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Target Concentration Intervention

Dose Individualization using Monitoring of Patient Response

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Objectives

1) Appreciate how a target concentration (TC) strategy is essential for rational clinical use of medicines
2) Understand when and why individual patient monitoring can be used for dose individualization
3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)

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Target Concentration in Clinical Use of Medicines

Target Conc = Target Effect x C50 / (Emax-Target Effect)

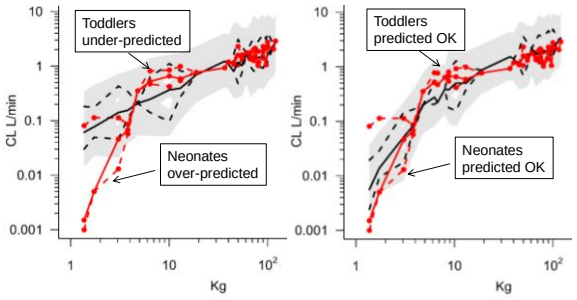
Target Conc	Dose Model
Initial Peak	Loading Dose = Target Conc x Volume of Distribution
Average Steady State	Maintenance Dose Rate = Target Conc x Clearance

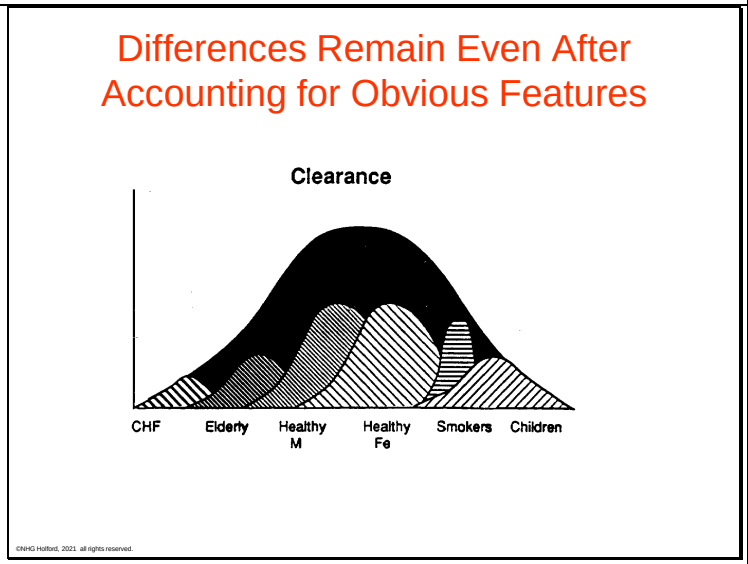
Ideal dose prediction requires **individual** estimates of **Emax, C50, V and CL**

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 4		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). Hale et al (1998) and Shaffer et al (2002) are examples of TCI trials used to determine the exposure-response relationship. 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. 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. Shaffer CL, Gal P, Ransom JL, Carlos RQ, Smith MS, Davey AM, et al. Effect of age and birth weight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. Crit Care Med. 2002;30(2):343-8.
Slide 5	**Why does PKPD vary?** ➢ Systematic (predictable) » Body size » Disease state (liver, kidney) » Genotype » etc... ➢ Random (not predictable) » Between Subject Variability » Within Subject Variability ©NHG Holford, 2021 all rights reserved.	
Slide 6	**Predictable Variability Size and Maturation** ¾ Allometry Alone explains 67% of CL variability ¾ Allometry + Maturation explains 80% of CL variability  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. ©NHG Holford, 2021 all rights reserved.	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 7		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 8	**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 9	**Which Drugs for TCI?** 1. Usefulness is hard to measure (drug is working when the clinical outcome is not easily observable) » Anti-arrhythmics e.g. lignocaine » Anti-convulsants e.g. phenytoin » Anti-coagulants e.g. warfarin 2. Big unpredictable variability (after using weight, renal function,etc) and small within subject variability » Too much variability means either inadequate beneficial effect or too much adverse effect » Observing patient response can predict future dose needs 	The first reason for using TCI is when the effect of treatment on the desired outcome cannot be easily measured. Cardiac anti-arrhythmic drugs and brain anti-arrhythmic drugs (anti-convulsants) may be having a useful effect but often arrythmias (heart or brain) occur only intermittently so it hard by direct observation to know if they are effective. TCI can be used here to ensure that drug concentration, a surrogate for anti-arrhythmic effect, is at a target which is known to be effective in most people. The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce between subject variability enough. Group based dosing removes the predictable component of between subject variability but the remaining unpredictable component may still be too large for the medicine to be used safely and effectively. This is where the use of individual patient response can further reduce variability and improve the probability of patients being within

		a acceptable range around the target concentration. Eventually a limit is reached attributable to within subject variability that cannot be influenced by TCI.
Slide 10		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

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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**	7 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

Target concentrations and PK parameters are known for most medicines which are helped by TCI.

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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

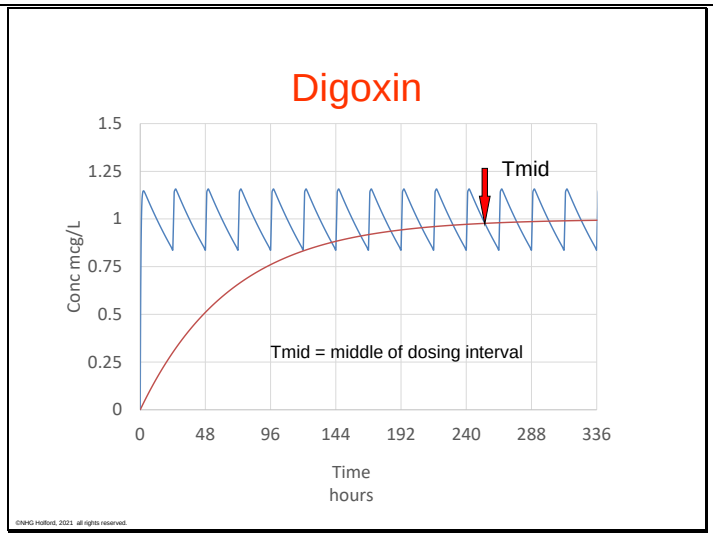
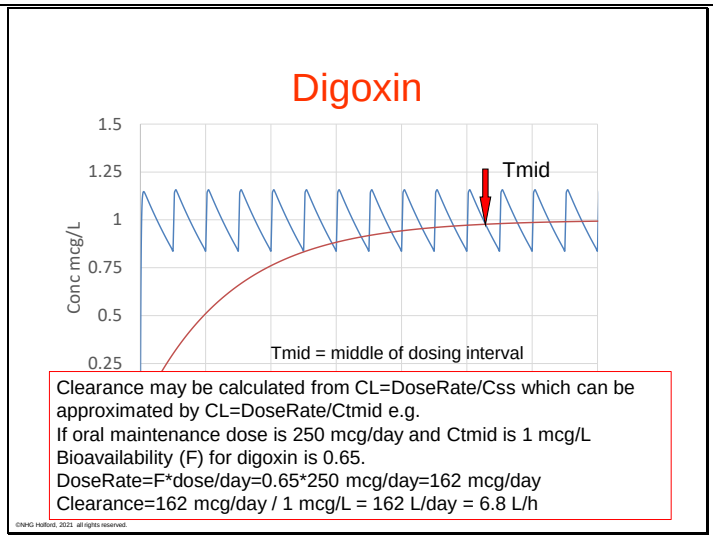
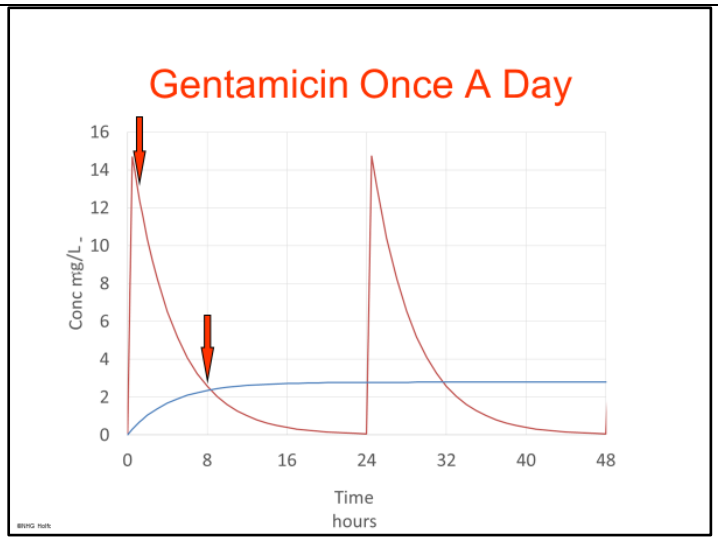
The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.

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 13	**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 14	**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 15	**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 16		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.
Slide 17	 Clearance may be calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/Ctmid e.g. If oral maintenance dose is 250 mcg/day and Ctmid is 1 mcg/L Bioavailability (F) for digoxin is 0.65. DoseRate=F*dose/day=0.65*250 mcg/day=162 mcg/day Clearance=162 mcg/day / 1 mcg/L = 162 L/day = 6.8 L/h	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.
Slide 18		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

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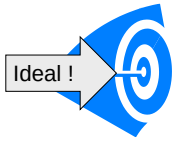
TDM or TCI?

- Therapeutic Drug Monitoring
  - » TDM Therapeutic Window
  - ☹ 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 window 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 window 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 the window'. 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. Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020; doi:10.1111/bcp.14434
Slide 20	**Principles of TDM and TCI** Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020; doi:10.1111/bcp.14434 	
Slide 21	**Assessment Short Answer Question Examples** 1. Define what is meant by a target concentration. 2. Give an example of a medicine and the response used for individual patient monitoring and dose individualization. 3. List the principles of target concentration intervention which distinguish it from therapeutic drug monitoring. 	

Principle	TDM	TCI
Has a single target	TDM does not have a target. It provides a range ("therapeutic window") that does not directly lead to a suitable dose.	TCI has a single target. The target can be used easily to calculate a suitable dose.
Uses PKPD principles	TDM only provides a measured concentration.	TCI uses PKPD principles to estimate individual parameters which can then be used to calculate a suitable dose.
Provides guidance to the clinician for the next dose	TDM does not provide guidance except through a "therapeutic" window which cannot be used to calculate a suitable dose. Dose adjustments are often empirical, rather than based on quantitative pharmacological rationale.	TCI uses the target and individual parameters such as clearance to recommend to the clinician a suitable dose.