Additional file 1. Brief description of AdAM sub-studies

SUB-STUDY BIELEFELD. HEALTH-ECONOMIC ANALYSIS.

The aim of this sub-study is to estimate the cost-effectiveness of the AdAM intervention compared to usual care.

The economic analysis will be conducted from a third-party payer perspective, which is the perspective of the statutory health insurance funds in Germany. Health effects will be measured by use of the composite endpoint of the clinical study combining hospital admissions and deaths.

The analysis of all reimbursed direct health care costs will be based on health insurance claims data comprising details on physician visits, inpatient hospital stays, pharmaceuticals (prescription medication), outpatient health care services provided by non-physicians and therapeutic appliances, rehabilitation, and sick pay. Arising costs, such as costs of IT-infrastructure, coordination, maintenance, training and fees, will be used to estimate the overall costs of the AdAM intervention. Fees for physicians will be varied in sensitivity analysis.

The cost-effectiveness of the intervention will be measured by the incremental cost-effectiveness ratio (ICER), which is expressed as the ratio of the difference in overall costs between the control and the intervention group and the difference in effects between both groups. For the ICER calculation of the base case, mean values of costs and effects will be used. In sensitivity analysis, also median values will be used.

Further analyses will be based on the composite endpoint's components (hospital admissions and deaths), on life years gained (LYs), and on quality-adjusted life years (QALYs). To determine the LYs, the remaining life expectancy in both the control and intervention group will be estimated using mortality tables. In order to take into account differences in quality of life between ages when calculating QALYs, age-dependent utility values will be obtained from the literature.

All future costs and health effects will be discounted by 3% per year according to recommendations by the German institute for efficiency and quality in health care (IQWiG). In sensitivity analysis, the discount rate will be varied from of 0% to 5%.

SUB-STUDY KÖLN. ANALYSIS OF BARRIERS AND FACILITATORS: QUALITATIVE INTERVIEWS AND FOCUS GROUPS WITH PHYSICIANS.

The aim of this sub-study is to identify factors facilitating or hindering the successful implementation of the intervention from a general practitioner's point of view and evaluate which factors facilitate or hinder the effective performance of systematic medication-checks and optimization. Hereby is expected to get insights how the intervention can be optimized and adapted for general practitioners' high-level acceptance and effectiveness of optimized medication-checks by area-wide implementation.

Therefore a multistage mixed-methods-Approach will be conducted (combination of qualitative and quantitative outcomes) (1).

Level 1: To analyze general practitioners subjectively perceived barriers and resources regarding implementation, guided expert-interviews will be conducted (n= 5-10) (face-to-face-interviews or telephone-interviews) (2,3) to explore the field. Therefore, a convenient sample strategy will be applied. Furthermore, formative evaluation will take part during the trial with two additional time points of qualitative data collection related to relevant emerging topics concerning successful implementation.

Level 2: Results of qualitative data collection will be used for understanding practical orientation patterns of general practitioners (how do they actually use AdAM in real life settings) and their conjunctive experiential space (4). Focus groups with general practitioners of intervention and control group (total, n= 4) will be conducted concerning their experiences and expectations of the project.

Level 3: Results of qualitative data collection will be used to prepare a quantitative general practitioners survey, in which ~~all~~ participating physicians of the intervention group will be asked about barriers and facilitators of the implementation. The survey aims representative detection of general practitioners factors, which facilitate or hinder implementation and identify specific attributes of 'early adapters' and 'late adapters' (5). Quantitative data will be evaluated descriptive and by applying appropriate multiple regression models.

The quality of the qualitative research data collection and analysis in interviews and focus groups is assured by audio recording as well as by transcription according to established standards and by independent coding and subsequent interpretation by a group of researchers. Data analysis will comprise qualitative content analysis according to Kuckartz (6).

Quality assurance concerning the survey conduct is assured by standards of survey development, pretesting, Dillman's Total Design (7) method for increasing response rates and data preparation with the Teleform® software.

SUB-STUDY FRANKFURT. ANALYSIS OF BARRIERS, FACILITATORS AND UNINTENDED CONSEQUENCES: QUALITATIVE INTERVIEWS WITH PATIENTS

The aim of this sub-study is to identify factors facilitating or hindering the successful implementation of the intervention. We especially focus on patient-perceived unintended consequences of the intervention, e.g. fear resulting from the exchange of information between several doctors or resentments towards the implemented technology.

The sub-study starts after the positive ethics vote dedicated to the qualitative study has been received (second vote). Patients who have already received the intervention, can be included in the study (inclusion criterion: invoiced EBM-code). Patients will be recruited by their general practitioners. General practitioners are trustful "gatekeepers" with the potential to motivate patients to participate (8). After written informed consent, contact details will be forwarded to the Institute of General Practice in Frankfurt/Main. A target sample of 20 patients (balanced with regard to sex, age) out of two or more practices will be included in the study.

We will interview the patients via telephone (9); the interviews are expected to take 20-40 minutes each. The interviewer will use a semi-structured interview guide, which will be pilot-tested in three to four think-aloud-interviews beforehand. Interviews will be audio recorded after informed consent and transcribed verbatim according to established standards (10). Data analysis will comprise qualitative content analysis according to Kuckartz (10). Data will be independently coded and subsequently interpreted by two researchers. The strategy of subsumption will be used to develop content categories mixed deductively-inductively. Data will be evaluated supported by software MAXQDA© at Goethe University in the Institute of General Practice in Frankfurt/Main.

ADAM PROCESS EVALUATION

A process evaluation is an essential part of the evaluation of complex medical interventions. The process evaluation in AdAM will study the following aspects:

1) Numbers of patients per practice from the list of potentially eligible patients that participated in AdAM ("reach")
2) Enrolment rate of GPs, general practices and patients measured as the number of GPs, general practices and patients per potentially eligible number of GPs, general practices and patients during the 15 months from baseline minus baseline (T1–T0) ("reach").
3) Number of patients per practice that were not included in the list of potentially eligible patients that participated in AdAM to evaluate the number of patients who benefit from the AdAM service.
4) Quantitative aspects of the intervention: to which extent was the intervention eMMa® applied to patients ("dose")?
    a. Number of GPs and general practices who use eMMa® to print a medication plan 15 months (once a year and more than once a year) from baseline minus baseline (T1–T0).
    b. Number of safety key figures retrievals and use of patient safety examination to ensure the frequency of use of eMMa® safety functionalities (BRAVO quality indicators).
5) Qualitative aspects of the intervention: was the intervention eMMa® applied as planned ("fidelity")?
6) Adaptation of the intervention: which modifications were made to adjust the intervention to heterogeneous processes in participating practices ("tailoring")?

Software log files provided by RpDoc®Solutions GmbH will comprise the data needed for analyses. Pseudonyms will be used to prevent identification of individual patients, practices or doctors.

Further details of the process evaluation (detailed research questions, MDS) will be provided a priori to the planned analyses.

ADAM SUSTAINABILITY ASSESSMENT

A fading effect over time in interventions for the improvement of drug management has been mentioned in the literature (11). This sustainability assessment aims to analyze such temporary effects. The goal is to determine if improvements in the prescription of drugs due to eMMa® can still be found after more than five quartiles. Therefore, it is necessary for both the intervention group and the control group to receive the intervention, i.e. eMMa®.

The sustainability assessment is meant to provide insights on the planned rollout on larger groups. Therefore, it is necessary for the control group to receive the full intervention.

Any further details will be pre-specified in a separate protocol.

SUB-STUDY WUPPERTAL: QCAS TO EXPLORE THE RELATIONSHIP BETWEEN ORGANIZATIONAL CONTEXT, IMPLEMENTATION PROCESS AND QUALITY OF CARE

The aim of this sub-study is to examine the process of effectiveness development, the interaction among key drivers (configurations of success) and to investigate, how these key drivers influence effect sustainability. The analyses of this sub-study will be based on practices of the intervention group of the parallel cluster-randomised controlled trial (c-RCT) and those practices of the control group who joined the intervention mode 15 months after their recruitment. We will include all control group practices who change intervention status at least until 30/06/2020.

QCAs will be based on a conceptual model comprising contextual and implementation process factors affecting intervention's effectiveness. Research suggests that attributes characterising the organisational context are important for the development of habitual behaviour and the successful adoption of interventions (12). In addition, contemporary definitions of organisations have evolved from a closed-system perspective (organisations = isolated systems with no interaction with their environment) to an open-system perspective. Therefore, organisational attributes will be defined on three distinct levels of analysis: 1) the behaviour of individuals, 2) the structural features and 3) the organisation viewed as an entity operating in a larger system of relations (13).

Analytic methods

In a first step, fuzzy set qualitative comparative analysis will be used to identify pathways – that is, different combinations of organisational attributes and implementation process characteristics – associated with:

1. sites' success in attaining a relative risk reduction in the primary end point at the end of the c-RCT (change is measured in comparison to the control groups' results) – QCA 1,
2. short term effects (change of secondary endpoints after the first five months of intervention) – QCA 2.

In a second step, the findings of the first QCA will be integrated in a multilevel model (two-level HML) in which the cross-level interactions of the pathways will be investigated and mechanisms suited for reaching sustainability at the end of a three month follow-up phase will be explored.

To prepare results of the first QCA for use in HLM, a categorisation of each study site as a member of one of the pathways is planned. Only those practices will be included in the multilevel model that are member of a configuration sufficient for outcome and part of c-RCT's intervention group. To explore mechanisms suited for a sustainable intervention effect, the two-level HLM will be estimated with the pathways (configurations) at the macro level. At the micro level a variable, which measures the stability of the attained performance level (dichotomous definition: "1" if there is no increase in all-causes hospital admissions and all-causes deaths per practice over the follow-up phase, otherwise "0") will be included. As explanatory variables the four constructs of the normalisation process theory (NPT; coherence, cognitive participation, collective action, reflexive monitoring) will be considered. This construct will be measured at the beginning of the follow-up phase and by applying the instrument NoMAD (14). They will describe physicians' views about how an intervention impacts on their work, and their expectations about whether it could become a routine part of their work.

Site sampling and data source:

The first QCA and the multilevel model will include only practices of the intervention group. The second QCA will use practices of the control group as well, after this group has joined the intervention mode.

Parameters corresponding to factors in the conceptual model will be derived from a survey, which is organised in two waves (first in 2019, second in 2020). The outcome measure will be based on secondary data (claims data). In addition, structural data of the practices (e.g. practice infrastructure, patient structure) and use of support will be obtained from other project partners (e.g. by extracting information out of CDSS log files).

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