

# BMJ Open Prospective single-centre clinical observational study on electronically monitored medication non-adherence, its psychosocial risk factors and lifestyle behaviours after heart transplantation: a study protocol

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## ABSTRACT

**Introduction** In heart transplant recipients (HTRs), non-adherence (NA) to immunosuppressive (IS) medication and to recommended lifestyle behaviours are a common phenomenon and associated with higher risk of allograft rejection, organ loss and mortality. Risk factors for NA are highly diverse and still insufficiently researched. Precise measures of NA and an accurate understanding of its aetiology are of undisputable importance to detect patients at risk and intervene accordingly. The aim of this study is to assess the accuracy and concordance of different measures for NA as well as to determine potential risk factors.

**Methods and analysis** This is a single-centre prospective observational trial. HTRs who are at least aged 18 are no less than 6 months post-transplant and receive tacrolimus (Prograf or Advagraf), cyclosporine (Sandimmun) or everolimus (Certican) as their prescribed IS medication are eligible for participation. We only include patients during the phase of medication implementation. At study enrolment, we assess depression, health-related quality of life, self-efficacy, social support, attachment, experiences and attitudes towards IS medication, emotional responses after transplantation, satisfaction with information about IS medication and perceptions and beliefs about medications. We further ask patients to rate their lifestyle behaviours concerning alcohol, smoking, diet, physical activity, sun protection and appointment keeping via questionnaires. Three different measurement methods for NA are applied at T0: self-reports, physician's estimates and IS trough levels. NA is monitored prospectively using an electronic multicompartiment pillbox (MEMS, VAICA) over a 3-month period. Meanwhile, participants receive phone calls every second week to obtain additional self-reports, resulting in a total of seven measurement points.

**Ethics and dissemination** The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg). Written informed consent is attained from all participants. The results of this study will be published in peer-reviewed journals and presented at conferences.

**Trial registration number** DRKS00020496.

## Strengths and limitations of this study

- This is the first study assessing potential risk factors of immunosuppressive (IS) non-adherence (NA) and non-pharmacological NA by prospectively applying electronic monitoring in heart transplant recipients.
- This study combines different measurement methods for NA, such as electronic monitoring, self-reports, physician's estimates and IS trough-level variability.
- One limitation of our study is a potential initial intervention effect induced by electronic monitoring; however, adherence behaviour is likely to stabilise after approximately 40 days.
- This is a single-centre study with a moderate sample size.

## INTRODUCTION

Adherence is defined as 'the process by which patients take their medication as prescribed'.<sup>1</sup> Especially in transplant recipients, regular and accurate intake of immunosuppressants is vital for organ survival.<sup>2-3</sup> Immunosuppressive (IS) non-adherence (NA) rates in transplant recipients differ greatly depending on the respective organ, with a mean prevalence of approximately 22.6% of patients per year.<sup>4-10</sup> For heart transplant recipients (HTRs), NA rates range between 4.6% and 39.2%,<sup>4-7 11 12</sup> influenced by the choice of measurement methods, operational definitions and case finding methods. Due to a rising awareness of its detrimental impact on allograft rejection, organ loss and mortality,<sup>2 13</sup> research on NA in HTRs has increased substantially in recent years. Already minor deviations from the medical regimen have been associated with hazardous effects on organ and patient survival.<sup>14</sup>

Various assessment tools for NA are currently available, comprising both indirect and direct measures. Direct measures include direct observation and blood assays, whereas for indirect measures pill counts, self-reports, collateral reports and electronic monitoring are used.<sup>15 16</sup> The most frequently employed NA measure for HTRs is self-report.<sup>16</sup> Despite their susceptibility to errors, such as memory bias and social desirability, self-reports are considered practical and inexpensive tools for NA assessment.<sup>15 17–20</sup> Although electronic monitoring allows insights into patterns of adherence behaviour, its use can be quite expensive and labour intensive.<sup>15 17</sup> Except for few studies,<sup>25 14</sup> electronic monitoring is only very sparsely used in HTRs.<sup>16</sup> Blood assays such as the trough-level variability are also frequently applied as an adherence measure, since they have increasingly been associated with rejection and mortality in HTRs.<sup>13 21 22</sup> Collateral reports, however, are mostly considered unreliable measurement methods for NA.<sup>23</sup> To increase sensitivity, some studies also use a combination of measurement methods to assess NA, which mostly results in very high NA rates.<sup>5 15</sup> Few studies have examined the accuracy and concordance of these NA measures<sup>17 24–28</sup>; especially in HTRs, research is scarce. However, an accurate assessment of NA seems crucial in order to detect patients at risk and to intervene accordingly.

Besides the relevancy of immunosuppressant intake, certain lifestyle habits can also adversely affect organ survival as well as patient morbidity and mortality after transplantation.<sup>29–33</sup> Nonetheless, a considerable amount of HTRs insufficiently adheres to certain lifestyle recommendations. Compared with other types of organs, HTRs display particularly high NA rates for physical exercise, with prevalences ranging between 33.7% and 49.1%.<sup>4 11 29 34</sup> For following dietary recommendations, NA rates between 22.9% and 46% were observed, while those for keeping follow-up appointments varied between 5.7% and 37.3%.<sup>4 11 29 30 34</sup> Alcohol use was found for approximately 4.9% to 27.8% of HTRs, while tobacco use was confirmed by 3.2% to 9.1%.<sup>4 11 29 34</sup> Helmy *et al*<sup>29</sup> further revealed that up to 39.9% of HTRs did not apply sun protection as recommended. Correlations between the various domains of lifestyle habits could not be detected,<sup>11</sup> whereas IS NA was found to be inter-related with appointment keeping<sup>30</sup> and smoking.<sup>12</sup> Research on non-pharmacological NA is sparse and only few have examined the occurrence of and interrelations between various NA areas. However, research on solid organ transplant recipients that included HTRs found certain patient-related risk factors for unhealthy lifestyle behaviours. Post-transplant smoking was found to be more prevalent in men, but less in older patients and those with comorbid physical diseases such as diabetes and hypertension.<sup>33</sup> Smoking in turn was found to be a risk factor for post-transplant at-risk drinking, while post-transplant alcohol use in general could be linked with male gender, being employed, and a history of psychiatric illness, among others.<sup>35</sup> No significant risk factors were

found for low physical exercise.<sup>36</sup> Most of these studies are based on the results of kidney recipients, while research on heart recipients is rare. Especially studies connecting non-pharmacological NA with electronically monitored IS NA in HTRs are missing.

Risk factors for IS NA on the other hand are well examined, although highly diverse and multifactorial in nature. They can reach from health system factors and behaviours of healthcare providers to factors on the individual patient level.<sup>37</sup> When developing interventions, especially the identification of modifiable factors on the patient level is of primary interest. A broad literature search on studies comprising HTRs revealed a variety of patient-related factors such as depression,<sup>38</sup> lower social support,<sup>4 6 11 39</sup> lower quality of life,<sup>34</sup> non-white ethnicity,<sup>4 13</sup> negative feelings,<sup>40 41</sup> attitudes to medication or treatment,<sup>41–43</sup> higher frequency of medication intake,<sup>44</sup> longer time since transplantation<sup>6 40 42</sup> and younger age<sup>40</sup> to be associated with NA. In renal transplant recipients, also anxiety,<sup>45</sup> male sex,<sup>45 46</sup> lower self-efficacy<sup>47–49</sup> and avoidant attachment<sup>50</sup> were found to be linked to increased NA. Although a considerable amount of research is devoted to the reasons and risk factors for IS NA, there is still a wide array of contradictory and heterogeneous results. Further, research examining risk factors exclusively in HTRs is sparse. Most studies examining risk factors for NA use self-reports, physicians' estimates or trough levels. To our knowledge, no study has examined potential risk factors for NA in HTRs that were measured by applying electronic monitoring. What is more, studies on risk factors for NA to recommended lifestyle behaviours are missing. In order to develop adequate adherence interventions, assessing the accuracy of NA measures as well as determining factors that promote NA is of paramount importance. With this study, we cover relevant topics on adherence after heart transplantation and wish to fill substantial gaps in current research.

## STUDY AIMS

The aim of our study is to investigate electronically monitored NA in HTRs over a period of 3 months during the phase of medication implementation.<sup>1 51</sup> The following three research questions (RQs) will be addressed:

1. Measurement methods: Do different measurement methods of NA correlate with each other at the beginning of the study? Does electronically monitored NA coincide with self-reported NA during the course of the study?
2. Psychosocial predictors: Can certain psychosocial factors predict electronically monitored NA in HTRs?
3. Non-pharmacological adherence and lifestyle behaviours: To what extent do HTRs comply with lifestyle requirements? Does IS medication coincide with healthy lifestyle behaviours? What are potential risk factors for these behaviours?

## METHODS AND ANALYSIS

### Setting and recruitment

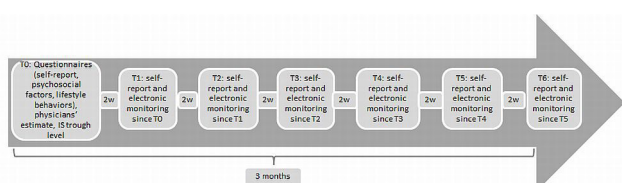
This work is part of the APT (Adherence and psychological health after transplantation) research project of the Department of Psychosomatic Medicine and Psychotherapy and takes place in cooperation with the Department of Cardiac Surgery and the Department of Nephrology and Hypertension in Erlangen. This substudy is conducted at the outpatient clinic of the Department of Cardiac Surgery of the University Hospital of Erlangen. During the course of 1 year, the sample is consecutively derived from HTRs undergoing their routine follow-up examination. Prior to their appointment, eligible patients are contacted via telephone and receive study information and questionnaires by mail, if interested.

### Study population

Inclusion criteria for the study are patients who are at least 18 years old, have undergone heart transplantation at least 6 months ago and receive either tacrolimus (Advagraf or Prograf), cyclosporine (Sandimmun) or everolimus (Certican) as their prescribed IS medication. Patients with neurocognitive disabilities, who have no sufficient knowledge of the German language, and/or have severe mental disorders will be excluded from the study. Medication adherence was no eligibility criterion. We specifically focus on medication implementation and exclude cases of initiation.<sup>1 51</sup> Of 100 eligible patients per year, we expect a responder rate of approximately 50%, resulting in a potential sample of 50 HTRs. We attain written informed consent from all participating patients (see online supplemental files 1 and 2). The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU).

### Study design and measurement points

This is a prospective clinical observational trial. At study enrolment, each patient is asked to fill in a questionnaire battery on potential psychosocial predictors of NA and recommended lifestyle behaviours. Further, self-reports, collateral reports and IS trough levels are assessed. Electronic monitoring will take place for 3 months. Meanwhile, each participant will receive phone calls in an interval of 2 weeks. Self-reports on potential incidents of NA referring to the last 2 weeks will be obtained. At the end of the study, patients will receive a feedback on their medication intake behaviour. The timeline of our study procedure is viewed in figure 1.



**Figure 1** Timeline of study procedure. 2w=2 weeks.

## MEASUREMENT METHODS

### IS adherence measures

#### Collateral report

Adherence assessments are made after the patients' appointments with their treating physician. The respective cardiologist is asked to rate the patients' IS adherence both on a 5-point Likert Scale (1=very good, 5=very bad) and on a 10 cm (0%–100%) Visual Analogue Scale (VAS) according to their subjective estimate of the patients' global adherence behaviour. Similar measures were used in the previous research.<sup>23 24</sup>

#### Self-report

As a means to assess self-reported NA, the patients equally receive a 10 cm (0%–100%) VAS (part of the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS)<sup>20</sup>) Interview, in order to reach comparability with the collateral report. We further apply the BAASIS Questionnaire<sup>20</sup>, which consists of four items that relate to the medication taking behaviour of the last 4 weeks. It assesses four types of IS NA (dose taking, drug holiday, timing adherence >2 hour and dose reduction) that can be rated on a 6-point scale (0=never, 5=everyday). Patients who consent to at least one of these four items are classified as non-adherent. We added a further question on timing adherence covering an additional intake interval of  $\pm 30$  min. During the course of the study, we also ask for the absolute frequency of IS intake deviations since the last phone call (recall period of approximately 2 weeks).

#### IS trough-level variability

IS levels are routinely checked at each follow-up examination at the outpatient clinic as well as at the patients' respective resident doctors every 8–10 weeks. We will use the IS trough level that is measured at study enrolment as well as up to three antecedent measures,<sup>52</sup> since reliability improves with an increased number of measurement points.<sup>23 53</sup> For frame of reference, each IS level is positioned with respect to its respective target level that can be changed individually by the treating cardiologist depending on the clinical course and time since transplantation. The graded standard target levels for the different IS regimens can be viewed in the online supplemental file 3. We then will assess IS trough level variability (CV%: percent coefficient of variation<sup>53</sup>) that has been associated with graft rejection, mortality and NA.<sup>21 22 54</sup> For the calculation of CV%, each IS level will be standardised by dividing it by its respective target level. For each standardised IS trough level, we will calculate means and SD. By dividing the SD by the mean and multiplying it by 100, we will gain the CV%.<sup>53 54</sup> Higher CV% are associated with a higher fluctuation of IS trough levels.<sup>53</sup> The IS trough levels for the different IS regimens will be dealt with equally.

#### Electronic monitoring

Electronic monitoring of NA is taking place with a multicompartiment pillbox (VAICA SimpleMed), which provides medication storage for 7 days with up to four doses per day. Medication extraction is automatically

**Table 1** Psychosocial constructs and applied questionnaires

Psychosocial construct	Instrument	Information
Depression	PHQ-9 <sup>74 75</sup>	Self-report screening instrument of depression, nine items, 4-point scale
Perceived social support	FSozU-7 <sup>76</sup>	Self-report instrument on social support (practical support, emotional support, social integration), short form of F-SozU, seven items, 5-point scale
Perceived health-related quality of life	WHOQoL-BREF <sup>77</sup>	Self-report instrument on perceived health-related quality of life (physical health, psychological health, social relationships, environment), short form of WHOQoL-100, 26 items, 5-point scale
Self-efficacy	SWE <sup>78 79</sup>	Self-report questionnaire, 10 items, 4-point scale
Attachment	RSQ <sup>80 81</sup>	Self-report questionnaire, 30 items, 5-point scale
Subjective experiences and attitudes towards immunosuppressive medication	MESI <sup>82</sup>	Self-report questionnaire, seven items, 5-point scale
Emotional responses after organ transplantation	TxEQ <sup>83 84</sup>	Self-report questionnaire on emotional responses after Tx (guilt, worry, disclosure, adherence, responsibility), 23 items, 5-point scale
Satisfaction with information about immunosuppressive medication	SIMS-D <sup>85 86</sup>	Self-report questionnaire, 17 items, 5-point scale
Perceptions of and beliefs about medications	BMQ <sup>87 88</sup>	Self-report questionnaire, 18 items, 5-point scale

PHQ-9: Patient Health Questionnaire [Gesundheitsfragebogen für Patienten], FSozU-7: Fragebogen zur sozialen Unterstützung, WHOQoL-BREF: World Health Organization Quality of Life - Short Form, SWF: General Self Efficacy Scale [Skala zur allgemeinen Selbstwirksamkeitserwartung], RSQ: Relationship Scales Questionnaire, MESI: Medication Experience Scale for Immunosuppressants [Medikamenten-Erfahrungs-Skala für Immunsuppressiva], TxEQ: The Transplant Effects Questionnaire [Fragebogen zur psychischen Verarbeitung einer Organtransplantation], SIMS-D: The Satisfaction with Information about Medicines Scale, BMQ: The Beliefs about Medicines Questionnaire.

recorded and transferred to a web portal where the individual IS medication schedules of each patient are registered. Data transfer is done using cellular reception. For timing adherence, we set intervals at  $\pm 30$  min and  $\pm 2$  hours. Reminder functions (visual/acoustic signals) are disabled to keep a possible intervention effect at a minimum. In addition, participants are requested to keep a diary for incidences when medication extraction does not coincide with pill intake or the medication is taken from another source (pocket, take-away box etc). Irrespective of each patient's dosing frequency and regimen, the percentage of (on time) taken immunosuppressants will be calculated per day, for each measurement point (T1–T6), as well as for the whole study course, attaining values between 0% and 100%. If the patient does not use the pill box for a certain period (due to hospital stay, vacation, bad reception), the respective days are registered as missing.

### Psychosocial variables

For the assessment of patient-related psychosocial risk factors, a variety of instruments is applied (see [table 1](#)). The choice of potential determinants is limited to individual patient-related factors amenable to change and modifiable by interventions.

### Non-pharmacological NA and lifestyle behaviour

To assess non-pharmacological NA to recommended lifestyle behaviours, we use self-report data on physical activity, diet, sun protection, smoking, appointment keeping and alcohol use. For better comparability, we apply similar measurement methods used in the previous research.<sup>29</sup> How each component is measured is viewed in [table 2](#).

### Patient and public involvement

Patients and the public are not involved in the design, recruitment and conduction of this study.

### Statistical analysis plan

Data will be analysed using SPSS V.21 for Microsoft Windows as well as the nlme-package<sup>55</sup> and the lme4-package<sup>56</sup> for R V.3.5.1. For descriptive statistics, we will depict frequencies, mean values, SDs and ranges. For group comparisons (non-responder-analyses), we will use independent T-tests, Mann-Whitney-U-tests and  $\chi^2$  tests. Cohen's kappa and the Intraclass correlation coefficient (ICC) will be used to conduct analyses on the association of measurement methods and the relation between lifestyle behaviours and NA (RQs 1 and 3). For prospective analyses, we will perform multiple linear regressions with the percentage frequency of electronically monitored NA

**Table 2** Methods to assess non-pharmacological NA to recommended lifestyle behaviours

Variable	Instrument	Information
Physical activity	Brief physical activity assessment tool <sup>89</sup>	Two items, frequency of intense and moderate physical activity during an average week (adherent: sufficiently active, non-adherent: insufficiently active)
Smoking	Self-developed (based on measure used by Helmy <i>et al</i> <sup>29</sup> )	One item on current smoking status (adherent: never smoked/stopped before HTx, non-adherent: stopped after HTx, smokes sometimes/several times a week/daily)
Alcohol use	Self-developed (based on measure used by Helmy <i>et al</i> <sup>29</sup> )	Two items on current alcohol use (frequency of alcohol use per average week, usual quantity of alcohol intake), non-adherent:>1 drink/day (0.33 L) (women), >2 drinks/day (men)
Sun protection	According to measure developed by Helmy <i>et al</i> <sup>29</sup>	Four items on current sun protection (using sun screen, wearing protective clothing, staying in the shade, being sensitive to the time of day), 5-point scale, adherent: always using ≥1 of protection methods, non-adherent: not always using at least 1
Diet	According to measure developed by Helmy <i>et al</i> <sup>29</sup>	One item on adherence to general dietary recommendations, four items on daily diet (sugar, low calorie, low saturated fats and low salt), 5-point scale, adherent: min. score 4–5 on all dietary recommendation, non-adherent: scores of 1–3 on any scale
Appointment keeping	Self-developed (based on measure used by Helmy <i>et al</i> <sup>29</sup> )	One item, frequency of unexcused absence at scheduled follow-up appointments since transplantation (adherent: 0, non-adherent:≥1)

HTx, heart transplantation.

as the outcome variable (RQs 1 and 2). To assess changes in probability of adherence over time, two alternative linear mixed models (strictly linear and piecewise linear) on the percentage frequency of NA of each measurement point (T1–T6) will be conducted (RQ 1). In order to examine potential risk factors for non-pharmacological adherence, logistic regression analyses will be applied (RQ 3). If predictor count in regression analyses is restricted due to limited sample size, we will conduct preliminary analyses (eg, Spearman's  $\rho$ , Pearson's  $r$ , ICC) in order to insert only variables that significantly correlate with the outcome. Bonferroni-Holm corrections will be made for all statistical tests in order to adjust for the alpha-error of multiple testing. Results will be interpreted on a significance level of  $p < 0.05$ .

### Progress

Recruitment started in September 2019. Of 48 eligible patients, 45 could be contacted via telephone before their follow-up examination. Of those, 18 (40%) agreed to participate and are currently taking part in our study, whereas 27 declined participation. Reasons for refusal are lack of study interest, lack of time, sickness and inconvenience or impossibility to integrate the pillbox into daily routine. Sociodemographic and biomedical data of all patients already included in our study are depicted in [table 3](#).

### DISCUSSION

To our knowledge, this is the first study assessing potential risk factors of IS NA and non-pharmacological NA by prospectively applying electronic monitoring as the main

NA measure. To date, no study has combined electronic monitoring, self-reports, physicians' estimates and IS trough level variability to measure NA in HTRs. Although,

**Table 3** Sociodemographic and biomedical data of current participants

	Patients (N=18)
Age (M, SD, range)	56.93 ( $\pm 15.59$ ), 32–82
Sex (n, %)	
Male	18 (100)
Female	0 (0)
Marital status (n, %)	
Single	3 (16.67)
Married/in a relationship	11 (61.11)
Separated/divorced	1 (5.56)
No information	3 (16.67)
Immunosuppressive medication (n, %)	
Advagraf (once daily)	1 (5.6)
Prograf (two times daily)	7 (38.89)
Sandimmun (two times daily)	6 (33.3)
Certican (two times daily)	2 (11.1)
Combination of Certican and Sandimmun	1 (5.56)
Combination of Certican and Prograf	1 (5.56)
Last transplantation (median, SD, range)	2010 ( $\pm 4.72$ ), 2003–2017



measuring NA might induce an intervention effect resulting in temporarily improved adherence, adherence behaviour is likely to stabilise on its base level after approximately 35–40 days.<sup>57–58</sup> Yet, by applying a combination of NA measures, especially electronic monitoring, more accurate statements about prevalences of NA and its potential risk factors in HTRs can be made. Precise measures and a detailed knowledge of potential determinants are crucial in order to develop adequate adherence interventions and reduce the fatal consequences of NA. In recent years, several well-designed interventions for the improvement of IS adherence have been published.<sup>59–63</sup> Most of these interventions are tailored to meet the needs of renal transplant recipients. Interventions specifically for HTRs are sparse or non-existent, especially since research on prevalences and risk factors of NA are mostly focused on renal transplant recipients.<sup>4</sup>

Further, more research on lifestyle behaviours is required to fully understand its reasons as well as potential implications on rejection and organ survival in HTRs. The potentially harmful consequences of insufficient physical activity, inadequate sun protection, tobacco and alcohol use and unhealthy diet are already well established in healthy populations.<sup>64–68</sup> But especially HTRs who are obliged to lifelong immunosuppression intake are at an even greater risk of developing chronic diseases and health issues when engaging in unhealthy lifestyle behaviours.<sup>29–69–70</sup> In order to prevent comorbid diseases and health damages, the development of interventions specifically targeting lifestyle habits and its potential risk factors<sup>33–35</sup> are substantial. Two recent studies on renal transplant recipients showed an improvement of sun-protective behaviour after an educational intervention.<sup>71–73</sup> Interventions for the improvement of other lifestyle behaviours are lacking. For the development of adequate lifestyle interventions, the investigation of reasons and risk factors for these unhealthy behaviours is a prerequisite that we wish to meet with this study.

If patients with acute forms of severe depression, excessive substance abuse or other self-harming behaviours are detected during study recruitment, immediate interventions or transferrals to the respective outpatient clinics can be initiated.

With the combination of lifestyle habits, psychosocial factors and a bandwidth of IS NA measures, especially electronic monitoring, our study will provide a promising opportunity to shed further light onto highly clinically relevant topics. We expect that our findings will contribute to the refinement of NA measures as well as the development of comprehensive interventions for HTRs.

## ETHICS AND DISSEMINATION

The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU). Written informed consent is attained from all participants. Patient data are pseudonymised. Each patient receives a three-digit code

under which personal and medical data are saved. In a password protected file, the patients' name can be linked to the three-digit code to which only the study director has access to. At the end of the project, the file on patient allocation will be deleted. The results of this study will be published in peer-reviewed journals and presented at national and international conferences.

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**Contributors** ML designed and drafted the manuscript and is currently conducting the study. YE supervises and supports the conceptualisation and conduction of the study. MW enabled the initiation of this project and supervises study coordination. MS supports patient recruitment. All authors revised the manuscript critically for important intellectual content, have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Competing interests** None declared.

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## REFERENCES

- Vrijens B, De Geest S, Hughes DA, *et al.* A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
- Dobbels F, De Geest S, van Cleemput J, *et al.* Effect of late medication non-compliance on outcome after heart transplantation: a 5-year follow-up. *J Heart Lung Transplant* 2004;23:1245–51.
- Denhaerynck K, Dobbels F, Cleemput I, *et al.* Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005;18:1121–33.
- Dew MA, DiMartini AF, De Vito Dabbs A, *et al.* Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007;83:858–73.
- De Bleser L, Dobbels F, Berben L, *et al.* The spectrum of nonadherence with medication in heart, liver, and lung transplant patients assessed in various ways. *Transpl Int* 2011;24:882–91.
- Dew MA, Dabbs AD, Myaskovsky L, *et al.* Meta-Analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation* 2009;88:736–46.
- De Geest S, Burkhalter H, Bogert L, *et al.* Describing the evolution of medication nonadherence from pretransplant until 3 years post-transplant and determining pretransplant medication nonadherence as risk factor for post-transplant nonadherence to immunosuppressives: the Swiss transplant cohort study. *Transpl Int* 2014;27:657–66.
- Villeneuve C, Rousseau A, Rerolle J-P, *et al.* Adherence profiles in kidney transplant patients: causes and consequences. *Patient Educ Couns* 2020;103:189–98.
- Bertram A, Fuge J, Suhling H, *et al.* Adherence is associated with a favorable outcome after lung transplantation. *PLoS One* 2019;14:e0226167.
- Paterson TSE, Demian M, Shapiro RJ, *et al.* Impact of Once- versus twice-daily tacrolimus dosing on medication adherence in stable renal transplant recipients: a Canadian single-center randomized controlled trial. *Can J Kidney Health Dis* 2019;6:205435811986799.

- 11 Dew MA, Dimartini AF, De Vito Dabbs A, *et al.* Adherence to the medical regimen during the first two years after lung transplantation. *Transplantation* 2008;85:193–202.
- 12 Denhaerynck K, Berben L, Dobbels F, *et al.* Multilevel factors are associated with immunosuppressant nonadherence in heart transplant recipients: the International BRIGHT study. *Am J Transplant* 2018;18:1447–60.
- 13 Oliva M, Singh TP, Gauvreau K, *et al.* Impact of medication non-adherence on survival after pediatric heart transplantation in the U.S.A. *J Heart Lung Transplant* 2013;32:881–8.
- 14 De Geest S, Abraham I, Moons P, *et al.* Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998;17:854–63.
- 15 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
- 16 Senft Y, Kirsch M, Denhaerynck K, *et al.* Practice patterns to improve pre and post-transplant medication adherence in heart transplant centres: a secondary data analysis of the International bright study. *Eur J Cardiovasc Nurs* 2017;1474515117747577.
- 17 Monnette A, Zhang Y, Shao H, *et al.* Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices: an updated review. *Pharmacoeconomics* 2018;36:17–27.
- 18 J. Foster B, L.H. Pai A. Adherence in adolescent and young adult kidney transplant recipients. *Open Urol Nephrol J* 2014;7:133–43.
- 19 Nevins TE, Nickerson PW, Dew MA. Understanding medication nonadherence after kidney transplant. *J Am Soc Nephrol* 2017;28:2290–301.
- 20 Dobbels F, Berben L, De Geest S, *et al.* The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. *Transplantation* 2010;90:205–19.
- 21 Flippin MS, Canter CE, Balzer DT. Increased morbidity and high variability of cyclosporine levels in pediatric heart transplant recipients. *J Heart Lung Transplant* 2000;19:343–9.
- 22 Ringwald JM, Gidding SS, Crawford SE, *et al.* Nonadherence is associated with late rejection in pediatric heart transplant recipients. *J Pediatr* 2001;139:75–8.
- 23 Pabst S, Bertram A, Zimmermann T, *et al.* Physician reported adherence to immunosuppressants in renal transplant patients: prevalence, agreement, and correlates. *J Psychosom Res* 2015;79:364–71.
- 24 Lieb M, Hepp T, Schiffer M, *et al.* Accuracy and concordance of measurement methods to assess non-adherence after renal transplantation - a prospective study. *BMC Nephrol* 2020;21:114.
- 25 El Allili M, Vrijens B, Demonceau J, *et al.* A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol* 2016;82:268–79.
- 26 Denhaerynck K, Steiger J, Bock A, *et al.* Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. *Am J Transplant* 2007;7:108–16.
- 27 Butler JA, Peveler RC, Roderick P, *et al.* Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation* 2004;77:786–9.
- 28 Schäfer-Keller P, Steiger J, Bock A, *et al.* Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant* 2008;8:616–26.
- 29 Helmy R, Duerinckx N, De Geest S, *et al.* The International prevalence and variability of nonadherence to the nonpharmacologic treatment regimen after heart transplantation: findings from the cross-sectional BRIGHT study. *Clin Transplant* 2018;32:e13280.
- 30 De Geest S, Dobbels F, Martin S, *et al.* Clinical risk associated with appointment noncompliance in heart transplant recipients. *Prog Transplant* 2000;10:162–8.
- 31 Weinrauch LA, Claggett B, Liu J, *et al.* Smoking and outcomes in kidney transplant recipients: a post hoc survival analysis of the FAVORIT trial. *Int J Nephrol Renovasc Dis* 2018;11:155–64.
- 32 Opelz G, Döhler B. Influence of current and previous smoking on cancer and mortality after kidney transplantation. *Transplantation* 2016;100:227–32.
- 33 Duerinckx N, Burkhalter H, Engberg SJ, *et al.* Correlates and outcomes of posttransplant smoking in solid organ transplant recipients: a systematic literature review and meta-analysis. *Transplantation* 2016;100:2252–63.
- 34 Brocks Y, Zittermann A, Grisse D, *et al.* Adherence of heart transplant recipients to prescribed medication and recommended lifestyle habits. *Prog Transplant* 2017;27:160–6.
- 35 Dobbels F, Denhaerynck K, Klem ML, *et al.* Correlates and outcomes of alcohol use after single solid organ transplantation: a systematic review and meta-analysis. *Transplant Rev* 2019;33:17–28.
- 36 Berben L, Engberg SJ, Rossmessl A, *et al.* Correlates and outcomes of low physical activity posttransplant: a systematic review and meta-analysis. *Transplantation* 2019;103:679–88.
- 37 World Health Organisation. Adherence to long-term therapies: evidence for action, 2003. Available: [https://www.who.int/chp/knowledge/publications/adherence\\_report/en/](https://www.who.int/chp/knowledge/publications/adherence_report/en/)
- 38 Delibasic M, Mohamedali B, Dobrilovic N, *et al.* Pre-Transplant depression as a predictor of adherence and morbidities after orthotopic heart transplantation. *J Cardiothorac Surg* 2017;12:62.
- 39 Dobbels F, Vanhaecke J, Dupont L, *et al.* Pretransplant predictors of posttransplant adherence and clinical outcome: an evidence base for pretransplant psychosocial screening. *Transplantation* 2009;87:1497–504.
- 40 Shemesh Y, Peles-Bortz A, Peled Y, *et al.* Feelings of indebtedness and guilt toward donor and immunosuppressive medication adherence among heart transplant (HTx) patients, as assessed in a cross-sectional study with the Basel assessment of adherence to immunosuppressive medications scale (BAASIS). *Clin Transplant* 2017;31:e13053.
- 41 Kung M, Koschwanez HE, Painter L, *et al.* Immunosuppressant nonadherence in heart, liver, and lung transplant patients: associations with medication beliefs and illness perceptions. *Transplantation* 2012;93:958–63.
- 42 Cherubini P, Rumiati R, Bigoni M, *et al.* Long-Term decrease in subjective perceived efficacy of immunosuppressive treatment after heart transplantation. *J Heart Lung Transplant* 2003;22:1376–80.
- 43 Hugon A, Roustit M, Lehmann A, *et al.* Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation* 2014;98:222–8.
- 44 Doesch AO, Mueller S, Akyol C, *et al.* Increased adherence eight months after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation. *Drug Des Devel Ther* 2013;7:1253–8.
- 45 Belaiche S, Décaudin B, Dharancy S, *et al.* Factors relevant to medication non-adherence in kidney transplant: a systematic review. *Int J Clin Pharm* 2017;39:582–93.
- 46 Prihodova L, Nagyova I, Rosenberger J, *et al.* Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study. *J Adv Nurs* 2014;70:2871–83.
- 47 Calia R, Lai C, Aceto P, *et al.* Emotional self-efficacy and alexithymia may affect compliance, renal function and quality of life in kidney transplant recipients: results from a preliminary cross-sectional study. *Physiol Behav* 2015;142:152–4.
- 48 Russell CL, Ashbaugh C, Peace L, *et al.* Time-in-a-bottle (TIAB): a longitudinal, correlational study of patterns, potential predictors, and outcomes of immunosuppressive medication adherence in adult kidney transplant recipients. *Clin Transplant* 2013;27:E580–90.
- 49 Silva AN, Moratelli L, Tavares PL, *et al.* Self-Efficacy beliefs, locus of control, religiosity and non-adherence to immunosuppressive medications in kidney transplant patients. *Nephrology* 2016;21:938–43.
- 50 Calia R, Lai C, Aceto P, *et al.* Attachment style predict compliance, quality of life and renal function in adult patients after kidney transplant: preliminary results. *Ren Fail* 2015;37:678–80.
- 51 De Geest S, Zullig LL, Dunbar-Jacob J, *et al.* ESPACOMP medication adherence reporting guideline (EMERGE). *Ann Intern Med* 2018;169:30–5.
- 52 Scheel J, Reber S, Stoessel L, *et al.* Patient-Reported non-adherence and immunosuppressant Trough levels are associated with rejection after renal transplantation. *BMC Nephrol* 2017;18:107.
- 53 Hsiao M, Fernandez HE, Gjertson D, *et al.* Monitoring nonadherence and acute rejection with variation in blood immunosuppressant levels in pediatric renal transplantation. *Transplantation* 2011;92:918–22.
- 54 Gueta I, Markovits N, Yarden-Bilavsky H, *et al.* High tacrolimus Trough level variability is associated with rejections after heart transplant. *Am J Transplant* 2018;18:2571–8.
- 55 Pinheiro J, Bates D, DebRoy S, *et al.* Nlme: linear and nonlinear mixed effect models. *R Package Version* 2014;3:1–117.
- 56 Bates D, Mächler M, Bolker B, *et al.* Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw* 2015;67:1–48.
- 57 Ekberg H, Tedesco-Silva H, Demirbas A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007;357:2562–75.
- 58 Denhaerynck K, Schäfer-Keller P, Young J, *et al.* Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application

- on a European sample of kidney transplant patients. *BMC Med Res Methodol* 2008;8:5.
- 59 Foster BJ, Pai ALH, Zelikovsky N, *et al.* A randomized trial of a multicomponent intervention to promote medication adherence: the teen adherence in kidney transplant effectiveness of intervention trial (TAKE-IT). *Am J Kidney Dis* 2018;72:30–41.
- 60 Panyi N, Erim Y. [Manualized psychotherapy for the optimization of immunosuppressant adherence following kidney transplantation: Results of a feasibility study]. *Z Psychosom Med Psychother* 2017;63:189–201.
- 61 Reese PP, Bloom RD, Trofe-Clark J, *et al.* Automated reminders and physician notification to promote immunosuppression adherence among kidney transplant recipients: a randomized trial. *Am J Kidney Dis* 2017;69:400–9.
- 62 Russell C, Conn V, Ashbaugh C, *et al.* Taking immunosuppressive medications effectively (TIMELink): a pilot randomized controlled trial in adult kidney transplant recipients. *Clin Transplant* 2011;25:864–70.
- 63 Russell CL, Moore S, Hathaway D, *et al.* MAGIC study: aims, design and methods using SystemCHANGE™ to improve immunosuppressive medication adherence in adult kidney transplant recipients. *BMC Nephrol* 2016;17:84.
- 64 Shield KD, Parry C, Rehm J. Chronic diseases and conditions related to alcohol use. *Alcohol Res* 2013;35:155–73.
- 65 Hernandez SL, Banks HE, Bailey AE, *et al.* Relationships among chewing tobacco, cigarette smoking, and chronic health conditions in males 18–44 years of age. *J Prim Prev* 2017;38:505–14.
- 66 Lim SS, Vos T, Flaxman AD, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2224–60.
- 67 Leskinen T, Stenholm S, Aalto V, *et al.* Physical activity level as a predictor of healthy and chronic disease-free life expectancy between ages 50 and 75. *Age Ageing* 2018;47:423–9.
- 68 Green AC, Williams GM, Logan V, *et al.* Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011;29:257–63.
- 69 Naldi L, Fortina AB, Lovati S, *et al.* Risk of nonmelanoma skin cancer in Italian organ transplant recipients. A registry-based study. *Transplantation* 2000;70:1479–84.
- 70 Söderlund C, Rådegran G. Immunosuppressive therapies after heart transplantation--The balance between under- and over-immunosuppression. *Transplant Rev* 2015;29:181–9.
- 71 Wu SZ, Jiang P, DeCaro JE, *et al.* A qualitative systematic review of the efficacy of sun protection education in organ transplant recipients. *J Am Acad Dermatol* 2016;75:1238–44.
- 72 Robinson JK, Guevara Y, Gaber R, *et al.* Efficacy of a sun protection workbook for kidney transplant recipients: a randomized controlled trial of a culturally sensitive educational intervention. *Am J Transplant* 2014;14:2821–9.
- 73 Robinson JK, Friedewald JJ, Desai A, *et al.* A randomized controlled trial of a mobile medical APP for kidney transplant recipients: effect on use of sun protection. *Transplant Direct* 2016;2.
- 74 Löwe B, Spitzer R, Zipfel S, *et al.* *Gesundheitsfragebogen für Patienten (PHQ-D). Komplettversion und Kurzform. Testmappe MIT manual, Fragebögen, Schablonen.* Pfizer: Karlsruhe, 2002.
- 75 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
- 76 Fydrich T, Geyer M, Hessel A, *et al.* Fragebogen zur Sozialen Unterstützung (F-SozU): Normierung einer repräsentativen Stichprobe. *Diagnostica* 1999;45:212–6.
- 77 Angermeyer C, Kilian R, Matschinger H. Deutschsprachige version Der who Instrumente Zur Erfassung von Lebensqualität WHOQOL-100 und WHOQOL-BREFM. *Z Med Psychol* 2002;11:44–8.
- 78 Schwarzer R, Jerusalem M. Generalized self-efficacy scale. In: Weinman J, Wright S, Johnston M, eds. *Measures in health psychology: A user's portfolio Causal and control beliefs.* Windsor, England: Nfer-Nelson, 1995: p. 35–7.
- 79 Schwarzer R, Jerusalem M. *Skalen Zur Erfassung von Lehrer- und Schülermerkmalen: Dokumentation Der psychometrischen Verfahren Im Rahmen Der Wissenschaftlichen Begleitung Des Modellversuchs Selbstwirksame Schulen.* Berlin: Freie Universität Berlin, 1999.
- 80 Steffanowski M, Oppl J, Meyerberg J, *et al.* Psychometrische Überprüfung einer deutschsprachigen Version des Relationship Scales Questionnaire (RSQ). In: Bassler M, ed. *Störungsspezifische Therapieansätze - Konzepte und Ergebnisse.* Gießen, 2001.
- 81 Griffin DW, Bartholomew K. The metaphysics of measurement: The case of adult attachment. In: Bartholomew K, Perlman D, eds. *Attachment processes in adulthood advances in personal relationships.* Jessica Kingsley, 1994: 5. p. 17.
- 82 Goetzmann L, Klaghofer R, Spindler A, *et al.* [The "Medication Experience Scale for Immunosuppressants" (MESI): initial results for a new screening instrument in transplant medicine]. *Psychother Psychosom Med Psychol* 2006;56:49–55.
- 83 Klaghofer R, Sarac N, Schwegler K, *et al.* Fragebogen zur psychischen Verarbeitung einer Organtransplantation: Deutsche Validierung des Transplant Effects Questionnaire (TxEQ) [Questionnaire on emotional response after organ transplantation: German validation of the Transplant Effect Questionnaire (TxEQ-D)]. *Z Psychosom Med Psychother* 2008;54:174–88.
- 84 Ziegelmann JP, Griva K, Hankins M, *et al.* The Transplant Effects Questionnaire (TxEQ): The development of a questionnaire for assessing the multidimensional outcome of organ transplantation - example of end stage renal disease (ESRD). *Br J Health Psychol* 2002;7:393–408.
- 85 Mahler C, Jank S, Hermann K, *et al.* Psychometric properties of a German version of the "Satisfaction with Information about Medicines Scale" (SIMS-D). *Value Health* 2009;12:1176–9.
- 86 Horne R, Hankins M, Jenkins R. The satisfaction with information about medicines scale (SIMS): a new measurement tool for audit and research. *Qual Health Care* 2001;10:135–40.
- 87 Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health* 1999;14:1–24.
- 88 Mahler C, Hermann K, Horne R, *et al.* Patients' beliefs about medicines in a primary care setting in Germany. *J Eval Clin Pract* 2012;18:409–13.
- 89 Marshall AL, Smith BJ, Bauman AE, *et al.* Reliability and validity of a brief physical activity assessment for use by family doctors. *Br J Sports Med* 2005;39:294–7. discussion - 7.