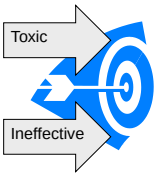
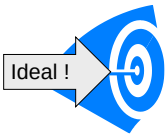
Slide 1	# TDM is Dead! # Long Live TCI! Dose Individualization using Monitoring of Patient Response Nick Holford University of Auckland 	TDM = Therapeutic Drug Monitoring TCI = Target Concentration Intervention
Slide 2	# Objectives 1) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM) 2) Appreciate how a target concentration (TC) strategy is essential for rational clinical use of medicines 3) Understand when and why individual patient monitoring can be used for dose individualization 	
Slide 3	# TDM or TCI? ➢ Therapeutic Drug Monitoring » TDM Therapeutic Range ☹ Imprecise » Sub-optimal at borders of the range  ➢ Target Concentration Intervention » TCI Single Target ☺ Accurate » Optimal – do the best you can  	Therapeutic drug monitoring (TDM) is a traditional concept associated with empirical 'seat of the pants' dose adjustment determined by a measurement being outside a 'therapeutic range'. The therapeutic range is hard to identify and is often mistakenly justified because it seems to be similar to the normal reference range for endogenous substances. A concentration at the bottom of the range has a very different meaning (close to being ineffective) from one at the top (close to being toxic) but TDM practitioners usually ignore this and are happy to do nothing as long as the concentration is 'within range'. TDM is typically limited to measuring a response such as concentration without any clear understanding that the response needs to be used to predict the required dose and to then to administer that dose. Target concentration intervention (TCI) is a science based method that uses pharmacokinetic and pharmacodynamic principles to identify how patients are different in terms of parameters such as

		CL, V, Emax and C50 and give the dose needed to reach the target. The first component of TCI is to use the individual parameters to predict the dose required to achieve the target as explained above. The second component of TCI is administer the predicted dose in order to achieve the therapeutic target. It has been shown to improve clinical outcome as well as being a cost-effective use of health resources. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998;338(8):499-505. van Lent-Evers NAEM, MathÃ´t RAA, Geus WP, van Hout BA, Vinks AATMM. Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. Ther Drug Monit. 1999;21(1):63-73. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503. Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.
Slide 4	**The Evidence - Mycophenolate** ➢ TCI » Use of TCI linked to reduced renal transplant rejection – Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs. – Le Meur 2008 (APOMYGYRE): Fixed Dose vs Target AUC ➢ TDM » Use of TDM had no effect in reducing renal transplant rejection – van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Range AUC – Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Range Trough TCI = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were not given dosing advice. 	Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503. van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation. 2008;86(8):1043-51. Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. Am J Transplant. 2009;9(7):1607-19. Rousseau A, Laroche M-L, Venisse N, Loichot-Roselmac C, Turcant A, Hoizey G, et al. Cost-Effectiveness Analysis of Individualized Mycophenolate Mofetil Dosing in Kidney Transplant Patients in the APOMYGRE Trial. Transplantation. 2010;89(10):1255-62.

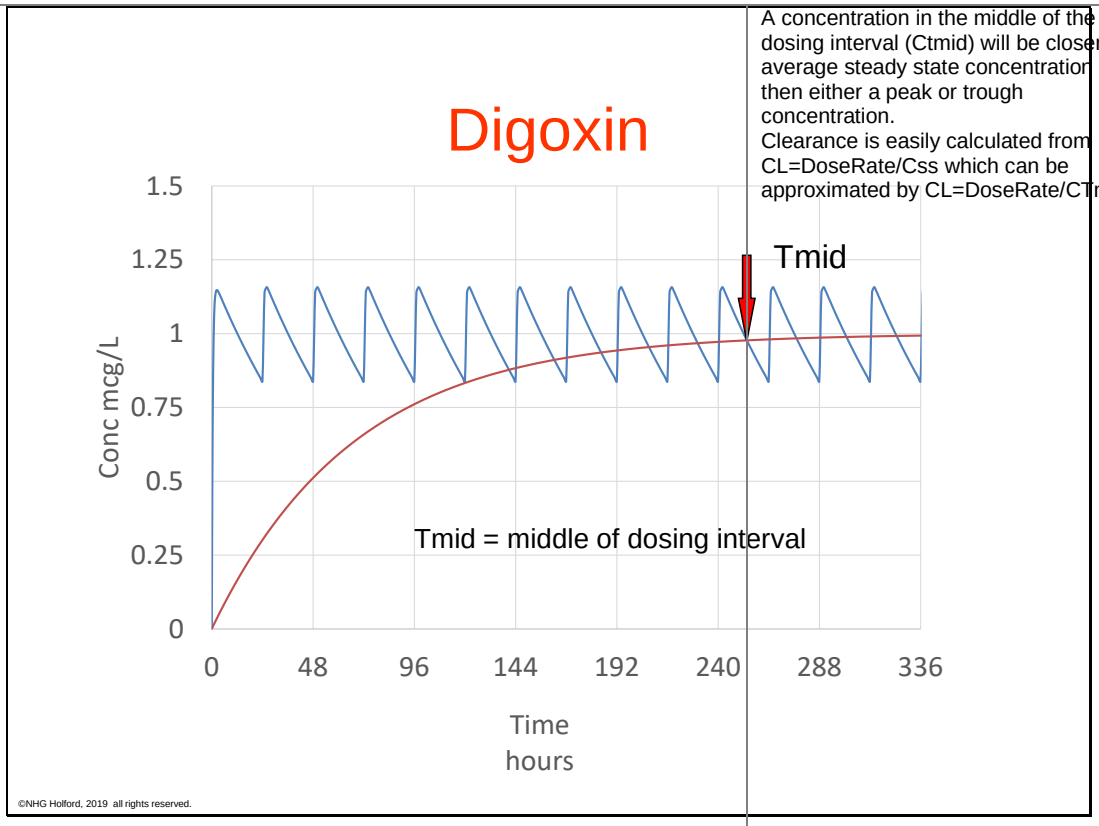
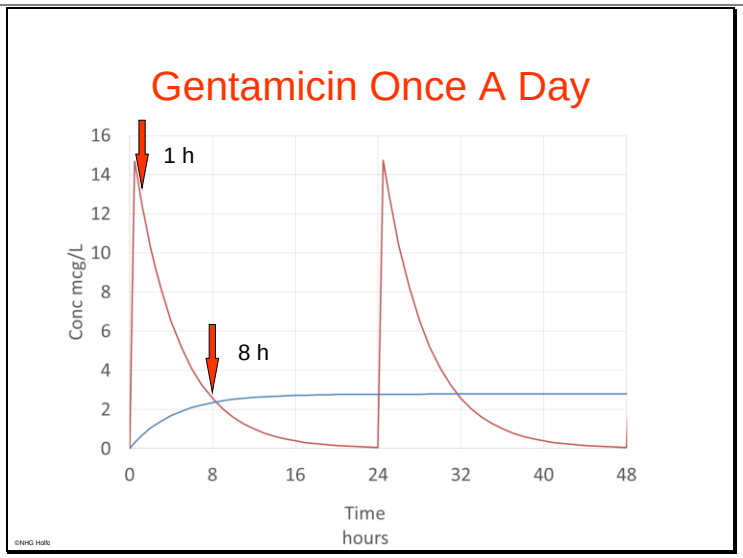
Slide 5	**The Evidence - Tacrolimus** ➢ TDM » Use of TDM had no effect in reducing renal transplant rejection – Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic range) – Anutrakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic range, more delayed graft function) TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were given dosing advice. 	Anutrakulchai S, Pongskul C, Kritmetapak K, Limwattananon C, Vannaprasaht S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol. 2019;85(9):1964-73. Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-6.
Slide 6	**Why TDM Cannot Work** ➢ TDM proposes a range of concentrations to judge if an individual is getting the right dose ➢ It is not reasonable to prescribe a range of doses in order to match the range of concentrations ➢ Therefore the therapeutic range cannot be used to get the right dose ➢ There is only one dose that can achieve the target concentration that will produce the target effect 	
Slide 7	**Target Concentration in Clinical Use of Medicines** **Target Conc = Target Effect x C50 / (Emax-Target Effect)** **Target Conc** | **Dose Model** Initial Peak | Loading Dose = **Target Conc** x **Volume of Distribution** Average Steady State | Maintenance Dose Rate = **Target Conc** x **Clearance** Ideal dose prediction requires **individual** estimates of **Emax, C50, V and CL** 	The target concentration approach links pharmacokinetics (PK) with pharmacodynamics (PD) to predict the right dose for a patient. How can the target concentration be calculated if there is no pharmacodynamic model available? Suppose the target effect for morphine is to reduce post-operative pain to an acceptably mild degree without unacceptable adverse effects. A commonly recommended dose of morphine sulfate is 5 mg repeated every 4 h according to response (New Zealand Formulary 2019). Because morphine sulfate is only 75% morphine this corresponds to a morphine dose of 3.76 mg/4h or 0.94 mg/h. The plasma clearance is about 86 L/h/70 kg (Holford, Ma et al. 2012) so the steady state target concentration is 0.94/86 = 0.011 mg/L. The steady state volume of distribution of morphine is about 350 L/70 kg so the intravenous loading dose is 350 L x 0.011 mg/L which is about 3.8 mg morphine or 5.1 mg morphine sulfate. This loading

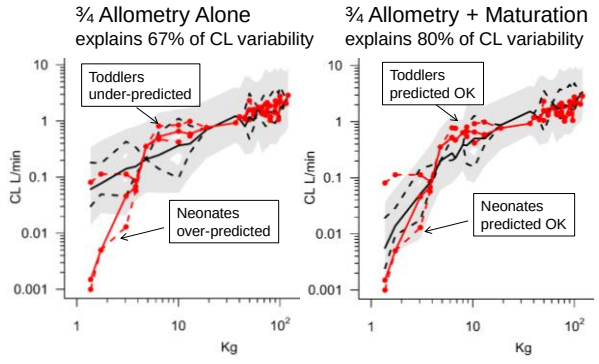
		dose is consistent with the usual starting dose of 5 mg morphine sulfate. This shows how the target concentration can be worked out based on doses that have already been worked out by trial and error. Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. Paediatr Anaesth. 2012;22(3):209-22. New Zealand Formulary. Morphine monograph https://nzf.org.nz/nzf_2515 2019
Slide 8	**Target Effects** **Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, C50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.** **Drug** / **Target Effect** / **Emax** / **C50** Aminoglycosides / "cure" / ? / ? Tacrolimus / "prevention of rejection" / ? / ? Phenytoin / "prevention of seizures" / ? / ? Digoxin / "control of atrial fibrillation" / ? / ? Theophylline / "normal PEFR" / 344 L/min / 11 mg/L Warfarin / INR 2-3 / 100% * / 1.5 mg/L • Inhibition of prothrombin complex synthesis 	The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration. Holford NHG, Black P, Briant R, Couch R, Kennedy J. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. *Clinical Pharmacokinetics* 1993; 25:495-505 Holford NHG, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial. *Clinical Pharmacokinetics* 1993; 25:506-515 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):1810-52.

Slide 9	**Target Concentrations** **Target Concentrations and Pharmacokinetic Parameters for Selected Medicines (70 kg standard individual). Css is the average steady state concentration.** | Drug | Target Conc | Clearance | Volume of distribution | | --- | --- | --- | --- | | Aminoglycosides | Peak 20 mg/L* Css 3 mg/L | 6 L/h | 18 L | | Tacrolimus** | 10 mcg/L | 20 L/h | 100 L | | Phenytoin | 10 mg/L | Vmax=415 mg/d, Km= 4mg/L | 45 L | | Digoxin | 1 ng/mL | 9 L/h | 500 L | | Theophylline | 10 mg/L | 3 L/h | 35 L | * 24 hour dosing ** whole blood standardized to haematocrit 45% 	Target concentrations and PK parameters are known for most medicines which are helped by TCI.
Slide 10	**How to Find the Target?** Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford*[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1] 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand ➢ Randomized concentration controlled trials are the gold standard 	For some drugs a so called therapeutic window of concentrations has been established by a similar trial and error approach. This range of concentrations is better thought of as an acceptable range but it does not define the target concentration. With the initial guidance of the acceptable range a clinical trial can compare potential target concentrations. This approach was used find the target concentration for starting treatment with theophylline in patients with severe airways obstruction (Holford, Black et al. 1993). Patients were randomized to targets of 10 and 20 mg/L and clinicians adjusted the dose after measuring concentrations to reach the target. This trial showed 10 mg/L was better than 20 mg/L. It produced a reasonable bronchodilator effect without serious adverse effects. The results were subsequently analyse to develop a pharmacodynamic model for theophylline(Holford, Hashimoto et al. 1993) (Holford 2017) Holford, N., P. Black, R. Couch, J. Kennedy and R. Briant (1993). "Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial." Clin Pharmacokinet **25**(6): 495-505. Holford, N., Y. Hashimoto and L. B. Sheiner (1993). "Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial." Clin Pharmacokinet **25**(6): 506-515. Holford, N. (2017). "Pharmacodynamic principles and the time course of immediate drug effects." Transl Clin Pharmacol **25**(4): 157-161.

Slide 11	**How to Dose?** **Target Concentration Strategy** 1. Choose Target Concentration 2. Determine V and CL using WT etc. 3. Calculate LD and MDR 4. Measure Response (e.g. Conc [,INR]) 5. Interpret Response Revise V and CL [,C50] 6. Goto Step 3 	The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration (Sheiner and Tozer 1978). A group value for volume (V) and or clearance (CL) is determined before the medicine is given. These PK parameters are then used to calculate the initial loading dose (LD) and maintenance dose rate (MDR). A response is measured reflecting how the individual is different from the group of patients who are otherwise similar in weight, renal function, etc. If the response is a measure of drug effect e.g. INR, then it can be used to revise the target conc. If the response is a concentration then it can be used to revise V and CL. Most commonly the focus will be on CL so that a new individualized maintenance dose rate can be calculated. Sheiner, L. and T. Tozer (1978). Clinical pharmacokinetics: The use of plasma concentrations of drugs. *Clinical Pharmacology: Basic Principles of Therapeutics*. K. Melmon and H. Morelli. New York, Macmillan**:** 71-109
Slide 12	**Determine Group V and CL** **(predictable variability)** ➢ Volume of Distribution » size $V = V_{pop} \times WT/WT_{std}$ » body composition ➢ Clearance » size $CL = Cl_{pop} \times (WT/WT_{std})^{3/4}$ » renal function » hepatic function » concomitant drugs 	WT=patient weight WTstd=standard weight e.g. 70 kg Vpop, CLpop=population volume and clearance in a standard subject e.g. 70 kg.

Slide 13	**Calculate LD and MDR e.g. Gentamicin** ➢ LD = TC x V = 20 mg/L x 20 L = 400 mg ➢ MDR = TC x CL = 3 mg/L x 6 L/h = 18 mg/h = 400 mg/day 	
Slide 14	**When to Measure Concs?** Goal is to estimate PK e.g. CL ➢ Number of Samples » Most medicines 1 » Gentamicin 2 ➢ Timing of Sample - As soon as possible » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" 	A rational approach to measuring drug concentrations is based on using the measurement to predict pharmacokinetic parameters – most commonly clearance. The least informative time to measure concentrations is just before the next dose (the 'trough' concentration) unless this is paired with another 'peak' concentration. This is because clearance determines the average concentration. So measuring a concentration in the middle of the dosing interval will be closer to the average and therefore more useful for predicting clearance. Gentamicin concentrations vary widely in a dosing interval so two concentrations are needed to reliably estimate clearance. The sooner the sample is taken the sooner concentrations can be used to improve dosing.

Slide 15		A concentration in the middle of the dosing interval (Ctmid) will be closer to the average steady state concentration (Css) then either a peak or trough concentration. Clearance is easily calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/CTmid.
Slide 16		Gentamicin concentrations with once a day dosing vary considerably. The trough concentration at 24 h is often unmeasurable because it is below the limit of quantitation. Concentrations are best measured 1h and 8 h after the dose. In this example a dose of 240 mg was given every 24 hours. V can be approximated from the first conc (C1 ~= 13 mg/L) assuming about 15% of the dose is eliminated in 1 hour. V=0.85*Dose/C1 e.g. 0.85*240 mg/13 mg/L=15.7 L Half-life can be estimated from C1 at time T1 (1 h) and the second conc (C2 ~= 2.5 mg/L) at time T2 (8 h): K=ln(C1/C2)/(T2-T1)=ln(13/8)/(8-1)=0.236 h-1 Thalf=ln(2)/K=2.94 h CL can then be calculated: CL=V*K=3.7 L/h

Slide 17	**Why does PKPD vary?** ➢ Systematic (predictable) » Body size » Disease state (liver, kidney) » Genotype » etc... ➢ Random (not predictable) » Between Subject Variability » Within Subject Variability 	
Slide 18	**Predictable Variability Size and Maturation**  Original data from Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75. 	Propofol is a commonly used intravenous anaesthetic whose dose is largely predictable from weight and age (Figure 1). This figure shows observed clearance values (red) over a wide range of weight and ages. Predictions of clearance based only in weight (allometry) or weight combined with age (maturation) show that upto 80% of variation in clearance is predictable and this can be used to work out the infusion rate of propofol. The plasma clearance of propofol in a 70 kg adult is about 2 L/min or 120 L/h and the target concentration is 5 mg/L so the required infusion rate is 600 mg/h. Holford NHG. Target concentration intervention - can we hit the targets? 6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects; Noordwijkerhout. LACDR; 2010. Original data from Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75.

Slide 19

Differences Remain Even After Accounting for Obvious Features

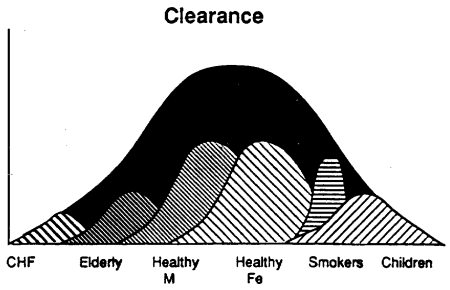


Figure originally drawn by Dr N.Sambol CDDS/SUMC1997

It shows the frequency distribution of clearance (expressed per kg body weight) for a medicine eliminated largely by metabolism with the distribution of clearance in specific sub-populations. Despite the use of weight, sex, age, disease, concomitant medications there remains a substantial variability of clearance within each sub-population. This remaining variability is what TCI can reduce. The limiting variability for the benefit of TCI is within subject variability.

Theophylline is metabolized by CYP1A2. This enzyme is induced by polycyclic hydrocarbons in cigarette smoke. Enzyme induction reduces variability because there is a maximum biological limit on the extent of enzyme induction.

Note that the naïve per kg method of scaling leads to an apparent higher clearance in children but in fact the clearance in children is the same as adults when scaled based on allometric theory (Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.)

Slide 20

Unexplained Clearance Variability

Drug	BSV_U %	WSV_U %	Source
Metoprolol	53	35	Lunn (1997)
Fenoterol	12	16	Bouillon (1996)
Riluzole	51	28	Bruno (1997)
Felodipine	34	33	Wade (1995)
Drug A	57	29	Karlsson (1993)
Drug B	35	19	Karlsson (1993)
Drug B	33	19	Jonsson (1996)
Moxonidine	22	15	Karlsson (1998)
Artemisinin	48	53	Sidhu (1998)
Average	**41**	**30**	

BSV_U=Between Subject **WSV_U=Within Subject**

Slide 21	**Safe and Effective Variability** ➢ CLINICAL JUDGMENT Suppose medicine use is safe and effective if: 1. Individual Css is on average at the Target Conc – Aim for the optimum target 2. 90% of the time Css is within 80%-125% of Target Conc – 'acceptable range' with optimum target ➢ STATISTICS Assume log-normal distribution for Css 90% of Css must lie within ± 1.64 x SD – Therefore SD must be 0.136 The Safe and Effective Variability (SEV) is 13.6% 	
Slide 22	**The Acceptable Range** ➢ Target Concentration Intervention proposes an acceptable range. ➢ This is similar to the therapeutic range but is applied at the level of the population not the individual. ➢ The acceptable range is used to decide on a dosing strategy for the population in order to determine the acceptable dose individualization method. 	The concept of an acceptable range for the population was first described in Matthews et al. 2004. It was subsequently explained in more detail in Holford & Buclin (2012). In order to avoid confusion with the therapeutic range used with TDM it is preferable to use the term acceptable range. Matthews I, Kirkpatrick C, Holford N. Quantitative justification for target concentration intervention--parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. Br J Clin Pharmacol. 2004;58(1):8-19. Holford NHG, Buclin TMD. Safe and effective variaality - A criterion for dose individualization. Ther Drug Monit. 2012;34(5):565-8.
Slide 23	**Three Ways to Dose** ➢ Population » Same dose for everyone – The dream dosing method! (often used in adults) ➢ Group (Covariate guided) » Same dose for similar group – e.g. same weight, CLcr, genotype (usually used for children) ➢ Individual » Dose determined by individual response – e.g. BP, INR, blood conc 	There are 3 ways to think about choosing the dose. The population dosing method uses the same dose for everyone. It is the most commonly used method but usually just for convenience. This means that some patients are either under-dosed or over-dosed. The group dosing method uses patient factors (also known as covariates) to predict the dose suitable for a group of patients with similar factors. Dosing in children is nearly always based on weight or age. The use of weight or renal function to adjust the dose is recommended for some medicines but probably not used as often as it should be. Individual dosing based on patient response is widely used when the response is easily measured. For example anti-hypertensive doses are usually adjusted based on the blood pressure response. The use of other response markers such as the international normalized ratio (INR) response to warfarin or the concentration of an

		antibiotic such as gentamicin are also examples. CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.
Slide 24	**Dosing Individualization Method Depends on Safe and Effective Variability (SEV)** Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3 PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5 BSV_P=sqrt(PPV_{total}^2 – BSV_u^2)=0.57 **SEV** / **Method Criteria** / **Example** / **Dosing Strategy** 0.9 / SEV>PPV_{total} / **0.9>0.7** / Population dosing 0.55 / PPV_{total} > SEV SEV>PPV_u / 0.7>0.55 **0.55>0.5** / Group dosing (WT, CLcr, etc) (BSV_P ⇨ 0) 0.35 / PPV_u > SEV SEV>WSV_u / 0.5>0.35 **0.35>0.3** / Individual response dosing (TCI) (BSV_U ⇨ 0) Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68 ©NHG Holford, 2019 all rights reserved.	
Slide 25	**Safe and Effective Variability (SEV) Aminoglycosides** **PPV_U** / **BSV_U** / **WSV_U** 0.33 / 0.30 / 0.13 ➢ Suggested Therapeutic Success Criterion 90% of Concs Within 80%-125% of Target Css ∴ SEV is 0.136 (log normal SD) ➢ Unpredictable PPV_U is 0.33 and is > SEV ∴ Covariate (WT, CLcr) prediction alone will be inadequate ➢ Unpredictable WSV_U is 0.13 and is < SEV (just!) ∴ TCI can achieve safe and effective target Matthews I, Kirkpatrick C, Holford NHG. Quantitative justification for target concentration intervention - Parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. British Journal of Clinical Pharmacology 2004;58(1):8-19 ©NHG Holford, 2019 all rights reserved.	

Slide 26	# Know Your Target Be Courageous ➢ Target for drug development is to learn » **the concentration effect relationship** » **safe and effective variability** ➢ Target for clinical practice is to confirm » **Target effect and target concentration** » **Best method for achieving the target effect for the patient** ➢ PKPD provides the tools to achieve the targets » **time to move away from traditional empirical approaches**. » **drug developers and clinicians must have courage to change** ➢ **Take Aim and Hit the Target!** 	