

ORIGINAL ARTICLE

Effects, costs and implementation of monitoring kidney transplant patients' tacrolimus levels with dried blood spot sampling: A randomized controlled hybrid implementation trial

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Funding information

Astellas Pharma Europe; Netherlands Organization for Health Research and Development (ZonMw, The Hague, Netherlands). Grant/Award Number: 836044004

Aims: Dried blood spot (DBS) home sampling allows monitoring creatinine levels and tacrolimus trough levels as an alternative for blood sampling in the hospital, which is important in kidney transplant patient follow-up. This study aims to assess whether DBS home sampling results in decreased patient travel burden and lower societal costs.

Methods: In this single-centre randomized controlled hybrid implementation trial, adult kidney transplant patients were enrolled. The intervention group ($n = 25$) used DBS home sampling on top of usual care in the first 6 months after transplantation. The control group ($n = 23$) received usual care only. The primary endpoint was the number of outpatient visits. Other endpoints were costs per patient, patient satisfaction and implementation.

Results: There was no statistically significant difference in the average number of outpatient visits between the DBS group (11.2, standard deviation: 1.7) and the control group (10.9, standard deviation: 1.4; $P = .48$). Average costs per visit in the DBS group were not significantly different (€542, 95% confidence interval €316–990) compared to the control group (€533, 95% confidence interval €278–1093; $P = .66$). Most patients ($n = 19/23$, 82.6%) were willing to perform DBS home-sampling if this would reduce the number of hospital visits. Only 55.9% ($n = 143/256$) of the expected DBS samples were received and 1/5 analysed on time ($n = 52/256$).

Conclusion: Adult kidney transplant patients are willing to perform DBS home sampling. However, to decrease patient travel burden and costs in post-transplant care, optimization of the logistical process concerning mailing and analysis of DBS samples is crucial.

KEYWORDS

cost-effectiveness, dried blood spots, implementation, randomized controlled trial

The authors confirm that the Principal Investigator for this paper is Daniël Johannes Touw and that he had direct clinical responsibility for the patients in this trial.

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1 | INTRODUCTION

Tacrolimus is currently the most used immunosuppressant in allograft rejection prevention in kidney transplant patients.¹ While effective at the correct dose, high tacrolimus trough levels are associated with severe adverse effects, while low tacrolimus levels increase the risk of acute rejection.² To find a balance between subtherapeutic and toxic effects of this drug in transplant patients, lifelong monitoring of blood drug levels using therapeutic drug monitoring (TDM) is therefore mandatory.^{2,3} Current clinical practice requires transplant patients to frequently travel to the hospital for venous blood sampling. In general, TDM is performed weekly in the first month post-discharge after renal transplantation. Over a period of approximately 1 year, the frequency is tapered to 3-monthly visits. Given the time delay between blood sampling and availability of analytical results, tacrolimus blood trough levels are usually not yet available when the nephrologist sees the patient and only become available in the evening of the day of sampling or the following day. This requires the patient to sample a few days earlier, or requires the nephrologist to schedule another appointment (usually by telephone) to discuss the TDM results. For both patient and nephrologist, this workflow is suboptimal.

Recently, dried blood spot (DBS) sampling was introduced as a novel tool that allows patients to sample at home. Using a fingerprick, blood can be applied to a sampling card, which can subsequently be mailed to the hospital laboratory a few days before a consultation with the nephrologist. DBS provides reliable results for both tacrolimus and creatinine levels.⁴⁻⁷ This results in up-to-date blood-drug levels at the time the patient consults the nephrologist. In theory, DBS sampling may result in a decreased patient travel burden, a more efficient workflow for the nephrologist, fewer outpatient visits and lower societal costs with improved quality of care.⁴ While promising, apart from a scenario analysis evaluating DBS home sampling for TDM of immunosuppressants, no clinical studies have assessed the cost-effectiveness of DBS home sampling.⁸ Only 1 study addressed the feasibility and implementation of home-based microsampling for tacrolimus TDM in children, but this study lacked a control group.⁹ Other studies focused on the feasibility of DBS home sampling in the context of patient sampling performance and sample quality.¹⁰⁻¹⁴

Given that using DBS home sampling could result in up-to-date blood levels of tacrolimus readily available at every consultation, we hypothesized that implementing DBS would increase the rate of tapering of outpatient visits and therefore would lower total health care costs. In this randomized controlled hybrid implementation trial, we aimed to assess whether the use of DBS home sampling in the first 6 months after kidney transplantation would result in fewer clinical consultations and lower costs from a societal perspective compared to usual care. In addition, the implementation of DBS home sampling was evaluated with regards to sampling logistics.

What is already known about this subject

- To prevent allograft rejection and drug toxicity, kidney transplant patients require frequent monitoring of tacrolimus trough levels during the first 6 months after transplantation.
- The dried blood spot (DBS) fingerprick sampling method can be used by transplant patients at home and tacrolimus and creatinine results of DBS are interchangeable with results of conventional venous sampling.
- DBS home sampling could lead to decreased patient travel burden and cost savings, but this had not been evaluated in a clinical study.

What this study adds

- Implementation of DBS sampling did not show a decreased patient travel burden in this study, mainly due to logistical problems concerning the sending and analysis of samples.
- Implementation of novel sampling techniques requires proper reminder systems for both patients and physicians, and high quality and traceable logistics.
- Adult kidney transplant patients are willing to perform DBS home sampling if this leads to a reduced number of outpatient visits to the hospital.

2 | MATERIALS AND METHODS

2.1 | Study design

In this single-centre randomized controlled trial, the intervention group used DBS sampling on top of usual care in the first 6 months after kidney transplantation, while the control group received usual care only. This study was designed as a hybrid implementation trial where a clinical intervention is tested while observing and gathering information on implementation.¹⁵ Therefore, an implementation strategy was not part of this study. This study is reported in accordance with the Standards for Reporting Implementation Studies (StaRI), see supplement S1.^{16,17} This study was conducted in accordance with the declaration of Helsinki, the EMA guideline for good clinical practice E6(R2) and the CONSORT 2010 guideline, see Supplement S2.^{18,19} The study protocol was approved by the medical ethical committee of the UMCG (NL56927.042.16.). The study protocol stated that, because of the nature of the study, no (serious) adverse events have to be reported. The trial protocol was registered in the Dutch Trial Register (Trial NL7721).

2.2 | Study population

All adult patients who were hospitalized at the University Medical Center Groningen (UMCG) after receiving a renal transplantation were screened. The inclusion criteria were: age ≥ 18 years, still hospitalized after renal transplantation, use of tacrolimus, proficiency of the Dutch language and ability to use the DBS sampling method.²⁰ The study follow-up period was 6 months. Patients who withdrew from the study during the enrolment period for any reason were replaced. Patients who switched, during the study, to another immunosuppressant that could also be monitored with DBS such as cyclosporin A, sirolimus or everolimus were not excluded.^{4,21} Written informed consent was obtained from all participants included in the study as described by the International Committee of Medical Journal Editors.²²

2.3 | DBS training and administration schedule

The intervention group received training in DBS sampling using a previously described method while still hospitalized after transplantation.²⁰ This 15-minute training included studying and practicing the complete sampling procedure under supervision of an experienced study-coordinator until deemed satisfactory.^{9,23} At each patients consultation, the nephrologist placed orders for DBS home sampling for the following consultation. During the first 4 weeks after kidney transplantation, patients were scheduled to visit the outpatient clinic every week and sampled 5 days prior to the visit. Subsequently, patients received instructions to sample 7 days prior to a scheduled visit. Upon receiving the DBS samples, the hospital laboratory routinely analysed the blood extracted from the DBS samples twice weekly, using previously validated method.⁴⁻⁶

2.4 | Study context and usual care

Patients in both the DBS and control groups received usual care as described by transplantation protocols in the UMCG. During the first year post-transplantation, all patients are treated in the academic hospital (the UMCG) where the transplantation was performed. This treatment consists of transplantation nephrologist consultation in the out-patient clinic. Patients arrive in the out-patient clinic before 10 AM for venous blood sampling because of the need to obtain a tacrolimus trough concentration, in addition to other clinical chemical parameters and serum creatinine. Nephrologist consultation is usually between 9 and 12 AM and takes on average 10 minutes. Tacrolimus trough concentrations are usually available in the late afternoon. Therefore, a telephone consult of, on average, 7.5 minutes takes place in the evening or the next day if, based on tacrolimus trough concentration, adjustment of the tacrolimus dose is needed. The frequency of outpatient visits is predetermined (weekly visits) in the first month postdischarge after adult renal transplantation. After that, follow-up visit frequency is planned based on clinical observation by the

nephrologist. Given that using DBS home sampling would result in up-to-date blood levels of tacrolimus and creatinine readily available at every outpatient visit, we hypothesized that implementing DBS would increase the rate of tapering of outpatient visits and therefore would lower the number of outpatient visits during the first 6 months after transplantation. On a yearly basis, approximately 170 adult kidney transplantations are performed in the UMCG. Patient travelling distance to the outpatient clinic is usually between 1 and 150 km.

2.5 | Effectiveness outcomes

The primary endpoint of this study was the number of outpatient visits per patient. Secondary endpoints were costs and patient satisfaction. Cost differences were measured between the DBS group and the control group using standard health resources use questionnaires and the formal Dutch reference prices of care, further detailed in the *Data collection* and *Cost evaluation* sections.²⁴

2.6 | Implementation outcomes

Implementation outcomes were the number of tacrolimus dose adjustments communicated by phone. If DBS results were available during the patient's visit, no phone calls discussing tacrolimus dosing would be needed. Other implementation and logistics measures included: (i) the number of DBS results that were on time, defined as the analytical results that were available in the patient's electronic health record (EHR) prior to the outpatient visit to the nephrologist; (ii) the time between sampling by the patient and receiving the sample at the laboratory as well as the analysis time, obtained from the EHR; and (iii) the number of printed prescriptions for tacrolimus, obtained from the EHR.

2.7 | Cost evaluation

To perform the cost evaluation from a societal point of view, 3 cost categories were identified: patient costs (parking costs and travelling expenses), costs related to loss of productivity (patients' travel time and time in the hospital, caregivers time) and healthcare costs (outpatient clinic visits, laboratory costs, nephrologist phone call, DBS sampling kit and analysis costs).⁸ Patient parking costs and traveling distance (in km) were obtained from the Institute for Medical Technology Assessment (iMTA) questionnaire (Supplement S3).²⁵⁻²⁷ To calculate traveling time (by car) an average speed of 80 km/h was assumed. The time in the hospital was calculated by the time difference between the moment of venous blood sampling and the start of the scheduled appointment plus 30 minutes to account for the duration of the scheduled appointment with the nephrologist (15 minutes) and the queue for venous sampling by a phlebotomist (15 minutes). Information about the presence of a caregiver and the patient's occupation was obtained from the iMTA questionnaire. Depending on

the occupation of a patient (employed, not-employed), a rate for loss of productivity was chosen for the cost calculation as stated by the formal Dutch national tariff, cost year 2017 (Table 1).²⁴ All laboratory results from the patients were obtained and prices were calculated using the tariff listing of the UMCG of 2017. Laboratory ordering was done using fixed sets of clinical chemical and haematological parameters. There are 3 types of order sets used, which are defined as *small*, *normal* and *extensive* (Table 1). Additional parameters such as blood drug levels and viral antibody titres are ordered separately (Table 1). The costs for an outpatient visit, the nephrologist telephone call and DBS training was based on the Dutch national tariff.²⁴ Since DBS-training was performed while patients were still hospitalized, no loss of productivity occurred. The costs for the DBS sampling kit and analysis was fixed (see Table 1). The 1-time costs of the implementation were calculated. Since, prior to the start of the implementation, the

TABLE 1 Reference prices as defined by the Dutch national tariff of 2017 and the university medical Centre Groningen tariff list of 2017

Type	Costs	Per
Patient costs		
Travel expenses (car)	€0.19	km
Parking costs	€3.00	Visit
Loss of productivity		
Productivity cost, paid, working women	€32.00	hr
Productivity cost, paid, working men	€38.00	hr
Unpaid work, replacement costs	€14.00	hr
Caregiver, replacement costs	€14.00	hr
Healthcare costs		
Patient visit to an academic outpatient clinic	€163.00	Visit
Nephrologist time	€113.00	hr
Nephrologist phone call	€14.13	Call
Study coordinator costs	€24.70	hr
DBS training (time and materials)	€13,68	Training
DBS sampling kit	€7.50	Kit
DBS analysis (tacrolimus + creatinine)	€50.00	Analysis
<i>Small</i> laboratory	€41.52	Analysis
<i>Normal</i> laboratory	€110.49	Analysis
<i>Extensive</i> laboratory	€348.34	Analysis
Tacrolimus whole blood	€44.03	Analysis
Mycophenolic acid whole blood	€44.03	Analysis
BK IgG	€93.87	Analysis
CMV IgG	€227.17	Analysis
EBV IgG	€227.17	Analysis

BK IgG, BK virus antibodies. CMV IgG, cytomegalovirus antibodies; DBS, dried blood spots; EBV IgG, Epstein-Barr virus antibodies.

DBS analytical method and DBS instruction method were already present, the development of these methods was not added to the implementation costs.²⁸ Based on the labour tariffs of the UMCG in the year 2017, the hourly costs of the study coordinator who performed the implementation was calculated (Table 1).

2.8 | Data collection

2.8.1 | Demographic and clinical data

Demographic, clinical and biochemical data were retrospectively collected from the EHR at baseline and during study follow-up. This included total bodyweight, height, time and date of transplantation, donor (living/deceased), donor age, donor sex, diabetes at baseline, immunosuppressive medication, delayed graft function and hospitalization time after transplantation.

The number of visits to the transplantation outpatient clinic was recorded, including date, tacrolimus dose (adjustments) and accompanying physician notes. The number of tacrolimus dose changes communicated by nephrologist' phone calls was obtained from the EHR. The number of written prescriptions for tacrolimus was obtained from the electronic prescribing system. For the DBS samples, data about date and time of sampling were recorded by patients at time of sampling. Data about reception of the sample at the laboratory, analysis time and time the results were available were collected from the EHR.

2.8.2 | Cost and patient satisfaction data

Four weeks after inclusion, all patients received a questionnaire about loss of (work) time due to the routine outpatient visits based on the Medical Consumption Questionnaire, the iMTA Valuation of Informal Care Questionnaire and the Productivity Cost Questionnaire, developed by the iMTA of the Erasmus University Rotterdam.²⁵⁻²⁷ These questionnaires are validated to perform cost-effectiveness research from a societal point of view in the Netherlands. Patients in the DBS group also completed a survey on patient satisfaction and feasibility of DBS sampling. The (Dutch) questionnaires can be found in Supplement S3. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.9 | Sample size

Based on the kidney transplant protocols used in our hospital and retrospective data, we expected an average of 10 visits to the outpatient clinic per patient during the study period. Based on expert opinion by several experienced nephrologists, the number of visits per patient could be reduced to 9 when using the DBS sampling method. With an expected reduction of 10%, assuming a standard deviation (SD) of 1, 5% error and a power of 90% resulted in a sample size of 22 patients per group. To account for 10% expected loss to follow-up

during the study, a minimum of 25 patients per group were to be included.

2.10 | Randomization

Randomization was done using computer-generated random numbers with equal allocation in 2 groups by an independent researcher who was not part of this study. The allocation was concealed in sequentially numbered, sealed envelopes. Patients were screened, enrolled and trained by 1 study coordinator. Due to the nature of the intervention, participant blinding was not possible.

2.11 | Statistical analysis

All categorical data are expressed as percentages, normally distributed numeric data as average \pm SD. Normality was tested using a Shapiro-Wilk test. When not normally distributed, the data are expressed as median with an interquartile range. Normally distributed cost data are expressed as an average with 95% confidence interval (95%CI) based on SD. When cost data were not normally distributed, the 95%CI was obtained by non-parametric bootstrapping ($n = 1000$ resampled data sets, bootstrap estimates 2.5th to 97.5th percentiles). The differences in patient visits were analysed both per-protocol and as intention-to-treat. Differences in continuous variables were assessed by a 2-tailed, unpaired t test. All statistical analyses were performed using SPSS, version 23 (SPSS, Chicago, IL, USA) or Anlyse It for Excel 4.81.6 (Leeds, UK). A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

In total, 83 patients were screened between May 2016 and May 2017 of whom 54 patients were randomized (for flow diagram, see Figure 1). In the DBS group, 3 patients were excluded, resulting in 25 patients included in the analysis. In the control group, 3 patients were excluded resulting in 23 patients included in the analysis. Reasons for exclusion can be found in Figure 1. All patients were Caucasian and received standard triple immunosuppressive therapy after transplantation consisting of tacrolimus, mycophenolic acid and prednisolon. Baseline characteristics were comparable in both groups (Table 2).

4 | EFFECTIVENESS OUTCOMES

4.1 | Number of visits

There was no statistically significant difference in the average number of visits between the DBS group and the control group ($P = .48$) as shown in Table 3.

4.2 | Patient satisfaction

In the DBS group, 23 out of 25 patients (92%) completed the questionnaire on DBS sampling satisfaction. Qualitative results can be found in Table 4. DBS sampling was manageable for most patients (82.6%, $n = 19/23$) and most patients (82.6%, $n = 19/23$) were willing to perform DBS home-sampling if this would reduce the number of hospital visits.

4.3 | Costs

In total, 23 patients in the DBS group and 23 patients in the control group completed the cost questionnaire and were included in the cost analysis. Because only 56% (see Results section 'implementation outcomes') of the expected number of DBS were analysed, the costs related to DBS analysis were corrected (Table 5). A Shapiro-Wilk test showed that costs were not normally distributed in both the DBS ($P < .0001$) and control ($P < .0001$) group. Therefore, costs are shown as a median in Table 5. However, because average costs are often used in decision making, this is also shown in Table 5. In the DBS group almost 80% ($n = 18/23$) of the patients were accompanied by a caregiver during the visit, in the control group this was about 50% ($n = 12/23$). Average costs in the DBS group were slightly higher, but not significantly different from the control group ($P = .66$). If the cost for DBS were subtracted, the average total costs for a patient visit in the DBS and control group were similar (€508; 95%CI €294-949 and €533; 95%CI €278-1093, respectively). The costs of patient training were €13.68 per patient; since these costs are 1-time only, they were not included in Table 5.

4.4 | Implementation outcomes

There were no statistically significant differences in the average number of tacrolimus dose adjustments communicated by phone and the number of printed tacrolimus prescriptions (Table 3).

The implementation took a total of 6 months' time for the study coordinator. The total (1-time) implementation costs were €19,244.

In the DBS group, according to the study protocol, a total of 256 DBS samples were expected to be sent to the hospital laboratory. During the study, a total of 143 (55.9%) of the expected number of DBS samples were received at the hospital. Of those, slightly over 1/3 ($n = 52$) of the results were on time. Seven DBS samples (4.9%) were rejected because of insufficient quality. For the intention-to-treat group, the average number of DBS samples per patient that was on time was 2.1 ± 2.0 (range 0-7). A per protocol analysis was performed on a subset of 6 patients who had ≥ 4 visits, where results of the DBS analysis were available in the EHR at the time of nephrologist consultation. There was no statistically significant difference in the per protocol group compared to the control group for the number of visits, tacrolimus dose adjustments communicated by phone and number of printed prescriptions as shown in Table 3.

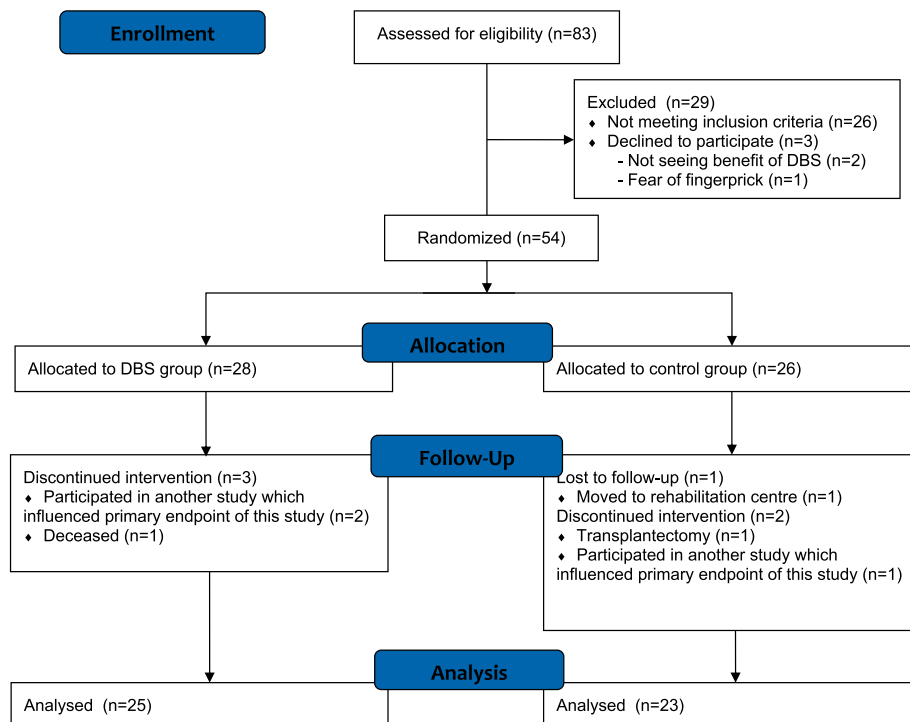


FIGURE 1 CONSORT diagram. DBS = dried blood spots

TABLE 2 Demographics and baseline characteristics of the patients

Participants	DBS group (n = 25)	Control group (n = 23)
Male sex, n (%)	17 (68.0)	12 (52.2)
Age, years ± SD	52.8 ± 14.1	50.9 ± 14.3
Body weight, kg ± SD	83.7 ± 15.6	79.2 ± 15.1
BMI, kg/m ² ± SD	27.7 ± 4.6	26.3 ± 4.7
Hospitalization time after transplantation, days ± SD	8.3 ± 2.3	9.3 ± 4.1
Delayed graft function, n (%)	5 (25.0)	4 (17.4)
Diabetes at baseline, n (%)	5 (25.0)	4 (17.4)
Induction, n (%)		
rATG	1 (4.0)	2 (8.7)
Basiliximab	5 (20.0)	5 (21.7)
Rituximab	2 (8.0)	0 (0.0)
Alemtuzumab	0 (0.0)	1 (4.3)
Donor		
Average age, y ± SD	55.3 ± 11.3	50.0 ± 15.9
Male, n (%)	18 (72.0)	17 (73.9)
Donor category, n (%)		
Living	17 (68.0)	12 (52.1)
Deceased, heart beating	0 (0.0)	5 (21.7)
Deceased, no heart beat	8 (32.0)	6 (26.1)

BMI, body mass index; DBS, dried blood spots; rATG, rabbit anti-thymocyte globulin; SD, standard deviation.

If dose adjustment occurred, this was communicated to the patient by the nephrologist per phone in 92.6% of the cases in the control group. For the intention-to-treat and per-protocol groups this was 89.9 and 79.3%, respectively. This difference was not statistically significant for either group compared to the control group ($P = .66$ and $.34$ respectively).

The average time between patient home sampling and receiving the sample in the hospital was 3.9 ± 6.6 days. The average time between receiving the sample and results available in the EHR (analysis time) was 2.6 ± 2.3 days. The total time between patient home sampling and results available in the EHR was 6.5 ± 6.6 days.

5 | DISCUSSION

Although DBS sampling is a promising tool to improve kidney transplant patient healthcare from both costs and patient satisfaction perspectives, this study showed no decrease in the number of outpatient visits. In addition, there were no reductions in costs, written tacrolimus prescriptions or dose adjustments communicated by phone when comparing the DBS group to the control group. Of note, implementation of DBS sampling, analysis and logistics were far from optimal, with 56% of DBS samples received and only 1 out of 5 DBS results being available on time.

The low availability of timely DBS results (20%) seems a plausible explanation for the absence of differences in primary or secondary endpoints in this study. Although these values are low, this is in line with the low DBS availability in a study by Al-Uzri et al. where

TABLE 3 Average number of visits to the outpatient clinic per patient per group

	DBS group		Control group (n = 23)	P value	
	Intention to treat (n = 25)	Per protocol* (n = 6)		Intention to treat	Per protocol*
Average number of visits per patient \pm SD	11.2 (1.7)	11.2 (0.9)	10.9 (1.4)	.48	.63
Average number of tacrolimus dose adjustments communicated by phone \pm SD	3.9 (1.6)	3.8 (2.0)	3.3 (2.0)	.23	.57
Average number of printed prescriptions for tacrolimus per patient \pm SD	3.4 (1.2)	4.0 (1.2)	3.1 (1.5)	.45	.18

*The per protocol group consists of 6 patients who had ≥ 4 visits where results of DBS analysis were available in the electronic health records at the time of nephrologist consultation.

DBS, dried blood spots; SD, standard deviation.

TABLE 4 Qualitative results of patient questionnaire on dried blood spot (DBS) sampling feasibility (n = 23)

Already experienced with fingerprick sampling	No (11)	Yes (8)	Slightly (4)
Able to produce a sufficient quality DBS sample with given instructions	Too hard (3)	Hard, but manageable (3)	Reasonably/easily (17)
Preferred way of blood sampling	Finger prick (5)	Venous sampling (6)	No preference (12)
Willing to provide multiple DBS a year if this can reduce the number of hospital visits	No (3)	Yes (19)	I don't know (1)

28 paediatric transplant patients were expected to provide a total of 279 DBS samples in a 12-month period.⁹ In this latter study, a total of 77% of the expected DBS were received by the laboratory, and 38% were considered on time (within 7 days after sampling). However, in contrast to our study, in the study by Al-Uzri et al., patients received a reminder phone call when no DBS sample was received.⁹ Upfront, we expected that patients would be highly motivated to perform DBS sampling at home, because the results of DBS would be available to them at the time of nephrologist consultation. A possible explanation for the low adherence to DBS sampling could be that patients performed DBS on top of conventional venous sampling instead of a complete substitute for venous sampling. Another possibility is the logistical problems concerning sending of DBS samples. The Dutch public posting service assures that if a medical sample is sent during working hours, it should be delivered the next morning. However, we calculated an average of 3.9 ± 6.6 days between patient sampling and receiving the sample at the laboratory. It is not possible to assess the reason for this, but possible explanations could be: (i) the patient forgot to send the sample; (ii) delays by the Dutch postal service; and (iii) delays in the hospitals' internal distribution system. Logistical delays might have led to a number of DBS results not being available on time, which could have resulted in decreased motivation and adherence to DBS sampling, as was mentioned by 3 patients.

Only 3 out of 23 patients found DBS home sampling too difficult to perform, mainly due to tremor in the hands, a well-known side-effect of tacrolimus. This is in accordance with other studies in which 91% (n = 55) and 93% (n = 36) of the patients were able to perform DBS sampling at home.^{11,13} Only 4.9% of the received samples was of insufficient quality, which is comparable to the performance of DBS

sampling by trained phlebotomists^{4,23} and is better than reported in other DBS feasibility studies, where 20% of the obtained samples were unfit for analysis.^{9,10} This shows that the used instruction method is adequate for patients to perform DBS home sampling. Preference of DBS sampling over venous sampling in this study was relatively low (21.1%) compared to other studies that report values between 37–61%.^{10–13} This can probably be explained by the previously mentioned reasons on patient motivation. However, 82.6% of the patients were willing to perform DBS sampling, if this leads to a reduced number of outpatient visits.

This study showed that kidney transplant patients required an average of 11 outpatient clinic visits in the first 6 months after transplantation at an average cost of €520 per visit (excluding costs for DBS analysis). If DBS home sampling is used as intended and a reduction of 1 visit per patient in the first 6 months after transplantation is realized, DBS sampling will save around €3 per patient if it is used on top of usual care. If DBS sampling would replace venous sampling for tacrolimus and creatinine, is used as intended and therefore reduces 1 visit per patient in the first 6 months after transplantation this will lead to a cost reduction of €399 per patient. In our centre, 192 adult kidney transplantations were performed in 2017. Thus, this could potentially lead to an annual societal cost-reduction of €76,608. Patients who are >12 months post-transplantation usually visit the outpatient hospital on a 3-monthly basis. It is possible that introduction of DBS home sampling for these patients on a 2–3 monthly basis might reduce the need for an outpatient visit every 3 months resulting in even further cost reduction.

Although not significant, this study shows a trend towards fewer telephone calls needed to discuss tacrolimus dose adjustments if DBS

TABLE 5 Average costs per visit of the patient to the outpatient clinic from a societal point of view

Time and costs per visit to the polyclinic	DBS group (n = 23)			Control group (n = 23)				
	Average volume/unit n ± SD	Average costs € (95%CI)	Median volume/unit n (IQR)	Median costs € (IQR range)	Average volume/unit n ± SD	Average costs € (95%CI)	Median volume/unit n (IQR)	Median costs € (IQR range)
<i>Patient costs</i>								
Parking costs		€2.61 (€0.00–3.00)		€3.00 (€3.00–3.00)		€1.62 (€0.00–€3.60)		€3.00 (€0.00–3.00)
Travel expenses	73 ± 46 km	€29.52 (€2.13–70.47)	76 km (42–92)	€29.15 (€15.81–39.14)	90 ± 60 km	€34.02 (€0.18–88.16)	94 km (32–140)	€35.61 (€12.29–53.20)
<i>Loss of productivity</i>								
Travel time	109 ± 69 min	€40.88 (€2.13–149.32)	115 min (62–137)	€32.03 (€20.62–60.55)	132 ± 85 min	€43.21 (€5.53–117.41)	120 min (49–210)	€32.80 (€17.27–61.09)
Time in hospital	90 ± 34 min	€36.66 (€7.00–87.89)	87 min (70–111)	€30.10 (€18.67–51.20)	91 ± 40 min	€32.93 (€7.00–93.84)	91 min (67–109)	€30.10 (€17.03–45.33)
Companion		€37.30 (€17.06–90.67)		€45.96 (€36.43–58.22)		€33.06 (€21.67–109.50)		€45.96 (€36.43–58.22)
<i>Healthcare costs</i>								
Visit to the polyclinic		€163.00*		€163.00*		€163.00*		€163.00*
Nephrologist telephone call		€4.97 (€0.00–€14.13)		€0.00 (€0.00–14.13)		€4.25 (€0.00–14.13)		€0.00 (€0.00–14.13)
Laboratory costs		€194.94 (€57.29–653.25)		€154.52 (€85.55–179.42)		€218.77 (€84.01–731.14)		€154.52 (€85.55–248.39)
DBS set	0.56	€4.33 (€0.00–7.50)		€7.50 (€0.00–7.50)				
DBS analysis	0.56	€28.85 (€0.00–50.00)		€50.00 (€0.00–50.00)				
Total		€541.55 (€315.78–990.19)		€492.68 ± (€415.63–601.20)		€532.73 (€278.09–1092.57)		€479.55 (€399.83–581.86)

*Costs are fixed, so no IQR or 95%CI is given.

SD = standard deviation; IQR = interquartile range; DBS = dried blood spots; 95%CI = 95% confidence interval obtained by nonparametric bootstrapping.

results are available on time. This indicates that the workflow for the nephrologist is potentially less time consuming and might increase the cost-reduction.

A strength of this study is that this is the first study that calculates costs of DBS sampling from a societal perspective in an outpatient setting. The design was chosen to be highly reflective of real-world practice of kidney transplant outpatient follow-up. To reflect daily practice, we deliberately chose to not interfere with usual care (e.g. send reminders to nephrologists and patients to sample DBS) and make the patient and nephrologist responsible for timely DBS sampling. This study shows that implementation of a novel home sampling method requires more time and a proper reminder system before it can be a part of routine patient care, replacing conventional venous sampling. Another implementation study including an implementation strategy and evaluation, prior to performing a cost evaluation study, might help in achieving this goal.²⁹ In addition, logistical challenges need to be overcome. Possible solutions could be: (i) automated reminders by (smart)phone or e-mail to tell the patient when to perform DBS home sampling; (ii) increasing the time between sampling and the visit to the outpatient clinic (>7 days) to account for logistic delays; and (iii) sending the samples with track-and-trace to be able to gain insight in logistical processes.

A limitation is that this study was performed in a Dutch setting, which can be different from other countries. However, since the Netherlands is more densely populated than most countries, patient costs saved due to DBS sampling might be higher in other countries due to longer travel distances to the hospital. Another limitation is the sample size, which was calculated on the primary endpoint. The sample size might not be fit for measuring secondary endpoints, meaning that caution is warranted when interpreting these results.

Although DBS home sampling seems promising, improving logistical methods for DBS samples is required to reduce the average of 4 days between patient sampling and receiving the sample at the laboratory to make DBS sampling feasible. A standard day for sampling, sending the sample and analysis in the laboratory might reduce both the time between sampling by the patient and analysis, as well as the time between analysis and results becoming available. However, this might make DBS sampling less feasible in the first 4 weeks after transplantation when visits are scheduled weekly. In future trials, a feasibility study should be performed prior to a cost-evaluation study on DBS to account for logistical hurdles. This study should be designed as an implementation study using available implementation strategies, such as the Consolidated Framework for Implementation Research.²⁹ The results from a feasibility study can also help provide a more accurate sample size calculation. If the number of visits and the SD observed in this study were used for the power calculation mentioned in the Methods section, the number of patients per group would be 48.

In conclusion, this study did not show a reduction in the number of outpatient visits when DBS home sampling for tacrolimus monitoring was offered to kidney transplant patients. Although DBS seems promising, the logistical process concerning timely sending and analysis of DBS samples should be optimized before effectiveness

assessment. Potentially, successful implementation of DBS offers a more efficient workflow for nephrologists, requiring fewer telephone calls to communicate dose adjustments. Transplant patients are willing to perform DBS home sampling if logistical hurdles are overcome and DBS home sampling is properly implemented in routine transplant care. If DBS is optimally implemented, eventually, this might lead to increased patient satisfaction, lower patient travel burden and lower societal costs.

ACKNOWLEDGEMENTS

This work was supported by the Netherlands Organization for Health Research and Development (ZonMw, The Hague, Netherlands) grant 836044004 and an unrestricted grant from Astellas Pharma Europe Ltd.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

H.V. and J.F.M.B. participated in conception, design, analysis and interpretation of data, drafting and revising the article, providing intellectual content and approved the final version of the manuscript. A.V.D.V. participated in analysis and interpretation of data, revising the manuscript, providing intellectual content and approved the final version of the manuscript. S.J.L.B., S.P.B. and D.J.T. participated in conception, design and interpretation of data, revising the article, providing intellectual content and approved the final version of the manuscript.

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SUPPORTING INFORMATION

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

How to cite this article: 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;86:1357-1366. <https://doi.org/10.1111/bcp.14249>