Received: 31 January 2024 | Revised: 22 April 2024 | Accepted: 25 April 2024

DOI: 10.1111/bcp.16121

THEMED ISSUE REVIEW

Removing the physician from the equation: Patient-controlled, home-based therapeutic drug self-monitoring of tacrolimus

Marinus Hazenbroek[1,2] | Liset H. M. Pengel[1] | Sebastiaan D. T. Sassen[3,4] | Emma K. Massey[2] | Marlies E. J. Reinders[1,2] | Brenda C. M. de Winter[3,4] | Dennis A. Hesselink[1,2]

[1]Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

[2]Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

[3]Erasmus MC, Rotterdam Clinical Pharmacometrics Group, Rotterdam, the Netherlands

[4]Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

Correspondence
Marinus Hazenbroek, Erasmus MC Transplant Institute, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
Email: m.hazenbroek@erasmusmc.nl

The dosing of tacrolimus, which forms the backbone of immunosuppressive therapy after kidney transplantation, is complex. This is due to its variable pharmacokinetics (both between and within individual patients), narrow therapeutic index, and the severe consequences of over- and underexposure, which may cause toxicity and rejection, respectively. Tacrolimus is, therefore, routinely dosed by means of therapeutic drug monitoring (TDM). TDM is performed for as long as the transplant functions and frequent and often lifelong sampling is therefore the rule. This puts a significant burden on patients and transplant professionals and is associated with high healthcare-associated costs. Furthermore, by its very nature, TDM is reactive and has no predictive power. Finally, the current practice of TDM does not foresee in an active role for patients themselves. Rather, the physician or pharmacist prescribes the next tacrolimus dose after obtaining the concentration measurement test results. In this article, we propose a strategy of patient-controlled, home-based, self-TDM of the immunosuppressant tacrolimus after transplantation. We argue that with the combined use of population tacrolimus pharmacokinetic models, home-based sampling by means of dried blood spotting and implementation of telemedicine, this may become a feasible approach in the near future.

KEYWORDS
Dried Blood Spot, Home-monitoring, Kidney Transplantation, Tacrolimus, Telemonitoring, Therapeutic Drug Monitoring

1 | INTRODUCTION

The ever-increasing demand for healthcare is taking its toll on healthcare systems all over the world.[1] Overcrowded outpatient clinics have become the norm, as have long waiting lists for surgical procedures.[2] This is, at least in part, due to the aging population and number of people living longer with chronic conditions. Compounding this are limitations of the healthcare system, such as the dwindling number of nursing staff and physicians per capita and ever-increasing healthcare costs. Transplantation medicine is no exception. The incidence of end-stage kidney disease has increased as a result of aging of the population and the epidemic of the metabolic syndrome.[3] At the same time,

Abbreviations: AI, artificial intelligence; AUC, area under the concentration *vs*. time curve; C_0, trough level; DBS, dried blood spot; EHR, electronic health record; PK, pharmacokinetics; PopPK, population pharmacokinetics; TDM, therapeutic drug monitoring.

the age of patients eligible for transplantation has increased and comorbid conditions are often no longer an absolute contraindication for transplantation.[4,5] This has resulted in an increased number of patients being waitlisted for transplantation.[6]

Meanwhile, the role of the patient has changed over the last decade. Patients now often desire a more active role in the treatment of their disease or condition, and shared decision making is considered good clinical practice.[7] While physicians encourage patient participation, this can put additional strain on health care professionals (e.g. time spent on consultations),[8] which may cause problems as evidenced by the high burn-out rates among transplant surgeons.[9] This issue, together with the increasing patient numbers and the need for cost-effectiveness of treatments, could be solved by introducing technological innovations such as telemedicine to support effective health care delivery.

Technological advances, such as the increasing use of smart phones and tablets, have opened the door for innovative methods to provide healthcare at a distance. Consultation via video, remote monitoring of vital functions or tracking medication intake using web-based interfaces or applications are all examples of what is now commonly referred to as telemedicine.[10,11] Telemedicine was found to improve access to care in rural areas and helped to reduce the number of visits to the outpatient clinic, with increased patient satisfaction, cost savings and reduced travel time.[12]

Telemedicine is also increasingly being used in the field of transplantation. This development was fuelled by the COVID-19 pandemic.[13] A recent literature review by Hezer *et al*. confirmed that the application of telemedicine in transplantation leads to improved adherence to (immunosuppressive) therapy and medication, increased patient satisfaction, reduced travel time and, in theory, a reduction of health expenditure.[14] Nonetheless, several barriers for the implementation of telemedicine remain, including limited information technology infrastructure, adequate reimbursement and legislative issues.[14]

In this article we propose a strategy of patient-controlled, home-based therapeutic drug monitoring (TDM) of the immunosuppressant **tacrolimus** after transplantation. We aim to provide evidence from the literature for the benefits and feasibility of such an approach. Tacrolimus is the backbone of current immunosuppressive therapy after solid organ transplantation and its dose is routinely adjusted by TDM. We believe that home-based, TDM by transplant recipients themselves may lead to more precise dosing of tacrolimus, with increased patient adherence and participation, improved quality of life, and reduced healthcare-associated costs.

2 | CURRENT TDM OF TACROLIMUS

Tacrolimus is routinely dosed to achieve an empirically defined whole blood concentration range (the so-called *target* range), which depends on the type of organ transplanted, the time after transplantation, and the concomitant immunosuppressive medication. For this purpose, the predose (C_0 or trough) concentration is routinely used, although some centres rely on limited sampling strategies and more extensive pharmacokinetic (PK) profiling.[15,16]

The current practice of TDM of tacrolimus has several limitations, as recently described by Holford and colleagues.[17] The main limitation being that TDM is reactive in nature, basically a question of trial and error, and that it has no predictive power. Another important limitation is the fact that the tacrolimus C_0 has a poor correlation with adverse clinical outcomes, including acute rejection.[18] Although the total tacrolimus exposure within a dosing interval (as measured by the area under the concentration *vs*. time curve [AUC]) may correlate better with clinical outcome,[15] the extensive sampling which is required puts a considerable burden on patients and nursing and laboratory staff, and is more expensive.

3 | DOSING OF TACROLIMUS WITH ALGORITHMS AND ARTICIFIAL INTELLIGENCE

The PK of tacrolimus can be described with population PK (PopPK) models.[19,20] Importantly, such PopPK models can also be used to predict the PK of tacrolimus after transplantation. PopPK models have been successfully used to guide both the tacrolimus starting dose and follow-up dosing. A starting dose can be calculated using algorithms derived from PopPK models, which can be described as *a priori* model-informed precision dosing, because it solely depends on the covariates in the model and does not rely on previously measured tacrolimus concentrations. On the contrary, follow-up dosing relies on PopPK models and *a posteriori* Bayesian prediction using measured tacrolimus concentrations.[21–24] This practice can be referred to as model-informed precision dosing. Taken together, studies investigating the benefits of algorithm-guided dosing have, in general, demonstrated that this strategy leads to a higher percentage of patients reaching the target concentration range at first steady state and maintaining patients on target. However, clear clinical benefits, such as less acute rejection or less tacrolimus-related toxicity, have not been convincingly demonstrated.[21,22,24] Nonetheless, model-informed follow-up dosing may have other advantages over traditional TDM. These include more standardized tacrolimus dosing and advice regarding the timing of tacrolimus concentration measurements.[23]

The lack of a clinical benefit, despite improved achievement of the target exposure, is partly explained by the fact that most of the studies investigating the benefits of algorithm/PopPK-guided tacrolimus dosing were powered for PK endpoints and not powered or designed to show differences in pharmacodynamic endpoints, the relation between exposure/concentration and demonstrate clinical benefits.[21,24] A recent randomized, controlled trial followed newly-transplanted patients for 90 days and compared standard TDM ($n = 45$) with combined algorithm-based starting and follow-up dosing using Bayesian prediction ($n = 40$).[22] The authors observed an improvement in PK endpoints in the intervention group (a shorter time to reach the target range, and less off-target exposure thereafter), but, again, no improvement in terms of acute rejection rate, graft

survival or the incidence of delayed graft function was observed. Like in previous studies comparing standard *vs.* algorithm-based tacrolimus dosing,[21,24] the limited number of patients included in this trial may have been too small to demonstrate clinical and/or statistically significant benefits of algorithm-based dosing.[22] Importantly, the association between tacrolimus exposure and rejection risk remains a topic of debate.[15] In low-exposure tacrolimus regimens, which are now standard in most centres,[25] no clear association between the tacrolimus C_0 and the risk of acute rejection has been demonstrated.[18] Furthermore, acute rejection is also determined by factors other than tacrolimus exposure and these include the number of human leucocyte antigen mismatches, patient adherence, the presence of donor-specific anti-human leucocyte antigen antibodies (resulting from prior transplantations, pregnancy or transfusions), cold ischaemia time and the exposure to concomitant immunosuppressive drugs.[26]

Clinical benefits may only become apparent if the performance of PopPK models improves in terms of achieving and maintaining tacrolimus target concentrations. The models by Francke *et al.* and Lloberas *et al.* resulted in 58 and 55% of patients being within the target concentration range at first steady state, respectively.[21,22] Fifty-eight percent of patients within target range using model-based dosing is a clinically meaningful improvement from 37.4% target range attainment in bodyweight-based dosing, but obviously there still is room for improvement of algorithms.[21] To further improve models, new covariates should be included in PopPK models and dosing algorithms. Such covariates may include the influence of gut microbiota and body composition.[27–29]

Recently, the use of artificial intelligence (AI) to develop models as an alternative to PopPK models has generated considerable enthusiasm as AI models use any amount and type of covariates without any assumptions to increase its predictive capacity.[30,31] AI is considered a valuable complementary asset to PopPK modelling and with tools such as *data mining* additional covariates can be identified.[30,32] Moreover, new software has been developed to combine machine learning with model building programmes to generate an infinite number of models from a dataset, an impossible feat to accomplish manually.[33] However, such AI models may be limited by overfitting, limited generalisability and lack of physiological explanation.[30,34] Collaboration between experts from the clinical and technological fields is necessary to determine the role of AI in precision dosing. Ultimately, the goal would be to move from a concentration target range towards a personalized exposure target range, to minimize side effects and optimize efficacy of therapy. However, reported outcomes on minimizing tacrolimus exposure differ due to differences in treatment strategies and study protocols, which make it difficult to choose an exposure target range.[15,35,36] These differences do suggest that subpopulations of transplant recipients might be identified that tolerate less restrictive immunosuppressive regimens without worse clinical outcomes and vice versa. When model-based dosing is implemented and patients' PK and clinical characteristics accumulate over time, it might be possible to stratify patients to low and high tacrolimus exposure based on their immunological risk.

3.1 | Dried blood spot

Tacrolimus in whole blood is largely bound to erythrocytes (the intraerythrocytic fraction makes up 74–95% of the whole blood concentration), with the plasma fraction (24.5% of the whole blood concentration) being largely bound to plasma proteins. There is only a limited amount of unbound tacrolimus in blood and this free fraction of tacrolimus makes up 0.1–1.5% of the total whole blood concentration.[37] In general, whole blood is the matrix used for TDM of tacrolimus in clinical practice. This is, however, limited by the need for repetitive venipuncture and the resulting burden for patients and personnel, and the healthcare workflow.

A proposed solution could be the use of dried blood spot (DBS) sampling. It is now possible to measure several analytes from a single spot, including creatinine, making it a valuable asset for algorithm-based dosing and home-monitoring.[38–40] There are multiple theoretical advantages to DBS sampling, which include (but are not limited to): the possibility to collect multiple samples (for the measurement of an AUC); the convenience of not having to visit the outpatient clinic for (self-)sampling; and DBS being less invasive compared to venapuncture.[38,39] While DBS is still invasive and potentially painful to patients, the fingerprick was preferred to venipuncture by patients within the context of DBS.[41] Additionally, self-sampling with DBS gives patients the freedom to follow their usual routine while sampling, reduces travel time and costs, as was described in a hypothetical study.[42] When DBS was tested in addition to standard care, Veenhof *et al.* found no difference in average costs compared to standard care for the healthcare organization. They did calculate a theoretical cost-reduction of 399 euro per patient in the first year after transplantation if DBS replaced venous sampling completely and could avoid the need for 1 consultation.[43] This calculation did not take into account the possible cost-reduction of reduced nephrologist and phlebotomist workflow.[43]

Before DBS can be applied it is essential to develop a method of sampling and subsequently perform a validation of this method (for an overview, see Capiau *et al.*).[44] An important factor to consider in the process of validation is the type of DBS filter paper, as this affects the analyte and its recovery.[45–47] Furthermore, the sample can be collected volumetrically or nonvolumetrically (free-fall drop from a patient's finger). Nonvolumetric samples need to be corrected for haematocrit levels during analysis,[48] while volumetric samples largely remove the need for correction.[49] When compared in practice, nonvolumetric samples were found to be superior in terms of clinical criteria, quality and cost compared to volumetric samples.[50,51] An overview of important aspects for clinical implementation was recently provided and highlighted the importance of both patient training to ensure sample quality and field testing of the transit of DBS cards to assure that these are analysed in time.[52]

4 | CLOSING THE LOOP

We envisage a future for TDM on the basis of patient controlled, home-based, TDM using DBS and dosing algorithms based on PopPK

models. Patients will sample their blood using DBS and receive dosing advice through a digital interface after analysis of the DBS by the laboratory (Figure 1). This digital interface could be built using a developed software programme from our hospital pharmacy, called MEDD-AIM. It was developed to improve the dosing process of vancomycin in critically ill patients,[53] who also have variable kinetics, by having multiple dosing recommendations calculated for a specific patient by established PK models. The physician enters the patient identification number, after which the programme extracts the necessary data (e.g. covariates) from the electronic health record (EHR). The programme uses the data to select a combination of models to run dosing simulations. Subsequently, the programme determines an optimal dose to achieve the target concentration at the requested time. For starting dose recommendations, the models do so without previous vancomycin levels (*a priori*), while for follow-up dosing the programme integrates previously administered dosages and vancomycin trough levels (*a posteriori*).

The main advantage of this tool is that the interface is simple and user-friendly, while it allows for healthcare professionals to view each separate model calculation in a combined plot of all concentration–time curves. MEDD-AIM might also be upgraded with an extension for tacrolimus dose recommendations by adding the tacrolimus models. This may seem like a moonshot, but we argue that this will become feasible within the next few years, as there are examples of closed loop systems in other areas of medicine. For instance, within the field of diabetes mellitus, patients monitor and control their own insulin therapy by means of measuring glucose concentrations in blood either by fingerprick or interstitial fluid using flash glucose monitoring devices (e.g. Freestyle libre). For the latter, it has been shown that glycaemic control improves and discontinuation rates of measuring decrease compared to standard blood glucose concentration monitoring.[54,55] Moreover, there is evidence regarding the safety and efficacy of self-monitoring or self-managing (dosing their own medication) among patients on oral anticoagulation (vitamin K antagonists). A Cochrane review including nearly 9000 participants found a 50% reduction in the occurrence of thrombo-embolisms and no increase in bleeding complications compared to standard of care.[56] However, in both fields it was noted that these results might not be reproducible when participants are less motivated, lack digital skills or lack trainability, due to a variety of reasons including physical limitations, failing to

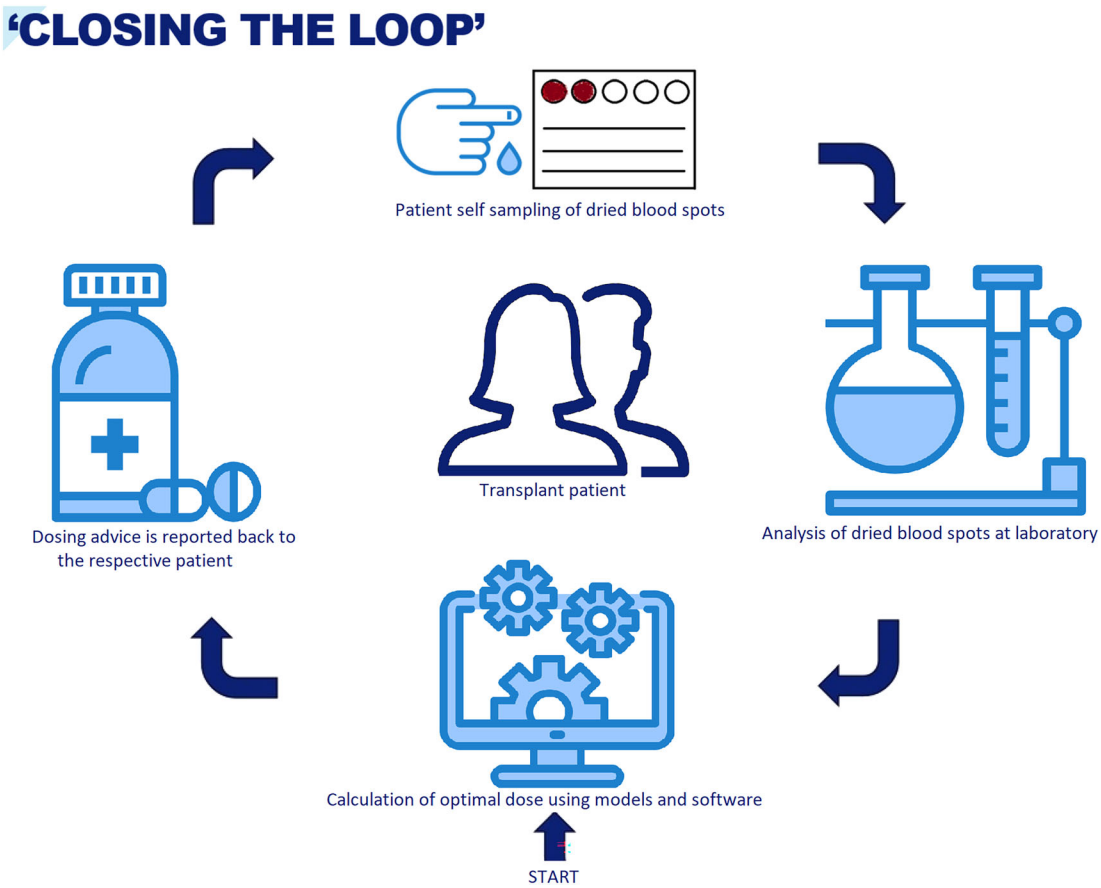

FIGURE 1 The *closing-the-loop* concept visualized. The MEDD-AIM software (below) calculates a starting dose based on available data (covariates) for an individual patient. When patients sample their own blood using dried blood spot cards (top), it can be sent to the laboratory through the postal service for analysis (right). The results and tacrolimus trough level will then be used as input for the algorithm to calculate a dose specific for an individual patient (bottom), after which the dose will be communicated to the patient through a digital interface (left). This process is repeated iteratively, forming a closed loop.

attend training or failing the assessment.[56] The impact of costs must not be understated, as this can make patients reluctant to partake in self-monitoring.[56]

Motivation, skills and/or trainability, and costs influenced the uptake and succes of these interventions in insulin and anticoagulant therapy, and these may apply to the transplant population as well and pose the first question that needs answering.

In the overview of home-monitoring by Hezer *et al*., the authors concluded that patient preferences, perceived burdens and needs have to be explored and subsequently integrated into the design of methods for home-monitoring.[14] This also applies to the proposed *closing-the-loop* principle. The feasibility of implementation and subsequent integration of this innovation into the patients' treatment regimen will meet with greater success and hopefully lead to prolonged adherence if patients' needs are taken into account. Moreover, studies among patients who are the potential end-users may help identify solutions to potential barriers and inform educational strategies on the system.

It is equally important to take the opinions of healthcare professionals into account. A Cochrane review regarding perceptions of and experiences with telemedicine in primary care showed ambiguous results across multiple aspects of telemedicine. For example, some physicians appreciated the decisional tools while others thought it threatened their clinical skills.[57] Ultimately, the question is under which conditions might *closing the loop* on TDM be acceptable to healthcare professionals? How do physicians and pharmacists perceive a closed loop TDM system, which patients do they see as potential candidates for use, what do they perceive as barriers to implementation in clinical care and how might we overcome them. Is there still a need to double-check an algorithm-based dosing recommendation by a pharmacist/physician or can it be more or less automated without checks by professionals? In the developmental process of software programs, it is mandatory to build in checkpoints for data validation according to the EU MDR and ISO 13485.[58,59] Moreover, the extent of most of these checks can be at the discretion of the developer, these measures do not avoid liability. It is important to explore these questions with healthcare professionals as the removal of checkpoints has implications for patient safety and professional liability, which may become a barrier to implementation. As mentioned before, tacrolimus dosing is both complex and critical for transplant healthcare and changes in the patients' health status and current medication use may rapidly succeed 1 another. These *real-world* changes make it difficult for algorithms to predict doses correctly as was shown for concomitant azole-therapy during tacrolimus therapy.[60] It is important to know the limitations of these models, as many do not account for drug interactions or (switching to) different tacrolimus formulations[61] or side effects such as diarrhoea.[62] In case of these clinical events, we do not expect these models to give an adequate dosing recoomendation. Coming back to our opening statement of this paragraph, we can not expect this concept to remove the need for involvement of health professionals, because they are responsible for their patients and their clinical outcomes. However, we could view this as a valuable part of the toolbox of the physician, which could also take work off their hands. For example, patients who are *stable* for a reasonable time post-transplantation might benefit from the increased autonomy provided by the closing-the-loop concept, possibly by also replacing the bulk of physical consultations with teleconsultations. We acknowledge the possible implications of omitting the physical examination during follow-up for the patient–provider relationship[63] or missed tumours in this high-risk population,[64] but this could be solved in multiple ways, including regular visits to the general practitioner or self-monitoring or self-examination combined with teleconsultations.

Essential for this concept is the development of a model (or a combination of models) that is applicable to (almost) all individual kidney transplant recipients, like the MEDD-AIM software for vancomycin. As mentioned before, problems with external validation and thus clinical implementation have been described,[65] which were probably due to differences between model structures, selection of covariates and differences between populations.[66,67] These findings highlight the importance of externally validating models before implementing them in clinical practice. To bridge the gap to a model applicable to a larger pool of (kidney) transplant recipients we propose to develop a digital interface which integrates established PopPK models to *fit* an individual patient to the best model or a combination of models using weighted model-averaging using clinical data from the EHR as input for the models.[61] This continuous learning approach, i.e. continuously updating a model using clinical data has previously been shown to successfully improve prediction models, for example when predicting the exposure to the antibiotic vancomycin.[68] The digital interface could then be tested prospectively for its performance in different cohorts of kidney transplant recipients. Subsequently, it would be easier to perform long-term trials with larger groups of patients from different transplant centres in a uniform way using the dosing interface, which would be powered to potentially show clinical benefits like improved graft survival and fewer rejection episodes. Moreover, the use of AI/machine learning could be beneficial, as patient data can be *mined* for important unexplored covariates to more accurately describe PK characteristics of the population. Furthermore, implementing techniques such as reducing the weight of model priors relative to the actual observations of patients (flattened priors) or model-averaging techniques can improve prediction accuracy if patients are not well-described by a model.[69,70]

Additionally, the interface might help elaborate reference values for pharmacological parameters of interest such as peak concentration or C_{max} and C_0 within the population and even for individuals. It has been established that fast metabolizers of tacrolimus need higher doses of tacrolimus to reach the target C_0, possibly leading to higher Cmax values, which in turn leads to toxicity by overexposure.[71,72] Conversely, it can help define a target C_0 or AUC to reduce underexposure.

Another area requiring further investigation is transit times, performing field tests for transit times of DBS samples is essential for having results in time.[52] For successful implementation this process will need to be optimized (e.g. more reliable transportation or working with local laboratories), but this will be quite a challenge to realize as

liquid chromatography–tandem mass spectrometry is expensive and requires dedicated and trained personnel, making wide-scale implementation in the near future difficult. It might be better to opt for a centralized strategy, starting with the validation in larger (academic) hospitals before further implementation. Starting in the larger centres with transplantation experience will also help the development of the technique, making it easier to evaluate clinical benefits and facilitate a regional rollout afterwards. Once validated in kidney transplant recipients, the strategy can serve as a proof of concept for other organ transplant populations.

Importantly, implementation of this technique requires a good information technology infrastructure. Digitalization of healthcare has been a slow process. For example, electronic health records (EHR) have only been routinely used for about 15 years in the United States of America due to financial reimbursement after the passing of the HITECH act (part of the Recovery and Reinvestment act).[73] It is important to acknowledge the multiple barriers to the implementation of the EHRs such as technical, time-related, social and legal barriers as well as the interrelationships between these barriers.[74] For instance, the perceived lack of adequate computer skills (technological barrier) and the additional time spent per patient (time barrier) may form a combined barrier to implementation. We need to take into consideration that the digital interface might be hampered by the same barriers and their interactions, which has its implications for possible facilitators. Potential facilitators include a robust infrastructure to guarantee fast and safe data management, and a dedicated support team to guarantee operability and adequate support with troubleshooting. A software programme such as MEDD-AIM relies on other digital systems for source data and adequate communication between these systems (Figure 2).

The digital interface could be embedded within the EHR or a standalone software programme, but it needs access to patient's sample data to give a dosing recommendation to either healthcare professionals or patients. While the choice of a modality may depend on several aspects including developmental/strategic choices, the possibility of collaborating with EHR providers and preferences from healthcare professionals and patients, it is clear that the interface will both generate and use a lot of sensitive data. Privacy and patient–physician confidentiality are of great importance, which is why legislative and safety issues are important to discuss in the early stages of development.[75] Concerning the legislative aspects, the digital interface will need to be accepted by the appropriate regulatory authority (e.g. MDR for the European Union) when implementation is at hand, ensuring its compliance to standard regulations.[59]

In conclusion, we believe that the future of TDM of tacrolimus will include patient controlled, home-based dosing using algorithms—the closing the loop concept. Important steps (see Table 1) to achieve this goal start with the optimisation and implementation of the DBS technique. Next, the focus should move towards the development of a model(s) that is capable of providing an accurate dosing recommendation for a large proportion of kidney transplant

TABLE 1 Steps to realize *closing-the-loop* concept.

1	Optimize and implement the use of DBS sampling in clinical practice
2	Explore barriers and facilitators among patients and healthcare professionals
3	Build a dosing interface to dose tacrolimus tailored to an individual patient
4	Retrospectively test the dosing interface
5	Acquire legislative certification for the dosing interface
6	Prospectively test the dosing interface *vs.* standard TDM in population of interest
7	Implement the dosing interface in clinical care
8	Monitor results after clinical implementation

Abbreviations: DBS = dried blood spot; TDM = therapeutic drug monitoring.

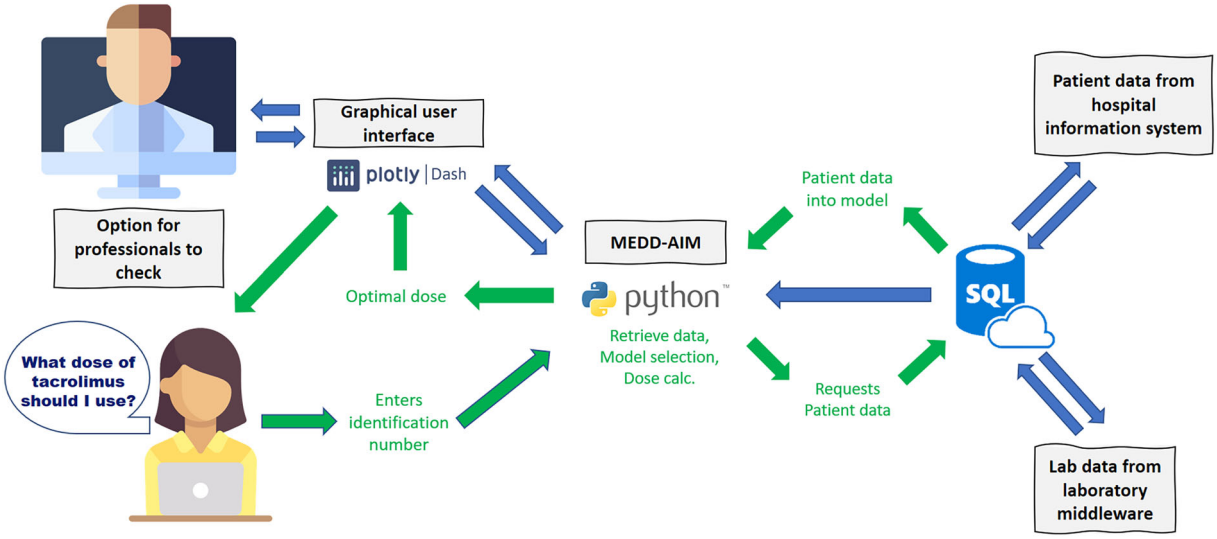

FIGURE 2 Visualization of dataflow behind the software programme MEDD-AIM.

recipients. The subsequent integration of this model in a digital interface or software programme needs to take into account stakeholders' needs and preferences in order to make successful implementation feasible and successful. Lastly, the platform needs to demonstrate superiority to the current, standard practice of TDM, preferably in terms of clinical endpoints rather than (surrogate) PK parameters. For now, the current practice of TDM will remain standard of care, albeit expensive and resource intensive. However, we have argued that algorithm-based dosing could become standard of care in the foreseeable future and potentially transform current post-transplant care delivery by taking the physician out of the equation.

4.1 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.[76]

AUTHOR CONTRIBUTIONS

M.H., D.A.H. and B.W. contributed to the design and writing of the manuscript. L.P. and E.M. revised the English. L.P., S.S., E.M., M.R., D.A.H. and B.W. commented on the manuscript. All authors provided critical feedback and contributed to the final manuscript.

CONFLICT OF INTEREST STATEMENT

D.A. Hesselink has received lecture fees and consulting fees from Astellas Pharma, Astra Zeneca, Chiesi Pharma, Medincell, Novartis Pharma, Sangamo Therapeutics and Vifor Pharma. He has received grant support from Astellas Pharma, Bristol-Myers Squibb and Chiesi Pharma (paid to his institution). D.A. Hesselink does not have employment or stock ownership at any of these companies, and neither does he have patents or patent applications.

DATA AVAILABILITY STATEMENT

Data-sharing not applicable - no new data generated.

ORCID

Marinus Hazenbroek https://orcid.org/0009-0004-1823-7003
Liset H. M. Pengel https://orcid.org/0000-0001-9620-8639
Sebastiaan D. T. Sassen https://orcid.org/0000-0002-4525-638X
Emma K. Massey https://orcid.org/0000-0002-9017-1924
Marlies E. J. Reinders https://orcid.org/0000-0001-9543-567X
Brenda C. M. de Winter https://orcid.org/0000-0002-4452-8443

REFERENCES

1. World Health Organization World report on ageing and health. World Health Organization: Geneva P. 2015;246.
2. OECD. *Waiting times for health services*; 2020. doi:10.1787/242e3c8c-en
3. Kovesdy, C.P., Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* (2011), 2022. 12(1): p. 7–11, doi:10.1016/j.kisu.2021.11.003.
4. Pérez-Sáez MJ, Arcos E, Comas J, et al. Survival benefit from kidney transplantation using kidneys from deceased donors aged ≥75 years: a time-dependent analysis. *Am J Transplant*. 2016;16(9):2724-2733. doi:10.1111/ajt.13800
5. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725-1730. doi:10.1056/NEJM199912023412303
6. Nederlandse Transplantatie Stichting Cijfers wachtlijst organen. 2023 30-01-2024 [cited 2024 22-01-2024]. Available from: https://www.transplantatiestichting.nl/medisch-professionals/cijfers-nts/wachtlijsten-organen
7. Barry MJ, Edgman-Levitan S. Shared decision making — the pinnacle of patient-centered care. *New England Journal of Medicine*. 2012;366(9):780-781. doi:10.1056/NEJMp1109283
8. Stacey D, Légaré F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017;4(4):CD001431. doi:10.1002/14651858.CD001431.pub5
9. Jesse MT, Abouljoud M, Eshelman A. Determinants of burnout among transplant surgeons: a national survey in the United States. *Am J Transplant*. 2015;15(3):772-778. doi:10.1111/ajt.13056
10. Lambooy S, Krishnasamy R, Pollock A, Hilder G, Gray NA. Telemedicine for outpatient Care of Kidney Transplant and CKD patients. *Kidney Int Rep*. 2021;6(5):1265-1272. doi:10.1016/j.ekir.2021.02.016
11. Schmid A, Hils S, Kramer-Zucker A, et al. Telemedically supported case Management of Living-Donor Renal Transplant Recipients to optimize routine evidence-based aftercare: a single-center randomized controlled trial. *Am J Transplant*. 2017;17(6):1594-1605. doi:10.1111/ajt.14138
12. Orlando JF, Beard M, Kumar S. Systematic review of patient and caregivers' satisfaction with telehealth videoconferencing as a mode of service delivery in managing patients' health. *PLoS ONE*. 2019;14(8):e0221848. doi:10.1371/journal.pone.0221848
13. Omboni S, Padwal RS, Alessa T, et al. The worldwide impact of telemedicine during COVID-19: current evidence and recommendations for the future. *Connect Health*. 2022;1:7-35. doi:10.20517/ch.2021.03
14. Hezer B, Massey EK, Reinders MEJ, et al. Telemedicine for kidney transplant recipients: current state, advantages, and barriers. *Transplantation*. 2023;108(2):409-420. doi:10.1097/TP.0000000000004660
15. Brunet M, van Gelder T, Åsberg A, et al. Therapeutic drug monitoring of Tacrolimus-personalized therapy: second consensus report. *Ther Drug Monit*. 2019;41(3):261-307. doi:10.1097/FTD.0000000000000640
16. Lemaitre F, Hesselink DA. TDM is alive and kicking! *Ther Drug Monit*. 2023;45(1):3-5. doi:10.1097/FTD.0000000000001034
17. Holford N, Ma G, Metz D. TDM is dead. Long live TCI! *Br J Clin Pharmacol*. 2022;88(4):1406-1413. doi:10.1111/bcp.14434
18. Bouamar R, Shuker N, Hesselink DA, et al. Tacrolimus predose concentrations do not predict the risk of acute rejection after renal transplantation: a pooled analysis from three randomized-controlled clinical trials(†). *Am J Transplant*. 2013;13(5):1253-1261. doi:10.1111/ajt.12191
19. Schagen MR, Volarevic H, Francke MI, et al. Individualized dosing algorithms for tacrolimus in kidney transplant recipients: current status and unmet needs. *Expert Opin Drug Metab Toxicol*. 2023;19(7):429-445. doi:10.1080/17425255.2023.2250251
20. Andrews LM, Riva N, de Winter BC, et al. Dosing algorithms for initiation of immunosuppressive drugs in solid organ transplant recipients. *Expert Opin Drug Metab Toxicol*. 2015;11(6):921-936. doi:10.1517/17425255.2015.1033397
21. Francke MI, Andrews LM, le HL, et al. Avoiding Tacrolimus underexposure and overexposure with a dosing algorithm for renal transplant

recipients: a single arm prospective intervention trial. *Clin Pharmacol Ther*. 2021;110(1):169-178. doi:10.1002/cpt.2163
22. Lloberas N, Grinyó JM, Colom H, et al. A prospective controlled, randomized clinical trial of kidney transplant recipients developed personalized tacrolimus dosing using model-based Bayesian prediction. *Kidney Int*. 2023;104(4):840-850. doi:10.1016/j.kint.2023.06.021
23. Francke MI, Hesselink DA, Andrews LM, van Gelder T, Keizer RJ, de Winter BCM. Model-based Tacrolimus follow-up dosing in adult renal transplant recipients: a simulation trial. *Ther Drug Monit*. 2022;44(5):606-614. doi:10.1097/FTD.0000000000000979
24. Størset, E., Åsberg A., Skauby M., Neely M., Bergan S., Bremer S., Midtvedt K., *Improved Tacrolimus Target Concentration Achievement Using Computerized Dosing in Renal Transplant Recipients--A Prospective, Randomized Study Transplantation*, 2015. 99(10): p. 2158–2166, Improved Tacrolimus Target Concentration Achievement Using Computerized Dosing in Renal Transplant Recipients—A Prospective, Randomized Study, doi:10.1097/TP.0000000000000708.
25. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357(25):2562-2575. doi:10.1056/NEJMoa067411
26. Eckardt K-U, Kasiske BL, Zeier MG. Special issue: KDIGO clinical practice guideline for the Care of Kidney Transplant Recipients. *Am J Transplant*. 2009;9:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x
27. Degraeve AL, Bindels LB, Haufroid V, et al. Tacrolimus pharmacokinetics is associated with gut microbiota diversity in kidney transplant patients: results from a pilot cross-sectional study. *Clinical Pharmacology & Therapeutics*. 2024;115(1):104-115. doi:10.1002/cpt.3077
28. Degraeve AL, Haufroid V, Loriot A, et al. Gut microbiome modulates tacrolimus pharmacokinetics through the transcriptional regulation of ABCB1. *Microbiome*. 2023;11(1):138. doi:10.1186/s40168-023-01578-y
29. Francke MI, Visser WJ, Severs D, de Mik - van Egmond AME, Hesselink DA, de Winter BCM. Body composition is associated with tacrolimus pharmacokinetics in kidney transplant recipients. *Eur J Clin Pharmacol*. 2022;78(8):1273-1287. doi:10.1007/s00228-022-03323-0
30. Woillard JB, Labriffe M, Debord J, Marquet P. Tacrolimus exposure prediction using machine learning. *Clin Pharmacol Ther*. 2021;110(2):361-369. doi:10.1002/cpt.2123
31. Zhang Q, Tian X, Chen G, et al. A prediction model for Tacrolimus daily dose in kidney transplant recipients with machine learning and deep learning techniques. *Front Med (Lausanne)*. 2022;9:813117. doi:10.3389/fmed.2022.813117
32. van Gelder T, Vinks AA. Machine learning as a novel method to support therapeutic drug management and precision dosing. *Clin Pharmacol Ther*. 2021;110(2):273-276. doi:10.1002/cpt.2326
33. Li X et al. pyDarwin: a machine learning enhanced automated nonlinear mixed-effect model selection toolbox. *Clin Pharmacol Ther*. 2024 Apr;115(4):758-773. doi: 10.1002/cpt.3114
34. Chekroud AM, Hawrilenko M, Loho H, et al. Illusory generalizability of clinical prediction models. *Science*. 2024;383(6679):164-167. doi:10.1126/science.adg8538
35. Ekberg H, van Gelder T, Kaplan B, Bernasconi C. Relationship of tacrolimus exposure and mycophenolate mofetil dose with renal function after renal transplantation. *Transplantation*. 2011;92(1):82-87. doi:10.1097/TP.0b013e31821fad06
36. Gatault P, Kamar N, Büchler M, et al. Reduction of extended-release Tacrolimus dose in low-immunological-risk kidney transplant recipients increases risk of rejection and appearance of donor-specific antibodies: a randomized study. *Am J Transplant*. 2017;17(5):1370-1379. doi:10.1111/ajt.14109
37. Zahir H, McCaughan G, Gleeson M, Nand RA, McLachlan AJ. Factors affecting variability in distribution of tacrolimus in liver transplant recipients. *Br J Clin Pharmacol*. 2004;57(3):298-309. doi:10.1046/j.1365-2125.2003.02008.x
38. Koop DR, Bleyle LA, Munar M, Cherala G, al-Uzri A. Analysis of tacrolimus and creatinine from a single dried blood spot using liquid chromatography tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2013;926:54-61. doi:10.1016/j.jchromb.2013.02.035
39. Veenhof H, Koster RA, Alffenaar JWC, Berger SP, Bakker SJL, Touw DJ. Clinical validation of simultaneous analysis of Tacrolimus, cyclosporine A, and creatinine in dried blood spots in kidney transplant patients. *Transplantation*. 2017;101(7):1727-1733. doi:10.1097/TP.0000000000001591
40. Koster RA, Alffenaar JWC, Greijdanus B, Uges DRA. Fast LC-MS/MS analysis of tacrolimus, sirolimus, everolimus and cyclosporin a in dried blood spots and the influence of the hematocrit and immunosuppressant concentration on recovery. *Talanta*. 2013;115:47-54. doi:10.1016/j.talanta.2013.04.027
41. van der Elst KC et al. Dried blood spot analysis suitable for therapeutic drug monitoring of voriconazole, fluconazole, and posaconazole. *Antimicrob Agents Chemother*. 2013;57(10):4999-5004. doi:10.1128/AAC.00707-13
42. Martial LC, Aarnoutse RE, Schreuder MF, Henriet SS, Brüggemann RJM, Joore MA. Cost evaluation of dried blood spot home sampling as compared to conventional sampling for therapeutic drug monitoring in children. *PLoS ONE*. 2016;11(12):e0167433. doi:10.1371/journal.pone.0167433
43. Veenhof H, van Boven JFM, van der Voort A, Berger SP, Bakker SJL, Touw DJ. Effects, costs and implementation of monitoring kidney transplant patients' tacrolimus levels with dried blood spot sampling: a randomized controlled hybrid implementation trial. *Br J Clin Pharmacol*. 2020;86(7):1357-1366. doi:10.1111/bcp.14249
44. Capiau S, Veenhof H, Koster RA, et al. Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology Guideline: development and validation of dried blood spot-based methods for therapeutic drug monitoring. *Ther Drug Monit*. 2019;41(4):409-430. doi:10.1097/FTD.0000000000000643
45. Capiau S, Stove VV, Lambert WE, Stove CP. Prediction of the hematocrit of dried blood spots via potassium measurement on a routine clinical chemistry analyzer. *Anal Chem*. 2013;85(1):404-410. doi:10.1021/ac303014b
46. Cheung CY, van der Heijden J, Hoogtanders K, et al. Dried blood spot measurement: application in tacrolimus monitoring using limited sampling strategy and abbreviated AUC estimation. *Transpl Int*. 2008;21(2):140-145. doi:10.1097/01.tp.0000331126.42103.63
47. Delahaye L, Heughebaert L, Lühr C, Lambrecht S, Stove CP. Near-infrared-based hematocrit prediction of dried blood spots: an in-depth evaluation. *Clin Chim Acta*. 2021;523:239-246. doi:10.1016/j.cca.2021.10.002
48. van de Velde D, van der Graaf JL, Boussaidi M, et al. Development and validation of hematocrit level measurement in dried blood spots using near-infrared spectroscopy. *Ther Drug Monit*. 2021;43(3):351-357. doi:10.1097/FTD.0000000000000834
49. De Kesel PM, Lambert WE, Stove CP. Does volumetric absorptive microsampling eliminate the hematocrit bias for caffeine and paraxanthine in dried blood samples? *A Comparative Study Anal Chim Acta*. 2015;881:65-73. doi:10.1016/j.aca.2015.04.056
50. Paniagua-González L, Lendoiro E, Otero-Antón E, López-Rivadulla M, de-Castro-Ríos A, Cruz A. Comparison of conventional dried blood spots and volumetric absorptive microsampling for tacrolimus and mycophenolic acid determination. *J Pharm Biomed Anal*. 2022;208:114443. doi:10.1016/j.jpba.2021.114443
51. Veenhof H, Koster RA, Junier LAT, Berger SP, Bakker SJL, Touw DJ. Volumetric absorptive microsampling and dried blood spot microsampling vs. conventional venous sampling for tacrolimus trough

concentration monitoring. *Clin Chem Lab Med*. 2020;58(10):1687-1695. doi:10.1515/cclm-2019-1260

52. Francke MI, Peeters LEJ, Hesselink DA, et al. Best practices to implement dried blood spot sampling for therapeutic drug monitoring in clinical practice. *Ther Drug Monit*. 2022;44(5):696-700. doi:10.1097/FTD.0000000000000994
53. Álvarez R, López Cortés LE, Molina J, Cisneros JM, Pachón J. Optimizing the clinical use of vancomycin. *Antimicrob Agents Chemother*. 2016;60(5):2601-2609. doi:10.1128/AAC.03147-14
54. Castellana M, Parisi C, di Molfetta S, et al. Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. 2020;8(1):e001092. doi:10.1136/bmjdrc-2019-001092
55. Stevens S, Gallagher S, Andrews T, Ashall-Payne L, Humphreys L, Leigh S. The effectiveness of digital health technologies for patients with diabetes mellitus: a systematic review. *Front Clin Diabetes Healthc*. 2022;3:936752. doi:10.3389/fcdhc.2022.936752
56. Heneghan CJ et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev*. 2016;7(7):CD003839.
57. Odendaal WA, Anstey Watkins J, Leon N, et al. Health workers' perceptions and experiences of using mHealth technologies to deliver primary healthcare services: a qualitative evidence synthesis. *Cochrane Database Syst Rev*. 2020;3(3):CD011942. doi:10.1002/14651858.CD011942.pub2
58. ISO *13485:2016*, International Organization for Standardization Editor. 2016–03.
59. *European commission regulation (EU) 2017/745 of the European Parliament and of the council of 5 April 2017 on medical devices*. European Union; 2023.
60. Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the magnitude of interaction between Tacrolimus and Voriconazole/Posaconazole in solid organ recipients. *Am J Transplant*. 2017;17(9):2372-2380. doi:10.1111/ajt.14232
61. Kirubakaran R, Stocker SL, Hennig S, Day RO, Carland JE. Population pharmacokinetic models of Tacrolimus in adult transplant recipients: a systematic review. *Clin Pharmacokinet*. 2020;59(11):1357-1392. doi:10.1007/s40262-020-00922-x
62. Maes BD, Lemahieu W, Kuypers D, et al. Differential effect of diarrhea on FK506 versus cyclosporine a trough levels and resultant prevention of allograft rejection in renal transplant recipients. *Am J Transplant*. 2002;2(10):989-992. doi:10.1034/j.1600-6143.2002.21018.x
63. Kravitz RL, Callahan EJ. Patients' perceptions of omitted examinations and tests: a qualitative analysis. *J Gen Intern Med*. 2000;15(1):38-45. doi:10.1046/j.1525-1497.2000.12058.x
64. Ietto G, Gritti M, Pettinato G, Carcano G, Gasperina DD. Tumors after kidney transplantation: a population study. *World J Surg Oncol*. 2023;21(1):18. doi:10.1186/s12957-023-02892-3
65. Boughton O, Borgulya G, Cecconi M, Fredericks S, Moreton-Clack M, MacPhee IAM. A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. *Br J Clin Pharmacol*. 2013;76(3):425-431. doi:10.1111/bcp.12076
66. Brooks E, Tett SE, Isbel NM, Staatz CE. Population pharmacokinetic modelling and Bayesian estimation of Tacrolimus exposure: is this clinically useful for dosage prediction yet? *Clin Pharmacokinet*. 2016;55(11):1295-1335. doi:10.1007/s40262-016-0396-1
67. Nanga TM, Doan TTP, Marquet P, Musuamba FT. Toward a robust tool for pharmacokinetic-based personalization of treatment with tacrolimus in solid organ transplantation: a model-based meta-analysis approach. *Br J Clin Pharmacol*. 2019;85(12):2793-2823. doi:10.1111/bcp.14110
68. Hughes JH, Tong DMH, Lucas SS, Faldasz JD, Goswami S, Keizer RJ. Continuous learning in model-informed precision dosing: a case study in pediatric dosing of vancomycin. *Clin Pharmacol Ther*. 2021;109(1):233-242. doi:10.1002/cpt.2088
69. Uster DW, Stocker SL, Carland JE, et al. A model averaging/selection approach improves the predictive performance of model-informed precision dosing: vancomycin as a case study. *Clinical Pharmacology & Therapeutics*. 2021;109(1):175-183. doi:10.1002/cpt.2065
70. Hughes JH, Keizer RJ. A hybrid machine learning/pharmacokinetic approach outperforms maximum a posteriori Bayesian estimation by selectively flattening model priors. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(10):1150-1160. doi:10.1002/psp4.12684
71. Jouve T, Fonrose X, Noble J, et al. The TOMATO study (Tacrolimus Metabolization in kidney transplantation): impact of the concentration-dose ratio on death-censored graft survival. *Transplantation*. 2020;104(6):1263-1271. doi:10.1097/TP.0000000000002920
72. van Gelder T, Meziyerh S, Swen JJ, de Vries APJ, Moes DJAR. The clinical impact of the C(0)/D ratio and the CYP3A5 genotype on outcome in Tacrolimus treated kidney transplant recipients. *Front Pharmacol*. 2020;11:1142. doi:10.3389/fphar.2020.01142
73. Steinbrook R. Health care and the American recovery and reinvestment act. *New England Journal of Medicine*. 2009;360(11):1057-1060. doi:10.1056/NEJMp0900665
74. Boonstra A, Broekhuis M. Barriers to the acceptance of electronic medical records by physicians from systematic review to taxonomy and interventions. *BMC Health Serv Res*. 2010;10(1):231. doi:10.1186/1472-6963-10-231
75. Grimson J, Grimson W, Hasselbring W. The SI challenge in health care. *Communications of the ACM*. 2000;43(6):48-55. doi:10.1145/336460.336474
76. Alexander SPH et al. The concise guide to PHARMACOLOGY 2023/24: ion channels. *Br J Pharmacol*. 2023;180(Suppl 2):S145-S222.

How to cite this article: Hazenbroek M, Pengel LHM, Sassen SDT, et al. Removing the physician from the equation: Patient-controlled, home-based therapeutic drug self-monitoring of tacrolimus. *Br J Clin Pharmacol*. 2024;1-9. doi:10.1111/bcp.16121