↓
(2%, 4%, 7%)	0%	3%	12%	84%	18.3	1	12%	0%	1.3%
(2%, 5%, 10%)	1%	5%	20%	74%	18.4	1.3	14%	0%	1.7%
(5%, 10%, 30%)	4%	21%	60%	15%	18.3	2.6	21%	0%	3.9%
(5%, 30%, 50%)	4%	78%	18%	1%	18.1	3.3	15%	0%	2.8%
(10%, 30%, 50%)	16%	69%	15%	1%	16.9	3.4	14%	0%	5.3%
(30%, 50%, 70%)	80%	20%	1%	0%	10	3.4	1%	0%	24.5%

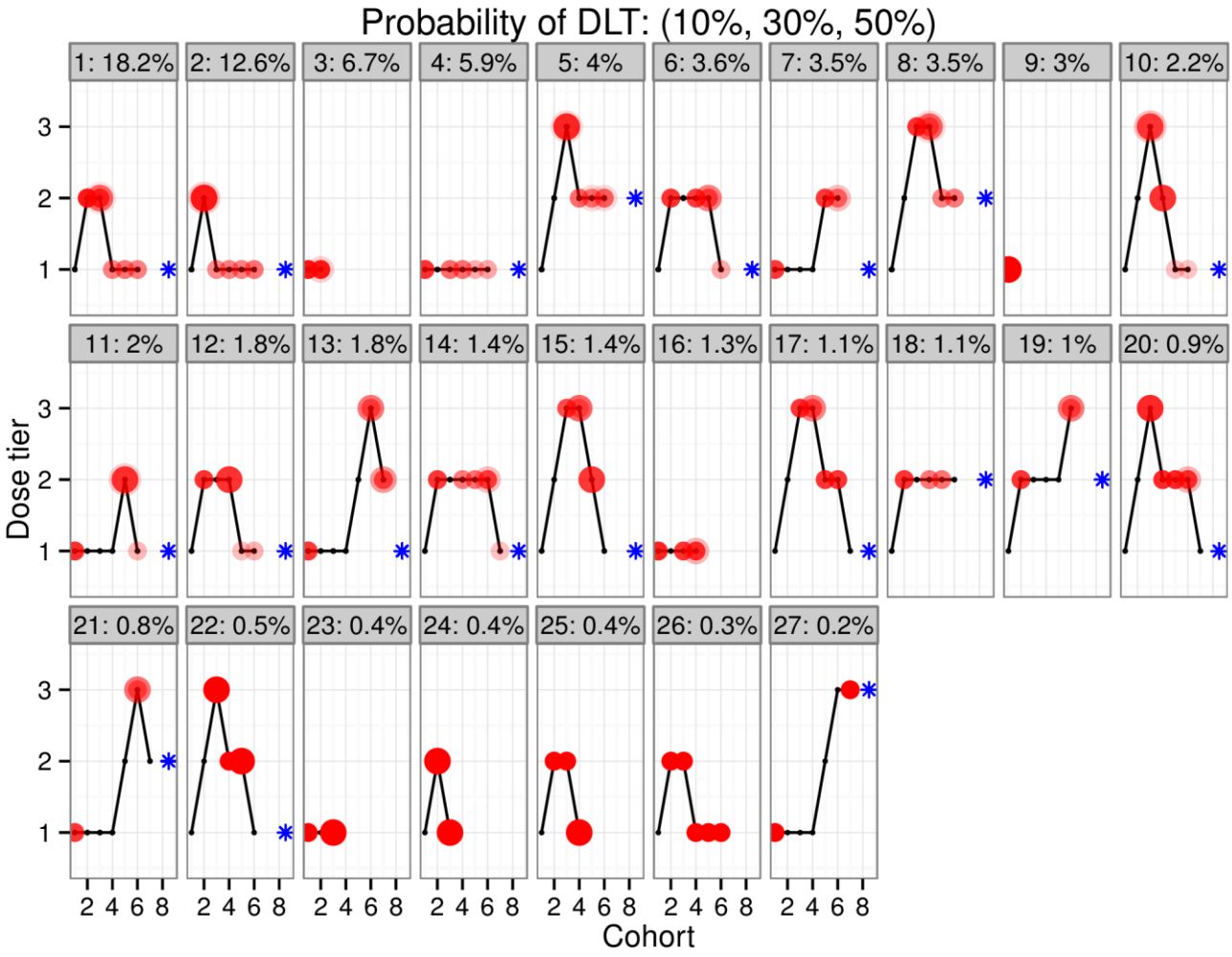
[1] The simulation results included in the study protocol and presented in the body of the manuscript were a subset of a larger set of simulations, thus due to a different flow of random numbers the values are not exactly replicated in this more limited set.

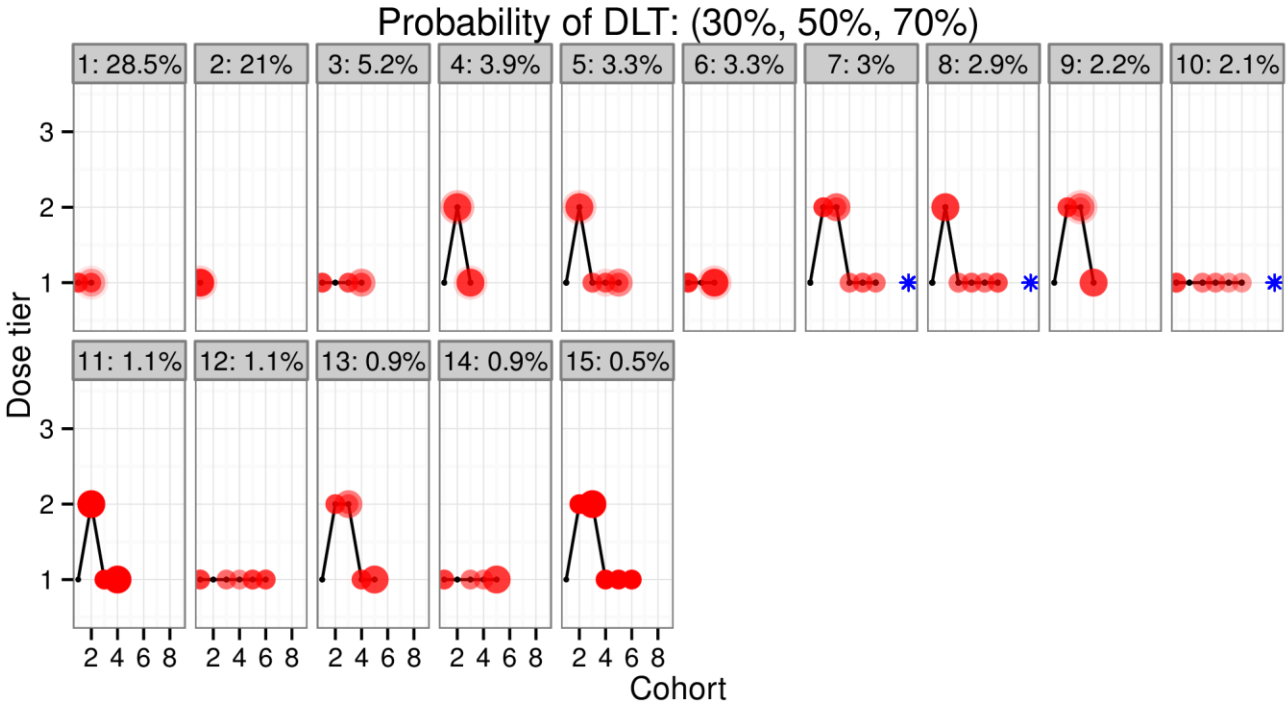
Figure I. Possible realizations of trial paths and MTD with probabilities for 10% target toxicity cumulatively covering 80% of all outcomes. The red points show DLTs observed in the given cohort, with the size showing the number of DLTs and the density showing their probability. The blue stars at the right indicate the selected MTD.




Probability of DLT: (5%, 10%, 30%)
1: 19.9%
2: 12%
3: 10.3%
4: 5%
5: 5%
6: 4.4%
7: 3.8%
8: 3.1%
9: 2.6%
10: 2%
11: 2%
12: 1.8%
13: 1.6%
14: 1.4%
15: 1.2%
16: 1.1%
17: 0.8%
18: 0.7%
19: 0.6%
20: 0.6%
Dose tier
Cohort


Probability of DLT: (5%, 30%, 50%)
1: 23.6%
2: 15.8%
3: 5.4%
4: 4%
5: 3.9%
6: 3.4%
7: 2.4%
8: 2.3%
9: 2.2%
10: 2.2%
11: 1.8%
12: 1.8%
13: 1.8%
14: 1.8%
15: 1.3%
16: 1.3%
17: 1.2%
18: 1.2%
19: 0.8%
20: 0.8%
21: 0.5%
22: 0.3%
Dose tier
Cohort
1
2
3
2 4 6 8


Probability of DLT: (10%, 30%, 50%)
1: 18.2%
2: 12.6%
3: 6.7%
4: 5.9%
5: 4%
6: 3.6%
7: 3.5%
8: 3.5%
9: 3%
10: 2.2%
11: 2%
12: 1.8%
13: 1.8%
14: 1.4%
15: 1.4%
16: 1.3%
17: 1.1%
18: 1.1%
19: 1%
20: 0.9%
21: 0.8%
22: 0.5%
23: 0.4%
24: 0.4%
25: 0.4%
26: 0.3%
27: 0.2%
Dose tier
Cohort



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