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Review article

Medication adherence interventions in transplantation lack information on how to implement findings from randomized controlled trials in real-world settings: A systematic review

Barbora Kostalova [a,1], Janette Ribaut [b,c,1], Fabienne Dobbels [b,d], Sabine Gerull [c,e], Katerina Mala-Ladova [a], Leah L. Zullig [f,g], Sabina De Geest [b,d,*]

[a] Department of Social and Clinical Pharmacy, Faculty of Pharmacy in Hradec Kralove, Charles University, Akademika Heyrovskeho 1203, 500 05 Hradec Kralove, Czech Republic
[b] Institute of Nursing Science, Department of Public Health, University of Basel, Bernoullistrasse 28, 4056 Basel, Switzerland
[c] Department of Theragnostic, Hematology, University Hospital of Basel, Petersgraben 4, 4031 Basel, Switzerland
[d] Academic Center for Nursing and Midwifery, Department of Public Health and Primary Care, KU Leuven, Kapucijnenvoer 35 blok d, box 7001, 3000 Leuven, Belgium
[e] Department of Hematology, Cantonal Hospital of Aarau, Tellstrasse 25, 5001 Aarau, Switzerland
[f] Department of Population Health Science, Duke University, 215 Morris St, Durham, NC 27701, USA
[g] Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), Durham Veterans Affairs Health Care System, 508 Fulton St, Durham, NC 27705, USA

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ABSTRACT

Background: Growing numbers of randomized controlled trials (RCTs) are showing the effectiveness of interventions to improve medication adherence in transplantation recipients. However, real-world implementation is still a major challenge. This systematic review assesses the range of information available in RCTs supporting these interventions' clinical adoption in adult transplant populations.
Methods: We included RCTs of interventions that a) targeted any phase of medication adherence in solid organ or allogeneic stem cell transplantation recipients and b) were published between January 2015 and November 2020. We excluded study protocols, conference abstracts and studies focusing only on pediatric populations. We identified relevant database and trial registries as well as traced references backward and citations forward. Implementation-relevant information was evaluated using adapted versions of Peters' ten criteria: 1. *healthcare/organizational context*; 2. *social/economic/policy context*; 3. *patient involvement*; 4. *other stakeholder involvement*; 5. *sample representativeness*; 6. *trial conducted in a real-world-setting*; 7. *presence of feasibility study*; 8. *implementation strategy*; 9. *process evaluation*; 10. *implementation outcomes*, using a stoplight color-rating system.
Results: Screening 17′004 titles/abstracts resulted in 23 eligible RCTs, including 2′339 patients (n = 19–209/study). All included studies focused on the implementation phase of medication adherence. The best-reported criteria were *feasibility study* (43%), *representative sample* (17%) and *conducted in a real-world-setting* (17%). Least reported were *context* (9%), *implementation strategies* (4%), *process evaluation* (4%).
Conclusions: RCTs testing medication adherence interventions tend to report limited implementation-relevant information. This hinders their translation to real-world transplant settings. Integrating implementation

Abbreviations: alloSCT, Allogeneic hematopoietic stem cell transplantation; ERIC, Expert Recommendations for Implementing Change; ICT, information and communication technology; MeSH, Medical Subject Headings; N, denominator; BCT, behavioral change techniques; Pocket PATH, Pocket Personal Assistant for Tracking Health (study acronym); PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International prospective register of systematic reviews; RE-AIM, Reach, Effectiveness, Adoption, Implementation, and Maintenance framework; RCT, Randomized controlled trial; SMILe, Integrated Model of Care in Long-Term Follow-Up after Allogeneic Hematopoietic SteM Cell TransplantatIon faciLitated by eHealth Technology (study acronym); SOT, Solid organ transplantation; TRANSIT, Transitioning to adult care (study acronym); BRIGHT, Building research initiative group: chronic illness management and adherence in transplantation (Study acronym).

* Corresponding author at: Institute of Nursing Science, University of Basel, Bernoullistrasse 28, CH-4056 Basel, Switzerland.
E-mail addresses: vankovb@faf.cuni.cz (B. Kostalova), janette.ribaut@unibas.ch (J. Ribaut), fabienne.dobbels@kuleuven.be (F. Dobbels), sabine.gerull@ksa.ch (S. Gerull), ladovaka@faf.cuni.cz (K. Mala-Ladova), leah.zullig@duke.edu (L.L. Zullig), sabina.degeest@unibas.ch (S. De Geest).
[1] Shared first authorship, contributed equally.

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science principles early in the conceptualization of RCTs would fuel real-world-translation, reducing research waste.

1. Introduction

Medication adherence is "*the process by which patients take their medications as prescribed, and is composed of initiation, implementation and discontinuation*" [1]. Following solid organ transplantation (SOT) and allogeneic stem cell transplantation (alloSCT), immunosuppressant medication non-adherence is associated with poor clinical outcomes including graft rejection or graft-versus-host disease, leading to increased care costs [2–10].

Immunosuppressant *initiation,* the patient taking the first dose, occurs immediately after transplantation at the hospital [11]. *Implementation* of the immunosuppressive regimen concerns how closely a patient's adherence (regarding intake, dosing and timing) corresponds to that regimen. Problems with this phase are reported in 10% to >60% of patients [10,12–15]. The third phase, *discontinuation,* ending intake, occurs in 0.5 to 3% of transplant patients [10,14,15].

Considering the prevalence of medication non-adherence, its potential outcomes and the shortage of donor organs [2–9,11], medication adherence measurement is recommended as routine post-transplant follow-up [16].

An increasing body of evidence encourages routine medication adherence support in transplant settings [11]. Systematic reviews recommend combining (e.g., educational, behavioral and psychological) components to produce complex interventions [11,17–20]. One recent meta-analysis showed that randomized controlled trials (RCTs) of interventions combining self-monitoring and electronic monitoring-based feedback on medication intake, plus social support, action planning and problem solving led to increased immunosuppressant adherence, while the effect on other outcomes such as rejection were uncertain [21]. However, how fully the analyzed trials' reports support the translation of their findings to real-world settings has not been evaluated.

An implementation science perspective can guide such an evaluation. Implementation science is "*the scientific study of methods to promote the integration of research findings and evidence-based interventions into healthcare policy and practice*" [22]. This approach focuses on methods to support lasting adoption of proven medication adherence interventions into clinical practice [23,24].

Peters et al. have published criteria on the translation process [25]. However, in chronically ill populations (e.g., statin users, HIV or asthma patients, but not transplant recipients), Zullig et al.'s recent systematic review showed that even high quality medication adherence intervention RCTs rarely included much implementation-relevant information. This lack would hinder their adoption into real-world-settings [26]. Therefore, this review's goal was to assess the type and extent of information available in published SOT and alloSCT adult medication adherence intervention RCTs to support real-world implementation of adherence-enhancing interventions.

2. Methods

2.1. Design

This article complies with the Cochrane Guidelines for systematic reviews [27]. The manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [28].

2.2. Protocol and registration

This review is registered at International prospective register of systematic reviews (PROSPERO) (CRD42020161710, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=161710). No other protocol has been published.

2.3. Eligibility criteria

This systematic review included RCTs of medication adherence interventions published during the last six years (01.01.2015–11.11.2020). We chose this period mainly because implementation science is an emerging field. The term 'implementation science' was only added to the Medical Subject Headings (MeSH) lexicon in 2019 [29], however, the range of related theoretical frameworks and taxonomies is growing rapidly [24]. Another reason is that looking at implementation only makes sense if the intervention can indeed improve adherence. Several reviews pointed to the poor methodological quality and the fact that not many interventions were effective in improving adherence. It took time before well-designed effective interventions to appeared in the literature.

The included papers fulfilled five selection criteria: 1) They focused on patients following heart, liver, kidney, lung, pancreas or combined transplantations (e.g., kidney-liver) or alloSCT; 2) Their subjects were adults or mixed populations (e.g., during transition from pediatric to adult care); 3) They included assessments of the *initiation*, *implementation* or *discontinuation* phases of medication adherence; 4) They were in English, French, German, Dutch, Spanish, Italian, Portuguese, Czech or Slovak; and 5) Full-text versions were available. Exclusion criteria were: 1) No original quantitative results (e.g., study protocols or conference abstracts); 2) Non-RCT research designs (e.g., quasi-experimental or descriptive studies); 3) A focus on uterus, islet, small intestine, egg cell, eye cornea, hands, feet, face transplantation or autologous stem cell transplantation; or 4) A focus exclusively on a pediatric population (<18 years).

2.4. Information sources

Literature searches queried five databases: MEDLINE OvidSP, CENTRAL (via Cochrane), Embase OvidSP, CINAHL EBSCOhost and Web of Science. We also searched trial registers (clinicaltrials.gov, WHO trial registry). Based on information in other reviews [19–21,30] and included RCTs, we used backward reference searches and forward citation tracing.

2.5. Search string

We developed our MEDLINE search string by combining key MeSH and free text terms. For other databases we adapted these (see Supplementary Material, Material and Methods). The MeSH and free-text terms reflected four concepts: *transplantation*, *medication adherence*, *RCT* and *adults*. The *adults* concept excluded articles focusing entirely on pediatric subjects, but kept mixed and adult populations. Our search string was reviewed by a medical information specialist at the University of Basel. Based on his recommendations and the Cochrane Guidelines [27], to maximize returns, no filters were applied (e.g., no time restrictions) as this could lead to incomplete results.

2.6. Data collection process

Identified titles and abstracts were independently screened by two reviewers (BK and JR). Full texts were assessed by the same reviewers using the criteria noted above. In case of disagreement, an independent third researcher (SDG) contributed to consensus finding.

Identified RCTs were searched for accompanying articles, e.g., study

protocols or pilot studies. Even if these articles were released before 2015, we used their content to complement the data item summary.

2.7. Risk of bias in individual studies

Identified studies' quality was independently assessed by two reviewers (BK and KML) using version 2 of the Cochrane risk of bias tool for RCTs [31]. Conflicting assessment ratings were resolved by consensus. This quality assessment did not exclude any studies.

2.8. Data items, summary measures and synthesis of the results

We used quantitative descriptions to summarize information on the first author, publication year, country, setting, study duration, population, sample size, intervention/control group characteristics (organized using the taxonomy of behavior change techniques, i.e., active intervention components, BCTs) [32], medication adherence phase and measurement, medication adherence outcome, clinical and other outcome(s). Although the prime focus of this review was on implementation relevant information, we also included some basic information on effectiveness outcomes. The latter outcomes have been addressed in other reviews [17–21].

We synthesized the selected studies' reporting elements using Zullig's adaptation [25] of Peters' ten implementation science assessment criteria [26]: *1) healthcare/organizational context; 2) social/economic/policy context* described [33]; *3) patient involvement; 4) other relevant stakeholder* involvement [34]; and *5) sample representative* of the target population; *6) trial conducted in real-world setting* [25]; 7) *feasibility study* conducted before main study; *8) implementation strategies reported* (methods to enhance adoption, implementation, sustainment, and scale-up of program or practice) [11,35,36]; *9) process evaluation* conducted parallel to outcome evaluation; and *10) implementation outcomes* measured and reported [37].

A detailed description of each criterion, including definitions and examples, is available in Table 1. Every RCT was independently rated by two reviewers (BK and JR). The reviewers presented their results in a table using a color rating system: green = intervention component well-reported, measured and addressed; orange = intervention component partly reported but uncertainly or unclearly addressed; and red = intervention component not reported. In cases of disagreement, an independent third researcher (LZ) decided on the rating.

2.9. Ethics approval

Because all data were publicly available, no ethics approval was necessary.

3. Results

3.1. Study selection

The selection process is presented in the PRISMA flow diagram (Fig. 1). Using the search strategy described above, we identified 17′004 titles, of which 15′048 were non-duplicates. Of these, 5′966 were published in or after 2015. After screening of titles and abstracts, 58 full-text articles were assessed for eligibility. Thirty-five were excluded: eight were not on RCTs, 21 were conference abstracts or proposals without results, four did not include medication adherence-enhancing interventions and two did not measure medication adherence as an outcome. Our analysis included 23 unique RCTs, from which we identified 18 accompanying papers (i.e., five protocols, five pilot/feasibility studies, one case study from an original RCT, six follow-up papers and one doctoral thesis).

Table 1
Adapted Peters' criteria and description of implementation research components [25,26].

	Implementation component [25,26]	Description
1	Did the investigators describe the health care and organizational context?	Context means the milieu where health care takes place. It includes interactions between the institution, practice patterns, attitudes of different stakeholders and varies between different health care systems and organizations. The implementation of new interventions is affected by a wide range of contextual factors, e.g., epidemiological or legal issues. These factors typically interact with each other, the intervention and the implementation and change over time [25].
2	Did the investigators describe the social, economic and policy context?	This question covers multilevel interactions between the policy and economic situation (e.g., insurance coverage of medication costs) as well as demographic and epidemiological conditions [25]. Providing a table on the demographics of the participants is important and necessary, but does not fully address the context. Ideally, authors will report on the underlying context in which the study is set. This could mean reporting the demographics of the sample in a table while also describing the social context in the text. For example, the context includes all relevant organizational or health policies, historical events (e.g., COVID-19), and other contextual factors that might influence the study.
3	Were patients and/or their family members involved in designing or evaluating the study?	When implementing interventions in a specific context, the interests and priorities of the end-users, i.e. the patients and their families, should be considered and involved at all stages of the research process [37]. A true partnership with patients and/or family members is needed at every stage of a research project, from the planning of the methods and designing of the intervention, throughout the study until the evaluation and dissemination of the findings.
4	Were other stakeholders, besides patients, involved in designing or evaluating the study?	When implementing interventions in a specific context, the interests and priorities of relevant stakeholders such as physicians, nurses or pharmacists as well as insurers or policy makers should be considered and involved at all stages of the research process [37]. True partnerships with all relevant stakeholders are needed throughout a research project from the planning of the methods and designing of the intervention until the evaluation and dissemination of the findings.
5	Was the included sample representative of the studied population?	Implementation science attempts to understand and work under real-world conditions, rather than controlling or eliminating them. Therefore, the aim is to include the broad population groups that an intervention will target, rather than a narrowly defined selection that may not represent the target population (e.g., including healthy volunteers, excluding patients with comorbidities) [25].

(*continued on next page*)

Table 1 (*continued*)

	Implementation component [25,26]	Description
		Broad selection criteria for participants recruited directly from the clinical setting improves both the results' representativeness for the investigated population and those results' external validity [24,26].
6	Was the research conducted in a real-world setting?	Implementation science attempts to understand the conditions of the real world and to work under them, instead of controlling these conditions or eliminating their influence. Therefore, the aim is to conduct the intervention with resources available in real-world-settings instead of performing highly effective, but overly complex, elaborate and expensive interventions [25]. Recruitment of participants directly from the clinical context and conducting research in real-world settings improves both the results' representativeness of the investigated population and their external validity [24,26].
7	Was a feasibility or pilot study conducted before the evaluation study?	A feasibility/pilot study aims to do a preliminary hypothesis test, estimate the sample size and costs, test the study procedures (e.g., feasibility of in−/exclusion criteria, randomization or data collection process) as well as the intervention's feasibility, acceptability and safety [38,39]. To support successful implementation, a feasibility/pilot study explores any uncertainties that have arisen during development without claiming to be a scale model of the planned study. A feasibility/pilot study using a small number of the target population within the targeted setting has the potential to reveal any problems with the design or intervention at an early stage and to address them proactively before spending too much effort, time and money [40].
8	Was an implementation strategy reported? [41,42]	Implementation strategies are measures to support interventions' adoption and sustainable implementation. These might include building stakeholder coalitions or auditing and providing feedback for clinicians or study personnel [35]. The application and evaluation of implementation strategies is essential to understand which measures support the adoption of medication adherence interventions and in which contexts. The Expert Recommendations for Implementing Change (ERIC) project provides a taxonomy for the description of implementation strategies in order to support a common language and reproducibility [35].
9	Was a process evaluation conducted parallel to the outcome evaluation?	Process evaluations examine the intervention's execution, as well as identifying its implementation and contextual factors. They promote an understanding of why an intervention fails or works and how it can be optimized [43]. A process evaluation conducted in parallel to (not as a substitute for) the outcome evaluation is essential to create a sustainable intervention which can be reproduced in other settings [33].
10	Were implementation outcomes such as adoption and costs measured? [37]	Implementation outcomes reflect the success of an implementation, its processes and its service system outcomes. An intervention or treatment can only show positive summative outcomes (e.g., medication adherence, graft rejection) following a successful implementation [37]. Implementation outcomes provide valuable insights into why an intervention has worked in a specific setting and how the chosen implementation strategies can be optimized to increase the implementation and effectiveness of a proven intervention in other settings [37,44]. Proctor et al.'s taxonomy of implementation outcomes provides clear definitions and description as well as measurement options for implementation outcomes. Some implementation outcomes are visible immediately after an intervention's implementation, others can only be evaluated after implementation. The following list provides an overview of established implementation outcomes defined in Proctor et al.'s definition, moving from proximal to distal outcomes [37]. Acceptability: Intervention is perceived as agreeable by stakeholders Appropriateness: Intervention is perceived as fitting or relevant in a specific setting. Adoption: Intention to use an intervention. Fidelity: How fully the intervention can be performed as intended. Feasibility: How extensively the intervention can be performed within a specific environment. Cost: Financial expenses related to the implementation effort and intervention. Penetration: Inclusion of an intervention in a specific clinical setting. Sustainability: How extensively the intervention persists or is formalized in a specific setting.

3.2. Study characteristics

3.2.1. Location

All included studies were written in English. Roughly two-thirds of the RCTs were conducted in four countries: the USA (n = 8, 35%) [45–52], Canada (n = 3, 13%) [53–55], South Korea (n = 3, 13%) [56–58] and Brazil (n = 2, 9%) [59,60]. One study each was performed in Australia [61], Belgium [62], Denmark [63], France [64], Germany [65] and Sweden [66]. The twenty-third study was performed in both the USA and Canada [67].

3.2.2. Population and study duration

The included RCTs involved 2′339 patients (n = 19–209 per study). The most frequently examined population was kidney transplant recipients (kidney transplantation alone (n = 16, 70%) [45,46,51,52,54–61,64–67]; kidney transplantation in combination with other organs (n = 2, 9%) [47,50]. Other studies included patients after lung transplantation (n = 2, 9%) [48,63]; heart (n = 1, 4%) [49]; heart, liver, and lung transplantation (n = 1, 4%) [62] or heart, kidney,

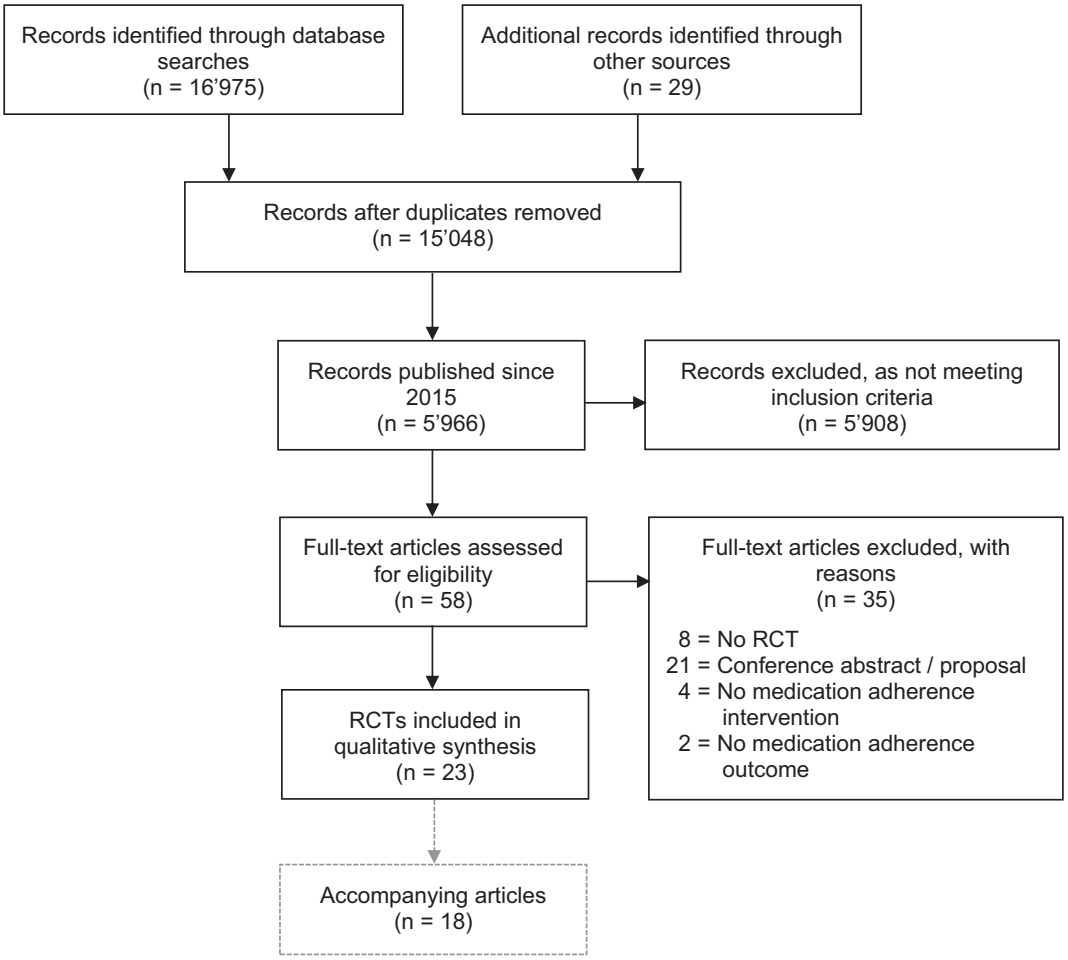


Fig. 1. Study flow diagram.

liver, lung and pancreas transplantation (n = 1, 4%) [53,62]. We did not find any RCTs on alloSCT.

Study duration (active phase including intervention delivery) ranged from two weeks [46] to twelve months [48,65,67]. Fourteen studies (61%) had no follow-up period [47,49,50,52,53,55–58,60,63,65–67]; nine (39%) had a mean follow-up period of two years (range: six weeks [46] to ten years [64]. Median overall study period (RCT and follow-up) was 26 weeks (range four weeks [63] to ten years and eight weeks [64]).

3.2.3. Adherence measurement

Although the majority of reviewed RCTs measured the medication implementation adherence phase, the majority did not operationalize adherence using the ABC taxonomy [1]. Six RCTs (26%) used a single measurement method [45,50–52,56,59], while eight (35%) used two [46,49,54,60,62–64,66], five (22%) used three [47,55,57,58,67] and one (4%) used four [61]. Three RCTs (13%) combined two to three measurement methods to produce composite adherence scores [48,53,65]. The most common measurement methods were self-report questionnaires (n = 20, 87%) [47–49,52–65,67], followed by assay level (n = 11, 48%) [46,47,49,50,53,60,61,64–67] and electronic monitoring (n = 10, 43%) [45,47,51,55,57,58,61,62,66,67]. Less often, studies relied on pharmacy refills (i.e., medication possession ratio) (n = 2, 9%) [55,61], pill counts (n = 2, 9%) [66,68], collateral reports by caregiver and physician/nurse reports (each n = 1, 4%) [48,65].

3.2.4. Intervention components

Only four RCTs (17%) reported on single-component interventions [52,55,56,63]. The rest reported on multi-component interventions. The BCTs most often used as part of the tested adherence interventions involved informing patients about health consequences (i.e., education) (n = 18, 78%) [45,46,48–51,53,54,57,59–65,67,68], feedback on behavior (n = 10, 43%) [45,47,48,51,54,62,65–68], prompts and cues (e.g., reminders, n = 8, 35%) [45,47,50,57,62,66–68], problem solving (n = 8, 34%) [46,48,51,54,61,62,65,67] and action planning (n = 7, 30%) [49,51,59,61,62,64,65].

3.2.5. Outcomes

While all RCTs reported adherence outcomes (inclusion criterion), 18 (78%) also reported clinical or service delivery outcomes [46–49,51,52,55–60,62,64–67,69–71]. Thirteen RCTs (57%) reported significantly improved adherence outcomes [46–49,51,55,59,62–65,67,69]; two of 18 (11%) reported significant improvement in clinical outcomes: A small proof of concept study reported significant group differences in systolic blood pressure at some, but not at all measurement time points [69,70]. However, this was not confirmed in the following efficacy trial [45]. Another RCT reported significant improvement in biopsy-verified rejection which was only observed in the univariate, but not in the multivariate analysis [66]. Furthermore, one open-label RCT (6%) reported a significant improvement in service delivery outcomes such as unplanned hospitalizations, length of unplanned stay and costs [65,71]. On the other hand, one RCT (6%) reported significantly more cytomegalovirus infections in the intervention than the control group which could be pointing to over-immunosuppression in adherent patients [67]. All RCTs that studied clinical or service delivery outcomes also reported no significant effects on abovementioned outcomes [48,49,51,52,55–57,59,60,62,65–67,71]

as well as on other infections [51,52,60,67], several laboratory values (e.g., estimated glomerular filtration rate [55–58,60,65,67], mean creatinine and/or creatinine clearance [51,52,55,59,66], hemoglobin [55]), incidence of development of de novo anti-HLA antibodies [58], bronchiolitis obliterans syndrome [48], clinically significant anxiety or depression symptoms [75], interstitial fibrosis/tubular atrophy [52], median ambulatory care visits [65], graft loss [47,52,56,60,62,64,65,67] and death [47–49,51,52,56,60,64]. Descriptions of all included RCTs can be found in Table S1.

3.2.6. *Risk of bias within studies*

Ten (43%) RCTs had an overall high risk of bias [45,49,50,53,54,56–58,64,66]; ten (43%) RCTs raised "some concerns" [46–48,52,55,59–61,63,65] and the remaining three (13%) had an overall low risk of bias [51,62,67]. The most problematic domain was missing outcome data: several high-risk studies did not have outcome data available for all, or almost all randomized patients and did not provide evidence that the result was not biased by missing outcome data. In addition, several trials made changes to the protocol after the study had already started, inadequately labelled adverse events or were insufficiently monitored by an independent body. A summary plot is presented in Fig. S1. Fig. S2 includes an assessment of each study.

3.3. *Relevant information on the implementation of medication adherence interventions in transplantation*

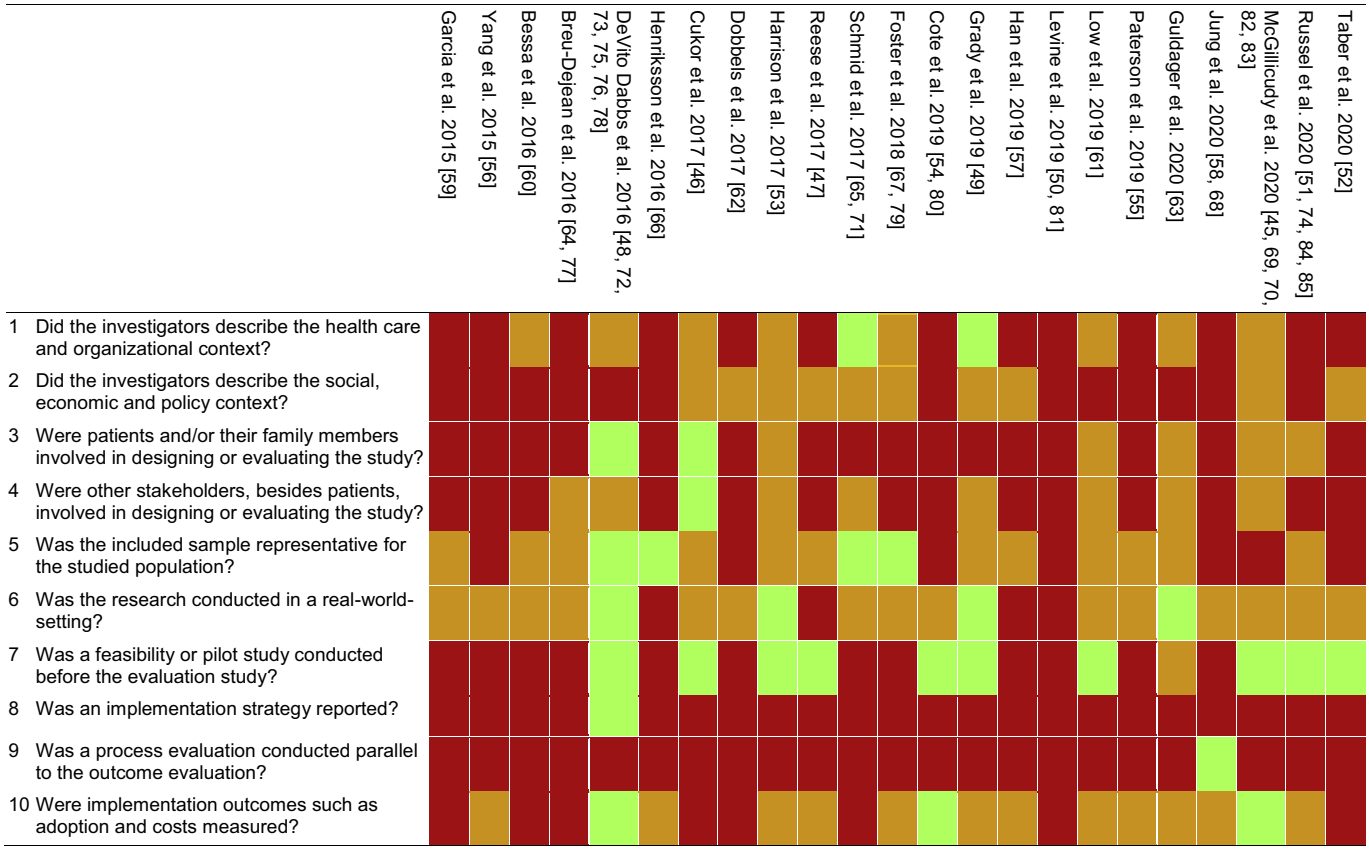
Regarding the ten adapted Peters' criteria, the included RCTs included limited information relevant to real-life implementation of the tested interventions (Table 2). One (4%) study clearly satisfied six criteria [48]; three (13%) satisfied three [46,49,65], three (13%) more fulfilled two [45,53,54] and eight (35%) only one each [47,51,52,58,61,63,66,67]. Of the remaining eight studies, four (17%) partly covered three criteria [55,57,60,64], and three (13%) partly addressed two [56,59,62]. One (4%) study fulfilled no implementation-relevant criteria [50]. The most reported criterion was the running of a feasibility study ($n = 10$, 43%) [45–47,49,52–54,61,74,76], while none clearly described a social, economic and policy context.

The following paragraphs summarize how fully the selected studies fulfilled Peters' modified criteria.

1) Only two studies (9%) clearly described their *healthcare and organizational contexts* [49,65]. For instance, the multicentric TRANSIT study described the current transition programs in its participating centers as well as the rate of patients who received necessary services to transition from pediatric to adult care [49]. 2) While all studies reported some socio-demographic characteristics, none gave full information on *social/economic/policy context.*

3) Two RCTs (9%) fully reported *involving patient/family* [46,76] in designing and evaluating the overall trial procedures, five others reported this criterion partially [45,51,53,61,63]. 4) While one RCT (4%) fully reported *involving other stakeholders* [46], eight reported it partially [45,49,53,61,63–65,76]. For example, Cukor et al. [46] developed an adherence promotion program based on patients' and healthcare providers' feedback during surveys ($n = 50$) and focus groups ($n = 15$). In that case, the authors also modified their study procedures according to the patients' input, e.g., they did not offer a placebo treatment [46]. In nine RCTs (39%), stakeholders participated in the intervention's content development but not in the development of the trial methodology [45,49,51,53,61,63–65,76].

Table 2
Implementation research components reported in medication adherence intervention studies in transplantation published 2015–2020 [73,77,79–85].



Green* = fully reported, orange* = partially reported, red* = not reported.
*The colors have been chosen to have enough contrast even for readers with color deficiency or color blindness, as well as in black and white mode.

5) Four studies (17%) included clear statements on the *representativeness of the included sample* [48,65–67]. 6) Four (17%) also reported being *conducted in a real-world-setting* [48,49,53,63]. E.g., the Pocket PATH study team [48] approached all adult patients who had received lung transplants during their predetermined periods. They were able to recruit and keep a sample similar to the lung transplant population as a whole regarding age, gender, health conditions and education [48].

7) Ten RCTs (43%) conducted *feasibility studies* [45–47,49,52–54,61,74,76]; however, most of these focused on the feasibility of study procedures and less on the study's implementation aspects.

8) *Implementation strategies* were clearly reported in one study (4%) [78]. To do so, the authors of the Pocket PATH study used audit and feedback (e.g., routine verification with feedback that all critical values were identified and appropriately addressed according to protocol) [78].

9) Similarly, only one study (4%) clearly described a *process evaluation* in parallel to the outcome evaluation [68]. Jung et al. evaluated the translatability and feasibility of an information and communication technology (ICT)-based centralized monitoring system to support medication adherence in kidney transplant recipients. To do so, they used the RE-AIM framework, which is often used to evaluate how well interventions are implemented [86]. RE-AIM stands for Reach (participation rate of eligible kidney transplant recipients), Effectiveness (improvement in medication adherence), Adoption (hospitals' willingness to participate in the RCT), Implementation (percentage of participants who follow the intervention as intended) and Maintenance (extent to which the ICT-based monitoring system became part of standard medication adherence monitoring) [68].

10) Three RCTs (13%) reported established (mainly proximal) *implementation outcomes* — acceptability, feasibility, satisfaction [45,54,72,78], while twelve addressed them partially [47,49,53,55–58,61,63,66,67,74]. For example, Jung et al. [58] assessed satisfaction with the ICT-based monitoring system including its convenience, safety, and accuracy. To test this, they used the ICT-based clinical trial system satisfaction questionnaire. The intervention achieved overall high satisfaction scores which increased during the study period. Although Jung et al. [58] clearly described the process evaluation, to date they have reported only satisfaction with the system.

4. Discussion

Non-adherence to immunosuppressants is a well-known risk-factor for poor outcomes in transplantation [11]. However, it is generally not well managed. And even with strong evidence bases supporting their adoption, few medication adherence interventions are translated into daily clinical practice. As our BRIGHT study has showed, medication adherence practice patterns vary worldwide at the transplant center level [87]. Various other surveys in SOT [88,89] and alloSCT [90] confirm this observation. Transplant centers are increasingly finding behavioral interventions more effective for behavioral change than education alone.

Although the impact on other outcomes remains unclear, recent RCTs recommend a combination of adherence interventions to improve medication adherence [19,21,91]. Our findings confirm these results as more than half of the included studies reported significantly improved adherence outcomes, but the majority showed no effect on any clinical outcomes. The most likely interpretation is that such interventions did not actually improve clinical outcomes. The reason for this is probably that included RCTs did not correspond to the real-world, which was also reflected in our evaluation of Peter's criteria. Despite many efforts, it seems that trials failed to recruit seriously non-adherent patients. The interventions worked in a sense of improving medication adherence measured in the trial-world. This might be inadequate in clinical practice as the interventions might be inappropriate for truly non-adherent patients. Another explanation for the lack of improvement in clinical outcomes could be due, on the one hand, to the fact that most RCTs were not powered for clinical outcomes and, on the other hand, the relatively short overall median study period, as intervention effects on medication adherence are typically observed after a short period of time, whereas clinical outcomes such as graft loss or death may occur later. Considering the negative consequences of medication non-adherence [2–10], routine adherence support in clinical practice is essential.

Medication adherence intervention studies should follow the same rigor as any RCT. For example, the serious adverse events should be closely monitored and reasons why they appeared should be addressed in future studies. Several studies were of low quality and/or inadequately labelled adverse events. Failure to ensure fidelity to basic study designs due to lack of regulatory oversight reduces the generalizability of results and thus compromises relevance in the real-world. This relevance begins with strict compliance to a study design that leads to generalizable results. This includes pre-defining a robust, important, and clinically relevant primary outcome and pre-defining a statistical analysis plan, not changing study designs or outcome measures midstream, and consistent monitoring, reporting, and investigation of adverse events. Nevertheless, real-world translation of the insights generated by even high-quality RCTs is hindered by a lack of focus on *how to translate this evidence into real-world-settings* [11,24,26,92], which are typically less resource-rich and more chaotic than trial-world settings.

Any delay in real-world translation is a major source of research waste. Indeed, many effective interventions are only implemented into daily (transplant) care years or even decades after RCTs have confirmed their value [93]. More importantly, for transplant patients, whose medications tend to have very low tolerances for non-adherence, this lag could carry a high cost in terms of health outcomes [24].

Shining a light on elements that can speed the implementation of (future) effective medication adherence interventions into clinical practice is a crucial step to support translational efforts. For this systematic review, we applied Zullig et al.'s adapted version of Peters et al.'s translatability criteria [25,26] to our sample of 23 RCTs on medication adherence interventions. Not one of the selected studies fulfilled all ten criteria for targeted implementation into real-world-settings [25,26]: the maximum was six, the minimum zero.

While information on *a feasibility study* was common, very little was written about *other stakeholder involvement*, *implementation strategies* or *process evaluation;* and nothing was available on *social/economic/policy context*. This suggests that studies on transplant adherence typically lack information vital to real-world translation of medication adherence interventions. As a finding, it is congruent with those of Zullig et al. in their 2019 review of high-quality non-transplant RCTs of medication adherence interventions [26].

Preventing such information gaps will require a research paradigm built on the principles of implementation science [24]. With an eye constantly on the clinical outcomes, these principles are best applied when planning a new study. For example, even while laying the groundwork to develop and test a medication adherence intervention, implementation science methodology would be guiding researchers to identify and prepare for possible barriers to real-world translation [72]. Implementation science implies a whole range of methodological considerations that reach beyond the standard clinical research methods. This includes a dual focus on effectiveness and implementation outcomes.

More specifically, because medication adherence interventions need to be integrated with related care processes within a specific clinical practice setting, an implementation science study would begin with a *contextual analysis* guided by theory. A full contextual analysis involves a preliminary mixed methods study that maps relevant context characteristics (e.g., geographical, epidemiological, legal) at the micro, meso and macro levels [37] as well as practice patterns and other relevant factors (e.g., barriers/facilitators for implementation) [24,33,94].

In addition to the scientific evidence and theoretical base (available via a literature search), an implementation science approach demands

stakeholder involvement throughout the research cycle. For example, end users such as target clinicians and patients, who will eventually receive or roll out the intervention, are included wherever possible in the intervention planning and creation processes. Only two studies in our review reported stakeholder involvement.

Rather than controlling or eliminating real-world conditions, an implementation science approach involves attempting to understand and work under them [25]. In our review, few RCTs involved *representative samples* and/or were conducted *in a real-world-setting*. Furthermore, few measures were reported to target and recruit seriously non-adherent patients. Thus, there is no certainty that such patients were not inadvertently excluded. This limits their results' generalizability and relevance to the clinical practice. For RCTs, recruiting a representative sample — regarding patient (e.g., age, gender, education) and clinical setting characteristics — allows the research team to conduct the project in real-world settings. By improving both the representativeness and external validity [24,26], this makes the results much easier to adapt and apply to clinical practice settings.

Implementation science projects usually also include *feasibility/pilot studies*. These are designed to allow researchers to save time, effort and costs by identifying and addressing potential barriers before they arise [38,39]. However, simply conducting such a study does not imply the use of implementation science methodology. Several of the studies we reviewed reported using feasibility/pilot studies without including any aspects of implementation science.

Transplant-related clinical settings are often quite chaotic and suffer from resource shortages. Therefore, to minimize waste, it is recommended to employ contextually adapted *implementation strategies*. These are intervention components that specifically support the chosen intervention's implementation [35]. Examples include providing local technical assistance or interprofessional education, changing the record system, setting up contracts with transplant centers, or organizing clinician meetings to manage implementation processes [35,95,96]. So far, we have found only one RCT in transplantation that reported clear information on implementation strategies [78].

Implementation science studies are guided by theoretical frameworks. In addition to supporting overall study design, these increase the efficiency of contextual analyses and intervention development. They also focus on ongoing evaluation of outcomes related not only to effectiveness (e.g., medication adherence, acute rejections) but also to implementation (e.g., acceptability, feasibility). Even after the study period has ended, they are useful to evaluate the *implementation pathway,* clarifying how and why the implementation or its components worked or failed. Hybrid designs with dual focus — one on effectiveness outcomes, the other on *implementation outcomes* — are common in implementation science [97,98]. Omitting these aspects means that if the intervention does not show effectiveness, we do not know if the intervention is not working or if it was simply not implemented.

Within transplantation medication adherence RCTs, integrating implementation principles right from the start of the study design and intervention development processes can be a game changer in at least two major ways. First, it increases the pace at which new evidence is implemented in daily clinical practice and optimizes daily management of medication adherence interventions [11,24,37,44]. Second, by shortening the transplant research pipeline from intervention development to sustainable implementation, it greatly increases both financial and societal returns on research investments.

As an example of a research project focusing on implementation from the beginning, we are using the ongoing SMILe study to develop, implement and test an eHealth-facilitated integrated care model for long-term follow-up of allogeneic stem cell transplant patients. This study will use a dual-focus effectiveness-implementation hybrid design. That is, its target outcomes include increased medication adherence (https://smile.nursing.unibas.ch/, https://vimeo.com/259739507 [94,99,100]) and smooth, sustainable implementation. From the earliest stages, the study team have been applying all principles of implementation science. This study is an example of how the new research paradigm of implementation science can be embraced in adherence research in transplantation.

5. Limitations

This review has several notable limitations. For example, we only included RCTs, although other designs such as quasi-experimental studies are common in medication adherence research. We chose RCTs because we aimed to focus on the studies that offered the strongest evidence base, but that limited the biases that reduce other study designs' reliability. We focused on adult or mixed population only, even that real-world translation of research findings is also important in pediatrics. The decision was based on the assumption that pediatric setting is very specific and needs to consider different aspects than the adult setting (e.g., parental involvement).

Also, we only included studies published since 2015. As noted above, we focused on this recent time period because implementation science, while not a new field, has gained momentum in recent years with an exponential growth in study and protocol publications [24]. Our results would likely show the same or even show worse reporting in the literature if we had included a longer time period.

As the focus of this paper was on implementation relevant information in medication adherence RCTs in transplantation, effectiveness outcomes were only limitedly reported to provide a basic description of the included studies. Effectiveness outcomes have been the focus of systematic reviews and meta-analyses [17–21,101,102]. The focus on implementation is novel and a missing link in the clinical application of lessons learned of medication adherence management so far. Despite current limited evidence on effectiveness of medication adherence interventions on clinical outcomes, evidence shows the relation of medication non-adherence and poor clinical outcome in longitudinal studies. International guidelines call for investment in support for medication adherence. The found higher infection rates in the intervention arms of clinical trials might be the expression of overimmunosuppression in adherent patients, a hypothesis to be further explored [67]. Finally, as we relied entirely on published information, we cannot exclude the possibility that some studies used implementation science methods without reporting them due to word count limits. We did not contact the authors of the included studies to check this possibility, but searched for accompanying papers that might point towards implementation science. We included all available information in our analysis but cannot rule out the possibility that relevant implementation information may have been considered and just not reported. Our review may serve as a basis for further research, where information from authors of included RCTs may clarify the real adoption of tested interventions and their sustainability in daily clinical practice in more detail.

6. Conclusions

This systematic review highlights the lack of both, high-quality RCTs showing an effect on clinical outcomes, a prerequisite before implementation, as well as implementation-relevant information in RCTs that tested medication adherence interventions in transplantation. With no specific focus on clinical implementation, even promising findings are commonly shelved for years or decades before translation into clinical practice. In addition to creating research waste, this deprives transplant patients of effective interventions.

Zullig's adapted version of Peters' ten implementation science criteria [25,26] offers a useful systematic approach to assess implementation-relevant information reported in studies.

To overcome current barriers to clinical adoption, we recommend strict compliance to a study design that leads to generalizable results. In addition, implementation science principles such as contextual information, stakeholder involvement, representativeness of samples and settings, feasibility studies, implementation strategies, and evaluations

of implementation-specific pathways and outcomes should be integrated early in the conceptualization of RCTs. Additionally, they should be reported in publications. We fully expect that implementation science methodology will both accelerate and increase the sustainability of medication adherence interventions' translation into real-world transplantation settings, thereby reducing research waste and helping patients.

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Authorship

The study was conceptualized by SDG (corresponding author: sabina.degeest@unibas.ch), BK and JR. Articles were located, identified and evaluated by BK, JR and SDG. Data were extracted and checked by BK, JR, KML, FD, SG and LZ. The manuscript was drafted and edited by JR with close revision and feedback from BK, SDG and SG as well as regular review and feedback from all other co-authors. Before publication, the final revision was reviewed and approved by all co-authors.

Declaration of Competing Interest

FD was the principal investigator and SDG a co-author of the included MAESTRO-Tx study. LZ has received research funding awarded to Duke University from the PhRMA Foundation and Proteus Digital Health, as well as consulting for Novartis and Pfizer. The authors are not aware of any further affiliations, memberships or funding that might affect the objectivity of this review.

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Appendix A. Supplementary data

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