Acknowledging Parameter Uncertainty in the Simulation-Based Design of an Actinomycin-D Pharmacokinetic Study in Pediatric Patients With Wilms' Tumor or Rhabdomyosarcoma

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Actinomycin-D

Background

- Wilms' tumor, Rhabdomyosarcoma
- Clinical use > 40 years
- No PK information to guide dosing
- Dosing regimens modified to minimize toxicity (VOD, myelosuppression)
- Toxicity rates in children < 1 year double
- Dosing modifications < 1 year

Actinomycin-D

Background

- Open label trial of actinomycin-D (AMD) in children with Wilms' Tumor or Rhabdomyosarcoma proposed
- Examine AMD PK properties with the goal of providing dosing guidance
- Need to understand Dose → Exposure in children < 1 year old

Simulation With Uncertainty

Background

- Incorporate uncertainty in the parameter estimates via probability density functions
- Uncertainty in parameters implemented as inter-trial variability

R/NONMEM Toolbox for Simulation from Posterior Parameter (Uncertainty) Distributions - Gibiansky

NMSUDS: R/NONMEM® Toolbox for Simulations from Uncertainty Distributions

http://metruminstitute.org/downloads/index.shtml

Objectives

1. Construct Pop PK model to describe AMD disposition in children

2. Perform clinical trial simulations incorporating parameter uncertainty for the design and evaluation of a prospective large-scale AMD trial in pediatric cancer patients, and subsequent sensitivity analysis

3. Power the study to be able to accurately and precisely estimate clearance for children < 1 year

Model Characteristics

- Developed from PK data in 33 children, ages 1.5 to 20 years
- Nonlinear mixed-effects modeling with NONMEM
- 3 compartment, allometric scaling
- Log-transformed parameters
- THETA prior distribution – NONMEM variance/covariance matrix (multivariate normal)
- OMEGA prior distribution – mode, df (inverse Wishart)

Simulations With Uncertainty

Procedure

1. Create NMTRAN template data file Simulation of 500 sets of unbiased parameters from the population posterior distributions
2. Simulation 500 replicate PK data sets
3. Reference model fit to PK data
4. Parameter estimates and model diagnostic information collected
5. Bias and precision calculated
6. Global sensitivity analysis
7. Study design refinement
8. Repeat process until informative design identified

Methods

Study Design Assessment

- Feasibility of study design
- Ability to accurately estimate V1, CL
- Bias +/- 20%, no trends over range of unbiased parameters
- Powered accurately estimate clearance for children < 1 year

Methods

Initial Study Design

n=200

Group 1:

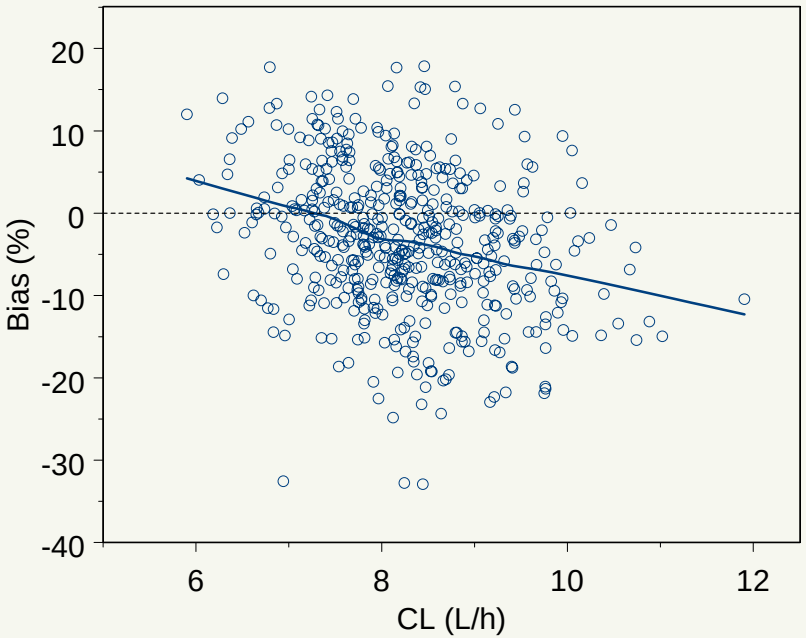
- 5 to 15 minutes
- 0.75 to 1.5 hours
- 3.5 to 4.5 hours
- 48 - 96 hours (n=50)

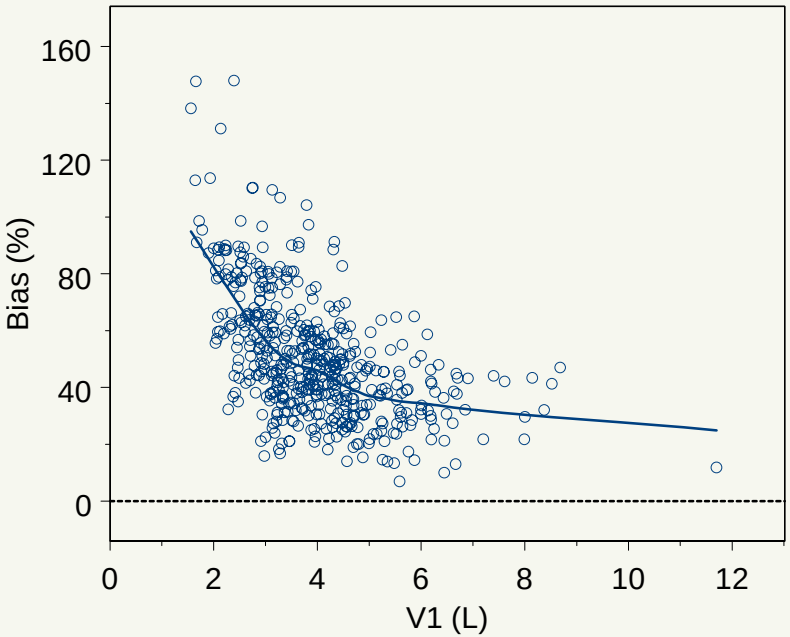
Group 2:

- 15 to 30 minutes
- 2 to 3 hours
- 5 to 6 hours
- 48 - 96 hours (n=50)

Results

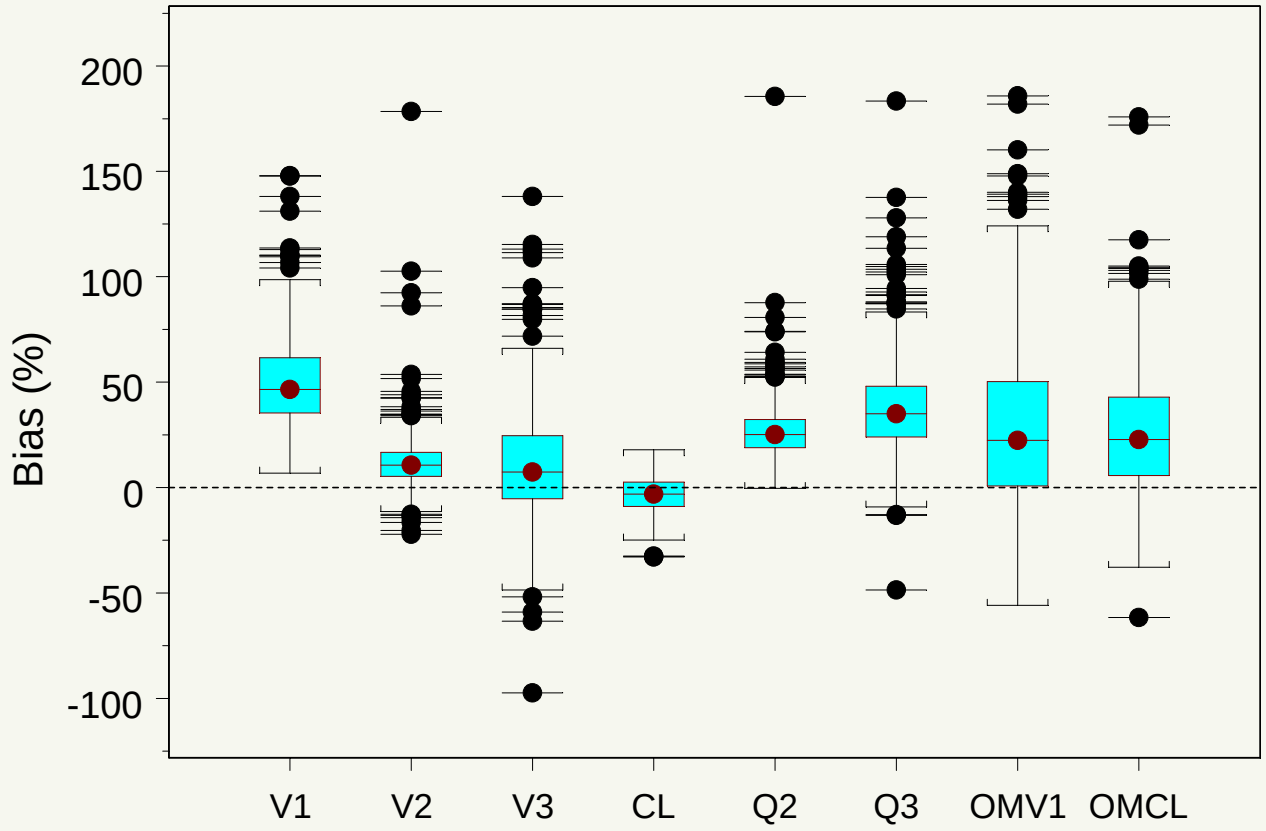
Initial Design





Results

Initial Design



Study Design Refinement

1. 24 hour sample added in 50% of patients
2. A rich sampling schedule was examined to evaluate the proposed sampling windows
3. Patients with a sample collected 48 – 96 hours increased to 50%
4. Sample fixed at 5 minutes included for both schedules
5. Sampling windows adjusted for remaining times

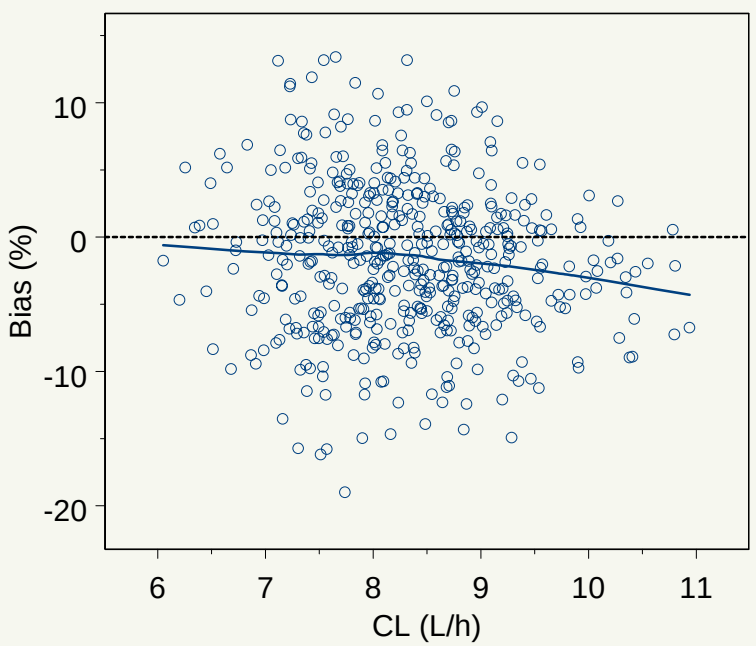
Final Study Design

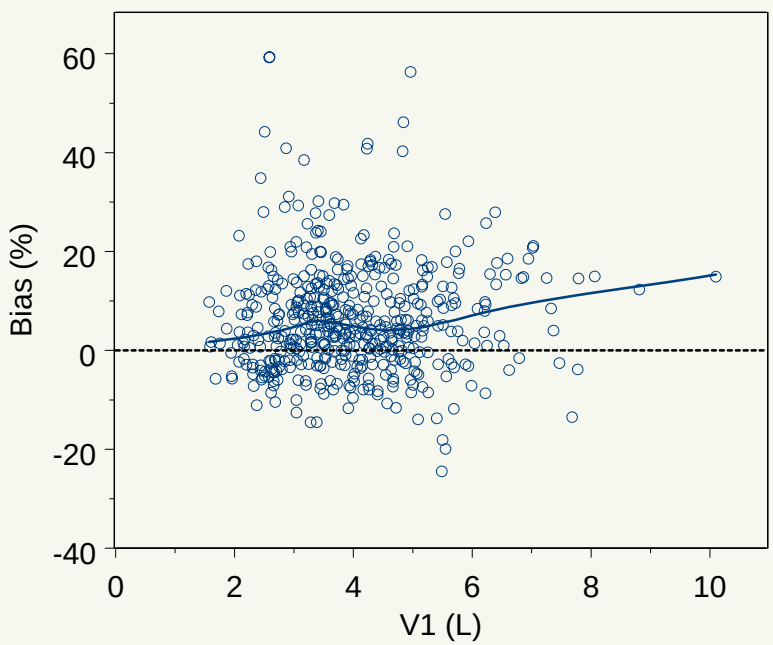
n=200

- Group 1:
  - 5 minutes fixed
  - 10 minutes fixed
  - 2 - 3 hours
  - 24 - 28 hours (n=100)
  - 48 - 96 hours (n=100)
- Group 2:
  - 5 minutes fixed
  - 0.75 - 1.5 hours
  - 5 - 6 hours
  - 24 - 28 hours (n=100)
  - 48 - 96 hours (n=100)

Results

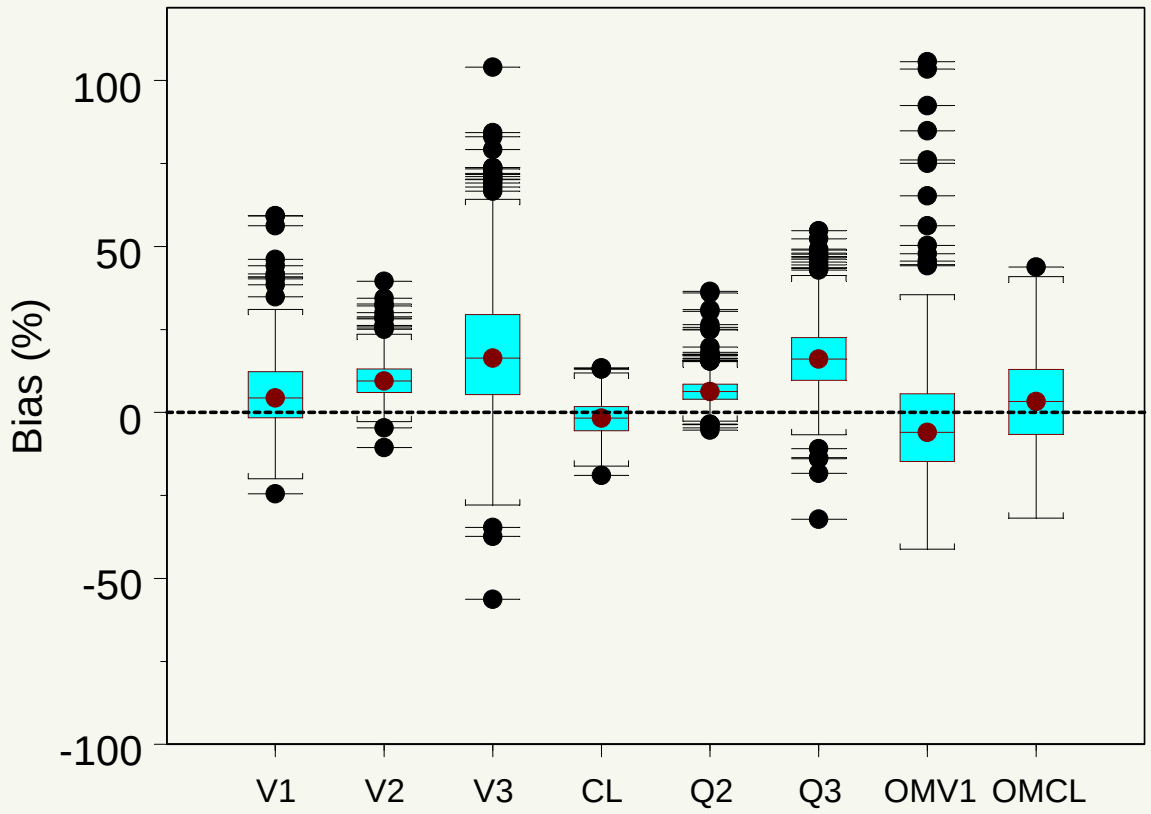
Final Study Design





Results

Final Study Design



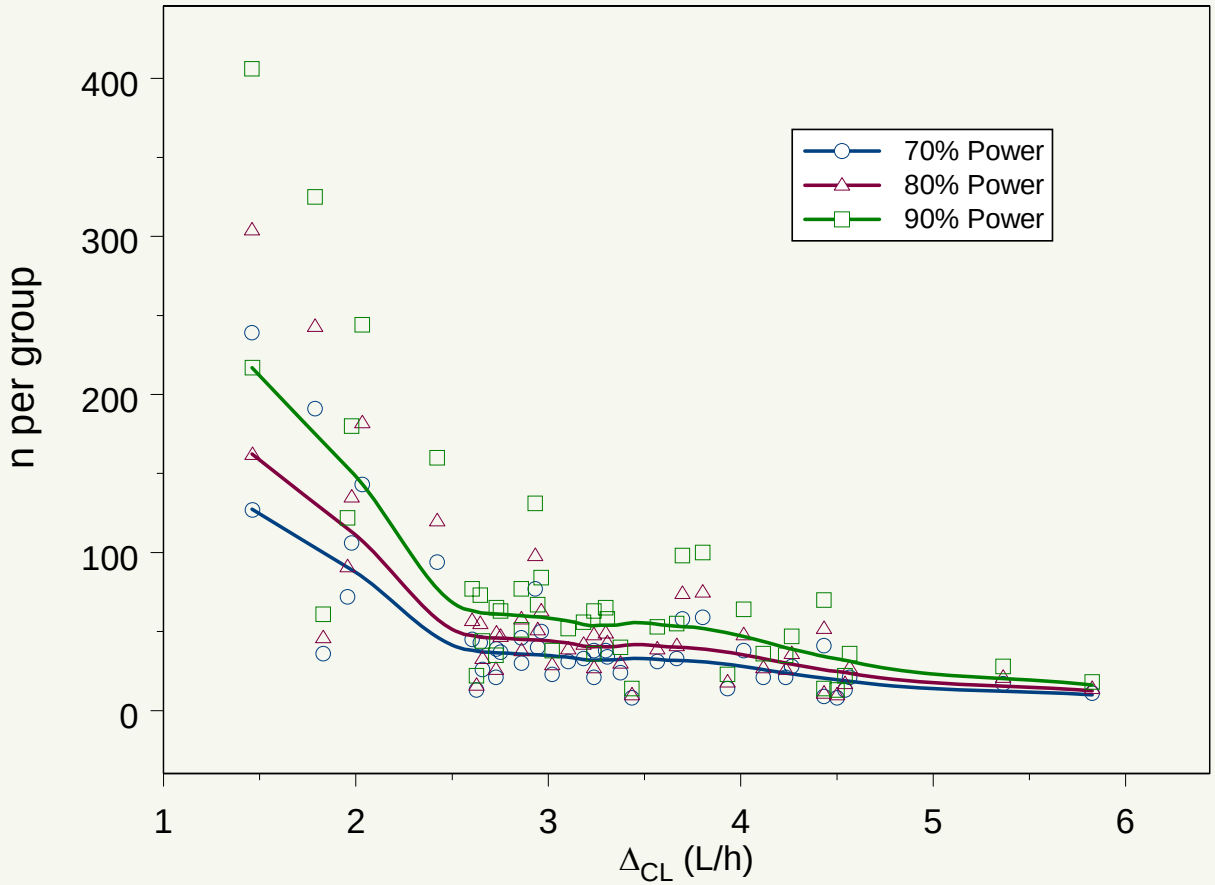
Age Effect

- Age effect on CL added to model

```
AEFF=0
IF(AGE.LE.1) THEN
AEFF=THETA(7)
ENDIF
TVCL = THETA(4)+0.75*LOG(WT/70)+AEFF*LOG(AGE)
LCL  = TVCL+ETA(2)
CL   = EXP(LCL)
```

- 500 values for AEFF drawn from RUNIF between 0 and 0.5

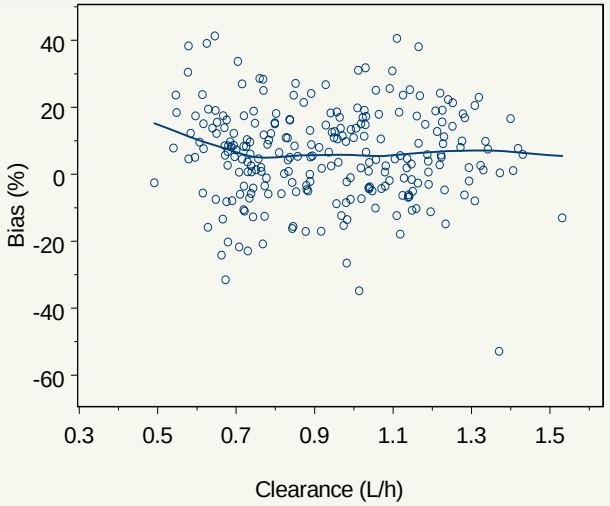
Age Effect
Power Analysis

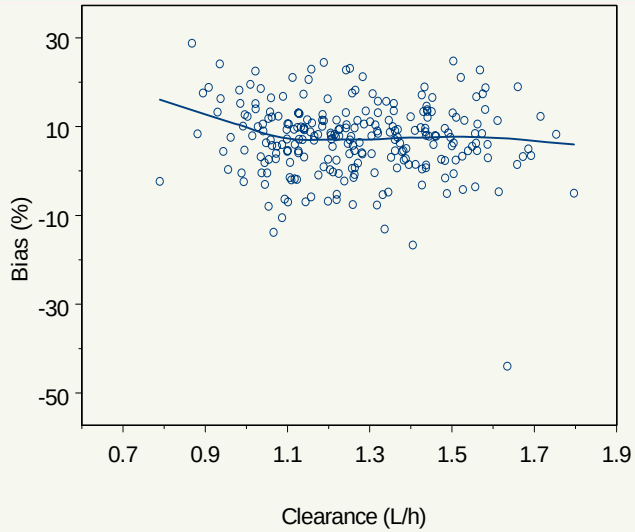


Age Effect

n=50

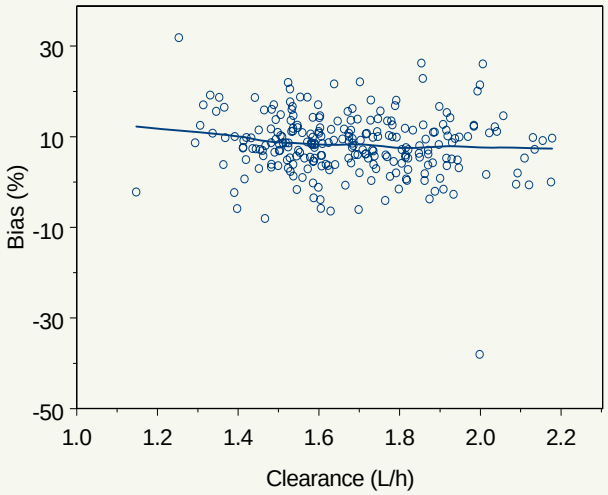
Age = 3 mos

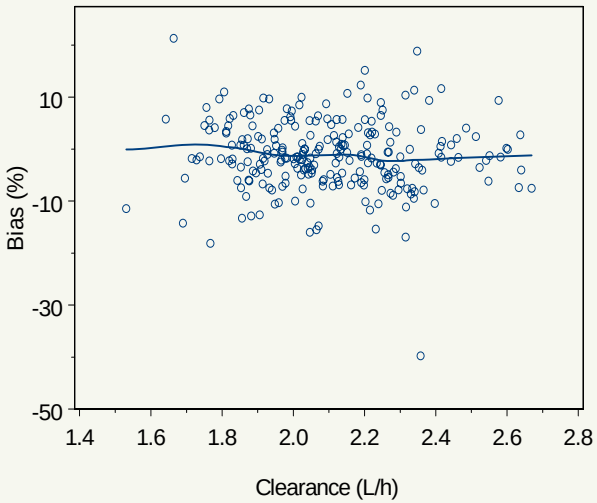




Age = 6 mos

Age = 9 mos





Age = 4 yrs

Conclusions

- A feasible and informative trial design was identified for an AMD clinical trial in pediatric patients with Wilms' tumor or Rhabdomyosarcoma

- Design was modified to be robust across the uncertainty in key parameters

Conclusions

- Appropriately powered to capture potential clearance differences in children < 1 year

- Results of this effort have been incorporated into a prospective trial protocol to be conducted through the Children's Oncology Group Phase I Consortium