Slide 1

PKPD Variability

Quantifying Variability to aid Dose Individualization

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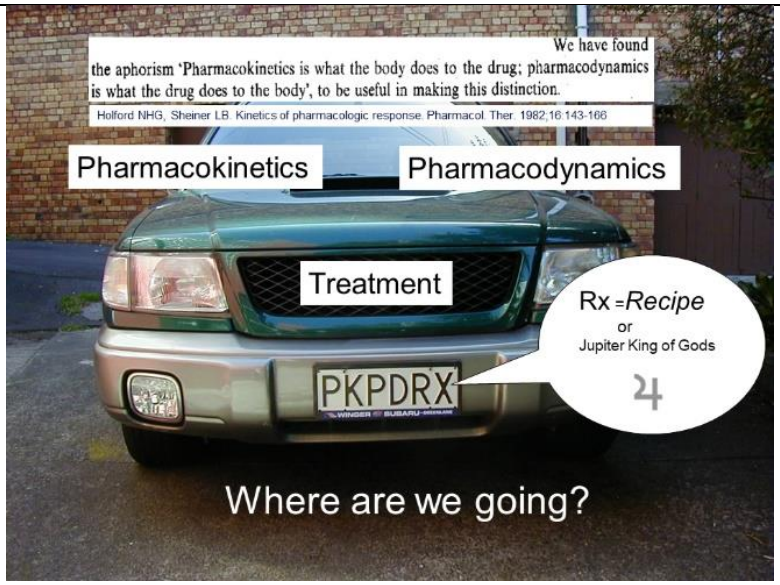
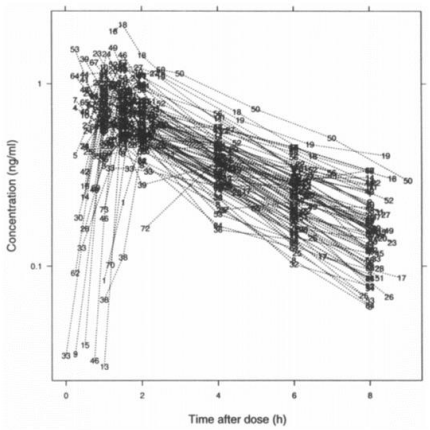
Slide 2

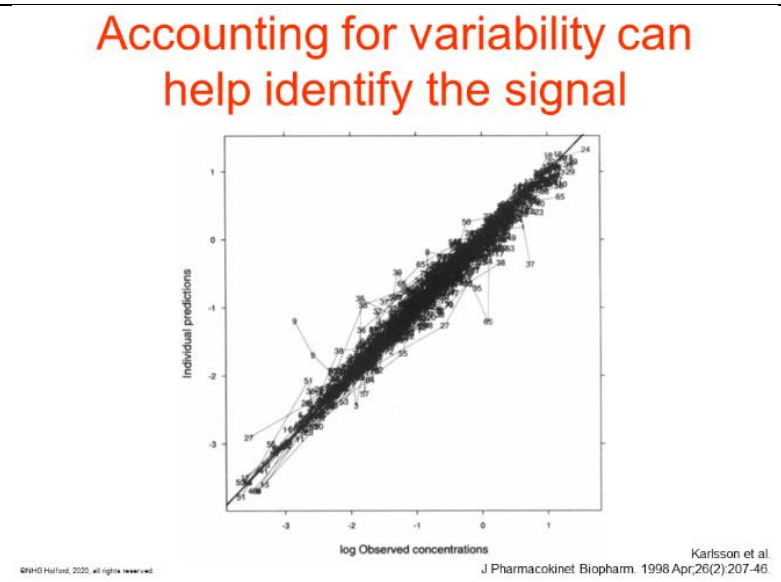
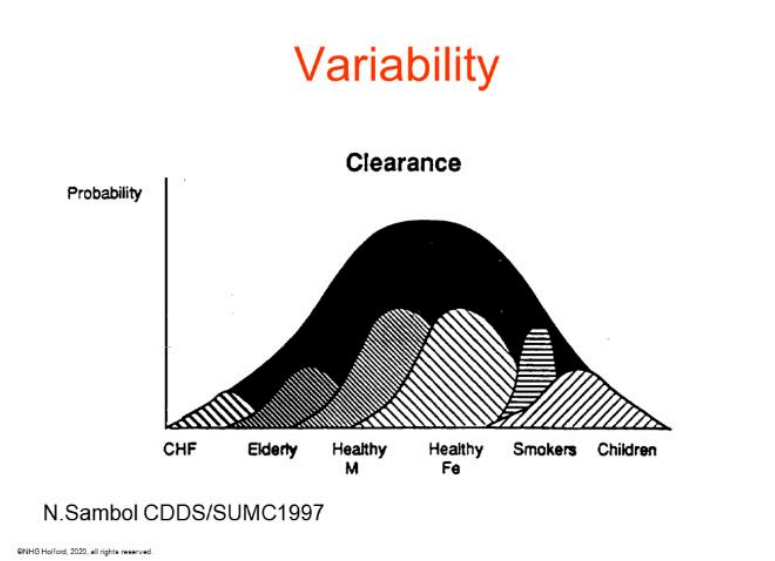
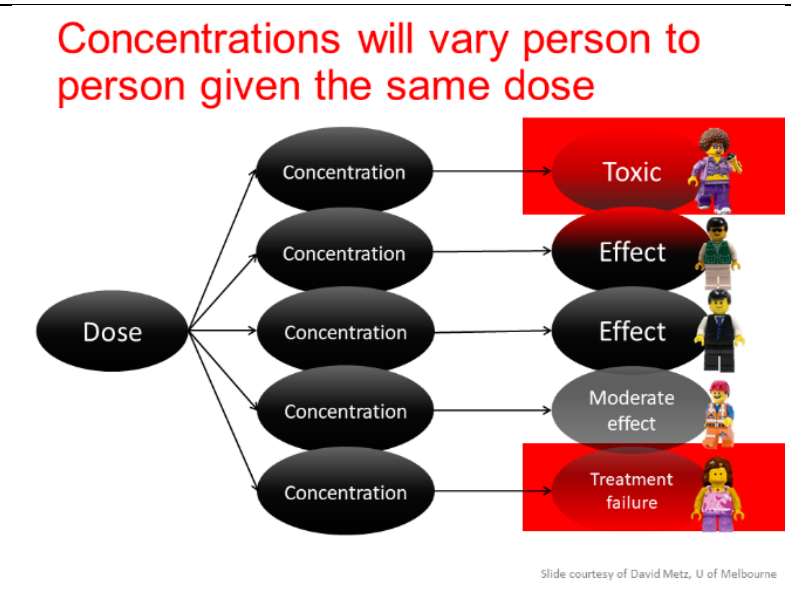


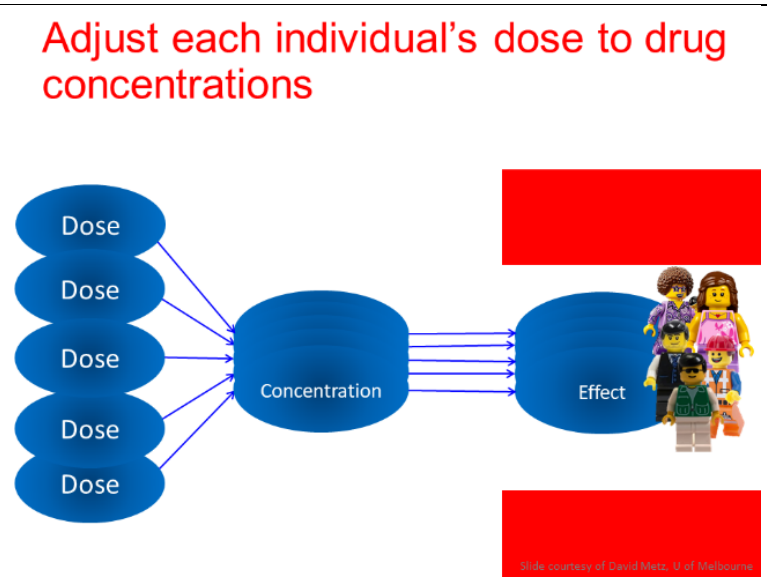
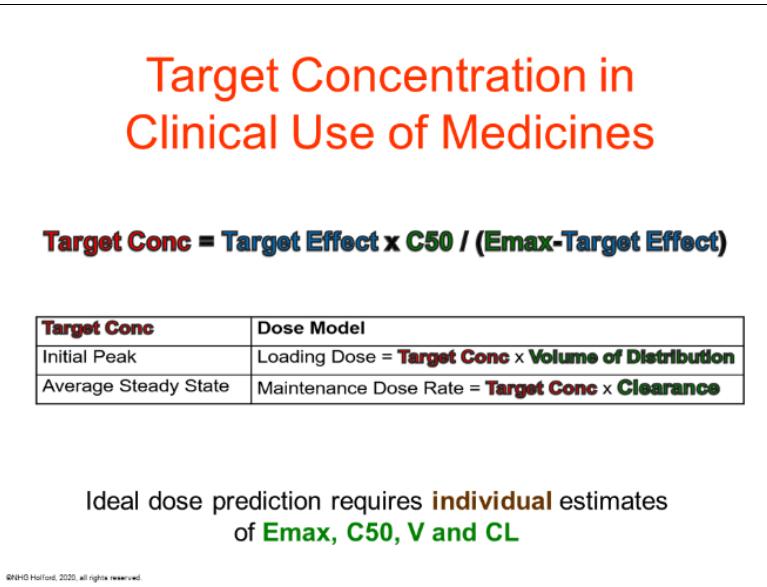
Slide 3

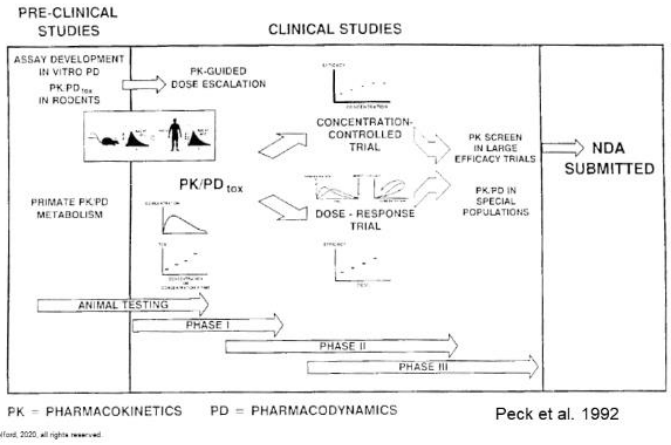
Objectives

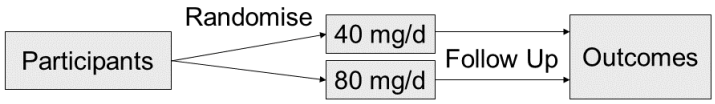
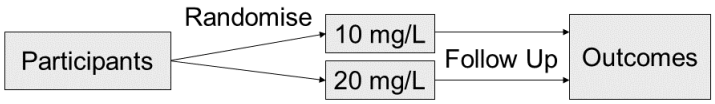
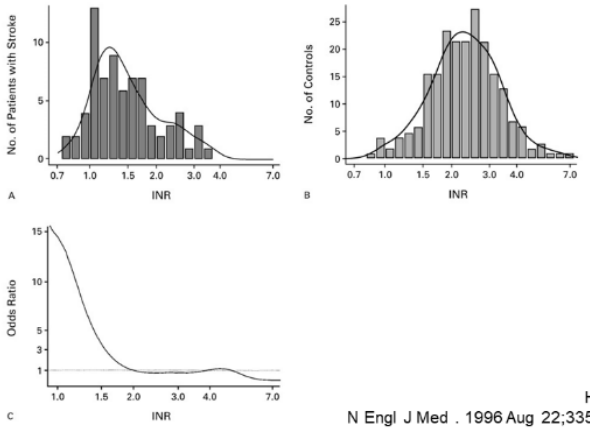
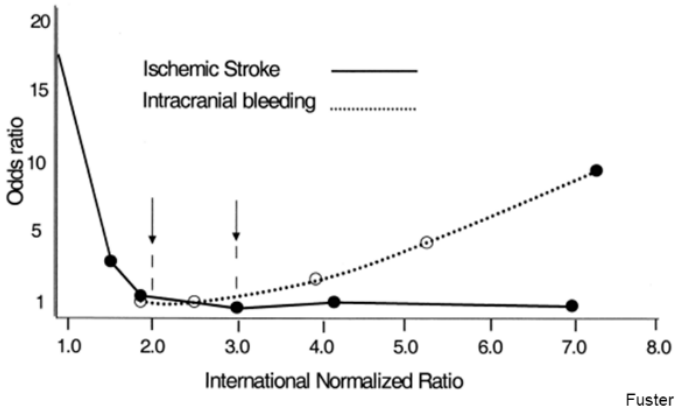
1) Learn about the sources of variability in clinical pharmacology
2) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use
3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)
4) Understand how to make rational choices for dose individualization

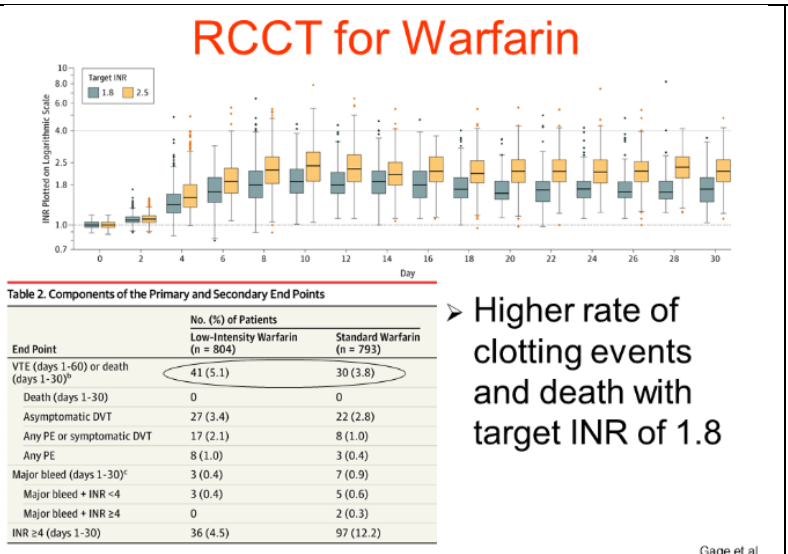
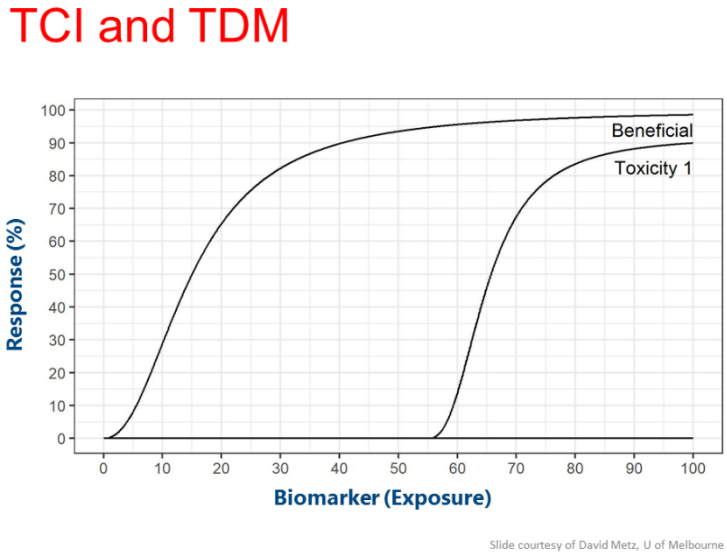
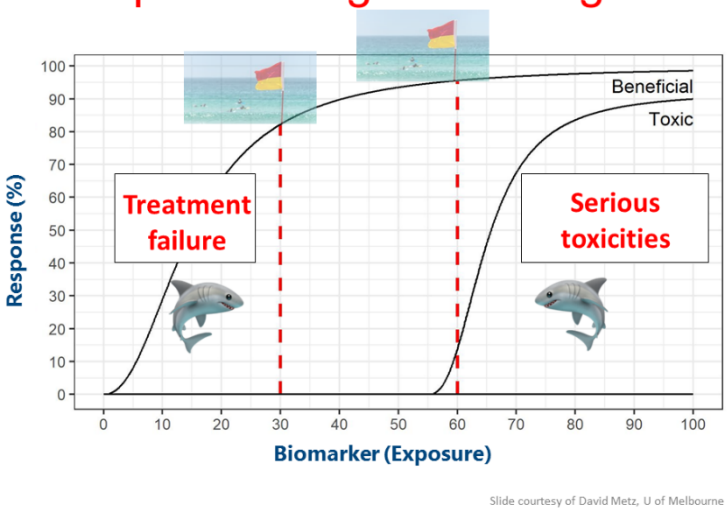
Slide 4	# Coursework Assignment Critical review of a New Zealand medicine data sheet ➢ The essay should discuss the overall scope and content of the data sheet. ➢ It must also include a specific focus on the application of the target concentration approach to dose individualization and recommendations for improving the information given to clinicians and patients. 	
Slide 5	# Clinical Pharmacology Pharmacokinetics Pharmacodynamics CL V Emax C50 Dose Concentration Effect 	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. A fundamental principle of clinical pharmacology is that drug effects are caused by drug concentrations—not drug doses. Drug concentration is not as easily observable as doses or 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). Individual differences in the dose–effect relationship can be understood in terms of the PK parameters (CL, V) and the PD parameters (Emax, C50) for both therapeutic and toxic effects.
Slide 6	# Clinical Data is Messy  Karlsson et al. J Pharmacokinet Biopharm. 1998 Apr;26(2):207-46. 	This example illustrates the variability in time course of concentration following a dose.

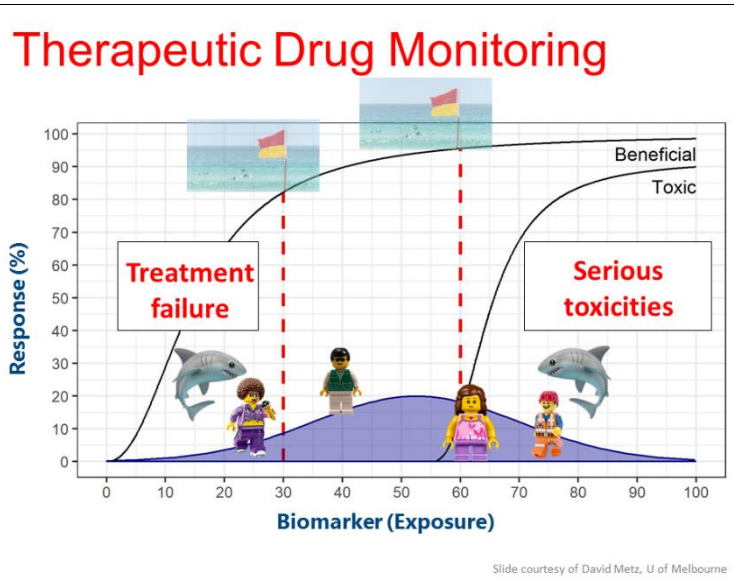
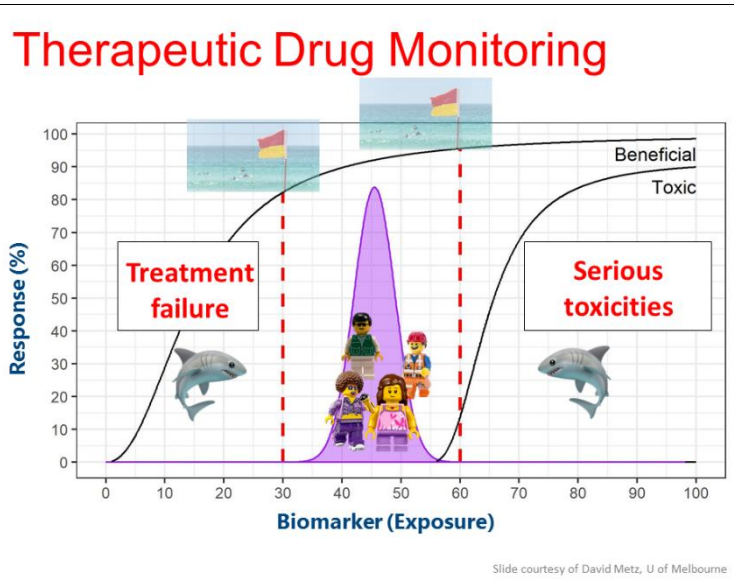
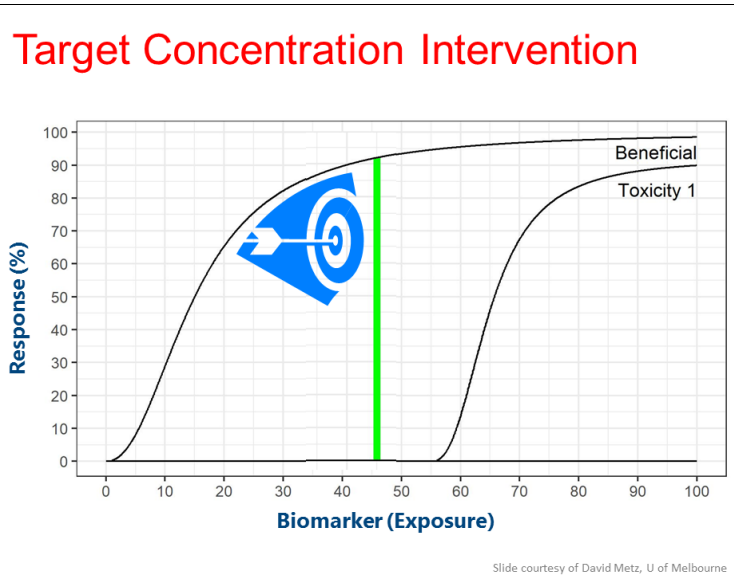
Slide 7		By accounting for sources of variability we an predict PK or PD such that our predictions line up with our observations. We aim to account for sources of variability such that our treatment is rational, safe and effective for our patient. We live in an age of personalised medicine. We recognise that patients are not identical, but rather they differ in how they respond to dose.
Slide 8		This graph shows the frequency distribution of clearance. Despite the use of patient factors (e.g. sex, age) there remains a substantial variability of clearance within each sub-population. We might be able to identify and quantify some of the factors that influence clearance in the population. Nevertheless, differences will remain even after accounting for obvious features; the black area of the graph shows that some of the variability in clearance can't be adequately described.
Slide 9		Personalised therapy should involve selection of a suitable medicine to treat the disease, and selection of the right dose. In the clinic if we give everyone the same dose, we can expect concentration to vary from person to person. This will lead to toxicity for some, failure for others. This is what we think about as a therapeutic or acceptable window.

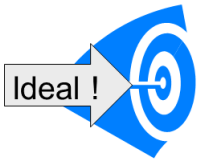
Slide 10		A better approach is to adjust each individuals dose to achieve the same concentration. This maximises the opportunity of being in acceptable range. Therapeutic drug monitoring and target concentration intervention are two ways of dose individualisation.
Slide 11		The target concentration approach links PKPD to prediction of the right dose for a patient. All drug effects are linked to concentration and that link is defined by a PD model. The Emax model is widely used: Effect=Emax×Conc/(C50+Conc). This can be rearranged to predict the target concentration required to achieve the target effect. The loading dose and maintenance dose rates needed to achieve the target concentration depend upon the volume of distribution or clearance in the patient. If Emax and C50 and Target Effect are not known then the Target Conc may be estimated: Target Conc = Typical Average Daily Dose/Typical Clearance The choice of target effect is always a balance between therapeutic benefit and toxicity and this requires clinical judgement along with comprehensive knowledge of the properties of the medicine. Further Reading Holford NH. Target concentration intervention: beyond Y2K. Br J Clin Pharmacol. 1999 Jul;48(1):9-13. Holford NH. Pharmacodynamic principles and target concentration intervention. Transl Clin Pharmacol. 2018 Dec; 26(4): 150–154.

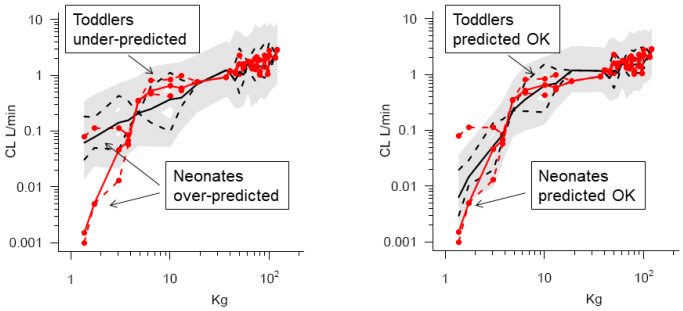
Slide 12	# Target Concentration ## Drug Development and Clinical Use ➢ Effective drug development needs a plan » A good plan has a clear objective » Target Concentration provides a clear objective in all phases of drug development ➢ TC is the rational basis for dose individualization » Choose the target effect to determine the TC » Use TC to predict individual dose Holford NHG. The target concentration approach to clinical drug development. Clin Pharmacokinet. 1995;29(5):287-91. 	
Slide 13	# Target Concentration in Drug Development  	The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients. Further Reading Peck et al. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. J Clin Pharmacol. 1994 Feb;34(2):111-9.
Slide 14	# 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 	When we need to dose individualise, we should choose a target concentration to achieve a target effect, and this target concentration guides dose individualisation. Now we want to think about how can we find the target?

Slide 15	# Randomised Controlled Trial Designs ➢ RDCT – Randomise to Dose Group  ➢ RCCT – Randomise to Concentration Group  	In a randomised dose controlled trial (RDCT) participants are randomised to different groups and followed up over a period of time. In a randomised concentration controlled trial (RCCT) participants are randomised to different target concentrations and followed up over a period of time. We believe that achievement of a target concentration will be associated with improved outcome. A RCCT allows us to learn and confirm whether a proposed target concentration is optimal. It is up to the clinician to determine the most appropriate dose to achieve the target concentration. In contrast to empirical dose adjustment, the target concentration intervention provides a method to link dose to concentration. See Sanathanan LP, Peck CC. The randomized concentration-controlled trial: an evaluation of its sample size efficiency. Control Clin Trials. 1991 Dec;12(6):780-94.
Slide 16	# Finding the target using Observational Data  Hylek et al. N Engl J Med . 1996 Aug 22;335(8):540-6.	Experimental study designs can often be resource intensive (eg, due to the number of patients, duration of follow-up, economic costs). Observational study designs can help find a target concentration using existing data. This example illustrates the odds of stroke relative to INR for patients with atrial fibrillation taking warfarin for stroke prevention. The top graphs show the distribution of INR (a measure of anticoagulation) among patients treated with warfarin who experienced a stroke, and among warfarin patients who did not experience a stroke (controls). The bottom graph presents the odds ratio (calculated using data from the top two graphs), and shows that the odds of stroke decreases as the INR approaches two; further increasing INR does not reduce the odds of a stroke while on warfarin.
Slide 17	# Finding the target using Observational Data  Fuster et al. Circulation 2001 Oct 23;104(17):2118-50.	Conversely we also need to balance treatment benefit (the reduced stroke risk), with the risk of treatment harm (increased bleeding risk due to warfarin over-anticoagulation). This data suggests that an INR of 2.5 to be a good balance, though a lower INR (1.8) may also be acceptable.

Slide 18		Experimental studies can be used to confirm what is learnt from observational data. This is an RCCT which examines whether a target INR of 1.8 would be better than 2.5; participants were randomised to a target INR of 1.8 (n=804) or 2.5 (n=793). The trial results in the table show that targeting a lower INR (1.8) was associated with marginally higher rates of clotting events or death (5.1 v 3.8%). A target INR of 2.5 was not associated with a drastically higher rate of major bleeds (0.4 v 0.9%). This data confirms the appropriateness of a target INR of 2.5
Slide 19		Up to this point we have discussed the concept that are strategies available to help us individualise dose. We now focus our attention on differentiating between a target concentration intervention and therapeutic drug monitoring approach to dose individualisation. Let us consider the exposure response curve for benefit and that for toxicity; for simplicity, we only have one curve for toxicity though in reality there may many (different) curves for toxicity.
Slide 20		In the therapeutic drug monitoring approach we consider a toxic limit and a treatment failure limit. Analogous to swimming between the flags.

Slide 21		In the clinic patients will have exposure within, at the limit of, and outside the acceptable range. They will be distributed within and across the therapeutic window. The therapeutic drug monitoring approach, assumes, that all our patients sit within the flags. This assumption is not correct.
Slide 22		The second fallacy of TDM is what is done with a concentration measurement; what should be the magnitude of the dose change given a measured concentration? What should we do if the measurement is just inside or outside the acceptable range (e.g. 28 or 31 in this example)? Furthermore this approach assumes that there is a range of doses which match the acceptable range of concentrations. The maintenance dose rate is related to the target concentration and clearance. Clearance will time with time, but is constant at a single point in time. The target concentration can only be achieved by a single maintenance dose. It is not possible to have a range of targets (e.g. 28 to 31) as this will require a range of maintenance dose rates.
Slide 23		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. Target concentration intervention also 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 24	# TDM or TCI ➢ Therapeutic Drug Monitoring » Relies upon the therapeutic range concept » Concentrations are stratified into sub-therapeutic, acceptable, or toxic » Considers concentrations at the top and bottom of the acceptable window to be the same » Assumes that there is a range of doses which match the acceptable range of concentrations – There is only one dose that can achieve the target concentration that will produce the target effect – The therapeutic range cannot be used to get the right dose 	
Slide 25	# TDM or TCI ➢ Target Concentration Intervention » Aims for a specific concentration » Dose adjustments focus on an optimal point of balance between benefit and toxicity » Dose can be calculated from the target concentration 	
Slide 26	# 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  	TDM is imprecise and sub-optimal at the borders of the range. TCI is more accurate and provides a plan to do the best that we can. Further reading Holford NHG. Target concentration intervention: beyond Y2K. Br J Clin Pharmacol. 1999 Jul; 48(1): 9–13. Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020 Jun 16.doi: 10.1111/bcp.14434. Online ahead of print.

Slide 27	# Why does PKPD vary? ➢ Systematic (predictable) » Body size » Disease state (liver, kidney) » Genotype » etc... ➢ Random (not predictable) » Between Subject Variability » Within Subject Variability 	Some sources of variability are predictable, and some are not. Further reading Holford NH. Pharmacodynamic principles and target concentration intervention. Transl Clin Pharmacol. 2018 Dec; 26(4): 150–154. Holford N. Pharmacokinetic variability due to environmental differences. Transl Clin Pharmacol. 2017 Jun; 25(2): 59–62.
Slide 28	# 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. 	This example demonstrates how accounting for predictable sources of variability, in this example size and age, can help explain some of the variability in clearance of propofol. These plots are visual predictive checks. These plot a summary of the observed data against data simulated from a model which we believe describes the clearance of propofol. The solid red line is the median of the observations and dashed red lines indicate the 90th percentiles of the observations. The solid black line is the median of the simulated data, whereas the dashed black line indicate the 90th percentiles of the simulated data. The shaded areas (not important in this example) describe the 95% confidence intervals associated with the percentiles. The left graph is generated using a model with only considers size (weight). It can be seen that in neonates the model (black lines) over-predict clearance compared to the observed data (red lines). Likewise for toddlers, the model under-predicts clearance. Overall by only considering weight alone, 67% of clearance variability is predictable. The right graph considers both size and maturation (age). It can be seen that the model predicted lines (black) are much closer to that observed. By taking both size and maturation into consideration, more of the variability in clearance can be explained.

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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**

While patient factors explain some of the variability in PKPD parameters, there will always remain some variability that cannot be predicted (unexplained).

One component of unexplained variability is variability between subjects (BSV). Another component that of unexplained variability is within subject variability (WSV); for example clearance may be different from one dosing interval to another.

The table illustrates that the unexplainable, (random) component of variability differs by medicine.

Note unexplained between subject variability (BSV_U) and unexplained within subject variability (WSV_U) are expressed as a percentage of an apparent co-efficient of variation.

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Three Ways to Dose

- Population
  - » Same dose for everyone
    - – The dream dosing method!
- Group (Covariate guided)
  - » Same dose for similar group
    - – e.g. same weight, CLcr, genotype
- Individual
  - » Dose determined by individual response
    - – e.g. BP, INR, blood conc

Since the predictable and random (unpredictable) sources of variability will be different for each medicine, we now can examine whether a criterion can be used to help us determine whether or not we need to dose individualize a medicine. Before we can consider this criterion, we first need to consider the different dosing strategies as well as identify/describe the different sources of variability.

The simplest method is a population dose - the same dose for everyone. It is commonly used due to its convenience. By treating everyone as though they were the same, it ignores differences between patients. This means that some patients are either under-dosed or over-dosed.

We may also stratify/group patients based upon covariates. The same dose is used for patents with similar characteristics

Doses may also be individualized according to individual response. For example based upon blood pressure.

We can also consider our dosing strategies for initial and subsequent dosing. For initial dosing (e.g. when the patient is started on a treatment), we can use either the population or group based dosing strategy, subsequently once we can measure how the patient responds to the treatment and adjust the dose based on the individual response; alternatively subsequent dosing is not based on individual response and the dose is continued on the population or group based dosing strategy.

Slide 31

Three Ways to Dose

In TCI: MDR = CL x TC

- Population CL
- Group CL
  - » e.g. CL_{GRP} = CL_{POP} x Size x Maturation
- Individual
  - » e.g. $CL_{individual}$ (influenced by CL_{GRP} and measured concentration)

We can also consider these three strategies in the context of target concentration intervention. Recall that we can describe MDR using CL and TC.

In population dosing we assume that there is no variability in clearance, that is, clearance is the same in everyone. We can think of the population clearance (CL_{POP}) as the typical value in the population.

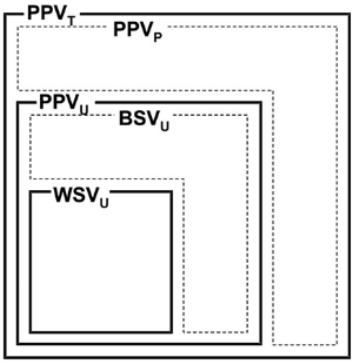
In group guided dosing, the population CL is adjusted according to patient specific factors which we know can account for variability. Therefore the clearance in each group is the same, but clearance will be differ amongst groups.

Measured concentration (or other biomarker) tells us how the individual patient is different from other patients in the group. Therefore we may further individualize clearance by starting at CL_{GRP} and adjust this according to the individual response, leading to an individualized estimate of clearance ($CL_{individual}$).

Slide 32

Identifying Variability

- **PPV_P**=Population Parameter Variability that is predictable
- **BSV_P**=Between Subject Variability that is predictable
- **PPV_U**=Population Parameter Variability that is unexplained
- **BSV_U**=Between Subject Variability that is unpredictable
- **WSV_U**=Within Subject Variability that is unpredictable



Holford NHG, Buclin TMD. Ther Drug Monit 2012; 34: 565-68

PPV_{Total} describes the total variability from predictable and unexplained sources.

At any given dose rate, steady-state average concentrations are determined by the variability in the pharmacokinetic parameters (e.g. clearance). This variability is called population parameter variability (PPV).

The total variability (PPV_T) can be broken down into predictable (PPV_P) and unpredictable (PPV_U) variability.

Some of the variability that is predictable (PPV_P) is BSV (BSV_P not shown in figure). For propofol, size and maturation predict some of the BSV in clearance.

PPV_U in consists of 2 components. Seemingly random between-subject variability (BSV_U) which is unpredictable from covariates and describes the variability of the individual's average parameter across subjects. Unpredictable within-subject variability (WSV_U). Some values for BSV_U and WSV_U were shown in the previous slide.

Slide 33

Safe and Effective Variability

- CLINICAL JUDGMENT
  Suppose medicine use is safe and effective if:
  1. Individual C_{ss} is on average at the Target Conc
     – Aim for the optimum target
  2. 90% of the time C_{ss} is within 80%-125% of Target Conc
     – 'therapeutic 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%

Suppose we determine a medicine is safe and effective if the individual steady state concentration typically lies a the target concentration. If our tolerance of risk and benefit requires us to have treatment with 90% of the population having Css measurements within 80-125% of the target, then we have a SEV of 13.6%.

Css = Average steady state concentration
SD = Standard Deviation
SEV=Safe and Effect Variability around target concentration

Further Reading
Holford NHG, Buclin T. Safe and effective variability-a criterion for dose individualization. Ther Drug Monit. 2012 Oct;34(5):565-8.

Slide 34

Dosing Individualization Method Depends on SEV

- SEV > PPV_T
  - » Population dosing (same dose for all)
- PPV_T > SEV > PPV_U
  - » Group dosing (i.e. based on covariates)
- PPV_U > SEV > WSV_U
  - » Target concentration intervention
- SEV < WSV_U
  - » Safe & effective dosing is impossible

Holford NHG, Buclin TMD. Ther Drug Monit 2012; 34: 565-68

Quantification of PPV_T, PPV_U, and WSV allows the use of SEV as a quantitative criterion to decide on a dose individualisation method.

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Dosing Individualization Method Depends on 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)

Note: If SEV<WSV_u then medicine cannot be used safely

For this example we will consider a medicine that has PPV_T of 0.7, BSV_U of 0.4, WSV_U of 0.3, PPV_U of 0.5 and BSV_P of 0.57.

If we set SEV as 0.9 then this medicine is suitable for population dosing (SEV>PPV_T), that is all patients could be given the same dose.

If SEV is set as 0.55, then this is lower than PPV_T and thus population dosing would be inadequate. As SEV is greater than PPV_U, a group based approach (e.g based on weight) would be suitable.

If SEV is set as 0.35, then a group based approach would not be adequate as SEV is less than PPV_U. As SEV is greater then WSV_U, dosing according to individual response should be considered.

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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

Using aminoglycoside antibiotics as an example.

PPV_U, BSV_U and WSV_U have been characterised as 0.33, 0.3 and 0.13 respectively. If we use an SEV criterion of 0.136, this is less than PPV_U and more than WSV_U, therefore population and covariate guided dosing alone (e.g. based sole on weight and creatinine clearance) would be inadequate, and an individualised approach (e.g. target concentration intervention) should be used.

Slide 37

Which Way to Aim?

- Phase 2 Drug Development
  - » PK and PKPD relationships (Target Effect ⟶ Target Conc)
  - » Predictable and Unpredictable variability (PPV_T)
  - » Between (BSV_U) and within subject (WSV_U)
- Phase 3 Drug Development
  - » Safe and effective variability (SEV)
  - » The BIG difficulty is deciding on SEV !
- Clinical Use of Medicines
  - » Use quantitative criteria to decide on dosing method
    - » Covariate Dosing if PPV_T>SEV>PPV_U
    - » TCI Dosing if PPV_U>SEV>WSV_U

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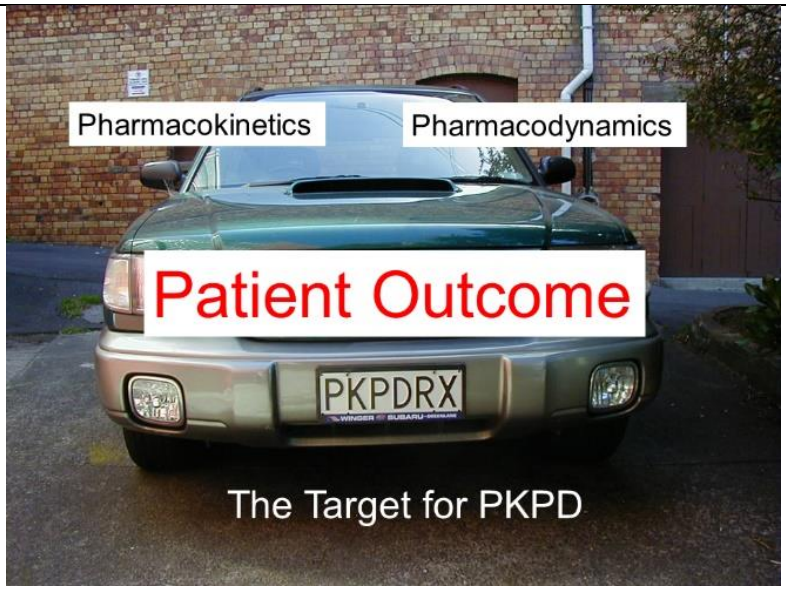

The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect

Slide 39

Why TCI?

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

- How can a target concentration of 10 mg/L be achieved and maintained?

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Which Drugs for TCI?

1. Effect is hard to measure (drug is working when the response is not observable)
   - » Anti-arrhythmics e.g. lignocaine
   - » Anti-convulsants e.g. phenytoin
   - » Anti-coagulants e.g. warfarin
2. Big unpredictable variability (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 uses a response, such as BP, as a substitute for being able to measure the clinical disease state that is being treated. When the medicine is working well or it is not working at all the clinical disease state may appear to be the same. It is assumed that trying to reach a typical response that is usually associated with benefit is better than giving everyone the same dose.

The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce the between subject variability so that the medicine can be used safely and effectively. TCI can only work however if the within subject variability (that cannot be influenced by TCI) is small enough so that dose individualization is really predictive for future use of the medicine in the same patient.

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How?
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. INR)
   Revise Target Conc
5. Measure Concs
   Revise V and CL
6. Goto Step 3

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration based on pharmacodynamic studies. A group value for volume (V) and or clearance (CL) can be 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, genotype, 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.

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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
Ciclosporin**	150 ng/mL	17 L/h	245 L
Phenytoin	10 mg/L	Vmax=415 mg/d, Km= 4mg/L	45 L
Digoxin	2 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.

Slide 43

Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, EC50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.

Drug	Target Effect	Emax	EC50
Aminoglycosides	"cure"	?	?
Cyclosporine	"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

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Determine Group V and CL

- 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.

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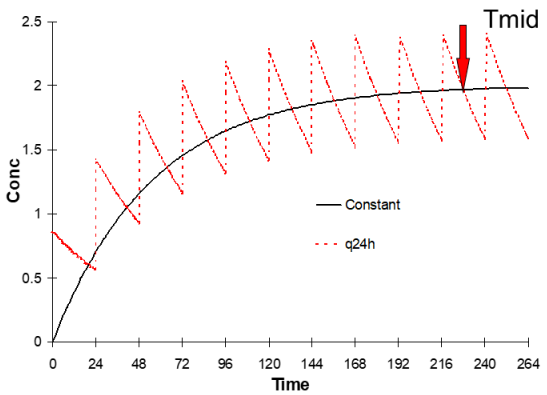
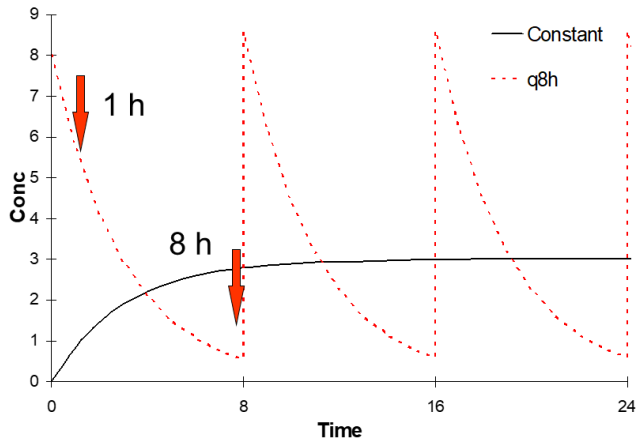
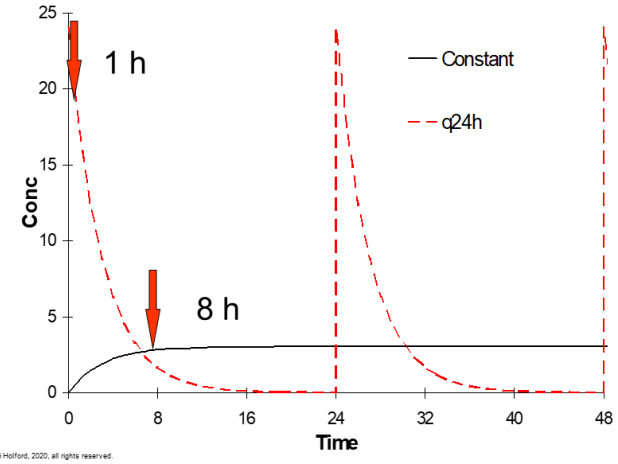
Calculate LD and MDR e.g. gentamicin

- 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

Slide 46	**When to Measure Concs?** **Goal is to estimate PK e.g. CL** ➢ Number of Samples » Most medicines 1 » Gentamicin 2 ➢ Timing of Sample » 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.
Slide 47	**When to Measure Concs?** **Goal is to estimate PK e.g. CL** ➢ Number of Samples » Most medicines 1 » Gentamicin 2 ➢ Timing of Sample » 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.
Slide 48	**Digoxin**  Tmid = middle of dosing interval 	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 49	# Gentamicin TDS  	
Slide 50	# Gentamicin OD  	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.
Slide 51	# References Bouillon T, Meineke I, Port R, Hildebrandt R, Günther K, Gundert-Remy, U. Concentration-effect relationship of the positive chronotropic and hypokalaemic effects of fenoterol in healthy women of childbearing age. Eur J Clin Pharmacol 1996;51:153-160. Bruno R, Vivier N, Le Libouix A, Powe LK, Delumeau JC, Rhodes GR. Population pharmacokinetics of riluzole in patients with amuyotrophic lateral sclerosis. Clin Pharmacol Ther 1997;62:518-526. Holford NHG, Tett S. Therapeutic Drug Monitoring. Chapter in Avery's Drug Treatment (4th Edition) Eds. Speight T, Holford NHG. 1997; Adis Intl, Auckland Holford NHG. Target Concentration Intervention: Beyond Y2K. British Journal Clinical Pharmacology 1999; 48: 9-13 Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020;Early View(doi:10.1111/bcp.14434). Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68 Jonsson EN, Wade JR, Karlsson MO. Comparison of some practical sampling strategies for population pharmacokinetic studies. J Pharmacokin Biopharm 1996;24:245-263. Karlsson MO and Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. J Pharmacokinet Biopharm 1993;21:735-750 Karlsson MO, Jonsson EN, Wilste CG, Wade JR. Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. J Pharmacokin Biopharm 1998;26:207-246. Lunn DJ and Aarons LJ. Markov Chain Monte Carlo techniques for studying interoccasion and intersubject variability: application to pharmacokinetics data. Appl Statist 1997;46:73-91 Sidhu JS, Ashton M et al. Artemisinin population pharmacokinetics in children and adults with uncomplicated falciparum malaria. Br J Clin Pharmacol 1998;45:347-354 Wade JR, Sambol NC. Felodipine population dose-response and concentration-response relationships in patients with essential hypertension. Clin Pharmacol Ther 57, 569-81, 1995 	