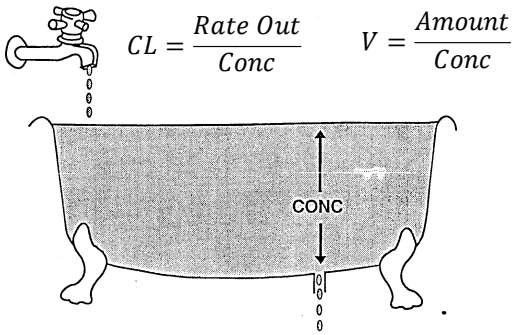
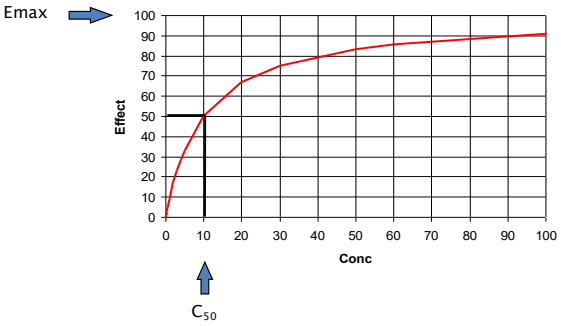
Slide 1	# Concentration Guided Dosing Nick Holford MBChB, FRACP Dept Pharmacology & Clinical Pharmacology University of Auckland	
Slide 2	 ## Clinical Pharmacology Pharmacokinetics Pharmacodynamics CL V Emax C50 Dose ← Concentration Effect **Concentration Guided Dosing** Auckland Pharmacometrics Group Copyright N.Holford 2026	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50). Effects do not determine the dose. The effect is determined by concentration. Concentration determines the dose needed for the effect. Thus concentration guided dosing provides the scientific basis for achieving the right dose.

Slide 3	 **Clearance & Volume**  Auckland Pharmacometrics Group Copyright N.Holford 2026	http://clinpharmacol.fmhs.auckland.ac.nz/docs/clearance.pdf The bathtub provides a physical model to explain how clearance determines drug elimination. This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time). Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state). Clearance is determined by the size of the hole in the bathtub.
Slide 4	 **Emax & C50**  Auckland Pharmacometrics Group Copyright N.Holford 2026	http://clinpharmacol.fmhs.auckland.ac.nz/docs/immediate-time-course-of-drug-effect.pdf http://clinpharmacol.fmhs.auckland.ac.nz/docs/ligand-binding.pdf Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the C50 will be the same as the Kd (the equilibrium binding constant). Notice that Emax can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the C50 only reaches 90% of Emax.
Slide 5	 **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, Volume and Clearance** Auckland Pharmacometrics Group Copyright N.Holford 2026	The target concentration approach links PKPD to prediction of the right dose for a patient.

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History of terminology and applicatons related to CGD

Term	Origin and Use
TDM Therapeutic Drug Monitoring	1960. TDM is the process of sampling, measurement and reporting to clinicians, typically without providing specific dosing advice (Buchthal, Svensmark et al. 1960).
TCS Target Concentration Strategy	1978. TCS provided the foundation for target concentration intervention with dosing based on a therapeutic window approach (Sheiner and Tozer 1978).
Bayesian Modelling Method	1982. First proposed use of Bayesian modelling for individualized dosing (Sheiner and Beal 1982).
TCI Target Concentration Intervention	1999. TCI is based on PKPD principles to calculate a target dose iteratively to reach a single target concentration or biomarker value (Holford 1999).
CGD+TCI Dosing Tool	2012. Collaborative web-based tool, Bayesian PKPD, target concentration intervention dosing approach (Holford, Turkistani et al. 2012).
MIPD Model-informed Precision Dosing	2016. The term was borrowed from precision medicine (Darwich, Ogungbenro et al. 2017). Despite the name, typically does not specify the dosing approach.
TDM Therapeutic Drug Management	2017. The term implies that the clinician takes an active role in proposing an adequate dose following the monitoring process (Jelliffe and Neely 2017). The word "management" highlights the clinician's involvement, similar to "intervention" in the TCI approach.

Holford, N. and Z. Petric (2025). "The Rational Basis for Personalized Treatment Using Concentration-Guided Dosing." Therapeutic Drug Monitoring **47(6): 705-712.**

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Buchthal, F., O. Svensmark and P. J. Schiller (1960). "Clinical and electroencephalographic correlations with serum levels of diphenylhydanotin." Arch Neurol 2: 624-630." Archives of Neurology **2: 624–630.**

Sheiner, L. B. and T. N. Tozer (1978). Clinical pharmacokinetics: The use of plasma concentrations of drugs. *Clinical Pharmacology: Basic Principles of Therapeutics. K. L. Melmon and H. F. Morelli. New York, Macmillan: **71–109.***

Sheiner, L. and S. Beal (1982). "Bayesian Individualization of pharmacokinetics: Simple implementation and comparison with Non-Bayesian Methods." J Pharm Sci **71(1344-48).**

Holford, N. H. (1999). "Target concentration intervention: beyond Y2K." Br J Clin Pharmacol **48(1): 9–13.**

Holford, S. D., A. Turkistani, H. Madhavaram and N. H. G. Holford (2012). "NextDose - A web based collaborative tool for dose individualisation." PAGANZ http://www.paganz.org/abstract/1295 **Accessed 13 Septl 2025.**

Darwich, A. S., K. Ogungbenro, A. A. Vinks, J. R. Powell, J.-L. Reny, N. Marsousi, Y. Daali, D. Fairman, J. Cook, L. J. Lesko, J. S. McCune, C. A. J. Knibbe, S. N. de Wildt, J. S. Leeder, M. Neely, A. F. Zuppa, P. Vicini, L. Aarons, T. N. Johnson, J. Boiani and A. Rostami-Hodjegan (2017). "Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future." Clinical Pharmacology & Therapeutics **101(5): 646–656.**

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Holford, N. and Z. Petric (2025). "The Rational Basis for Personalized Treatment Using Concentration-Guided Dosing." Therapeutic Drug Monitoring **47(6): 705–712.**

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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 (usually used for children), CLcr, genotype
- Individual
  - Dose determined by individual response
    - e.g. BP, INR, blood conc

Holford, N. H. G. and T. M. D. Buclin (2012). "Safe and effective variability – A criterion for dose individualization." Therapeutic Drug Monitoring **34(5): 565–568.**

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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, N. H. G. and T. M. D. Buclin (2012). "Safe and effective variability - A criterion for dose individualization." Therapeutic Drug Monitoring **34(5): 565–568.**

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.

Slide 8

Two Approaches to Dosing

- Therapeutic Window Approach
  - Range of concentrations within a "window" are used to decide whether to change the dose
- Target Concentration Approach
  - A single, optimal target concentration is used to adjust the dose to achieve the target

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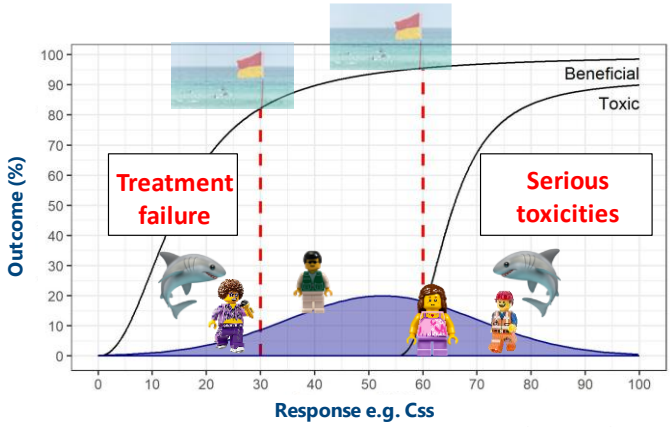
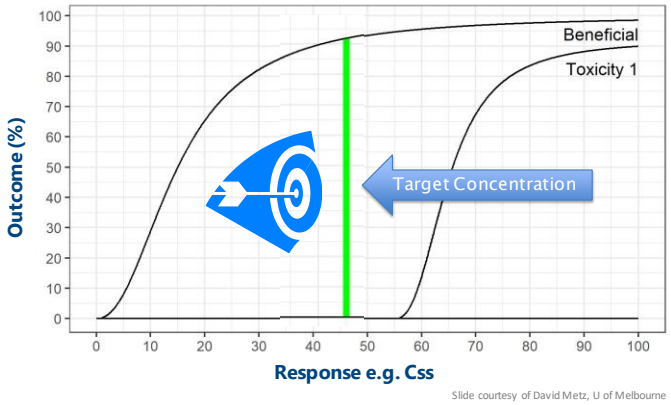
Therapeutic Window



Slide courtesy of David Metz, U of Melbourne

Slide 10

Target Concentration

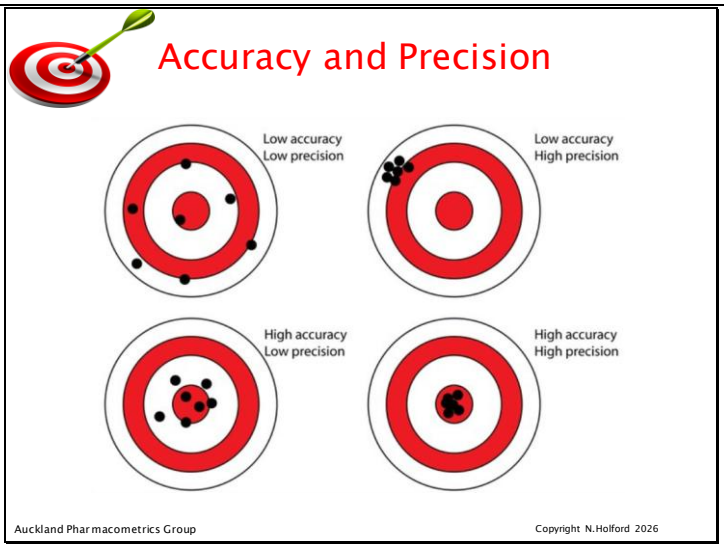
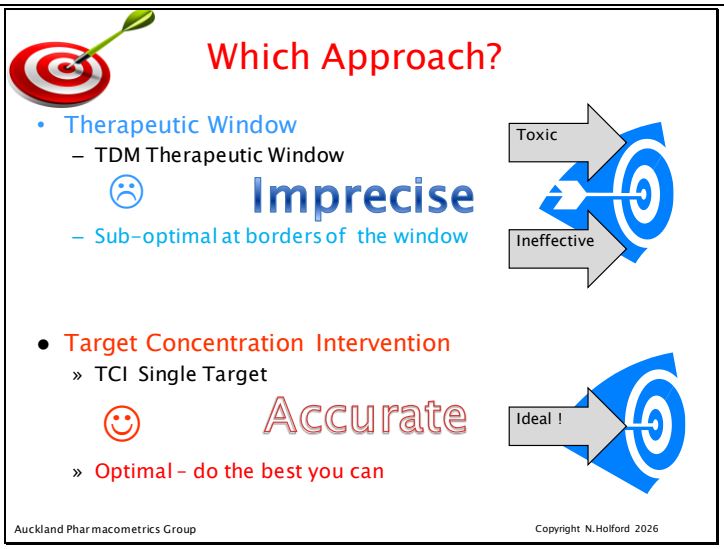


Slide courtesy of David Metz, U of Melbourne

We can be more accurate and precise if we remove the flags and aim for a specific target. In the target concentration intervention approach, every measurement is used to guide dose adjustment to achieve a target concentration a measure which is correlated with improved outcomes.

As described previously, maintenance dose rate is related to the target concentration and clearance. Therefore, if we know the clearance for an individual, then the maintenance dose rate is known.

The target concentration intervention approach provides a method to link target concentration with dose. This means that the clinician is provided a proposed dose that will achieve the target.

Slide 11		Note the difference between precision and accuracy. It is possible to have group shots at a target so that they are close together and thus precise – but not at the centre of the target. An accurate group of shots will be centred on the target. The term "precision dosing' is not the same as "accurate dosing". That is why target concentration intervention is a better description of individualized dosing method than precision dosing. Figure from: https://www.researchgate.net/publication/304674901_Digital_Close-Range_Photogrammetry_-_A_Modern_Method_to_Document_Forensic_Mass_Graves/figures?lo=1
Slide 12		http://clinpharmacol.fmhs.auckland.ac.nz/docs/target-concentration-intervention.pdf Note the difference between precision and accuracy. It is possible to have group shots at a target so that they are close together and thus precise – but not at the centre of the target. An accurate group of shots will be centred on the target. The term "precision dosing' is not the same as "accurate dosing". That is why target concentration intervention is a better description of individualized dosing method than precision dosing.

Slide 13	 **Why TWA Cannot Work** • TWA proposes a range of concentrations to judge if an individual is getting the right dose • It is not practical to prescribe a range of doses in order to match the range of concentrations • Therefore the therapeutic window 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 Auckland Pharmacometrics Group Copyright N.Holford 2026	
Slide 14	 **TWA - Tacrolimus** • TWA – Use of TWA had no effect in reducing renal transplant rejection • Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic window) • Anutrakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic window, more delayed graft function) TWA = goal was to reach exposure within therapeutic range in every patient. Clinicians were given dosing advice. Auckland Pharmacometrics Group Copyright N.Holford 2026	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 15	 **TCA vs TWA - Mycophenolate** • TCA – Use of TCA reduced renal transplant rejection • Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs. • Le Meur 2008 (APOMYGYRE): Fixed Dose vs Target AUC • TWA – Use of TWA had no effect in reducing renal transplant rejection • van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Window AUC • Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Window Trough TCA = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation. TWA = goal was to reach exposure within therapeutic range in every patient. Clinicians were not given dosing advice. Auckland Pharmacometrics Group Copyright N.Holford 2026	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 16	 TCA vs TWA – Vancomycin • 3 published studies compared TCA with historical TWA • All showed TCA achieved more patients in the therapeutic window than TWA • All showed reduced nephrotoxicity with TCA ➢ *TCA confirmed in Auckland, NZ using NextDose* TCA = goal was to reach target AUC in every patient. Clinicians were given dosing advice using Bayesian estimation. TWA = goal was to reach target trough within therapeutic window in every patient. Clinicians may have been given dosing advice (varied by study). Truong et al. Int Med J (2012), Neely et al. Antimicrob Agents Chemo (2018), Meng et al. Pharmacotherapy (2019) Auckland Pharmacometrics Group Copyright N.Holford 2026	Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(4):433-42. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Internal Medicine Journal. 2012;42(1):23-9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62(2):e02042-17.

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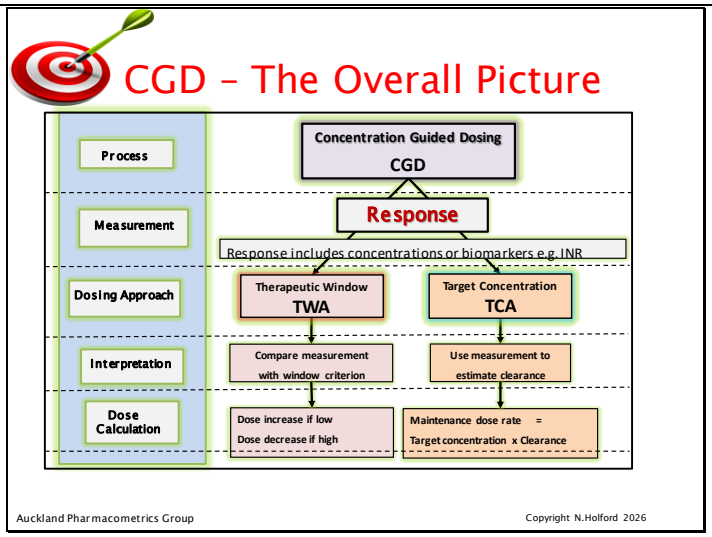

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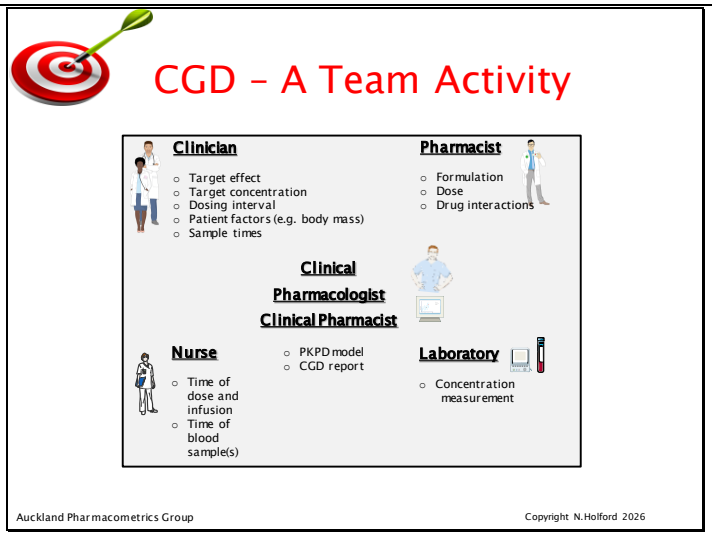

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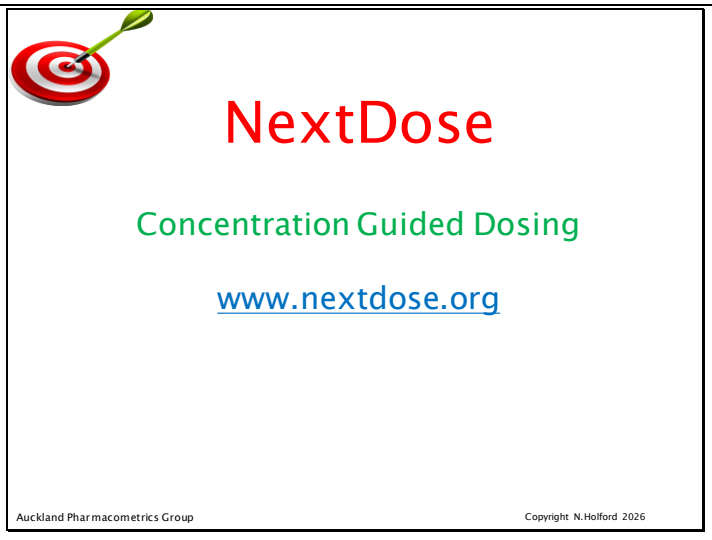

Slide 20	 ## Conclusion Received: 6 February 2020 | Revised: 28 April 2020 | Accepted: 19 May 2020 DOI: 10.1111/bcp.14434 **REVIEW-THEMED ISSUE** **TDM is dead. Long live TCI!** Nick Holford[1] | Guangda Ma[1] | David Metz[2] Holford et al Brit J Clin Pharmacol 2020 	Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020; (doi:10.1111/bcp.14434).
Slide 21	 ## Acknowledgements • Thanks to heads of department, my colleagues and students who have supported and shared this journey • Thanks to the University of Auckland for salary and computing resources 	