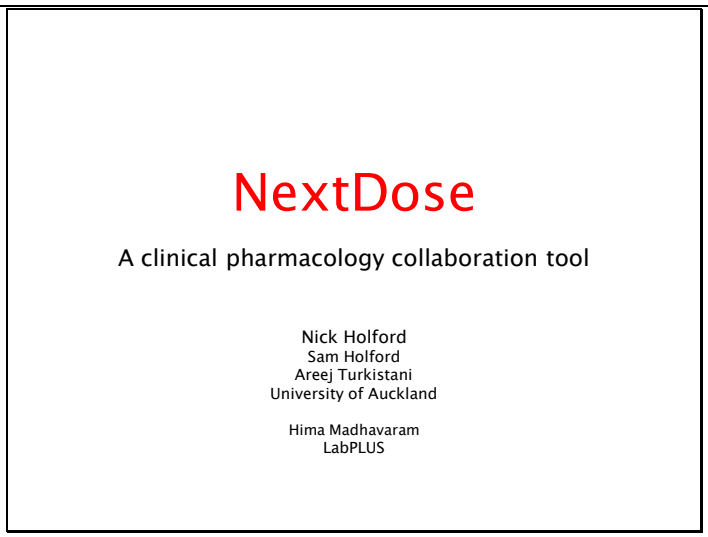
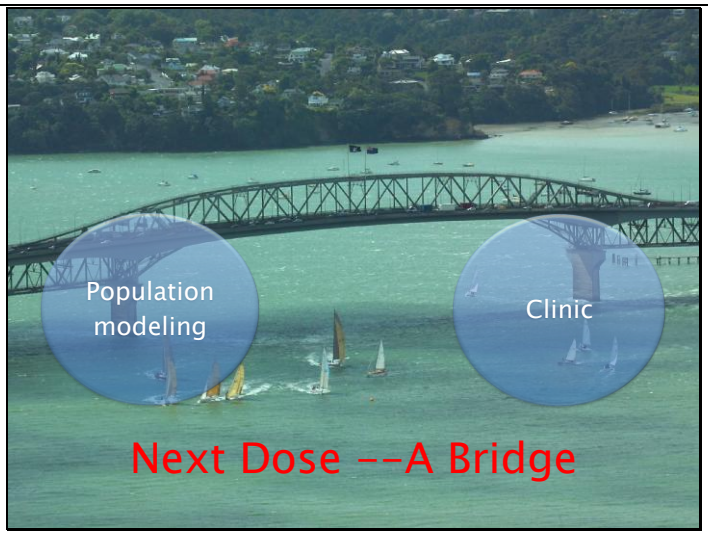
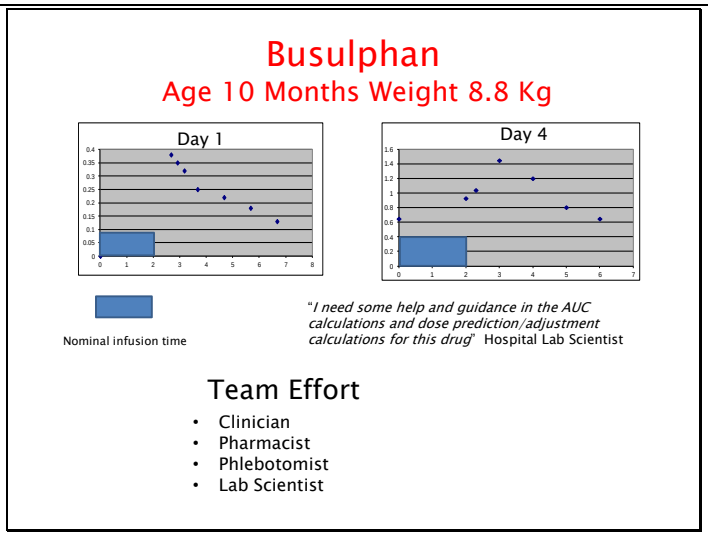
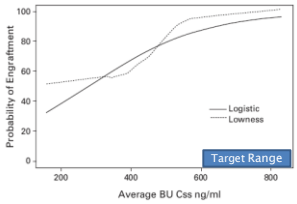
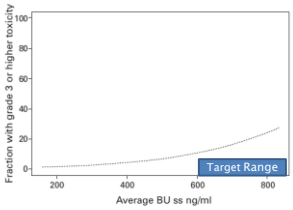
Slide 1		
Slide 2		
Slide 3		Note rising concentrations after nominal end of infusion means there must be an error in either dosing history (e.g. longer infusion than 2 hours) or the way that blood samples were obtained (e.g. contamination from catheter used for infusion).

Slide 4	**Pharmacodynamics Children**  **Figure 1** Probability of engraftment compared to Bu Css (ng/ml).  **Figure 2** Fraction of patients with toxicity as related to Bu Css (ng/ml). Target Range 0.6 to 0.9 mg/L; Target Concentration 0.77 mg/L Corresponds to Target AUC of 1125 umoL*min q6h dosing Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.	Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.
Slide 5	**AUC Dose Adjustment** **from Busulfex label (PDL 2006)** **Dose Adjustment Based on Therapeutic Drug Monitoring** Instructions for measuring the AUC of busulfan at dose 1 (see **Blood Sample Collection for AUC Determination**), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125 µM•min), are provided below. Adjusted dose (mg) = Actual Dose (mg) x Target AUC (µM•min)/Actual AUC (µM•min) For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800 µM•min. for a target AUC of 1125 µM•min, the target mg dose would be: Mg dose = 11 mg x 1125 µM•min / 800 µM•min = 15.5 mg Busulfex dose adjustment may be made using this formula and instructions below. ***Blood Sample Collection for AUC Determination:*** Calculate the AUC (µM•min) based on blood samples collected at the following time points: For dose 1: 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). Actual sampling times should be recorded. For doses other than dose 1: Pre-infusion (baseline), 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). AUC calculations based on fewer than the three specified samples may result in inaccurate AUC determinations. For each scheduled blood sample, collect one to three mL of blood into heparinized (Na or Li heparin) Vacutainer® tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within one hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at -20°C. All plasma samples are to be sent in a frozen state (i.e., on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations. **Calculation of AUC:** BUSULFEX AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula: Dose 1 $AUC_{infinity}$ Calculation: $AUC_{infinity} = AUC_{0-day} + AUC_{extrapolated}$ where AUC_{0-day} is to be estimated using the linear trapezoidal rule and AUC extrapolated can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant, λ_z. The λ_z must be calculated from the terminal elimination phase of the busulfan concentration vs. time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC. If the AUC is assessed subsequent to Dose 1, steady-state AUC_{ss} (AUC_{0-day}) is to be estimated from the trough, 2 hr, 4 hr and 6 hr concentrations using the linear trapezoidal rule. ***Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring:*** An administration set with minimal residual hold up (priming) volume (1-3 mL) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment. Prime the administration set tubing with drug solution to allow accurate documentation of the start time of BUSULFEX infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), **DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING** to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hr), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the BUSULFEX infusion. When recording the BUSULFEX infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the two-hour infusion.	PDL. Busulfex Product Label http://www.ivbusulfex.com/Busulfex_Marketing.Pi.8.06.pdf. 2006.
Slide 6	**Bayesian Dose Adjustment** • Well established methodology for TCI based dose prediction – Sheiner 1977 – Applied to busulphan paedatric BMT (Bleyzac 2001, Salinger 2010) • Flexible – Not affected by sampling times (provided they are accurate) – Loading dose can be different from maintenance dose • Output – Estimate of patient's clearance (CL) and dose – Any dosing interval (e.g. q6h, daily, continuous infusion) Dose mg q interval h = TargetConc (mg/L) * CL (L/h) * interval (h) 265 mg q 24 h = 0.770 mg/L * 14.3 L/h * 24 h	Sheiner LB, Rosenburg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm. 1977;5:445-79. Bleyzac N, Souillet G, Magron P, Janoly A, Martin P, Bertrand Y, et al. Improved clinical outcome of paediatric bone marrow recipients using a test dose and Bayesian pharmacokinetic individualization of busulfan dosage regimens. Bone Marrow Transplant. 2001;28(8):743-51.

Slide 7	**NextDose** • Collaboration Tool Recognizing Responsibility – Clinicians (age, weight, disease) – Pharmacists (formulation, dose, time) – Phlebotomists (blood sample time) – Laboratory (concentration measurement) • Extensible – Medicines – Covariates – Security	
Slide 8	**Demonstration** nextdose.org	
Slide 9	**Questions** • Practical – Number and timing of blood samples for busulphan measurement? • Clinical – Intermittent doses or continuous infusion? • Theoretical – Should doses be adjusted to achieve total treatment target AUC target or target AUC/conc after the first dose(s)?	