Duke Clinical Research Institute

Use of clinical practice data and PK/PD modeling to aid classification of narrow therapeutic index drugs

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Background

- Narrow therapeutic index (NTI) drugs
  - *Small differences in concentrations = toxicities or therapeutic failures*
- FDA has tightened bioequivalence standards for NTI drugs
  - *90% CI of 90-111.11%*
- Broad implementation of new standards is challenging
  - *Most drugs with potential NTI lack NTI classification*
- Lack of NTI classification in part due to uncharacterized therapeutic index
  - *Therapeutic index = toxic exposure / efficacy exposure*
- There is a need to define the therapeutic index of potential NTI drugs

Objective

- Use clinical practice data and PK/PD modeling to characterize the drug dose/concentration-response relationship to aid in classification of drugs with NTI

3-prong approach, proof of concept

- Step 1: Literature review and data extraction
  - *Safety, efficacy, TDM, PK/PD*
- Step 2: Electronic medical records at Duke
  - *Safety, efficacy, drug levels, dosing history*
  - *Inpatient*
- Step 3: PK/PD modeling
  - *Characterize concentration-response relationship*
  - *Simulate concentration-response relationship*

Data not peer reviewed

Lamotrigine (LTG) case example

- Indicated for seizures and bipolar disorder
- Therapeutic index is poorly defined
- Use of TDM in clinical practice varies substantially
- Adverse events (e.g. rash) possibly related to dose

Step 1: Literature review and data extraction

Epilepsy indication in adults

Literature Search — All publications from Embase and Pubmed searches compiled

Preliminary Review — •Titles and abstracts reviewed. • Preliminary list of articles for extraction created

Publication Retrieval — Preliminary list of publications downloaded for review

Final Review and Extraction — •All relevant articles are entered in organizational worksheet •Data extracted

Pubmed: N=384
Embase: N=187

Articles in study database: N=132

Data extracted: N=78

PK: N=34
Safety: N=21
Efficacy/PD: N=43

Examples of LTG literature efficacy data

Reference	Number of subjects	Outcome measure	Efficacy results	Dose range
Mohanraj et al, 2005	249	Reduction in seizure frequency	Successful monotherapy in 61% of subjects	25–600 mg
Reunanen M et al, 1996	226	Percentage of subjects who were seizure- free during 7 weeks	60.4% of subjects were seizure-free at end of 7 weeks	100–200 mg
Gilliam et al, 2000	156	Percentage of subjects on monotherapy	56% patients on monotherapy	100–500 mg
Mauri et al, 2005	222	Percentage of patients who were seizure- free during 1 year	89% of patients were seizure- free after 1 year of treatment	50–150 mg
Brodie et al, 1995	131	Percentage of patients who were seizure- free during 40 weeks	26% of patients seizure-free at 40 weeks	100–300 mg

Examples of LTG literature safety data

Reference	N	Type	Severity	Incidence	Range of drug doses
Matsuo et al, 1996 Binnie et al, 1989 Schachter et al, 1995	8 – 334	Rash	Moderate/ serious	1%, 3%, 8%	100–500 mg (serious), 100 mg (moderate)
Gilliam et al, 1998 Schachter et al, 1995	156 – 334	Stevens-Johnson syndrome	Serious	0.1%, 1%	300–400 mg (study #99), 300 mg/day, and 250 mg bid (study #65)
Baulac et al, 2010	141	Grand mal seizures	Serious	1%	300–400 mg/day
Jozwiak et al, 2000	126	Diplopia	Serious	1%	250 mg
Schachter et al, 1995	334	Dizziness	Serious	0.6%	100–500 mg
Schachter et al, 1995	334	Vision blurred	Serious	0.6%	100–500 mg
Schachter et al, 1995	334	Ataxia	Serious	0.3%	100–500 mg
Schachter et al, 1995	334	Nausea	Serious	0.3%	100–500 mg

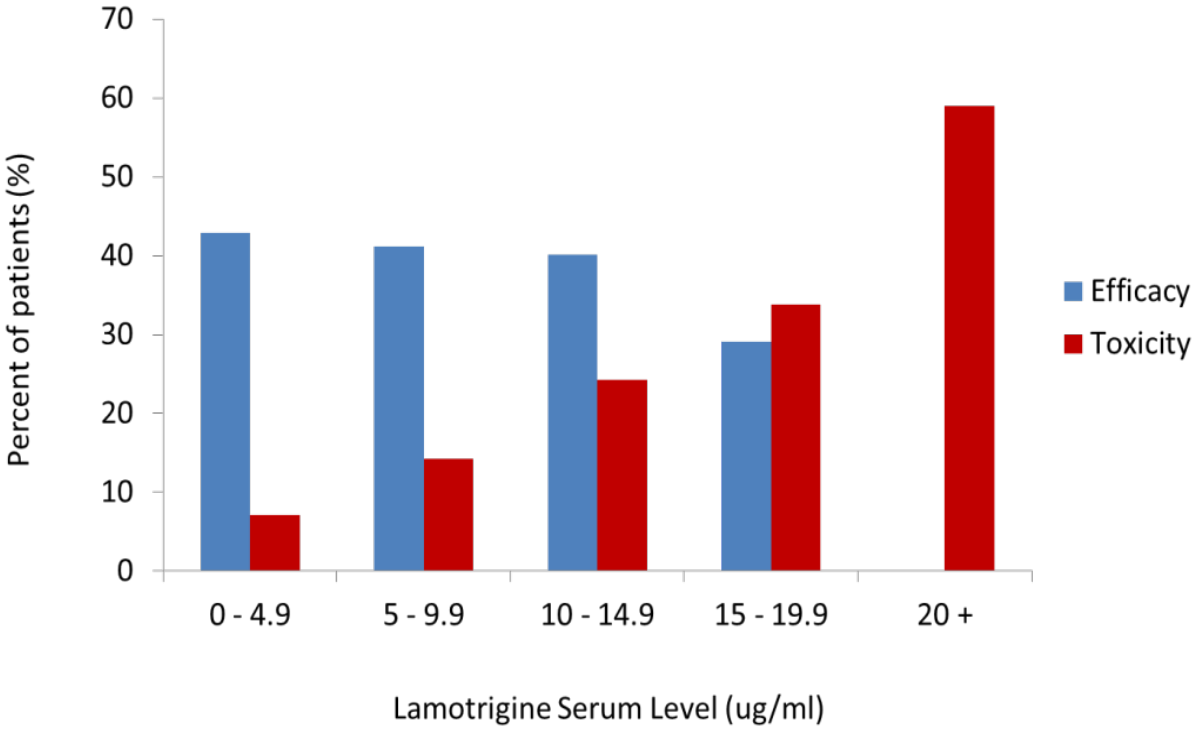
Example of LTG literature TDM data

Retrospective study (N=**811**)

Monotherapy or combination therapy

Toxicity: side effects significant enough to decrease dose or change to another AED

Therapeutic index ~4-20



Hirsch et al. Neurology 2004; 63 (6): 1022-1026

Step 2: LTG EMR data

- Adult inpatients with seizures
- Parameters of interest
  - *LTG dosing*
  - *LTG concentrations*
  - *Seizure events*
  - *Safety events*
    - Warnings & Precautions on drug label

Table. Extracted EMR data	
Basic demographics	
Concomitant AEDs	
Seizures (y/n)	
"Routine" EEG (y/n)	
Continuous EEG monitoring (y/n)	
LTG dose info • Amount • Formulation • Date • Time	
LTG concentrations (date/time)	
Lab values • Hematology • AST, ALT • BUN, Creatinine	
Adverse events	
• Anemia	• Multiorgan failure
• Leukopenia	• Neutropenia
• Thrombocytopenia	• Suicidal ideation or behavior
• Serious rash	• Stevens-Johnson

Step 2: LTG EMR data - inpatients (N=46)

Age (years)	41.5 (16.16)
Weight (kg)	84.9 (31.07)
Height (cm)	170.9 (11.04)
Male gender	23 (50%)
Race	
White	30 (65%)
Black	15 (15%)
Asian	1 (2%)
Number of lamotrigine doses	244
Doses per subject	5.3 (4.17)
Number of lamotrigine levels	55
Number of PK samples per subject	1.2 (0.40)
Concomitant medications	
Carbamazepine	1/46 (2%)
Valproic acid	5/46 (11%)
Phenytoin	6/46 (13%)
Primidone	0/46 (0%)
Any AED	12/46 (26%)

*mean (SD) reported; Data extraction period: 01/2012-12/2013; AED: Anti-Epileptic Drug

Outcomes

Seizure Frequency

N days with ≥ one seizure	22/170 (13%)
N subjects with ≥ one seizure	12/46 (26%)
Mean (SD) seizures per day	1.5 (10.93)
Method of seizure diagnosis Clinical Electrographic	 17 (77%) 5 (23%)

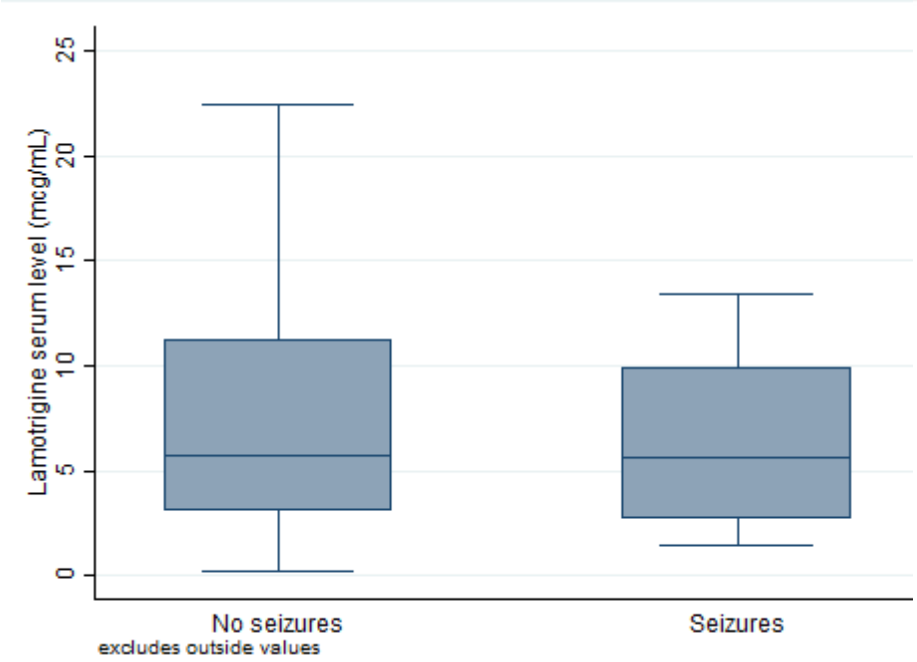
Safety

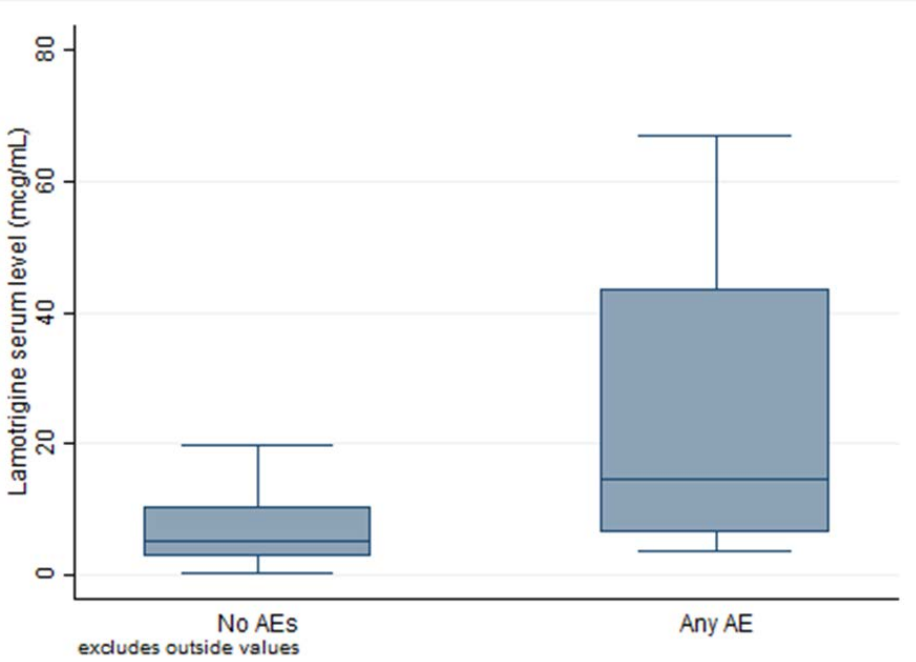
Anemia	5/46 (11%)
Thrombocytopenia	4/46 (9%)
Leukopenia	1/46 (2%)
Drug decrease due to AE	1/46 (2%)
Any adverse event	8/46 (18%)

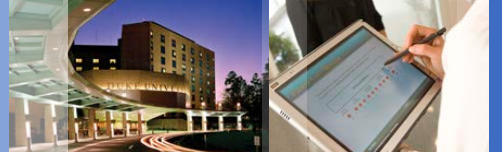
Lamotrigine Levels (mcg/mL)

	All days	Days with seizure	Days without seizure	p
Mean (SD)	8.9 (10.20)	6.4 (4.20)	9.6 (11.30)	0.35
Median (IQR)	5.7 (3.1, 10.5)	5.7 (2.7, 9.9)	5.7 (3.1, 11.2)	0.74
Min, Max	0.2, 67.1	1.4, 13.4	0.2, 67.1	NA

Observed data: LTG exposure and response







Step 3: PK/PD Modeling

- Goal
  - *Characterize the exposure-response relationship*
  - *Increase exposure data via simulation*
- Process
  - *Identify published PK/PD models of LTG in the literature*
  - *Select the appropriate literature PK/PD model*
    - Observed factors: patient population, sample size, robustness
    - Model performance (structural PK and covariate model maintained)
      - De novo estimation of PK/PD parameters using the Duke EMR data
      - Predictive performance using literature PK/PD parameters
  - *Simulate LTG exposure in patients from the Duke EMR*
    - Maximum concentration of the day (Daymax)
    - Maximum trough concentration of the day (C_{trough})
    - Average concentration of the day ($C_{average}$)
  - *Evaluate LTG exposure-response relationship*

Candidate PK models identified in the literature

Ethnicity/ Country	Patient Population	N	Covariates	CL (L/h)	V (L)	Reference
Serbian	Adult/pediatric	38	CBZ, VPA	1.97	78.9	Milovanovic 2009
Spanish and German	Adults	600	WT, CBZ, VPA, PHT, PRM	1.96	NE	Rivas 2008
USA (Whites, Blacks, and Hispanics)	Elderly	148	BUN/SCR ratio, WT, PHT	2.84	117	Punyawudho 2008
Chinese	Pediatric	165	AGE, VPA	1.16	40.2	Zhang 2008
Australia	Adults	124	VPA, PHT	2.14	78.1	Chan 2001
Whites/Non-Whites	Adults	474/53	Enzyme inducers, race	4.06	125.3	Grasela 1997
Whites/Asians	Adults	158/5	Race	2.28	77.4	Gidal 2000
USA	Adults	62	WT, VPA, Enzyme inducers	~1.95	NR	Mallaysamy 2013
Indian	Adults	95	WT, CBZ, VPA	2.27	53.6	Brzakovic 2014
Serbian	Adult/pediatric	53	WT, CBZ, VPA	4.23	NE	He 2012
Chinese	Pediatric	284	WT, CBZ, VPA, PB	1.01	16.7	[11]

No PK/PD models

Cannot identify covariate effects

Auto-induction

Missing info

Different pop.

CBZ: carbamazepine; VPA: valproate; PHT: phenytoin; PB: phenobarbital; PRM: primidone

Demographics from PK model and EMR

	Rivas Study Median [25th-75th percentile]	EMR Data Median [25th – 75th percentile] Mean (Range)
No. of patients	600	45
Male/female	337/263	23/22
Age (y)	38-39 [26.8 – 51.3]	43 [31 – 50] 41.8 (20 – 74)
Body weight (kg)	70.0-76.0 [61.8 – 85.0]	78.5 [65.8 – 99.3] 85.3 (46 – 175)
Caucasian/Non-Caucasian	NR	29/16
Number of LTG levels	1699	53
Mean number of levels per subject	2.8	1.2

NR: not reported.

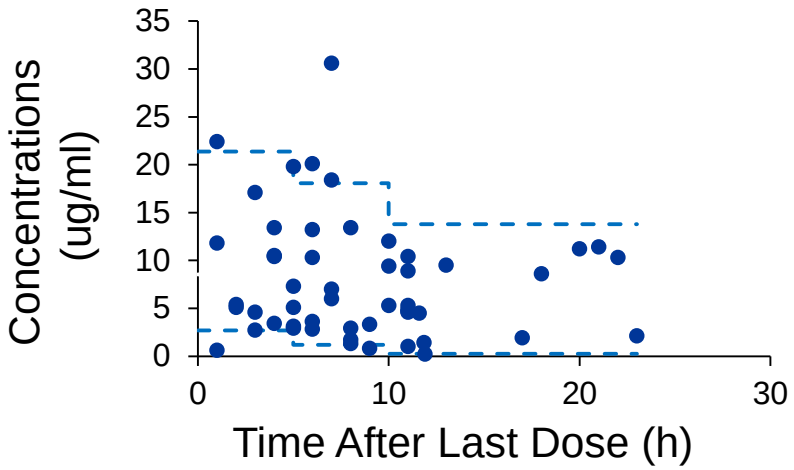
De Novo Estimation of PK Parameters

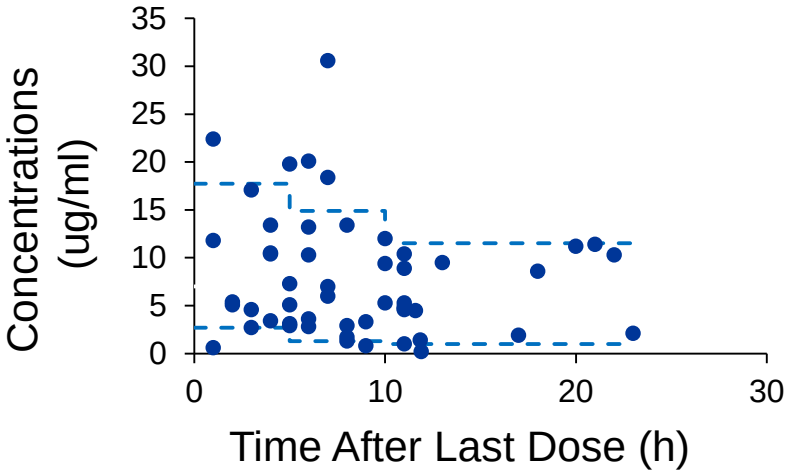
	Rivas Paper		Estimates from our data	
Parameters	Point Estimate (RSE)	IIV, CV% (RSE)	Point Estimate (RSE)	IIV, CV% (RSE)
θ1, L/h/kg	0.028 (2.1%)	27.5% (9.4%)	0.023 (11%)	62.4% (15%)
V, L/kg	1.5 Fixed	NE	1.19 (23%)	154.9% (15%)
Ka, 1/h	1.3 Fixed	NE	1.3 Fixed	NE
θ2 (VPA)	-0.713 (7.7%)	NA	-0.713 Fixed	NA
θ3 (PHT)	0.663 (10%)	NA	0.663 Fixed	NA
θ4 (PB or PRM)	0.588 (8.7%)	NA	0.588 Fixed	NA
θ5 (CBZ)	0.467 (30%)	NA	0.467 Fixed	NA
θ6 (IND)	0.864 (12%)	NA	0.864 Fixed	NA
Additive residual error	1.25 (8.2%)	NA	1.46 (39%)	NA

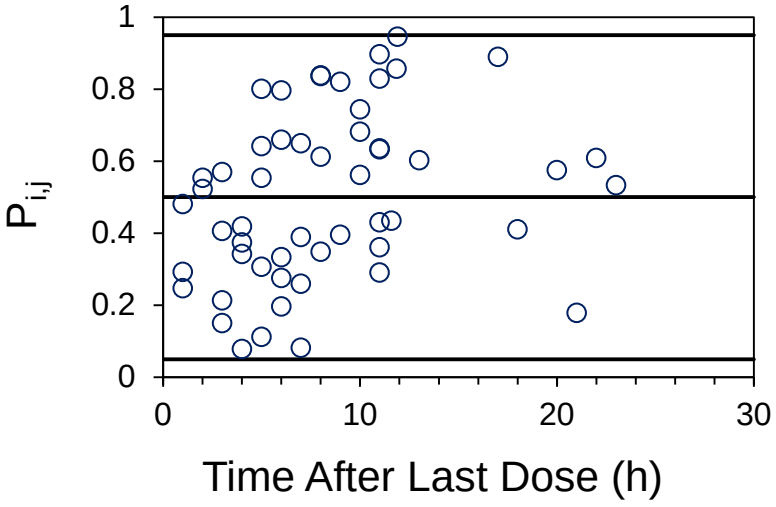
NE: not estimated; NA: not applicable.

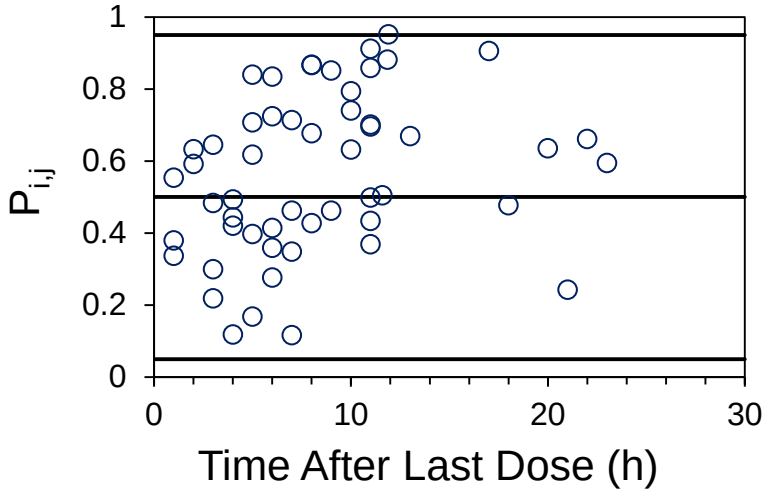
$$CL\ (L/h) = \theta 1 * BW * e^{-\theta 2*VPA} * e^{\theta 3*PHT} * e^{\theta 4*(PB\ or\ PRM)} * e^{\theta 5*CBZ} * e^{\theta 6*IND}$$

PK model performance: de novo and predictive







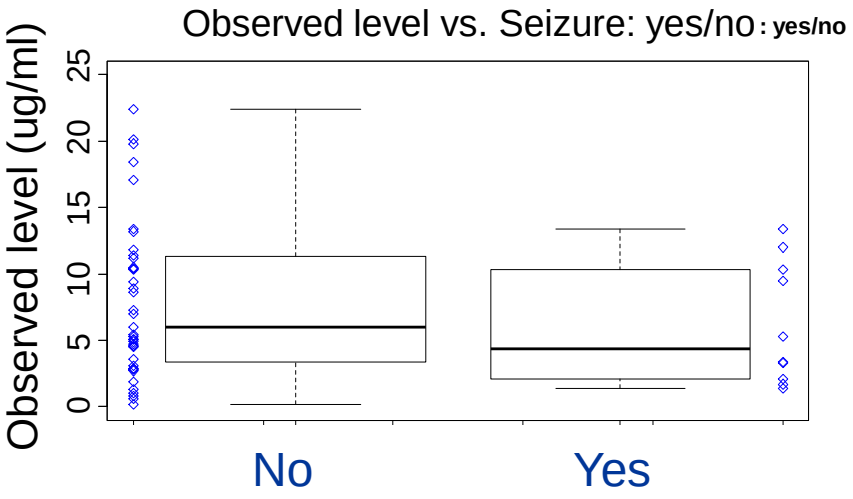


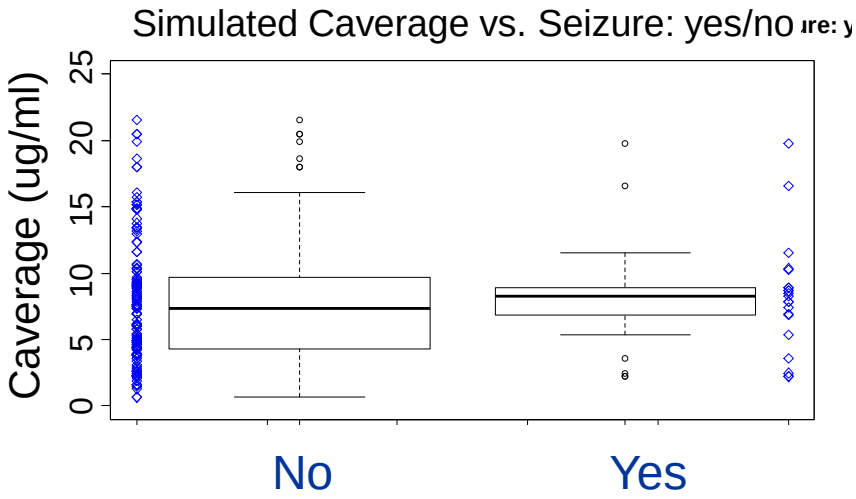
LTG exposure-response relationship: simulations

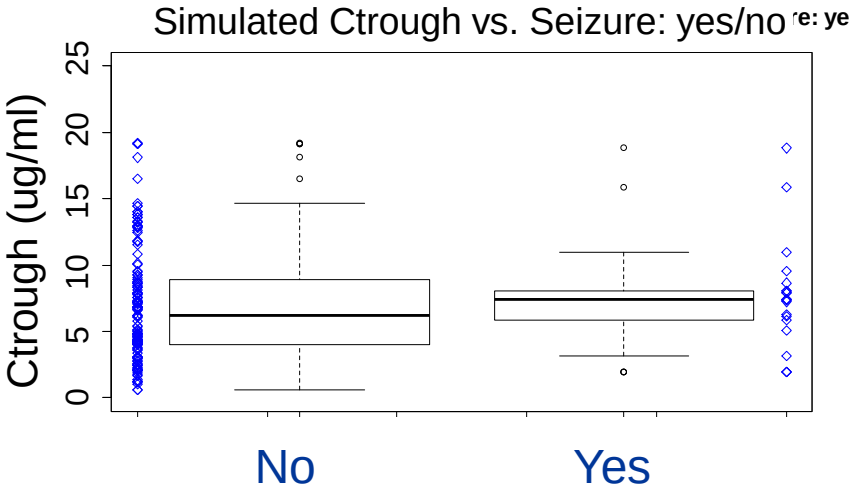
	# observed events with levels	# Pts with observed events and levels	# observed events with simulated levels	# Pts with observed events with simulated levels
Seizures	10	10	22	12
Multiple seizures	5	5	10	7
Anemia	7	6	31	8
Thrombocytopenia	6	4	20	5
Leukopenia	2	2	6	2
Any adverse events	11	8	43	9

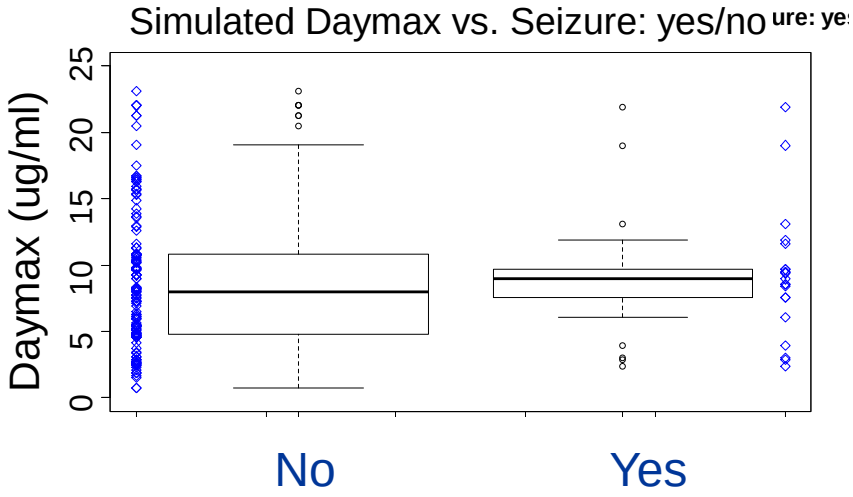
Increase in sample size and number of events

Observed and Simulated LTG vs. Seizures

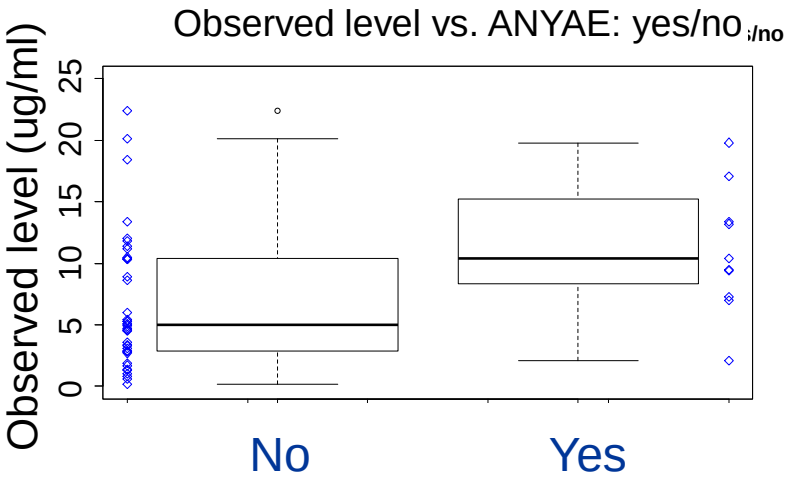


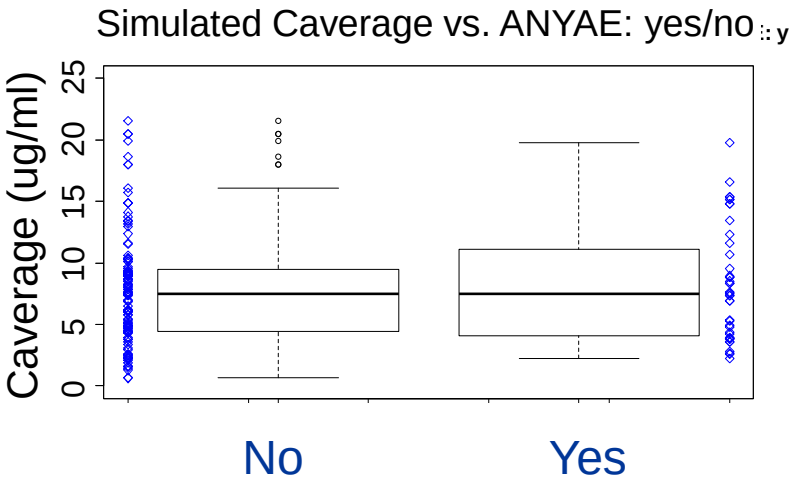


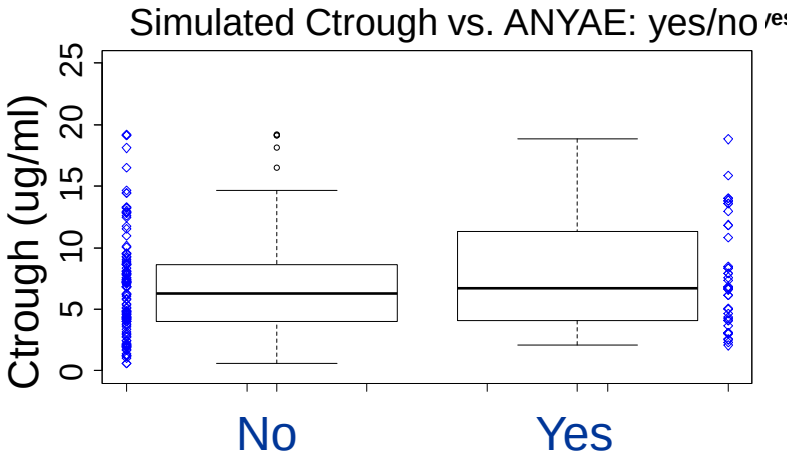


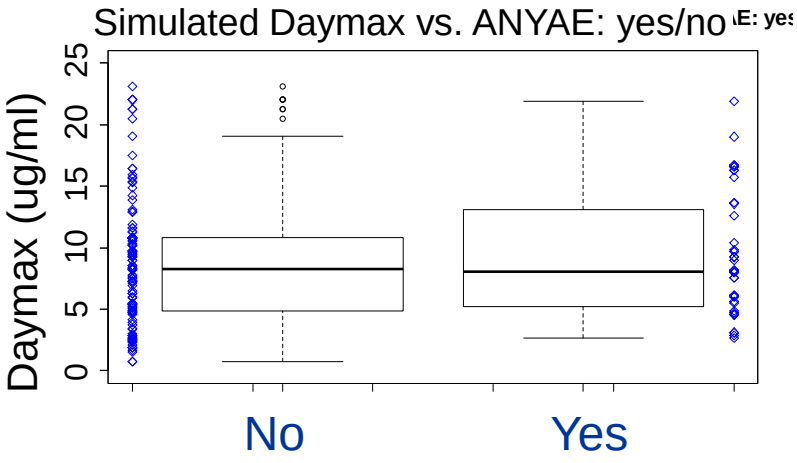


Observed and Simulated LTG vs. Any Adverse Events

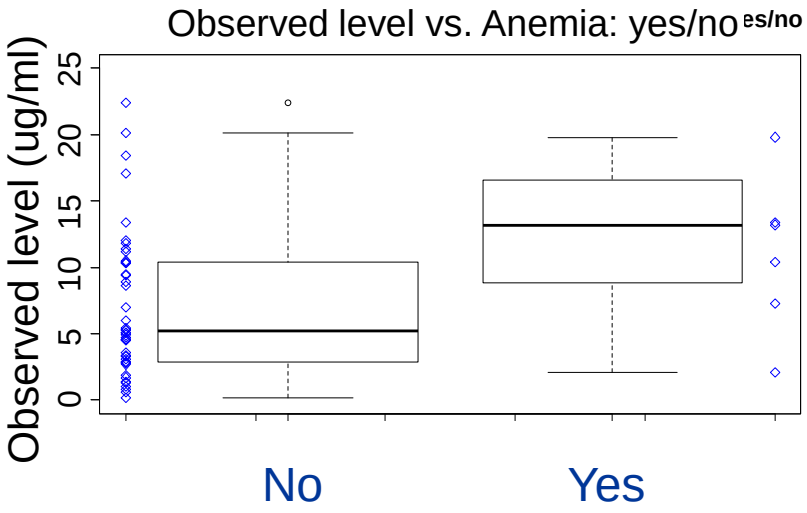


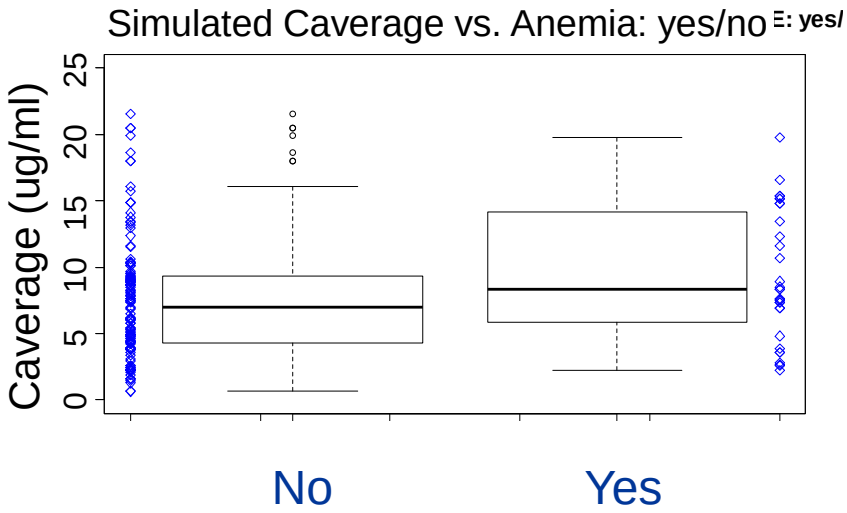


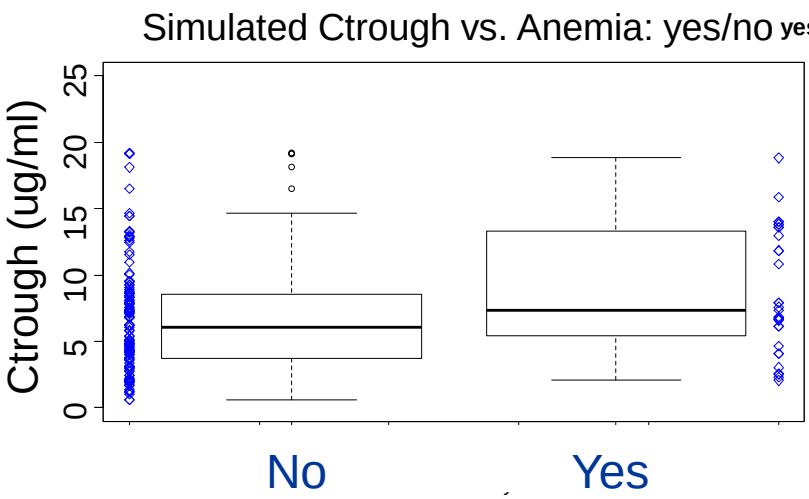


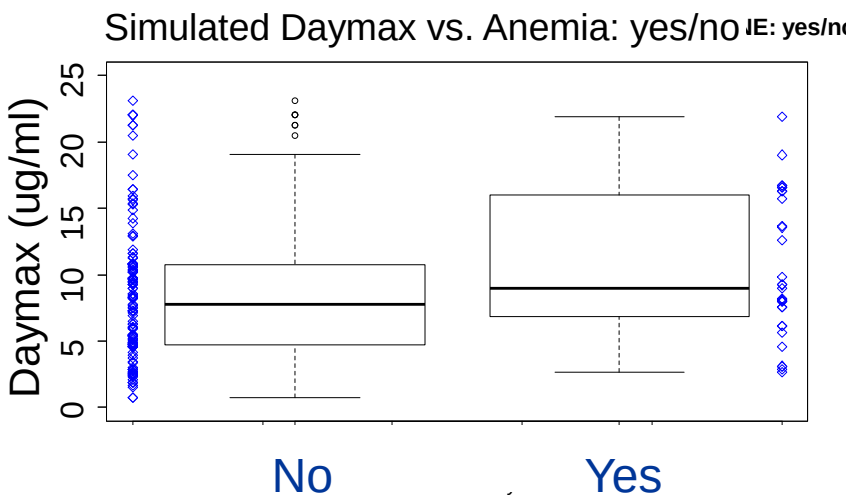


Observed and Simulated LTG vs. Anemia

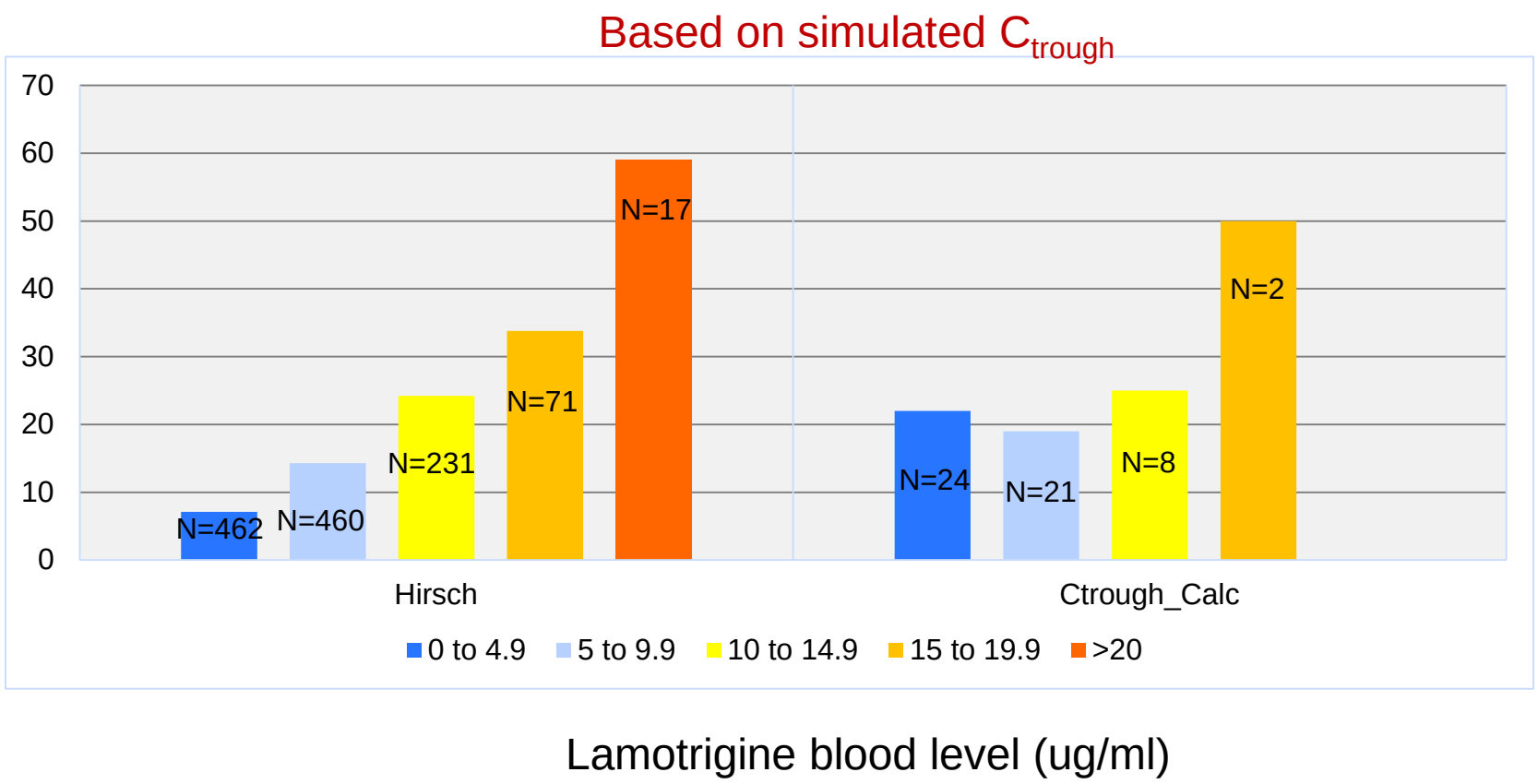




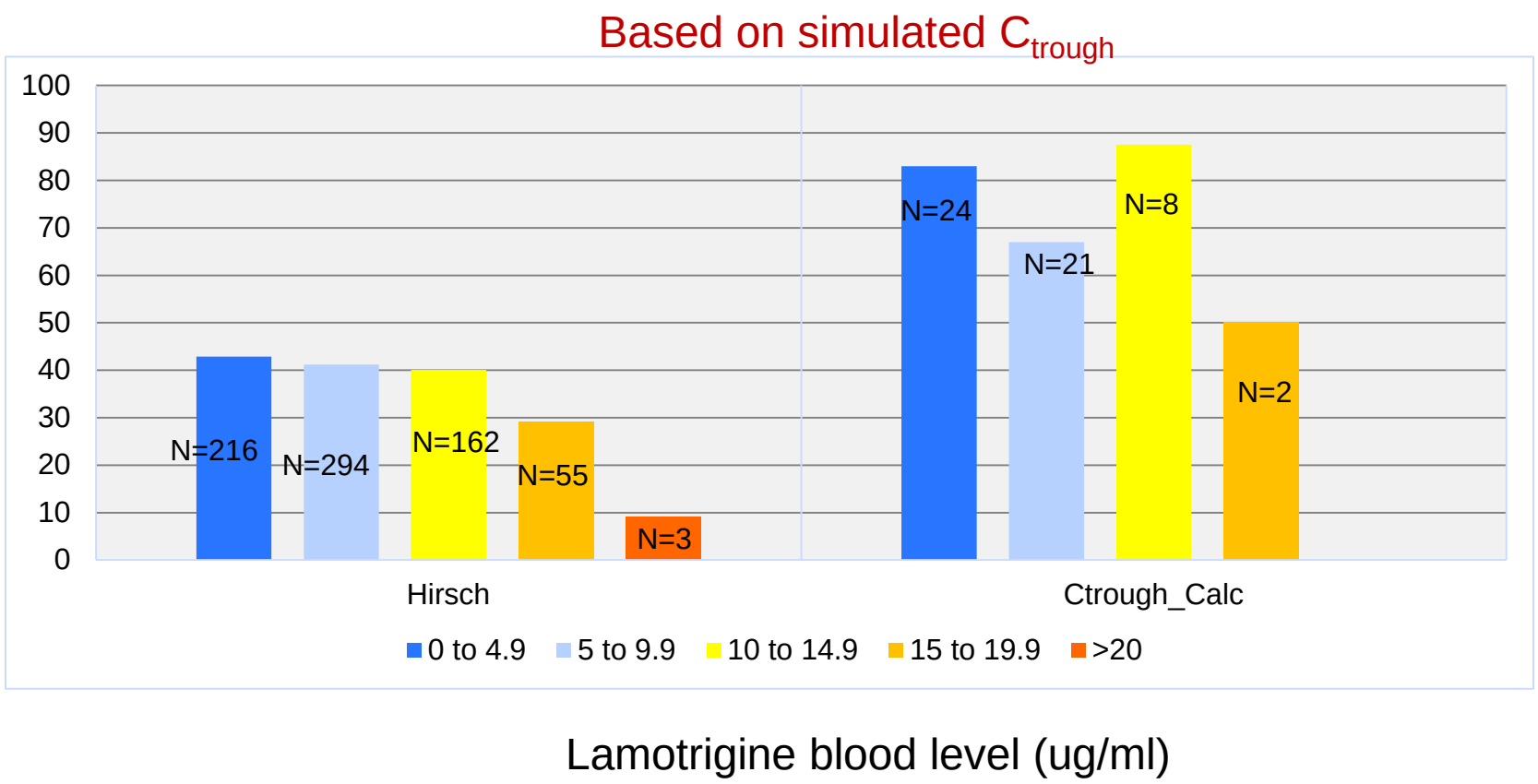




Literature Data vs. Duke Data: Safety vs. C_{trough}



Literature Data vs. Duke Data: Efficacy vs. C_{trough}



Summary of results for LTG

- A literature search yielded important information about the LTG therapeutic index
  - *~4-20*
- A LTG PK model was selected from the literature and was suitable to characterize Duke EMR data
- PK simulations increased the sample size and number of events in the Duke EMR data
- Similar trends of the exposure-response relationship were shown for observed and simulated data
- Based on the therapeutic index data alone
  - *LTG should not be classified as NTI*

Conclusions

- The proposed 3 prong-approach is promising to define the therapeutic index of drugs with potential NTI
- Quality of the data used to “evaluate” published PK models is important
- Sample size can be a limiting factor of the approach

Future Steps

- Increase the sample size for modeling
  - *Clinical trial data*
    - LTG, collaboration Univ. of Maryland
  - *Outpatient data*
    - Sirolimus
- Evaluate approach with known NTI drug as probe and compare to “potential” NTI
  - *Phenytoin vs. LTG*
- Collect clinical practice prescription data

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