


The detection and prevention of adverse drug events in nursing home and home care patients: Study protocol of a quasi-experimental study

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Abstract

Aim: To estimate the cost-effectiveness of an intervention facilitating the early detection of adverse drug events through the means of health professional training and the application of a digital screening tool.

Design: Multi-centred non-randomized controlled trial from August 2018 to March 2020 including 65 nursing homes or home care providers.

Methods: We aim to estimate the effect of the intervention on the rate of adverse drug events as primary outcome through a quasi-experimental empirical study design. As secondary outcomes, we use hospital admissions and falls. All outcomes will be measured on patient-month level. Once the causal effect of the intervention is estimated, cost-effectiveness will be calculated. For cost-effectiveness, we include all patient costs observed by the German statutory health insurance.

Results: The results of this study will inform about the cost-effectiveness of the optimized drug supply intervention and provide evidence for potential reimbursement within the German statutory health insurance system.

KEYWORDS

adverse drug events, home care intervention, hospital admissions, nursing home intervention, quasi-experimental study design

1 | BACKGROUND

Polypharmacy, most commonly defined as the concurrent intake of more than five drugs regularly (Bushardt et al., 2008; Hilmer & Gnjidic, 2009), is disproportionately prevalent in the elderly (Kantor et al., 2015). When prescribed reasonably, polypharmacy can yield clinical benefits (Wise, 2013). However, many elderly are exposed to an extend of polypharmacy where health-related utility is no longer given, for example due to adverse drug events (ADEs) (Calderón-Larrañaga et al., 2012; Shah & Hajjar, 2012), cognitive and/or physical decline or increased hospital admissions (Fried et al., 2014). Evidence suggests that patients taking more than eight drugs regularly have an increased ADE risk by a factor of 2.3, respectively (Nguyen et al., 2006).

Recent evidence from Sweden suggests that almost half of the elderly, aged 65 and older, is subject to polypharmacy, while almost 12 percent took more than ten drugs regularly (excessive polypharmacy) (Morin et al., 2018). Even higher rates were found for elderly living in German nursing homes, with 53 percent of residents subject to polypharmacy and 16 percent subject to excessive polypharmacy (Dörks et al., 2016). The general elder population in Germany has lower rates of polypharmacy of about 42 percent. Those living in nursing homes have substantially higher average levels of regularly consumed medications, compared to elderly not living in nursing homes. Further, the risk of being exposed to excessive polypharmacy

is increased modestly in nursing home residents (Morin et al., 2018). In France, the average medications intake is 6.9 medications per nursing home resident, and the prevalence of excessive polypharmacy is 21.1 percent. Almost half of French nursing homes residents take potentially inappropriate medications, with benzodiazepines and anticholinergics having the highest prevalence (Herr et al., 2017). Potentially inappropriate medications were also highly prevalent in the German elder population (Schubert et al., 2013). Unfortunately, there is no evidence available about the prevalence of polypharmacy in German home care patients. In a study based on a sample of home care patients in six European countries including Germany, the authors conclude that 39 percent of patients in home care settings were subject to polypharmacy and 23 percent to excessive polypharmacy (Giovannini et al., 2018).

Given the above summarized studies, there is strong evidence of high prevalence of polypharmacy in elderly from several nations. Further, polypharmacy is especially prevalent in nursing home residents. The following intervention aims to reduce ADEs in a sample of more than 1,500 patients in 65 nursing facilities in Germany (see Figure 1). Of the 65 nursing facilities, 58 were nursing homes and seven home care providers, respectively. Training nurses and utilizing a software tool to detect ADEs, we aim to reduce ADEs in the first place and further hospital admissions and falls in nursing facility patients in the second place. ADEs, hospital admissions and falls will be measured monthly per patient.

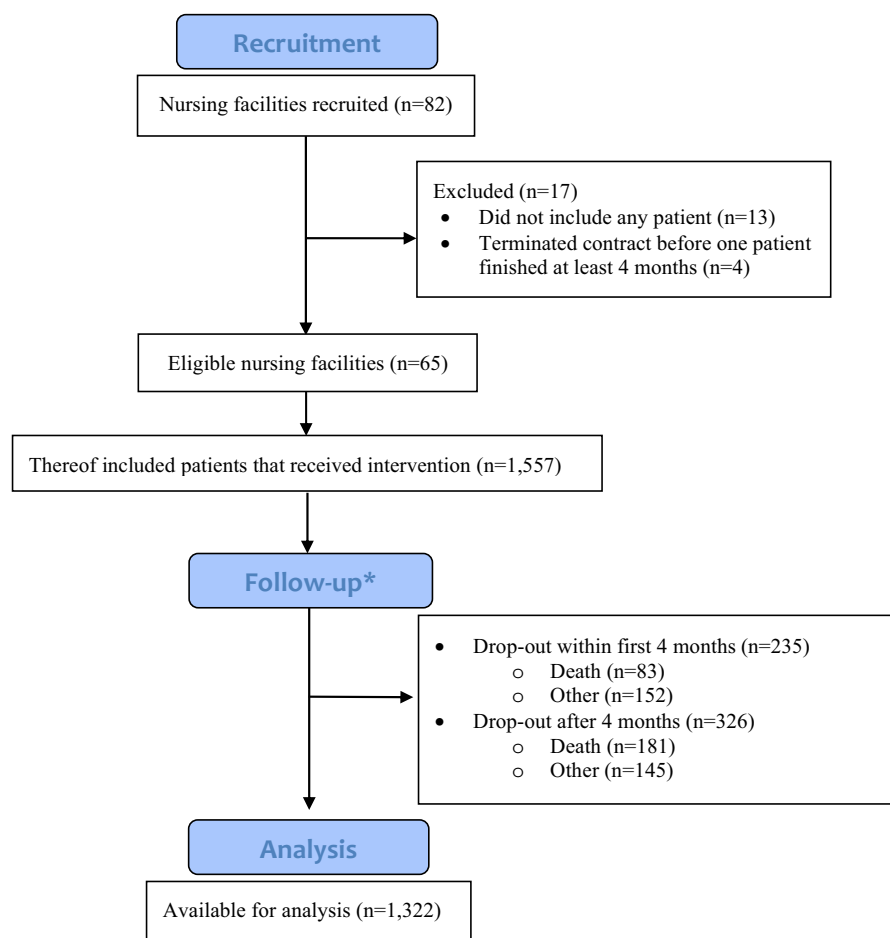


FIGURE 1 Flow chart of nursing facility and patient recruitment based on the CONSORT Statement, 2010 (Moher et al., 2010)

Further, we calculate the cost-effectiveness of our intervention, utilizing sickness fund cost and claims data for all relevant health services to derive the incremental cost-effectiveness ratio (ICER). The study is conducted from the social insurance perspective. Specifically, this includes sickness funds, care insurance and rehabilitation.

2 | METHODS/DESIGN

2.1 | Overall study design

The study is conducted as a multicentre, non-randomized intervention study with two study arms. To derive causal estimates, we aim to implement a quasi-experimental evaluation exploiting difference-in-difference design, and additionally propensity score matching. The intervention group consists of nursing facility patients, namely nursing home residents and patients cared by home care providers. Nurses in the intervention nursing facilities were trained by experts (geriatric pharmacists) to increase their sensibility to detect ADEs. Besides that, patient medications were continually screened by a digital tool called VERIKO PT (pharmacotherapy)[®]. The tool is developed by Gero PharmCare GmbH, Cologne and screens patient's medications with respect to potential drugs yielding adverse effects in geriatric patients. Following ADE identification, risk and medication analysis will be performed. Finally, risk coping strategies will be implemented, with the aim to reduce adverse drug events in geriatric patients. For individuals in the control group, regular nursing care will be provided. Thus, control individuals will be selected randomly out of a set of non-participating nursing facilities.

2.2 | Ethics, consent, permissions and funding

The study is funded by the Innovation Fund of the German Federal Joint Committee (G-BA) from 1st of October 2017 until 30th of September 2021. The study is conducted in line with the Declaration of Helsinki and listed in the German Joint Federal Committees ("Gemeinsamer Bundesausschuss") public accessible project list¹ and has been registered in the German register of clinical trials on 23rd of December 2020 (ID: DRKS00023757). The study has been ethically confirmed by the Ethics Committee of the University Witten/Herdecke on 29th of June 2018 with a positive votum (application number: 76/2018). Nursing facilities were recruited in the German federal states Berlin, Brandenburg, Mecklenburg-Vorpommern and North Rhine-Westphalia. Only patients insured by AOK Nordost, Innungskrankenkasse Brandenburg und Berlin and VIACTIV were eligible to be included in the intervention group. Nursing facilities were recruited by contacting relevant associations, presentations of the project on relevant symposia or on congresses, or direct acquisition. Overall,

more than 545 nursing facilities were contacted through one of the stated ways. Nurses, physicians and pharmacies were recruited using Open-House tendering processes.

Informed consent must have been provided from nursing facilities to participate in the study. Once the respective nursing facilities provided informed consent, additional informed consent must have been provided from patients living in a participating nursing facility in order to take part. All patients fitting the eligibility criteria in included nursing facilities have been informed by trained nurses working in the participating nursing facilities both verbally and by text about the intervention and their possibility to take part in the study. Informed consent was collected by nursing facilities and forwarded to the project leading institution.

Participants could take part in other studies except those that address or affect drug safety issues. Within nursing facilities, there was no group of patients defined to be ineligible for participation in the study.

In accordance with the data protection guidelines (declaration of unreasonableness), obtaining informed consent from control group individuals was unreasonable. Therefore, it was not necessary to obtain informed consent from control individuals. As with nursing facility residents of the intervention group, data from control group individuals have been pseudonymized at sickness fund level, upfront data transfer to the evaluator.

2.3 | Study setting

The study started on 1st of August 2018 with the recruitment of the first patient. The last patient in the intervention arm was included on 31st of March 2020. The intervention is implemented at least for 12 months for included patients. Analysing the results of the study, we aim to distinguish between a per-protocol analysis (PPA) and an intention-to-treat analysis (ITT). In the former, we include only patients that participated at least 12 months in the study. In the latter, we include all individuals that participated at least 4 months in the study, even if they dropped out before the a priori minimum required per protocol study period of 12 months. Thus, individuals considered as drop-out vary with the analytical framework we apply. For the ITT analysis, the drop-out rate on the 12th of July 2021 was 3.7 percent, while for the PPA, it was 31.2 percent, respectively. In general, reasons for drop-out may be demotivation, change of sickness fund, death, or others.

To detect potential ADEs in geriatric patients appropriately, nurses and physicians in the participating care entities are trained to detect ADEs. Trainings are held by specialized geriatric pharmacists. Further, a digital tool called VERIKO PT[®] is used for patients participating in the intervention group. This digital tool can detect risks associated with active ingredients in drugs. Both the digital VERIKO PT[®] and detection by medical staff are together referred to as VERIKO[®]. Within VERIKO[®], 70–80 percent of ADEs are detected by medical staff, while 20–30 percent are detected by VERIKO PT[®].

Data will be provided up to 18 months pre-intervention as well as at least for 12 months since intervention start for individuals of both the intervention and control group.

2.4 | Sample size

Based on previous research, we expect the effect of the intervention to be as large as a 30 percent reduction in ADE probability (Henschel et al., 2015). In order to yield proper estimates and provide reasonable pre-intervention time trends, it is required to have at least four pre-intervention time points of outcome measurements (Somers et al., 2013). With 18 pre-intervention observations per individual (18 months), we satisfy this condition.

To date, 24th of February 2021, 1,557 individuals participated in the intervention arm, residing in 65 nursing facilities (clusters), with an average of 24.4 individuals per cluster. As the intervention to control group ratio will be 1:2, we will include 3,114 individuals from 130 nursing facilities in the control group, coming up with 4,671 individuals in total.

2.5 | Eligibility criteria

Eligible were all patients insured at either AOK Nordost, Innungskrankenkasse Brandenburg und Berlin or VIACTIV living in a participating nursing facility during the intervention time, that is, between 1st of August 2018 and 31st of March 2020. To participate in the intervention, the nursing facility which takes care of the patient must have provided informed consent. Besides that, patients needed to provide informed consent additionally. Patients for which no data are available for the period 18 months prior to intervention will be excluded from the analysis. In the per-protocol analysis, patients not providing data for at least 12 months after the intervention started will be excluded. For the intention-to-treat analysis, the participation time must be at least 4 months.

2.6 | Participant timeline

Participants were able to participate in the study from 1st of August 2018 until 31st of March 2020. Once included, patients were told to participate at least for 12 months in the study. However, study participants could withdraw from the study any time. If patients did not complete the 12 months participation time, they are considered dropouts in the per-protocol analysis. In the intention-to-treat analysis, patients are considered dropouts if they participated <4 months in the intervention. There was no maximum time set for patients after which they needed to automatically end the intervention. Instead, they are potentially able to participate for as long as from 1st of August 2018 until 31st of March 2021 in the intervention.

2.7 | Intervention

The OAV ("Optimierte Arzneimittelversorgung für pflegebedürftige geriatrische Patienten") intervention aims to reduce ADEs in geriatric patients that receive care either in a home care or nursing home setting. The set of nurses, physicians and pharmacists working in, or in cooperation with the respective nursing facility, are together referred to as geriatric care teams. The intervention facilitates the reduction in iatrogenesis. Iatrogenesis is the process that leads to an adverse effect from medical treatment to the patient, mostly due to drugs (Mitty, 2010).

To reduce ADEs, the intervention provides training for nurses and physicians to detect potential ADEs as well as inappropriate medications. Five experienced medication- and risk managers (geriatric pharmacists) as well as one operative project coordinator guiding and training the decentralized geriatric care teams make up the training team. Geriatric care teams consist of physicians, nurses and pharmacists. The trainings were held 2 days before the beginning of the intervention as a theory class. During theory class, the participating geriatric care teams receive education about ADE detection in nursing facility patients from the expert-level geriatric pharmacists. This educational concept is the base for geriatric teams to detect ADEs in practice. After theory classes, ADE detection started in the respective nursing homes. To support geriatric teams during the first 3 days of the intervention, nurses will be practically testing their skills by applying what they learned in the theory classes as a process of "learning by doing," while being observed by the experts.

Afterwards, regular risk screening is starting. Apart from emergency ADE detection and intervention, potential ADEs detected both by geriatric care teams and VERIKO PT[®] (see section below) during risk screening are discussed in monthly ADE boards. ADE boards are held with all relevant members of the geriatric care teams and aim to establish geriatric-pharmaceutical risk profiles of the positively screened patients. With the help of both risk-screening approaches (medical staff and VERIKO PT[®], together referred to as VERIKO[®]), the aim of the intervention is to detect potential risks of ADEs due to polypharmacy in nursing facility patients. This part of the intervention is referred to as *risk identification*. Both patients detected by geriatric care teams and by VERIKO PT[®] will be identified to be at risk, also when only one of either the geriatric care teams or VERIKO PT[®] identified the risk. If identified as at risk of ADEs, the risk is analysed in the *risk analysis*. The risk analysis is discussed in the monthly ADE boards. In this step, both a trained pharmacist, at least one trained nurse and a physician analyse the patient's medical documentation, vital parameters and drug documentation. Once done, the patient is categorized as either in need of a targeted medication analysis, or not. If a *medication analysis* appears necessary, the patient's physician (GP or medical specialist) checks the documentation provided by the former *risk analysis* including the result of a *risk evaluation* from the respective physician. After evaluation, the risks will be coped by optimizing patients drug supply during *risk coping*. Finally, success (or non-success) of the intervention will be evaluated in the *risk evaluation*.

Quarterly and additionally to that standardized, operative process, interdisciplinary case conferences discussing risk-benefit

evaluations of individual high-risk patients are conducted to strengthen the expertise of the geriatric care teams. Twice a year, meetings with associations of the included occupational groups in the geriatric care teams were held, following regular audits. Based on the audit results regarding high-risk processes, organizational design and structures were improved. On a regular basis, continuously measured successes and failures will be reflected in PDCA (Plan-Do-Check-Act) cycles (also referred to as optimization cycles in this project) (see Figure 2).

2.8 | Software-based ADE risk screening

The software tool VERIKO PT[®] from Gero PharmCare GmbH includes a database of more than 2,400 active ingredients typically prescribed to geriatric patients. After entering a patient's medications into the system, it detects active ingredients that are potentially harmful for geriatric patients. Organ system or functional impairments associated with the respective active ingredient, such as gait, cognitive, kidney or gastrointestinal as well as other impairments, are shown in VERIKO PT[®] and categorized into risk groups. For each risk group, each active ingredient can potentially increase the risk of suffering from a respective impairment. If the active ingredient is known to yield such effects, the risk group affected by the active ingredient receives a label of either low, medium or high risk. This is called the risk class and is calculated for each risk group and individual (Gero PharmCare GmbH, 2021).

3 | DATA

3.1 | Nursing home, Gero PharmCare GmbH and insurance claims data

During the intervention period, nursing homes gather data about patients for whom potential ADEs are detected and thus for whom

medication analysis are requested. Gero PharmCare GmbH stores data about the date of medication analysis request, birthdate, name and sickness fund of the patient.

Health insurance claims data are obtained for all participating patients in the intervention group and the control group. Participating sickness funds provide cost and claims data of the following health services: Hospital care, outpatient care, pharmaceuticals, remedies and aids, transportation costs, nursing care, outpatient nursing care, participation in a disease management programme, specialist outpatient palliative care services, palliative care services and general practitioner centred care ("hausarztzentrierte Versorgung" in German).

3.2 | Control group

Considering that we aim to apply a difference-in-difference design mixed with propensity score matching (see Section 3.5), we implement a four-stage approach to select a reasonable control group that is expected to be subject to comparable unobservable factors as the intervention group.

The four stages are the following:

1. We only select potential control nursing facilities from the same federal state as the intervention NE to control for unobservable time-varying state effects.
2. We categorize both nursing homes and home care providers regarding their structural factors. For nursing homes, we stratify both intervention and control nursing homes into categories of 20 beds with respect to their maximal capacity. For home care providers, we stratify in categories of insured individuals, with steps of 20 individuals per category. We only select control nursing facilities within the same structural category as the intervention category randomly, with a proportion of intervention to control nursing facilities of 1:6 respectively.

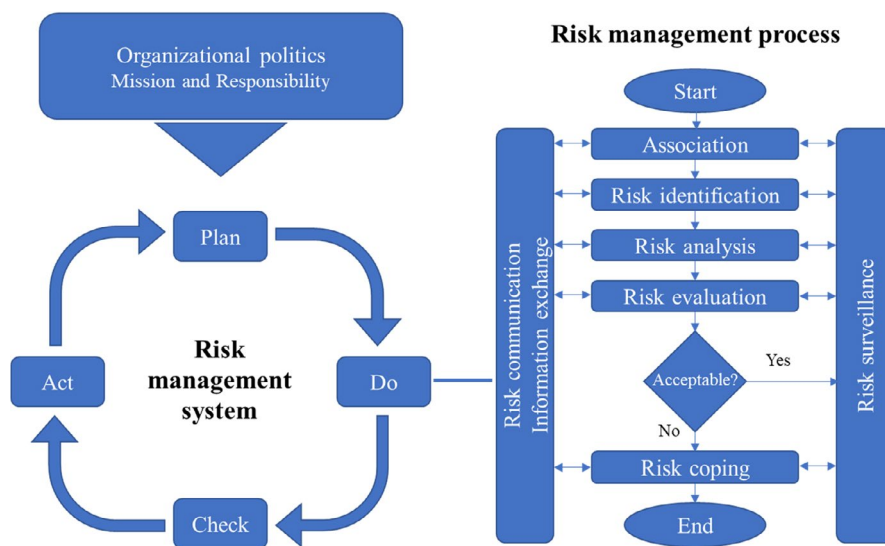


FIGURE 2 Optimization cycles applied in the OAV project

3. We only select individuals as potential controls observed during the same period of time as the intervention individuals were observed.
4. Out of the remaining potential control individuals, we select the ones as controls with a ratio of twice the amount as intervention individuals with propensity score matching, based on the variables we observe commonly for both control and intervention individuals.

3.3 | Data storage, transfer and safety

When nurses in nursing facilities detect a potential ADE, they forward a request of medication and risk analysis to Gero PharmCare GmbH. The request is not pseudonymized and includes patient name, birth date, sickness fund number, and day of request of medication and risk analysis. All requests for all patients that needed a medication- and risk analysis are forwarded by Gero PharmCare GmbH to the participating sickness funds, including the date of the medication and risk analysis. For each sickness fund, the process will be conducted using software tools that satisfy the high standards of data security, encryption and protection for patient data transfer. Note that data transferred from Gero PharmCare GmbH to sickness funds are not pseudonymized since data of Gero PharmCare GmbH will be merged with sickness fund data at the sickness funds.

As a next step, healthcare cost and claims data from sickness funds combined with data received from Gero PharmCare GmbH are pseudonymized at the level of sickness fund before transferred to an aggregated database where all sickness fund data merged will be stored. The platform at which the aggregated sickness fund data are stored is the SAHRA platform, in the following SAHRA, from the company data experts GmbH, Neubrandenburg, Germany.

All sickness funds transfer the merged and pseudonymized Gero PharmCare GmbH and sickness fund data cost and claims data via a secure data transfer mechanism to the SAHRA platform, ensuring that data protection, encryption and safety are guaranteed.

Finally, data are provided to export for the evaluator (TU Berlin) using a SAHRA-SFTP-Server. TU Berlin can download the data from the SAHRA-SFTP-Server via VPN. Finally, data will be analysed by the evaluator.

3.4 | Outcomes

As main outcome, we define a binary variable indicating whether an individual received an ADE during the period of observation (see Table 1). ADEs are defined as unintended events that occur during treatment of a patient with a drug, but where the causality of the drug leading to the adverse event is not necessarily given. As a subset of ADEs, adverse drug reactions have been defined as those ADEs where causality of the unintended events comes from the respective drug, taken at normal doses (World Health Organisation

[WHO], 1972). As we operationalize ADEs exploiting ICD-10-GM codes, we need to carefully select ICD-10-GM codes indicating ADEs. Thus, we define ADEs as the most prevalent and most likely causally related ICD-10-GM codes with respect to ADEs derived by Stausberg & Hasford, 2011 and Hohl et al., 2014. With respect to estimated effect size, previous research gives us reason to expect an effect of about 30 per cent reduction in ADEs due to the intervention (Henschel et al., 2015).

As secondary health-related outcome (see Table 1), we take whether a patient was subject to any hospital admission within a given study period (ITT or PPA). This outcome is likely to be associated with ADEs, since ADEs can lead to hospital admissions. Also related to ADEs, our second secondary outcome is defined as the number of falls per patient per intervention period. Falls are operationalized utilizing the ICD-10-GM codes S72.0x and S72.1x, since both diagnoses have shown to be caused primarily by falls (Cumming & Klineberg, 1994; Taeger et al., 2000).

Further, we aim to estimate to which extend the intervention reduces the intake of potentially harmful drugs. Thus, we measure the delta in frequency and combinations of certain ATC codes given to patients. Our criteria for detecting potentially harmful ATC are Beers criteria from the American Geriatrics Society ("American Geriatrics Society, 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults," 2015).

Finally, to conduct cost-effectiveness analysis, we aim to measure all costs of patients available to the participating sickness funds (see Table 1), namely the costs summarized in section "Nursing home, Gero PharmCare GmbH and insurance claims data."

3.5 | Statistical analysis

We exploit a quasi-experimental approach in order to estimate the causal impact of our intervention on primary and secondary outcomes, that is, a difference-in-difference design (Angrist & Pischke, 2009). In addition to the classical difference-in-difference design, only two observation periods (one pre- and one post-treatment) are present, and we add several pre- and post-treatment observation periods. To account for this special data structure in our difference-in-difference specification, we will implement period fixed effects (Angrist & Pischke, 2009). In case of necessity, we can also add group or nursing facility specific time trends to account for varying trends in the outcome variable on group nursing facility level. If we implement group or nursing facility specific time trends, our design can also be referred to as controlled interrupted time series, as described by Somers et al. (2013). This case will be of special relevance in case the common trends assumption for difference-in-differences does not hold for our data (Somers et al., 2013). In a controlled interrupted time series, time trends of both the intervention and control groups on the outcome variable need to be modelled correctly or to the same extend incorrectly for both control and the intervention group, while within the pre-intervention trend, different slopes between control and intervention group can be captured (Somers et al., 2013).

TABLE 1 Input and outcome data available for the purpose of this study

Claims and cost data	Health-related outcomes
<ul style="list-style-type: none"> • Hospital care • Outpatient care • Pharmaceuticals • Remedies and aids • Transportation • Nursing care (in- and outpatient) • Disease management programme participation • Specialist outpatient palliative care service 	<p>Primary</p> <ul style="list-style-type: none"> • Adverse drug events (Stausberg & Hasford, 2011 and Hohl et al., 2014) <p>Secondary</p> <ul style="list-style-type: none"> • Hospital admissions • Falls (ICD-10-GM codes S72.0x and S72.1x)

Additional to the statistical specification, it is important to reasonably choose the control group. The control group should be chosen so that potential unobservable shall affect the control group the same way as the intervention group. Thus, the control group needs to be chosen so that unobservable factors that occur in the intervention group are also likely to occur in the control group (Jacob et al., 2016; Somers et al., 2013). For that reason, we choose the control group as individuals from nursing facilities with geo-political proximity (federal state level) as well as individuals within those nursing facilities with propensity score matching. For further details, see Section "Control group."

3.6 | Study management

The study is led by the sickness fund AOK Nordost. The whole study team consists of project managers from the sickness funds Innungskrankenkasse Brandenburg und Berlin, VIACTIV and AOK Nordost. Innungskrankenkasse Brandenburg und Berlin is responsible for project implementation in Berlin and Brandenburg, VIACTIV for North Rhine-Westphalia and AOK Nordost also for the implementation in Berlin and Brandenburg, as well as in Mecklenburg-Vorpommern. Further, each sickness fund provides at least one data specialist for data preparation and data transfer for the reason of this study. TU Berlin is responsible for scientific evaluation of the intervention. Finally, the Chamber of Pharmacists of North Rhine is accountable for the construction and distribution of geriatric teams.

All project partners with at least one delegate participate in a six-week rhythm standardized meeting to discuss project status, progress and upcoming or solved issues. Both the project lead sickness fund AOK Nordost and Gero PharmCare GmbH are always available for participating nursing homes to provide information and answer requests.

4 | DISCUSSION

4.1 | Limitations

Our study comes with several limitations. The first limitation is inherited in the design of the study. Even though we apply both difference-in-differences and propensity score matching, our

estimates may still be biased. The reason for this is that we do not conduct a randomized controlled trial (RCT) but select the control group postintervention and rely on observational data. Explicitly, we cannot eliminate the potential that the control group is subject to time-varying unobservable that influence the outcomes of interest, but that do not affect the outcomes of the intervention group, or vice versa. This is a risk RCTs get rid of by design, namely by randomization upfront treatment (Dehejia & Wahba, 2002). Even though we randomly select controls based on propensity scores, it is possible that we miss a relevant variable while calculating the propensity score that has an impact on the likelihood to receive treatment. This could be, for example, a certain individual trait that NE nurses recruiting patients know from experience, but that is not observable to us. Further, nursing facilities participating in the study might have a different motivation with respect to innovative concepts affecting their patient's treatments than non-participating nursing homes. Such factors cannot be captured in our analysis since we rely on the objectivity of nurses recruiting patients in nursing homes or at home care providers, as well as we cannot randomly select nursing facilities participating in the study.

The second major limitation is due to an external, unforeseeable factor from the perspective of the beginning of the study, namely the SARS-CoV-2 pandemic. The pandemic, which hit Germany in February/March 2020 and then throughout 2020, had an impact on intervention effectiveness, especially in the first and second quarter of the year 2020, even though we established measures to reduce the pandemic impact on the intervention. First, monthly ADE boards were switched from physical meetings to phone calls to prohibit virus transmissions. To keep up key factors of our intervention, ADEs detected during risk identification were still forwarded to physicians to be present during their visits. Second, case and risk conferences as well as pharmaceutical audits have been stopped during the first wave of the pandemic. These parts of the intervention rather focus on mid- and long-term success and could be paused for a period without jeopardizing key features of the intervention. Third, in case pharmacies were no longer able to participate in phone calls in ADE meetings, Gero PharmCare GmbH, which also employs pharmacists, supported with pharmaceutical advice from their employed pharmacists. Fourth, trainings were held remotely via an online application rather than physically, as done before. The pandemic forced some participating nursing facilities to pause or stop their participation in the study. In general, nursing homes that already made far progress in project implementation were more likely to continue the project

without huge deviations, while nursing homes with less progress in implementation were less likely to proceed during the pandemic successfully. Additionally, the pandemic might have hit certain nursing facilities harder than others, either due to regional variation in SARS-CoV-2 cases or variation of SARS-CoV-2 cases across nursing facilities within the same region, or also due to regional (communal level) variation in pandemic response, as well as nursing facility level variation in response. Nursing care patients are among the most vulnerable groups during the pandemic. Jeopardizing business as usual, the SARS-CoV-2 pandemic could have shifted the focus of the personnel to other factors than the intervention, and efforts to detect ADEs might have diminished. In case of an outbreak within a nursing home, the situation was often life-threatening for patients. To limit transmission, patients in nursing homes often were not allowed to see their relatives. Further, visits from personnel other than nurses or physicians (e.g. ergo- or physiotherapist) were strictly limited during 2020. Consequentially, bio-psychosocial stress was highly increased for nurses during that time. In order to better understand the situation in nursing facilities, especially nursing homes, Gero PharmCare GmbH contacted entities both orally and per mail to get an overview of the situation within nursing homes.

However, limitations due to the SARS-CoV-2 pandemic would impact the estimated effect of the intervention downwards, yielding more conservative estimates than without pandemic conditions. Further, power also is likely negatively affected due to a reduction in the potential sample size. *Ceteris paribus*, if we detect an effect in the evaluation, the likelihood is increased that the effect is non-random and probably larger in size than it will be detected in our evaluation.

5 | TRIAL STATUS

The protocol was written on January 10, 2020. The first date of recruitment was 1st of August, 2018. Recruitment was completed on 31st of March 2020 with 1,557 individuals respectively.

CONFLICT OF INTEREST

FH is CEO of the company Gero PharmCare GmbH. FH is further affiliated with the University of Witten Herdecke, where OAV is part of his Habilitation. HJH is associated with research projects from research college of the Robert-Bosch-Foundation, science forum geriatrics, Deutsche Bank and the innovations fund from the G-BA. HJH further receives lecture fees from Pfizer Pharma, Bayer Health Care and AO Trauma Europe. He further offers consulting services for Pfizer Pharma.

AUTHOR CONTRIBUTIONS

BL wrote a first draft of this manuscript and revised it upon comments of VV. Afterwards, the draft was forwarded to all other co-authors which commented the draft. Comments were adopted from BL and VV.

ETHICAL APPROVAL

The study was ethically approved by the ethics committee of the University of Witten/Herdecke on 29th of June 2018 with a positive votum (application number: 76/2018).

DATA AVAILABILITY STATEMENT

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

CONSENT FOR PUBLICATION

Not applicable.

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ENDNOTE

¹ URL: <https://innovationsfonds.g-ba.de/projekte/neue-versorgung-sformen/oav-optimierte-arzneimittelversorgung-fuer-pflegebeduerftige-geriatriche-patienten.111>, last access on 24th of February 2021.

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