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Busulfan TCI Audit and Model Evaluation

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Background

- Intravenous high dose busulfan is used for bone marrow conditioning prior to bone marrow transplant
- Target concentration intervention for busulfan is recommended in the FDA label (AUC method)
- Bayesian TCI has been in use at Auckland Starship and Auckland City hospital for all busulfan bone marrow conditioning since March 2012

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Busulfan Audit

- Ethical approval from HDEC to conduct a clinical audit of busulfan use
- LabPlus (Auckland) performs all busulfan concentration measurements
- Laboratory scientists at LabPlus trained to use NextDose to enter demographic, dose and concentration data
- LabPlus provides NextDose report to clinical staff with future maintenance dose proposal

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Audit Summary

69 Reports March 2012-Jan 2015

- Target
  - 4800 umol/L*min with dosing interval of 24 h (49 reports)
  - 2400 umol/L*min with dosing interval of 12 h (1 reports)
  - 0.77 mg/L (10 reports)
- Target Errors
  - AUC 4800 umol/L*min with dosing interval of 2 h (8 reports)
  - Conc of 4800 umol/L (1182 mg/L) (1 report)
- Documentation
  - 13 clinical consultants
  - Clinical consultant not identified (27 reports)

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TCI Model Evaluation

Booth 2007	NextDose 2012	McCune 2014
24 children, teenagers ~384 observations 3 occasions	67 infants, children, adults 371 observations 1 to 4 occasions	1610 infants, children, adults 12,380 observations 1 to 3 occasions
1 compartment Empirical allometry Total body weight No maturation .	1 compartment Theory based allometry Total Body weight Best guess maturation Post-menstrual age	2 compartment Theory based allometry Normal fat mass Estimated maturation Post-menstrual age Sex (V), Time (CL)
BSV + BOV No correlation	BSV + BOV BSV Correlation CL and V	BSV + BOV BSV & BOV Correlation CL,V1,Q,V2 (full block)

Booth 2007: Booth BP, Rahman A, Dagher R, Griebel D, Lennon S, Fuller D, et al. Population pharmacokinetic-based dosing of intravenous busulfan in pediatric patients. J Clin Pharmacol. 2007;47(1):101-11.

NextDose 2012: Holford SD, Turkistani A, Madhavaram H, Holford NHG. NextDose - A web based collaborative tool for dose individualisation. PAGANZ http://wwwpaganzorg/abstract/1295 2012;Accessed 11 July 2013.

McCune 2014: McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63.

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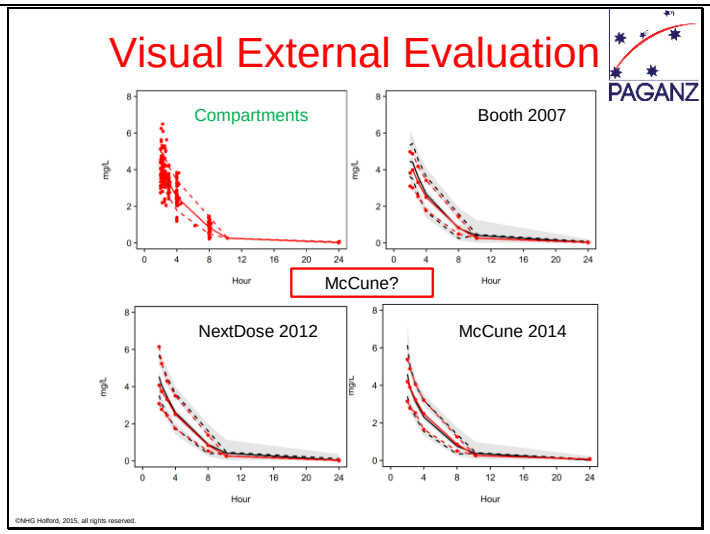
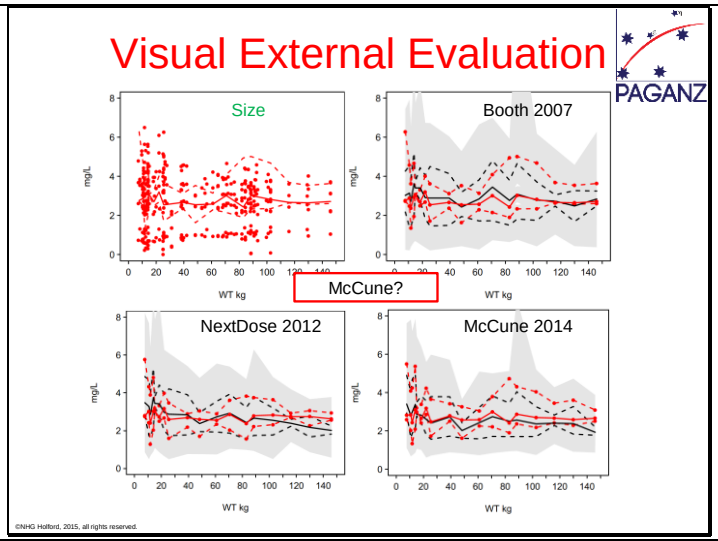
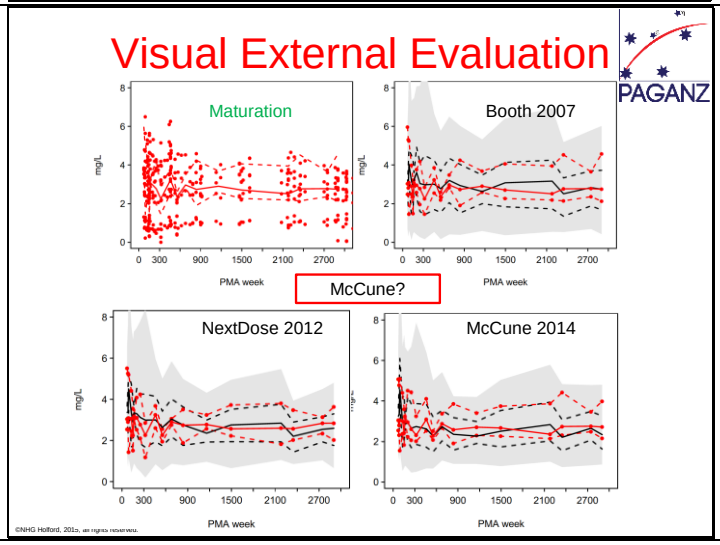
Objective Function Value

MAXEVAL=0

Booth 2007	NextDose 2012	McCune 2014
-489	-534	-387
	NextDose?	

Total: 395 observations
1 occasion: 69 subjects
2 occasions: 10 subjects
3 occasions: 2 subjects
4 occasions: 1 subject

Slide 7		PRED corrected VPC
Slide 8		PRED corrected VPC
Slide 9		PRED corrected VPC

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Clearance Prediction Error

Booth 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Average	0.0%	1.0%	1.2%	2.2%	1.9%	2.1%
StDev	0.0%	4.8%	3.6%	6.1%	2.5%	**4.1%**

NextDose 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Average	-1.1%	**-0.1%**	0.0%	1.0%	0.8%	1.0%
StDev	3.5%	5.6%	0.0%	**4.6%**	3.8%	5.0%

McCune 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Average	-1.8%	-0.8%	-0.6%	0.3%	0.0%	**0.2%**
StDev	2.4%	4.2%	3.7%	5.3%	0.0%	**2.5%**

McCune?

"true" clearance for each subject in each model was estimated from the empirical Bayes estimate using all occasions (Occall) Best prediction was based on performance of each model prediction of occasion 1 clearance (Occ1)

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Clearance Prediction Error

NextDose 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Min	0.0%	**-1.0%**	-7.7%	-7.7%	-2.4%	-2.4%
Max	0.0%	36.4%	9.8%	40.5%	10.0%	**24.0%**

NextDose 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Min	-8.9%	-8.9%	0.0%	**-0.1%**	-6.4%	-6.4%
Max	8.3%	31.4%	0.0%	35.4%	12.5%	**19.4%**

McCune 'True'	Booth Occ all	Booth Occ 1	NextDose Occ all	NextDose Occ 1	McCune Occ all	McCune Occ 1
Min	-9.1%	-7.1%	-11.1%	-11.1%	0.0%	**-4.6%**
Max	2.4%	29.3%	6.8%	33.2%	0.0%	**17.5%**

McCune?

"true" clearance for each subject in each model was estimated from the empirical Bayes estimate using all occasions (Occall) Best prediction was based on performance of each model prediction of occasion 1 clearance (Occ1)

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Evaluation Summary

Evaluation Method	Best Model
Objective Function Value	NextDose 2012
VEE Compartments	McCune 2014
VEE Size	McCune 2014
VEE Maturation	McCune 2014
CL Prediction Error Average	McCune 2014
CL Prediction Error SD	McCune 2014
CL Prediction Error Min	NextDose 2014
CL Prediction Error Max	McCune 2014

Best TCI Model
McCune 2014

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Summary

- Audit
  - NextDose usable by clinical laboratory staff without specialist TCI guidance
  - 1 serious dose error on Nextdose report due to mistaken entry of target AUC value with conc units
  - 8 moderate errors on NextDose report due to mistaken dosing interval
- Model Evaluation
  - McCune 2014 model more complex but overall better prediction of observed concentrations and future dosing