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Psychometric Properties of the BAASIS: A Meta-analysis of Individual Participant Data

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Background. Nonadherence to immunosuppressives, a risk factor for poor posttransplant outcomes, can be assessed by self-report using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS). Available in written and interview versions, and previously validated on content, the BAASIS is widely used in research and clinical practice. The aim of this study was to investigate its psychometric properties. **Methods.** Using a literature search and our BAASIS database, this meta-analysis identified completed studies in adult transplant recipients whose data were usable to examine the BAASIS' reliability and 3 validity aspects: (1) relationships with other variables (electronic monitoring, other self-report scales, tacrolimus blood-level variability, collateral report, depressive symptoms, psycho-behavioral constructs, and interventions); (2) response processes; and (3) internal structure. Testing used random-effects logistic regressions. **Results.** Our sample included 12 109 graft recipients from 26 studies. Of these 26, a total of 20 provided individual participant data. Evidence of the BAASIS' stability over time supports its reliability. Validity testing of relationships with other variables showed that BAASIS-assessed nonadherence was significantly associated with the selected variables: electronically monitored nonadherence ($P < 0.03$), other self- and collaterally-reported nonadherence ($P < 0.001$), higher variability in tacrolimus concentrations ($P = 0.02$), higher barriers ($P < 0.001$), lower self-efficacy ($P < 0.001$), lower intention ($P < 0.001$), and higher worries ($P = 0.02$). Nonadherence also decreased after regimen change interventions ($P = 0.03$). Response process evaluation indicated good readability and slightly higher nonadherence with the written version. Structurally, items on taking and timing shared variability. **Conclusions.** The BAASIS shows good validity and reliability as a self-report instrument to assess medication nonadherence in transplantation.

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K.D., F.D., B.K., and S.D.G. conceived, designed, supervised the study, and drafted the article. K.D. performed the statistical analysis. K.D., F.D., B.K., S.D.G., and the members of the BAASIS consortium provided data for the meta-analysis and critically revised the article for important intellectual content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final article.

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INTRODUCTION

Medication nonadherence (NA) is a critical behavioral risk factor for poor posttransplant clinical and economic outcomes.[1] To identify transplant recipients at risk, the international Consensus on Managing Modifiable Risk in Transplantation (COMMIT) guidelines recommend monitoring NA to immunosuppressive drugs as a fifth vital sign.[2] Adherence to a medication regimen, defined in the Ascertaining Barriers for Compliance (ABC) taxonomy as the process by which patients take their medications as prescribed, consists of 3 interrelated phases: initiation, implementation, and (dis)continuation.[3] Initiation occurs when the patient takes the first dose of a prescribed medication. Implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose, and has 2 aspects, that is, taking (as prescribed versus skipped, extra, or reduced dosing) and timing (as prescribed vs late or early).[4] Within the context of NA, discontinuation occurs when the patient stops taking the prescribed medication against a clinician's advice.

Because these phases are determined by different risk factors, which call for different interventional strategies to remediate, they need to be assessed separately. Numerous (non-)adherence assessment methods exist, with varying degrees of error and bias. Some are objective and generate a rich data collection (eg, electronic monitoring); others result in sparser data collection. These include drug or drug metabolite monitoring or pharmacy refill records. More subjective sparse sampling methods include collateral reports by healthcare workers or family members, pill counts, and retrospective self-report questionnaires. A richer but still biased method is the use of a patient diary (pen-and-paper or electronic).

No single method can be regarded as a gold standard.[1] Although the richest and most objective methods may yield very useful or accurate data, these methods are not necessarily feasible and usable in daily clinical practice. Self-report is inexpensive and easy to integrate in daily clinical routine; however, it has its drawbacks. One is its inherent underreporting bias.[5] Another is that, although several self-report measures have been proposed or are being used in transplantation, they often lack a conceptual basis and have unestablished psychometric properties.[6]

The Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) is a self-report instrument (see Table 1) that is conceptually embedded in the ABC taxonomy and widely used in clinical practice and research projects. The latest version is a 6-item instrument assessing implementation (4 items), discontinuation (1 item), and initiation of related comedications (1 item added in 2019). The instrument, currently translated into 11 languages, is available in a written version and a patient interview (to be executed in a nonthreatening and nonjudgmental manner).[7] Although some single-center studies provide information on its validity,[8,9] its psychometric properties have not been extensively investigated.

The American Educational Research Association, the American Psychological Association, and the National Council on Measurement in Education provide guidance for studying psychometric properties of self-report instruments by assessing their reliability (ie, the extent to which random errors of measurement determine the consistency/precision of the scoring) and validity (ie, the degree to which evidence and theory support the interpretation of test scores for their proposed uses).[10] Validity is considered a unitary concept consisting of 5 dimensions: test content-based evidence, relations to other variables, response processes, internal structure, and the consequences of the testing. This study's aim was to address the validity of the BAASIS regarding its response processes, internal structure, and relations to other variables as well as to study its reliability.

MATERIALS AND METHODS

Design and Sample

We conducted a meta-analysis of the individual participant data, including data sets requested from the eligible studies' corresponding authors or principal investigators. These persons were identified after searching the peer-reviewed literature and our BAASIS database of clinical and research projects that had obtained permission to use the copyrighted scale.[7] The literature search queried PubMed, Embase, and the Cochrane library until July 2020 using BAASIS and Basel assessment of adherence as search terms. Eligible studies employed the BAASIS to assess adherence to immunosuppressives of adult (≥18 years) transplant patients, and tested relationships between NA and other variables. Two reviewers (B.K. and K.D.) independently screened abstracts and obtained full articles if deemed potentially useful; then, both reviewers further examined the full texts independently regarding eligibility. As a final selection step, each candidate study was discussed among the 4 primary authors. Our own BAASIS database of clinical and research projects functioned as an additional source of candidate research, from which studies could be selected according to the same eligibility criteria as were used for those selected from the abstract databases.

Principle investigators or corresponding authors of eligible studies were sent emails to invite them to share data, with 1 reminder sent in case of nonresponse. Those who responded received a list of variables to be shared and a link on a secured server, allowing them to upload the requested data (see later). They all also became members of the BAASIS consortium (see authorship list). In any case in which individual participants' data were not available for a set of studies, the option of pooling the studies' published aggregated results for standard meta-analysis was also left open.

The variable selection process was guided by our previous work on determinants of NA. In addition to a limited set of basic criteria regarding sample characterization or variables necessary for a (proper) statistical analysis, 2 topics were of particular interest: alternative measures of NA[11] and variables with a record of established associations with adherence.[12–14] The selection process did not focus on reliability testing; however, when eligible studies allowed such testing, we collected the relevant data.

Ethical Considerations

As a secondary data analysis of existing data, no ethical approval was obtained. However, we verified that the included studies had obtained ethical approval and

TABLE 1.

Content of the BAASIS and alternative self-report NA assessment instruments

		BAASIS		Measure of adherence to treatment	Morisky Medication Adherence Scale	Immunosuppressant Therapy Adherence Scale
Subject/dimension	**Item content**	**Binary answer**	**Frequency indication**	**Frequency indication**	**Binary answer**	**Frequency indication**
Adherence: implementation	Taking NA	Yes/no	1, 2, 3, 4, >4	–	Yes/no (2 weeks); yes/no (yesterday)	>50%, 21%–50%, 1%–20%, 0% of NA
	Drug holidays	Yes/no (if taking NA = yes)	1, 2, 3, 4, >4	–	–	–
	Timing NA	Yes/no	1, 2–3, 4–5 times, every 2–3 days, almost every day	Always (1) to never (6)	–	–
	Dose alteration	Yes/no	–	–	/	/
Adherence: discontinuation	Stopped	Yes/no	–	–	/	/
Adherence: initiation	New prescription filled and started	Yes/no	–	–	–	–
Barriers	Forgetting	–	–	Always (1) to never (6)	Yes/no	>50%, 21%–50%, 1%–20%, 0% of NA
	Difficult remembering	–	–	Always (1) to never (6)	Yes/no	–
	Dose alteration because forgetting day before	–	–	Always (1) to never (6)	–	–
	Forgetting because of travel	–	–	Always (1) to never (6)	Yes/no	–
	Running out of drugs	–	–	Always (1) to never (6)	–	–
	Reasons beyond control	–	–	–	–	–
	Carelessness	–	–	–	–	>50%, 21%–50%, 1%–20%, 0% of NA
Attitudes	Feeling better/good	–	–	Always (1) to never (6)	Yes/no	–
	Feeling worse	–	–	Always (1) to never (6)	Yes/no	>50%, 21%–50%, 1%–20%, 0% of NA
	Feeling hassled	–	–	–	Yes/no	–
Total score		NA if yes on ≥1 implementation item			Lower total scores equal higher NA	

BAASIS, Basel Assessment of Adherence to Immunosuppressive Medications Scale; NA, nonadherence.

followed guidelines regarding human patients. All data were anonymized before uploading. If local legislation required ethical approval for use of data in secondary analyses necessitating data sharing, this was obtained from the appropriate review boards.

Variables and Measurement

The following participant-level variables were requested from the original studies: demographics: age and sex; clinical: type of transplanted organ and months since transplantation; setting-related: transplant center; and study design-specific: study group allocation and time point of measurement for repeated-measurement studies. We also noted item responses on the BAASIS and ancillary information on the version used (eg, written or interview and language).

A detailed explanation of the BAASIS questionnaire can be found on its website.[7] In short, each of the 3 phases of adherence is covered by at least 1 yes/no question. Initiation and discontinuation are queried over a 1-y recall period, whereas the 4 implementation phase questions cover the past 4 wk. A frequency indication (on a 5-point scale) is also requested for 3 of the 4 implementation phase questions, that is, questions on taking adherence, drug holidays (skipping 2 or more doses in a row), and timing/regularity of medication intake (within 2 h of prescribed times). For an overview of items and their scoring, see Table 1. We handled implementation NA dichotomously: respondents who answered even one of the implementation questions positively were classed as nonadherent.[15]

To establish validity using evidence of the BAASIS' relations to other variables, 3 groups of variables could be discerned. The first group consisted of data collected via other adherence measures (ie, electronic monitoring [EM], other self-report adherence measures, drug or drug metabolite monitoring, and collateral report); the second of psycho-behavioral constructs known to be associated with (non)-adherence; and the third of interventions to enhance adherence in transplant recipients.

For EM, we calculated the following 3 parameters, all of which were congruent with the BAASIS recall period: the percentage of prescribed doses taken (taking adherence); the percentage of rightly timed doses taken (timing adherence); and the number of doses skipped consecutively per monitored mo (drug holidays).

To determine adherence scores of other self-report instruments, we first calculated their scores according to their respective scoring manuals. We then standardized the scores with a mean of 0 and SD of 1. Details regarding the individual instruments can be found in Table 1.

For the drug monitoring assessment, we calculated the coefficient of variation over available tacrolimus trough levels because it was the most frequently used immunosuppressive drug and variability of its assays has previously been linked to NA.[16]

Regarding collateral report estimates from healthcare workers in routine patient care (ie, physicians and nurses), if any doubt was noted concerning the patient's medication taking behavior, these were considered as NA.

The analyzable psycho-behavioral constructs we focused on were depressive symptomatology—a construct known to be positively associated with NA[17]—and 6 variables included in the Integrative Model of Behavioral Prediction. From a theoretical perspective, these are expected to correlate with NA.[18] In particular, barriers and unfavorable attitudes/beliefs are hypothesized to be positively associated with NA, while intention to adhere, self-efficacy, and favorable attitudes/beliefs and social norms should be negatively associated with it. Attitudes and norms are expected to show weaker associations because they influence behavior only distally, via the mediator variable of intention.

In terms of responsiveness to an intervention, we examined whether the BAASIS was able to distinguish changes in adherence behavior following adherence-enhancing interventions. A number of randomized controlled trials of complex behavioral interventions were available to check this aspect of validity. One set of studies, all using prepost study designs, also tested the effect of dosing regimen alterations (from 2 to 1 daily) on patients' adherence reporting.

Our examination of validity evidence based on response processes focused on the readability of the BAASIS, that is, ensuring that the majority of respondents understand its questions. The used Flesch formula, which we applied to the text of the written questionnaire, yields a score between 0 and 100. Scores of 60–69 are considered standard, corresponding to the reading levels of grade 8 to 9, or normal 13- to 15-y-old students.[19] Higher scores, which indicate that texts are easier to comprehend,[20] would be beneficial for the instrument's overall applicability. To ensure that people with low literacy are able to understand questions and instructions correctly, an appropriate reading level would be grade 5 to 6 (ages 10–12 y). We also checked whether responses differed between the written and interview versions.

Examination of evidence based on internal structure involved checking interrelationships among 3 items of the implementation dimension. Because the fourth question (on drug holidays) depends on the taking adherence answer, it was excluded. This analysis partly overlaps with the reliability check of the scale's internal consistency. A further analysis of reliability dealt with testing response stability of items over time for those studies that used repeated measurements.

Statistical Analysis

Included variables are described per study and overall using frequencies, percentages, means, medians, SDs, and interquartile ranges, as appropriate. Standardized variables are described in their transformed versions.

Testing validity evidence based on relations to other variables required hypothesis testing (ie, comparison of the BAASIS with other adherence measures, psycho-behavioral constructs, and adherence-enhancing interventions). For this step, we used generalized linear mixed modeling, regressing the validation variables onto both the individual responses for the dichotomous BAASIS questions on taking and timing NA and on the overall implementation score. We accounted for clustering at the study level, or in cases of multicenter studies, at each participating center, using random intercepts. For longitudinal studies, an extra random intercept was added to capture the time series nested within patients. If only published results were available, odds ratios (ORs) and their variances were extracted or reconstructed, then logarithmized and combined into an overall estimate using linear mixed modeling.[21] In those cases, 2 random intercepts represented the different studies and their repeated measurements.

To examine evidence based on internal structure and reliability, we used a Spearman's rho interitem correlation matrix and a principal component analysis. To evaluate stability over time in patients who had repeated BAASIS measurements, we used intracluster correlation, expressing random-intercept variance (reflecting patients' adherence level) as a percentage of total variability.

All effect sizes of individual and pooled studies are presented in forest plots, along with 95% confidence intervals (CIs), probability values, and descriptive statistics. An alpha level of 0.05 was considered statistically significant. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Sample Characteristics

Of a total of 84 original studies using the BAASIS, we contacted the authors of 35 (41.7%) to request data (Figure 1). Reasons for noneligibility were the inclusion of nontransplant or pediatric transplant populations (n = 20), lack of sufficient content to allow hypothesized relationship testing, for example, prevalence studies (n = 17), and studies either that were still in the data collection phase or could not be fully scrutinized because they had not yet been published as full-text articles (n = 11). Of the selection of 35 eligible studies, 26 (74.3%) could be used in this meta-analysis—20 with individual participant data[8,9,11,12,22-41] (of which 1 was found through our own BAASIS database and was only available as a manuscript at the time of our analysis)[22] and 6 using aggregated results extracted from the publications.[42-48]

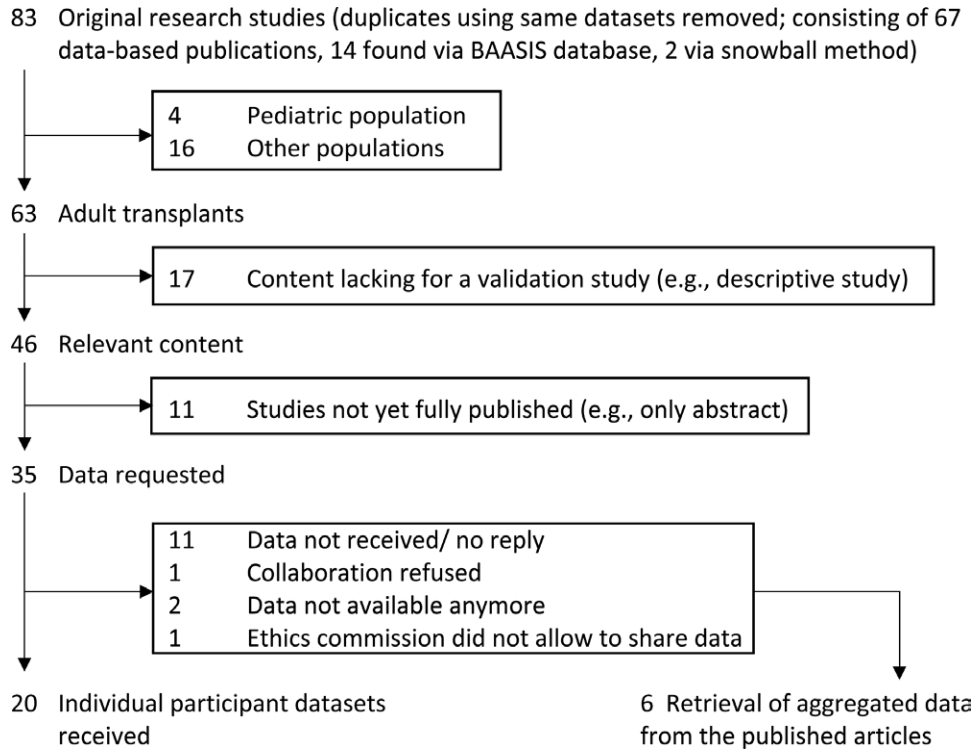

FIGURE 1. Flow chart of the sampling process. BAASIS, Basel Assessment of Adherence to Immunosuppressive Medications Scale.

Of the 9 studies that could not be used, 1 did not receive the needed ethics committee approval, 1 had no data available, 1 declined our invitation to participate in the BAASIS collaboration, and 6 did not respond to our invitation.

The included studies covered 17 countries and had variable study designs—mostly cross-sectional observational studies with retro or prospective elements (depending on the variables studied) (Table 2). Half were multicenter studies. Thirteen employed the interview version of the BAASIS and 11 the written version and 2 versions were not known. All used 2 or more BAASIS questions to assess implementation of the immunosuppressive regimen. Nine included the discontinuation item, and 1 asked about medication therapy initiation.

The included studies provided data on 12 109 transplant recipients (Table 3). Individual-level data were provided for 11 474 (94.8%) of these; for the remaining 635 (5.2%), data were aggregated at the study level. Patients' mean age was 53.2 ± 13.3 y. Slightly fewer than two-thirds were male (64.1%), and at a mean of 43.8 ± 60.1 mo after transplantation. The majority had received kidney grafts (62.7%), followed by hearts (15.3%), livers (15.0%), and lungs (7.0%).

Overall, 14.6% reported having missed doses; skipping >1 dose occurred in 1.6% of respondents (Table 4). Self-reported timing NA was 31.2%; 1.9% reported self-initiated dose alterations. The percentage of recipients who checked yes for at least 1 implementation item was 38.3%. Discontinuation issues were only reported in 0.4% of answers. A detailed description of the scoring frequencies of all the BAASIS items of the different studies is available in the supplemental materials (**Table S1, SDC**, http://links.lww.com/TP/C727 to **Table S5, SDC**, http://links.lww.com/TP/C727).

Details of studies included in the various psychometric analyses are shown in Table 5. Results are summarized in Figure 2 and presented with at the individual study level in supplemental **Figure S1, SDC**, http://links.lww.com/TP/C727 to **Figure S15, SDC**, http://links.lww.com/TP/C727.

Evidence Based on Relations to Other Variables (Part 1: Other Adherence Measures)

Self-reported taking NA, as measured by the BAASIS, was modeled using the predictor variable EM-measured percentages of prescribed medications taken (**Figure S1, SDC**, http://links.lww.com/TP/C727). The resulting model indicated that for each 10% higher the intake level was, the odds of self-reported NA were significantly lower (OR = 0.84; [95% CI, 0.72-0.99]; $P = 0.03$). Likewise, the odds of BAASIS-assessed timing NA were lower for each higher 10% bracket of correctly timed doses as registered by EM (OR = 0.82; [95% CI, 0.72-0.93]; $P = 0.002$). With respect to drug holidays, although 63 instances of consecutive dose missing were registered by EM regarding a total of 14 962 prescribed doses (0.4%) in 293 patients,[27,33] none were reported on the BAASIS.

Association of the BAASIS with alternative self-report adherence scales showed that a 1 SD increase in their total scores (indicating higher adherence levels) correlated with significantly lower odds for taking (OR = 0.36; [95% CI, 0.28-0.46]; $P < 0.001$), timing (OR = 0.50; [95% CI, 0.40-0.61]; $P < 0.001$), and overall implementation NA (OR = 0.34; [95% CI, 0.26-0.45]; $P < 0.001$; **Figure S2, SDC**, http://links.lww.com/TP/C727).

TABLE 2.

Overview of studies

No	Ref	Country; no. of centers	Aim	Design	BAASIS
Individual participant data					
1	Bessa[23]	PT; 1	Efficacy of pharmacists-led educational intervention to enhance adherence and clinical outcomes	RCT	Interview; implementation (4 items)[a]; at day 28 and 90
2	Burkhalter[24]	CH; 3	Association of daytime sleepiness; depressive symptoms with NA	CS	Written; implementation (4 items)[b] + discontinuation; at inclusion
3	De Geest[25,26]	CH; 6	Countrywide extensive cohort study with biobank	Prospective	Written; implementation (2 items: taking [ordinal][a] + missing consecutive doses [no/yes]); at inclusion (6 months post-Tx), month 12, and yearly thereafter
4	Denhaerynck[12]	AU, BE, BR, CA, CH, DE, ES, FR, IT, GB, US; 36	Psychosocial, behavioral and clinical multilevel Correlates of NA	CS	Interview; implementation (4 items)[b] + discontinuation; at inclusion
5	Dobbels[27]	BE; 1	Efficacy of multicomponent, nurse-led, tailored behavioral intervention to enhance adherence	RCT	Interview; implementation (4 items)[a]; at inclusion, 3 (randomization), 6, 9, and 15 mos
6	Ducci[28]	IT; 1	Psychosocial correlates and clinical consequences of NA	CS/prospective	Written; implementation (4 items)[a]; at inclusion
7	Eisenga[29]	NL; 1	Extensive cohort study with biobank	Prospective	Written; implementation (4 items)[a]; between Tx/post-Tx inclusion and 3 mos, 3, 6 mos, 1, 2, 3, and 5 y after Tx or post-Tx inclusion
8	Godinas[30]	BE; 1	Conversion of twice to once-daily tacrolimus	Prepost intervention	Written; implementation (4 items)[b] + discontinuation; at inclusion and year 1
9	Gustavsen sample 1[31]	NO; 1	Routine capture of NA: comparison of frequent vs single-point measurement of NA on NA capture and NA prevalence	RCT	Written; implementation (taking and timing, binary); at week 8 and year 1
	Gustavsen sample 2[31]			Prospective	At year 1
10	Košťálová[22]	CZ; 1	Associations of attitudes and blood assays to NA	CS/prospective	Written; implementation (4 items),[b] discontinuation, initiation[c]; at inclusion
11	Lieb[8]	DE; 1	Accuracy and concordance of measurement methods of NA	Longitudinal retrospective and prospective	Interview; implementation (4 items)[a]; at inclusion and 6 following measurements spaced 2 wks apart
12	Liu[32]	CN; 1	Prevalence NA and associations with beliefs	CS	Written; implementation (4 items)[a]; at inclusion
13	Low[33] [d]	AU; 4	Efficacy of a multicomponent, tailored behavioral intervention to enhance adherence	RCT	Interview; implementation (4 items)[a]; at inclusion and 4 follow-ups 3 mos apart
14	Marsicano[9,34]	BR; 1	Psychosocial and clinical multilevel correlates of NA	Retrospective	Interview; implementation (4 items; only binary); at inclusion
15	Silva[35]	BR; 1	Psychosocial correlates of NA	Retrospective	Interview; implementation (4 items; only binary); at inclusion
16	Sanders-Pinheiro [36]	BR; 20	Psychosocial, behavioral and clinical multilevel correlates of NA	CS/retrospective	Interview; implementation (4 items)[a]; at inclusion
17	Schäfer[11]	CH; 2 main centers + small other category	Psychosocial, behavioral, and clinical correlates of NA; diagnostic accuracy of NA measurements; clinical consequences of NA	CS	Written; implementation (1 item; 4 items on a subgroup of n = 10)[a]; at inclusion
18	Schmid[37]	CH; 1	Psychosocial correlates of NA (Integrative Model of Behavioral Prediction)	CS	Interview; implementation (4 items)[a]; at inclusion
19	Scheel[38,39]	DE; 3	Psychosocial correlates and clinical consequences of NA	CS/retrospective	Written; implementation (4 items)[b]; at inclusion
20	Tielen[40,41]	NL; 1	Association of NA with beliefs and clinical consequences of NA	CS/prospective	Interview; implementation (4 items)[b] + discontinuation; at inclusion (6 wks post-Tx), 6 mos, and 18 mos

Continued next page

TABLE 2. (Continued)

No	Ref	Country; no. of centers	Aim	Design	BAASIS
Published studies (aggregate data)					
21	Abedini[42]	NO; 14	Conversion of twice to once-daily tacrolimus	Prospective	Written; implementation (4 items) + discontinuation; at inclusion and 1, 3, 6, and 12 months postconversion
22	Beckebaum[43]	DE; 1	Conversion of twice to once-daily tacrolimus	Prospective	Interview; implementation (4 items; frequency estimation unknown); at inclusion and 12 mos postconversion
23	Doesch[44,45]	DE; 1	Conversion of twice calcineurin inhibitor to once-daily tacrolimus	Prospective	Interview; implementation (4 items); at inclusion and 4 mos postconversion
24	Fellström[46]	SE; 19	Conversion of twice to once-daily tacrolimus	Prospective	Version unknown; implementation (4 items) + discontinuation; at inclusion and 3, 6, 12 mos postconversion
25	Lehner[47]	DE; 7	Conversion of twice to once-daily tacrolimus	Prospective	Version unknown; implementation (4 items); at inclusion, and 18 mos postconversion
26	Valente[48]	IT; 1	Conversion of twice to once-daily tacrolimus	Prospective	Interview, implementation (4 items); at inclusion, and 6 mos postconversion

[a]Original frequency scoring (once a month, every 2 wk, every week, more than once a week, or every day).
[b]Adapted frequency scoring (item 1A, 1B: once, twice, 3 times, 4 times, >4 times; item 2: once, 2–3 times, 4–5 times, every 2–3 d, or almost every day).
[c]Initiation item related to comedications added in 2019.
[d]Human research ethics number for inclusion in this meta-analysis: HREC/13/SHB/10.
AU, Australia; BAASIS, Basel Assessment of Adherence to Immunosuppressive Medications Scale; BE, Belgium; BR, Brazil; CA, Canada; CH, Switzerland; CN, China; CS, cross-sectional; CZ, Czech Republic; DE, Germany; ES, Spain; FR, France; GB, Great Britain; HTx, heart transplant; IT, Italy; KTx, kidney transplant; LiTx, liver transplant; LuTx, lung transplant; NA, nonadherence; NL, the Netherlands; NO, Norway; PT, Portugal; RCT, randomized controlled trial; SE, Sweden; Tx, transplantation; US, United States.

Concerning the relationship between the BAASIS and drug or drug metabolite monitoring, we found that the odds of taking NA (OR = 1.013; [95% CI, 1.002–1.023]; $P = 0.02$) increased with higher coefficients of variation between available tacrolimus blood assays; however, this relationship was quite inconsistent among participating studies, with no corresponding relationship to timing or overall NA (**Figure S3, SDC**, http://links.lww.com/TP/C727).

Collateral reports predicting implementation problems were congruent with the BAASIS (**Figure S4, SDC**, http://links.lww.com/TP/C727 and **Figure S5, SDC**, http://links.lww.com/TP/C727) for both physicians (OR = 1.78; [95% CI, 1.49-2.13]; $P < 0.001$) and nurses (OR = 2.56; [95% CI, 2.09-3.15]; $P < 0.001$).

Evidence Based on Relations to Other Variables (Part 2: Psycho-behavioral Constructs)

With regard to associations between the BAASIS and variables of the Integrative Model of Behavioral Prediction, the overall BAASIS implementation NA score was predicted as hypothesized (**Figure S6, SDC**, http://links.lww.com/TP/C727 to **Figure S11, SDC** http://links.lww.com/TP/C727) by barriers (OR = 5.50; [95% CI, 3.92-7.71; $P < 0.001$), self-efficacy (OR = 0.62; [95% CI, 0.55-0.71]; $P < 0.001$), intention (OR = 0.61; [95% CI, 0.50-0.73]; $P < 0.001$), and beliefs (the worrying side of the belief spectrum: OR = 1.21; [95% CI, 1.09-1.35]; $P < 0.001$). Beliefs regarding future outlook predicted taking adherence (OR = 0.83; [95% CI, 0.71-0.97]; $P = 0.018$). An association with norms was nonsignificant (OR = 1.04; [95% CI, 0.88-1.24]; $P = 0.65$). Patients' BAASIS scores were also associated with assessments of depressive symptomatology (OR = 1.17; [95% CI, 1.09-1.27]; $P < 0.001$; **Figure S12, SDC**, http://links.lww.com/TP/C727).

Evidence Based on Relations to Other Variables (Part 3: Responsiveness to Interventions)

Although the 3 randomized controlled trials that tested the efficacy of tailored psychosocial/behavioral interventions to improve adherence generally favored the intervention groups (**Figure S13, SDC**, http://links.lww.com/TP/C727), a pooled analysis of the interventions' impact on the participants' BAASIS responses did not yield statistically significant results (OR = 0.70; [95% CI, 0.49-1.01]; $P = 0.06$). On the contrary, pooling results of trials testing a switch from twice- to once-daily tacrolimus regimens (**Figure S14, SDC**, http://links.lww.com/TP/C727) showed decreased total implementation (OR = 0.78; [95% CI, 0.61-1.00]; $P = 0.048$) and taking NA (OR = 0.67; [95% CI, 0.47-0.95]; $P = 0.03$).

Evidence Based on Response Processes

The BAASIS' Flesch Reading Ease score was 70, indicating a relatively easy (7th grade) reading level. No differences were found between the written and interview version regarding taking adherence (OR = 0.92; [95% CI, 0.82-1.03]; $P = 0.16$). However, timing issues were more frequently reported in the written version (OR = 1.30; [1.18-1.44]; $P < 0.001$). The same was true for the total implementation score (OR = 1.25; [1.14-1.37]; $P < 0.001$).

Reliability and Validity Evidence Based on Internal Structure

Despite having model convergence problems with the calculation of the intracluster correlation to estimate the degree of intrapatient stability of the BAASIS scores over time, 30% to 60% of longitudinal variability could be attributed to patient-specific adherence levels (**Figure**

TABLE 3.

Characteristics of the included samples

Ref	N	Organs, n (%)	Study groups, n (%)	Sex: male, n (%)	Months after Tx: mean (SD); median (IQR)	Age: mean (SD); median (IQR), y
Individual participant data						
Bessa[23]	128	KTx	I: 64; C: 64	80 (62.50)	0.0 (0.1); 0.0 (0.0)	44.5 (12.1); 45.0 (21.0)
Burkhalter[24]	926	KTx	–	586 (63.28)	11.5 (9.3); 9.5 (11.0)	58.7 (12.3); 60.0 (18.0)
De Geest[25]	3280	KTx 2058 (62.74) LiTx 672 (20.49) LuTx 324 (9.88) HTx 226 (6.89)	–	2103 (64.12)	8.1 (7.1); 6.0 (0.9)	52.6 (13.6); 55.0 (18.0)
Denhaerynck[12]	1397	HTx	–	1018 (72.87)	39.9 (16.5); 39.0 (27.0)	53.2 (13.2); 56.0 (18.0)
Dobbels[27]	247	LuTx 111 (44.94) HTx 80 (32.39) LiTx 56 (22.67)	I: 103; C: 102	140 (56.68)	52.8 (34.3); 47.0 (57.0)	54.9 (12.8); 58.0 (16.0)
Ducci[28]	268	LiTx	–	206 (76.87)	33.9 (15.7); 33.0 (24.0)	54.4 (8.9); 56.0 (13.0)
Eisenga[29]	1737	KTx 1036 (59.64) LiTx 381 (21.93) LuTx 248 (14.28) HTx 72 (4.15)	–	1020 (58.72)	84.0 (94.9); 48.0 (126.0)	55.8 (13.2); 58.0 (18.0)
Godinas[30]	166	LuTx	–	79 (47.59)	81.3 (55.6); 67.0 (69.0)	56.8 (12.7); 61.0 (14.0)
Gustavsen 1[31]	195	KTx	I: 100; C:95	139 (71.28)	0.1 (0.0); 0.1 (0.0)	55.3 (14.1); 57.5 (20.3)
Gustavsen 2[31]	100	KTx	–	75 (75.00)	12.0 (0.0); 12.0 (0.0)	54.1 (13.9); 56.0 (18.5)
Košťálová[22]	361	KTx	–	323 (64.27)	97.7 (73.3); 79.2 (108.7)	57.7 (11.7); 60.2 (18.8)
Lieb[8]	78	KTx	–	56 (71.79)	5.6 (4.2); 5.0 (6.0)	55.3 (11.5); 56.5 (17.0)
Liu[32]	296	LiTx	–	223 (75.34)	–	53.4 (10.1); 55.0 (13.0)
Low[33]	69	KTx	I: 35; C: 34	39 (56.52)	32.3 (16.6); 28.0 (20.0)	50.7 (11.4); 51.2 (15.9)
Marsicano[9,34]	100	KTx	–	65 (65.00)	72.3 (42.4); 72.0 (57.5)	45.0 (13.5); 44.5 (23.0)
Silva[35]	88	KTx	–	56 (63.64)	108.7 (43.9); 107.0 (59.0)	47.2 (12.9); 47.0 (21.0)
Sanders-Pinheiro[36]	1105	KTx	–	647 (58.55)	74.4 (57.7); 57.6 (75.6)	47.6 (12.6); 48.4 (19.2)
Schäfer[11]	349	KTx	–	200 (57.31)	100.2 (78.8); 91.0 (104.0)	53.0 (13.6); 53.5 (20.5)
Schmid[37]	114	KTx	–	74 (64.91)	32.9 (14.8); 31.5 (25.0)	53.6 (11.9); 56.0 (15.0)
Scheel[38,39]	357	KTx	–	232 (64.99)	77.0 (73.5); 48.0 (82.0)	52.9 (13.8); 54.0 (21.0)
Tielen[40,41]	113	KTx	–	73 (64.60)	1.0 (0.1); 1.0 (0.0)	50.8 (13.5); 53.0 (18.0)
Subtotal	11 474	KTx 7177 (62.55) HTx 1775 (15.47) LiTx 1673 (14.58) LuTx 849 (7.40)	–	7344 (64.00)	42.9 (60.5); 18.0 (48.0)	53.4 (13.3); 55.7 (18.6)
Published data						
Abedini[42]	91	KTx	–	58 (63.7)	49.2 (52.8); 36.0	47.7 (14.3); 47.0
Beckebaum[43]	110	LiTx	–	70 (63.2)	77.4 (59.6)	51.0 (13.9)
Doesch[44,45]	72	HTx	–	55 (76.3)	57.6 (52.8)	46.0 (14.4)
Fellström[46]	175	KTx	–	113 (64.6)	49.2 (49.2); 32.4	49.4 (14.0); 50.0
Lehner[47]	153	KTx	–	96 (62.7)	69.6 (55.2)	51.1 (12.3)
Valente[48]	34	LiTx	–	27 (79.4)	38	60.0
Subtotal	635	KTx 419 (65.98) LiTx 144 (22.68) HTx 72 (11.34)	–	419 (66.1)	59.4 (52.3)[a]	50.0 (13.3)[a]
Total	12 109	KTx 7596 (62.73) HTx 1847 (15.25) LiTx 1817 (15.01) LuTx 849 (7.01)	–	7736 (64.1)	43.8 (60.1)[a]	53.2 (13.3)[a]

[a]Weighted average using mean or median (if mean not available); pooled SD.

C, control group; HTx, heart transplant; I, intervention group; IQR, interquartile range; KTx, kidney transplant; LiTx, liver transplant; LuTx, lung transplant.

TABLE 4.

Descriptive statistics of responses to the BAASIS (summary statistics of Table S1, SDC, http://links.lww.com/TP/C727 to Table S5, SDC, http://links.lww.com/TP/C727).

		Frequencies	
Dimension	**Item content**	**Yes, n (%)**	**Frequency indication, n (%)**
Implementation	Taking NA	3281 (14.57)	2422 (10.76)
			400 (1.78)
			116 (0.52)
			70 (0.31)
			102 (0.45)
	Drug holidays	371 (1.64)	130 (1.31)
			30 (0.30)
			16 (0.16)
			13 (0.13)
			12 (0.12)
	Timing NA	3379 (31.19)	1472 (15.39)
			797 (8.33)
			351 (3.67)
			198 (2.07)
			81 (0.85)
	Dose alteration	196 (1.91)	
Discontinuation	Stopped	12 (0.35)	
Initiation	New prescription filled and started	98 (100.00)	
Implementation	Overall score	4027 (38.33)	
All dimensions simultaneously	Overall score	8 (0.26)	

Basel Assessment of Adherence to Immunosuppressive Medications Scale; NA, nonadherence.

S15, SDC, http://links.lww.com/TP/C727). Furthermore, regarding the implementation section's internal consistency, Table 6 indicates moderate correlations between the 2 items on taking and timing (rho values ≈ 0.30); however, their correlation with dose reduction was quite weak (rho ≈ 0.10). A principal component analysis confirmed these interitem correlations, showing that the rotated 2-factor solution separated the dose-reduction item's response pattern from those of the taking and timing items. This implies some overlap in the information gathered by the taking and timing items, but only a negligible overlap between the responses on dose reduction and those on taking and timing NA.

DISCUSSION

Although NA to prescribed immunosuppressives is a risk factor of poor outcomes in transplant recipients, few studies in the transplant and general adherence literature have examined the psychometric properties of self-report NA instruments such as the BAASIS. Using a sample that reflects a variety of settings and transplant populations, and following a method considered state-of-the-art in the meta-analytic field (ie, relating to individual participant data),[49] our analysis supports the BAASIS' ability to assess NA to immunosuppressives in a sufficiently precise and targeted way: associations were confirmed with almost all of the hypothesized relationships; and the reliability testing shows that the BAASIS distinguishes a patients' personal level of adherence, a signal that differs from mere measurement error. Therefore, the BAASIS lives up to its status as one of the COMMIT group's recommended self-report instruments[2]—a recommendation that, until now, has relied on content validity arguments. This study confirms and extends other validity aspects that have since been added.[6,31]

Specifically, regarding its relationship to other assessment methods for NA, we found a clear association between the BAASIS and EM, which is currently considered the most accurate (although still indirect) method of measuring NA. This indicates that the BAASIS' self-reported subjective appraisal of NA is in line with a method that is independent of self-perception. Given EM's intrusiveness in daily life and high costs, self-report can function as a low-tech, inexpensive alternative in which EM is not feasible (eg, in daily clinics and large studies/registries).[50]

The direct measurement of tacrolimus blood variability as a NA barometer was only weakly associated with the BAASIS. Variability in blood levels of medications or their metabolites are known to be influenced by numerous factors, such as the timing of the blood sampling, absorption of the medication (eg, with or without food), interactions with food and other drugs, genetics, dosing changes, or even white coat adherence (ie, increased adherence prior to a clinic visit).[51–54] Once these factors are accounted for, NA's contribution to blood-level variability is barely discernible.[55] Still, although blood assays provide little useful information on the implementation aspect of adherence, they are considered able to detect aspects our available data did not allow us to check, that is, noninitiation or discontinuation of the medication regime.[1]

Strong relationships were found with other self-report measures of NA, including the Immunosuppressant Therapy Adherence Scale,[56] which is also endorsed by the COMMIT group.[2] The BAASIS is different from this and most other self-report measures in that it incorporates all NA dimensions as

TABLE 5.

Methodological details of the various analyses

Ref	Time frame[a]	Operational definitions of (in)dependent variables or random variables	Timing BAASIS measurements
Validation analysis of the relationship of the BAASIS to other variables (part 1: other adherence measures): EM			
Dobbels[27]	Concurrent	EM assessment of same prior month as covered by the BAASIS recall period, expressed in parameters of taking adherence (% prescribed doses taken), timing adherence (% of expected intakes with an interdose interval deviating <25% from prescribed) and omissions of >1 consecutive doses. Parameters were calculated from the raw data.	Baseline,[b] 3 (randomization), 6,[c] and 9[c] mos
Lieb[8]	Concurrent	EM assessment of same prior 2 wks as covered by the BAASIS recall period, expressed in parameters of taking adherence (% prescribed doses taken) and timing adherence (% of intakes within 2-h time window around the intake time). Data were delivered as parameter calculations from the authors.	Baseline, 2, 4, 6, 10, and 12 weeks. Note: The recall period was changed to 2 wks.
Low[33]	Concurrent	EM assessment of same prior month as covered by the BAASIS recall period, expressed in parameters of taking adherence (% prescribed doses taken), timing adherence (% of expected intakes with an interdose interval deviating <25% from prescribed) and omissions of >1 consecutive doses. Parameters were calculated from the raw data.	Baseline (randomization),[b] 3,[c] 6,[c] 9,[c] and 12[c] mos
Schäfer[11]	Prospective	3 mos of EM assessment following BAASIS measurement, expressed in parameters of taking adherence (% prescribed doses taken), timing adherence (% of expected intakes with an interdose interval deviating <25% from prescribed), and omissions of >1 consecutive doses. Parameters were calculated from the raw data.	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 1: other adherence measures): self-report instruments			
Ducci[28]	Concurrent	Immunosuppressant Therapy Adherence Scale	At inclusion
Low[33]	Concurrent	Morisky Medication Adherence Scale	At inclusion and four 3 monthly visits[c]
Marsicano[9,34]	Concurrent	Measure of adherence to treatment	At inclusion
Schmid[37]	Concurrent	Immunosuppressant Therapy Adherence Scale	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 1: other adherence measures): blood assay			
Bessa[23]	Concurrent	Coefficient of variation of tacrolimus trough levels obtained at days 10, 14, 21, and 28 d after Tx (n = 248)	At day 28[c]
Dobbels[27]	Concurrent/ prospective	Coefficient of variation of tacrolimus trough levels obtained at inclusion, 3, 6, 9, and 15 mos (between 2 and 5 measurements; n = 368)	At inclusion[c]
Eisenga[29]	Concurrent/ prospective	Coefficient of variation of tacrolimus levels 3 to 12 mos after Tx (between 2 and 4 measurements) (n = 1795)	At inclusion (1st available measurement post-Tx)
Godinas[30]	Concurrent/ prospective	Coefficient of variation of 3 prior tacrolimus trough levels (n = 498)	At inclusion
Gustavsen 2[31]	Concurrent/ prospective	Coefficient of variation of 6 tacrolimus levels 6–9 wks after Tx (n = 570)	At week 8[c]
Košťálová[22]	Prospective	Coefficient of variation of 7 tacrolimus trough levels at consecutive visits between 3 and 22 mos apart (n = 1635)	At inclusion
Lieb[8]	Retrospective/ concurrent	Coefficient of variation of tacrolimus of trough levels at inclusion + 3 antecedent measures (n = 302)	At inclusion
Schäfer[11]	Prospective	Coefficient of variation of tacrolimus trough levels right before inclusion till end of EM measurement (between 2 and 17 measurements; n = 306)	At inclusion
Scheel[38,39]	Retrospective	Coefficient of variation of 4 tacrolimus trough levels within the last 12 months before BAASIS measurement (between 4 and 43 measurements; n = 2058)	At inclusion
Tielen[40,41]	Concurrent	Coefficient of variation of tacrolimus blood levels at inclusion and 2 prior weeks (between 4 and 10 measurements; n = 572)	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 1: other adherence measures): collateral report			
Denhaerynck[12]	Retrospective/ concurrent	Physician and nurse estimates, blinded to patient self-report – 1 excellent; 2 fair; 3 poor adherence; dichotomized into adherent (1) and NA (2 and 3)	At inclusion
Dobbels[27]	Retrospective/ concurrent	Physician and nurse estimates, blinded to patient self-report – 1 excellent; 2 fair; 3 poor adherence; dichotomized into adherent (1) and NA (2 and 3)	At inclusion
Gustavsen[31]	Retrospective/ concurrent	Physician/nurse estimate – 1 excellent, 2 suboptimal, 3 poor adherence, dichotomized into adherent (1) and NA (2 and 3)	At inclusion
Lieb[8]	Retrospective/ concurrent	Physician estimate – 1 = very good adherence to 5 = very poor adherence, dichotomized into adherent (1) and NA (2–5)	At inclusion
Marsicano[9,34]	Retrospective/ concurrent	Assistant physician and nurse estimates, blinded to patient self-report – 1 good, 2 fair, 3 poor adherence, dichotomized into adherent (1) and NA (2 and 3)	At inclusion

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TABLE 5. (Continued)

Ref	Time frame[a]	Operational definitions of (in)dependent variables or random variables	Timing BAASIS measurements
Scheel[38,39]	Retrospective/ concurrent	Physician estimate, blinded to patient self-report – 1 = very good adherence to 5 = very poor adherence, dichotomized into adherent (1) and NA (2–5)	At inclusion
Sanders-Pinheiro[36]	Retrospective/ concurrent	Nephrologist and nurse estimates (one or both), blinded to patient's self-report – binary score	At inclusion
Schäfer[11]	Retrospective/ concurrent	Several physicians' and several nurses' estimates, blinded to patient's self-report – 1 good, 2 fair, 3 poor adherence, dichotomized into adherent and NA if at least one of the physicians or nurses considered the patient not having good adherence	At inclusion
Schmid[37]	Retrospective/ concurrent	Physician and nurse estimates, blinded to patient's self-report – 1 good, 2 fair, 3 poor adherence, dichotomized into adherent (1) and NA (2 and 3)	At inclusion
Silva[35]	Retrospective/ concurrent	Assistant physician and nurse estimates, blinded to patient's self-report – 1 good, 2 fair, 3 poor adherence, dichotomized into adherent (1) and NA (2 and 3)	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 2: psycho-behavioral constructs): cognitive behavioral theory			
Denhaerynck[12]	Concurrent	Integrative Model of Behavioral Prediction (barriers, intention, self-efficacy, beliefs, norms)	At inclusion
Dobbels[27]	Concurrent	Integrative Model of Behavioral Prediction (barriers)	At inclusion and 15 mos[d]
Ducci[28]	Concurrent	Integrative Model of Behavioral Prediction (barriers, intention, self-efficacy, beliefs, norms)	At inclusion
Godinas[30]	Concurrent	Integrative Model of Behavioral Prediction (barriers)	At inclusion
Schmid[37]	Concurrent	Integrative Model of Behavioral Prediction (barriers, intention, self-efficacy, beliefs, norms)	At inclusion
Schäfer[11]	Concurrent	Integrative Model of Behavioral Prediction (self-efficacy, beliefs)	At inclusion
Tielen[40,41]	Concurrent	Integrative Model of Behavioral Prediction (self-efficacy, beliefs)	At inclusion, 6, and 18 mos
Košťálová[22]	Concurrent	Integrative Model of Behavioral Prediction (beliefs)	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 2: psycho-behavioral constructs): depressive symptoms			
Burkhalter[24]	Concurrent	Depressive symptomatology: Depression, Anxiety, and Stress Scale	At inclusion
De Geest[25]	Prospective	Depressive symptomatology: Depression, Anxiety, and Stress Scale	NA predicted by depressive symptoms at previous visit
Denhaerynck[12]	Concurrent	Hospital anxiety and depression scale (depression part)	At inclusion
Liu[32]	Concurrent	Hospital anxiety and depression scale (depression part)	At inclusion
Scheel[38,39]	Concurrent	Hospital anxiety and depression scale (depression part)	At inclusion
Schäfer[11]	Concurrent	Beck depression inventory	At inclusion
Validation analysis of the relationship of the BAASIS to other variables (part 3: responsiveness to adherence-enhancing interventions)			
Bessa[23]		Postintervention assessments comparison of intervention vs control group (original primary outcome: CV%)	Days 28 and 90
Dobbels[27]		Postintervention assessments comparison of intervention vs control group (original primary outcome: EM)	Months 6, 9, and 15
Low[33]		Postintervention assessments comparison of intervention vs control group (original primary outcome: EM)	Months 3, 6, 9, and 12
Abedini[42]		Postconversion vs inclusion assessments	Inclusion, months 1, 3, 6, and 12
Beckebaum[43]		Postconversion vs inclusion assessments	Inclusion, month 12
Doesch[44,45]		Postconversion vs inclusion assessments	Inclusion, months 4 and 8
Lehner[47]		Postconversion vs inclusion assessments (paired data unknown)	Inclusion, month 18
Fellström[46]		Postconversion vs inclusion assessments	Inclusion, months 3, 6, and 12
Godinas[30]		Postconversion vs inclusion assessments	Inclusion, month 12
Valente[48]		Postconversion vs inclusion assessments (paired data unknown)	Inclusion, month 6
Validation analysis of the internal structure of the BAASIS			
Studies with individual participant data			All available data points (see Table 2)

Continued next page

TABLE 5. (Continued)

Ref	Time frame[a]	Operational definitions of (in)dependent variables or random variables	Timing BAASIS measurements
Reliability analysis of stability over time of individual responses			
Bessa[23]		Patient number as a random intercept	Day 28 and 90[c]
De Geest[25,26]		Patient number as a random intercept	Inclusion, year 1 and yearly visits
Dobbels[27]		Patient number as a random intercept	Inclusion, month 3, 6, 9, and 15[d]
Eisenga[29]		Patient number as a random intercept	Inclusion, month 3, 6, 12, 24, 36, 60
Gustavsen[31]		Patient number as a random intercept	Week 8 and year 1[c]
Lieb[8]		Patient number as a random intercept	Inclusion and six 2-weekly visits
Low[33]		Patient number as a random intercept	Inclusion and four 3-monthly visits[c]
Tielen[40,41]		Patient number as a random intercept	Inclusion, month 6 and 18

Concurrent means that the study falls within the recall period of the BAASIS. Retrospective means that the study falls before the recall period of the BAASIS. Prospective means that the assay was done after the BAASIS measurement.

[a]Adapted to each research question pertaining to the 4-wk recall period for NA during the implementation phase.

[b]Baseline data are not relevant for concurrent adherence testing, because EM is not yet available for the prior month.

[c]Control group only.

[d]Control group, preallocated, and nonallocated participants.

BAASIS, Basel Assessment of Adherence to Immunosuppressive Medications Scale; CV%, coefficient of variation; EM, electronic monitoring; HTx, heart transplant; KTx, kidney transplant; LiTx, liver transplant; LuTx, lung transplant; NA, nonadherence; RCT, randomized controlled trial.

outlined in the conceptual ABC taxonomy framework[3] while covering the taking and timing aspects of implementation. It fulfills these tasks without querying any causal indicators (ie, reasons) of NA as part of the instrument itself.[57] Therefore, the causal indicators were assessed separately (ie, using the variables within the Integrative Model of Behavioral Prediction), which also provided us with validity evidence of the BAASIS' expected relations to these concepts. Those in theoretical closeness to NA behavior were confirmed (ie, barriers, self-efficacy, and intentions).

Regarding responsiveness to interventions, adherence enhancements were only detected for regimen change studies; not with the 3 complex adherence-enhancing interventions. Considering that 2 of these 3 trials also employed EM and neither detected any intervention effect using EM, a lack of intervention efficacy was probably the reason for the lack of a relationship.[23,33]

Because of increased attention in the literature to the topic of health literacy, our response process examination included a seldom-performed check of the instrument's reading level. The BAASIS' readability level was judged fairly easy to read, corresponding to the level of the 7th grade, or a reader of about 12 to 13 y old. At this level, the majority of respondents should understand the questions and instructions; however, those with very low literacy may still experience difficulties. For such individuals, the interview version may be indicated.

The slightly lower reporting of timing errors in the interview version may indicate that patients feel more comfortable with the written version; however, it may also reflect variation in included studies. It would have been useful to check whether responses differed between interviewers, which would at the same time have documented the BAASIS' interrater reliability. However, not enough data were available to do this test.

As with all methods of assessing medication taking behavior, self-report has its advantages and shortcomings. Although feasible and affordable, it is considered somewhat bias-prone (eg, recall bias and social desirability bias) and provides less rich data collection than some other measures.[1] Nonetheless, validation studies such as this one provide sufficient evidence of its reliability and validity to justify its intended application. Possible next steps in this instrument's continuous validation process include determining its diagnostic accuracy in comparison to that of other assessment methods, to optimize its assessment by combining different available methods,[11] and to examine its predictive validity toward clinical outcomes.[40,50]

Although NA is increasingly recognized as a major behavioral risk factor for poor outcomes in transplantation, routine assessment either of NA or of NA risk is not yet standard practice. Achieving effective, sustainable adherence monitoring in real-world settings is an attainable goal but will demand the use of suitable methods aimed at implementing adherence assessment. Involvement of the full range of stakeholders will inform context-specific strategies to maximize the acceptability and feasibility of evidence-based adherence measurement methods. Although self-report is often falsely regarded as a substandard measurement method, reliable patient-report instruments can easily and affordably be integrated into clinical practice and add considerable value. This is particularly true in combination with other commonly used assessment methods.[6,11]

CONCLUSIONS

This study on the psychometric properties of the BAASIS, a self-report instrument assessing NA to immunosuppressive

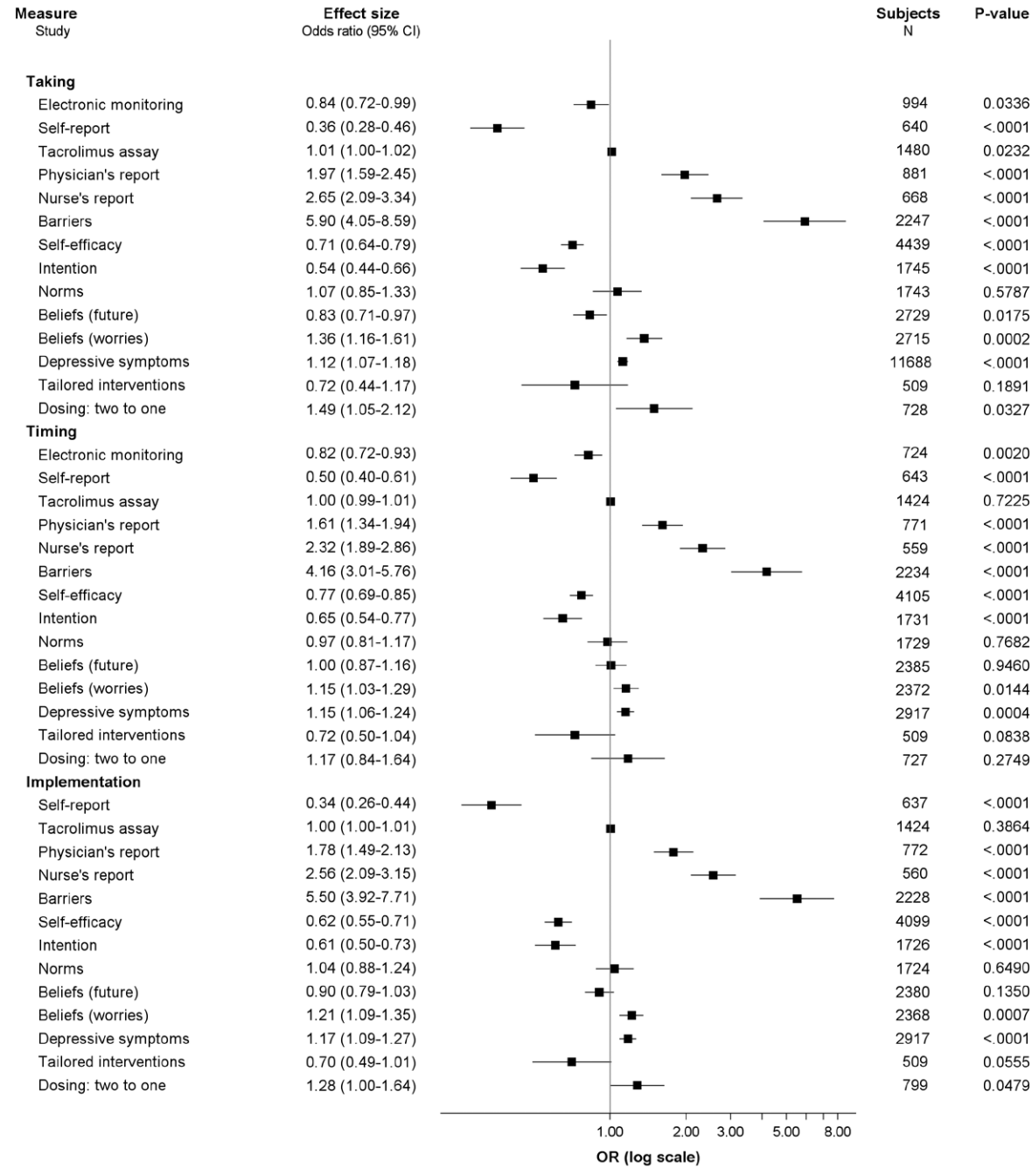

FIGURE 2. Summary of pooled (overall) effect sizes (for details see **Figures S1, SDC**, http://links.lww.com/TP/C727–S14 http://links.lww.com/TP/C727). 95% CI, 95% confidence interval; OR, odds ratio.

TABLE 6.

Reliability and validity evidence based on internal structure: internal consistency of the 3 independent items on the implementation aspect

	Interitem correlations (Spearman's rho)			Principal component analysis: factor loadings (Pearson's *r*)	
	Taking	**Timing**	**Dosing**	**Factor 1**	**Factor 2**
				N = 12 125; N = 8966	
Taking		rho = 0.31; N = 11 888	rho = 0.11; N = 9023	*r = 0.79*; r = 0.79	*r = 0.00*; r = –0.02
Timing	*rho = 0.28*; *N = 12 557*		rho = 0.10; N = 8985	*r = 0.81*; r = 0.83	*r = 0.09*; r = 0.15
Dosing	*rho = 0.11*; *N = 12 157*	*rho = 0.08*; *N = 12 137*		*r = 0.06*; r = 0.07	*r = 1.00*; r = 0.99

Italic font indicates a binary score and nonitalic an ordinal score.

medication, shows a favorable validity and reliability profile. Although the scale undoubtedly shares the limitations of any self-report instrument, the fact that almost all hypothesized relationships were confirmed—and if not, circumstantial evidence could explain that lack—provides evidence that the BAASIS does capture medication taking behavior. Because it is easy and inexpensive to administer and interpret, self-report is extremely useful as a screening tool in the clinic, or to assess NA of larger samples in a study or registry setting.

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REFERENCES

1. De Geest S, Ribaut J, Denhaerynck K, et al. Adherence management in transplantation: creating impact in real world settings based on state of the art evidence. In: Cukor D, Cohen S, Kimmel PL, eds. *Psychosocial Aspects of Chronic Kidney Disease: Exploring the Impact of CKD, Dialysis, and Transplantation on Patients*. Academic Press; 2021:409–448.
2. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017;101:S1–S56.
3. Vrijens B, De Geest S, Hughes DA, et al.; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691–705.
4. 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;17:854–863.
5. Dang J, King KM, Inzlicht M. Why are self-report and behavioral measures weakly correlated? *Trends Cogn Sci*. 2020;24:267–269.
6. Dobbels F, Berben L, De Geest S, et al.; Transplant360 Task Force. The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. *Transplantation*. 2010;90:205–219.
7. Institute of Nursing Science. The Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS©). Available at https://baasis.nursing.unibas.ch/. Accessed March 9, 2022.
8. 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.
9. Marsicano Ede O, Fernandes Nda S, Colugnati F, et al. Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. *BMC Nephrol*. 2013;14:108.
10. *Joint Committee on the Standards for Educational and Psychological Testing. The Standards for Educational and Psychological Testing*. AERA Publications; 2014.
11. Schafer-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;8:616–626.
12. Denhaerynck K, Berben L, Dobbels F, et al.; BRIGHT study team. Multilevel factors are associated with immunosuppressant nonadherence in heart transplant recipients: the international BRIGHT study. *Am J Transplant*. 2018;18:1447–1460.
13. 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;18:1121–1133.
14. De Geest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. *Transplantation*. 1995;59:340–347.
15. De Geest S, Denhaerynck K, Dobbels F. Clinical and economic consequences of nonadherence to immunosuppressive drugs in adult solid organ transplantation. In: Oppenheimer F, ed. *Compliance in Solid Organ Transplantation*. Permanyer Publications; 2011:63–81.
16. McGillicuddy JW, Chandler JL, Sox LR, et al. Exploratory analysis of the impact of an mHealth medication adherence intervention on tacrolimus trough concentration variability: post hoc results of a randomized controlled trial. *Ann Pharmacother*. 2020;54:1185–1193.
17. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160:2101–2107.
18. Fishbein M, Hennessy M, Yzer M, et al. Can we explain why some people do and some do not act on their intentions? *Psychol Health Med*. 2003;8:3–18.
19. Flesch R. A new readability yardstick. *J Appl Psychol*. 1948;32:221–233.
20. Readability Formulas. *Readability formulas*. Available at https://readabilityformulas.com/free-readability-formula-tests.php. Accessed October 30, 2021.
21. Sheu CF, Suzuki S. Meta-analysis using linear mixed models. *Behav Res Methods Instrum Comput*. 2001;33:102–107.
22. Kostalova B, Mala-Ladova K, Dusilova-Sulkova S, et al. Comparison of different methods to assess tacrolimus concentration intra-patient variability as potential marker of medication non-adherence. *Front Pharmacol*. 2022;13:973564.
23. Bessa AB, Felipe CR, Hannun P, et al. Prospective randomized trial investigating the influence of pharmaceutical care on the intra-individual variability of tacrolimus concentrations early after kidney transplant. *Ther Drug Monit*. 2016;38:447–455.
24. Burkhalter H, Wirz-Justice A, Cajochen C, et al. Daytime sleepiness in renal transplant recipients is associated with immunosuppressive non-adherence: a cross-sectional, multi-center study. *Clin Transplant*. 2014;28:58–66.
25. De Geest S, Burkhalter H, Berben L, et al.; Psychosocial Interest Group, Swiss Transplant Cohort Study. The Swiss Transplant Cohort Study's framework for assessing lifelong psychosocial factors in solid-organ transplants. *Prog Transplant*. 2013;23:235–246.
26. Koller MT, van Delden C, Muller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *Eur J Epidemiol*. 2013;28:347–355.
27. Dobbels F, De Bleser L, Berben L, et al. Efficacy of a medication adherence enhancing intervention in transplantation: the MAESTRO-Tx trial. *J Heart Lung Transplant*. 2017;36:499–508.
28. Ducci J, De Simone P, Denhaerynck K, et al. Clinical consequences of subclinical non adherence to immunosuppression after liver transplantation. *Transpl Int*. 2013;26:146.
29. Eisenga MF, Gomes-Neto AW, van Londen M, et al. Rationale and design of TransplantLines: a prospective cohort study and biobank of solid organ transplant recipients. *BMJ Open*. 2018;8:e024502.
30. Godinas L, Dobbels F, Hulst L, et al. Once daily tacrolimus conversion in lung transplantation: A prospective study on safety and medication adherence. *J Heart Lung Transplant*. 2021;40:467–477.
31. Gustavsen MT, Midtvedt K, Lonning K, et al. Evaluation of tools for annual capture of adherence to immunosuppressive medications after renal transplantation - a single-centre open prospective trial. *Transpl Int*. 2019;32:614–625.
32. Liu HX, Teng S, Lin XH, et al. The application of the necessity-concerns framework in investigating adherence and beliefs about immunosuppressive medication among Chinese liver transplant recipients. *Chin Nurs Res*. 2017;4:14–17.
33. Low JK, Manias E, Crawford K, et al. Improving medication adherence in adult kidney transplantation (IMAKT): a pilot randomised controlled trial. *Sci Rep*. 2019;9:7734.
34. Marsicano EO, Fernandes NS, Colugnati FA, et al. Multilevel correlates of non-adherence in kidney transplant patients benefitting from full cost coverage for immunosuppressives: a cross-sectional study. *PLoS One*. 2015;10:e0138869.
35. 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 (Carlton)*. 2016;21:938–943.
36. Sanders-Pinheiro H, Colugnati FAB, Denhaerynck K, et al.; ADHERE BRAZIL Study Team. Multilevel correlates of immunosuppressive nonadherence in kidney transplant patients: the multicenter ADHERE BRAZIL study. *Transplantation*. 2021;105:255–266.
37. Schmid-Mohler G, Thut MP, Wuthrich RP, et al. Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the Integrative Model of Behavioral Prediction: a cross-sectional study. *Clin Transplant*. 2010;24:213–222.

38. Scheel JF, Schieber K, Reber S, et al. Psychosocial variables associated with immunosuppressive medication non-adherence after renal transplantation. *Front Psychiatry*. 2018;9:23.
39. 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.
40. Tielen M, Laging M, Beck DK, et al. Importance of early medication adherence for long-term graft survival: a prospective, single-centre cohort study. *Transplantation*. 2016;100:S431.
41. Tielen M, van Exel J, Laging M, et al. Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. *J Transplant*. 2014;2014:675301.
42. Abedini S, Goransson L, Cockburn E, et al. Immunosuppression adherence in stable kidney transplant patients converted from immediate- to prolonged-release tacrolimus in clinical practice: a Norwegian study. *Transplant Direct*. 2018;4:e338.
43. Beckebaum S, Iacob S, Sweid D, et al. Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. *Transpl Int*. 2011;24:666–675.
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;7:1253–1258.
45. Doesch AO, Mueller S, Konstandin M, et al. Increased adherence after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation: a pre-experimental study. *Transplant Proc*. 2010;42:4238–4242.
46. Fellstrom B, Holmdahl J, Sundvall N, et al. Adherence of renal transplant recipients to once-daily, prolonged-release and twice-daily, immediate-release tacrolimus-based regimens in a real-life setting in Sweden. *Transplant Proc*. 2018;50:3275–3282.
47. Lehner LJ, Reinke P, Horstrup JH, et al. Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf) in kidney transplant patients in Germany: a multicenter, noninterventional study. *Clin Transplant*. 2018;32:1–9.
48. Valente G, Rinaldi L, Sgambato M, et al. Conversion from twice-daily to once-daily tacrolimus in stable liver transplant patients: effectiveness in a real-world setting. *Transplant Proc*. 2013;45:1273–1275.
49. Ioannidis JP, Rosenberg PS, Goedert JJ, et al.; International Meta-analysis of HIV Host Genetics. Commentary: meta-analysis of individual participants' data in genetic epidemiology. *Am J Epidemiol*. 2002;156:204–210.
50. Tong A, Oberbauer R, Bellini MI, et al. Patient-reported outcomes as endpoints in clinical trials of kidney transplantation interventions. *Transpl Int*. 2022;35:10134.
51. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group: Kasiske BL, Zeier MG, Craig JC, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9:S112–S124.
52. Hwang YH, Kim H, Min K, et al. Tacrolimus trough levels in kidney transplant recipients. *BMC Nephrol*. 2021;22:405.
53. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.
54. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. *Clin Pharmacol Ther*. 2014;95:617–626.
55. Leino AD, Abuls KM, Rodgers JKL, et al. Evaluation of the relationship between medication adherence and tacrolimus coefficient of variation. *Prog Transplant*. 2022;32:184–189.
56. Chisholm MA, Lance CE, Williamson GM, et al. Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Educ Couns*. 2005;59:13–20.
57. Voils CI, Hoyle RH, Thorpe CT, et al. Improving the measurement of self-reported medication nonadherence. *J Clin Epidemiol*. 2011;64:250–254.