

## REVIEW-THEMED ISSUE

# TDM is dead. Long live TCI!

Nick Holford<sup>1</sup>  | Guangda Ma<sup>1</sup>  | David Metz<sup>2</sup> 

<sup>1</sup>Department of Pharmacology & Clinical Pharmacology, University of Auckland, Auckland, New Zealand

<sup>2</sup>Department of Pediatrics, University of Melbourne, Melbourne, Victoria, Australia

### Correspondence

Professor Nick Holford, Dept Pharmacology & Clinical Pharmacology, 85 Park Road, Auckland 1042, New Zealand.

Email: n.holford@auckland.ac.nz

Twenty years ago, target concentration intervention (TCI) was distinguished from therapeutic drug monitoring (TDM). It was proposed that TCI would bring more clinical benefit because of the precision of the approach and the ability to link TCI to principles of pharmacokinetics and pharmacodynamics to predict the dose required by an individual (1). We examine the theory and clinical trial evidence supporting the benefits of TCI over TDM and conclude that in the digital age TDM should be abandoned and replaced by TCI.

## 1 | INTRODUCTION

“Target concentration intervention (TCI) is proposed as an alternative conceptual strategy to therapeutic drug monitoring (TDM). It is argued that the idea of a therapeutic range has limited the interpretation of measured drug concentrations and diminished the anticipated clinical benefit to patients by use of an oversimplified pharmacodynamic model. TCI on the other hand embraces pharmacokinetic and pharmacodynamic concepts and uses the idea of a target effect and associated target concentration to make rational individual dose decisions.” Holford (1999)<sup>1</sup>

Just over 20 years ago target concentration intervention (TCI) was distinguished from therapeutic drug monitoring (TDM).<sup>1</sup> Both TCI and TDM can be considered as approaches to concentration-controlled dosing (CCD) of individual patients (Table 1). This commentary focuses on how these approaches differ in achieving individualized dosing. The distinguishing principles of the TDM and TCI approaches continue today but the clinical importance of understanding why TCI is superior to TDM is still not widely recognized. This review will describe the principles and clinical trial results that show that the TDM approach is often ineffective or inferior, and the benefits that arise from understanding and applying the TCI approach.

## 2 | PRINCIPLES OF THERAPEUTIC DRUG MONITORING

In 2020 the most widespread definition of TDM still focuses on the *measurement* of concentrations of medicines:

“*Therapeutic drug monitoring* (TDM) is a branch of clinical chemistry and clinical pharmacology that specializes in the measurement of medication concentrations in blood”.<sup>2</sup>

The rationale for TDM and what is done with the measurements is linked to the concept of a therapeutic window.

“The *therapeutic window* (or pharmaceutical window) of a drug is the range of drug dosages which can treat disease effectively without having toxic effects”. The Wikipedia description of the therapeutic window defines it as a “range of doses” (not concentration) and rather naively defines this window as “[effective] treatment without toxic effects” as if this was true across the whole window.<sup>3</sup>

The term “therapeutic window” is also commonly referred to as the therapeutic range, but an important distinction should be drawn between these terms (see below).

The International Association of Therapeutic Drug Monitoring and Clinical Toxicology<sup>4</sup> provides a definition of *a posteriori* TDM that is mainly about measurement without emphasis on using these measurements to individualize dose.<sup>5</sup> Its journal, *Therapeutic Drug Monitoring*, states “The journal presents studies detailing the various factors that affect the rate and extent drugs are absorbed, metabolized, and excreted.” without mention of how these studies might be used.<sup>6</sup> Elsewhere it defines TDM as “a multi-disciplinary clinical specialty

**TABLE 1** Comparison of TDM and TCI approaches to concentration-controlled dosing

Property	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.

aimed at improving patient care by individually adjusting the dose of drugs for which clinical experience or clinical trials have shown it improves outcome in the general or special populations. TDM can be based on *a priori* pharmacogenetic, demographic and clinical information, and/or on the *a posteriori* measurement of blood concentrations of drugs (pharmacokinetic monitoring) and/or biomarkers [pharmacodynamic (PD) monitoring].<sup>7</sup> Again, the emphasis is on measurement without explicit detail on dose individualization and how this should be done.

Other statements in the published literature include:

“Therapeutic drug monitoring (TDM) can be defined as the measurement of drug in biological samples to individualise treatment by adapting drug dose to improve efficacy and/or reduce toxicity”<sup>8</sup>

“Therapeutic Drug Monitoring (TDM) – Measuring the concentration of a drug in the blood at scheduled intervals. Therapeutic drug monitoring (TDM) is used to determine the dose at which a drug will be the most safe and effective.”<sup>9</sup>

These definitions come from easily accessible, peer-moderated sources and are consistent with the way that TDM is currently

practiced and has been practiced for decades: The process of TDM typically involves three steps:

1. measuring a drug concentration in a blood sample usually taken just before the next dose<sup>10</sup>
2. comparing the measurement with a therapeutic window (which is often poorly defined<sup>11</sup>)
3. adjusting the dose based on criteria that are usually not specified but typically if the measurement is outside the window the dose is changed otherwise it is left unchanged. The dose adjustment step is rarely mentioned in articles about TDM and is implicitly left to the prescribing clinician.<sup>12</sup>

The first weakness of TDM is the lack of pharmacological rationale for the number and timing of concentration measurements. These are typically guided by previous exploratory studies without clear justification for what measurements are intended to achieve. A pharmacological rationale can be made for achieving a target steady-state concentration (or equivalent in terms of an area under the concentration time curve [AUC]). The dose rate to achieve this target is easily predicted if the drug clearance is known.

Often a trough concentration is recommended, although this may be a poor measurement time to help estimate drug clearance. In the pragmatic clinical environment, concentration measurements are often *ad hoc* and not always one dosing interval after the preceding dose.<sup>13</sup> The acceptable time window (e.g. within 1 hour of the intended time) for a concentration measurement such as a trough is rarely defined. This may mean that a measurement that is accepted as a trough in one study may not meet the acceptable time window in another study.

The second weakness of TDM is that the measured value is compared to a range of concentrations (the therapeutic window). Such an approach naïvely categorizes drug concentrations into “sub-therapeutic”, “therapeutic” and “toxic”, and incorrectly considers concentrations at the upper and lower limits of the window equivalent. Furthermore, to use a medicine, it is only possible to prescribe a specific dose. It is not practically possible to translate a range of concentrations to a single dose. Thus, the therapeutic window concept used with TDM cannot be expected to aid the clinician in prescribing the right individual dose.

The third and most important weakness of TDM is that it does not describe how to use the measured concentration to improve dosing. The failure of the TDM approach to provide an explicit link between the desired target (drug or biomarker concentration) to the dose needed to achieve the target means dose adjustments are typically *ad hoc* and empirical rather than science based. While a trial and error approach can eventually lead to attainment of the right dose for the individual, using a pharmacokinetic model to inform dose adjustments can reduce the number of cycles to attain the right dose, reducing time spent under- or overtreated.

A recent example published in this journal (reference deliberately not included) illustrates the problem with the TDM approach. A study of the drug pharmacokinetics was used to propose a

selection of exposure targets based on maximum concentration ( $C_{max}$ ) and area under the curve from 0-24 hours ( $AUC_{0-24}$ ) with variants obtained by dividing by the minimum inhibitory concentration (MIC). No pharmacological rationale is provided for these targets. The clinician does not have a target but a table of four different targets with ranges of values for each target that vary depending on the time after dose. In all there are 48 numbers suggested from which a single individual dose must be calculated and prescribed, an essentially impossible task. This illustrates the second (comparison with a range) and third (no dosing algorithm) weaknesses of TDM.

It seems that clinicians ask for drug concentration measurements to check to see if the measurement is within the therapeutic range just as they do for other analytes such as sodium or glucose, which have a reference range. If the measured value is within range, then it is considered “normal” and no further action is taken. The hallmark of TDM is a focus on the measured value, a “normal range” of measured concentrations and no patient-specific actionable rationale for dose individualization. We have used quotation marks for “normal” to indicate this is a common clinical usage (just as with other analytes) but it is an incorrect interpretation. There are of course no physiologically “normal” ranges for exogenous medicines, rather concentration targets or acceptable ranges based on clinical outcome data.

### 3 | PRINCIPLES OF TARGET CONCENTRATION INTERVENTION

The principles of TCI are as follows:

1. Define and use a *target* (eg, drug concentration or biomarker) to guide the dose required for optimal treatment.
2. Use *pharmacological principles* to predict the dose required to achieve the target.
3. Apply an *intervention* method for using individual patient measurement of response to recommend the next dose to achieve the target.

### 4 | DEFINING A TARGET

The concept of TCI is built on the idea that, following treatment with a medicine, there is a measurable explanatory variable (eg, concentration) that can act as a useful predictor of individual clinical outcome. While for some drugs a physiological measure (eg, blood pressure) may be used, the target used in TCI is typically a measure of either drug exposure in the body (eg, concentration in blood) or of drug effect, such as a pharmacodynamic biomarker on the causal path between drug concentration and clinical outcome. An example of a pharmacodynamic biomarker is the International Normalized Ratio (INR).<sup>14</sup>

The essential property of a useful TCI target is that it can be linked to drug concentration and thus to a dose which is predictable from pharmacokinetic principles. The target may be based on the desired outcome either based on empirical association or preferably on pharmacodynamic principles. The predicted dose may be a single dose but more commonly it is a maintenance dose with associated dosing interval.

#### 4.1 | What is a target?

TCI is thus based on the idea that there is a target (drug concentration or biomarker) that is associated with safe and effective treatment. It is necessarily an optimum obtained by comparing the benefits and adverse effects of treatment. For many drugs the target reflects the risk-benefit profile in the population, thus the same target is used for all patients. When there is sufficient information, the target for each individual may differ, reflecting their individual risk-benefit profile, for example the target INR for warfarin therapy when used for mechanical heart valves may be 2.5, 3 or 3.5 depending on prosthesis, thrombogenicity and patient-related risk factors.<sup>15</sup> In all cases the target is a single value, which means that a single specific dose required to achieve the target can be predicted.

#### 4.2 | Target $C_{ss}$ or AUC?

In most cases the use of TCI is to predict and use a maintenance dose with a particular dosing interval (DI) that will achieve a steady-state target exposure. Drug exposure can be described equivalently by the average steady-state concentration ( $C_{ssAVG}$ ) or by the steady-state area under the concentration-time curve over the dosing interval ( $AUC_{0-DI}$ ). Note that the numerical value of  $AUC_{0-DI}$  is dependent on the choice of dosing interval whereas  $C_{ssAVG}$  is independent of the interval. If the dosing interval is known, then these parameters are easily interconvertible ( $C_{ssAVG} = AUC_{0-DI}/DI$ ). For drugs in which the dosing interval may vary, eg, busulfan, commonly used with either 6- or 24-hour dosing intervals, the AUC value has to be clearly identified with a corresponding dosing interval although this is rarely done in a consistent fashion even in approved drug labels.<sup>16</sup> Given that the achieved exposure will be the same, it is simpler and less error prone to define the target using  $C_{ssAVG}$  and avoid the need to specify the dosing interval.

#### 4.3 | Measurement of the response

In TCI, the primary purpose of measuring the drug concentration or pharmacodynamic biomarker is to identify the parameter(s) (such as clearance) which can be used to predict the dose for the individual patient. Thus, the timing and number of samples should be chosen to optimize the estimation of these parameter(s).

#### 4.4 | Acceptable range and therapeutic window

A quantitative understanding of pharmacokinetic variability has led to the concept of safe and effective variability (SEV).<sup>17</sup> SEV describes the variation around the target concentration in terms of an acceptable range of concentration and a population goal of the percentage of patients who will have concentrations within this range when using TCI. A suggested acceptable range might be within 80-125% of the target concentration with 95% of patients within this range. This is achievable for busulfan because most PK variability is either predictable from factors such as weight and age or due to between-subject variability, which can be quantified using Bayesian dose prediction.<sup>18</sup>

The term “acceptable range” can be considered equivalent to a therapeutic range, but acceptable range is preferable to avoid confusion with therapeutic window. It is defined in terms of the population and is not used to determine the individual dose. In contrast, the therapeutic window is a TDM concept applied to an individual dosing decision.

#### 4.5 | Interpretation: using pharmacological principles

TDM interprets the measured response in relation to the therapeutic window but offers no pharmacological principles to guide dose prediction. With TCI the interpretation of a measured response (drug concentration or biomarker) is aimed at individualizing the estimates of parameters linking dose to the target response. In the simplest case, this involves estimating clearance to predict the maintenance dose rate required to achieve a target average steady-state concentration. Details of these interpretation methods are beyond the scope of this review. Following the pioneering work of Sheiner and Peck in the late 1970s the idea of using Bayesian principles to combine prior information with the measured responses has been widely implemented.

#### 4.6 | Intervention: recommending the next dose

TDM does not recommend a dose. TCI requires that the output of the interpretation method should propose the next dose (usually with a dosing interval) which is expected to achieve the target response. This leads to the intervention component of TCI. The proposed dose can then be considered by the clinician to achieve the desired clinical outcome.

### 5 | EVIDENCE THAT TCI IS BETTER THAN TDM

#### 5.1 | Vancomycin

Vancomycin is routinely used for the treatment of gram-positive bacterial infections, including methicillin-resistant species of *Staphylococcus aureus*. Over the last decade, dosing and monitoring

strategies for vancomycin therapy have evolved, with current clinical evidence supporting exposure, as measured by the 24-hour area under the concentration-time curve ( $AUC_{24}$ ), rather than trough concentration(s).<sup>19</sup>

The TCI and TDM approaches have both been used to guide vancomycin therapy. The TCI approach for vancomycin focuses on adjusting dose to achieve a stated, discrete target (eg,  $AUC_{24}$  of 400 mg/L-h, equivalent to  $C_{ssAvg}$  of 16.67 mg/L) with the aid of an explicit calculation method to determine the dose to achieve the target. Rather than focus on a discrete target, the TDM strategy focuses on maintenance of vancomycin within a therapeutic window, with dose adjustments only considered if the measurement of exposure (AUC or concentration) is outside the therapeutic window.

There have been three published studies<sup>13,20,21</sup> which have directly compared a TCI approach (where vancomycin therapy is intended to achieve a discrete target guided by an explicit dosing algorithm) to a TDM approach (aiming for a therapeutic window with or without a dosing algorithm) (Table 2). Details of the search strategy are provided in Supporting Information. All three studies examined achievement of therapeutic exposure as the primary outcome, along with nephrotoxicity, one of the most serious adverse outcomes attributable to vancomycin therapy. Whilst there was heterogeneity in the quantification of achievement, or definition of nephrotoxicity amongst these studies, all three studies reported a higher proportion of individuals achieving the target therapeutic exposure and a lower frequency of nephrotoxicity with TCI-guided therapy compared to TDM (Table 2). The findings reported by Neely et al<sup>13</sup> also suggest that TCI may reduce resource use, with a reported decrease in the length of vancomycin therapy, as well as the number of samples needed.

All three studies shared a before-after (historical control) design, with two of the three studies evaluating a shift from concentration-guided TDM to  $AUC_{24}$ -guided TCI. TDM tends to be favoured in a concentration-guided approach due to the entrenched clinical dogma of comparing concentration measurements to a therapeutic window, and only adjusting dose outside this window. In contrast, the  $AUC$ -guided approach tends to favour TCI as computational help is needed to estimate AUC, and once AUC is estimated the magnitude of dose adjustment is simply proportional to the ratio of the target AUC to the estimated AUC. The gold standard for estimation of  $AUC_{24}$  is Bayesian estimation of vancomycin clearance underpinned by a PK model appropriate for the patient population, though accurate and precise estimation of AUC may also be achieved using a closed-form PK equation.<sup>22</sup>

For vancomycin, changing to AUC-guided dosing can improve care not only by shifting towards a more rational clinical target, but also through implementation of the TCI strategy to individualize the dose to achieve the target.

#### 5.2 | Mycophenolate

The superiority of TCI over TDM has been firmly demonstrated by studies of mycophenolate mofetil (MMF) in preventing graft rejection

**TABLE 2** Summary of studies comparing TDM and TCI dosing for vancomycin

Study	Design	TDM dosing	TCI dosing	Therapeutic exposure	Nephrotoxicity
Meng <sup>21</sup>	Before-after study	Trough-based dosing strategy aiming for therapeutic trough concentration between 10 and 20 mg/L (n = 179)	Hospital-wide implementation of an AUC-based dosing strategy using two-point sampling (peak and trough) and the trapezoidal rule. Dose adjustment using Excel spreadsheet with default AUC <sub>24</sub> target of 500 mg/L·h (n = 117)	TCI: 74% achieved initial AUCs within acceptable range TDM: 55% achieved initial trough concentrations within acceptable range	TCI: 9.4% TDM: 11%
Truong <sup>20</sup>	Retrospective matched audit	Matched-cohort with initial kilogram-based dosing and adjustment according to trough concentration (n = 50)	Consecutive patients with initial kilogram-based dosing and subsequent dose adjustment to trough target of 12 or 15 mg/L (n = 50)	TCI: 84% within acceptable range at 48 h (88% at 72 h; 93% at 96 h). TDM: 29% within acceptable range at 48 h (61% at 72 h; 78% at 96 h)	TCI: 8.3% TDM: 14%
Neely <sup>13</sup>	Serial cohort study	Year 1: Trough-based dosing strategy aiming for therapeutic trough concentration between 10-20 mg/L (n = 75)	Year 2 (TCI only): Hospital-wide implementation of an AUC-based vancomycin dosing using the multiple-model Bayesian adaptive control algorithm in BestDose. AUC target 400 mg/L·h (n = 88) Year 3 (TCI + optimal sampling): AUC targeting using BestDose + multiple-model optimal sampling to calculate the most informative date and time to measure the next vancomycin concentration for each patient (n = 89)	70% of AUCs were therapeutic 19% of trough concentrations were acceptable	TCI: 0% TCI + optimal Sampling: 2% TDM: 8%

after kidney transplantation.<sup>23</sup> Previously the benefit of CCD for MMF has been subject to debate.<sup>24,25</sup> However, the failure to recognize the fundamental difference in concentration control methods and outcomes between the TDM trials and TCI trials<sup>23</sup> has led to the incorrect interpretation that the evidence does not support CCD.<sup>24</sup>

There have been four randomized controlled trials (RCTs) testing the benefit of mycophenolate CCD (a fifth is excluded due to a confounded design<sup>26</sup> and is discussed elsewhere<sup>23</sup>). These RCTs are summarized in Table 3, and details of search strategy are given in the Supporting Information.

Two RCTs have used TDM for the CCD intervention approach rather than TCI. In the first, the fixed-dose concentration-controlled trial (FDCC),<sup>30</sup> exposure within the range of 30-60 mg/L·h was proposed as the therapeutic window<sup>30</sup>; in the second, the Opticcept trial,<sup>31</sup> the goal was a lower-bound therapeutic window with a trough concentration  $\geq 1.9$  mg/L.<sup>31</sup> In both trials, clinicians were provided with just the AUC or trough value, respectively, leaving the decision to adjust, and by how much, to the clinician.

TDM failed to control MPA exposure. In the FDCC, "mean MPA AUC values, and the proportion of patients achieving AUC values within the therapeutic range of 30 to 60 mg hr/L ... was similar in the

concentration-controlled and fixed-dose groups", leading to near-identical outcomes.<sup>30</sup> In Opticcept, whilst MMF dosing was higher in the TDM arm (ie, attempts were made to optimize exposure), MPA trough concentrations were "identical at all time points" between arms.<sup>31</sup> Again, unsurprisingly, clinical benefits were not seen.

In contrast, two RCTs have used TCI for the CCD intervention, with quite different results to the two TDM trials. Both TCI trials used maximum *a posteriori* Bayesian estimation (MAPBE) to predict doses. The first TCI trial involved random assignment of subjects into one of three MPA exposure target arms,<sup>27,28</sup> a technique considered the gold standard in testing the exposure-response relationship.<sup>32-34</sup> TCI successfully separated the groups into three distinct exposure arms.<sup>27</sup> This led to a significant reduction in biopsy proven acute rejection (BPAR) (14.9% vs 27.5%, with a further small reduction in the highest exposure group, 11.5%).<sup>27,28</sup> With random assignment of exposure target, the association between AUC and BPAR was highly significant, whilst that between MMF dose and BPAR was not.<sup>28</sup>

The second TCI trial, APOMYGRE, compared MMF TCI with fixed dosing.<sup>29</sup> Again TCI was successful in controlling MPA exposure<sup>29</sup> and led to a substantial reduction in BPAR in the TCI compared with the fixed dose arm (7.7% vs 24.6%).<sup>29</sup>

**TABLE 3** Summary of studies of TDM or TCI concentration-controlled dosing of mycophenolate

Study	Design	Dosing strategy in CCD arms	Therapeutic exposure	Outcomes
Hale et al <sup>27</sup> and van Gelder et al <sup>28</sup>	Multitarget RCCT in kidney transplant recipients (n = 150)	Target MPA AUC <sub>0-12</sub> of either 16.1, 32.2 or 60.6 mg/L·h (low, medium or high target arms)  Dose recommendation from MAPBE supplied to clinician	Successful separation of intervention arms into three distinct MPA exposure groups	BPAR 27.5%, 14.9% and 11.5% in low, medium and high target groups respectively (P = 0.043, low vs medium target group)
Le Meur et al <sup>29</sup>	RCT of TCI vs fixed dosing in kidney transplant recipients (n = 137)	Target MPA AUC <sub>0-12</sub> target of 40 mg/L·h  Dose recommendation from MAPBE supplied to clinician	In TCI arm, increased proportion within range of 30-60 mg/L·h at all post-adjustment time points over the 12-month period	Treatment failure in 47.7% vs 29.2% (P = 0.03) and BPAR in 24.6% vs 7.7% (P = 0.01), fixed dose vs. TCI arm respectively
Van Gelder et al <sup>30</sup>	RCT of TDM vs fixed dosing in kidney transplant recipients (n = 901)	MPA AUC <sub>0-12</sub> between 30 and 60 mg/L·h deemed acceptable  Observed MPA AUC <sub>0-12</sub> supplied to clinician without dose adjustment recommendation	TDM failed to improve exposure, with similar mean MPA AUC <sub>0-12</sub> and proportion in range between treatment arms	No difference in outcomes. Treatment failure in 25.7% vs 25.6% (P = 0.81) and BPAR in 15.5% vs 14.9%, in the fixed dose and TDM arm, respectively
Gaston et al <sup>31</sup>	RCT of TDM vs fixed dosing in 720 kidney transplant recipients: TDM and reduced CNI (group A), TDM and standard CNI (group B), fixed dosing and standard CNI (group C)	Goal trough MPA > 1.3 mg/L (cyclosporine co-therapy) or > 1.9 mg/L (tacrolimus co-therapy)  Observed MPA trough concentration supplied to clinician without dose adjustment recommendation	TDM failed to improve exposure, with MPA trough concentrations "identical at all time points with or without monitored dosing"	Noninferiority group A vs group C (primary outcome measure)  Treatment failure in 55 (22.6%), 67 (28.3%), and 67 (27.9%) subjects in groups A, B and C, respectively (P = 0.13 for A vs B and P = 0.18 for A vs C)

Abbreviations: AUC, area under the concentration-time curve; BPAR, biopsy proven acute rejection; CCD, concentration-controlled dosing; CNI, calcineurin inhibitor; MAPBE, maximum *a posteriori* Bayesian estimation; MPA, mycophenolic acid; RCCT, randomized concentration-controlled trial; RCT, randomized controlled trial; TCI, target concentration intervention; TDM, therapeutic drug monitoring.

Together these two RCTs show the effectiveness of TCI in achieving the desired MPA exposure, and confirm causal association between MPA exposure and rejection.<sup>27-29</sup> The latter trial in addition showed superiority of TCI over fixed dosing.<sup>29</sup>

For mycophenolate the difference in outcome between CCD methods is stark. CCD using a TDM strategy has proven ineffective in achieving desired MPA exposure,<sup>30,31</sup> to the extent that outcomes were no better than "one-size-fits-all" mycophenolate dosing. With TCI, however, desired MPA exposure can be effectively achieved – as shown in prospective trials<sup>26,27,29</sup> and routine care<sup>35</sup> – leading to substantial clinical benefit.<sup>27,29</sup>

### 5.3 | Other Immunosuppressants

The limitations of TDM have been shown for other immunosuppressants. For example, the landmark Elite-Symphony trial compared tacrolimus, cyclosporine and sirolimus, each dosed by TDM.<sup>36</sup> They reported between 30% and 50% of subjects outside of the desired acceptable range over much of the trial, and "few patients ... consistently within target range".<sup>36</sup>

One RCT has directly compared TDM with TCI for tacrolimus.<sup>37</sup> In the TCI group, dose adjustment was determined by MAPBE. In the control group, dosing was managed by highly experienced transplant physicians. The primary outcome was the proportion of concentrations within the acceptable range.

Target concentration attainment was superior in the TCI arm compared to TDM. In the standard risk subpopulation, the proportion of concentrations per patient within the acceptable range was significantly higher with TCI: 90% vs 78% for TDM.<sup>37</sup> The same was seen in high-risk patients: 77% vs 59%.<sup>37</sup>

## 6 | DISCUSSION

The published evidence demonstrates that clinical outcomes are superior when TCI is used. This is especially clear for reducing transplant rejection with mycophenolate, with two randomized controlled trials showing a major improvement with TCI and two randomized trials showing no benefit with TDM. For vancomycin and tacrolimus, TCI demonstrated superior achievement of exposure goal as well as clinical benefits when the design was appropriate. We have used

the examples of vancomycin, mycophenolate and tacrolimus to illustrate how TCI is a better approach to dose individualization, but the approach can be applied to any treatment with an observable response, including treatment with biological agents. The TCI approach describes what to do with an observation, so it can be used with any kind of response regardless of whether the response can be observed quickly (eg, rapid point of care assays) or takes some time to be reported from a specialist laboratory. We have not attempted to comment on the wide variety of methodologies available to clinicians for interpreting responses, ranging from empirical dose adjustment to complex models integrating multiple responses. The focus of this commentary is on the principles of the TCI approach – a concentration *target* and an explicit *intervention strategy* – rather than a review of implementations.

The main practical challenge for use of TCI is entering essential information into a TCI dosing tool. This is not a problem for TDM because the dosing decision workflow is simple and based on comparing the measured concentration to the therapeutic window. When a dose change is needed, TDM-based dose changes do not take account of the dosing history or patient characteristics such as weight and renal function, they just use the measured concentration. Nevertheless, as has been shown, this leads to inferior dose individualization and inferior outcomes. Digitization of healthcare records and integration with clinical decision support tools means TCI is becoming easier to use and its benefits can be delivered in practice.

## 7 | CONCLUSION

In the era of individualized medicine, TCI rather than TDM should be the standard of care for dose individualization. Both on the basis of scientific principles and clinical evidence the better treatment strategy is TCI.

### COMPETING INTERESTS

There are no competing interests to declare.

### ORCID

Nick Holford  <https://orcid.org/0000-0002-4031-2514>

Guangda Ma  <https://orcid.org/0000-0002-9743-1389>

David Metz  <https://orcid.org/0000-0003-4478-5308>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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